НАЦІОНАЛЬНА АКАДЕМІЯ НАУК УКРАЇНИ
ІНСТИТУТ ОРГАНІЧНОЇ ХІМІЇ НАН УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

Рік заснування – 1966

ЖУРНАЛ ОРГАНІЧНОЇ ТА ФАРМАЦЕВТИЧНОЇ ХІМІЇ

JOURNAL OF ORGANIC AND PHARMACEUTICAL CHEMISTRY

2024 — том 22, випуск 3 (87)

Харків
НФаУ

У журналі розглянуто проблеми синтезу й аналізу органічних та елементоорганічних сполук, аналогів природних сполук і лікарських субстанцій, наведено результати фізико-хімічних досліджень у вищезазначених напрямах. Також з погляду (біо)органічної, фармацевтичної, аналітичної та фізичної хімії проаналізовано питання з різних аспектів рослинництва, ґрунтознавства й дослідження навколишнього середовища.

Для працівників науково-дослідних установ, вищих навчальних закладів та фахівців хімічного, фармацевтичного, біологічного, медичного і сільськогосподарського профілів.

«Журнал органічної та фармацевтичної хімії» внесено до затвердженого МОН України Переліку наукових фахових видань України (категорія «Б») для опублікування результатів дисертаційних робіт за спеціальністю 102 – Хімія та 226 – Фармація, промислова фармація (наказ МОН України від 28.12.2019 р. № 1643); індексовано в наукометричних базах даних: Chemical Abstracts (CAS), Index Copernicus; внесено до каталогів та пошукових систем: Directory of Open Access Journals (DOAJ), Bielefeld Academic Search Engine (BASE), Directory of Open Access scholarly Resources (ROAD), PKP Index, Ulrich's periodicals, Worldcat, НБУ ім. В. І. Вернадського і УРЖ «Джерело».

Затверджено до друку вченою радою Інституту органічної хімії НАН України, протокол № 22 від 10.12.2024 р.

Затверджено до друку вченою радою Національного фармацевтичного університету, протокол № 10 від 28.11.2024 р.

Адреса для листування: 61002, м. Харків, вул. Григорія Сковороди, 53, Національний фармацевтичний університет, редакція «Журналу органічної та фармацевтичної хімії». E-mail: publish@nuph.edu.ua, orgpharm-journal@nuph.edu.ua. Сайт: http://ophcj.nuph.edu.ua

Рішення Національної ради України з питань телебачення і радіомовлення № 1911 (протокол № 17 від 30.05.2024 р.) "Про заяви Національного фармацевтичного університету, м. Харків, щодо реєстрації суб'єкта у сфері друкованих медіа" (ідентифікатор медіа R30-05024)

Підписано до друку 19.12.2024 р. Формат 60 × 84 1/8.

Папір офсетний. Друк ризо. Умовн. друк. арк. 9,3. Обліков.-вид. арк. 10,76. Тираж 50 прим.

Редактори — О. Ю. Гурко, Л. І. Дубовик. Комп'ютерне верстання — О. М. Білинська

«Журнал органічної та фармацевтичної хімії». Том 22, випуск 3 (87), 2024

ISSN 2308-8303 (Print)

ISSN 2518-1548 (Online)

Journal of Organic and Pharmaceutical Chemistry

Original Research

OPEN ACCESS
Freely available online on
http://ophcj.nuph.edu.ua

UDC 547.513+547.514+546.16

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Synthesis and Physicochemical Characteristics of 6,6-Difluorobicyclo[3.2.0]heptane Derivatives

Abstract

The gram-scale synthesis of 6,6-difluorobicyclo[3.2.0]heptane-derived building blocks (i.e., primary amine and carboxylic acid) was performed *via* the deoxofluorination of the corresponding bicyclic keto ester with diethylaminosulfur trifluride (DAST). Physicochemical properties of the compounds obtained (i.e., pK_a) or their model benzamide / anilide derivatives (i.e., Log*P*) were determined experimentally and compared to those of monocyclic and non-fluorinated bicyclic counterparts. It was found that *gem*-difluorination expectedly decreased the pK_a values by 0.3–0.5 units, whereas the Log*P* values were decreased by 0.54–0.55 units. Meanwhile, the bicyclic system itself had a negligible impact on the compounds' acidity and lipophilicity compared to the monocyclic counterparts.

***Keywords*:** fluorine; bicyclic compounds; acidity; lipophilicity; building blocks

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Синтез та фізико-хімічні характеристики похідних 6,6-дифлуоробіцикло[3.2.0]гептану

Анотація

Здійснено синтез будівельних блоків на основі 6,6-дифлуоробіцикло[3.2.0]гептану (а саме, первинного аміну та карбонової кислоти) у грамових кількостях шляхом деоксофлуорування відповідного кетоестеру. Експериментальним шляхом визначено фізико-хімічні властивості одержаних сполук (зокрема pK_a) або їх модельних бензамідних / анілідних похідних (зокрема Log*P*), а результати зіставлено з даними для моноциклічних та нефлуорованих біциклічних аналогів. Виявлено, що *гем*-дифлуорування очікувано зменшило значення pK_a на 0.3–0.5 одиниці, тоді як значення Log*P* зменшилось на 0.54–0.55 одиниці. Водночас власне біциклічна система мала незначний вплив на кислотні властивості та ліпофільність сполук, якщо порівнювати з моноциклічними аналогами.

***Ключові слова*:** Флуор; біциклічні сполуки; кислотність; ліпофільність; будівельні блоки

Citation: Moroz, B. L.; Holovach, S. M.; Melnykov, K. P.; Lesyk, D. S.; Filatov, A. A.; Grygorenko, O. O. Synthesis and physicochemical characteristics of 6,6-difluorobicyclo[3.2.0]heptane derivatives. *Journal of Organic and Pharmaceutical Chemistry* **2024**, *22* (3), 3–9
https://doi.org/10.24959/ophcj.24.314176
Supporting information: Copies of ^{1}H, ^{13}C and ^{19}F NMR spectra.
Received: *15 October 2024*; **Revised:** *3 November 2024*; **Accepted:** *5 November 2024*

Funding: The work was supported by Enamine Ltd., Ministry of Education and Science of Ukraine (grant No. 0122U001962 (22BF037-02)), and the National Academy of Sciences of Ukraine (grant No. 0119U102718).
Conflict of interests: The authors are employees or consulting scientists at Enamine Ltd. that offers the title compounds from the company's catalog.

■ Introduction

Fluorinated derivatives of saturated rings have attracted much attention recently, and several drug molecules of this class have entered the market over the last decade [1, 2]. On the other hand, conformational restriction through the introduction of a bicyclic ring system is a well-recognized design approach in medicinal chemistry, providing unique chemotypes with improved physicochemical and biological properties [3–5]. In this view, building blocks derived from fluorinated saturated bicyclic scaffolds can be considered advantageous to early drug discovery; however, only limited examples thereof can be found in the literature to date (**Figure 1**) [6–8].

In this work, we propose a novel fluorinated saturated bicyclic scaffold of potential interest to the drug discovery – 6,6-difluorobicyclo[3.2.0]heptane. We describe the synthesis of its functionalized derivatives – building blocks **1** and **2**, their physicochemical characteristics in terms of acid-base properties and lipophilicity, and comparison with non-fluorinated and monocyclic counterparts.

■ Results and discussion

Our synthesis of compounds **1** and **2** was very straightforward and started from commercially available keto ester **3** that could also be prepared through [2+2] cycloaddition according the protocols [9] previously reported (**Scheme 1**). Deoxofluorination of compound **3** proceeded smoothly upon the action of DAST in refluxing CH_2Cl_2 and provided a target *gem*-difluorinated derivative **4** in the yield of 62%. A mild alkaline hydrolysis of ester **4** gave diastereopure carboxylic acid **1** in the yield of 86%. Its further DPPA-mediated Curtius reaction followed by the interception of the intermediate isocyanate with *t*BuOH and *N*-Boc deprotection gave amine **2** (59% yield, as hydrochloride).

Acid-base titrations of compounds **1** and **2**×HCl, as well as their non-fluorinated counterparts **5** and **6** were performed according to the protocol [10] previously reported. The results are summarized in **Figure 2** along with the data for the corresponding cyclohexane and cycloheptane derivatives **7**–**10** [10]. It was found that the *gem*-difluorination decreased acidity of the COOH and NH_3^+ functions by 0.3 and 0.5 pK_a units, respectively. Meanwhile, the impact of the bicyclic system on the compounds' acidity was negligible.

To evaluate the lipophilicity increment of the title scaffold, model benzamide or anilide derivatives were prepared from building blocks **1**, **2**×HCl, **5**, and **6** using chloro-*N*,*N*,*N*′,*N*′-tetramethylformamidinium hexafluorophosphate (TCFH) as an

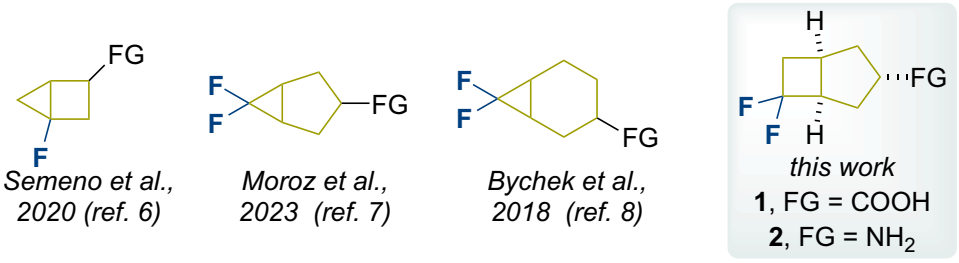
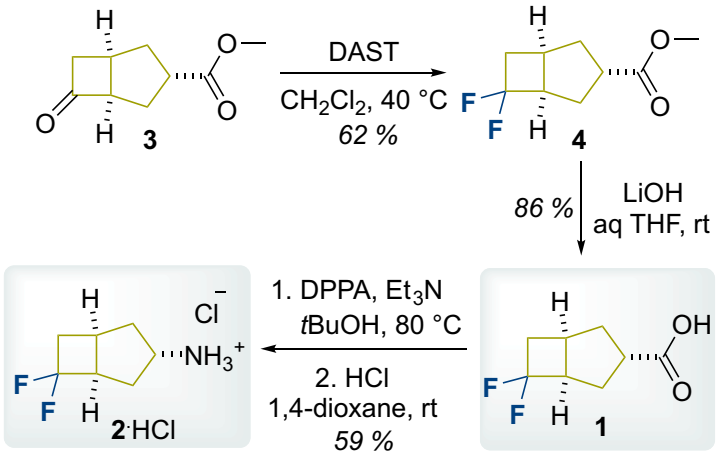


Figure 1. Selected examples of fluorinated fused bicyclic building blocks, including 6,6-difluorobicyclo[3.2.0]heptanes described in this work (FG = NH_2 or COOH)



Scheme 1. The synthesis of building blocks **1** and **2**×HCl

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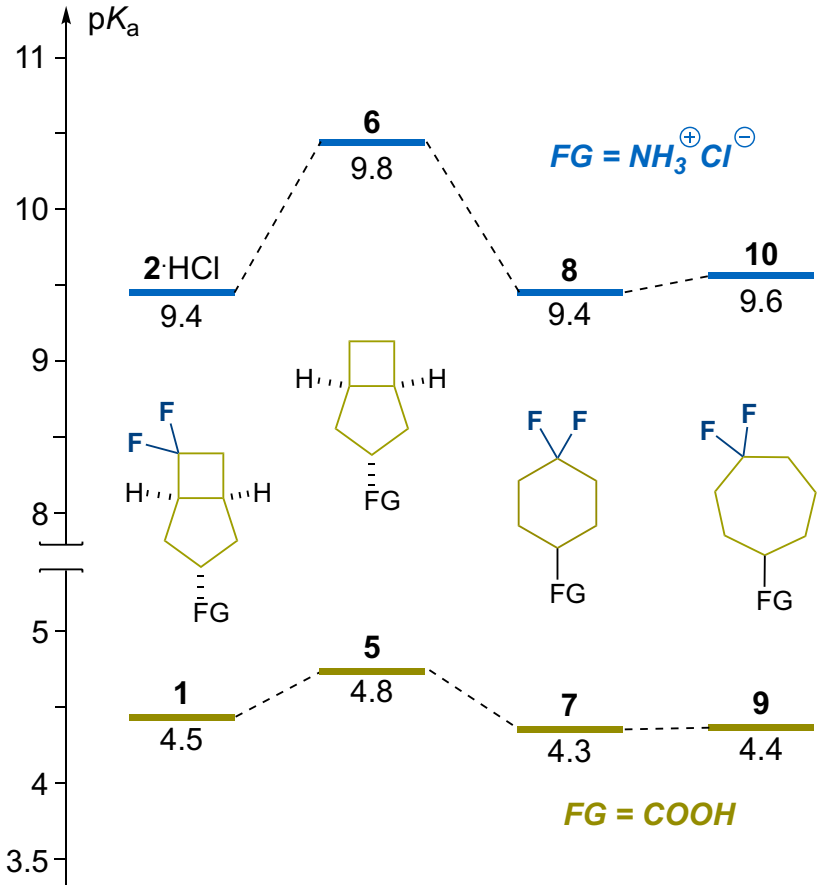
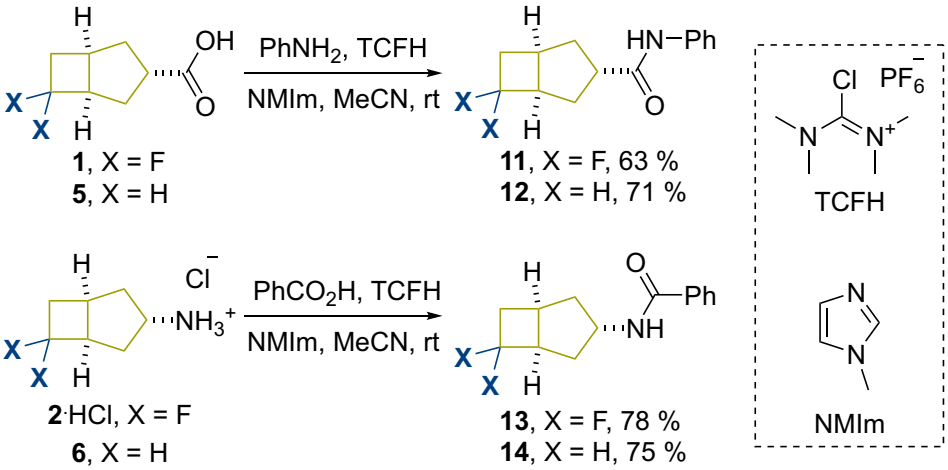


Figure 2. The pK_a values for compounds **1**, **2**×HCl, and **5**–**10**

activator (**Scheme 2**). The Log*P* values were determined using the shape-flask method [11]. The results are given in **Figure 3** along with the data previously reported for *gem*-difluorinated cycloalkanes **15**–**18**. It is apparent that *gem*-difluorination of the bicyclo[3.2.0]heptane system resulted in a decrease of the Log*P* values by 0.54–0.55 units, whereas the conformational restriction imposed by the bicyclic system did not have a considerable effect (compare **13**/**17** and **14**/**18** pairs). This is contrary to the previous results on the disubstituted bicyclic ring systems where diminished lipophilicity was noted compared to the monocyclic counterparts [12].

■ Conclusions

A straightforward gram-scale synthesis of 6,6-difluorobicyclo[3.2.0]heptane-derived building blocks was described. The method is based on the deoxofluorination of the corresponding commercially available bicyclic ketoester with DAST. After the standard functional group transformations (i.e., ester hydrolysis and modified Curtius



Scheme 2. The synthesis of anilides / benzamides **11**–**14**

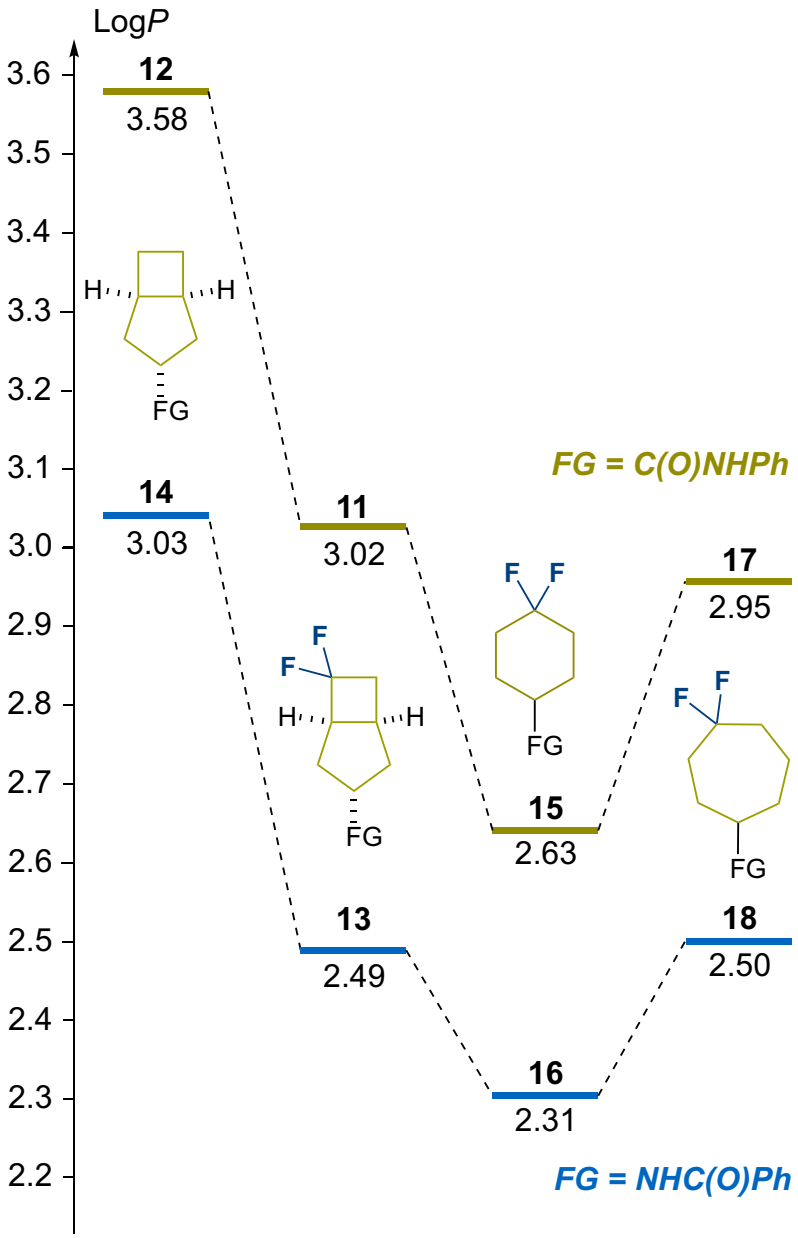


Figure 3. Log*P* values for compounds **11**–**18**

reaction), the corresponding carboxylic acid and primary amine hydrochloride were obtained in good overall yields. The acid-base titration of the products obtained, as well as their non-fluorinated and monocyclic counterparts showed that *gem*-difluorination expectedly decreased the compound's acidity (by 0.3–0.5 units). Lipophilicity was also decreased by 0.54–0.55 Log*P* units. Meanwhile, the bicyclic system itself did not have significant impact on either acidity or lipophilicity.

■ Experimental part

The solvents were purified according to the standard procedures [13]. Diethyl(trifluoro-λ⁴-sulfanyl)amine (DAST), diphenyl phosphoryl azide (DPPA), tetramethylchloroformamidinium hexafluorophosphate (TCFH), starting compounds **3**, **5**, and **6** were obtained from Enamine stock; all other starting materials were available commercially. Melting points were measured on the MPA100 OptiMelt automated melting point system. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR), on an Agilent ProPulse 600 spectrometer (at 151 MHz for ^{13}C) and a Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts were reported in ppm (δ scale) downfield from TMS as an internal standard and were referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. For ^{19}F NMR CCl_3F was

ISSN 2308-8303 (Print) / 2518-1548 (Online)

used as an internal standard. Coupling constants (*J*) were given in Hz. The column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. The reverse phase high-performance liquid chromatography (RP-HPLC) was performed on an Agilent 1260 Infinity instrument with an UV/VIS detection.

Methyl (1*R,3*S**,5*R**)-6,6-difluorobicyclo[3.2.0]heptane-3-carboxylate (4)**

To a solution of keto ester **3** (5.00 g, 29.7 mmol) in CH_2Cl_2 (150 mL), a neat DAST (39.3 mL, 0.297 mol) was added dropwise at 0 °C. The reaction mixture was warmed to rt and stirred at reflux (bath temperature 40 °C) overnight, then cooled and carefully poured onto ice-cold water. The biphasic solution was neutralized with saturated aq. $NaHCO_3$ to pH 6–7 and then extracted with CH_2Cl_2 (2×200 mL). The organic layer was washed with brine (100 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The product was purified by flash chromatography (gradient hexanes/*t*BuOMe 20:1 to 10:1 (*v*/*v*) as eluent) to give product **4**.

A yellowish oil. Yield – 3.50 g (62%). Anal. Calcd for $C_9H_{12}F_2O_2$, %: C 56.84, H 6.36. Found, %: C 57.05, H 6.31. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.77–1.88 (2H, m, CH_2), 1.95 (1H, dd, J_{HF} = 13.0 Hz, J_{HF} = 6.5 Hz, CH_2), 2.01–2.13 (1H, m, CH_2), 2.26 (1H, dd, J_{HF} = 13.6 Hz, J_{HF} = 6.7 Hz, CH), 2.64–2.80 (2H, m, CH_2), 3.02 (1H, hept, J_{HF} = 6.3 Hz, CH), 3.15–3.25 (1H, m, CH), 3.70 (3H, s, CH_3). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$), δ, ppm: 28.2 (dd, J_{CF} = 10.7 Hz, J_{CF} = 7.9 Hz), 29.7 (t, J_{CF} = 4.6 Hz), 36.3 (d, J_{CF} = 3.2 Hz), 39.5 (t, J_{CF} = 23.1 Hz), 43.0, 50.7 (dd, J_{CF} = 24.0 Hz, J_{CF} = 21.8 Hz), 52.0, 120.5 (dd, J_{CF} = 288.9 Hz, J_{CF} = 277.9 Hz), 175.4. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$), δ, ppm: –90.7 (d, J_{FF} = 196.6 Hz, CF_2), –98.8 (d, J_{FF} = 196.6 Hz, CF_2).

(1*R,3*S**,5*R**)-6,6-Difluorobicyclo[3.2.0]heptane-3-carboxylic acid (1)**

To a solution of carboxylate **4** (2.50 g, 13.2 mmol) in THF (30 mL), a solution of LiOH·H_2O (1.11 g, 26.4 mmol) in water (8 mL) was added at rt, and the resulting mixture was stirred overnight. The volatiles were evaporated under reduced pressure (bath temperature below 40 °C), then the aqueous residue was acidified with aq. HCl (2 M, 35 mL) upon cooling in an ice water bath, and the product was extracted with CH_2Cl_2 (3×30 mL). The organic layer was washed with water (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give product **1**.

A brownish powder. Yield – 2.00 g (86%). M. p. 99–102 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.62–1.78 (2H, m, CH_2), 1.88 (1H, dd, J_{HF} = 12.8 Hz, J_{HF} = 6.4 Hz, CH_2), 2.06 (1H, dd, J_{HF} = 13.6 Hz, J_{HF} = 6.7 Hz, CH_2), 2.11–2.26 (1H, m, CH), 2.59–2.73 (2H, m, CH_2), 2.90 (1H, hept, J_{HF} = 6.6 Hz, CH), 3.09–3.21 (1H, m, CH). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6), δ, ppm: 27.5 (dd, J_{CF} = 11.3 Hz, J_{CF} = 7.6 Hz), 28.9 (t, J_{CF} = 4.7 Hz), 35.2 (d, J_{CF} = 3.3 Hz), 38.3 (t, J_{CF} = 22.4 Hz), 42.5, 49.9 (dd, J_{CF} = 23.5 Hz, J_{CF} = 21.4 Hz), 120.9 (dd, J_{CF} = 289.6 Hz, J = 276.7 Hz), 175.3. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6), δ, ppm: –96.8 (d, J_{FF}= 193.4 Hz, CF_2), –88.9 (d, J_{FF} = 193.4 Hz, CF_2). HRMS (ESI/QTOF), *m*/*z*: Calcd for $C_8H_9F_2O_2^-$ 175.0576 [M–H]$^-$. Found: 175.0579.

(1*R,3*S**,5*R**)-6,6-Difluorobicyclo[3.2.0]-heptan-3-amine hydrochloride (2×HCl)**

To a solution of carboxylic acid **1** (1.30 g, 7.38 mmol) in *t*BuOH (20.0 mL), Et_3N (1.13 mL, 8.12 mmol) and DPPA (1.91 mL, 8.85 mmol) were added sequentially at 80 °C. The reaction mixture was slowly heated to reflux and stirred at the same temperature overnight. Then, the solution was cooled, diluted with EtOAc (100 mL), and washed with brine (3×30 mL); the organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The residual crude *N*-Boc-protected amine was dissolved in anhydrous HCl (*ca.* 3.6 M in dioxane, 15 mL) and stirred at room temperature overnight. The resulting precipitate was filtered and washed with *t*BuOMe (4×10 mL) to give product **2**×HCl.

A brownish amorphous solid. Yield – 0.800 g (59%). ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.67–1.81 (2H, m, CH_2), 2.00 (1H, dd, J_{HF} = 12.7 Hz, J_{HF} = 6.3 Hz, 0.5×CH_2), 2.15–2.27 (2H, m, 0.5×CH_2+CH), 2.62–2.77 (2H, m, CH_2), 3.15–3.30 (1H, m, CH), 3.55–3.69 (1H, m, CH), 8.45 (3H, br. s, NH_3^+). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6), δ, ppm: 26.0 (t, J_{CF} = 9.3 Hz), 29.7, 35.4, 38.5 (t, J_{CF} = 22.4 Hz), 48.6 (m), 50.3, 120.7 (dd, J_{CF} = 288.1 Hz, J_{CF} = 277.8 Hz). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6), δ, ppm: –96.3 (d, J_{FF} = 194.1 Hz, CF_2), –89.2 (d, J_{FF} = 194.3 Hz, CF_2). HRMS (ESI/QTOF), *m*/*z*: Calcd for $C_7H_{12}F_2N^+$ 148.0932 [M + H]$^+$. Found: 148.0928.

(1*R,3*S**,5*R**)-6,6-Difluoro-*N*-phenylbicyclo[3.2.0]heptane-3-carbox-amide (11)**

To a solution of compound **1** (0.200 g, 1.14 mmol) in CH_3CN (10.0 mL), aniline (110.0 μL, 1.25 mmol),

1-methyl-1*H*-imidazole (270.0 μL, 3.41 mmol, 0.280 g) and TCFH (0.351 g, 1.25 mmol) were sequentially added. The reaction mixture was stirred at room temperature overnight. The crude solution was then purified by RP-HPLC (column: CHROMATOREX C18 100×19 mm, 5 μm, 30 mL/min; 23–50% CH_3CN/H_2O gradient) to yield a pure product **11**.

A yellow powder. Yield – 0.180 g (63%). M. p. 158–160 °C. Anal. Calcd for $C_{14}H_{15}F_2NO$, %: C 66.92, H 6.02, N 5.57. Found, %: C 67.28, H 6.21, N 5.71. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.72–1.94 (3H, m, CH_2+CH), 2.04–2.15 (2H, m, CH_2), 2.65–2.80 (2H, m, CH_2), 3.08 (1H, m, CH), 3.17–3.27 (1H, br. m, CH_2), 7.03 (1H, t, J_{HH} = 7.6 Hz, PhH), 7.29 (2H, m, PhH), 7.62 (2H, d, J_{HH} = 8.0 Hz, PhH), 10.05 (1H, s, NH). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6), δ, ppm: 27.8 (dd, J_{CF} = 11.2 Hz, J_{CF} = 7.6 Hz), 29.4 (t, J_{CF} = 4.5 Hz), 36.1 (d, J_{CF} = 3.1 Hz), 38.6 (t, J_{CF} = 22.4 Hz), 44.2, 50.2 (t, J_{CF} = 22.3 Hz), 119.1, 121.1 (dd, J_{CF} = 289.8 Hz, J_{CF} = 276.5 Hz), 123.0, 128.6, 139.2, 172.0. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6), δ, ppm: –96.1 (d, J_{FF} = 193.1 Hz, CF_2), –88.9 (d, J_{FF} = 192.9 Hz, CF_2).

***N*-[(1*R**,3*S**,5*R**)-6,6-Difluorobicyclo[3.2.0]-heptan-3-yl]benzamide (12)**

To a solution of compound **2**×HCl (0.307 g, 1.67 mmol) in CH_3CN (10.0 mL), benzoic acid (0.225 g, 1.84 mmol), 1-methyl-1*H*-imidazole (530.0 μL, 6.69 mmol, 0.549 g) and TCFH (0.515 g, 1.84 mmol) were sequentially added. The reaction mixture was stirred at room temperature overnight. The crude solution was then purified by RP-HPLC (column: XBridge BEH C18 100×19 mm, 5 μm, 30 mL/min; 18–40% CH_3CN/H_2O gradient) to yield a pure product **12**.

A yellowish powder. Yield – 0.300 g (71%). M. p. 155–157 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.71–1.86 (2H, m, CH_2), 1.90 (1H, dd, J_{HF} = 12.9 Hz, J_{HF} = 6.6 Hz, CH_2), 2.03–2.19 (2H, m, 0.5×CH_2+CH), 2.65–2.82 (2H, m, CH_2), 3.07 (1H, hept, J_{HF} = 6.5 Hz, CH), 3.20–3.25 (1H, m, CH), 7.03 (1H, t, J_{HH} = 7.4 Hz, PhH), 7.29 (2H, t, J_{HH} = 7.7 Hz, PhH), 7.62 (2H, d, J_{HH} = 8.0 Hz, PhH), 10.04 (1H, s, PhH). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6), δ, ppm: 25.8 (dd, J_{CF} = 10.9 Hz, J_{CF} = 7.5 Hz), 31.0 (t, J_{CF} = 4.2 Hz), 36.7 (d, J_{CF} = 3.0 Hz), 38.9 (t, J_{CF} = 22.7 Hz, overlapped with the solvent residual peak), 48.5 (t, J_{CF} = 22.5 Hz), 49.5, 121.2 (dd, J_{CF} = 289.3 Hz, J_{CF} = 277.3 Hz), 127.2, 128.1, 131.0, 134.5, 166.0. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6), δ, ppm: –96.3 (d, J_{FF} = 193.3 Hz, CF_2), –88.6 (d, J_{FF} = 193.3 Hz, CF_2). HRMS (ESI/QTOF), *m*/*z*: Calcd for $C_{14}H_{16}F_2NO^+$ 252.1194 $[M + H]^+$. Found 252.1189.

(1*R,3*S**,5*S**)-N-Phenylbicyclo[3.2.0]heptane-3-carboxamide (13)**

To a solution of carboxylic acid **5** (0.200 g, 1.43 mmol) in CH_3CN (10.0 ml), aniline (140.0 μL, 1.57 mmol), 1-methyl-1*H*-imidazole (340.0 μL, 28 mmol, 3.0 equiv) and TCFH (0.439 g, 1.57 mmol) were sequentially added. The reaction mixture was then stirred at room temperature overnight. The crude solution was purified by RP-HPLC (column: CHROMATOREX C18 SMB100–5T 100×19 mm, 5 μm, 30 mL/min; 23–50% CH_3CN/H_2O gradient) to yield product **13**.

A beige powder. Yield – 0.240 g (78%). M. p. 175–178 °C. ^{1}H NMR (500 MHz, $CDCl_3$), the compound exists as *ca.* 3:1 mixture of rotamers, δ, ppm: 1.42–1.55 (0.75×2H, br. m, CH_2), 1.70–1.79 (0.25×2H, m, CH_2), 1.82 (0.75×2H, dd, J_{HH} = 12.7 Hz, J_{HH} = 6.4 Hz, CH_2), 1.86–2.04 (0.75×2H and 0.25×2H, m, CH_2), 2.15–2.29 (0.75×2H and 0.25×4H, m, CH_2), 2.68–2.78 (0.25×3H, m, 3×CH), 2.91 (0.75×2H, br. s, 2×CH), 3.18 (0.75×1H, hept, J_{HH} = 6.4 Hz, CH), 7.10 (1H, t, J_{HH} = 7.5 Hz, PhH), 7.32 (2H, t, J_{HH} = 7.8 Hz, PhH), 7.43 (1H, br. s, NH), 7.56 (2H, d, J_{HH} = 7.8 Hz, PhH). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$), the compound exists as a mixture of rotamers, δ, ppm: 24.4 and 25.6, 38.1 and 38.2, 38.6 and 39.2, 46.2 and 51.3, 119.9, 124.2, 129.1, 138.3, 173.7. HRMS (ESI/QTOF), m/z: Calcd for $C_{14}H_{18}NO^+$ 216.1383 $[M + H]^+$. Found 216.1378.

