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

2025 — том 23, випуск 1 (89)

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.

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«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 № 6 від 15.04.2025 р.

Затверджено до друку вченою радою Національного фармацевтичного університету, протокол № 3 від 28.03.2025 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 17.04.2025 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 23, випуск 1 (89), 2025

ISSN 2308-8303 (Print)

ISSN 2518-1548 (Online)

Journal of Organic and Pharmaceutical Chemistry

Opinion

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

UDC 615.214:544

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Balancing Physicochemical Properties between the Molecules of Mercy (Non-Addictive Drugs) and the Molecules of Mysticism (Often Addictive Drugs)

Abstract

The fundamental physicochemical features of drugs acting on the central nervous system (CNS) determine their ability to penetrate the blood-brain barrier (BBB) and be active against the CNS activities. In this paper, we study two well-known groups of drugs used or prescribed by physicists to treat CNS disorders. One group of drugs belongs to pain killers (the Molecules of Mercy), and the other group belongs to the mind-changers (the Molecules of Mysticism). These two groups of CNS drugs differ in a number of physicochemical parameters: molecular weight, lipophilicity, hydrogen bound acceptor count, hydrogen bond donor count, polar surface area, polarizability, flexibility, bioavailability, and their behavior (agreement or disagreement) related to specific structural conditions, in particular the Lipinski's rule, Ghose filter, Veber's rule, Multi-Drug Data Report (MDDR) criteria. In the study of 41 well-known drugs that affect the CNS (both approved or illegal), it has been found that painkillers that do not cause addiction have a physicochemical profile other than those of mind-changer drugs that are very often addictive.

The features of physicochemical parameters associated with the profiles of "pain killer" and "mind-changer" drugs are discussed.

Keywords: CNS-drugs discovery; pain killers; mind-changers; physicochemical properties; therapeutic drugs

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Балансування фізико-хімічних властивостей між молекулами милосердя (неадиктивними препаратами) і молекулами містицизму (часто адиктивними препаратами)

Анотація

Фундаментальні фізико-хімічні характеристики лікарських засобів, що діють на центральну нервову систему (ЦНС), визначають їхню здатність проникати через гематоенцефалічний бар'єр (ГЕБ) і проявляти активність щодо ЦНС. У цій роботі досліджено дві відомі групи препаратів, які застосовують для лікування розладів ЦНС. Перша група належить до анальгетиків (молекули милосердя), а друга – до психоактивних речовин (молекули містицизму). Ці дві групи лікарських засобів відрізняються за деякими фізико-хімічними параметрами: молекулярною масою, ліпофільністю, кількістю акцепторів і донорів водневого зв'язку, площею полярної поверхні, поляризованістю, «гнучкістю», біодоступністю, а також за відповідністю або невідповідністю певним структурним критеріям, зокрема правилу Ліпінські, фільтру Гоуза, правилу Вебера та критеріям Multi-Drug Data Report (MDDR). У ході дослідження 41 добре відомого лікарського засобу, що впливають на ЦНС (як затверджених, так і нелегальних), було виявлено, що анальгетики, які не викликають залежності, мають фізико-хімічний профіль, відмінний від профілю психоактивних речовин, які часто є адиктивними. У статті розглянуто особливості фізико-хімічних параметрів, пов'язані з профілями «анальгетичних препаратів» та «психоактивних препаратів».

Ключові слова: розробка препаратів для ЦНС; анальгетики; психоактивні препарати; фізико-хімічні властивості; терапевтичні препарати

Citation: Kraus, J.-L. Balancing Physicochemical Properties between Molecules of the Mercy (Non-Addictive Drugs) and Molecules of Mysticism (Often Addictive Drugs) *Journal of Organic and Pharmaceutical Chemistry* **2025**, *23* (1), 3–10.
https://doi.org/10.24959/ophcj.25.321860
Received: *17 October 2024*; **Revised:** *30 January 2025*; **Accepted:** *5 February 2025*

Funding: CNRS-Aix Marseille-University and Marseille Institute for Biology of Development (IBDM) are greatly acknowledged for the facilities offered and financial support.
Conflict of interest: The author has no conflict of interest to declare.
Ethics approval and consent to participate: This article does not contain any studies involving patients or animals as test objects.

■ Introduction

At all times, throughout his evolution and development, man has sought to protect himself against pain, whether physical or psychological. At first, he was looking for plants or natural compounds for this purpose. Then, taking care of the health and well-being, a person was seeking for new flavors, new tastes, new antibacterial drugs and new hormone regulators. Throughout this time, man has been creating a pharmacopoeia that contains several thousand molecules with a wide variety of chemical structures. Some of these molecules are of natural origin, while most of them are obtained as a result of chemical synthesis. Today, in order to cure specific pathologies or disorders, medical professionals have to make difficult choices between thousands of possible therapeutic molecules.

In their book, "Organic Molecules in Action" (1973), *Murray Goodman* and *Frank Morehouse* [1] have proposed to classify the pharmacopeial constitutive molecules into several classes of compounds, which represent millions of combinations between carbon, hydrogen, oxygen, sulfur, and other atoms upon which life itself is based:

- the Molecules of the code of life (nucleic acid and proteins);
- the Giant molecules (polymers);
- the Molecules of Mercy (pain killers or pain relievers);
- the Molecules of Mysticism (mind-changers);
- the Molecules of Might (germ killers);
- the Molecules of the steroid family (hormonal modulators);
- the Molecules of Growth and Health (vitamins);
- the Molecules of Senses (taste, odor, attraction).

Among these different classes of molecules, the Molecules of Mercy (pain relievers or pain killers) and the Molecules of Mysticism appeared of particular interest since both classes act at the Central Nervous System level (CNS), which requires crossing the blood-brain barrier (BBB).

This article will focus on these two groups of drugs, emphasizing their physicochemical properties that enable them to act as pain killers or as mind changers. From medicinal and chemical perspectives, the ability to design efficient pain reliever drugs in reducing their psychedelic side effect (mind changers) could be of high interest.

■ Materials and methods

The drugs included in this study are approved by the Food and Drug Administration (FDA) or have received approval from the European Medicines Agency (EMA). Some of these drugs are approved, others are banned, and some are obsolete molecules that have been replaced. However, all the drugs mentioned in this manuscript have been tested on patients for their effects on the CNS and are registered in the DrugBank database available at www.drugbank.com. According to literature recommendations, CNS drugs mentioned in this study are classified into two groups of drugs – *pain killers* (drugs of Mercy) and *mind-changers* (drugs of Mysticism) [1].

The group of Pain killers (*Molecules of Mercy*)

Pain killers or pain reliever molecules (Molecules of Mercy) are used to alleviate the common human aches and pains. Their action is often mediated through the prostaglandin production. The prostaglandin change is generally very low in uninflamed tissues, but increases immediately in acute inflammation [2]. Nevertheless, some compounds like capsaicin, codeine, and buprenorphine, listed below, do not act through the inhibition of prostaglandin effects.

The branded names of the drugs included in this group of painkillers, which refer to the international non-proprietary names (INN), are the following: Salicylic acid, Codeine, Buprenorphine, Methadone, Nalorphine, Celecoxib, Ibuprofen, Naproxen, Paracetamol, Pregabalin, Diclofenac, Oxycodone, Carbamazepine, Amitriptyline, Capsaicin, Meloxicam, Prednisolone, Meperidine, Butalbital, Naltrexone, Gabapentin, Morphine and Fentanyl[§].

[§] **Note**: it should be underlined that in this study Fentanyl and Morphine have been considered as Pain Killers, as well as Mind Changers.

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

The group of Mind-Changer Drugs (*Molecules of Mysticism*)

These molecules affect mental processes and fall under the classification of hallucinogenic or psychotomimetic drugs. They alter thinking, perception, and mood [3]. The international nonproprietary names of drugs belonging to the group of mind changers are as follows: Heroin, Cocaine, Ergotamine, LSD, Mescaline, Amphetamine, Psylocibin, Nikethamide, Serotonin, Epinephrine, Phenylethylamine, Methamphetamine, Bufotenine, Tetrahydrocannabinol, Methylphenidate (Ritalin), Cathinone, Morphine, and Fentanyl[§].

This study does not include prescribed drugs available to treat mental illness. Antidepressants used to treat depression, anxiety, and some types of personality disorders, or antipsychotic drugs to treat schizophrenia and bipolar disorders, as well as to restore the chemical balance of the brain are not mentioned [4]. The study presented includes only modern medicines, natural or synthetic, which are known to be active against the CNS as pain relievers or mind changers.

■ Results

Physical and chemical properties of the drugs studied (pain killers and mind-changers)

In the broad sense, moderately lipophilic drugs cross the BBB, by passive diffusion, and the hydrogen bonding properties of drugs can significantly influence their CNS uptake profile. Polar molecules are generally poor CNS drugs unless they undergo active transport across the CNS. Other properties (size, molecular weight, partition coefficient, molecular flexibility (rotational bonding), solubility, polar surface, polarizability, bioavailability) are also factors that can affect the transport of an organic molecule to cross the BBB [5, 6].

Pain killers and mind-changers possess tremendous chemical diversity and yet reach their target(s) in the brain. The question is, "*What physical and medicinal-chemical characteristics do they possess to induce their various activities: pain killers for the molecules of Mercy and mind changers for the molecules of Mysticism?*"

The most known molecules belonging to the group of the Molecules of Mysticism are the cannabinoids (hashish, marihuana) extracted from *Cannabis sativa*, which are the oldest and most broadly occurring hallucinogens. Cannabis ranks second after opium as the most widely used mind-altering drug today. The most active ingredient of cannabinoids is Δ^9-tetrahydrocannabinol (THC). In the late 1960s, researchers learned that there were specific areas in the brain controlling pain [7–9]. As for psychedelic drugs, hallucinogenic compounds, such as Δ^1-Tetrahydrocannabinol, Psylocibin, and LSD, exert their primary effects through activating serotonin 5-HT_{2A} receptors found predominantly in cortical regions [10]. The question that arises at the level of chemical structures and physicochemical properties is, "*How can the molecules of the group of pain killers be differentiated from those of mind-changers, taking into account that these two groups of compounds must penetrate the blood-brain barrier to reach their targets at the CNS level?*"

To answer this question, 23 drugs (US FDA approved or/and European marketing authorization) most prescribed for the treatment of pain (the Molecules of Mercy) and 18 molecules of well-known psychedelic drugs used for recreational purposes (the Molecules of Mysticism) and/or for mental disorders are included in this study. The physicochemical characteristics of these 41 molecules could be found in DrugBank Online data, offered to the public as a free-to-access resource [11]. For each drug, 11 representative structural physicochemical parameters were considered: Molecular weight (MW), Chemical formula, Water solubility (mg mL^{-1}), log *P*, log *S*, Hydrogen acceptor count, Hydrogen donor count, Rotatable bond count, Polar surface area ($Å^2$), Polarizability ($Å^3$), Bioavailability.

Table 1 and **Table 2** show the values of the physicochemical parameters for each drug belonging to both groups of drugs: 23 Molecules of Mercy (pain killers) and 19 Molecules of Mysticism (mind-changers), as well as their compliance with the Lipinski's rule (Rule of five), Ghose filter, Veber's rule, and MDDR-like rule.