***N*-[(1*R**,3*S**,5*S**)-bicyclo[3.2.0]heptan-3-yl]-benzamide (14)**

To a solution of hydrochloride **6** (0.200 g, 1.36 mmol) in CH_3CN (10.0 mL), benzoic acid (0.183 g, 1.50 mmol), 1-methyl-1*H*-imidazole (430.0 μL, 5.44 mmol, 0.447 g) and TCFH (0.419 g, 1.50 mmol) were sequentially added. The reaction mixture was stirred at room temperature overnight. The crude solution was then purified by RP-HPLC (column: XSelect FluoroPhenyl 100×19 mm, 5 μm, 30 mL/min; 8–35% H_2O/CH_3CN gradient) to yield a pure product **14**.

A colorless powder. Yield – 0.220 g (75%). M. p. 160–162 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.48–1.60 (4H, m, CH_2), 1.77 (2H, dd, J_{HH} = 12.2 Hz, J_{HH} = 6.3 Hz, CH_2), 2.15 (2H, dq, J_{HH} = 11.9 Hz, J_{HH} = 6.6 Hz, CH_2), 2.76 (2H, br.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

s, CH), 4.75–4.87 (1H, m, CH), 7.43 (2H, t, J_{HH} = 7.5 Hz, PhH), 7.46–7.53 (1H, m, PhH), 7.83 (2H, d, J_{HH} = 7.5 Hz, PhH), 8.28 (1H, d, J_{HH} = 7.9 Hz, NH). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6), δ, ppm: 23.9, 35.6, 38.8, 49.7, 127.2, 128.1, 130.9, 134.8, 166.0. HRMS (ESI/QTOF), *m/z*: Calcd for $C_{14}H_{18}NO^+$ 216.1383 $[M + H]^+$. Found 216.1381.

Acknowledgments

The authors express their gratitude to Olga Kovalenko and Margaryta Bolgova for pK_a titrations, Prof. Andriy O. Tolmachov for his encouragement and support, and all the brave defenders of Ukraine who made this publication possible.

References

1. Grygorenko, O. O.; Melnykov, K. P.; Holovach, S.; Demchuk, O. Fluorinated Cycloalkyl Building Blocks for Drug Discovery. *ChemMedChem* **2022**, *17* (21). https://doi.org/10.1002/cmdc.202200365.
2. Ryabukhin, S. V.; Bondarenko, D. V.; Trofymchuk, S. A.; Lega, D. A.; Volochnyuk, D. M. Aza-Heterocyclic Building Blocks with In-Ring CF_2 Fragment. *Chem. Rec.* **2023**, *24* (2). https://doi.org/10.1002/tcr.202300283.
3. de Sena M. Pinheiro, P.; Rodrigues, D. A.; do Couto Maia, R.; Thota, S.; Fraga, C. A. M. The Use of Conformational Restriction in Medicinal Chemistry. *Curr. Top. Med. Chem.* **2019**, *19* (19), 1712–1733. https://doi.org/10.2174/1568026619666190712205025.
4. Borsari, C.; Rageot, D.; Dall'Asen, A.; Bohnacker, T.; Melone, A.; Sele, A. M.; Jackson, E.; Langlois, J.-B.; Beaufils, F.; Hebeisen, P.; Fabbro, D.; Hillmann, P.; Wymann, M. P. A Conformational Restriction Strategy for the Identification of a Highly Selective Pyrimido-Pyrrolo-Oxazine MTOR Inhibitor. *J. Med. Chem.* **2019**, *62* (18), 8609–8630. https://doi.org/10.1021/acs.jmedchem.9b00972.
5. Grygorenko, O. O.; Volochnyuk, D. M.; Ryabukhin, S. V.; Judd, D. B. The Symbiotic Relationship between Drug Discovery and Organic Chemistry. *Chem.–Eur. J.* **2019**, *26* (6), 1196–1237. https://doi.org/10.1002/chem.201903232.
6. Semeno, V. V.; Vasylchenko, V. O.; Vashchenko, B. V.; Lutsenko, D. O.; Iminov, R. T.; Volovenko O.; Grygorenko, O. O. Building the Housane: Diastereoselective Synthesis and Characterization of Bicyclo[2.1.0]Pentane Carboxylic Acids. *J. Org. Chem.* **2019**, *85* (4), 2321–2337. https://doi.org/10.1021/acs.joc.9b03044.
7. Moroz, B.; Melnykov, K. P.; Holovach, S.; Filatov, A. A.; Raievskyi, O.; Platonov, M.; Liashuk, O.; Volochnyuk, D. M.; Grygorenko, O. O. 6,6-Difluorobicyclo[3.1.0]Hexane as a Rigidified 4,4-Difluorocyclohexane Mimetic: Multigram Synthesis, Physicochemical Characterization, and Incorporation into Maraviroc Analogs. *J. Fluorine Chem.* **2023**, *272*, 110215–110215. https://doi.org/10.1016/j.jfluchem.2023.110215.
8. Bychek, R. M.; Levterov, V. V.; Sadkova, I. V.; Tolmachev, A. A.; Mykhailiuk, P. K. Synthesis of Functionalized Difluorocyclopropanes: Unique Building Blocks for Drug Discovery. *Chem.–Eur. J.* **2018**, *24*, 12291–12297. https://doi.org/10.1002/chem.201705708.
9. Greene, A. E.; Luche, M. J.; Serra, A. A. An Efficient, Enantioconvergent Total Synthesis of Natural Hirsutic Acid C. *J. Org. Chem.* **1985**, *50* (21), 3957–3962. https://doi.org/10.1021/jo00221a001.
10. Holovach, S.; Melnykov, K. P.; Skreminskiy, A.; Herasymchuk, M.; Tavlui, O.; Aloshyn, D.; Borysko, P.; Rozhenko, A. B.; Ryabukhin, S. V.; Volochnyuk, D. M.; Grygorenko, O. O. Effect of Gem-Difluorination on the Key Physicochemical Properties Relevant to Medicinal Chemistry: The Case of Functionalized Cycloalkanes. *Chem.–Eur. J.* **2022**, *28* (19), e202200331. https://doi.org/10.1002/chem.202200331.
11. Liashuk, O. S.; Fedinchyk, A.; Melnykov, K. P.; Herasymchuk, M.; Alieksieieva, D.; Lesyk, D.; Bas, Y. P.; Keda, T. Y.; Yatsymyrskiy, A. V.; Holota, Y.; Borysko, P.; Yarmolchuk, V. S.; Grygorenko, O. O. 3,3-Difluorooxetane – A Versatile Functional Group for Bioisosteric Replacements in Drug Discovery. *Chem.–Eur. J.* **2024**, e202403277. https://doi.org/10.1002/chem.202403277.
12. Semeno, V. V.; Vasylchenko, V. O.; Fesun, I. M.; Ruzhylo, L. Y.; Kipriianov, M. O.; Melnykov, K. P.; Skreminskyi, A.; Iminov, R.; Mykhailiuk, P.; Vashchenko, B. V.; Grygorenko, O. O. Bicyclo[m.n.k]Alkane Building Blocks as Promising Benzene and Cycloalkane Isosteres: Multigram Synthesis, Physicochemical and Structural Characterization. *Chem.–Eur. J.* **2024**, *30* (12). https://doi.org/10.1002/chem.202303859.
13. Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*; Elsevier, 2009. https://doi.org/10.1016/c2009-0-26589-5.

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Journal of Organic and Pharmaceutical Chemistry

Review Article

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UDC 662.164.2

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Chemical Warfare Agents: Structure, Properties, Decontamination (Part 2)

Abstract

The review is aimed at summarizing and systematizing information about various methods of deactivation of chemical warfare agents that are necessary on the battlefield, as well as in laboratories, research institutions, and facilities of production, storage, and destruction of poisonous substances. The review presents the main directions of neutralizing warfare poisonous substances, which are the most effective in the conditions of their real use. In the second part of this work, the methods of deactivating warfare poisons using nucleophilic reagents, primarily α-nucleophiles, which have high efficiency and can react as nucleophiles and as oxidants, are considered in detail. A promising area of degradation of such products is the use of supernucleophilic systems based on functionalized detergents, as well as adsorption and photocatalytic deactivation methods. The material presented above shows the importance of general knowledge about the physical and chemical properties of chemical warfare agents, the rate of their decomposition, the advantages and disadvantages of certain available technologies for their application. This review can be useful for finding new and improving known methods for decontamination of chemical warfare agents and other ecotoxicants, and protecting the environment.

Keywords: chemical warfare agents; nerve agents; vesicants; decontamination; detection; protection

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Бойові отруйні речовини: структура, властивості, дезактивація (частина 2)

Анотація

Огляд спрямовано на узагальнення та систематизацію інформації про різні методи дезактивації бойових отруйних речовин, необхідних на полі бою, а також у лабораторіях, дослідних установах, на об'єктах виробництва, зберігання та знищення отруйних речовин. В огляді наведено основні напрями знешкодження бойових отруйних речовин, які є найбільш ефективними в умовах їх реального застосування. У другій частині цієї роботи докладно розглянуто методи дезактивації бойових отруйних речовин за допомогою використання нуклеофільних реагентів, насамперед α-нуклеофілів, які мають високу ефективність і можуть реагувати і як нуклеофіли, і як окислювачі. Перспективним напрямом деградації таких продуктів є застосування супернуклеофільних систем на основі функціоналізованих детергентів, а також методів адсорбції та фотокаталітичної дегазації. Викладений матеріал доводить важливість загальних знань про фізичні та хімічні властивості бойових отруйних речовин, швидкість їх розкладання, про переваги та недоліки тих чи інших доступних технологій їх застосування. Цей огляд може бути корисний для пошуку нових й удосконалення відомих методів дезактивації бойових отруйних речовин та інших екотоксикантів, захисту довкілля.

Ключові слова: бойові отруйні речовини; нервово-паралітичні речовини; шкірно-наривні речовини; дезактивація; виявлення; захист

ISSN 2308-8303 (Print) / 2518-1548 (Online)

Citation: Shumeiko, O. E.; Korotkikh, M. I. Chemical warfare agents: Structure, properties, decontamination (Part 2). *Journal of Organic and Pharmaceutical Chemistry* **2024**, *22* (3), 10–23.
https://doi.org/10.24959/ophcj.24.313307
Received: *3 August 2024*; **Revised:** *27 October 2024*; **Accepted:** *30 October 2024*

Funding: Grant of the Ukrainian National Academy of Sciences 6.2/2-2023.
Conflict of interests: The authors have no conflict of interests to declare.

■ Introduction

Deactivation on the battlefield is the rapid removal of chemical warfare agents (CWAs) from military equipment, other equipment, personnel, and various objects by both chemical and physical methods. Therefore, a solid surface that is contaminated with poisonous substances is the main object of decontamination. Actually, the surface's nature and its interaction with applied chemical agents are the main problems in the development of a CWAs decontamination system. In addition, one should keep in mind that deactivating agents are not supposed to cause corrosion or damage to surfaces after deactivation. This review describes the chemical reactions mainly for the four main warfare poisons. These are sarin, soman, mustard gas, and VX. This is due to their extremely strong toxicity and stability, as well as their large reserves in a number of countries around the world [1]. The main attention here is given to such methods of CWAs deactivation as oxidative/nucleophilic reactions, photocatalytic reactions, and adsorption methods of deactivation.

Thus, to neutralize CWAs, nucleophilic reagents can be used, primarily α-nucleophiles, which are highly effective and can act both as a nucleophile and as an oxidizing agent [2]. The methods of decontamination of CWAs with hydrogen peroxide solutions turned out to be very effective. However, it has a low reaction rate and requires activation with reagents, such as carbonates, molybdates, phthalates, etc. Studies of the reactivity of hydrogen peroxide and its activators have led to the creation of universal formulations of the nucleophilic-oxidizing mechanism of action, which are quite effective in relation to the main types of CWAs [3].

The way to increase the efficiency of systems for splitting CWAs should be sought not only in the structural modification of the corresponding agent, but also in the use of alternative methods of influencing the reaction rate, for example, by changing the properties of the medium. In this sense, the use of a microorganized medium (micellar solutions, microemulsions, ionic liquids, concentrated aqueous solutions of quaternary ammonium salts, etc.) is already widely used to solve a number of applied and fundamental problems [3, 4].

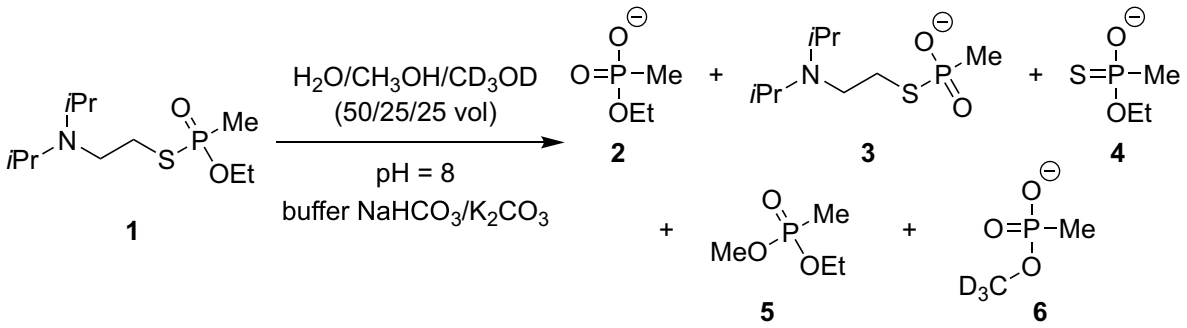
Works on the application of photocatalytic deactivation of CWAs using composites obtained on the basis of zirconium and terephthalic acid, which are made from plastic waste, seem very interesting [5]. This is important, taking into account the problems of ecology and the application of "green" chemistry methods.

Further, the most interesting works in this direction will be considered in detail, primarily those related to the practical use of the proposed methods of decomposition of warfare poisonous substances.

■ Nucleophilic/oxidative decontamination of warfare poisons

Nucleophilic reagents, primarily α-nucleophiles, which have high efficiency, can be used to decontaminate CWAs [1]. For example, work [2] provides data on deactivation of the nerve agent VX – an inhibitor of acetylcholinesterase **1**. Its deactivation by simple hydrolysis in an aqueous-alkaline medium does not give a satisfactory result due to the formation of a stable toxic product of hydrolysis **3** (**Scheme 1**) [3]. The formation of compounds **5** and **6** indicates the participation of alcohols in the process (as parallel transesterification to hydrolysis).

However, the combination of hydrolysis with an oxidation reaction is highly effective in achieving the complete destruction of the VX agent [4]. In this work, the authors studied the behavior of VX in relation to five α-nucleophiles: magnesium monoperoxyphthalate, metachloroperbenzoic acid, potassium monopersulfate, hydrogen peroxide, and hydrogen peroxide with boric acid. All reactions studied were carried out at pH 8. This pH value was chosen since it minimized the risk of corrosion when the metal surface was degassed. It was shown that during the VX hydrolysis in a water-methanol solution, the hydrolytic compound formation occurred due to nucleophilic attack of both water and methanol, mainly



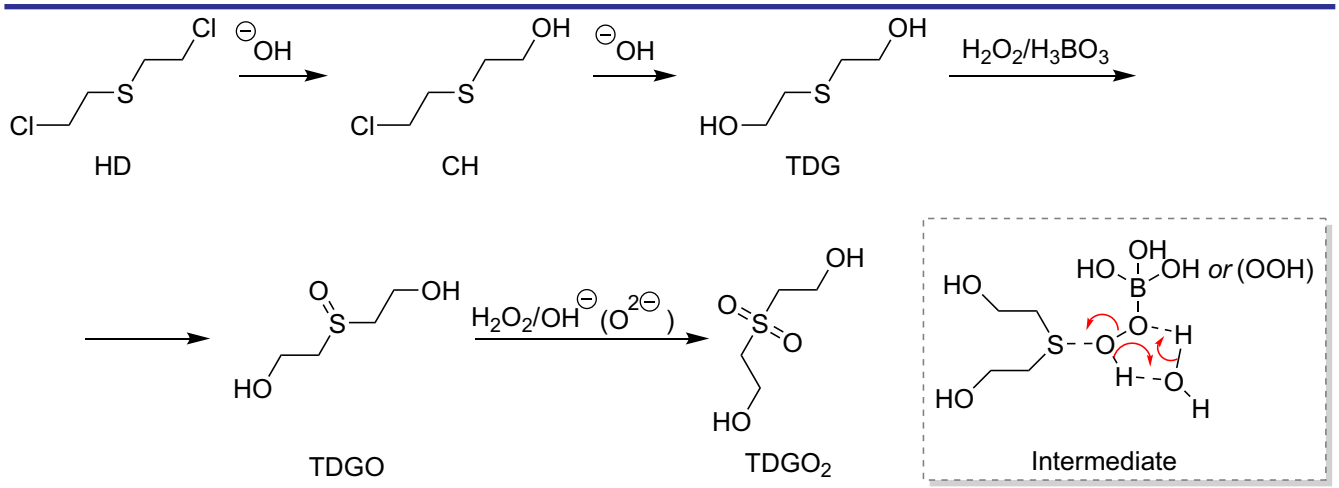
Scheme 1. Hydrolysis of VX (**1**) in solution $H_2O/CH_3OH/CD_3OD$

at the phosphorus atom. The oxidative-nucleophilic reaction involving α-nucleophiles increased from 200 to 2000 times compared to simple hydrolysis in a water-methanol solution at pH 8. Using 20 equivalents of magnesium monoperoxyphthalate, it was possible to achieve complete destruction of VX, which turned into non-toxic phosphonate **2** (**Scheme 1**). It should be noted that decontamination using magnesium monoperoxyphthalate was successfully extended to soman [5].

The methods of decontamination of CWAs with hydrogen peroxide solutions turned out to be very effective. However, H_2O_2 shows a low reaction rate and requires its activation by other reagents, such as HCO_3^- [6–8], MoO_4^{2-} [9–11], etc. Moreover, the rate of the activation reaction between H_2O_2 and HCO_3^- is not as high as expected [6, 12]. The activation of H_2O_2 using MoO_4^{2-} is much more effective, however, at the same time, there is a loss of active oxygen [13], which leads to a decrease in the rate of CWAs destruction within a fairly short time [9, 14].

Another disadvantage of MoO_4^{2-} as an activator of hydrogen peroxide is, for example, that mustard gas can be easily re-oxidized to the corresponding sulfone [9], which exhibits rather high toxicity. In work [15], the authors investigated boric acid as an activator of hydrogen peroxide reacting with H_2O_2 to form peroxoborates, which could quickly oxidize sulfur to sulfoxide [16]. The decomposition of peroxoborate itself occurs rather slowly, which gives a good perspective for using such solutions for the purpose of CWAs decontamination [17, 18]. In the work mentioned above [15], the nucleophilic/oxidative reactivity of the $B(OH)_3$–H_2O_2 system was studied, while special attention was paid to the influence of the pH of the medium and temperature on the reaction rate. Thioanisole and paraoxon were used as CWAs imitators. The ^{11}B NMR analysis showed that $B(OH)_3$ quickly reacted with H_2O_2 to form peroxoborates ($[B(OH)_{(4-x)}(OOH)_x]^-$). Their content depended on pH and solution temperature. It was shown that peroxoborates acted as oxidants for the primary oxidation of sulfide in the pH range of 8–12, and that O_2^- was responsible for further oxidation of sulfoxide.

Paraoxon decomposes due to OOH^- ions, and the rate of decomposition increases exponentially with pH increasing. The data provided suggest that mustard gas, soman, and VX are effectively decomposed into non-toxic products in a solution of $B(OH)_3 – H_2O_2$ at pH 9–11. **Scheme 2**



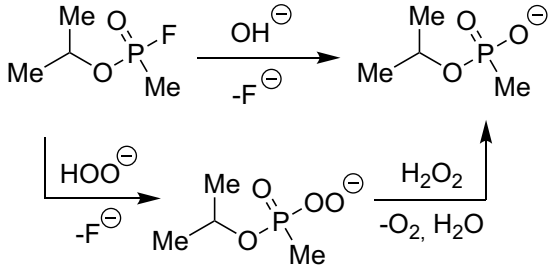
Scheme 2. Destruction of mustard gas in the system $B(OH)_3 – H_2O_2$ (HD – mustard gas, CH – 2-chloroethyl-2'-hydroxyethyl sulfide, TDG – thiodiglycol, TDGO – thiodiglycol sulfoxide, $TDGO_2$ – thiodiglycol sulfone)

ISSN 2308-8303 (Print) / 2518-1548 (Online)

shows the diagram of the mustard gas decomposition.

It should be noted that in the presence of activators, such as carbonates, bicarbonates, and molybdates, hydrogen peroxide, in organic co-solvents provides rapid decontamination of a wide range of warfare poisons, and it is important at low temperatures (-30 °C). Such solutions are non-toxic, do not cause corrosion, and are environmentally safe [14]. Concern for the environment became the reason to abandon the use of chlorine-containing products (for example, in bleaching processes) and replace them with systems based on hydrogen peroxide. These "green" peroxide products allow for avoiding the use of toxic and carcinogenic organochlorine compounds. Another advantage of peroxides is that they can be used for the CWAs deactivation in the cold season. For example, the freezing point of 50% H_2O_2 is -40 °C. Previously, *Menger* and *Rourk* [19] demonstrated effectiveness of microemulsion formulations using 30% H_2O_2. These microemulsions did not freeze or delaminate at -18 °C and were effective against various CWAs mimics. The scheme of the sarin deactivation reaction in the presence of activated $B(OH)_3$ is shown in **Scheme 3**.

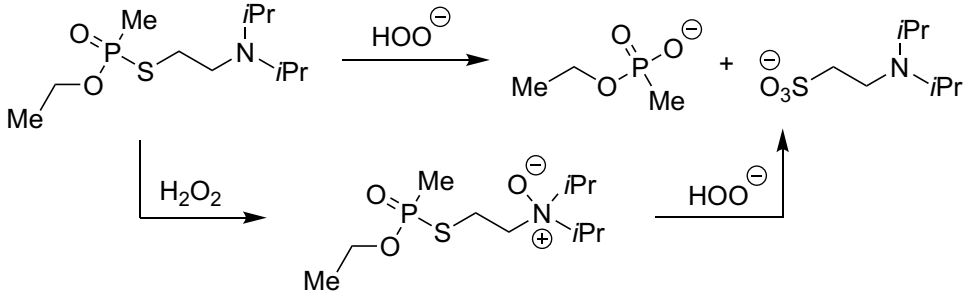
Inorganic α-nucleophiles – HOO^- and ClO^- ions exhibiting anomalously high reactivity are of particular interest as the basis of compositions for the breakdown of ecotoxicants and hazardous substances [20–23]. In the alkaline medium, VX-type CWAs are quickly destroyed due to the nucleophilic attack of the hydrogen peroxide ion on the phosphorus atom. Peroxyhydrolysis of VX takes place, according to the scheme given below (**Scheme 4**), with the formation of ethylmethylphosphonic acid. VX *N*-oxide is another reaction product, which further, at a slower stage, undergoes nucleophilic attack to form an acid. At the same time, the released thiol is oxidized to sulfonate [24].



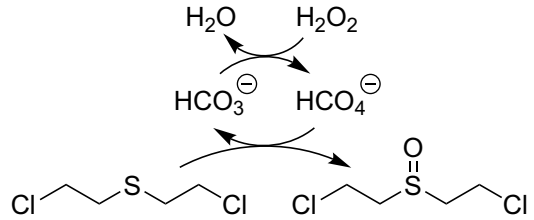
Scheme 3. The sarin deactivation reaction in the presence of activated $B(OH)_3$

The reaction of VX with the HOO^- anion proceeds approximately 40 times faster than with the more basic HO^- ion ($\tau_{1/2}$ = 45 s, 23 °C, [HOO^-] = 0.1 M), which allows for efficient splitting of VX in the alkaline medium by nucleophilic mechanism. Concentrated solutions of hydrogen peroxide, which exhibit oxidizing properties under these conditions, oxidize mustard gas and various ecotoxicants in neutral and acidic medium. To ensure the decomposition of ecotoxicants by both nucleophilic and oxidative mechanisms, the pH of the medium is of great importance [24, 25]. Since the optimal conditions for carrying out these reactions are different, and pK_a (H_2O_2) = 11.5–11.6, hydrogen peroxide can hardly be considered a universal deactivation agent [22]. Nevertheless, numerous studies of the reactivity of hydrogen peroxide and its activators (carbonates, molybdates, phthalates, etc.) led to the creation of universal formulations of the nucleophilic-oxidizing mechanism of action, which are quite effective in relation to the main types of CWAs [25]. Thus, the activation of H_2O_2 with sodium hydrogen carbonate leads to the appearance of a HCO_4^- anion in the reaction mixture in slightly alkaline media. It is a more powerful oxidant than H_2O_2, and this makes it possible to destroy not only sarin and VX, but mustard gas as well (**Scheme 5**).

The use of potassium molybdate as an activator of hydrogen peroxide in microemulsions of the oil/water type makes it possible to design universal systems for destructing CWAs of various nature [26]. The advantage of this system is that the oxidation of mustard gas mainly leads to the formation of sulfoxide, and not to highly toxic sulfone [26].



Scheme 4. The VX deactivation with a peroxyhydroxide ion



Scheme 5. The mustard gas deactivation using a HCO_4^- ion

Salts of hypochlorous acid have been widely used in the decomposition of CWAs and ecotoxicants [24]. Hypochlorites are deactivation substances of universal action and are used for detoxification of the human skin, equipment, and terrain [24]. In nucleophilic substitution reactions at the tetracoordinated phosphorus atom, the ClO^- ion acts as a true nucleophilic catalyst and decomposes sarin-type CWAs to phosphonic acids (**Scheme 6**).

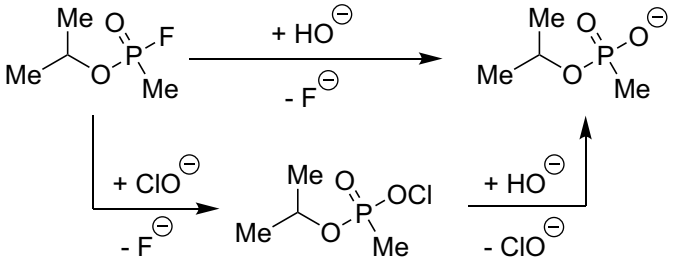
The high oxidizing activity of hypochlorous acid plays an important role in deactivation of mustard gas, which undergoes destruction in alkaline media with the formation of a number of oxidation and elimination products (**Scheme 7**). It should be emphasized that sulfoxide is formed at the first stage of this rather complex process, which is further transformed into other products.

Hypochlorite solutions can be used for the VX deactivation, especially at low pH values (**Scheme 8**). At the same time, only 3 moles of "active" chlorine are used to destroy 1 mole of VX. More than 10 moles of "active" chlorine are needed to oxidize 1 mole of VX in alkaline media.

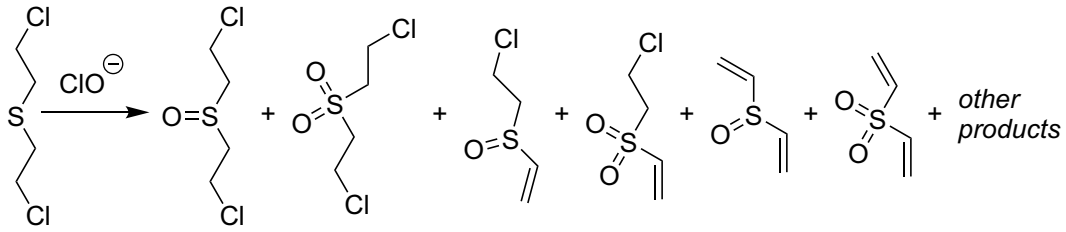
Thus, it can be concluded that the use of systems based on hydrogen peroxide for deactivation of CWAs is effective from the point of view of both the reaction rate and environmental protection.

Convenient for practical use, oxidizing systems consisting of one reagent have also been developed, both against combat poisonous substances and various ecotoxicants [27]. The reagent L–Gel proposed consists of an aqueous solution of a mild oxidizer Oxone TM (potassium peroxymonosulfate) together with a gel-forming agent based on silica gel Cab-O-Sil EH-5. L–Gel is non-toxic, environmentally friendly, does not cause corrosion, maximizes contact time due to its thixotropic nature, and sticks to any surface. **Table 1** shows comparative data on the effectiveness of decontamination of a mustard imitator – chlorodiethyl sulfide for various oxidizing systems compared to the "L–Gel" proposed.

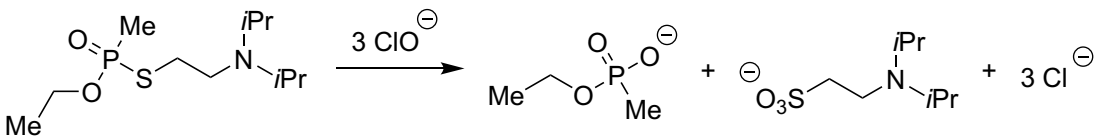
The reactions were carried out at pH = 3, except for sodium hypochlorite (pH = 12). The ratio of the oxidizing agent to chlorodiethyl sulfide was 2. In general, in many cases, chlorine-containing oxidizing reagents, such as NaOCl, $Ca(OCl)_2$ or dichloroisocyanurate salts, are used for deactivation of CWAs [24]. However, such processes strongly affect the environment and are



Scheme 6. The sarin deactivation using a hypochlorite anion



Scheme 7. The mustard gas deactivation using a hypochlorite-anion



Scheme 8. The VX deactivation scheme using a hypochlorite anion

ISSN 2308-8303 (Print) / 2518-1548 (Online)

Table 1. Oxidation of chlorodiethyl sulfide

Oxidant	Reaction time (min)	Percentage of oxidation
Sodium hypochlorite	30	91
Hydrogen peroxide	30	100
Ammonium peroxydisulfate	10	40
L-Gel	10	100

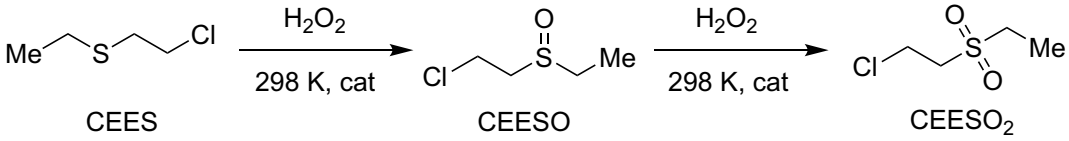
associated with high costs of disposal. With these shortcomings, a heterogeneous catalyst based on saponite clay containing Nb^V was proposed. It selectively converts toxic sulfur-containing chemical warfare agents into non-toxic products with a reduced negative impact on the environment under extremely mild conditions [28]. Due to the introduction of Nb^V centers into the saponite framework, a bifunctional catalyst with strong oxidizing and acidic properties was obtained. When it is used, high activity and selectivity for the oxidative deactivation of the mustard imitator – 2-chloroethyl ethyl sulfide in the presence of an aqueous solution of hydrogen peroxide at room temperature is observed. **Scheme 9** shows the specified reaction.

Porous oxides are also promising materials as they demonstrate remarkable chemical, physical and mechanical stability, as well as good dispersion of the catalytically active metal. Thus, nanostructured inorganic metal oxides, such as Al_2O_3, ZnO, and TiO_2, have been widely studied in relation to the CWAs oxidation or other methods of their destruction [29]. The process of deactivation of soman, mustard gas, and VX with such a combined reagent as a solution of sodium peroxycarbonate and tetraacetylethylenediamine was studied. It was shown that the optimal pH value for the degradation of mustard and VX was about 7.5–9.0 and 8.5–9.5, respectively, and the effectiveness of soman decontamination reached its maximum at pH 9.5–10.5 and a temperature from 0 °C to 45 °C [30]. To obtain a decontamination percentage of > 99%, the molar ratio between active oxygen and CWA should be at least 3, 2, and 10 for soman, mustard gas, and VX, respectively. The analysis of products using gas chromatography/mass spectrometry, liquid chromatography/mass spectrometry, and ion chromatography showed that the decomposition of soman was a process of perhydrolysis. It was indicated that the decomposition of mustard gas occurred by oxidation of atoms C and S and release of HCl. At the same time, the process of the VX decomposition was *via* the oxidation of atoms C, S, and N and the breaking of C-C, C-N, C-S, and P-S bonds.

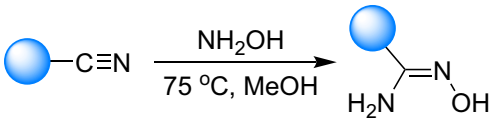
Attention was drawn to the work [31] where the authors found that palladium-on-carbon catalyzed the deep oxidation of organophosphorus and organosulfur compounds with oxygen in water at 90 °C in the presence of carbon monoxide. This system is the first example of catalytic cleavage of phosphorus-carbon bonds. Starting with trimethylphosphine oxide, the phosphorus-containing products formed during the sequential breaking of the *P-C* bond were dimethylphosphinic, methylphosphonic, and phosphoric acids. A similar sequence of reactions was observed for triethylphosphine oxide, except that intermediate products formed by partial oxidation of ethyl groups, such as phosphonoacetic acid, were also observed. Deep oxidation of dimethyl and diethyl sulfides occurs through the mediation of the corresponding sulfoxides. For methyl derivatives, the ease of oxidation decreases in the series: $(CH_3)_2S > (CH_3)_2SO > (CH_3)_2SO_2$ and corresponds to a system acting as an electrophilic oxidant. These results are important in the creation of systems for the deactivation of CWAs and various ecotoxicants.

Using polymer materials containing active nucleophilic centers capable of destructing phosphorus and sulfur esters seems promising. For example, in work [32], the processes of degradation of CWAs by polyacrylamideoxime and poly(*N*-hydroxyacrylamide) were studied. Those polymers are capable of generating nucleophilic oximate groups *via* dissociation of amidoxime or hydroxamic groups, respectively. They are environmentally friendly, economical, and non-toxic polymers, which are essentially products of one-stage addition of available polyacrylonitrile and polyacrylamide (**Scheme 10**).

The polymers were converted into their corresponding oximate salts at pH values higher than the pK_a of oximate or amidoximate groups – 7.5 and 10.8, respectively. The authors focused



Scheme 9. Deactivation of 2-chloroethyl ethyl sulfide (CEES) in the presence of a catalyst based on saponite-Nb^V and hydrogen peroxide. Oxidation products – CEESO (sulfoxide), $CEESO_2$ (sulfone)



Scheme 10. The reaction of the interaction of polyacrylonitrile with hydroxylamine with the formation of polyacrylamidoxime

on the characteristics of functional polymers as deactivating agents for such CWAs as VX, sarin, and soman. The considered polymeric amidoximes in the form of cross-linked polyamidoximate salts can act as effective dephosphorylating agents due to the formation of amidoximate ions on the surface of polymer salt particles without an excess of hydroxyl ions present. Such reactive polymers can be promising materials for the modification of surfaces, such as textiles, coatings, and sorbents. The half-life of VX during heterogeneous hydrolysis was 6 min in the presence of polyacrylamidoxime. Under the same conditions, the half-life for sarin was less than 3 minutes.

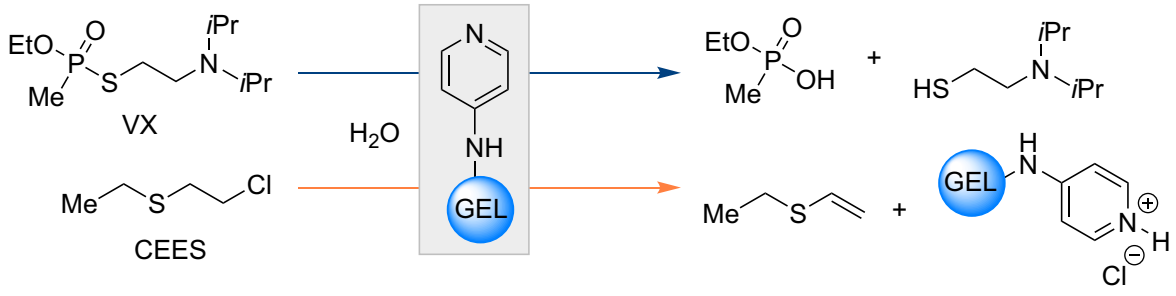
In the same aspect, the work [33] is of interest, in which water-soluble polymeric materials based on polyalkylamines modified with nucleophilic groups were introduced as catalysts for the hydrolysis of warfare poisons. The choice of polymer materials was based on the criteria of simplicity of their synthesis, solubility in water, and the rate of hydrolysis of CWAs imitators. The study involving diisopropyl fluorophosphate showed that at a constant pH value, 4-aminopyridine-substituted polyallylamines and polyvinylamines were the most effective for this process.

Hydrogel particles of 4-aminopyridine-substituted polyallylamines and polyvinylamines cross-linked with epichlorohydrin revealed pH-dependent swelling and ionization systems that affected the rate constants of the nucleophilic hydrolysis of diisopropylfluorophosphate [32]. The study was conducted on the deactivation of VX and soman in suspensions or gels of both polymers with a concentration of 2.5–3.7 wt.%, which swelled in water or in a mixture of DMSO/water. The half-life of soman was 12 and 770 min at pH 8.5 and 5, respectively. Adding VX to 3.5–3.7 wt.% suspensions in DMSO-d_6 and D_2O, with an initial VX concentration of 0.2 vol.%, led to 100% degradation of VX in less than 20 min. In addition, the gels of both polymers facilitated the reaction of dehydrochlorination of mustard gas and its analog – 2-chloroethylethyl sulfide (**Scheme 11**).

The ability of such aminopyridine-modified polyalkylamine materials to decompose the most stable CWAs in combination with water solubility and the presence of numerous amino groups, which provide convenient “handles” for covalent attachment to polymeric and inorganic carriers, opens prospects for their wide application, for example, in fabrics and other materials that contribute to quick and effective decontamination of CWAs.

■ Supernucleophilic systems based on functional detergents for the neutralization of chemical warfare agents

It is quite difficult to create a compound that would surpass the hydroxylamine anion in an aqueous solution in terms of its nucleophilic reactivity. Therefore, the way to increase the efficiency of systems for splitting CWAs should be sought not so much in the structural modification of the splitting agent, but in the use of alternative methods of influencing the reaction rate, for example, by changing the properties of the medium, in which it occurs [2, 33–35]. In this sense, the use of microorganized media (micellar solutions, microemulsions, ionic liquids, concentrated aqueous solutions of quaternary ammonium salts, etc. [36–42]) is already widely used to solve a number of applied and fundamental problems. The indisputable advantage of micellar systems compared to other organized microheterogeneous media is that a radical change in the properties of the medium is achieved by the introduction of rather small amounts of micelle-forming substances (in amounts above the critical concentration of micelle formation, which varies



Scheme 11. Deactivation reactions of VX and mustard imitator (CEES)

ISSN 2308-8303 (Print) / 2518-1548 (Online)

within 10^{-6}–10^{-2} mol L^{-1}) [38, 39]. At the same time, the main component of such systems in most cases is water, which makes them extremely attractive for practical use from the point of view of "green" chemistry [43].

The use of solutions of cationic surfactants as a medium for the destruction of CWAs with nucleophilic reagents allows for their effective solubilizing (most of CWAs are difficult to dissolve in water in the absence of detergents), and also ensures wetting of hydrophobic and highly developed surfaces [2, 35, 38, 44]. At the same time, achieving the effects of micellar catalysis leads to an additional increase in the rate of the process of splitting CWAs by nucleophilic reagents (hydroxide ion, oximate ion, etc.) by 10–10^3 times [45–57].

One of the most promising ways to increase the efficiency of the binding of nucleophilic reagents by micelles is the creation of functional detergents – surfactants, which have reactive fragments in their structure. When implementing this approach, the concentration of nucleophilic groups on the surface of micelles will always be equal to the concentration of a surfactant [58]. The most promising here is the use of an α-nucleophile fragment as a functional group, which ensures a sharp increase in the rate due to the implementation of the α-effect. Currently, the main types of functional surfactants containing a supernucleophilic fragment are detergents based on hydroxylamine derivatives and detergents containing peroxy- and iodoxocarboxylate groups. Oxime derivatives are of particular interest among this group of reagents. This is due to the ease of structural modification, which makes it possible to obtain oximes that split CWAs in a wide range of the medium acidity (neutral, slightly alkaline, alkaline) [59]. **Figure 1** shows some typical detergents based on alkylated imidazole and pyridine containing an oxime group.

CWAs imitators – 4-nitrophenyl esters of diethylphosphonic (**1**), diethylphosphoric (**2**) and toluenesulfonic (**3**) acids were most often used to study the reactivity of functional surfactants (**Figure 2**).

Below is the reaction scheme characterizing the reactivity of the oximate group of functionalized surfactants, which consists of a nucleophilic attack of the oximate fragment (Ox^-) of the functionalized surfactants on the electron-deficient phosphorus and sulfur atoms of the nitrophenolate ion (**Scheme 12**).

Table 2 shows data on half-life periods for decomposition reactions of CWAs imitators – paraxone and armine [33]. The half-life periods of organophosphorus compounds indicate that these functionalized surfactants have high reactivity and can be successfully used to destroy CWAs as part of personal protective equipment and mixtures for treating various surfaces.

■ Adsorption methods and photocatalytic deactivation of chemical warfare agents

Works on the application of photocatalytic deactivation of CWAs using composites obtained on the basis of zirconium and terephthalic acid, which are made from plastic waste, seem very interesting. This is important, based on the problems of ecology and the use of "green" chemistry methods. For example, the work [60] shows the synthesis of such composites and evaluates their photocatalytic activity in the degradation

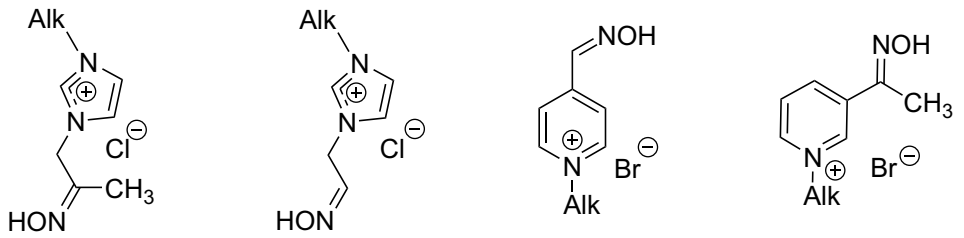
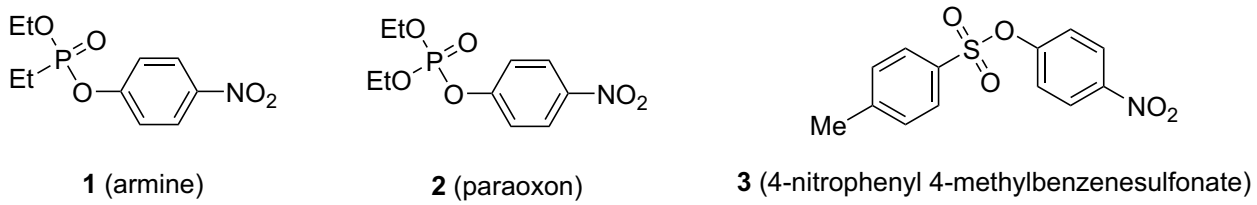
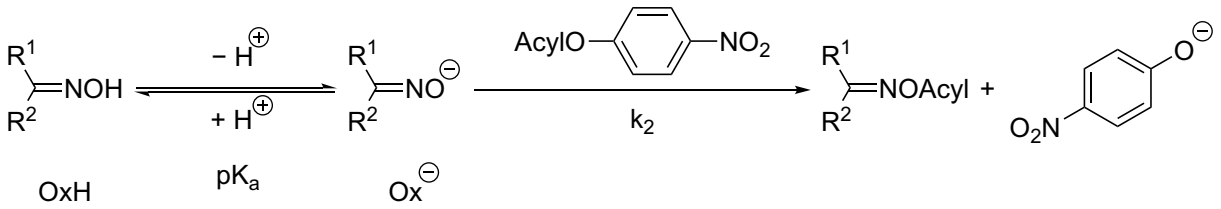


Figure 1. Structural formulas of some typical functionalized surfactants



1 (armine) **2** (paraoxon) **3** (4-nitrophenyl 4-methylbenzenesulfonate)

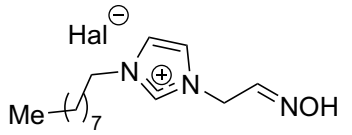
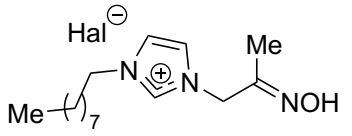
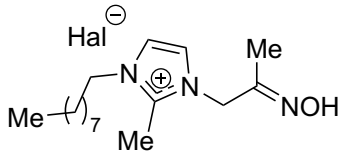
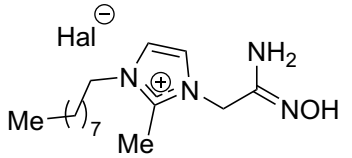
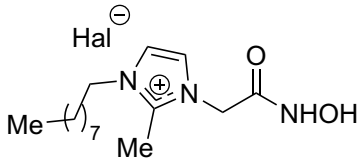
Figure 2. Structural formulas of substrates based on phosphorus and sulfur esters



Note: $R^1(R^2)C{=}NO^-$ – the corresponding anionic surfactant fragment (Ox^-)

Scheme 12. The reaction scheme of functional detergents with acyl-containing substrates

Table 2. Half-life periods ($\tau_{1/2}$) in the destruction of paraxone and armine (water, 25 °C) with the participation of functionalized detergents

Functional detergent	Paraxone $\tau_{1/2}$ (s)	Armine $\tau_{1/2}$ (s)
	14	2
	43	2
	45	3
	37	3
	180	20

of an imitator of a chemical warfare agent – dimethyl 4-nitrophenyl phosphate. The composite synthesized had a large surface area (1440 $m^2\ g^{-1}$) and a large pore volume (1.49 $cm^3\ g^{-1}$). Composite samples absorbed visible light with a band gap of 2.13–2.88 eV. They showed a high efficiency for the degradation of an imitator of sarin with a short half-life ($t_{1/2}$ = 2.17 min) at pH 7 by exposure to visible light. Capture experiments have confirmed that H^+ and O_2^- radicals play an important role in photocatalytic degradation. The composite performs two processes at the same time: hydrolysis and photocatalytic oxidation in water.

Noteworthy is the work [61], in which the authors found that barium titanate nanoparticles with sizes of 8–12 nm obtained by the gel collection method were effective photocatalytic detoxifiers of CWAs vapors, in particular, a mustard imitator (2-chlorodiethyl sulfide). Relatively monodisperse, homogeneously spherical nanoparticles of barium titanate, initially dispersed in alcohol solvents, form a stable and porous aggregated structure that resembles a nanostructured material with pores of an average diameter 4.6 nm and a relatively narrow distribution of their sizes (2.5–8 nm). Due to its porosity and polar chemically active surface, a large amount of CWAs imitator and its decomposition products are adsorbed on barium titanate. The reported absorption by weight of the CWAs simulant was the highest among a number of materials and nanocomposites known for their detoxification activity and tested under the same conditions (169 mg g^{-1} compared to 117 mg g^{-1} for zinc oxide and < 100 mg g^{-1} for other oxides transition metals). In addition to adsorption, barium titanate nanomaterial acts simultaneously as an effective heterogeneous catalyst, decomposing toxic vapors into alcohols, sulfides, and thiols – molecules with much lower toxicity than CWAs [62]. Hydrolysis and dehydrohalogenation were the predominant ways of detoxification through the formation of a cyclic sulfonium intermediate both in the light and in the dark. Irradiation with ambient light promoted photooxidation and photodegradation by radical intermediate products formed. It should be concluded that barium titanate nanoparticles with an oxygen-rich surface are being investigated as a potentially useful medium for photoreactive detoxification of chemical warfare agents.

It is worth paying attention to the study of photolytic and photocatalytic reactions of deactivating sarin, soman, mustard gas, and chlorocyanide in the air [63]. It has been shown that the vapors of these CWAs (except for chlorocyanide) can be effectively removed by UV light of a bactericidal lamp by photolysis or photocatalysis. Such a photocatalytic reaction leads to photoinduced polymerization directly under the action of UV irradiation, as well as the splitting of CWAs into small inorganic compounds on the surface of a TiO_2 catalyst. It has been confirmed

ISSN 2308-8303 (Print) / 2518-1548 (Online)

that the static photolysis approach can be used to decontaminate sarin vapors indoors. At the same time, it has been demonstrated that the dynamic photocatalytic approach to the destruction of sarin and soman vapors is much more effective than photolysis, and its use is considered appropriate for the disinfection of nerve-paralytic CWAs in the air. **Table 3** shows data on the rate constants of the corresponding CWAs cleavage reactions.

Interesting results were obtained by the authors [64], who used photocatalytic and sonophotocatalytic methods of processing reaction mixtures in aqueous TiO_2 suspensions. CWAs imitators were used as reagents – dimethyl methylphosphonate, diethyl phosphoramidate, pinacolyl methylphosphonate and butylaminoethanethiol. The complete conversion of imitators into inorganic products was achieved in 600 min, and only for butylaminoethanethiol it took more time. Sonolysis accelerated the photodegradation of dimethyl methylphosphonate. No degradation of imitators was observed without ultraviolet irradiation. The final decomposition products were PO_4^{3-}, CO_2, NO_3^-, NH_4^+, SO_4^{2-}.

Degradation of dimethyl methylphosphonate proceeds by sequential oxidation of methoxy groups and then methyl groups. Destruction of diethyl phosphoramidate begins with the breaking of the P–NH_2 bond with the formation of diethyl phosphate, which is further transformed into ethyl phosphate [65]. Destruction is also facilitated by the oxidation of α- and ß-carbons of ethoxy groups with the formation of ethylphosphonoamidate, hydroxyethylethylphosphonoamidate, and other products. Photocatalytic degradation of pinacolyl methylphosphonate begins with the oxidation of the pinacol fragment, which products are methylphosphonic acid and acetone. The results demonstrate the possibility of photocatalysis for the destruction of CWAs in the aqueous phase. The optimization of degradation conditions is necessary to achieve practical high efficiency.

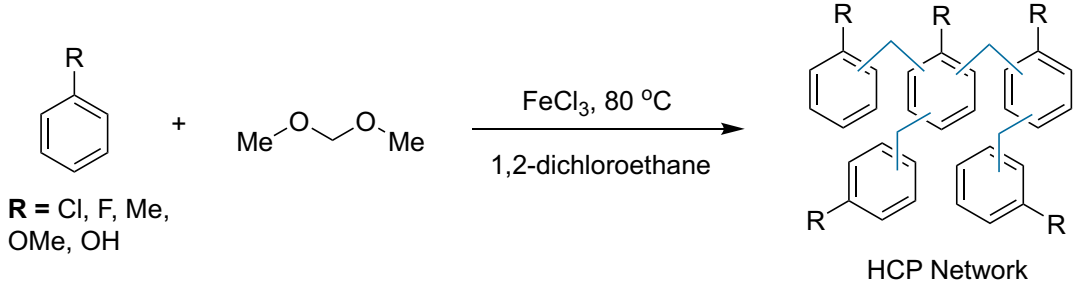
Table 3. Rate constants of the first-order reactions of photolysis and photocatalysis of CWAs vapors

CWAs	Initial concentration (mg L^{-1})	k × 10^2 (min^{-1})	
		Photolysis	Photocatalysis
Sarin	1.7	2.32	5.97
Soman	0.94	4.09	7.25
Mustard	0.42	2.54	1.19

The question of using polymer sorbents for CWAs deactivation is reflected in many recent publications. They provide the effective adsorption of CWAs and the possibility of their deactivation in large volumes and in a short period of time. Hyper-crosslinked polymers are a class of sorbents that are produced using a simple and controlled method called "linking" [66]. Several hyper-crosslinked polymers and their properties, including the absorption capacity in relation to CWAs imitators, were reported. A hyper-crosslinked polymer derived from fluorobenzene showed the greatest potential when used for CWAs neutralization and was tested against real agents, including sarin and mustard gas, showing absorption close to 20 mL g^{-1} [66]. **Scheme 13** shows a simplified scheme for the synthesis of such a polymer based on halobenzenes.

The ability of hyper-crosslinked polymers to absorb large volumes of liquid due to the swelling of porous networks is a property that can be used in many other areas, for example, in medical purposes for treating wounds. The maximum swelling of hyper-crosslinked polymers, along with the inclusion of catalytic groups in the network to ensure chemical deactivation of agents, will contribute to the development of a universal polymer material capable of absorbing and destroying stocks of all known CWAs.

It is known that sorbent materials are usually used for the physical removal of chemical warfare agents from contaminated surfaces. They remove CWAs in liquid form by their physical adsorption. After adsorption, the sorbent is removed by wiping until clean surfaces are



Scheme 13. The synthesis of hyper-crosslinked polymer meshes

obtained. One such work [67] presents data on the decontamination composition based on nanomaterials containing TiO_2, MgO, and ZnO nanoparticles for use against chemical warfare agents. This decontamination composition was prepared by mixing 90% of TiO_2 nanoparticles with a size of 5–15 nm, 8% of MgO nanoparticles with a size of 5–15 nm and 2% of ZnO nanoparticles with a size of 20–30 nm. As the authors showed, the composition prepared proved its effectiveness in physically removing 98–99% of contaminated glass, rubber, and metal surfaces [68]. It effectively removed chemical warfare agents from the contaminated skin. Examples of the chemical decomposition of 97% of mustard gas in 24 hours and 99.9% of sarin in 2 hours are given in contrast to Fuller's earth, which chemically decomposes only 63% of mustard gas and 59% of sarin in 24 hours.

■ Conclusions

The material presented in the review relates to the analysis of various methods of decontamination of chemical warfare agents, ecotoxicants, and various pollutants that are widely used to clean surfaces and air. The main degradation processes of CWAs that have been described above include hydrolysis, oxidation, photolysis. The use of these reactions, both individually and in various combinations, allows for creating unique formulations and technologies capable of a quick and efficient destruction of both chemical warfare agents and other ecotoxicants. An important method of CWAs deactivation is the use of nucleophilic/oxidizing systems, primarily α-nucleophiles, which are highly efficient and can react as nucleophiles and oxidants. It has been shown that the use of systems based on hydrogen peroxide for deactivation of CWAs is effective both from the point of view of the reaction rate and environmental protection. Being convenient for practical use, oxidizing systems consisting of one reagent have also been developed, both against chemical warfare agents and various pollutants.

An equally important method of decontamination of CWAs is the use of supernucleophilic systems based on functional detergents, which makes it possible to increase efficiency not only due to structural modification of the agent that breaks down ecotoxicants, but also by using alternative methods of influencing the reaction rate, for example, by changing properties of the solvent in which it occurs.

In this sense, microorganized systems (micellar solutions, microemulsions, ionic liquids, concentrated aqueous solutions of quaternary ammonium salts, etc.) are widely used to solve a number of applied and fundamental problems. The indisputable advantage of micellar systems compared to other organized microheterogeneous media, is that a significant change in the properties of the medium is achieved by the introduction of rather small amounts of micelle-forming substances, above the critical concentration of micelle formation, which varies within 10^{-6}–10^{-2} mol l^{-1}. At the same time, the main component of such systems, in most cases, is water, which makes them extremely attractive for practical use from the point of view of "green" chemistry.

Works on the application of photocatalytic deactivation of CWAs using composites obtained on the basis of zirconium and terephthalic acid, which are made from plastic waste, seem very interesting (this is important, based on environmental issues). It is worth paying attention to the research of photolytic and photocatalytic reactions of deactivation of sarin, soman, mustard gas and chlorocyanide in the air. Thus, vapors of these CWAs (except chlorocyanide) can be effectively removed by UV light from a germicidal lamp. Such a photocatalytic reaction leads to photoinduced polymerization directly under the action of UV irradiation, as well as the splitting of CWAs into small inorganic compounds on the surface of the TiO_2 catalyst. Photocatalytic and sonophotocatalytic methods of processing reaction mixtures in aqueous TiO_2 suspensions have also been developed. The question of using polymer sorbents for deactivating CWAs is reflected in many recent publications. They provide effective adsorption of CWAs and the possibility of their deactivation in large volumes and in a short period of time.

Thus, ensuring high reaction rates and forming decomposition products that are safe for nature and humans and their subsequent complete disposal should be the basis of methods and technologies for decontaminating chemical warfare agents.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

References

1. Popov, A.; Kapitanov, I.; Serdyuk, A.; Shumeiko, A. Reactivity of nucleophiles and α-effect in substitution processes at electron – deficiency centers (Part 1). *Ukr. Khim. Zh.* **2020**, *86* (7). https://doi.org/10.33609/2708-129X.86.7.2020.3-31.
2. Popov, A. F. Design of green microorganized systems for decontamination of ecotoxicants. *Pure Appl. Chem.* **2008**, *80* (7), 1381–1397. https://doi.org/10.1351/pac200880071381.
3. Yang, Y. C.; Szafraniec, L. L.; Beaudry, W. T.; Rohrbaugh, D. K. Oxidative detoxification of phosphonothiolates. *J. Am. Chem. Soc.* **1990**, *112* (18), 6621–6627. https://doi.org/10.1021/ja00174a025.
4. Popov, A.; Kapitanov, I.; Serdyuk, A.; Shumeiko, A. Reactivity of nucleophiles and α-effect in substitution processes at electron – deficiency centers (Part 2). *Ukr. Khem. Zh.* **2020**, *86* (8). https://doi.org/10.33609/2708-129X.86.8.2020.77-100.
5. Bromberg, L.; Hatton, T. A. Nerve Agent Destruction by Recyclable Catalytic Magnetic Nanoparticles. *Ind. Eng. Chem. Res.* **2005**, *44* (21), 7991–7998. https://doi.org/10.1021/ie0506926.
6. Richardson, D. E.; Yao, H.; Frank, K. M.; Bennett, D. A. Equilibria, Kinetics, and Mechanism in the Bicarbonate Activation of Hydrogen Peroxide: Oxidation of Sulfides by Peroxymonocarbonate. *J. Am. Chem. Soc.* **2000**, *122* (8), 1729–1739. https://doi.org/10.1021/ja9927467.
7. Bakhmutova-Albert, E. V.; Yao, H.; Denevan, D. E.; Richardson, D. E. Kinetics and Mechanism of Peroxymonocarbonate Formation. *Inorg. Chem.* **2010**, *49* (24), 11287–11296. https://doi.org/10.1021/ic1007389.
8. Wagner, G. W. Studies on Residue-Free Decontaminants for Chemical Warfare Agents. *Environ. Sci. Technol.* **2015**, *49* (6), 3755–3760. https://doi.org/10.1021/es506045a.
9. Wagner, G. W.; Procell, L. R.; Yang, Y.-C.; Bunton, C. A. Molybdate/Peroxide Oxidation of Mustard in Microemulsions. *Langmuir* **2001**, *17* (16), 4809–4811. https://doi.org/10.1021/la010334h.
10. Chiarini, M.; Bunton, C. A. Oxidation of Thioanisole by Peroxomolybdate in Alcohol-Modified Micelles of Cetylpyridinium Chloride. *Langmuir* **2002**, *18* (23), 8806–8812. https://doi.org/10.1021/la026156p.
11. Taube, F.; Hashimoto, M.; Andersson, I.; Pettersson, L. Characterisation of aqueous peroxomolybdate catalysts applicable to pulp bleaching. *J. Chem. Soc., Dalton Trans.* **2002**, (6), 1002–1008, 10.1039/B107936K. https://doi.org/10.1039/B107936K.
12. Zhao, S.; Xi, H.; Zuo, Y.; Wang, Q.; Wang, Z.; Yan, Z. Bicarbonate-activated hydrogen peroxide and efficient decontamination of toxic sulfur mustard and nerve gas simulants. *J. Hazard. Mater.* **2018**, *344*, 136–145. https://doi.org/10.1016/j.jhazmat.2017.09.055.
13. Nardello, V.; Marko, J.; Vermeersch, G.; Aubry, J. M. 90Mo NMR and kinetic studies of peroxomolybdic intermediates involved in the catalytic disproportionation of hydrogen peroxide by molybdate ions. *Inorg. Chem.* **1995**, *34* (20), 4950–4957. https://doi.org/10.1021/ic00124a007.
14. Singh, B.; Prasad, G.; Pandey, K.; Danikhel, R.; Vijayaraghavan, R. Decontamination of Chemical Warfare Agents (Review Article). *Def. Sci. J* **2010**, *60*, 428–441. https://doi.org/10.14429/dsj.60.487.
15. Zhao, S.; Xi, H.; Zuo, Y.; Han, S.; Zhu, Y.; Li, Z.; Yuan, L.; Wang, Z.; Liu, C. Rapid activation of basic hydrogen peroxide by borate and efficient destruction of toxic industrial chemicals (TICs) and chemical warfare agents (CWAs). *J. Hazard. Mater.* **2019**, *367*, 91–98. https://doi.org/10.1016/j.jhazmat.2018.12.075.
16. Davies, D. M.; Deary, M. E.; Quill, K.; Smith, R. A. Borate-catalyzed reactions of hydrogen peroxide: kinetics and mechanism of the oxidation of organic sulfides by peroxoborates. *Chem. Eur. J*. **2005**, *11 12*, 3552–3558. https://doi.org/10.1002/chem.200401209.
17. Deary, M. E.; Durrant, M. C.; Davies, D. M. A kinetic and theoretical study of the borate catalysed reactions of hydrogen peroxide: the role of dioxaborirane as the catalytic intermediate for a wide range of substrates. *Org. Biomol. Chem.* **2013**, *11* (2), 309–317. https://doi.org/10.1039/C2OB26842F.
18. Lobachev, V. L.; Zimtseva, G. P.; Matvienko, Y. V.; Rudakov, E. S. Kinetics of the oxidation of diethyl sulfide in the B(OH)3-H2O2/H2O system. *Theor. Exp. Chem.* **2007**, *43* (1), 44–49. https://doi.org/10.1007/s11237-007-0004-4.
19. Menger, F. M.; Rourk, M. J. Deactivation of mustard and nerve agent models via low-temperature microemulsions. *Langmuir* **1999**, *15*, 309–313. https://doi.org/10.1021/la980910i.
20. Picard, B.; Chataigner, I.; Maddaluno, J.; Legros, J. Introduction to chemical warfare agents, relevant simulants and modern neutralisation methods. *Org. Biomol. Chem.* **2019**, *17* (27), 6528–6537. https://doi.org/10.1039/C9OB00802K.
21. Wagner, G. W.; Sorrick, D. C.; Procell, L. R.; Brickhouse, M. D.; McVey, I. F.; Schwartz, L. I. Decontamination of VX, GD, and HD on a Surface Using Modified Vaporized Hydrogen Peroxide. *Langmuir* **2007**, *23* (3), 1178–1186. https://doi.org/10.1021/la062708i.
22. Mikutta, R.; Kleber, M.; Kaiser, K.; Jahn, R. Organic matter removal from soils using hydrogen peroxide, sodium hypochlorite, and disodium peroxodisulfate. *Soil Sci. Soc. Am. J.* **2005**, *69*, 120–135. https://doi.org/10.2136/sssaj2005.0120.
23. Wagner, G. W.; Yang, Y.-C. Rapid Nucleophilic/Oxidative Decontamination of Chemical Warfare Agents. *Ind. Eng. Chem. Res.* **2002**, *41* (8), 1925–1928. https://doi.org/10.1021/ie010732f.
24. Yang, Y. C.; Baker, J. A.; Ward, J. R. Decontamination of chemical warfare agents. *Chem. Rev.* **1992**, *92* (8), 1729–1743. https://doi.org/10.1021/cr00016a003.
25. Wagner, G.; Yang Y.-C. (US Department of Army). Universal Decontaminating Solution for Chemical Warfare Agents. US Patent US6245957B1, June 12, 2001.
26. Wagner, G.; Procell, L.; Yang Y.-C.; Bunton C. (US Department of Army). Molybdate/peroxide microemulsions useful for decontamination of chemical warfare agents. US Patent US6723891B1, April 20, 2004.
27. Raber, E.; McGuire, R. Oxidative decontamination of chemical and biological warfare agents using L-Gel. *J. Hazard. Mater.* **2002**, *93* (3), 339–352. https://doi.org/10.1016/S0304-3894(02)00051-1.
28. Carniato, F.; Bisio, C.; Psaro, R.; Marchese, L.; Guidotti, M. Niobium(V) Saponite Clay for the Catalytic Oxidative Abatement of Chemical Warfare Agents. *Angew. Chem., Int. Ed.* **2014**, *53* (38), 10095–10098. https://doi.org/10.1002/anie.201405134.
29. Shen, Z.; Zhong, J.-Y.; Yang, J.-C.; Cui, Y.; Zheng, H.; Wang, L.-Y.; Wang, J.-L. Decontamination of Chemical Warfare Agents by Zn2+ and Ge4+ co-doped TiO2 nanocrystals at sub-zero temperatures: A solid-state NMR and GC study. *Chem. Phys. Lett.* **2018**, *707*, 31–39. https://doi.org/10.1016/j.cplett.2018.07.033.
30. Qi, L.; Zuo, G.; Cheng, Z.; Wang, L.; Zhou, C. Treatment of chemical warfare agents by combined sodium percarbonate with tetraacetylethylenediamine solution. *Chem. Eng. J.* **2013**, *229*, 197–205. https://doi.org/10.1016/j.cej.2013.05.108.
31. Hogan, T.; Simpson, R.; Lin, M.; Sen, A. The deep oxidation of chemical warfare agent models: facile catalytic oxidative cleavage of phosphorus-carbon and sulfur-carbon bonds using dioxygen. *Catal. Lett.* **1997**, *49* (1), 59–63. https://doi.org/10.1023/A:1019088818029.