Notes to the descriptors that appear in **Tables 1** and **2** are given below:

MW – the molecular weight in g mol^{-1}. **Water Solubility** in mg mL^{-1}. **Log*P*** – the octanol-water partition coefficient [12]. **Log*S*** – the common solubility unit corresponding to the 10-based logarithm of the water solubility of a molecule measured in mol L^{-1}. $\mathbf{H_A}$ – the number of hydrogen bond acceptors. $\mathbf{H_D}$ – the number of hydrogen bond donors. **Rotatable bonds** – the number of single bonds which can freely rotate around their axis [13]. **Bioavailability** – representing the fraction (F) of the administered dose

Table 1. Molecules of Mercy (pain killers)

№	Generic names	MW	Chemical formula	Water solubility,[a] mg mL^{-1}	Log *P*[a]	Log *S*[a]	H_A[a]	H_D[a]	Rotatable bonds[a]	Bioavailability[a]	Polar surface area[a]	Polarizability[a]	Lipinskis rule[b] (Rule of five)	Ghose rule[b]	Vebers rule[b]	MDDR-like rule[b]
1	Salicylic acid	180	$C_9H_8O_4$	10	1.2	-	3	1	3	1	63.6	7.1	Yes	Yes	No	No
2	Codeine	299	$C_{18}H_{21}NO_3$	0.57	1.24	-2.7	4	1	1	1	41.93	31.9	Yes	Yes	No	No
3	Buprenorphine	467	$C_{29}H_{41}NO_4$	0.017	4.53	-4.4	5	2	5	1	65.07	53.35	Yes	No	No	No
4	Methadone	309	$C_{21}H_{27}NO$	0.006	4.14	-4.7	2	0	7	1	20.31	36.28	Yes	No	No	No
5	Nalorphine	311	$C_{19}H_{21}NO_3$	1.36	1.55	-2.4	4	2	2	1	52.93	33.3	Yes	Yes	No	No
6	Celecoxib	381	$C_{17}H_{14}F_3N_3O_2S$	0.005	3.99	-2.7	3	1	4	1	59.3	26.67	Yes	Yes	No	No
7	Ibuprofen	206	$C_{13}H_{18}O_2$	0.070.	3.5	-3.5	2	1	4	1	37.3	23.76	Yes	Yes	Yes	No
8	Naproxen	260	$C_{14}H_{14}O_3$	0.051	3.29	-3.6	3	3	1	1	46.53	24.8	Yes	Yes	No	No
9	Paracetamol	151	$C_8H_9NO_2$	4.15	0.51	-1.16	2	2	1	1	49.33	15.52	Yes	No	No	No
10	Pregabalin	159	$C_8H_{17}NO_2$	11.3	-1.4	-1.2	3	2	5	1	66.32	18.08	Yes	No	No	No
11	Diclofenac	296	$C_{14}H_{11}Cl_2N_20$	0.0045	4.98	-4.8	3	2	4	1	49.33	27.93	Yes	Yes	No	No
12	Oxycodone	315	$C_{18}H_{21}NO_4$	5.59.	1.04	-1.8	5	1	1	1	59	32.79	Yes	Yes	No	No
13	Carbamazepine	236	$C_{15}H_{12}N_2O$	0.152	2.1	-3.2	1	1	0	1	46.33	25	Yes	Yes	No	No
14	Amitriptyline	277	$C_{20}H_{23}N$	0.0045	5.1	-4.8	1	0	3	1	3.24	33.74	Yes	Yes	No	No
15	Capsaicin	305	$C_{14}H_{27}NO_3$		3.75	-	3	2	9	1	58.56	36.32	Yes	Yes	No	No
16	Meloxicam	351	$C_{14}H_{13}N_3O_4S_2$	0.154	2.28	-3.4	5	4	2	1	99.6	34.25	Yes	Yes	No	No
17	Prednisolone	360	$C_{21}H_{28}O_{50}$	0.2390	1.66	-3.2	5	3	2	4	94.83	38.69	Yes	Yes	No	No
18	Meperidine	247	$C_{15}H_{21}NO_2$	1.11	2.9	-2.4	2	0	4	1	29.54	28.09	Yes	Yes	No	No
19	Butalbital	224	$C_{11}H_{16}N_2O_3$	2.23.	1.47	-2	3	2	4	1	75.27	22.43	Yes	Yes	No	No
20	Naltrexone	341	$C_{20}H_{23}NO_4$	3.07	2.07	-2	5	2	2	1	70	36.03	Yes	Yes	No	No
21	Gabapentin	171	$C_9H_{17}NO_2$	4.34	- 1.9	-1.6	3	2	3	1	63.32	18.92	Yes	Yes	No	No
22	Morphine	285	$C_{17}H_{19}NO_3$	0.149	0.9	-1.4	4	2	0	1	52.93	29.94	Yes	Yes	No	No
23	Fentanyl	336	$C_{22}H_{28}N_2O$	0.024	4.12	-4.2	2	0	6	1	23.55	30.89	Yes	Yes	Yes	Yes

Notes: [a] Reported Values (Water solubility, log *P*, log *S*, H_A, H_D, Rotatable bonds, Bioavailability, Polar surface area, Polarizability) are **predicted values** through the ALOGPS 2.1 program; [b] Answers (Yes or Not) associated with the rules of Five, Ghose filter, Veber and MDDR-like, are **given according to DrugBank** database recommendations.

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

Table 2. Molecules of Mysticism (mind-changers)