32. Bromberg, L.; Schreuder-Gibson, H.; Creasy, W. R.; McGarvey, D. J.; Fry, R. A.; Hatton, T. A. Degradation of Chemical Warfare Agents by Reactive Polymers. *Ind. Eng. Chem. Res.* **2009**, *48* (3), 1650–1659. https://doi.org/10.1021/ie801150y.
33. Popov, A. F.; Savelova, V. A. Modern approaches to the construction of highly efficient nucleophilic systems. *Theor. Exp. Chem.* **1999**, *35* (1), 1–17. https://doi.org/10.1007/BF02511123.
34. Gonzaga, F.; Segues, B.; Perez, É.; Rico-Lattesh, I.; Lattes, A. Decontamination chimique. II. Oxydation de composés soufrés en milieu micellaire: rôle de la lipophilie des substrats. *C. R. Acad. Sci., Ser. IIc: Chim.* **1998**, *1* (3), 209–216. https://doi.org/10.1016/S1387-1609(99)80082-6.
35. Delfino, R. T.; Ribeiro, T. S.; Figueroa-Villar, J. D. Organophosphorus compounds as chemical warfare agents: a review. *J. Braz. Chem. Soc.* **2009**, *20*, 407–428. https://doi.org/10.1590/S0103-50532009000300003.
36. Ariga K.; Kunitake, T. *Supramolecular Chemistry–Fundamentals and Applications*; Springer: Heidelberg, 2006.
37. Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*; Wiley, 2008.
38. Holmberg, K. *Handbook of Applied Surface and Colloid Chemistry*; Wiley: Chichester, England; New York, 2002.
39. Lion, C.; Despagne, B.; Delmas, G.; Fosset, L. Destruction Du Paraoxon Par Une Nouvelle Série de Sels de N-Alkyl Hydroximinomethylpyridinium. *Bull. Soc. Chim. Belg.* **1991**, *100* (7), 549–554. https://doi.org/10.1002/bscb.19911000710.
40. Menger, F. M.; Elrington, A. R. Rapid Deactivation of Mustard via Microemulsion Technology. *J. Am. Chem. Soc.* **1990**, *112* (22), 8201–8203. https://doi.org/10.1021/ja00178a074.
41. Toullec, J.; Moukawim, M. Cetyltrimethylammonium Hydroperoxide: An Efficient Reagent for Promoting Phosphate Ester Hydrolysis. *Chem. Commun.* **1996**, No. 2, 221. https://doi.org/10.1039/cc9960000221.
42. Gonzaga, F.; Perez, E.; Rico–Lattes, I.; Lattes, A. New Microemulsions for Oxidative Decontamination of Mustard Gas Analogues and Polymer-Thickened Half-Mustard. *New J. Chem.* **2001**, *25* (1), 151–155. https://doi.org/10.1039/b003671o.
43. Zimmerman, J. B.; Anastas, P. T.; Erythropel, H. C.; Leitner, W. Designing for a Green Chemistry Future. *Science* **2020**, *367* (6476), 397–400. https://doi.org/10.1126/science.aay3060.
44. Marrs, T. C.; Maynard, R. L.; Sidell, F. R. *Chemical Warfare Agents: Toxicology and Treatment*; Wiley: Chichester, West Sussex, England; Hoboken, Nj, 2007.
45. Han, X.; Balakrishnan, V. K.; vanLoon, G. W.; Buncel, E. Degradation of the Pesticide Fenitrothion as Mediated by Cationic Surfactants and α-Nucleophilic Reagents. *Langmuir* **2006**, *22* (21), 9009–9017. https://doi.org/10.1021/la060641t.
46. Han, X.; Balakrishnan, V. K.; Buncel, E. Alkaline Degradation of the Organophosphorus Pesticide Fenitrothion as Mediated by Cationic C_{12}, C_{14}, C_{16}, and C_{18} Surfactants. *Langmuir* **2007**, *23* (12), 6519–6525. https://doi.org/10.1021/la063521u.
47. Balakrishnan, V. K.; Han, X.; vanLoon, G. W.; Dust, J. M.; Toullec, J.; Buncel, E. Acceleration of Nucleophilic Attack on an Organophosphorothioate Neurotoxin, Fenitrothion, by Reactive Counterion Cationic Micelles. Regioselectivity as a Probe of Substrate Orientation within the Micelle. *Langmuir* **2004**, *20* (16), 6586–6593. https://doi.org/10.1021/la049572d.
48. Omakor, J. E.; Ikenna Onyido; vanLoon, G. W.; Buncel, E. Mechanisms of Abiotic Degradation and Soil–Water Interactions of Pesticides and Other Hydrophobic Organic Compounds. Part 3. Nucleophilic Displacement at the Phosphorus Centre of the Pesticide Fenitrothion [O,O-Dimethyl O-(3-Methyl-4-Nitrophenyl) Phosphorothioate] by Oxygen Nucleophiles in Aqueous Solution: α-Effect and Mechanism†. *J. Chem. Soc., Perkin Trans. 2* **2001**, No. 3, 324–330. https://doi.org/10.1039/b008615k.
49. Martinek, K.; A.K. Yatsimirski; Osipov, A. P.; Berezin, I. V. Micellar Effects on Kinetics and Equilibrium of Synthesis and Hydrolysis of Benzylideneaniline. *Tetrahedron* **1973**, *29* (7), 963–969. https://doi.org/10.1016/0040-4020(73)80046-8.
50. A Comparative Analysis of Pseudophase Ion-Exchange (PIE) Model and Berezin Pseudophase (BPP) Model: Analysis of Kinetic Data for Ionic Micellar-Mediated Semi-Ionic Bimolecular Reaction. *Bull. Korean Chem. Soc.* **2007**, *28* (7), 1135–1140. https://doi.org/10.5012/bkcs.2007.28.7.1135.
51. Kapitanov, I. V.; Mirgorodskaya, A. B.; Valeeva, F. G.; Gathergood, N.; Kuca, K.; L. Ya. Zakharova; Yevgen Karpichev. Physicochemical Properties and Esterolytic Reactivity of Oxime Functionalized Surfactants in PH-Responsive Mixed Micellar System. *Colloids Surf., A* **2017**, *524*, 143–159. https://doi.org/10.1016/j.colsurfa.2017.04.039.
52. Quina, F. H.; Chaimovich, Hernan. Ion Exchange in Micellar Solutions. 1. Conceptual Framework for Ion Exchange in Micellar Solutions. *J. Phys. Chem.* **1979**, *83* (14), 1844–1850. https://doi.org/10.1021/j100477a010.
53. Menger, F. M.; Portnoy, C. E. Chemistry of Reactions Proceeding inside Molecular Aggregates. *J. Am. Chem. Soc.* **1967**, *89* (18), 4698–4703. https://doi.org/10.1021/ja00994a023.
54. Al-Lohedan, H.; Bunton, C. A. Ion Binding and Micellar Effects upon Reactions of Carboxylic Anhydrides and Carbonate Esters. *J. Org. Chem.* **1982**, *47* (7), 1160–1166. https://doi.org/10.1021/jo00346a003.
55. Bunton, C. A.; Lawrence Baylor Robinson. Micellar Effects upon the Reaction of P-Nitrophenyl Diphenyl Phosphate with Hydroxide and Fluoride Ions. *J. Org. Chem.* **1969**, *34* (4), 773–780. https://doi.org/10.1021/jo01256a002.
56. Bunton, C. A.; Ihara, Y. Micellar Effects upon Dephosphorylation and Deacylation by Oximate Ions. *J. Org. Chem.* **1977**, *42* (17), 2865–2869. https://doi.org/10.1021/jo00437a018.
57. Kapitanov, I.; Serdyuk, A.; Shumeiko, A.; Prokop'eva, T.; Popov, A. Acid-base properties of functionalized surfactants in micellar systems. *Ukr. Khim. Zh.* **2017**, *83* (8), 94–102 [*in Russian*].
58. Singh, N.; Karpichev, Y.; Tiwari, A. K.; Kuca, K.; Ghosh, K. K. Oxime Functionality in Surfactant Self-Assembly: An Overview on Combating Toxicity of Organophosphates. *J. Mol. Liq.* **2015**, *208*, 237–252. https://doi.org/10.1016/j.molliq.2015.04.010.
59. Le, D. V.; Nguyen, M. B.; Dang, P. T.; Lee, T.; Nguyen, T. D. Synthesis of a UiO-66/G-C3N4 Composite Using Terephthalic Acid Obtained from Waste Plastic for the Photocatalytic Degradation of the Chemical Warfare Agent Simulant, Methyl Paraoxon. *RSC Advances* **2022**, *12* (35), 22367–22376. https://doi.org/10.1039/D2RA03483B.
60. Giannakoudakis, D. A.; Pearsall, F.; Florent, M.; Lombardi, J.; O'Brien, S.; Bandosz, T. J. Barium Titanate Perovskite Nanoparticles as a Photoreactive Medium for Chemical Warfare Agent Detoxification. *J. Colloid Interface Sci.* **2018**, *531*, 233–244. https://doi.org/10.1016/j.jcis.2018.07.053.
61. Liu, Y.; Moon, S.-Y.; Hupp, J. T.; Farha, O. K. Dual-Function Metal–Organic Framework as a Versatile Catalyst for Detoxifying Chemical Warfare Agent Simulants. *ACS Nano* **2015**, *9* (12), 12358–12364. https://doi.org/10.1021/acsnano.5b05660.
62. Zuo, G.-M.; Cheng, Z.-X.; Li, G.-W.; Shi, W.-P.; Miao, T. Study on Photolytic and Photocatalytic Decontamination of Air Polluted by Chemical Warfare Agents (CWAs). *Chem. Eng. J.* **2007**, *128* (2-3), 135–140. https://doi.org/10.1016/j.cej.2006.10.006.
63. Vorontsov, A. V.; Davydov, L.; Reddy, E. P.; Lion, C.; Savinov, E. N.; Smirniotis, P. G. Routes of Photocatalytic Destruction of Chemical Warfare Agent Simulants. *New J. Chem.* **2002**, *26* (6), 732–744. https://doi.org/10.1039/b109837c.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

64. Horikoshi, S.; Watanabe, N.; Mukae, M.; Hidaka, H.; Serpone, N. Mechanistic Examination of the Titania Photocatalyzed Oxidation of Ethanolamines. *New J. Chem.* **2001**, *25* (8), 999–1005. https://doi.org/10.1039/b102186i.
65. Wilson, C.; Main, M.; N. John Cooper; Briggs, M. E.; Cooper, A. I.; Adams, D. J. Swellable Functional Hypercrosslinked Polymer Networks for the Uptake of Chemical Warfare Agents. *Polym. Chem.* **2017**, *8* (12), 1914–1922. https://doi.org/10.1039/c7py00040e.
66. DeCoste, J. B.; Peterson, G. W. Metal–Organic Frameworks for Air Purification of Toxic Chemicals. *Chem. Rev.* **2014**, *114* (11), 5695–5727. https://doi.org/10.1021/cr4006473.
67. Prasad, G. K.; Gautam, A.; Kannan, G. M.; Acharya, J.; Gupta, A. K.; Thakare, V. B.; Singh, B. Nanomaterials Based Decontamination Formulation for Use in Personal Decontamination Kit against Chemical Warfare Agents. *Defense Life Science Journal* **2017**, *3* (1), 5. https://doi.org/10.14429/dlsj.3.12056.
68. Szinicz, L. History of Chemical and Biological Warfare Agents. *Toxicology* **2005**, *214* (3), 167–181. https://doi.org/10.1016/j.tox.2005.06.011.

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UDC 54.057:[547.747+547.513]

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Multigram Synthesis of 2-Azabicyclo[2.1.1]hexane-1-Carboxylates (2,4-Methanoprolines) – Promising Bicyclic Proline Analogs

Abstract

An optimized approach towards 4-substituted 2,4-methanoproline derivatives is reported. Careful selection of the starting materials and optimized isolation procedure provided easy access to a key bicyclic building block in a preparative yield of 32 % over five laboratory steps of up to 0.7 kg. Further modifications allowed us to obtain a number of useful derivatives, including those containing NH_2, COOH, CH_2NH_2, and CH_2F fragments with orthogonally protected functionalities.

Keywords: bicyclic compounds; building blocks; proline analog; bridged pyrrolidine; amino acid

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Масштабований синтез похідних 2-азабіцикло[2.1.1]гексан-1-карбоксилату (2,4-метанопроліну) – перспективних біциклічних аналогів проліну

Анотація

Запропоновано оптимізований підхід до 4-заміщених похідних 2,4-метанопроліну. Ретельний відбір вихідних речовин та удосконалена процедура виділення забезпечили простий доступ до ключового біциклічного будівельного блоку з препаративним виходом 32 % за п'ять стадій у масштабі до 0,7 кг. Подальші перетворення дозволили одержати низку корисних похідних, зокрема тих, що містять фрагменти NH_2, COOH, CH_2NH_2 та CH_2F з ортогонально захищеними функціональними групами.

Ключові слова: біциклічні сполуки; будівельні блоки; аналог проліну; містковий піролідин; амінокислоти

Citation: Chernykh, A.V.; Liashuk, O.S.; Hurieva, A. M.; Volochnyuk, D. M.; Grygorenko, O. O. Multigram Synthesis of 2-Azabicyclo[2.1.1]hexane-1-Carboxylates (2,4-Methanoprolines) – Promising Bicyclic Proline Analogs. *Journal of Organic and Pharmaceutical Chemistry* **2024**, *22* (3), 24–37.
https://doi.org/10.24959/ophcj.24.314843
Received: *27 October 2024*; **Revised:** *10 November 2024*; **Accepted:** *11 November 2024*

Supporting information: Copies of NMR spectra of all the compounds synthesized within the framework of this article.
Funding: This work was supported by Enamine Ltd. O. O. Grygorenko received additional funding from the Ministry of Education and Science of Ukraine, grant No. 0122U001962 (22BF037-02).
Conflict of interests: The authors are employees or consulting scientists at Enamine Ltd. offering commercially available reagents and starting compounds from the company's catalog.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

Introduction

Introduced in the 2000s, the "escape from flatland" concept affected the medicinal chemistry paradigm considerably, setting novel trends in drug design [1, 2]. This catchphrase refers to shifting from the predominant use of planar (hetero)aromatic fragments to sp^3-enriched moieties with three-dimensional shapes in drug design [3–5]. The introduction of non-planar saturated structures may improve the compound's physicochemical parameters [6–8], lower binding entropic penalty [1, 9], provide precise spatial disposition of the side chain fragments [10], and increase metabolic stability [11]. As a part of this concept, the intensive development of structurally rigid analogs of naturally occurring compounds (especially amino acids) was observed. In particular, C_1-modified pyrrolidine analogs received considerable attention after the introduction of the antidiabetic agent "Boceprevir" [12] and the antihepatitic drug "Saxagliptin" [12, 13] (**Figure 1**, *B*). Since then, fused pyrrolidine analogs and approaches to their synthesis have been thoroughly studied, resulting in more than 6500 compounds reported in *Reaxys*® [14]. On the contrary, pyrrolidines with bridged C_1 units are less documented, either in biomedical application studies or in the development of synthetic approaches (**Figure 1**, *A*).

One of the bridged pyrrolidine scaffolds, 2-azabicyclo[2.1.1]hexane (2,4-methanopyrrolidine), has been of particular interest since the 1980s when the corresponding α-amino acid – 2,4-methanoproline (**1**, **Figure 2**, *A*, FG = H) – was isolated from *Ateleia Herbert smithii Pittier* [15, 16]. The conformational features introduced by the bicyclic skeleton of **1** were considered to stabilize the *trans*-amide bond configuration, which was of potential use in peptide-based drug design [17–20]. Thus, *Stammer* and colleagues studied a conformationally constrained analog of thyrotropin-releasing hormone (TRH) and demonstrated a determinative impact of the bicyclic core on the conformation of the whole molecule [21]. Furthermore, derivatives of 2,4-methanopyrrolidine demonstrated very promising results in the recent antimalarial discovery campaign [22] and the discovery of the potential nicotinic acetylcholine receptor (nAChR) ligands [23].

To date, several different approaches to the synthesis of 2,4-methanoproline (**1**) and its derivatives have been reported (**Figure 2**, *A*). The earliest method included intramolecular photochemical [2+2] cycloaddition of *N*-allylic dehydroalanine derivatives **2** [3, 24, 25]. In this way, carboxyalkyl-, alkyl-, F-, or non-substituted 2,4-methanoprolines could be obtained in moderate yields. Modification of the pre-formed 2-azabicyclo-[2.1.1]hexane core *via* the C–H lithiation – electrophile addition sequence gave the target unsubstituted product in the yield of 98% [26]. Alternative approaches were based on intramolecular nucleophilic substitution reactions. In particular, one-pot tandem Strecker reaction – S_N2-type nucleophilic cyclization (STRINC) of

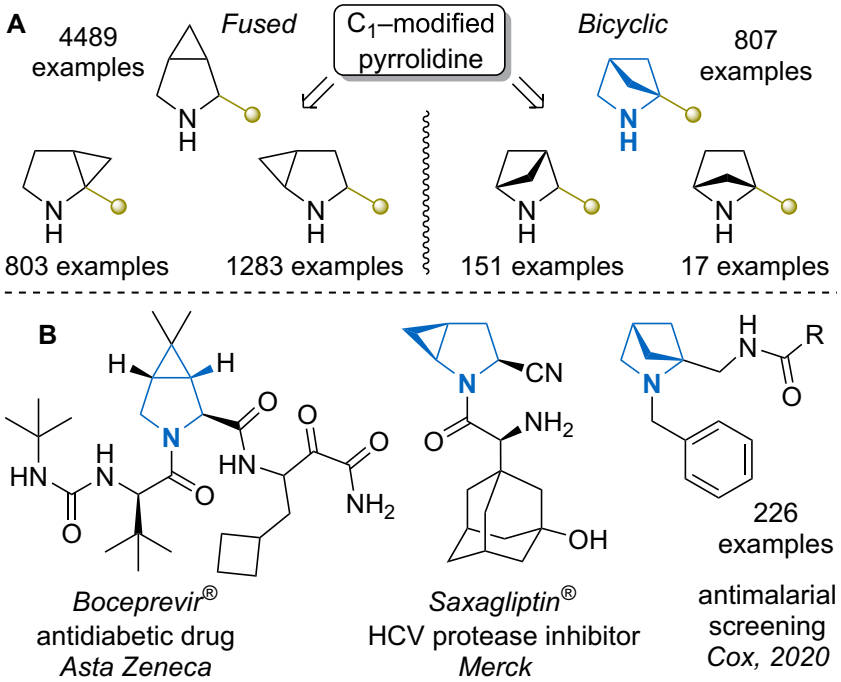

Figure 1. (*A*) Reported fused (left) and bridged (right) C_1-modified pyrrolidines ; (*B*) Drug substances with C_1-modified pyrrolidines

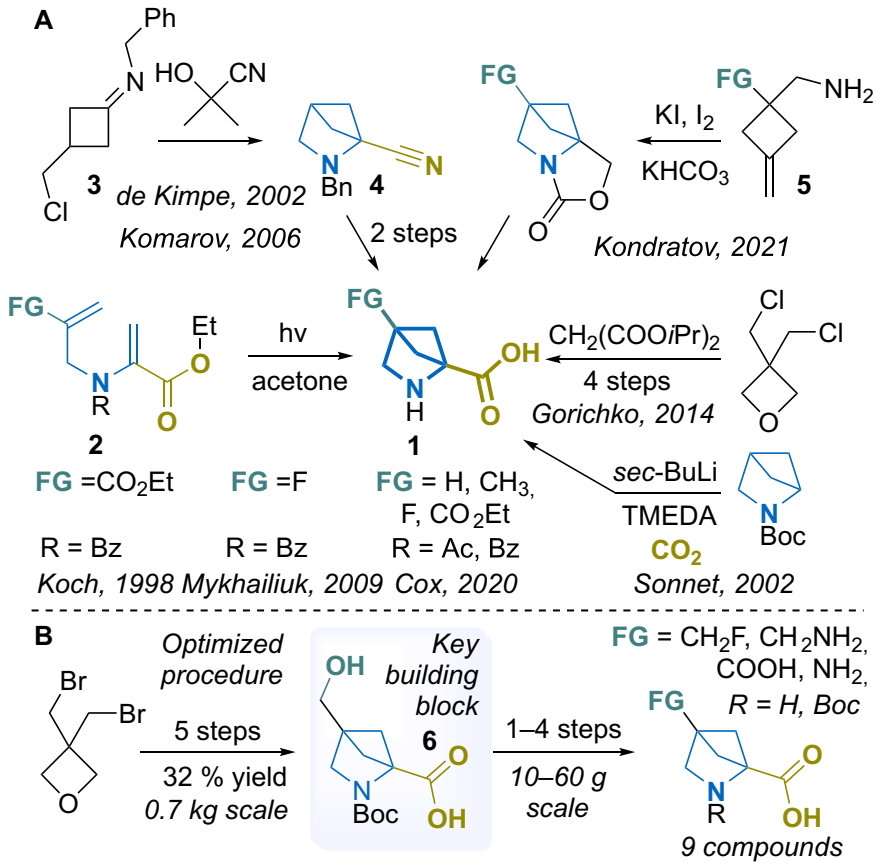

Figure 2. (*A*) Known synthesis of 2,4-methanoproline and its derivatives. (*B*) Results reported in this work

imine **3** produced nitrile **4** that could be easily converted to amino acid **1** in a few steps [27]. I_2-promoted cyclization of methylenecyclobutane **5** gave the corresponding tricyclic carbamate; the latter compound was converted to amino acid **1** upon the hydrolytic cleavage of the carbamate moiety with the subsequent oxidation of the hydroxymethyl fragment [28]. Finally, a sophisticated approach based on the double recyclization of oxetane ring allowed *Vasiuta* and *Gorichko* [29] the preparation of 4-hydroxymethyl-2-azabicyclo[2.1.1]hexane-1-carboxylic acid derivative (**1**, FG = CH_2OH) in only four steps.

In this work, we re-established the previously reported synthetic protocol towards *N*-Boc-4-hydroxymethyl-2,4-methanoproline (**6**) and adjusted it for the kilogram-scale production (**Figure 2**, *B*). The optimization of the starting points of the synthesis, as well as avoiding the product isolation with ion-exchange chromatography, allowed for the preparation of the key building block of up to 0.7 kg scale in a single run. Simple chemical transformations (including oxidation, deoxyfluorination, the Curtius reaction, or mesylation – nucleophilic substitution – azide reduction sequence) offered several valuable polyfunctionalized building blocks on a 10–60 g scale in preparative isolated yields.

■ Results and discussion

We started our investigation with the synthesis of the first important intermediate – bicyclic lactone **7** (**Scheme 1**). Repeating the original procedure [29], the application of dichloride **8** and diisopropyl malonate **9** as precursors led to spiro-derivative **10** in the yield of 64%, which upon acidic rearrangement produced compound **7** in the yield of 62% (40% over two-steps). Meanwhile, the use of the corresponding dibromide **11** and diethylmalonate **12** was more effective in our hands, giving products **13** and **7** in the yield of 77% (64% over two steps). Using these optimized procedures, the sequence was scaled up to 1.10 kg of product **7** with no noticeable loss in efficiency. The Curtius rearrangement of the carboxylic acid moiety with the subsequent recyclization of compound **14** under basic conditions afforded highly hydrophilic amino acid **15** (as a salt) in the yield of 80% (according to ^{1}H NMR spectra). The method reported for the isolation of this compound by ion-exchange column chromatography was considered impractical for the large-scale synthesis. To bypass the limitations caused by the amphiphilic nature of the amino acid obtained, compound **15** was converted to the corresponding *N*-Boc derivative by the treatment

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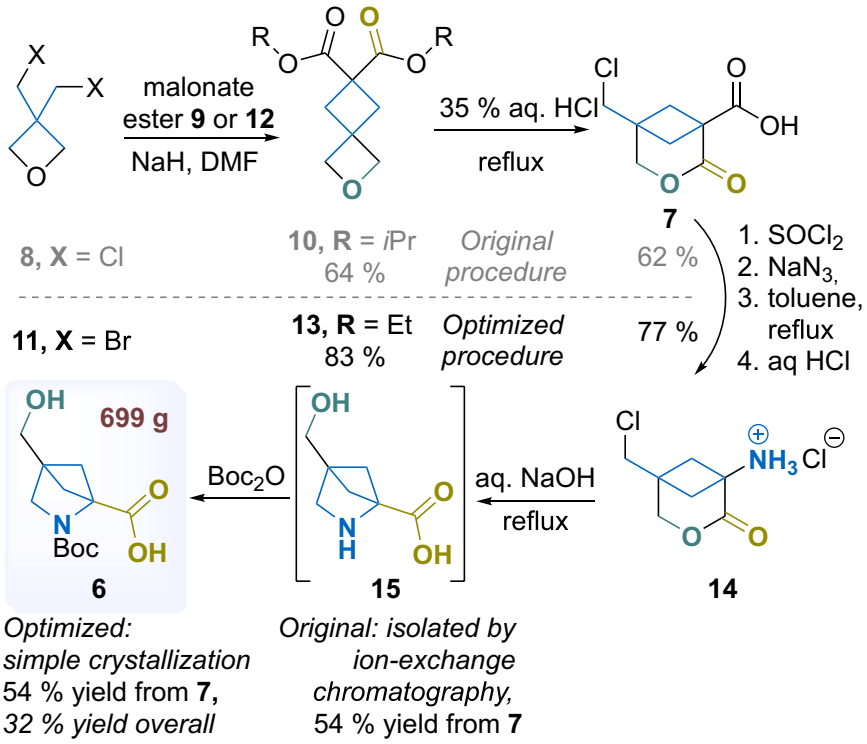
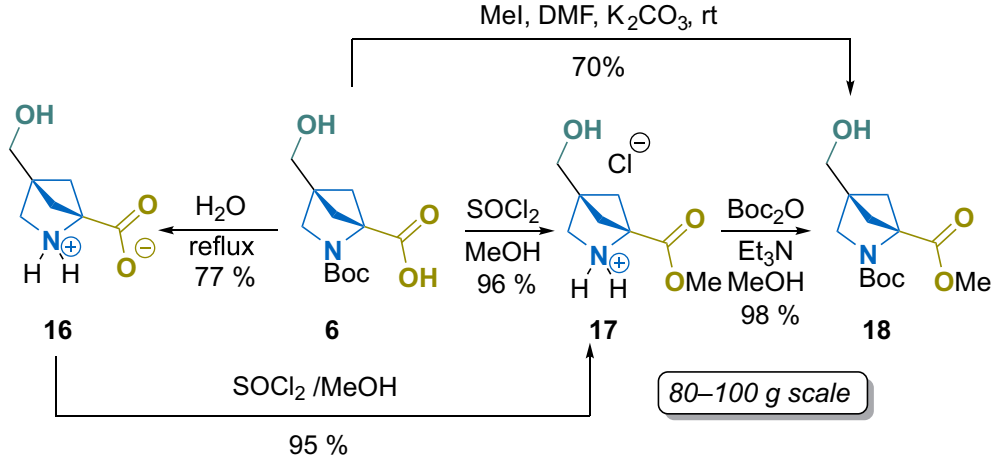


Scheme 1. Synthesis of key building block **6**

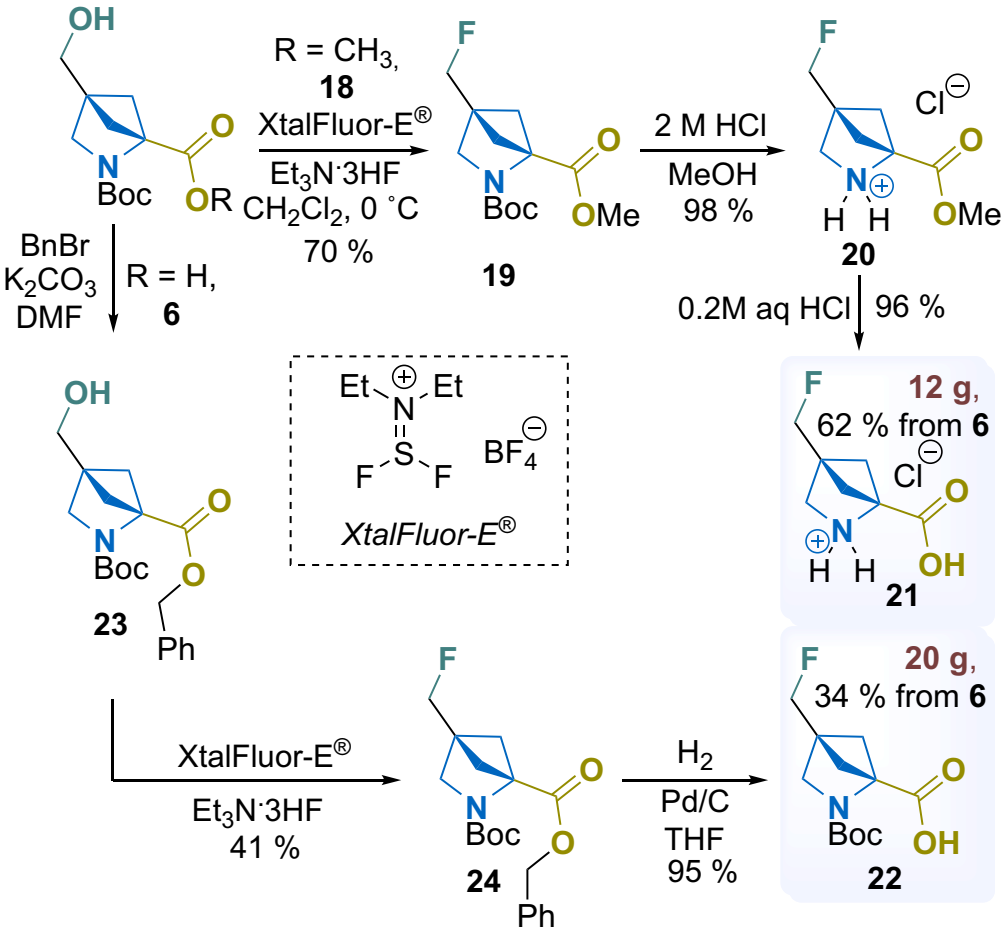
with Boc_2O without isolation. Upon completion of the reaction, pure *N*-Boc amino acid **6** was extracted from the aqueous solution after the acidification with $NaHSO_4$. This simple methodology allowed for the preparation of the key building block **6** on a 0.7 kg scale in a single run in the yield of 32% over four laboratory steps.

With a substantial amount of compound **6** in hand, we aimed to demonstrate its utility as the source of 2-azabicyclo[2.1.1]hexane derivatives (**Scheme 2**). Firstly, interconversions of the *N*,*O*-protective groups were performed. Refluxing the aqueous suspension of compound **6** led to amino acid **16** in the zwitterionic form in an isolated yield of 77%. $SOCl_2$-mediated esterification led to the simultaneous cleavage of the carbamate fragment, giving amine **17** as a HCl salt. The *N*-Boc-protection of the latter compound under basic conditions gave alcohol **18** (in the yield of 98%) that could also be obtained directly from *N*-Boc amino acid **6** using MeI – K_2CO_3 in DMF in an isolated yield of 70%.