№	Generic names	MW	Chemical formula	Water solubility, [a] mg mL^{-1}	Log *P*[a]	Log *S*[a]	H_A[a]	H_D[a]	Rotatable bonds[a]	Bioavailability[a]	Polar surface area [a]	Polarizability[a]	Lipinski's rule[b] (Rule of five)	Ghose rule[b]	Veber`s rule[b]	MDDR-like rule[b]
1	Heroin	369	$C_{21}H_{23}NO_5$	0.266	2.3	-3.1	4	0	0	1	65.07	38.19	Yes	Yes	No	No
2	Cocaine	303	$C_{17}H_{21}NO_4$	5.03	1.97	-1 8	3	0	5	1	55.84	32.02	Yes	Yes	No	No
3	Ergotamine	581	$C_{33}H_{35}N_5O_5$	0.233	2.95	-3.4	6	3	4	1	118.21	62.23	No	No	No	No
4	LSD	323	$C_{20}H_{25}N_3O$	0.27	3.3	-	2	1	3	1	39.34	37.54	Yes	Yes	Yes	No
5	Mescaline	211	$C_{11}H_{17}NO_3$	1.0	0.78	-	4	2	2	1	-	-	Yes	-	-	
6	Amphetamine	135	$C_9H_{13}N$	1.74	1.85	-1.9	1	1	2	1	26.02	16.17	Yes	No	Yes	No
7	Psylocibin	284	$C_{12}H_{17}N_2O_4P$	-	1.24	-	4	3	5	1	85.79	-	Yes	-	No	No
8	Nikethamide	178	$C_{10}H_{14}N_2O$	109.0	0.83	-0.21	2	0	3	1	33.2	19.56	Yes	Yes	Yes	No
9	Serotonin	176	$C_{10}H_{12}N_2O$	2.5	0.56	-1.8	2	3	2	1	62.04	19.31	Yes	Yes	No	No
10	Epinephrine	183	$C_9H_{13}NO_3$	0.1	-0.82	-0.99	4	4	3	1	77.72	19.04	Yes	No	No	No
11	Phenethylamine	121	$C_8H_{11}N$	2.19	1.41	-1.7	1	1	2	1	2602	14.36	Yes	No	Yes	No
12	Methamphetamine	149	$C_{10}H_{15}N$	0.928	2.23	-2.2	1	1	3	1	12.03	18.04	Yes	No	Yes	No
13	Bufotenine	204	$C_{12}H_{16}N_2O$	3.2	2.04	-1.8	2	2	3	1	39.26	23.29	Yes	Yes	Yes	No
14	Tetrahydrocannabinol	314	$C_{21}H_{30}O_2$	0.0026	7.29	-5.1	2	1	4	1	29.46	38.96	No	No	Yes	No
15	Methylphenidate	233	$C_{14}H_{19}NO_2$	0.182	1.47	-2.1	2	1	4	1	38.33	25.91	Yes	Yes	Yes	No
16	Cathinone	149	$C_9H_{11}NO$	2.46	0.51	-1.8	2	1	2	1	43.09	16.28	Yes	No	No	No
22	Morphine	285	$C_{17}H_{19}NO_3$	0.149	0.9	-1.4	4	2	0	1	52.93	29.94	Yes	Yes	No	No
23	Fentanyl	336	$C_{22}H_{28}N_2O$	0.024	4.12	-4.2	2	0	6	1	23.55	39.89	Yes	Yes	Yes	Yes

Notes: [a] Reported Values (Water solubility, log *P*, log *S*, H_A, H_D, Rotatable bonds, Bioavailability, Polar surface area, Polarizability) are **predicted values** through the ALOGPS 2.1 program; [b] Answers (Yes or Not) associated with the rules of Five, Ghose filter, Veber and MDDR-like, are **given according to DrugBank** database recommendations.

of a xenobiotic that reaches the systemic circulation, measured on a continuous range from 0 to 1 [14]. **Polar Surface Area** (PSA) – defined as the surface sum over all polar atoms or molecules, primarily oxygen and nitrogen, including also their attached hydrogen atoms [15, 16]. **Polarizability** – determines the response of the susceptibility of a molecule to an approaching charge. Larger molecules, atoms, or ions are more polarizable than smaller objects. Polarizability is expressed as the polarizability volume with units in $Å^3 = 10^{-24}$ cm^3 [17, 18]. **Rule of Five** (Lipinski's rule) – not more than 5 hydrogen bond donors; not more than 10 hydrogen bond acceptors; the molecular mass less than 500 Da [19]. **Ghose Filter** – the partition coefficient Log*P* from −0.4 to +5.6; the molecular refractivity from 40 to 130; the molecular weight from 180 to 480; the number of atoms from 20 to 70 (includes H-bond donors [e.g., OHs and NHs] and H-bond acceptors [e.g., Ns and Os]) [20]. **Veber's rule** – 10 or fewer rotatable bonds and the polar surface area equal to or less than 140 $Å^2$ or 12 or fewer H-bond donors and acceptors [21]. **MDDR-like rule** – the rule-of-five test cannot be used to discriminate between drugs and non-drugs. Descriptors used for the MDDR-like rule are the number of rings, the number of rigid bonds, and the number of rotatable bonds. The probability of finding a "druglike" compound is higher in the ranges: No. of rings ≥ 3, No. of rigid bonds ≥ 18, No. of rotatable bonds ≥ 6, while the probability of finding a 'nondrug-like' compound is higher in the ranges: No. of rings ≤ 2, No. of rigid bonds ≤ 17, No. of rotatable bonds ≤ 5 [22, 23].

Table 3. The average values of all the physicochemical values related to both groups of drugs

No.	Physicochemical properties	The Molecules of Mysticism (mind-changers)	The Molecules of Mercy (pain killers)
1	MW	263.8	192.88
2	Solubility (mg/ml)	4.37	0.96
3	Log *P*	2.28	1.55
4	Log *S*	-1.3	-2.17
5	H_A	2.56 (between 2 and 3)	3.2 (between 3 and 4)
6	H_D	1.2 (between 1 and 2)	1.3 (between 1 and 2)
7	Rotatable bonds	3	3
8	Polar Surface Area	30.58	54.14
9	Polarizability	29.01	31.51
10	Bioavailability	1	1
11	Rule of Five	Yes (18/18)	Yes (23/23)
12	Ghose Filter	Yes (9/17)	Yes (19/23)
13	Veber's rule	Yes (9/17)	Yes (2/23)
14	MDDR-like rule	Yes (2/18)	Yes (0/23)

Note: Values provided in **Table 3** correspond to the mean ones calculated based on data from **Tables 1** and **2**

Table 3 shows the average values of all the physicochemical parameters listed in **Tables 1** and **2** related to both groups of drugs: *Pain killers* and *Mind-changers*.