Since introducing fluorinated substituents into organic molecules is a widely recognized strategy for fine-tuning the compound's physicochemical properties [30–35], we considered installing a fluorine atom into the 2,4-methanoproline core. We found that the treatment of the *N*,*O*-protected building block **18** with commercially available deoxyfluorination agents (DAST (*N*,*N*-diethylaminosulfur trifluoride) or Morph-DAST) led to the formation of the fluoromethyl derivative **19**



Scheme 2. Variation of the protective functional groups in the building block **6**



Scheme 3. Preparation of fluoromethyl derivatives **21** and **22**

in the unsatisfactory yield of 26–30%. At the same time, the application of an alternative fluorine source – XtalFluor-E® (DAST difluorosulfinium salt) [36, 37] produced target compound **19** in the preparative yield of 70% (**Scheme 3**). The subsequent cleavage of the *N*- and *O*-protection groups gave the building block **20** and then – amino acid hydrochloride **21** in the yields of 98% and 96%, respectively. Considering the potential incompatibility of the masked neopentyl fluoride fragment with nucleophilic reagents [38], *N*-Boc protected amino acid **22** was prepared by an alternative sequence. The base-promoted benzylation of amino acid **6** gave hydroxyester **23** that was transformed into fluoride **24** in the yield of 41%. The hydrogenolysis of the benzyl protection group cleanly produced the target *N*-Boc-amino acid **22** in the yield of 95%.

The amination of the primary alcohol moiety in the molecule of **6** was achieved by a standard three-step sequence (**Scheme 4**) [39, 40]. The mesylation with MsCl under mild conditions cleanly afforded mesylate **25** (in the yield of 99%), which upon the treatment with NaN_3 was converted into azide **26** in a high yield of 94%. The catalytic hydrogenolysis over Pd/C was found to be sluggish, giving the complex mixture of unidentified compounds. However, using saturated ammonia methanol as a solvent suppressed the undesired reactivity, producing target aminomethyl derivative **27** in the yield of 91% on a 20 g scale.

Finally, oxidation of the alcohol moiety in **6** with $RuCl_3/NaIO_4$ mixture [41, 42] afforded carboxylic acid **28** in the yield of 89% (**Scheme 5**). Upon acidic cleavage of derivative **28**, a protected bicyclic glutamate analog **29** was obtained in the yield of 93% (overall 83% from **6**). The latter compounds can be of special interest to bioorganic and medicinal chemists since promising peptidomimetic properties of its derivatives were disclosed previously by *Esslinger* and co-workers [43]. The Curtius rearrangement of carboxylic acid **28** gave orthogonally protected diamine **30** in the yield of 62%. Its subsequent hydrogenolysis produced diamino acid derivative **31** in the yield of 98% (overall 54% from **6**) on *ca.* 20 g scale.

■ Conclusions

In this work, the multigram synthesis of 2-azabicyclo[2.1.1]hexane-1-carboxylate (2,4-methanoproline) derivatives has been developed. An optimized

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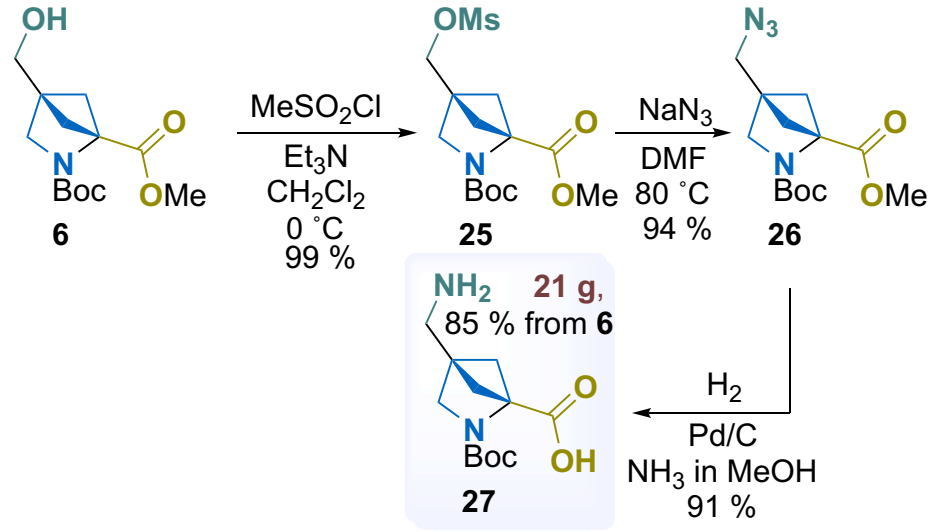
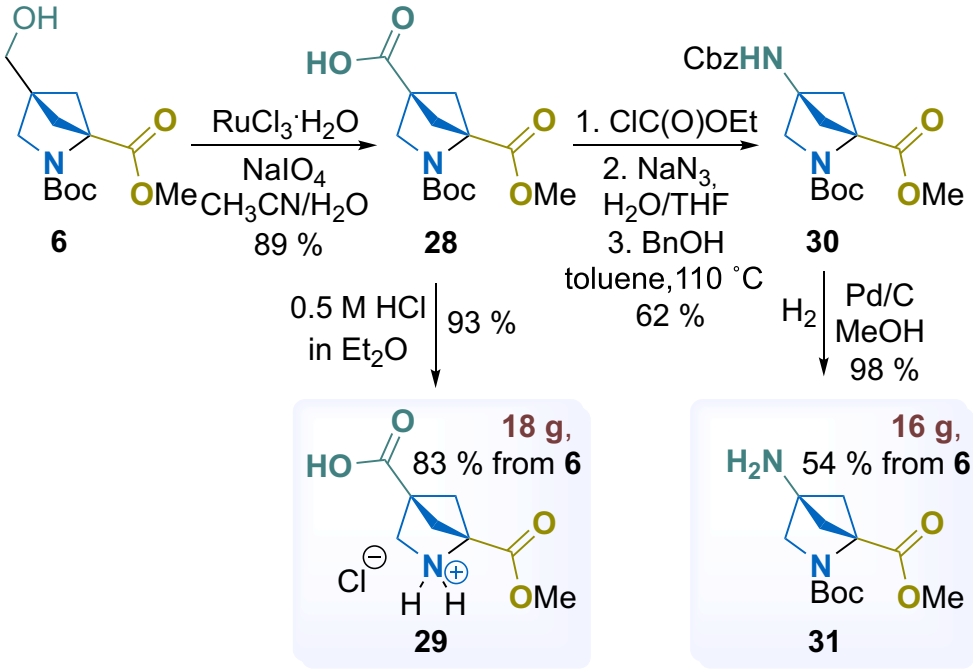


Scheme 4. Preparation of diamino acid derivative **27**



Scheme 5. Ru-mediated oxidation of alcohol **6** and further transformations

protocol for synthesizing the key building block – *N*-Boc-4-(hydroxymethyl)-2,4-methanoproline – has allowed for the preparation of the latter compound on a 700-g scale with the improved overall yield and avoiding the resource-demanding ion-exchange chromatography step. Further functional group transformations have offered several building blocks valuable for medicinal chemists, including those bearing CH_2F, CH_2NH_2, COOH, and NH_2 groups in position C-4. Operationally simple transformations, high overall yields, as well as large amounts of the products obtained, offer easy access to privileged saturated scaffolds. We believe that the results of this work will promote the use of the title chemotype in future drug development campaigns.

■ Experimental part

The solvents were purified according to the standard procedures [44]. Compound **11**, Xtal-Fluor-E® ((Diethylamino)difluorosulfonium tetrafluoroborate), and all other starting materials were obtained from Enamine Ltd. stock. Melting points were measured on the MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C{^{1}H} NMR), on an Agilent ProPulse 600

spectrometer (at 151 MHz for ^{13}C) and a Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for $^{13}C\{^{1}H\}$ NMR and 376 MHz for $^{19}F\{^{1}H\}$ NMR). NMR chemical shifts were reported in ppm (δ scale) downfield from TMS as an internal standard and referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. For $^{19}F\{^{1}H\}$, NMR CCl_3F was used as an internal standard. Coupling constants (*J*) were given in Hz. Spectra were reported as follows: chemical shift (δ, ppm), integration, multiplicity, coupling constants (Hz), and signals assignment if applicable. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

Diethyl 2-oxaspiro[3.3]heptane-6,6-dicarboxylate (13)

To the suspension of NaH pre-cooled to 0 °C (60% dispersion in mineral oil, 0.750 kg, 18.8 mol) in DMF (3.5 L), neat diethyl malonate (3.00 kg, 18.7 mol) was slowly added, keeping the temperature below 10 °C (CAUTION! Application of the mechanical stirring apparatus and intensive ventilation of the fume hood is necessary due to massive solidification of the reaction mixture and large amounts of the evolved gas!). The resulting mixture was stirred for 1 h at rt, then slowly heated to 60 °C, and the solution of 3,3-*bis*-(bromomethyl)oxetane (**11**) (2.20 kg, 9.02 mol) in DMF (0.5 L) was added gradually at this temperature. The resulting mixture was heated to reflux and stirred for 16 h at the same temperature. Upon completion of the reaction (concluded by ^{1}H NMR spectroscopy of the small aliquot of the reaction mixture), the mixture was cooled to rt, diluted with water (6 L), and extracted with *t*BuOMe (5 L). The organic layer was washed with water (2×2 L), dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The oily residue was distilled in a high vacuum to give the title compound **13**. The compound was mentioned previously in the literature without proper characterization [45].

A colorless liquid. Yield – 1.82 kg (83%). B. p. 95–98 °C (1 mmHg). Anal. Calcd. for $C_{12}H_{18}O_5$, %: C 59.49, H 7.49. Found, %: C 59.35, H 7.55. ^{1}H NMR (400 MHz, $CDCl_3$), *δ*, ppm: 1.23 (3H, t, *J* = 7.1 Hz, $\underline{CH_3}CH_2O$), 2.72 (2H, s, CH_2), 4.17 (2H, q, *J* = 7.1 Hz, $CH_3\underline{CH_2}O$), 4.65 (2H, s, CH_2). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$), *δ*, ppm: 171.5, 83.3, 77.2, 61.7, 48.1, 39.0, 38.3, 14.1.

5-(Chloromethyl)-2-oxo-3-oxabicyclo-[3.1.1]heptane-1-carboxylic acid (7)

To a refluxing aq. HCl (6 M, 900 mL), a neat compound **13** (100.0 g, 0.413 mol) was added within 2–3 min in a few portions. The resulting mixture was refluxed for 30 min and then concentrated under reduced pressure at 70 °C. The crude residue was triturated with Et_2O (400 mL), the precipitate formed was filtered off, washed with Et_2O (200 mL), and dried under a high vacuum (1 mmHg) at 50–60 °C with a P_2O_5 drying trap to give a pure compound **7**.

A colorless solid. Yield – 65.2 g (77%). M. p. >250 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$), *δ*, ppm: 2.26 (2H, dd, *J* = 7.3, 2.8 Hz, CH_2), 2.72 (2H, dd, *J* = 7.3, 2.9 Hz, CH_2), 3.62 (2H, s, CH_2Cl), 4.55 (2H, s, CH_2OCO). All other spectral data are in accordance with those reported in the literature [29].

1-Amino-5-(chloromethyl)-3-oxabicyclo-[3.1.1]heptan-2-one hydrochloride (14)

A neat $SOCl_2$ (1.92 kg, 16.128 mol) was slowly added to the solution of compound **7** (1.10 kg, 5.376 mol) in CH_2Cl_2 (5.6 L) and DMF (120 mL, 2% *v*/*v*) over *ca.* 1 hour at rt. The reaction mixture was heated to reflux for 3 h, then cooled to rt, and the solvent evaporated under reduced pressure. The solution of the residual compound, which was used in the next step as obtained (1.15 kg, 5.16 mol), in THF (2 L) was added to the solution of NaN_3 pre-cooled to 0 °C (2.00 kg, 30.8 mol) in water (4 L). The resulting mixture was stirred for 1 hour at rt, then poured on water (2 L) and extracted with toluene (4 L). The organic phase was separated, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to *ca.* 2.5 L, transferred to a dropping funnel, and the later was installed on a separate 10 L three-necked round bottom flask. A fresh portion of toluene (2.5 L) was added to this flask, heated to 85 °C, and the organic solution in a dropping funnel was slowly added to the heated solvent (*ca.* 1 h). The resulting mixture was heated to reflux and stirred for an additional 30 min at the same temperature, then left stirring without heating bath upon cooling to room temperature. The inhomogeneous mixture was carefully decanted from the precipitate, and the organic solvent was concentrated under reduced pressure to *ca.* 2–2.5 L. To the precipitate left, aq. HCl (8 M, 3L) was added in one portion, and the resulting mixture was slowly heated to reflux with intensive stirring

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(CAUTION! A possible violent gas evolution!). To the refluxing aqueous mixture, the toluene solution previously obtained was gradually added, controlling the addition rate by the rate of gas evolution. The resulting mixture was refluxed for an additional 2 hours, then cooled to room temperature, and the layers were separated. The aqueous phase was evaporated under reduced pressure, giving crude amine **14** as a HCl salt, which was used in the next step without purification. The analytical sample was obtained by trituration of the small amount of the crude material in Et_2O.

A colorless solid. M. p. 189–191 °C (*lit.* 194–196 °C [29]). ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.20 (2H, dd, J = 6.7, 3.0 Hz, CH_2), 2.64 (2H, d, J = 7.0 Hz, CH_2), 3.80 (2H, s, CH_2Cl), 4.44 (2H, s, CH_2OCO), 9.23 (3H, br. s, NH_3^+). All other spectral and physical data are in accordance with those reported in the literature [29].

2-[(*tert*-Butoxy)carbonyl]-4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid (6)

Product **14** was dissolved in 4 L of water, and then a solid NaOH (800.0 g, 20.0 mol) was added in portions, keeping the internal temperature below 40–45 °C. After additional stirring for 15 min, the mixture was cooled to rt, and the solution of Boc_2O (1.80 kg, 8.25 mol) in THF (1.8 L) was added dropwise. The resulting mixture was stirred for 3 h at rt, extracted with *t*BuOMe (2.0 L), and the aqueous layer was separated, acidified with $NaHSO_4$ to pH = 2, and extracted with EtOAc (3×2 L). The organic phases were combined, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was triturated with EtOAc (1.5 L) until solidification, and the precipitate formed was filtered to give a pure *N*-Boc-amino acid **6** (475.0 g, 1.85 mol, 36%). The filtrate was evaporated under reduced pressure to give a crude Boc-amino acid **6** (224.0 g, 0.871 mol, 17%) with sufficient purity, which could be used in the next step without purification.

A colorless solid. Yield – 699 g (53% from **7**). M. p. 143–146 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.36 (9H, s, $C(CH_3)_3$), 1.52 (2H, d, J = 5.0 Hz, CH_2), 1.85 (2H, d, J = 3.3 Hz, CH_2), 3.21 (2H, s, CH_2O), 3.56 (2H, d, J = 5.0 Hz, CH_2N), 4.71 (1H, t, J = 5.3 Hz, OH), 12.42 (1H, br. s, CO<u>OH</u>). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6), δ, ppm: 27.8, 43.0, 48.0, 53.4, 60.1, 67.8, 79.4, 156.4, 169.5. HRMS (ESI/QTOF), *m/z*: calcd for $C_{12}H_{19}NO_5Na^+$ 280.1155 $[M + Na]^+$, found 280.1156.

4-(Hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid (16)

A crude *N*-Boc-amino acid **6** (224.0 g, 0.871 mol) was mixed with 2 L of distilled water and heated to reflux with intensive stirring. Upon completion of the reaction (concluded by ^{1}H NMR spectrum of the small aliquot of the reaction mixture), the solvent was evaporated under reduced pressure to dryness, the solid residue was washed with a dry EtOH (1.0 L), filtered, and re-dissolved in a dry MeOH (3.4 L). Insoluble parts were filtered off, the filtrate was carefully evaporated under reduced pressure to give a pure amino acid **16**.

A colorless solid. Yield – 105.1 g (77%). M. p. 224–225 °C. Anal. Calcd. for $C_7H_{11}NO_3$, %: C 53.49, H 7.05, N 8.91. Found, %: C 53.41, H 6.98, N 8.83. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.55 (2H, d, J = 5.2 Hz, CH_2), 1.90 (2H, d, J = 5.3 Hz, CH_2), 2.99 (2H, s, CH_2N), 3.54 (2H, s, CH_2O), 4.82 (1H, s, CO<u>OH</u>). ^{13}C{^{1}H} NMR (101 MHz, D_2O), δ, ppm: 40.9, 49.4, 50.2, 59.8, 71.3, 172.1.

Methyl 4-(hydroxymethyl)-2-azabicyclo-[2.1.1]hexane-1-carboxylate hydrochloride (17)

A neat $SOCl_2$ (84.0 mL, 1.16 mol) was slowly added to a suspension of compound **6** pre-cooled to 0 °C (100.0 g, 0.389 mol) in MeOH (800 mL), keeping the internal temperature below 10 °C. The reaction mixture was heated to reflux and stirred at the same temperature for 40 min. Upon completion of the reaction (concluded by ^{1}H NMR spectrum of the small aliquot of the reaction mixture), the reaction mixture was cooled to room temperature, concentrated under reduced pressure, and co-evaporated the residue with fresh MeOH portions (2×350 mL). The residue was dried under a high vacuum (1 mmHg) to give a pure compound **17**. Yield – 77.3 g (96%).

An alternative method from **16**: A neat $SOCl_2$ (97.0 mL, 1.34 mol) was added dropwise to the solution of compound **16** pre-cooled to 0 °C (70.0 g, 0.445 mol) in MeOH (700 mL), keeping the internal temperature below 10 °C. The reaction mixture was heated to reflux and stirred at the same temperature for 40 min. Upon completion of the reaction (concluded by ^{1}H NMR spectrum of the small aliquot of the reaction mixture), the reaction mixture was cooled to room temperature, concentrated under reduced pressure, and co-evaporated the residue with fresh MeOH portions (2×350 mL). The residue was dried under a high vacuum (1 mmHg) to give a pure compound **17**.

A yellow powder. Yield – 87.8 g (95% from **16**). M. p. 150–153 °C. ^{1}H NMR (500 MHz, DMSO-d_6),

δ, ppm: 1.86 (2H, d, J = 5.1 Hz, CH_2), 2.18 (2H, d, J = 4.5 Hz, CH_2), 3.20 (2H, s, CH_2O), 3.61 (2H, s, CH_2N), 3.78 (3H, s, CH_3), 4.96 (1H, br. s, OH), 10.09 (2H, br. s, NH_2^+). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6), δ, ppm: 41.1, 48.7, 50.8, 52.9, 58.8, 67.0, 166.0. HRMS (ESI/QTOF), m/z: calcd for $C_8H_{14}NO_3^+$ 172.0968 $[M + H]^+$, found 172.0968.

2-*tert*-Butyl 1-methyl 4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate (18)

Method A. MeI (11.0 mL, 0.177 mol) was added to a mixture of compound **6** (22.0 g, 85.51 mmol) and K_2CO_3 (17.7 g, 128.3 mmol) in DMF (100 mL). The resulting suspension was stirred at room temperature overnight, poured on water (300 mL), and extracted with EtOAc (2×250 mL). The organic phases were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dried in a high vacuum (1 mmHg) to give a pure compound **18**. Yield – 16.21 g (70%).

Method B. The solution of Boc_2O (94.8 g, 0.435 mol) in MeOH (100 mL) was added to the solution of compound **17** (82.0 g, 0.395 mol) and Et_3N (137.6 ml, 0.987 mol) in MeOH (700 mL). The reaction mixture was stirred at room temperature overnight and then concentrated under reduced pressure. The residual oil was triturated with THF (500 mL), and the resulting cloudy mixture was filtered. The filtrate was evaporated under reduced pressure, triturated with *t*BuOMe (700 mL), and filtered, and the solvent was concentrated under reduced pressure to give product **18**.

A yellow viscous oil. Yield – 105.3 g (98% from **17**). Anal. Calcd. for $C_{13}H_{21}NO_5$, %: C 57.55, H 7.80, N 5.16. Found, %: C 57.46, H 7.72, N 4.96. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.40 (9H, s, $C(CH_3)_3$), 1.80–1.67 (2H, m, CH_2), 2.00 (2H, d, J = 3.5 Hz, CH_2), 2.44 (1H, s, OH), 3.36 (2H, s, CH_2O), 3.75 (3H, s, CH_3), 3.78 (2H, s, CH_2N). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ, ppm: 28.3, 43.7, 48.3, 52.1, 53.6, 61.9, 68.0, 81.0, 157.2, 169.2.

2-*tert*-Butyl 1-methyl 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate (19)

Et_3N×3HF (142.7 g, 0.885 mol) and Xtal-Fluor-E® (81.1 g, 0.354 mol) were sequentially added to the solution of compound **18** pre-cooled to 0 °C (80.0 g, 0.295 mol) in CH_2Cl_2 (1 L). The cooling bath was removed, and the resulting mixture was left overnight with stirring. The clear solution was slowly poured on sat. aq. $NaHCO_3$ (700 mL), the organic phase was washed with sat. aq. $NaHCO_3$ (500 mL), water (500 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The crude product obtained was purified by flash column chromatography (hexanes/EtOAc, gradient = 4:1 to 1:1 v/v) to give a pure compound **19**.

A yellow viscous oil. Yield – 56.5 g (70%). ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.34 (9H, s, $C(CH_3)_3$), 1.73 (2H, dd, J = 4.5, 1.5 Hz, CH_2), 2.00 (2H, d, J = 4.5 Hz, CH_2), 3.33 (2H, s, CH_2N), 3.70 (3H, s, CH_3), 4.50 (2H, d, J_{HF} = 47.2 Hz, CH_2F). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ, ppm: 28.1, 43.5 (d, J_{CF} = 4.6 Hz), 46.2 (d, J_{CF} = 21.9 Hz), 51.9, 52.7 (d, J_{CF} = 5.8 Hz), 67.9, 80.9, 81.9 (d, J_{CF} = 167.1 Hz), 156.9, 168.5. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$), δ, ppm: –226.3. HRMS (ESI/QTOF), m/z: calcd for $C_{13}H_{20}FNO_4Na^+$ 296.1269 $[M + Na]^+$, found 296.1267.

Methyl 4-(fluoromethyl)-2-azabicyclo[2.1.1]-hexane-1-carboxylate hydrochloride (20)

Compound **19** (55.0 g, 0.201 mol) was mixed with the anhydrous HCl methanolic solution (2 M, 500 mL) and stirred for 30 min at room temperature. After the gas evolution ceased, the solvent was carefully evaporated under reduced pressure at 30 °C. The crude residue was triturated with CH_3CN (100 mL), and the precipitate formed was collected by filtration to give a pure compound **20**.

A colorless solid. Yield – 41.5 g (98%). M. p. 196–199 °C. ^1H NMR (500 MHz, DMSO-d_6), δ, ppm: 2.03 (2H, d, J = 5.0 Hz, CH_2), 2.22–2.32 (2H, m, CH_2), 3.30 (2H, s, CH_2N), 3.77 (3H, s, CH_2), 4.71 (2H, d, J_{HF} = 47.0 Hz, CH_2F), 10.58 (2H, br. s, NH_2^+). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6), δ, ppm: 40.9 (d, J_{CF} = 4.9 Hz), 47.8 (d, J_{CF} = 5.3 Hz), 48.0 (d, J_{CF} = 21.8 Hz), 53.0, 67.2, 80.9 (d, J_{CF} = 161.7 Hz), 165.6. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6), δ, ppm: –227.3. HRMS (ESI/QTOF), m/z: calcd for $C_8H_{13}FNO_2^+$ 174.0925 $[M + H]^+$, found: 174.0925.

4-(Fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid hydrochloride (21)

Compound **20** (13.0 g, 0.062 mol) was dissolved in aq. HCl (0.2 M, 100 mL), and the resulting solution was heated to reflux. After additional stirring for 2 h, the mixture was cooled to rt, and the solvent was evaporated under reduced pressure to dryness. The residue was additionally dried in a high vacuum (1 mmHg) to give a pure compound **21**.

A colorless solid. Yield – 11.6 g (96%). M. p. 205–207 °C. ^1H NMR (500 MHz, D_2O), δ, ppm: 2.11 (2H, dd, J = 5.9, 2.3 Hz, CH_2), 2.58 (2H, d, J = 5.8 Hz, CH_2), 3.60 (2H, s, CH_2N), 4.84 (2H, d, J_{HF} = 46.6 Hz, CH_2F). $^{13}C\{^1H\}$ NMR (151 MHz, D_2O), δ, ppm: 41.0 (d, J_{CF} = 4.5 Hz), 48.3 (d, J_{CF} = 21.1 Hz), 49.0 (d, J_{CF} = 6.0 Hz), 69.1, 81.2 (d,

ISSN 2308-8303 (Print) / 2518-1548 (Online)

J_{CF} = 161.6 Hz), 168.5. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6), δ, ppm: –227.3. HRMS (ESI/QTOF), *m*/*z*: calcd for $C_7H_{11}FNO_2^+$ 160.0768 $[M + H]^+$, found: 160.0773.

2-[(*tert*-Butoxy)carbonyl]-4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid (22)

Compound **24** (28.0 g, 0.080 mol) was dissolved in THF (300 mL), and Pd/C (10% *w*/*w*, 5.00 g) was added in one portion. The flask was vacuumed and backfilled with H_2 from the balloon of the appropriate size, and the resulting mixture was stirred overnight. After the reaction was complete (concluded by ^1H NMR spectra of the small aliquot of the reaction mixture), the suspension was filtered through a celite pad, and the filtrate was concentrated under reduced pressure to give a pure compound **22**.

A colorless solid. Yield – 19.7 g (95%). M. p. 136–137 °C. ^1H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.50 (9H, s, $C(CH_3)_3$), 1.93 (2H, s, CH_2), 2.37 (2H, s, CH_2), 3.49 (2H, s, CH_2N), 4.59 (2H, d, J_{HF} = 47.1 Hz, CH_2F). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$), δ, ppm: 28.3, 44.9, 45.7 (d, J_{CF} = 22.9 Hz), 53.9, 70.0 (d, J_{CF} = 16.5 Hz), 82.1 (d, J_{CF} = 167.6 Hz), 82.9, 157.6, 169.7. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$), δ, ppm: –226.8. HRMS (ESI/QTOF), m/z: calcd for $C_{12}H_{18}FNO_4Na^+$ 282.1118 $[M + Na]^+$, found: 282.1112.

1-Benzyl 2-*tert*-butyl 4-(hydroxymethyl) bicyclo[2.1.1]hexane-1,2-dicarboxylate (23)

Benzyl bromide (30.5 mL, 0.257 mol) was added to a mixture of compound **6** (63.0 g, 0.245 mol) and K_2CO_3 (50.4 g, 0.365 mol) in DMF (400 mL) at room temperature. The resulting mixture was stirred at room temperature overnight, then diluted with water (1 L) and extracted with EtOAc (2×600 mL). The organic phases were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dried under a high vacuum (1 mmHg) to give a pure compound **23**.

A colorless solid. Yield – 73.6 g (87%). M. p. 68–69 °C. ^1H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.33 (9H, s, $C(CH_3)_3$), 1.68 (2H, s, CH_2), 1.93 (2H, s, CH_2), 2.87 (1H, s, OH), 3.29 (2H, s, CH_2O), 3.67 (2H, s, CH_2N), 5.11 (2H, s, $\underline{CH_2}Ph$), 7.26 (5H, s, PhH). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ, ppm: 28.2, 43.6, 48.3, 53.6, 61.6, 66.5, 67.9, 80.9, 128.0, 128.1, 128.5, 135.7, 157.2, 168.5. HRMS (ESI/QTOF), *m*/*z*: calcd for $C_{20}H_{26}O_5Na^+$ 370.1630 $[M + Na]^+$, found: 370.1625.

1-Benzyl 2-*tert*-butyl 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate (24)

$Et_3N{\cdot}3HF$ (164.0 mL, 1.01 mol) and XtalFluor-E® (69.2 g, 0.302 mol) were added sequentially to the solution of compound **23** pre-cooled to 0 °C (70.0 g, 0.202 mol) in DCM (1 L). The resulting mixture was slowly warmed to room temperature and stirred at the same temperature overnight. Then, the mixture was quenched with saturated aq. $NaHCO_3$ (2×700 mL), the organic layer was washed with water (700 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The crude product obtained was purified by flash column chromatography (hexanes/EtOAc, 5:1 to 1:1 gradient, *v*/*v*) to give a pure compound **24**.

A yellow viscous oil. Yield – 28.5 g (41%). ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.35 (9H, s, $C(CH_3)_3$), 1.75 (2H, d, J = 4.6 Hz, CH_2), 2.01 (2H, d, J = 4.3 Hz, CH_2), 3.33 (2H, s, CH_2N), 4.47 (2H, d, J_{HF} = 47.0 Hz, CH_2F), 5.13 (2H, s, $\underline{CH_2}Ph$), 6.96–7.59 (m, 5H, PhH). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ, ppm: 28.3, 43.6 (d, J_{CF} = 4.6 Hz), 46.4 (d, J_{CF} = 21.9 Hz), 52.9 (d, J_{CF} = 5.7 Hz), 66.7, 68.1, 81.0, 82.1 (d, J_{CF} = 167.4 Hz), 128.1, 128.2, 128.6, 135.8, 157.0, 168.0. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$), δ, ppm: –226.1. HRMS (ESI/QTOF), *m*/*z*: calcd for $C_{19}H_{24}FNO_4Na^+$: 372.1582 $[M + Na]^+$, Found: 372.1583.

2-*tert*-Butyl 1-methyl 4-[(methanesulfonyloxy)methyl]-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate (25)

To the solution of compound **6** pre-cooled to 0 °C (31.9 g, 0.118 mol) and Et_3N (25.0 mL, 0.179 mol) in CH_2Cl_2 (300 mL) under Ar atmosphere, a neat $MeSO_2Cl$ (16.2 g, 0.141 mol) was added dropwise keeping temperature below 5 °C. The resulting mixture was stirred for 1 h at the same temperature, washed with water (2×200 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dried in a high vacuum (1 mmHg) for 1 h at 35–38 °C to give compound **25**.

A yellow solid. Yield – 40.5 g (99%). M. p. 91–93 °C. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.39 (9H, s, $C(CH_3)_3$), 1.83–1.79 (2H, m, CH_2), 2.04–2.09 (2H, m, CH_2), 3.00 (3H, s, CH_3), 3.39 (2H, s, CH_2N), 3.74 (3H, s, CH_3), 4.36 (s, 2H, CH_2O). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$), δ, ppm: 28.2, 37.5, 44.0, 45.2, 52.1, 53.1, 67.9, 81.2, 156.8, 168.3. HRMS (ESI/QTOF), *m*/*z*: calcd for $C_{14}H_{23}NNaO_7S^+$ 372.1093 $[M + Na]^+$, found: 372.1088.

2-*tert*-Butyl 1-methyl 4-(azidomethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate (26)

To the solution of compound **25** (40.0 g, 0.114 mol) in DMF (300 mL), a solid NaN_3 (23.0 g, 0.354 mol) was added in one portion. The resulting mixture was stirred overnight at 80 °C, diluted with water (750 mL), and extracted with *t*BuOMe (750 mL). The organic layer was separated, washed with

brine (2×500 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give a pure compound **26**.

Yield – 31.9 g (94%). A yellow oil. Anal. Calcd. for $C_{13}H_{20}N_4O_4$, %: C 52.69; H 6.80; N 18.91. Found, %: C 52.38; H 6.87; N 19.25. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.41 (9H, s, $C(CH_3)_3$), 1.80 (2H, d, J = 3.6 Hz, CH_2), 2.03 (2H, d, J = 3.6 Hz, CH_2), 3.37 (2H, s, CH_2N), 3.53 (2H, s, CH_2N), 3.76 (3H, s, CH_3). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$), δ, ppm: 28.3, 44.5, 46.5, 51.8, 52.1, 53.9, 68.0, 81.1, 157.0, 168.6.

2-*tert*-Butyl 1-methyl 4-(aminomethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate (27)

The mixture of compound **26** (25.0 g, 84.4 mmol) and Pd/C (10% *w*/*w*, 5.00 g) in the saturated NH_3 methanolic solution (300 mL) was vacuumed and backfilled with H_2 from the balloon of the appropriate size. The resulting mixture was left overnight with intensive stirring. After the reaction was complete (concluded by ^{1}H NMR spectra of the small aliquot of the reaction mixture), the suspension was filtered through a thin celite pad, and the filtrate was evaporated under reduced pressure. The crude product was purified by flash column chromatography (hexanes/EtOAc/Et_3N = 1:4:0.25 *v*/*v*) to give a pure compound **27**.

A colorless solid. Yield – 20.8 g (91%). M. p. 57–60 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.43 (9H, s, $C(CH_3)_3$), 1.76 (2H, dd, J = 4.8, 1.8 Hz, CH_2), 1.91 (2H, br s, NH_2), 1.98 (2H, d, J = 4.5 Hz, CH_2), 2.98 (2H, s, CH_2N), 3.37 (2H, s, CH_2N), 3.78 (3H, s, CH_3). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$), δ, ppm: 28.4, 42.4, 43.8, 48.7, 52.1, 54.2, 67.9, 80.9, 157.2, 169.1. HRMS (ESI/QTOF), *m*/*z*: calcd for $C_{13}H_{23}N_2O_4^+$ 271.1652 $[M + H]^+$, found: 271.1646.

2-[(*tert*-Butoxy)carbonyl]-1-(methoxycarbonyl)-2-azabicyclo[2.1.1]hexane-4-carboxylic acid (28)

$RuCl_3 \times H_2O$ (1.07 g, 5.16 mmol) was added in one portion to the solution of alcohol **6** (56.0 g, 0.206 mol) and $NaIO_4$ (88.3 g, 0.413 mol) in the H_2O/MeCN mixture (900 mL, 2:1 *v*/*v*). The resulting solution was stirred for 2 h at rt, diluted with water (200 mL), and quenched with a solid $NaHCO_3$ to pH = 7 (CAUTION! Intensive stirring is required due to the heavy foaming effect). The suspension obtained was filtered, and the filtrate was extracted with $CHCl_3$ (400 mL). The organic layer was discarded, and the aqueous layer was acidified with 10% aq. $NaHSO_4$ to pH = 2 (CAUTION! Intensive stirring is required due to the heavy foaming effect) and extracted with EtOAc (2×700 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a pure acid **28**.

A colorless solid. Yield – 52.2 g (89%). M. p. 122–125 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.36 (9H, s, $C(CH_3)_3$), 1.88 (2H, d, J = 4.1 Hz, CH_2), 2.27 (2H, d, J = 4.4 Hz, CH_2), 3.48 (2H, s, CH_2N), 3.66 (3H, s, CH_3), 12.92 (1H, br. s, COOH). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6), δ, ppm: 27.8, 44.7, 47.0, 51.6, 52.4, 66.9, 80.0, 156.0, 167.5, 170.5. HRMS (ESI/QTOF), *m*/*z*: calcd for $C_{13}H_{19}NO_6Na^+$ 308.1105 $[M + Na]^+$, found: 308.1102.

1-(Methoxycarbonyl)-2-azabicyclo[2.1.1]-hexane-4-carboxylic acid hydrochloride (29)

Compound **28** (25.0 g, 87.6 mmol) was mixed with an anhydrous HCl ethereal solution (0.5 M, 300 mL). The reaction mixture was stirred for 24 h at room temperature, filtered, and the precipitate obtained was washed with Et_2O (150 mL) and dried on air to give a pure compound **29**.

A colorless powder. Yield – 18.1 g (93%). M. p. 196–198 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 2.19 (2H, dd, J = 5.3, 2.0 Hz, CH_2), 2.52 (2H, d, J = 1.9 Hz, CH_2 overlapped with the solvent residual peak), 3.46 (2H, s, CH_2N), 3.79 (3H, s, CH_3), 10.33 (2H, s, NH_2^+), 13.29 (1H, br. s, COOH). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6), δ, ppm: 42.8, 48.2, 49.0, 53.1, 66.7, 165.2, 168.8. HRMS (ESI/QTOF), *m*/*z*: calcd for $C_8H_{12}NO_4^+$ 186.0761 $[M + H]^+$, found: 186.0760.

2-*tert*-Butyl 1-methyl 4-{[(benzyloxy)carbonyl]amino}-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate (30)

To the solution of acid **28** pre-cooled to 0 °C (30.0 g, 0.105 mol) and Et_3N (22.0 mL, 0.158 mol) in THF (300 mL) under Ar atmosphere, a neat ethyl chloroformate (13.8 g, 0.127 mol) was added dropwise with mechanical stirring. The resulting mixture was stirred at 0 °C for 1 h, then cooled to –10 °C, and the solution of NaN_3 (50.0 g, 0.769 mol) in water (200 mL) was slowly added. The cooling bath was removed, and the reaction mixture was stirred for another 1 h, diluted with water (200 mL), and extracted with EtOAc (2×300 mL). The organic layer was separated, dried over Na_2SO_4, concentrated under reduced pressure to ca. 60 mL, and mixed with the benzylic alcohol (21.9 mL, 0.211 mol) solution in toluene (300 mL). The resulting mixture was gradually heated to reflux (over *ca.* 30 min) and stirred at the same temperature overnight. Upon completion, the mixture was concentrated under reduced pressure, and the crude residue was triturated with *t*BuOMe (75 mL). The resulting precipitate was filtered and dried on air to give a pure compound **30**.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

A colorless solid. Yield – 25.6 g (62%). M. p. 153–156 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.41 (9H, s, $C(CH_3)_3$), 2.06 (2H, s, CH_2), 2.39 (2H, br. s, CH_2), 3.51 (2H, s, CH_2N), 3.76 (3H, s, CH_3), 5.07 (2H, s, $\underline{CH_2}Ph$), 5.48 (1H, s, NH), 7.33 (5H, s, PhH). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ, ppm: 27.1, 28.3, 46.8, 52.2, 52.3, 53.6, 54.8, 65.3, 67.0, 77.2, 81.3, 128.3, 128.5, 128.7, 136.1, 155.0, 156.9, 168.5. HRMS (ESI/QTOF), *m*/*z*: calcd for $C_{20}H_{26}N_2O_6Na^+$ 413.1683 $[M + Na]^+$, found: 413.1680.

2-*tert*-Butyl 1-methyl 4-amino-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate (31)

Compound **30** (25.0 g, 64.1 mmol) was dissolved in MeOH (300 mL), and Pd/C (10% *w*/*w*, 5.00 g) was added in one portion. The reaction vessel was evacuated and backfilled with H_2 from a balloon (repeated 2 times), and the suspension was stirred under the H_2 atmosphere overnight. After the reaction was completed (concluded by ^{1}H NMR spectra of the small aliquot of the reaction mixture), the catalyst was filtered off through a short pad of celite, and the solvent was evaporated under reduced pressure to give a pure compound **31**.

A colorless solid. Yield – 16.1 g (98%). M. p. 98–99 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.42 (s, 9H, $C(CH_3)_3$), 1.93–2.05 (br. m, 6H, $2\times CH_2+NH_2$), 3.33 (s, 2H, CH_2N), 3.77 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$), δ, ppm: 28.4, 49.5, 52.1, 55.9, 57.3, 64.7, 81.0, 157.0, 168.9. HRMS (ESI/QTOF), *m*/*z*: calcd for $C_{12}H_{21}N_2O_4^+$ 257.1496 $[M + H]^+$, found: 257.1495.

Acknowledgments

The authors express their gratitude to Prof. Dr. A. O. Tolmachev for his encouragement and support and to all the brave defenders of Ukraine for making this publication possible.

References

1. Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing saturation as an approach to improving clinical success. *J. Med. Chem.* **2009**, *52* (21), 6752–6756. https://doi.org/10.1021/jm901241e.
2. Hamilton, D.J.; Dekker, T.; Klein, H. F.; Janssen, G. V.; Wijtmans, M.; O'Brien, P.; de Esch, I.J.P. Escape from planarity in fragment-based drug discovery: A physicochemical and 3D property analysis of synthetic 3D fragment libraries. *Drug Discov. Today: Technologies* **2020**, *38*, 77–90. https://doi.org/10.1016/J.DDTEC.2021.05.001.
3. Cox, B.; Zdorichenko, V.; Cox, P. B.; Booker-Milburn, K. I.; Paumier, R.; Elliott, L. D.; Robertson-Ralph, M.; Bloomfield, G. Escaping from Flatland: Substituted bridged pyrrolidine fragments with inherent three-dimensional character. *ACS Med. Chem. Lett.* **2020**, *11* (6), 1185–1190. https://doi.org/10.1021/acsmedchemlett.0c00039.
4. Aldeghi, M.; Malhotra, S.; Selwood, D. L.; Chan, A. W. E. Two- and three-dimensional rings in drugs. *Chem. Biol. Drug Des.* **2014**, *83*, 450–461. https://doi.org/10.1111/cbdd.12260.
5. Cox, B.; Booker-Milburn, K. I.; Elliott, L. D., Robertson-Ralph, M.; Zdorichenko, V. Escaping from flatland: [2+2] photocycloaddition; conformationally constrained sp^3-rich scaffolds for lead generation. *ACS Med. Chem. Lett.* **2019**, *10* (11), 1512–1517. https://doi.org/10.1021/acsmedchemlett.9b00409.
6. Degorce, S. L.; Bodnarchuk, M. S.; Cumming, I. A.; Scott, J. S. Lowering lipophilicity by adding carbon: One-carbon bridges of morpholines and piperazines. *J. Med. Chem.* **2018**, *61* (19), 8934–8943. https://doi.org/10.1021/acs.jmedchem.8b01148.
7. Smyrnov, O.; Melnykov, K. P.; Semeno, V.; Liashuk, O. S.; Grygorenko, O. O. α-CF_3-Substituted saturated bicyclic amines: Advanced building blocks for medicinal chemistry. *Eur. J. Org. Chem.* **2024**, *27* (1), e202300935. https://doi.org/10.1002/ejoc.202300935.
8. Meanwell, N. A. Applications of bioisosteres in the design of biologically active compounds. *J. Agric. Food Chem*. **2023**, *71* (47), 18087–18122. https://doi.org/10.1021/acs.jafc.3c00765.
9. Clemons, P. A.; Bodycombe, N. E.; Carrinski, H. A.; Wilson, J. A.; Shamji, A. F.; Wagner, B. K.; Koehler, A. N.; Schreiber, S. L. Small molecules of different origins have distinct distributions of structural complexity that correlate with protein-binding profiles. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107* (44), 18787–18792. https://doi.org/10.1073/pnas.1012741107.
10. Krzyzanowski, A.; Pahl, A.; Grigalunas, M.; Waldmann, H. Spacial score – a comprehensive topological indicator for small-molecule complexity. *J. Med. Chem.* **2023**, *66* (18), 12739–12750. https://doi.org/10.1021/acs.jmedchem.3c00689.
11. Mykhailiuk, P. K. Saturated bioisosteres of benzene: where to go next? *Org. Biomol. Chem*. **2019**, *17* (11) 2839–2849. https://doi.org/10.1039/C8OB02812E.
12. Liu, J.; Han, J.; Izawa, K.; Sato, T.; White, S.; Meanwell, N. A.; Soloshonok, V. A. Cyclic tailor-made amino acids in the design of modern pharmaceuticals, *Eur. J. Med. Chem.* **2020**, *208*, 112736. https://doi.org/10.1016/j.ejmech.2020.112736.
13. Boulton, D. W. Clinical Pharmacokinetics and Pharmacodynamics of Saxagliptin, a Dipeptidyl Peptidase-4 Inhibitor. *Clin. Pharmacokinet.* **2017**, *56* (1), 11–24. https://doi.org/10.1007/s40262-016-0421-4.
14. Reaxys® Database; https://www.reaxys.com/ (accessed on 03 Jun 2024).
15. Bell, E. A.; Qureshi, M. Y.; Pryce, R. J., Janzen, D. H.; Lemke, P.; Clardy, J. 2,4-Methanoproline (2-carboxy-2,4-methanopyrrolidine) and 2,4-methanoglutamic acid (1-amino-1,3-dicarboxycyclobutane) in seeds of Ateleia herbert smithii Pittier (Leguminosae). *J. Am. Chem. Soc.* **1980**, *102* (4), 1409–1412. https://doi.org/10.1021/ja00524a029.
16. Kite, G. C.; Ireland, H., Non-protein amino acids of Bocoa (Leguminosae; Papilionoideae). *Phytochem.* **2002,** *59* (2), 163–168. https://doi.org/10.1016/S0031-9422(01)00447-2.
17. Montelione, G. T.; Hughes, P.; Clardy, J.; Scheraga, H. A. Conformational properties of 2,4-methanoproline (2-carboxy-2,4-methanopyrrolidine) in peptides: determination of preferred peptide bond conformation in aqueous solution by proton Overhauser measurements. *J. Am. Chem. Soc.* **1986**, *108* (21), 6765–6773. https://doi.org/10.1021/ja00281a051.

18. Piela, L.; Nemethy, G.; Scheraga, H. A. Conformational properties of 2,4-methanoproline (2-carboxy-2,4-methanopyrrolidine) in peptides: theoretical conformational energy analysis of restrictions of the polypeptide chain conformation. *J. Am. Chem. Soc*. **1987**, *109* (15), 4477–4485. https://doi.org/10.1021/ja00249a009.
19. Mykhailiuk, P. K.; Kubyshkin, V.; Bach, T.; Budisa, N. Peptidyl-prolyl model study: How does the electronic effect influence the amide bond conformation? *J. Org. Chem.* **2017**, *82* (17), 8831–8841. https://doi.org/10.1021/acs.joc.7b00803.
20. Juvvadi, P.; Dooley, D. J.; Humblet, C. C.; Lu, G. H.; Lunney, E. A.; Panek, R. L.; Skeean, R.; Marshall, G. R. Bradykinin and angiotensin II analogs containing a conformationally constrained proline analog. *Int. J. Pept. Protein Res.* **1992**, *40* (3–4), 163–170. https://doi.org/10.1111/j.1399-3011.1992.tb00289.x.
21. Mapelli, C.; Halbeek, H. Van; Stammer, C. H. Synthesis and conformational studies by ^{1}H- and ^{13}C-NMR spectroscopy of a novel, sterically constrained analogue of thyrotropin-releasing hormone. *Biopolymers* **1990**, *29* (2), 407–422. https://doi.org/10.1002/bip.360290212.
22. Cox, B.; Duffy, J.; Zdorichenko, V.; Bellanger, C.; Hurcum, J.; Laleu, B.; Booker-Milburn, K. I.; Elliott, L. D.; Robertson-Ralph, M.; Swain, C. J., Bishop, S. J.; Hallyburton, I.; Anderson, M. Escaping from flatland: antimalarial activity of sp^3-rich bridged pyrrolidine derivatives. *ACS Med. Chem. Lett.* **2020**, *11* (12), 2497–2503. https://doi.org/10.1021/acsmedchemlett.0c00486.
23. Patel, A. B.; Malpass, J. R. Potential nicotinic acetylcholine receptor ligands from 2,4-methanoproline derivatives. *J. Med. Chem.* **2008**, *51* (21), 7005–7009. https://doi.org/10.1021/jm800537a.
24. Esslinger, C. S.; Koch, H. P.; Kavanaugh, M. P.; Philips, D. P.; Chamberlin, A. R.; Thompson, C. M.; Bridges, R. J. Structural determinants of substrates and inhibitors: probing glutamate transporters with 2,4-methanopyrroldidine-2,4-dicarboxylate. *Bioorg. Med. Chem. Lett.* **1998**, *8* (21), 3101–3106. https://doi.org/10.1016/S0960-894X(98)00560-5.
25. Levterov, V. V; Michurin, O.; Borysko, P. O.; Zozulya, S.; Sadkova, I. V; Tolmachev, A. A.; Mykhailiuk, P. K. Photochemical in-flow synthesis of 2,4-methanopyrrolidines: pyrrolidine analogues with improved water solubility and reduced lipophilicity. *J. Org. Chem.* **2018**, *83* (23), 14350–14361. https://doi.org/10.1021/acs.joc.8b02071.
26. Krow, G. R.; Herzon, S. B.; Lin, G.; Qiu, F.; Sonnet, P. E. Complex-induced proximity effects. Temperature-dependent regiochemical diversity in lithiation–electrophilic substitution reactions of *N*-Boc-2-azabicyclo[2.1.1]hexane. 2,4- and 3,5-Methanoprolines. *Org. Lett.* **2002**, *4* (18), 3151–3154. https://doi.org/10.1021/ol026509b.
27. Grygorenko, O. O.; Artamonov, O. S.; Palamarchuk, G. V; Zubatyuk, R. I.; Shishkin, O. V; Komarov, I. V Stereoselective synthesis of 2,4-methanoproline homologues. *Tetrahedron: Asymmetry* **2006**, *17* (2), 252–258. https://doi.org/10.1016/j.tetasy.2005.12.009.
28. Homon, A. A.; Hryshchuk, O. V.; Mykhailenko, O. V.; Vashchenko, B. V.; Melnykov, K. P.; Michurin, O. M.; Daniliuc, C. G.; Gerus, I. I.; Kovtunenko, V. O.; Kondratov, I. S.; Grygorenko, O. O. 4-(Di-/Trifluoromethyl)-2-heterabicyclo[2.1.1]hexanes: Advanced fluorinated phenyl isosteres and proline analogues. *Eur. J. Org. Chem.* **2021**, *2021* (47), 6580–6590. https://doi.org/10.1002/ejoc.202100414.
29. Vasiuta, R. I.; Gorichko, M. V Synthesis of 4-hydroxymethyl-2,4-methanoproline. *Tetrahedron Lett.* **2014**, *55* (2), 466–468. https://doi.org/10.1016/j.tetlet.2013.11.062.
30. Holovach, S.; Melnykov, K. P.; Skreminskiy, A.; Herasymchuk, M.; Tavlui, O.; Aloshyn, D.; Borysko, P.; Rozhenko, A.B.; Ryabukhin, S. V; Volochnyuk, D. M.; Grygorenko, O. O. Effect of *gem*-difluorination on the key physicochemical properties relevant to medicinal chemistry: the case of functionalized cycloalkanes. *Chem. Eur. J.* **2022**, *28* (19), e202200331. https://doi.org/10.1002/chem.202200331.
31. Nair, A. S.; Singh, A. K.; Kumar, A.; Kumar, S.; Sukumaran, S.; Koyiparambath, V. P.; Pappachen, L. K.; Rangarajan, T. M.; Kim, H., Mathew, B. FDA-approved trifluoromethyl group-containing drugs: A review of 20 years. *Processes* **2022**, *10* (10), 2054. https://doi.org/10.3390/pr10102054.
32. Han, J.; Remete, A. M.; Dobson, L. S.; Kiss, L.; Izawa, K.; Moriwaki, H.; Soloshonok, V. A.; O'Hagan, D. Next generation organofluorine containing blockbuster drugs. *J. Fluor. Chem.* **2020**, *239*, 109639. https://doi.org/10.1016/j.jfluchem.2020.109639.
33. der Born, D. Van; Pees, A.; Poot, A .J.; Orru, R. V. A., Windhorst, A. D.; Vugts, D. J. Fluorine-18 labelled building blocks for PET tracer synthesis. *Chem. Soc. Rev*. **2017**, *46* (15), 4709–4773. https://doi.org/10.1039/C6CS00492J.
34. Shah, P.; Westwell, A. D. The role of fluorine in medicinal chemistry. *J. Enzyme Inhib. and Med. Chem.* **2007**, *22* (5), 527–540. https://doi.org/10.1080/14756360701425014.
35. Henary, E.; Casa, S.; Dost, T. L.; Sloop, J. C.; Henary, M. The role of small molecules containing fluorine atoms in medicine and imaging applications. *Pharmaceuticals* **2024**, *17* (3). https://doi.org/10.3390/ph17030281.
36. L'heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; Laflamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. Aminodifluorosulfinium salts: selective fluorination reagents with enhanced thermal stability and ease of handling. *J. Org. Chem.* **2010**, *75* (10), 3401–11. https://doi.org/10.1021/jo100504x.
37. Mohammadkhani, L.; Heravi, M. M. XtalFluor-E: A useful and versatile reagent in organic transformations. *J. Fluorine Chem.* **2019**, *225*, 11–20. https://doi.org/10.1016/J.JFLUCHEM.2019.06.006.
38. Karabatsos, G. J.; Graham, J. D. Carbonium ion rearrangement of the neopentyl system. *J. Am. Chem. Soc.* **1960**, *82* (19), 5250–5251. https://doi.org/10.1021/ja01504a063.
39. Scriven, E.; Turnbull, K. Azides: their preparation and synthetic uses. *Chem. Rev.* **1988**, *88*(2), 297–368. https://doi.org/10.1021/cr00084a001.
40. Corey, E. J.; Link, J. O. A general, catalytic, and enantioselective synthesis of α-amino acids. *J. Am. Chem. Soc.* **1992**, *114* (5), 1906–1908. https://doi.org/10.1021/ja00031a069.
41. Carlsen, P.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. A greatly improved procedure for ruthenium tetroxide catalyzed oxidations of organic compounds. *J. Org. Chem.* **1981**, *46* (19), 3936–3938. https://doi.org/10.1021/jo00332a045.
42. Conti, P.; Caligiuri, A.; Pinto, A.; Roda, G.; Tamborini, L.; Nielsen, B.; Madsen, U.; Frydenvang, K.; Colombo, A.; De Micheli, C. Synthesis and pharmacological evaluation of novel conformationally constrained homologues of glutamic acid. *Eur. J. Med. Chem.* **2007**, *42* (8), 1059–1068. https://doi.org/10.1016/j.ejmech.2007.01.013.
43. Koch, H. P., Kavanaugh, M. P.; Esslinger, C. S.; Zerangue, N.; Humphrey, J. M.; Amara, S. G.; Chamberlin, A. R.; Bridges, R. J. Differentiation of Substrate and Nonsubstrate Inhibitors of the High-Affinity, Sodium-Dependent Glutamate Transporters. *Mol. Pharmacol.* **1999**, *56* (6), 1095–1104. https://doi.org/10.1124/mol.56.6.1095.
44. Armarego, W. L. F. *Purification of Laboratory Chemicals,* 9th ed.; Butterworth-Heinemann: Elsevier 2022 ISBN 978-0-12-805457-4
45. Cochrane, W. P.; Pauson, P. L.; Stevens, T. S. Synthesis of 3-oxabicyclo[3.1.1]heptanes by rearrangement of 3-oxaspiro[3.3]heptanes. *J. Chem. Soc., C: Organic* **1969**, *18*, 2346. https://doi.org/10.1039/j39690002346.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

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Journal of Organic and Pharmaceutical Chemistry

Advanced Research

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UDC 546.27:54.05

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Reevaluation of the *ortho*-Carborane Synthesis: Success with Mono-Substituted Acetylenes in the Presence of Silver Salts

Abstract

The study shows that traditional methods for synthesizing ortho-carboranes from *nido*-$B_{10}H_{14}$ and its complexes ($B_{10}H_{12}L_2$) using donor- and acceptor-disubstituted acetylenes yielding low efficiencies (yields 0–12 %). Attempts to improve yields with ionic liquids and silver salts as catalysts were unsuccessful with disubstituted acetylenes. However, it has been found that the use of mono-substituted acetylenes (phenylacetylene, ethyl propiolate) in the presence of silver salts in the reaction with $B_{10}H_{12}L_2$ substrates produces *ortho*-carboranes in high yields (~90 %). This suggests that the key step is the formation and subsequent addition of silver acetylenides, and not the donor-acceptor π-complexes previously assumed. This finding allows us to better understand the mechanisms of the *ortho*-carboranes formation and offers an efficient pathway for their synthesis.

Keywords: *ortho*-carborane; decaborane; acetylenes; silver; synthesis

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Перегляд синтезу *орто*-карборанів: успіх для монозаміщених ацетиленів у присутності солей срібла

Анотація

Дослідження засвідчує, що традиційні методи синтезу *орто*-карборанів з *нідо*-$B_{10}H_{14}$ та його комплексів ($B_{10}H_{12}L_2$) з використанням дизаміщених ацетиленів з донорними та акцепторними замісниками мають низьку ефективність (виходи 0–12 %). Спроби підвищити вихід продуктів за допомогою йонних рідин і солей срібла як каталізаторів були невдалими за використання дизаміщених ацетиленів. Проте було виявлено, що використання монозаміщених ацетиленів (фенілацетилен, етилпропіолат) у присутності солей срібла в реакції із субстратами $B_{10}H_{12}L_2$ призводить до утворення *орто*-карборанів з високим виходом (~90 %). Це свідчить про те, що ключовим етапом взаємодії є утворення та подальше приєднання ацетиленідів срібла, а не донорно-акцепторних π-комплексів, як передбачали раніше. Це відкриття дозволяє краще зрозуміти механізми утворення *орто*-карборанів і надає можливості для їх ефективного синтезу.

Ключові слова: *орто*-карборани; декаборан; ацетилени; срібло; синтез

ISSN 2308-8303 (Print) / 2518-1548 (Online)

Citation: Svaliavyn, O. V.; Mishchenko, A. M.; Lishchenko, Yu. L.; Mityuk, A. P.; Cherednichenko, A. S.; Shtil, N. A.; Turcheniuk, V. V.; Smaliy, R. V.; Rassukana, Yu. V.; Pashenko, O. Ye. Reevaluation of the ortho-Carborane Synthesis: Success with Mono-Substituted Acetylenes in the Presence of Silver Salts. *Journal of Organic and Pharmaceutical Chemistry* **2024**, *22* (3), 38–45.
https://doi.org/10.24959/ophcj.24.316200
Supporting information: Experimental details; spectral and analytical data for the synthetized compounds; copies of ^{1}H, ^{11}B and ^{13}C NMR spectra.
Received: *10 October 2024*; **Revised:** *13 November 2024*; **Accepted:** *23 November 2024*

Funding: The work was supported by National Research Foundation of Ukraine (grant No. 0123U104256).
Conflict of interests: The authors have no conflict of interests to declare.

■ Introduction

The transition from academic discovery to industrial application remains lengthy and complex, often necessitating the development of new or modification of existing production cycles. One illustrative example is the principle of isosterism proposed by Langmuir in 1919 [1], which has been successfully employed in medicinal chemistry over the years [2]. Recently, this concept has been expanded to include the replacement of benzene rings in molecules with more complex frameworks [3], including carboranes.

Carboranes are polyhedral clusters composed of boron, carbon, and hydrogen atoms, known for their unique chemical and physical properties. Initially investigated for the boron neutron capture therapy (BNCT), carboranes have emerged as valuable scaffolds in the development of new pharmaceuticals and chemical probes [4, 5]. Numerous successful applications of carboranes, specifically *ortho*-substituted ones, in medicinal chemistry have been reported, underscoring their great potential in pharmaceutical research [6, 7] (**Figure, B**). Beyond medicinal applications, carborane-based compounds exhibit exceptional properties that make them promising candidates in materials science [8, 9], particularly in the creation of heat-resistant polymers, ceramic precursors [10] (**Figure, A**), and extraction agents [11].

Existing methods for the *ortho*-carborane synthesis typically involve the reaction of decaborane or its complexes with acetylenes under specific conditions. These methods are limited to cycloadditions of precursors like $B_{10}H_{14}$ and its complexes $B_{10}H_{12}L_2$ with acetylenes in various conditions. Essentially, these reactions can be separated into three groups: a direct reaction between *nido*-$B_{10}H_{14}$ [12, 13] or $B_{10}H_{12}L_2$-complexes [14, 15] and acetylene precursors, and several modifications of reactions of $B_{10}H_{12}L_2$-complexes, which employ the metal catalysis [16, 17] or ionic liquids [18, 19]. For all these groups of reactions, very similar conditions are suggested, namely heating in toluene under an inert atmosphere. Although it looks solid on paper, we have found that all these approaches lack reproducibility and are hardly suitable for the up-scale optimization. Addressing these challenges is crucial for opening the opportunity for wider use of carborane derivatives in both medicinal chemistry and materials science. Only increasing the availability of *ortho*-carboranes and a systematic study of their chemical behavior can transform them from "exotic" to "widely used" agents for widespread use. Considering that synthetic routes to *ortho*-carboranes are deeply constrained, there is a pressing need to develop effective, scalable methods for their preparation.

In this work, we address the challenges in the *ortho*-carborane synthesis by optimizing existing methods. We conducted a comprehensive screening by reacting *nido*-$B_{10}H_{14}$ or $B_{10}H_{12}L_2$ complexes with various acetylenes under different conditions. The use of disubstituted acetylenes consistently yielded poor results (chromatographic

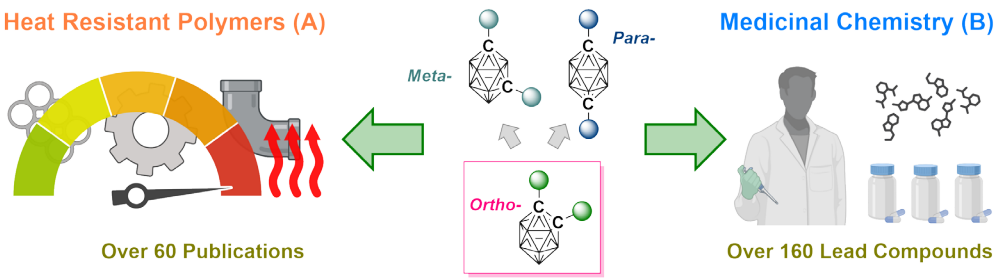


Figure. Carboranes: main fields of application

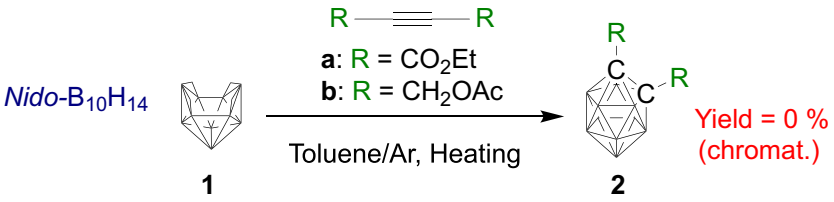
yields ≤12%), and we could not isolate the products. In contrast, employing mono-substituted acetylenes in the presence of silver salts led to significant improvements, achieving yields of approximately 90% with both donor (phenylacetylene) and acceptor (ethyl propiolate) reagents. This suggests that the key step in the silver-catalyzed reactions is the formation and addition of silver acetylenides, not the previously assumed donor-acceptor π-complexes alone [16]. Our study provides an efficient pathway for the *ortho*-carborane synthesis, facilitating their broader application in various fields.

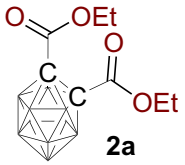
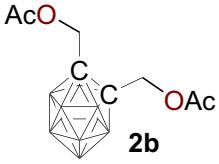
■ Results and discussion

The rigorous analysis of the literature sources showed that the direct addition of symmetrical acetylenes (starting from a bare acetylene molecule and expanding to variously substituted derivatives) to *nido*-decaborane $B_{10}H_{14}$ (**1, Table 1**) was described in the seminal [20] and several other early works [14] in good details, and offered seemingly straightforward protocols and reasonable yields. Considering that our long-term plans involved synthesizing all possible carborane isomers – the "parent" *ortho*-carborane and its thermocatalytic isomerization products [21], specifically *meta*- and *para*-carboranes – we opted for diethyl ester of acetylene dicarboxylic acid as the first-choice cycloaddition partner. *Ortho*-carborane dicarboxylic acid is not only a very convenient starting material for further derivatization (see cubane [22], cuneane [23], and stellane examples [24, 25]). It is also known to undergo isomerization to *meta*- and *para*-carborane dicarboxylic acids with good preparative yields [21]. However, our attempts to cyclize **1** with diethyl ester of acetylene dicarboxylic acid failed, resulting in only starting materials and some unidentified degradation products according to ^{1}H, ^{11}B, and ^{13}C NMR and LC/MS analysis (**Table 1**, entry 1). Repeating the experiment several times yielded similar results. This led us to assume that the strong electron-withdrawing character of diethyl ester of acetylene dicarboxylic acid was the key factor determining the outcome, despite the opposite being reported in the literature. We returned to the work where comprehensive screening of acetylene substrates was performed [15], and selected acetylene dimethoxy acetate as a new test reagent since it showed the best results (89% yield of the desired carborane **2b**) according to the paper. However, reacting this new acetylene with **1** under similar conditions led to the same outcome: no product was detected, and only starting materials with signs of degradation were found (**Table 1**, entry 2).

Further a logical step was to test the reactivity of decaborane complexes **3** ($B_{10}H_{12}L_2$) with various ligands according to the described procedures. Literature sources suggested that such complexes can be obtained *in situ* from $B_{10}H_{14}$ [15] or pre-made [26] and directly subjected to cyclization reactions. To avoid multi-parameter optimization within a single set of experiments, and lacking obviously superior options for acetylene counterparts, we used the same reagents (acetylenes with **R** = **a** and **b**) as in the previous set.