Discussion

A careful analysis of the reported values allows us to determine what are the physicochemical properties that support the ability of these CNS drugs to act as pain killers or pain relievers and what are the physicochemical parameters that induce a mind-changer effect (psychedelic activity) in this group of drugs. Let us first recall that all the values of the physicochemical parameters considered came from the same database, the Drug Bank, which is accessible freely online.

All the molecules cited in this manuscript are used in clinical practice, mainly as pain killers, and are therefore approved by the FDA; other substances in the group of mind-changers are used in clinical practice, while others are classified as prohibited and non-commercial. It is known that all the molecules analyzed act at the CNS level, which means that all these drugs must penetrate the blood-brain barrier. The analysis of the physicochemical parameters associated with each of the two groups – pain killers and mind-changer compounds – reveals differences in the average values of certain parameters.

As can be seen from **Table 3**, the molecular weight, solubility, Log *P,* and log *S* values for the mind changer drugs are lower than for pain killers. On the contrary, the values of polarizability, polar surface area, hydrogen acceptor count, and hydrogen donor count of the pain killers are higher than those of the mind-changer drugs.

From the results presented in **Table 3**, the following conclusions can be drawn:

- most of the drugs belonging to both groups, the Molecules of Mercy or the Molecules of Mysticism, corresponded to the *Lipinski's rule* as indicated in **Tables 1** and **2**;
- 9 of 23 compounds of the Mysticism group satisfy the *Veber's rule*, while only 2 of 23 compounds of the Mercy group satisfy this rule;
- the majority of the drugs (19/21) related to drugs of Mercy comply with the *Ghose filter*

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

rule, while only half of drugs of Mysticism comply with this rule;

- most of the drugs of these two groups do not support the *MDDR-like rules*.

Based on the data presented in **Tables 1**, **2**, and **3**, the development and synthesis of molecules for the treatment of pain in the CNS, in particular for end-of-life care, requires a targeted approach. Chemists developing new pain killers or improving existing ones through molecular modifications should ensure that the physicochemical properties of these molecules meet the criteria set out in **Table 3**.

For Molecules of Mercy (pain killers), these new structures will represent pharmacological profiles that would limit the side effects often associated with taking active painkiller ingredients (morphine and related analogs), mainly addiction effects. As indicated in **Table 3**, mind-changing drugs that act on the psyche (anxiety, depression) present physicochemical criteria significantly different from those of more specific molecules to combat pain.

■ Conclusion

When designing new CNS drugs, it is necessary to maintain a balance between physical and chemical requirements and achieve the best compromises in properties depending on the target therapeutic effect – pain killers or mind-changers. While all CNS drugs (41 compounds), pain killers, and mind-changers involved in this study comply well with the Lipinski's rule, it can be noted that pain killers mostly comply with the Ghose filter conditions, but do not satisfy the Veber's rule. In contrast, only half of the mind-changer drugs agree with the Veber's rule and satisfy the Ghose filter conditions. This observation indicates that other physicochemical parameters, such as polar surface area, polarizability, and flexibility, are important parameters that can be manipulated by medicinal chemists involved in the CNS drug design in order to modulate or improve the pharmacological effect of a new CNS drug depending on the desired target effect: pain reliever or mind changer activities. Of course, since we have focused only on approved or natural, well-known drugs that ensure the BBB penetration, the conclusions presented are restrictive. They could only be applied to drugs that satisfied the condition of the BBB penetration in order to orient the desired effect to the pain reliever effect rather than the mind changer effect. These results can be of interest since addictive psychedelic effects are often associated with the use of pain reliever drugs.

■ Acknowledgments

CNRS-Aix Marseille University and Marseille Institute for Biology of Development (IBDM), director Dr. L. Kodjabachian, are greatly acknowledged for the facilities offered and financial support.

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

Journal of Organic and Pharmaceutical Chemistry

Advanced Research

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UDC 54.057:547-304.2

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A Scalable Approach to Primary Amines *via* the Petasis Reaction

Abstract

The efficient and scalable synthesis of homoallylic amines is a subject of significant interest due to the potential applications of these compounds in medicinal and synthetic chemistry. The three-component Petasis reaction is an excellent approach for obtaining these compounds. Based on previous studies, this work explores the α-aminoallylation of ketones and aldehydes using allylboronic acid pinacol ester. Compared to classical methods, the protocol developed reduces the excess of reagents, increasing the environmental friendliness of the process, while maintaining high yields. A wide range of substrates, including various aliphatic, cyclic, and heterocyclic ketones, was studied to identify factors affecting the reactivity. The method was also successfully applied to aldehydes, producing amine-containing building blocks on a large scale. Various work-up procedures were optimized for efficient isolation of the homoallylamines synthesized without the need for chromatographic purification.

Keywords: Petasis reaction; three-component reaction; primary amines; multigram synthesis

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Масштабований синтез первинних амінів на основі реакції Петасіса

Анотація

Ефективний і масштабований синтез гомоаліламінів викликає значний інтерес через потенційне застосування цих сполук у медичній та синтетичній хімії. Трикомпонентна реакція Петасіса є чудовим підходом для їх одержання. Спираючись на попередні дослідження, у цій роботі розглянули α-аміноалілювання кетонів і альдегідів із використанням пінаколового естеру алілборонової кислоти. Проти класичних методів, розроблений протокол зменшує надлишок реагентів, підвищуючи екологічність процесу і водночас зберігаючи високі виходи. Досліджено широкий діапазон субстратів, зокрема різні аліфатичні, циклічні та гетероциклічні кетони, що дозволило виявити фактори, які впливають на реакційну здатність. Метод також успішно застосовано до альдегідів, що дало змогу отримати відповідні будівельні блоки у великому масштабі. Було оптимізовано різні методи очищення для ефективного виділення синтезованих гомоаліламінів без необхідності використання хроматографії.