Table 1. Probing *nido*-decaborane $B_{10}H_{14}$ (**1**) in reactions with symmetrically disubstituted acetylenes



#	Reagents/Reaction Conditions	t, °C	Reaction Time, hours	Yield, LCMS, %	Expected Product
1	Substrate: **1**; Acetylene: **R = a**	110	12 h	0	 **2a**
2	Substrate: **1**; Acetylene: **R = b**	110	12 h	0	 **2b**

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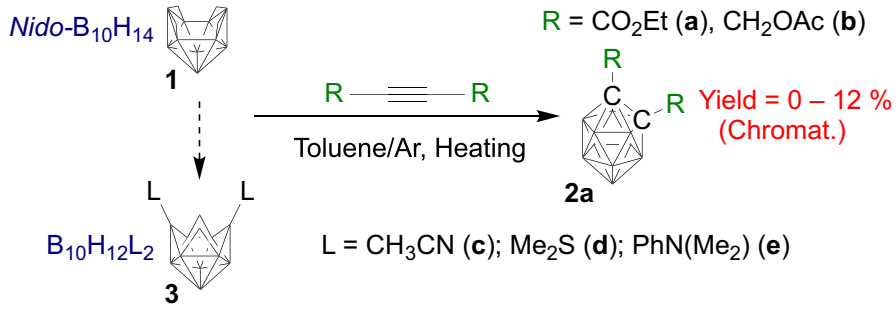
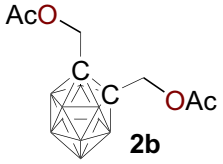
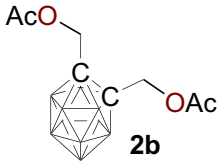
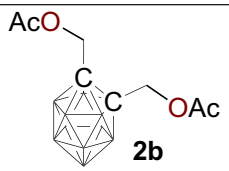
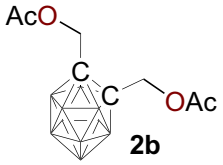
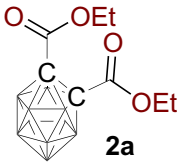
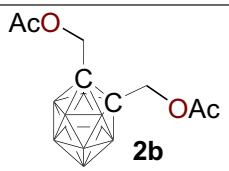
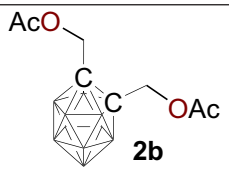
First, we investigated the methods *in situ* (**Table 2**, entries 1–4). To the toluene solution of substrate **1**, we added the ligand and acetylene **b**, then heated the mixture under vigorous reflux in an inert atmosphere for approximately 12 h. Heating acetonitrile (**c**) together with **1** and acetylene **b** [15] yielded the same results as before: the recovery of starting materials and the formation of unidentified degradation products (**Table 2**, entry 1). We then switched to a more basic ligand, dimethylaniline (**e**) [15], under similar conditions, which allowed us to detect the

Table 2. Probing the decaborane complexes $B_{10}H_{12}L_2$ (**3**) in reactions with symmetrically disubstituted acetylenes



#	Reagents/Reaction Conditions	t, °C	Reaction Time, hours	Yield, LCMS, %	Expected Product
1	Substrate: **1**; L = CH_3CN (**c**, 10 equiv., *in situ*); Acetylene: **R = b**	110	12 h	0%	 **2b**
2	Substrate: **1**; L = $PhN(CH_3)_2$ (**e**, 10 equiv., *in situ*); Acetylene: **R = b**	110	12 h	11%	 **2b**
3	1) Substrate: **1** + $PhN(CH_3)_2$ (**e**, 10 equiv., *in situ*); 2) Acetylene: **R = b**	1) 80; 2) 120	1) 2 h 2) 12 h	7%	 **2b**
4	1) Substrate*: **1** + $PhN(CH_3)_2$ (**e**, 10 equiv., *in situ*); 2) Acetylene: **R = b**	1) 80; 2) 120	1) 2 h 2) 48 h	8%	 **2b**
5	Substrate: **3c**; Acetylene: **R = a**	110	12 h	0	 **2a**
6	Substrate: **3d**; Acetylene: **R = b**	110	12 h	12%	 **2b**
7	Substrate: **3c**; Acetylene: **R = b**	110	12 h	10%	 **2b**

Note: *The Schlenk technique was used and additional all reagents and gases were subjected to additional drying according to standard protocols

target carborane **2b** using the LC/MS analysis with an 11% chromatographic yield (**Table 2**, entry 2).

Further attempts to improve this result involved implementing a two-step protocol. In the first step, decaborane **1** was heated with the ligand in toluene at 80 °C for 2 h. Then, acetylene **b** was added to the mixture, and heating was continued for an additional 12 h at 120 °C, leading to a 7% chromatographic yield of carborane **2b** (**Table 2**, entry 4). Using the Schlenk techniques and additional drying protocols for reagents, glassware, and gases did not improve the outcome, yielding 8% of **2b**.

We assumed that the low yields were due to insufficient time for forming $B_{10}H_{12}L_2$ under the given conditions and that the addition of acetylene hindered this reaction. To address this issue, we prepared samples of **3** ($B_{10}H_{12}L_2$) with the most common and reactive ligands reported in the literature (acetonitrile (**c**) and dimethylsulfide (**d**)) using standard protocols [26]. Applying this approach to both acetylenes previously tested resulted in no desired product with acetylene **a**, and similar low (chromatographic) yields of carborane **2b** with acetylene **b** when **3c** and **3d** were used as substrates (**Table 2**, entries 5–7).

These experiments demonstrate that while we could detect the formation of carborane **2b** analytically, we could not reproduce the classical methodologies of the carborane synthesis at the preparative level.

Since approaches involving the use of ionic liquids [18, 19] are impractical for scalability, we opted for metal-catalyzed cycloadditions of acetylenes to decaborane complexes $B_{10}H_{12}L_2$ (**3**), in particular reactions catalyzed by silver salts [16, 17]. The work by *Toppino et al.* [16] in 2013 suggested that π-complexes of acetylenes with silver ions were the reactive species that interacted directly with decaborane complexes to yield the desired carboranes. The following year, *El-Zaria et al.* [17] published a manuscript postulating that it was not the π-complexes, but bimetallic complexes that were the actual active species in these transformations. However, their reaction system proposed, while offering mild conditions, utilized an expensive organophosphorus silver complex as the source of soluble silver ions [17].

In this context, we decided to optimize the reaction conditions using readily available silver nitrate. As the first step in this series of tests, we reacted substrate **3c** with acetylene **b** in the presence of a catalytic amount of $AgNO_3$. Not surprisingly, this attempt (**Table 3**, entry 1) yielded results similar to the previous experiments, namely an 8% chromatographic yield of carborane **2b**. However, when we switched to monosubstituted acetylenes (entries 2 and 3, **Table 3**), we obtained the corresponding carboranes **2f** and **2g** with preparative yields of 69% and 90%, respectively. This result clearly indicates that the formation of silver acetylenides is the determining step in this reaction. These findings provide an opportunity for further optimization of reaction conditions and offer a potentially preparative approach to the synthesis of key carborane precursors suitable for further derivatization.

■ Conclusions

Our systematic study of the synthesis of *ortho*-carboranes has shown that traditional methods using disubstituted acetylenes with *nido*-$B_{10}H_{14}$ or its complexes $B_{10}H_{12}L_2$ consistently yield low amounts of the desired products (≤ 12%), which cannot be isolated. Attempts to enhance these yields through the silver salt catalysis were unsuccessful with disubstituted acetylenes.

On the contrary, the use of mono-substituted acetylenes in the presence of silver salts with $B_{10}H_{12}L_2$ where L = CH_3CN resulted in significantly higher production of *ortho*-carboranes, reaching a yield of up to 90%. This substantial improvement indicates that the formation and addition of silver acetylenides are crucial steps in the reaction mechanism, rather than the formation of donor-acceptor π-complexes as previously assumed.

This efficient and scalable method provides a practical pathway for the synthesis of *ortho*-carboranes, facilitating their potential broader application in medicinal chemistry and materials science. Our findings also offer new insights into the mechanistic aspects of the carborane formation, which could inform future research and optimization of related synthetic processes.

■ Experimental part

The solvents were purified according to the standard procedures. All starting materials were obtained from Enamine Ltd. Melting points were measured on an automated melting point system. ^1H, ^{11}B, ^{13}C, and NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 500 MHz for ^1H, 160 MHz for ^{11}B, and 126 MHz for ^{13}C) and Varian Unity Plus 400 spectrometers (at 400 MHz

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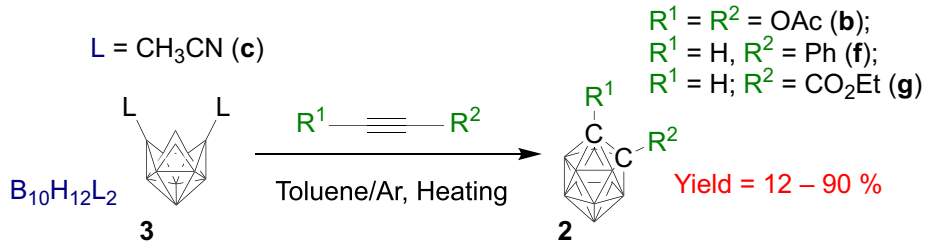
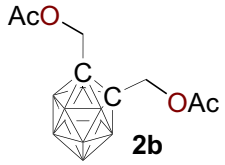
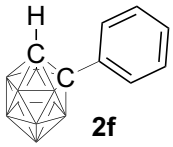
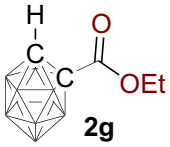
Table 3. Probing the decaborane complex $B_{10}H_{12}L_2$ (**3c**) in reactions with substituted acetylenes in the presence of silver nitrate



#	Reagents/Reaction Conditions	t, °C	Reaction Time, hours	Yield, LCMS, %	Expected Product
1	Substrate: **3c** Acetylene: **R = b** Catalyst: $AgNO_3$	110	8 h	8	 **2b**
2	Substrate: **3c** Acetylene: **R^1 = H; R^2 = Ph** Catalyst: $AgNO_3$	110	7 h	69*	 **2f**
3	Substrate: **3c** Acetylene: **R^1 = H; R^2 = COOEt** Catalyst: $AgNO_3$	110	1 h	90*	 **2g**

Note: *Preparative yields after isolating the title compound as a pure sample from the reaction mixture

for ^{1}H, 128 MHz for ^{11}B and 101 MHz for ^{13}C). Tetramethylsilane (^{1}H, ^{11}B, ^{13}C) was used as a standard. HPLC analyses were done on Agilent 1200. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)). Column chromatography was performed with silica gel (200–300 mesh).

The general protocol for reacting decaborane $B_{10}H_{14}$ (1) with acetylenes

A mixture of 1.0 equiv. of decaborane **1** ($B_{10}H_{14}$), 2.0 equiv. of acetylene (**a** or **b**), and toluene 5 L per mole of decaborane (**1**) was refluxed for 12 h under Ar atmosphere. Toluene was removed under reduced pressure, and the residue was treated with pentane to extract the product.

The general protocol for reacting decaborane $B_{10}H_{14}$ (1) with acetylenes in the presence of the nucleophilic ligand for *in situ* generating $B_{10}H_{12}L_2$ (3)

A mixture of 1.0 equiv. of decaborane **1** ($B_{10}H_{14}$), 10.0 equiv. of the ligand (L) source (L = CH_3CN (**c**); Me_2S (**d**); $PhN(Me_2)$ (**e**)), 2.0 equiv. of acetylene (**a** or **b**), and toluene 5 L per mole of decaborane (**1**) was refluxed for 12 h under Ar atmosphere. Toluene was removed under reduced pressure, and the residue was treated with pentane to extract the product.

The general protocol for reacting decaborane complexes $B_{10}H_{12}L_2$ (3) with acetylenes

A mixture of 1.0 equiv. of decaborane complex **3** ($B_{10}H_{12}L_2$) with ligands L = CH_3CN (**c**) or Me_2S (**d**), 2.0 equiv. of acetylene (**a** or **b**), and toluene 5 L per mole of the decaborane complex (**3**) was refluxed for 12 h under Ar atmosphere. The toluene was removed under reduced pressure, and the residue was treated with pentane to extract the product.

The general protocol for reacting decaborane complexes $B_{10}H_{12}L_2$ (3) with acetylenes in the presence of silver nitrate

1.0 equiv. of $B_{10}H_{12}(CH_3CN)_2$ (**3c**) and 2.0 equiv. of phenylacetylene were combined in the presence of $AgNO_3$ (7 mol%) in anhydrous toluene (1.2 L per mole of the decaborane complex (**3c**)) and heated at 100 °C for 1–8 h depending on the substrate under Ar atmosphere. After cooling the resulting mixture to room temperature and evaporating the solvent, the residue was purified via flash chromatography on silica gel.

■ Acknowledgment

We acknowledge BioRender.com for providing the graphical tools used to create **Figure**.

References

1. Langmuir, I. Isomorphism, Isosterism and Covalence. *J. Am. Chem. Soc.* **2002,** *41* (10), 1543–1559. https://doi.org/10.1021/ja02231a009.
2. Meanwell, N. A. Applications of Bioisosteres in the Design of Biologically Active Compounds. *J. Agric. Food Chem.* **2023**, *71* (47), 18087–18122. https://doi.org/10.1021/acs.jafc.3c00765.
3. Mykhailiuk, P. K. Saturated bioisosteres of benzene: where to go next? *Org. Biomol. Chem.* **2019,** *17* (11), 2839–2849. https://doi.org/10.1039/c8ob02812e.
4. Valliant, J. F.; Guenther, K. J.; King, A. S.; Morel, P.; Schaffer, P.; Sogbein, O. O.; Stephenson, K. A. The medicinal chemistry of carboranes. *Coord. Chem. Rev.* **2002,** *232* (1), 173–230. https://doi.org/10.1016/S0010-8545(02)00087-5.
5. Gruzdev, D. A.; Levit, G. L.; Krasnov, V. P.; Charushin, V. N. Carborane-containing amino acids and peptides: Synthesis, properties and applications. *Coordination Chemistry Reviews* **2021,** *433*, 213753. https://doi.org/10.1016/j.ccr.2020.213753.
6. Stockmann, P.; Gozzi, M.; Kuhnert, R.; Sarosi, M. B.; Hey-Hawkins, E. New keys for old locks: carborane-containing drugs as platforms for mechanism-based therapies. *Chem Soc Rev* **2019,** *48* (13), 3497–3512. https://doi.org/10.1039/c9cs00197b.
7. Emilia, O. Z.; Christian, A. M.; Mark, W. L., Jr. The Use of Carboranes in Cancer Drug Development. *International Journal of Cancer and Clinical Research* **2019,** *6* (2). https://doi.org/10.23937/2378-3419/1410110.
8. Nunez, R.; Tarres, M.; Ferrer-Ugalde, A.; de Biani, F. F.; Teixidor, F. Electrochemistry and Photoluminescence of Icosahedral Carboranes, Boranes, Metallacarboranes, and Their Derivatives. *Chem. Rev.* **2016,** *116* (23), 14307–14378. https://doi.org/10.1021/acs.chemrev.6b00198.
9. Dash, B. P.; Satapathy, R.; Maguire, J. A.; Hosmane, N. S. Polyhedral boron clusters in materials science. *New Journal of Chemistry* **2011,** *35* (10), 1955–1972. https://doi.org/10.1039/c1nj20228f.
10. Wang, C.; Huang, F.; Jiang, Y.; Li, J.; Zhou, Y.; Du, L. Oxidation behavior of carbon materials derived from a carborane- and silicon-incorporated polymer. *Ceram. Int.* **2012,** *38* (4), 3081–3088. https://doi.org/10.1016/j.ceramint.2011.12.007.
11. Keener, M.; Hunt, C.; Carroll, T. G.; Kampel, V.; Dobrovetsky, R.; Hayton, T. W.; Menard, G. Redox-switchable carboranes for uranium capture and release. *Nature* **2020,** *577* (7792), 652–655. https://doi.org/10.1038/s41586-019-1926-4.
12. Ditter, J. F.; Klusmann, E. B.; Oakes, J. D.; Williams, R. E. Direct synthesis of closo-carboranes. *Inorganic Chemistry* **2002,** *9* (4), 889–892. https://doi.org/10.1021/ic50086a039.
13. Heying, T. L.; Ager, J. W.; Clark, S. L.; Alexander, R. P.; Papetti, S.; Reid, J. A.; Trotz, S. I. A New Series of Organoboranes. III. Some Reactions of 1,2-Dicarbaclovododecaborane(12) and its Derivatives. *Inorganic Chemistry* **2002,** *2* (6), 1097–1105. https://doi.org/10.1021/ic50010a004.
14. Beall, H. Icosahedral carboranes. XVII. Simplified preparation of o-carborane. *Inorg. Chem.* **2002,** *11* (3), 637–638. https://doi.org/10.1021/ic50109a044.
15. Heying, T. L.; Ager, J. W.; Clark, S. L.; Mangold, D. J.; Goldstein, H. L.; Hillman, M.; Polak, R. J.; Szymanski, J. W. A New Series of Organoboranes. I. Carboranes from the Reaction of Decaborane with Acetylenic Compounds. *Inorg. Chem.* **2002,** *2* (6), 1089–1092. https://doi.org/10.1021/ic50010a002.
16. Toppino, A.; Genady, A. R.; El-Zaria, M. E.; Reeve, J.; Mostofian, F.; Kent, J.; Valliant, J. F. High yielding preparation of dicarba-closo-dodecaboranes using a silver(I) mediated dehydrogenative alkyne-insertion reaction. *Inorg. Chem.* **2013,** *52* (15), 8743–8749. https://doi.org/10.1021/ic400928v.
17. El-Zaria, M. E.; Keskar, K.; Genady, A. R.; Ioppolo, J. A.; McNulty, J.; Valliant, J. F. High yielding synthesis of carboranes under mild reaction conditions using a homogeneous silver(I) catalyst: direct evidence of a bimetallic intermediate. *Angew. Chem. Int. Ed.* **2014,** *53* (20), 5156–5160. https://doi.org/10.1002/anie.201311012.
18. Kusari, U.; Li, Y.; Bradley, M. G.; Sneddon, L. G. Polyborane reactions in ionic liquids: new efficient routes to functionalized decaborane and o-carborane clusters. *J. Am. Chem. Soc.* **2004,** *126* (28), 8662–8663. https://doi.org/10.1021/ja048018n.
19. Li, Y.; Carroll, P. J.; Sneddon, L. G. Ionic-liquid-promoted decaborane dehydrogenative alkyne-insertion reactions: a new route to o-carboranes. *Inorg. Chem.* **2008,** *47* (20), 9193–202. https://doi.org/10.1021/ic800999y.
20. Fein, M. M.; Grafstein, D.; Paustian, J. E.; Bobinski, J.; Lichstein, B. M.; Mayes, N.; Schwartz, N. N.; Cohen, M. S. Carboranes. II. The Preparation of 1- and 1,2-Substituted Carboranes. *Inorg. Chem.* **1963,** *2* (6), 1115–1119. https://doi.org/10.1021/ic50010a008.
21. Korshak, V. V.; Bekasova, N. I.; Solomatina, A. I.; Frunze, T. M.; Sakharova, A. A.; Mel'nik, O. A. Synthesis of unsaturated esters of m- and p-carboranedicarboxylic acids. *Bulletin of the Academy of Sciences of the USSR, Division of chemical science* **1982,** *31* (8), 1694–1695. https://doi.org/10.1007/BF00956914.
22. Collin, D. E.; Kovacic, K.; Light, M. E.; Linclau, B. Synthesis of Ortho-Functionalized 1,4-Cubanedicarboxylate Derivatives through Photochemical Chlorocarbonylation. *Org. Lett.* **2021**, *23* (13), 5164–5169. https://doi.org/10.1021/acs.orglett.1c01702.
23. Smith, E.; Jones, K. D.; O'Brien, L.; Argent, S. P.; Salome, C.; Lefebvre, Q.; Valery, A.; Bocu, M.; Newton, G. N.; Lam, H. W. Silver(I)-Catalyzed Synthesis of Cuneanes from Cubanes and their Investigation as Isosteres. *J. Am. Chem. Soc.* **2023,** *145* (30), 16365–16373. https://doi.org/10.1021/jacs.3c03207.
24. Smyrnov, O.; Melnykov, K.; Pashenko, O.; Volochnyuk, D.; Ryabukhin, S. Stellane at the Forefront: Derivatization and Reactivity Studies of a Promising Saturated Bioisostere of ortho-Substituted Benzenes. **2024**. https://doi.org/10.26434/chemrxiv-2024-rlf5q.
25. Smyrnov, O. K.; Melnykov, K. P.; Rusanov, E. B.; Suikov, S. Y.; E, O.; Fokin, A. A.; Volochnyuk, D. M.; Ryabukhin, S. V. Multigram Synthesis of Dimethyl Stellane-1,5-Dicarboxylate as a Key Precursor for the ortho-Benzene Mimics. *Chem.–Eur. J.* **2023**, e202302454. https://doi.org/10.1002/chem.202302454.
26. Islam, S.; Johnson, F. A.; Hill, W. E.; Silva-Trivino, L. M. Kinetics of ortho-carborane formation revisited. *Inorganica Chimica Acta* **1997,** *260* (1), 99–103. https://doi.org/10.1016/S0020-1693(96)05544-2.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

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Journal of Organic and Pharmaceutical Chemistry

Advanced Research

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UDC [547-304.2+547-32+546.27+546.28]54.057

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High-Temperature Polymer Components Reimagined: Scalable Syntheses and *de novo* Routes to Structurally Versatile Precursors

Abstract

Developing efficient and scalable synthetic protocols for key polymer precursors is crucial to advancing high-performance materials designed to withstand severe thermal environments. In this article, we report on the development of solid, high-yield methods for preparing structurally diverse building blocks, including *s*-triazine derivatives, phenyl-borosilane alkynyl oligomers, phthalonitrile-based monomers, and novel diamine curing agents on multi-gram to multi-hundred-gram scales. These carefully optimized procedures use readily available starting materials, mild conditions, and well-known synthetic transformations, thus addressing the longstanding challenges associated with their practical upscaling. The resulting library of monomers and oligomers offers a broad range of reactive functional groups (e.g., nitriles, alkynes, borosilane motifs), enabling future combinatorial-like strategies for the formation of advanced co-polymers with enhanced thermal stability, mechanical strength, and tunable properties suitable for high-temperature applications.

Keywords: heat-resistant polymers; monomers; oligomers; curing agents; triazine; phthalonitrile; borosilane; diamine; synthesis

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Переосмислення компонентів високотемпературних полімерів: масштабований синтез і *de novo* шляхи до структурно різноманітних прекурсорів

Анотація

Розробка ефективних і масштабованих синтетичних протоколів для одержання ключових прекурсорів полімерних продуктів має вирішальне значення для подальшого вдосконалення цих матеріалів, зокрема розроблених з метою витримувати суворі термічні умови. У цій статті ми повідомляємо про розробку надійних, високопродуктивних методів синтезу структурно різноманітних білдинг-блоків, включно з похідними *s*-триазину, фенілборосилан-алкініловими олігомерами, мономерами на основі фталонітрилу та новими діаміновими затверджувачами в масштабах від кількох грам до кількох сотень грам. Ретельно оптимізовані процедури використовують легкодоступні вихідні матеріали, м'які умови проведення взаємодій та добре відомі синтетичні перетворення, таким чином вирішуючи проблеми, пов'язані з їх практичним масштабуванням. Отримана бібліотека мономерів і олігомерів пропонує широкий спектр реакційно-здатних функціональних груп (наприклад, нітрилів, алкінів, боросиланових фрагментів), що дозволяє в майбутньому

ISSN 2308-8303 (Print) / 2518-1548 (Online)

за допомогою комбінаторних стратегій створювати передові кополімери з підвищеною термічною стабільністю, механічною міцністю та регульованими властивостями.

Ключові слова: термостійкі полімери; мономери; олігомери; затверджувачі; триазин; фталонітрил; боросилан; діамін; синтез

Citation: Kurganov, R. M.; Svaliavyn, O. V.; Pashchenko, Ye. O.; Savchenko, D. O.; Rozhenko, A. B.; Ryabukhin, S. V.; Volochnyuk, D. M. High-Temperature Polymer Components Reimagined: Scalable Syntheses and *de novo* Routes to Structurally Versatile Precursors. *Journal of Organic and Pharmaceutical Chemistry* **2024**, *22* (3), 46–55.
https://doi.org/10.24959/ophcj.24.317091
Supporting information: Details of experiments and synthesis; spectral and analytical data for the compounds synthesized; copies of ^{1}H, ^{11}B, and ^{13}C NMR spectra.
Received: *3 October 2024*; **Revised:** *18 November 2024*; **Accepted:** *22 November 2024*

Funding: The work was supported by the Ministry of Education and Science of Ukraine (grant No. 1/PH/25-024).
Conflict of interests: The authors have no conflict of interests to declare.

■ Introduction

The drive to develop heat-resistant polymers has been a major focus in material science due to the ever-increasing demands of industries like aerospace, electronics, and chemical processing that require materials capable of operating at high temperatures without degrading [1]. The inherent thermal stability of these materials is attributed to their molecular architecture, which often incorporates rigid aromatic backbones and robust heterocyclic structures specifically engineered to withstand high-temperature environments.

Among the various classes of heat-resistant polymers, several stand out and exhibit remarkable properties thanks to their unique chemical structures and bonding characteristics. Aromatic polyimides, as well as phthalonitriles, are highly valued for their mechanical robustness and thermal endurance [2–4] (**Figure 1**). These polymers are often synthesized using a two-step polymerization process that ensures high molecular weight and structural integrity [4, 5]. Similarly, polybenzoxazoles, polybenzimidazoles, and triazines-based polymers provide exceptional heat resistance and have been extensively studied for their application in harsher environments [3, 6]. The integration of elements like boron, silicon, and phosphorus has also been shown to significantly enhance thermal and oxidative stability, as explored in hybrid systems [3, 7, 8].

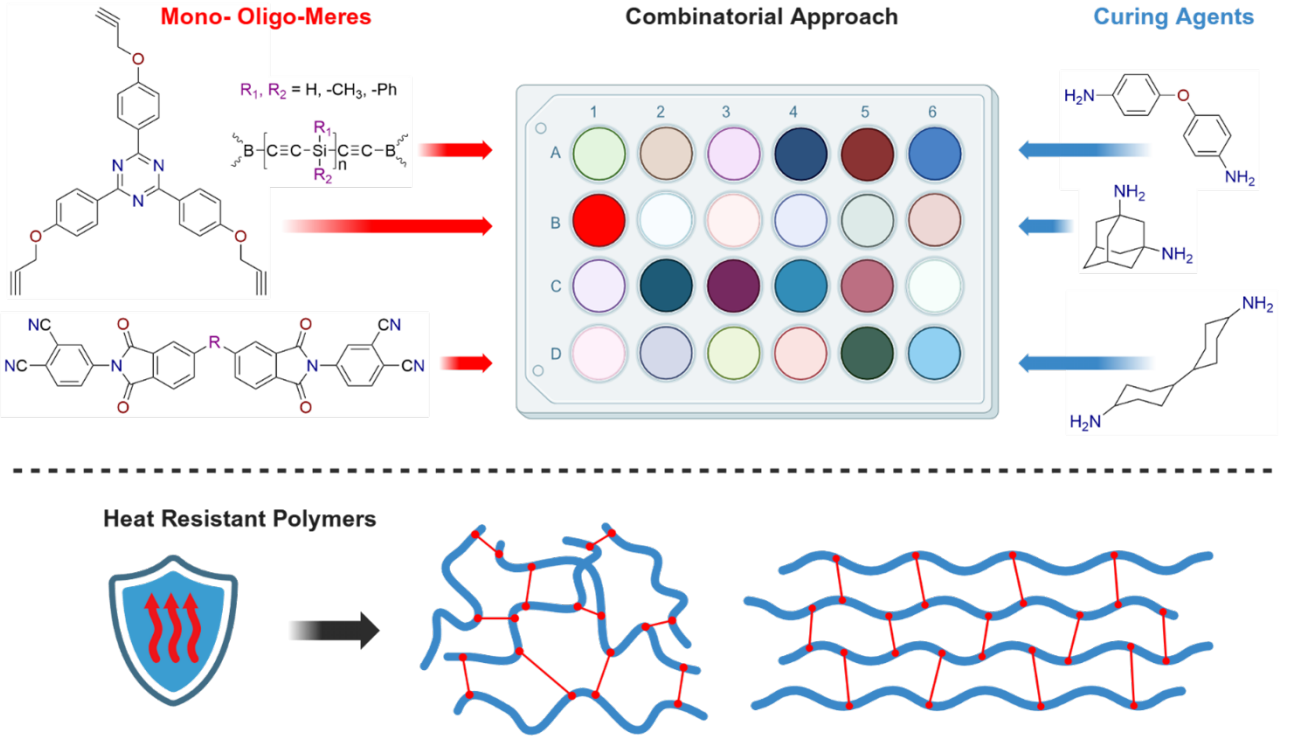


Figure 1. The visualization of the concept of the combinatorial chemistry-fashioned approach to the design of new heat-resistant materials

A particularly promising avenue is the development of composite polymers where combining different types of monomers and oligomers can lead to enhanced material properties. The compatibility of functional groups across these diverse classes allows for cross-linking and synergistic effects that optimize performance [9, 10]. This compatibility opens up opportunities for innovative composite designs that leverage the strengths of various polymer classes as seen in recent studies on silicon and boron-containing hybrids and *s*-triazine reinforced networks [7, 11] (**Figure 1**).

An effective strategy to further enhance the properties of these polymers may involve the use of polyamine curing agents of varying chemical nature, including aromatic, aliphatic, and saturated cage-like structures (**Figure 1**). These curing agents can react with functional groups present in the monomers and oligomers, such as nitriles and alkynes, facilitating cross-linking and the network formation [12, 13]. By selecting polyamines with different structural characteristics, it is possible to tailor the flexibility, cross-link density, and thermal properties of the resulting polymers. For example, aromatic polyamines can contribute to increased rigidity and thermal stability, while aliphatic and cage-like polyamines may improve toughness and impact resistance [14]. The incorporation of these diverse curing agents expands the potential of developing advanced materials with customized performance profiles suitable for demanding applications.

However, the synthesis of these monomers and oligomers, as well as amine curing agents, must be both efficient and scalable. Despite the availability of several synthetic pathways, few are optimized for large-scale production, which is crucial for practical applications. The challenge lies in developing protocols that maintain the integrity of the production sequence and use readily available and safe reagents in mild conditions, allowing for scale-up. It is critical to address this gap to transition these materials from the lab to industry, as highlighted in work on phthalonitriles, borosilane oligomers, and triazine-based precursors [4, 7, 11].

To address the need for scalable synthetic methods, our research focuses on developing robust, high-yield protocols for compounds, such as phthalonitriles, triazine-based monomers, aromatic borosilane oligomers, and a number of diamine curing agents [15]. These compounds are designed to participate readily in cross-polymerization reactions, leveraging their compatible functional groups to form complex, high-performance materials [10]. In the further stages of our research, through a parallel combinatorial-inspired series of polymerizations, we aim to assess the impact of each component on the final polymer characteristics (**Figure 1**). This systematic approach not only facilitates the identification of optimal polymer formulations, but also paves the way for novel applications in high-temperature environments.

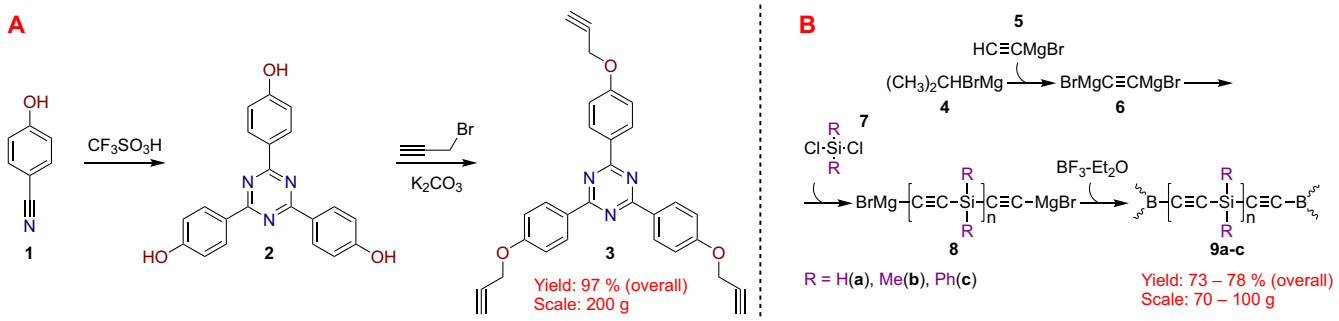
Our effort to establish scalable synthetic protocols is motivated by the promising potential of these materials in various technological fields. By examining the interaction and effects of different polymer components, we seek to develop a comprehensive framework for producing advanced heat-resistant polymers that meet the stringent demands of modern industry.