Ключові слова: реакція Петасіса; трикомпонентна реакція; первинні аміни; багатограмовий синтез

Citation: Herasymchuk, M. V.; Ryabukhin, S. V. A Scalable Approach to Primary Amines via the Petasis Reaction. *Journal of Organic and Pharmaceutical Chemistry* **2025**, *23* (1), 11–21.
https://doi.org/10.24959/ophcj.25.324183
Supporting information: Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra.
Received: *2 December 2024*; **Revised:** *27 February 2025*; **Accepted:** *3 March 2025*

Funding: The work was funded by the internal Enamine grant and the Ministry of Education and Science of Ukraine (grant number 0123U102102).
Conflict of interests: The authors have no conflict of interests to declare.

Introduction

The amino group is a fundamental structural and functional motif in medicinal chemistry, playing a crucial role in molecular interactions and drug design [1]. Its versatility stems from several key advantages. First, it facilitates strong binding interactions between a drug molecule and its biological target by acting as both a hydrogen bond donor and acceptor. Additionally, the presence of a basic nitrogen center allows for fine-tuning of physicochemical properties, which can significantly enhance the ADMET profile of lead compounds [2]. The nitrogen atom, capable of forming three bonds, serves as one of the essential structural elements for controlling molecular geometry and steric bulk. Furthermore, the synthetic accessibility of the NH_2 group makes it an attractive handle for a wide range of chemical transformations, enabling the construction of diverse organic compounds [3].

Taking into account these advantages, medicinal chemistry relies on a rich synthetic toolbox that provides numerous methodologies for introducing amino functionality into target molecules. Of particular interest are approaches that rapidly expand the chemical space, such as diversity-oriented synthesis (DOS) for building amine libraries relevant to fragment-based drug discovery (FBDD) [4]. One such approach is multicomponent reactions (MCRs), which have gained widespread use as complexity-generating transformations, enabling the rapid synthesis of diverse scaffolds of both synthetic and biological interest [5].

Among these, the Petasis reaction stands out as a particularly powerful and versatile three-component transformation. Originally reported in 1993 by Petasis and colleagues, this reaction involves a secondary amine, paraformaldehyde, and (*E*)-vinylboronic acid, providing a streamlined route to allylamines [6]. Over time, it has evolved into a general MCR incorporating amines, carbonyl compounds, and vinyl- or arylboronic acids, functioning as a modular assembly tool for rapidly constructing structurally complex amines from readily available (either synthetically or commercially) precursors. The reaction widespread adoption is reflected in numerous reviews covering its scope [7], including a 2019 comprehensive review by *Wu et al.*, which discusses substrate expansion, non-classical Petasis variants, asymmetric versions using chiral catalysts, and multistep cascade reactions leading to natural product-like heterocycles. Other recent reviews have explored novel catalytic variants [8], asymmetric approaches, and non-directed transformations [9], with the latest comprehensive review by *Pandit and Kamble* providing an up-to-date perspective on the reaction's utility [10].

Compared to other amine synthesis methods, the Petasis reaction offers a remarkable functional group tolerance, accommodating alcohols, carboxylic acids, and amines under mild conditions. Compatible organoboron species include vinylboronate esters, arylboronate esters, and potassium organotrifluoroborates, and the reaction does not require anhydrous or inert conditions. Notably, it serves as a highly selective method for the synthesis of α-amino acids, making it a valuable tool in combinatorial chemistry and drug discovery. The reaction stereoselectivity is particularly pronounced when chiral amines or aldehydes are used as substrates. Beyond its synthetic flexibility, the biological relevance of its products makes it an essential component in the probe compound development and drug discovery efforts. In fact, the Petasis reaction was originally applied in the synthesis of naftifine (Exoderil®), a widely used antifungal agent.

Further advancements in the Petasis reaction have introduced allylboronic components [11, 12], opening new avenues for the synthesis of homoallylamines – highly versatile intermediates in pharmaceutical chemistry, natural product synthesis, and heterocyclic compound development [13]. Despite several reports on allylboron reagents in the Petasis reaction, a comprehensive study of its scope and limitations remains largely unclear.

In our recent studies, we successfully applied this modification to two in-house projects, focusing on the multigram-scale synthesis of 3D-shaped spirocyclic piperidines and azepanes using the Petasis/Grubbs reaction sequence (**Figure 1**, *A*) [14]. Additionally, we developed a scalable preparation of δ-amino acids, employing the Petasis reaction between ketones, allylboronic acid pinacol ester, and methanolic ammonia, followed by the cross-metathesis (**Figure 1**, *B*) [15].

The later approach is particularly valuable as it yields derivatives with an unprotected NH_2 group, allowing for selective functionalization at a later stage, with the possibility of installing protecting groups or additional substituents. Furthermore, this strategy leverages ammonia – a cost-effective and versatile nitrogen source – instead of pre-functionalized amines, adding to its synthetic practicality. The foundational work on this transformation was laid in two seminal studies

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

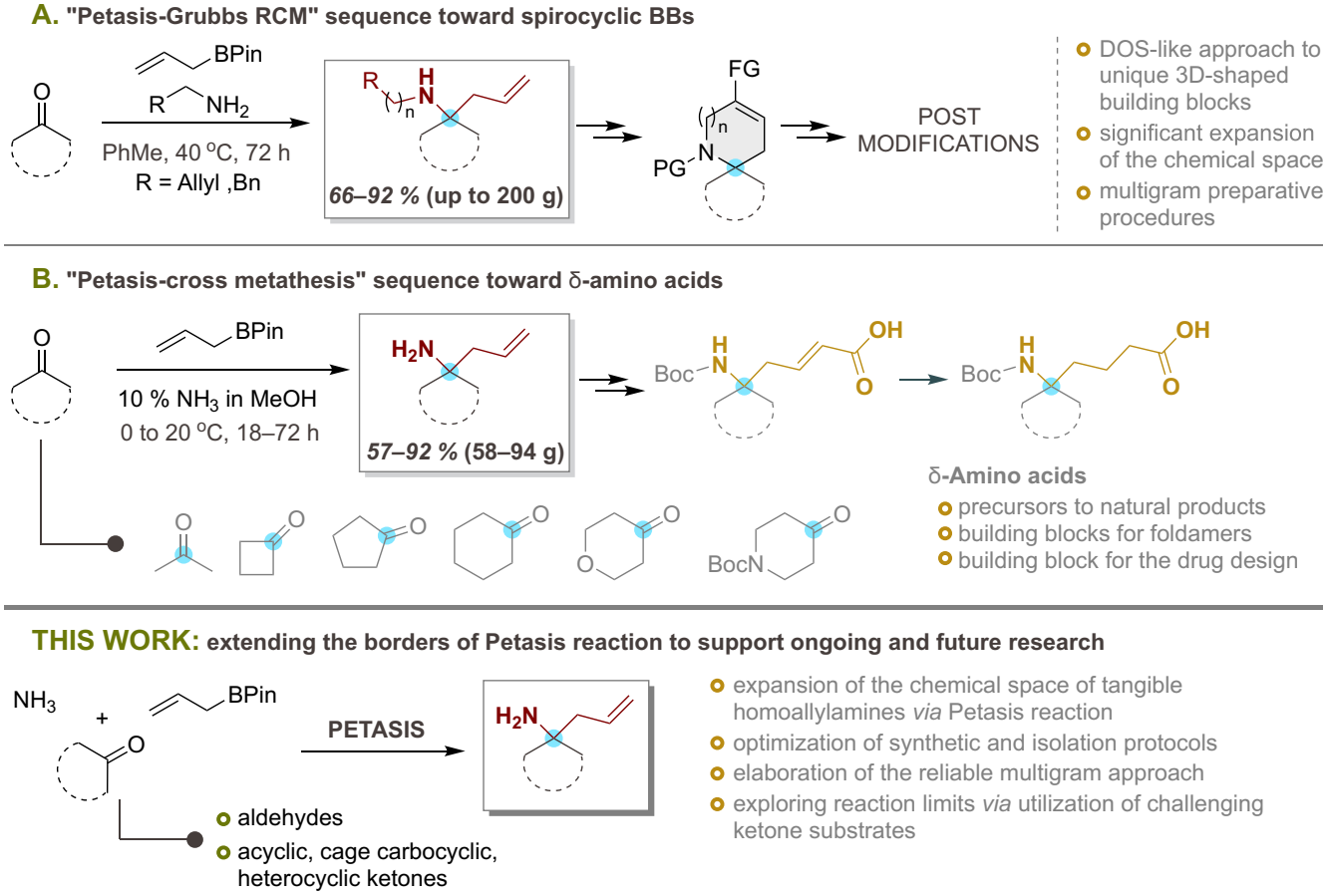

Figure 1. Background and synopsis of the work

by *Kobayashi et al.* [16], which demonstrated its applicability to aldehydes, producing homoallylic primary amines in high yields with excellent chemo- and stereoselectivity. Subsequent studies, such as those by *Dhudshia et al.* [17], extended the reaction to ketones, yet both investigations were conducted at sub-millimolar scales, significantly limiting their commercial potential and practical integration into drug discovery pipelines. Moreover, although this reaction was sometimes used for specific purposes in subsequent years, we have not found any other work exploring its further potential.

To bridge this gap, our recent work has focused on scaling up the Petasis reaction for the δ-amino acid synthesis, using acetone and simple carbo(hetero)cyclic ketones to generate six homoallylamines in moderate-to-high yields at a multigram scale (**Figure 1**, *B*). In this study, we continue expanding the synthetic potential of the Petasis reaction to create a diverse array of primary homoallylamines, with a specific emphasis on optimizing synthetic and isolation protocols, as well as exploring its applicability to structurally distinct ketones (**Figure 1**, *C*). This research is aimed not only at expanding the chemical field available for medicinal chemistry, but also at creating practical and scalable methodologies for integrating the Petasis reaction into modern drug discovery programs.

■ Results and discussion

Kobayashi et al. first demonstrated that the reaction of aldehydes with pinacol allylboronate and a large excess of ammonia (saturated in the solvent) at -10°C efficiently produced homoallylic primary amines with high yields, as well as excellent chemo- and stereoselectivity [16a]. Further optimization of the reaction conditions revealed that α-aminoallylation of aldehydes with allylboronate could also proceed smoothly in aqueous ammonia when surfactants (e.g., dodecylbenzene sulfonic acid) were present [16b]. However, in some cases, significant amounts of the competing alcohol by-product were observed. Expanding on this work, *Dhudshia et al.* explored the use of ketones in α-aminoallylation, identifying allylboronic acid as the most effective boronic reagent, while pinacol allylboronate proved the least efficient among the boronic components tested [17].

Preliminary experiments

At the beginning of our study, we used reaction conditions based on our previous work