Results and discussion

Monomers based on polynitriles, triazines with terminal alkynes, and borosilane alkynyl hybrid oligomers individually yield polymers renowned for their exceptional thermal and mechanical properties [4, 7, 11]. Each class contains functional groups that are chemically compatible for copolymerization, such as nitrile groups, terminal alkynes, and boron-silicon moieties. Grounding on the previous studies, we assume that when these monomers (oligomers) are combined in composite materials, the synergistic interactions among their functional groups can lead to enhanced properties, surpassing those of polymers derived from the individual components.

As the first step, we focused on the synthesis and study of the scale-up opportunities for *s*-triazines, particularly 2,4,6-*tris*(4-(prop-2-yn-1-yloxy)phenyl)-1,3,5-triazine (**3, Scheme 1**, *A*) proven high properties when used as the main component for polymerization [11] and borosilane alkynyl hybrid oligomers, which also exhibited excellent thermo-resistant performance [7]. For this purpose, we used reaction conditions similar to those described in the literature [11, 16], suggesting a two-step preparation using readily available components like 4-hydroxybenzonitrile (**1**) for the acid-catalyzed cyclization to 2,4,6-*tris*(4-(prop-2-yn-1-yloxy)phenyl)-1,3,5-triazine (**2**) at first, and then propargyl bromide for alkylating its phenol groups (**Scheme 1, A**). By optimizing reaction conditions, we were able to scale the preparation of triazine **3** to approximately 200 g per operation. Based on the scope of the

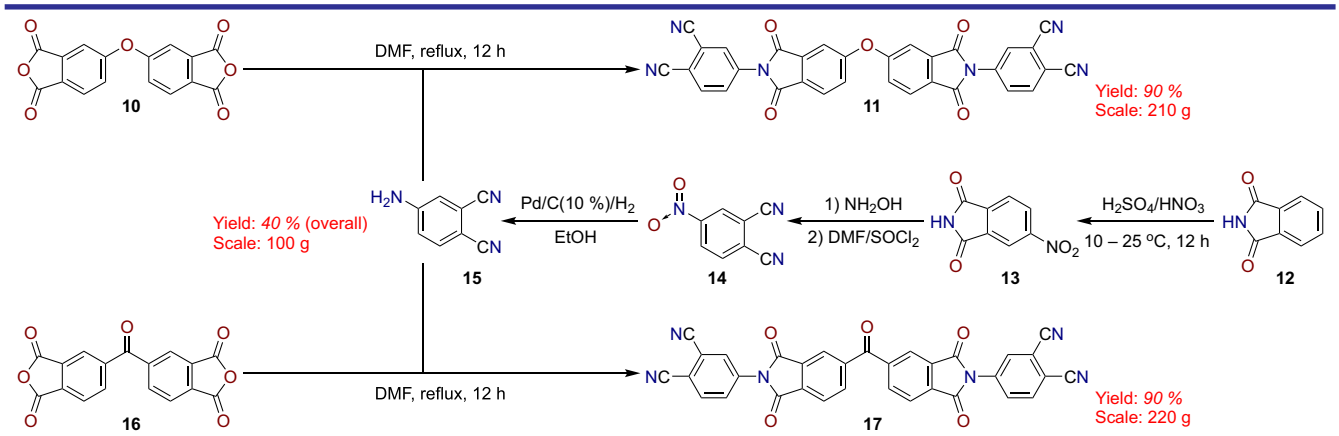
ISSN 2308-8303 (Print) / 2518-1548 (Online)



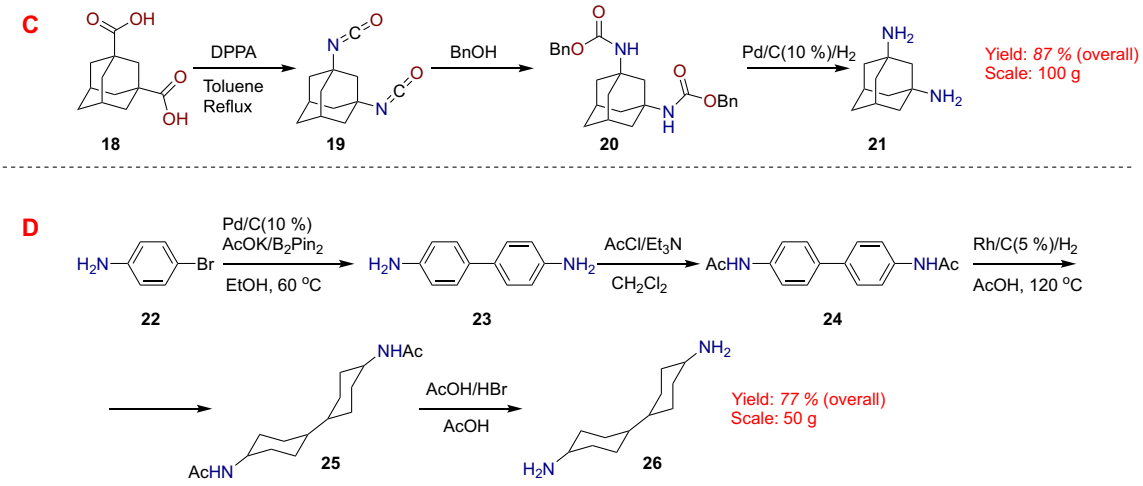
Scheme 1. The preparation of 2,4,6-*tris*(4-(prop-2-yn-1-yloxy)phenyl)-1,3,5-triazine (*A*, compound **3**) and phenyl-borosilane alkynyl hybrid oligomers (*B*, compounds **9a–c**)

borosilane alkynyl hybrid oligomers reported in the literature [7], we opted to prepare all three variants using different dichlorosilanes: dichloromethylsilane, dimethyldichlorosilane, and diphenyldichlorosilane. This approach was chosen to evaluate how various substituents influence the compatibility and, ultimately, the properties of the resulting polymers. The target oligomers (**9a**, **9b**, **9c**, **Scheme 1**, *B*) were synthesized *via* the Grignard reaction on a multigram scale, achieving high yields. To begin, a commercially available isopropylmagnesium bromide (1 equiv. of 3 M solution in 2-methyltetrahydrofuran (Me-THF), compound **4**, **Scheme 1**, *B*) was added to 1 equiv. of 3 M ethynylmagnesium bromide (**5, Scheme 1**, *B*) in the same solvent, and the mixture was refluxed for 2 h, forming a white precipitate of organic magnesium reagents. Utilizing commercial reagents significantly streamlined the process from a technological standpoint, and using Me-THF as a solvent enabled higher reaction temperatures, shorter reaction times, and improved yields while avoiding solvent decomposition products at every stage. To access three borosilane alkynyl hybrid oligomers (**9a–c, Scheme 1**, *B*), dichlorosilane, dimethyldichlorosilane, or diphenyldichlorosilane (0.45 equiv) in Me-THF were added dropwise over 30 min to the reaction mixture, which was then refluxed for additional 3 h. Subsequently, boron trifluoride etherate (0.3 equiv.) was introduced, and the reaction proceeded for 5 more h at room temperature. Quenching with aqueous hydrochloric acid, extracting with ethyl acetate, washing to neutrality, drying over sodium sulfate, and concentrating gave the corresponding yellowish viscous oligomers. Under these conditions, yields ranged from 73% to 78% for three oligomers (**9a–c, Scheme 1**, *B*) on up to 100 g per the operation scale (**Scheme 1**, *B*).

Polymers derived from tetranitriles, especially phthalonitriles, are renowned for their exceptional thermal stability and mechanical strength, making them highly valuable in advanced material applications. These superior properties arise from the extensive cross-linking facilitated by the multiple cyano-groups, which undergo cyclotrimerization to form stable triazine and phthalocyanine structures within the polymer matrix. Although the literature often treats phthalonitriles **11** and **17** (**Scheme 2**) as readily accessible [4], no single source actually describes their synthesis, even on the laboratory scale. To fill this gap, we started from inexpensive phthalimide (**12**) and converted it into the dicyanamine intermediate (**15**) in three straightforward steps. Using (**15**) and commercially available dianhydrides (**10** and **16**, **Scheme 2**) in refluxing DMF, we obtained target phthalonitriles **11** and **17** in



Scheme 2. The preparation of 4,4′-(oxybis(phthalimide))diphthalonitrile (**11**) and 4,4′-(carbonylbis(phthalimide))diphthalonitrile (**17**)



Scheme 3. The preparation of diamine-based curing agents: 1,3-diaminoadamantane (**21**) and 1,1'-bi(cyclohexane)]-4,4'-diamine (**26**)

the yield of about 90% each on over 200 g scale. This reliable, high-yield route not only provides these key phthalonitriles on a large scale, but also opens new opportunities for the subsequent (co-)polymerization studies and material development.

Amine curing agents are effectively utilized in the copolymerization of polynitriles with terminal alkynes to form highly cross-linked polymer networks with enhanced thermal and mechanical properties [17]. The amine groups react with nitrile functionalities through nucleophilic addition, forming amidine linkages, and they facilitate cyclization reactions that incorporate heterocyclic structures, such as triazine rings, into the polymer backbone [12]. Additionally, amines can interact with terminal alkynes via the hydroamination or addition reactions, further increasing the cross-link density [17]. This synergistic approach not only accelerates the polymerization process, but also allows for tailoring material properties, making it valuable for advanced applications in high-performance composites and adhesives. In this part of our study, we focused on saturated diamines, considering that aromatic counterparts like 4,4'-oxydianiline [4] were readily available from commercial sources. Two complementary synthetic routes (**Scheme 3,** *C* and *D*) were developed to access structurally diverse amine curing agents on a multi-gram scale, giving adamantane-based diamine (**21**) and diamine (**26**) featuring a flexible bis-cyclohexane backbone. In route **C** (upper pathway, **Scheme 3**), 1,3-adamantanedicarboxylic acid (**18**) was converted into a diisocyanate intermediate (**19**) *via* the reaction with diphenyl phosphoryl azide (DPPA) in refluxing toluene. The treatment of **19** with benzyl alcohol (BnOH) gave a Cbz-protected derivative (**20**), and the subsequent Pd/C-catalyzed hydrogenation allowed to completely remove the protecting group, yielding diamine **21** [15] in an excellent overall yield of 87% at a 100 g scale. In route **D** (lower pathway, **Scheme 3**), at the first step, a Suzuki coupling between 4-bromoaniline (**22**) and 4-aminophenylboronic acid pinacol ester (generated *in situ* from **22** and *bis*(pinacolato)diboron) yielded *bis*-aniline **23** (**Scheme 3**). A direct Rh-(or Pd-)-catalyzed hydrogenation of diamine **23** did not allow to completely reduce the substrate and led to the inseparable mixtures of the products. To address this issue, we first prepared the corresponding diacetyl amide (**24**). After optimizing the catalytic conditions, the Rh(5% on Carbon)-catalyzed hydrogenation was applied to fully saturate the aromatic rings, giving diacetamido-*bis*-cyclohexane (**25**) with a quantitative yield. After evaluating various hydrolysis conditions for **25**, including both acidic and basic protocols, we found that the HBr-mediated hydrolysis in acetic acid provided the best outcome. Under these optimized conditions, diamine **26** (**Scheme 3, B**) could be obtained in the 77% overall yield over five steps on a 50 g scale. It is worth noting that [1,1'-bi(cyclohexane)]-4,4'-diamine (**26, Scheme 3**) was synthesized for the first time using a *de novo* developed protocol. Together, routes **C** and **D** demonstrated robust, scalable methods for accessing diamines with distinct structural features.

■ Conclusions

This study has substantially advanced the methods available for producing critical building blocks of high-temperature polymers. We have shown that by fine-tuning synthetic conditions, employing cost-effective and readily available raw materials, and integrating mild reaction conditions,

ISSN 2308-8303 (Print) / 2518-1548 (Online)

it is possible to achieve reliable multi-gram to multi-hundred-gram scale preparations of structurally diverse intermediates, ranging from s-triazine derivatives and phthalonitriles to borosilane oligomers and novel diamine curing agents. Unlike many reports that focus solely on polymerization outcomes, our work has focused on developing reproducible procedures and adapting them to industrially significant quantities. This has allowed us to demonstrate that even complex components can be obtained in high yields, high purity, and at scales that transcend typical bench-level experiments.

Such an expanded synthetic toolkit promises a significant impact on the rational design of future advanced materials. Although we did not perform polymerizations here, the compounds prepared open the door to tailor-made architectures with specifically tuned properties. The presence of multiple reactive functionalities, including nitriles, alkynes, boron-silicon motifs, and amine groups, encourages a combinatorial-like approach to explore various cross-linked networks. This combinatorial exploration may help researchers systematically correlate structural modifications with the thermal, mechanical, and oxidative characteristics of the resulting polymers. Over time, this knowledge is expected to guide the development of new classes of polymers optimized for extreme operational conditions.

Ultimately, our work provides a practical foundation for bridging the gap between conceptual molecular designs and real-world material applications. The scalable production of key polymer precursors will be instrumental in ensuring a steady pipeline of innovative components, paving the way for next-generation materials with enhanced longevity, durability, and reliability in demanding high-temperature settings.

■ Experimental section

The general information and materials

The solvents were purified according to the standard procedures. All starting materials were obtained from Enamine Ltd. Melting points were measured on an automated melting point system. ^{1}H, ^{11}B, ^{13}C, and NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 500 MHz for ^{1}H, 160 MHz for ^{11}B and 126 MHz for ^{13}C) and Varian Unity Plus 400 spectrometers (at 400 MHz for ^{1}H, 128 MHz for ^{11}B and 101 MHz for ^{13}C). Tetramethylsilane (^{1}H, ^{11}B, ^{13}C) was used as a standard. HPLC analyses were done on Agilent 1200. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)). Column chromatography was performed with silica gel (200–300 mesh).

Experimental protocols

4,4',4"-(1,3,5-Triazine-2,4,6-triyl)triphenol (2)

In a dry flask, 200 g (1.68 mol) of *p*-cyanophenol (**1**) was dissolved in a minimal portion of dry chloroform, and 300 mL (2-fold molar excess) of trifluoromethanesulfonic acid was added slowly at stirring as one portion. During the first two hours of stirring at room temperature, a brown precipitate of target 4,4',4"-(1,3,5-Triazine-2,4,6-triyl)triphenol (**2**) was formed. The precipitate was collected and washed with several portions of cold water, upon which it turned pale yellow. Additional washes with hot chloroform were performed to stripe off the residual starting material, then product **2** was collected and dried on air. The yield of purified triazine (**2**) was 195 g (98%).

2,4,6-Tris(4-(prop-2-yn-1-yloxy)phenyl)-1,3,5-triazine (3)

Triazine **2** (150 g, 0.42 mol) was partially dissolved in 1500 mL of anhydrous acetonitrile (acetone may be used as an alternative solvent). Potassium carbonate (176 g, 3.1-fold excess) was then slowly added to the reaction mixture in one portion while stirring. The resulting mixture was brought to a gentle reflux, and an excess of propargyl bromide (156 g, 100 mL, 3.1 mol) was introduced as a slow stream *via* a dropping funnel. The heating at 80 °C continued for 24 h. After the completion, the mixture was poured into water, and the precipitated solid product was collected by filtration. The crude product **3** was thoroughly washed with several portions of cold water, followed by several portions of cold hexane. The final yield of triazine **3** was 198 g (99%).

Borosilane alkynyl hybrid oligomer (9b)

Under an argon atmosphere, 0.5 M solution of acetylene magnesium bromide **5** in Me-THF (700 mL, 0.45 mol) was placed in a dry flask. 2 M solution of isopropylmagnesium bromide **4** in Me-THF (245 mL, 0.5 mol) was then added dropwise, monitoring the course of the reaction by gas evolution (propane release). Once the gas evolution ceased, a white precipitate (**6**) formed, indicating the reaction had reached its completion. Next, dichlorodimethylsilane (**7**) (53.2 g, 0.21 mol) was added dropwise. As the addition proceeded, the white precipitate partially dissolved, and the mixture became nearly clear.

The reaction was stirred at room temperature for 5 h. Afterward, boron trifluoride etherate (20.3 g, 0.14 mol) was introduced gradually, and the mixture was stirred for an additional 15 h. Upon the completion, the reaction was quenched by cautiously adding dilute hydrochloric acid under continuous stirring. The resulting mixture was transferred to a separation funnel and extracted with ethyl acetate. The combined organic phase was washed with water until a neutral state, dried over sodium sulfate, and concentrated under reduced pressure to give a thick brown liquid. To remove impurities, the product was reprecipitated from ethyl acetate into hexane. After the evaporation of the solvents, the borosilane oligomer (**9b**) was obtained as a brown oil, which crystallized upon standing. The yield of oligomer (**9b**) was 80 g (75%).

Borosilane alkynyl hybrid oligomer (9a) was prepared according to the protocol used for the preparation of **9b**, its yield was 68 g (73%).

Borosilane alkynyl hybrid oligomer (9c) was prepared according to the protocol used for the preparation of **9b**, its yield was 97 g (78%).

4-Nitrophthalimide (13)

Phthalimide (**12**) (240 g, 1.63 mol) was added into the mixed acid, which was prepared from the fuming nitric acid (65%, 300 g) and the concentrated sulfuric acid (98%, 1500 g) at 10 °C. The reaction mixture was then allowed to warm slowly to 25 °C. After 12 h, the reaction product was precipitated by pouring into ice, filtered and washed with water until it was free of acid, and purified by crystallization from ethanol. The yield was 294 g (94%).

4-Nitrophthalonitrile (14)

Step 1. 4-Nitrophthalimide (**13**, 220 g, 1.14 mol) was suspended in 2 L of ethanol in a 5 L round-bottom flask equipped with a mechanical stirrer and a reflux condenser. A 25% aqueous hydroxylamine solution containing 3.42 mol NH_2OH (3.0 equiv. relative to 4-nitrophthalimide **13**) was added dropwise with vigorous stirring. The mixture was heated to 75–80 °C under reflux for 5 h, ensuring the complete conversion as monitored by HPLC. After cooling to room temperature, the mixture was further chilled in an ice bath to facilitate precipitation. The resulting solid was collected by the vacuum filtration, washed thoroughly with cold ethanol followed by cold water, and then dried under reduced pressure to give 4-nitrophthalamide 14 with the yield of 90% (200 g). The product was taken to the next step without the additional purification.

Step 2. Thionyl chloride (3.81 mol, 453 g, 278 mL) was added slowly to *N*,*N*-dimethylformamide (667 mL) at a temperature below 5 °C under the argon atmosphere. After the addition was complete, 4-nitrophthalamide from the previous step (200 g) was introduced slowly in one portion, and the mixture was stirred for 18 h at room temperature. The reaction mixture was then poured into ice-cold water, causing the product to precipitate. The solid was collected by filtration, washed thoroughly with cold water, and dried under reduced pressure to give the desired product in the yield of 89% (178 g).

4-Aminophthalonitrile (15)

4-Nitrophthalonitrile **14** (125 g, 0.72 mol) and Pd/C (10% on carbon, 18 g) were suspended in 5 L of 95% ethanol in a hydrogenation vessel. Hydrogen gas was passed through the vigorously stirred suspension for 3 h at ambient temperature and pressure. After the completion, the catalyst was removed by filtration through celite, and the solvent was evaporated under reduced pressure to yield 4-aminophthalonitrile as an off-white solid (97 g, 97% yield).

4,4'-(Oxybis(1,3-dioxoisoindoline-5,2-diyl))-diphthalonitrile (11)

In a 5 L round-bottom flask, *bis*-anhydride **10** (124 g, 0.70 mol) was combined with 4 L of glacial acetic acid and heated to reflux at 120 °C while stirring. Dinitrile **15** (94.7 g, 0.65 mol) was then added, and the reaction was maintained by stirring under reflux for an additional 12 h. Initially, the solution was clear and yellow, and as the reaction proceeded, a white precipitate of imide **11** formed. After the completion of the reaction (monitored by HPLC), the mixture was cooled to room temperature, and the solid was collected by filtration. The precipitate was thoroughly washed with water to remove residual acetic acid, then with ethyl acetate and finally with hexane. Drying the white solid under reduced pressure gave 210 g of imide **11** (95% yield).

4,4'-(Carbonylbis(1,3-dioxoisoindoline-5,2-diyl))diphthalonitrile (17)

In a 5 L round-bottom flask, compound **16** (132 g, 0.75 mol) was combined with 4.5 L of glacial acetic acid and heated to 120 °C under reflux while stirring. Dinitrile **15** (80 g, 0.54 mol) was then introduced, and the reaction mixture was stirred under reflux for an additional 12 h. Initially, the solution was clear and yellow; as the reaction progressed, imide **17** precipitated from the mixture. After the completion, the reaction was cooled to room temperature, and the

ISSN 2308-8303 (Print) / 2518-1548 (Online)

solid was collected by filtration. The precipitate was thoroughly washed with water to remove residual acetic acid, then with ethyl acetate, and finally with hexane. Drying the white solid under reduced pressure gave 220 g of imide **17** (95% yield).

Dibenzyl-(adamantane-1,3-diyl)dicarbamate (20)

In a 2 L round-bottom flask, 1,3-adamantanedicarboxylic acid (**18**) (50.5 g, 0.23 mol) was dissolved in 900 mL of toluene and heated to 80 °C under reflux. Triethylamine (70 mL, 50 g, 0.49 mol) was added, followed by the careful dropwise addition of diphenyl phosphorazidate (DPPA; 97 mL, 110 g, 0.35 mol). The reaction mixture was maintained at 80 °C for 1 h until the gas evolution ceased. The solution of benzyl alcohol (60 mL, 61 g, 0.56 mol) in triethylamine (70 mL, 50 g, 0.49 mol) was then introduced, and the mixture was kept at 80–85 °C for 48 h. After cooling to room temperature, the mixture was poured into cold water, the layers were separated and the aqueous layer was additionally extracted twice with ethyl acetate, and the combined organic layers were dried and concentrated under reduced pressure. The recrystallization of the residue from ethanol gave 96 g (99% yield) of carbamate **20**.

Adamantane-1,3-diamine dihydrochloride (21)

In a 2 L round-bottom flask, carbamate **20** (98 g, 0.32 mol) was dissolved in methanol (1.5 L). Palladium on carbon (Pd/C, 10%, 9.8 g) was added, and the flask was purged with hydrogen. The hydrogen atmosphere (1 atm) was maintained above the solution, ensuring a hydrogen supply of 110 mL per gram of substrate **20**. The mixture was stirred at room temperature for 18 h. After the completion, the catalyst was removed by filtration through celite, and the solvent was evaporated under reduced pressure, yielding a white powdery diamine **21**. Diethyl ether (500 mL) was added, followed by dioxane/HCl until the mixture became acidic. The resulting suspension was stirred, and the precipitated diamine **21** as a dihydrochloride salt was collected by filtration, washed, and dried under reduced pressure to give 96 g (98% yield) of the desired product.

1,1'-Biphenyl-4,4'-diamine (benzidine, 23)

4-Bromoaniline (107 g, 0.62 mol) was combined with *bis*(pinacolato)diboron (249 g, 0.94 mol) and potassium acetate (183.6 g, 1.87 mol) in anhydrous ethanol (1 L) within an argon-flushed, three-necked, 2 L round-bottom flask. To this mixture, 10% Pd/C catalyst (6.6 g) was added, and the reaction mixture was stirred and heated to 60 °C. The mixture was maintained at this temperature with continuous stirring for the duration necessary to achieve the complete consumption of the starting materials, as confirmed by HPLC. After the reaction was complete, the reactor was cooled to room temperature, and the reaction mixture was filtered through celite to remove the catalyst. The filtrate was concentrated under reduced pressure, and the residue was taken up in dichloromethane (3 × 0.5 L). The combined organic layers were then washed twice with water (2 × 0.5 L) and once with brine (0.25 L). The organic phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to yield a thick brown residue. This crude product was purified by flash chromatography on silica gel using petroleum ether as an eluent. The purified *bis*-aniline **23** was obtained as a white solid in the amount of 54 g, corresponding to the yield of 94%.

***N,N'*-([1,1'-biphenyl]-4,4'-diyl)diacetamide (24)**

In a 2 L round-bottom flask, compound **23** (66 g, 0.36 mol) was dissolved in 600 mL of dichloromethane at room temperature. Triethylamine (99 mL, 72 g, 0.71 mol) was added, followed by the dropwise addition of acetyl chloride (50 mL, 55.7 g, 0.71 mol) under ice-cooling. The mixture was stirred for 5 h, then the solvent was removed under reduced pressure. The resulting residue was washed thoroughly with water multiple times. After drying, diacetamide **24** was obtained in a quantitative yield (100%) as 96 g of the solid.

***N,N'*-([1,1'-bi(cyclohexane)]-4,4'-diyl)diacetamide (25)**

N,N'-([1,1'-biphenyl]-4,4'-diyl)diacetamide **24** (100 g, 0.37 mol) was dissolved in glacial acetic acid (1 L) and transferred into an autoclave equipped with mechanical stirring. Rhodium on carbon (Rh/C) catalyst (5 g of 5% Rh/C) was added, and the vessel was sealed under hydrogen at 120 °C. The mixture was stirred under these conditions for 7 days, and the reaction progress was monitored by ^{1}H NMR until aromatic signals completely disappeared, indicating the full hydrogenation to *N,N'*-([1,1'-bi(cyclohexane)]-4,4'-diyl)diacetamide (**25**). After cooling to room temperature, the mixture was filtered to remove the catalyst, and the solvent was evaporated under reduced pressure to give the product as an oil. The yield was 99%, providing 103 g of fully saturated acetamide **25**.

[1,1'-Bi(cyclohexane)]-4,4'-diamine (26)

N,N'-([1,1'-bi(cyclohexane)]-4,4'-diyl)diacetamide (**25**) (59.8 g, 0.21 mol) was dissolved in a mixture (1:1, *v*/*v*) of glacial acetic acid (1 L) and hydrobromic acid (1 L) and heated at 115 °C for 5 days. During the hydrolysis, water (100 mL) and additional HBr (50 mL) were added as needed. After the complete hydrolysis was confirmed by the mass spectrometric analysis, the mixture was concentrated under reduced pressure. The residue was neutralized with an aqueous base and extracted three times with MTBE (3 × 500 mL). The combined organic extracts were dried and evaporated to yield an oily residue, which was dissolved in anhydrous MTBE (200 mL). The dioxane/HCl solution was added until an acidic state, causing the precipitation of diamine **26** as dihydrochloride (white solid). After the filtration and drying, 55 g of the product was obtained, corresponding to a yield of 92%.

Acknowledgment

The authors thank Enamine Ltd. for access to the building blocks stock, Prof. Andrey A. Tolmachev, for his encouragement and support, and Halyna Buvailo for her major contribution to the preparation of Supporting Information. We acknowledge BioRender.com for providing the graphical tools used to create **Figure 1**.

References

1. Cassidy, P. E.; Aminabhavi, T. M.; Reddy, V. S. Heat-Resistant Polymers. In *Kirk-Othmer Encyclopedia of Chemical Technology*, 2000.
2. Mark, H. F. *Encyclopedia of polymer science and technology, 15 volume set*; Wiley New York, NY, USA, 2014.
3. Kumar, D.; Gupta, A. D.; Khullar, M. Heat-resistant thermosetting polymers based on a novel tetrakisaminophenoxycyclotriphosphazene. *Journal of Polymer Science Part A: Polymer Chemistry* **2003**, *31* (11), 2739–2745. https://doi.org/10.1002/pola.1993.080311109.
4. Kumar, D.; Razdan, U.; Gupta, A. D. Heat-resistant polymers from melt-processable bisimido-bisphthalonitriles. *Journal of Polymer Science Part A: Polymer Chemistry* **1993**, *31* (3), 797–804. https://doi.org/10.1002/pola.1993.080310326.
5. Butt, M. S.; Akhtar, Z.; Zafar-uz-Zaman, M.; Munir, A. Synthesis and characterization of some novel aromatic polyimides. *European Polymer Journal* **2005**, *41* (7), 1638–1646. https://doi.org/10.1016/j.eurpolymj.2005.01.016.
6. (a) Hasegawa, M.; Hoshino, Y.; Katsura, N.; Ishii, J. Superheat-resistant polymers with low coefficients of thermal expansion. *Polymer* **2017**, *111*, 91-102. https://doi.org/10.1016/j.polymer.2017.01.028. (b) Krishnaraj, C.; Jena, H. S.; Leus, K.; Van Der Voort, P. Covalent triazine frameworks – a sustainable perspective. *Green Chem.* **2020**, *22* (4), 1038–1071. https://doi.org/10.1039/c9gc03482j.
7. Zhou, H.; Zhou, Q.; Zhou, Q.; Ni, L.; Chen, Q. Highly heat resistant and thermo-oxidatively stable borosilane alkynyl hybrid polymers. *RSC Adv.* **2015**, *5* (16), 12161–12167. https://doi.org/10.1039/c4ra14352c.
8. Inoue, K.; Nakamura, H.; Ariyoshi, S.; Takagi, M.; Tanigaki, T. Heat-resistant polymers prepared from [(4'-(2-vinyl)-4-biphenylyl)oxy] pentachlorocyclotriphosphazene. *Macromolecules* **2002**, *22* (12), 4466–4469. https://doi.org/10.1021/ma00202a015.
9. Yu, G.; Liu, C.; Wang, J.; Li, X.; Jian, X. Heat-resistant aromatic S-triazine-containing ring-chain polymers based on bis(ether nitrile)s: Synthesis and properties. *Polymer Degradation and Stability* **2010**, *95* (12), 2445–2452. https://doi.org/10.1016/j.polymdegradstab.2010.08.011.
10. Achar, B. N.; Fohlen, G. M.; Parker, J. A. Studies on heat-resistant thermosetting phthalocyanine polymers. *Journal of Applied Polymer Science* **1984**, *29* (1), 353–359. https://doi.org/10.1002/app.1984.070290133.
11. Zhou, J.; Wang, J.; Jin, K.; Sun, J.; Fang, Q. s-Triazine-based functional monomers with thermocrosslinkable propargyl units: Synthesis and conversion to the heat-resistant polymers. *Polymer* **2016**, *102*, 301–307. https://doi.org/10.1016/j.polymer.2016.09.027.
12. Sastri, S. B.; Keller, T. M. Phthalonitrile polymers: Cure behavior and properties. *Journal of Polymer Science Part A: Polymer Chemistry* **1999**, *37* (13), 2105–2111. https://doi.org/10.1002/(sici)1099-0518(19990701)37:13<2105::aid-pola25>3.0.co;2-a.
13. (a) Zhang, Y.; Huang, Y.; Liu, X.; Yu, Y. Studies on the silicone resins cured with polymethylsilazanes at ambient temperature. *Journal of Applied Polymer Science* **2003**, *89* (6), 1702-1707. https://doi.org/10.1002/app.12433. (b) Takekoshi, T.; Terry, J. M. High-temperature thermoset polyimides containing disubstituted acetylene end groups. *Polymer* **1994**, *35* (22), 4874–4880. https://doi.org/10.1016/0032-3861(94)90746-3.
14. Burchill, P. J. On the formation and properties of a high-temperature resin from a bisphthalonitrile. *Journal of Polymer Science Part A: Polymer Chemistry* **2003**, *32* (1), 1–8. https://doi.org/10.1002/pola.1994.080320101.
15. Seino, H.; Mochizuki, A.; Ueda, M. Synthesis of aliphatic polyimides containing adamantyl units. *Journal of Polymer Science Part A: Polymer Chemistry* **1999**, *37* (18), 3584–3590. https://doi.org/10.1002/(sici)1099-0518(19990915)37:18<3584::aid-pola5>3.0.co;2-r.
16. Woiczechowski-Pop, A.; Dobra, I. L.; Roiban, G. D.; Terec, A.; Grosu, I. Synthesis and Structural Analysis of Some Podands with C_3 Symmetry. *Synth. Commun.* **2012**, *42* (24), 3579–3588. https://doi.org/10.1080/00397911.2011.585732.
17. Mika, T. F.; Bauer, R. S. Curing agents and modifiers. In *Epoxy resins*, Routledge, 2018; pp 465–550.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

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ISSN 2308-8303 (Print) / 2518-1548 (Online)