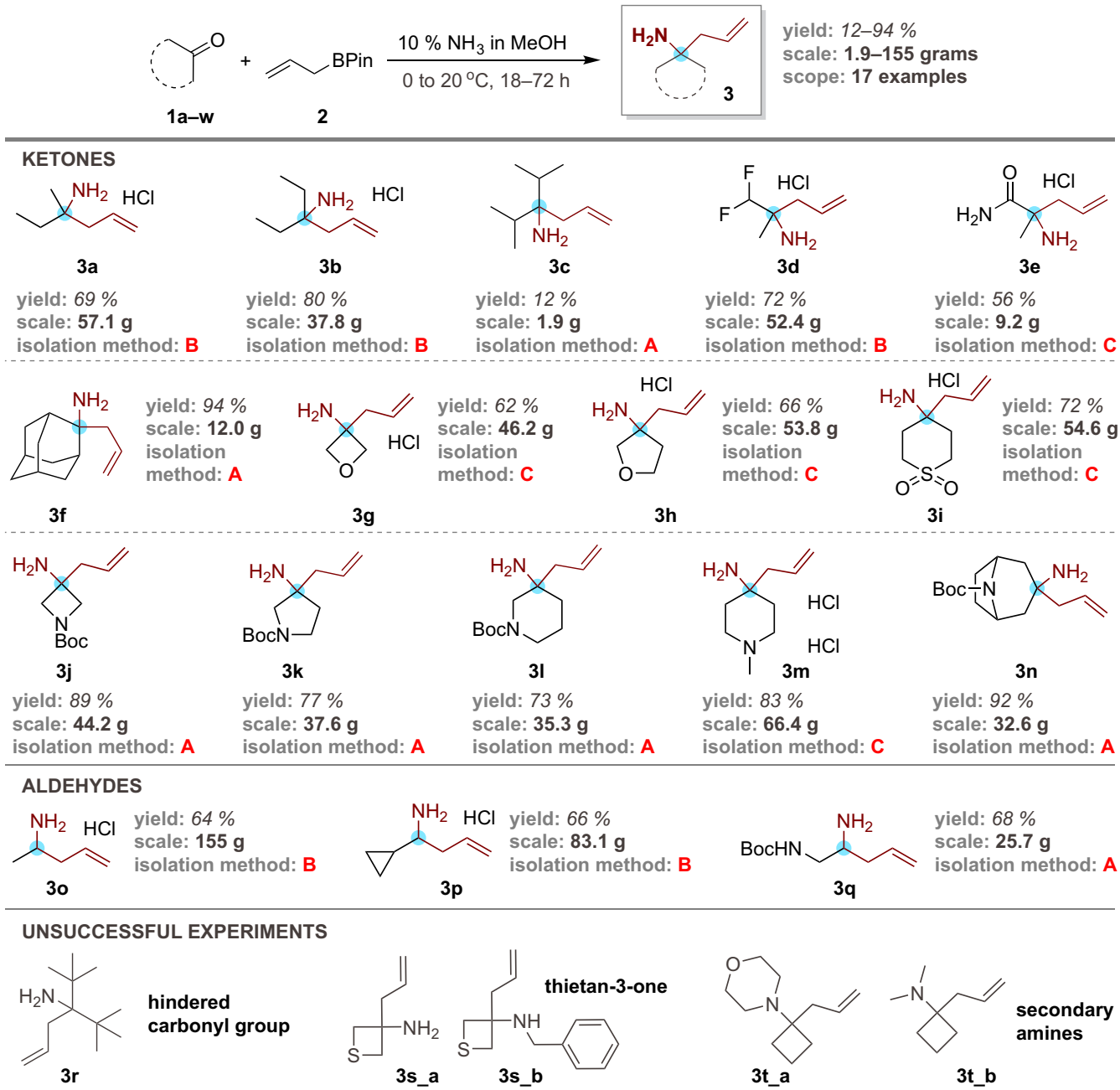

Figure 2. The scope, yields, and scales of achievable homoallylamines **3**

on δ-amino acids [15]. Since allylboronic acid is commercially unavailable, we opted for its readily accessible pinacol ester. The initial reaction was conducted using butanone (**1a**, 1.0 equiv) and allylboronic acid pinacol ester (**2**, 1.1 equiv) in a 10% ammonia solution in methanol (~5.8 equiv) at 0–20°C. Complete consumption of the ketone, monitored by GCMS, was observed in 18 hours. A straightforward acid-base extraction made it possible to obtain homoallylamine **3a** with a yield of 72% (on a 0.01 mol scale). Scaling up the reaction to 0.5 mol of butanone resulted in a comparable efficiency, yielding **3a** in 69% as its hydrochloride salt (for products **3** isolation *see below*). One critical detail observed during scale-up was the mode of addition of the pinacol ester. Adding it gradually from a dropping funnel led to the formation of a solid complex between ammonia and the boronic ester, producing a bulky precipitate that hindered further addition and complicated the process overall. To avoid this issue, the ester should be added in one portion. Notably, in contrast to the protocol used by *Dhudshia et al.*, we successfully reduced the excess of ammonia (from 10 equiv. to 5.8 equiv.) and the boronic ester (from 1.6 equiv. to 1.1 equiv.). Increasing the amounts of these reagents did not enhance the reaction efficiency. These optimizations rendered our method more sustainable and practical for the multigram-scale preparation of homoallylamines.

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

Substrate scope investigation

To evaluate the scope of the protocol, we tested a range of alicyclic and cyclic ketones, as well as aldehydes. Special attention was given to structurally diverse ketones as a recent study highlighted the challenges associated with ketimines in the homoallylic amine synthesis due to their low electrophilicity – contrasting with the well-established allylation of aldimines [18]. However, our successful results with butanone called this assumption into question, prompting a systematic study of the ketone reactivity.

We examined various aliphatic ketones, including functionalized derivatives (**1b–e,r**), cage-shaped adamantanone (**1f**), and heterocyclic ketones containing oxygen (**1g,h**), sulfur (**1i,s**), or nitrogen (**1j–n**).

Experiments proved that linear aliphatic ketones (**1b,d,e**) performed well, yielding homoallylamines in good to high yields on a large scale. However, steric hindrance around the carbonyl significantly impacted the reaction efficiency. For example, introducing two methyl groups in positions α and α' of pentan-2-one (diisopropyl ketone, **1c**) drastically reduced the yield of **3c** to just 12% under prolonged reaction conditions (60°C, 72 h, closed vial). In the case of *di*(*tert*-butyl) ketone (**1r**), no detectable (by ^{1}H NMR) homoallylamine was formed. Interestingly, adamantanone (**1f**), being structurally similar to diisopropyl ketone but conformationally locked, exhibited the highest efficiency among the ketones tested, providing **3f** in the yield of 94%. Apparently, the enhanced reactivity of adamantanone can be attributed to its conformational rigidity, which minimizes conformational penalties and locks the molecule into an optimal conformation for attack by the boronic ester.

Heterocyclic ketones generally gave the expected homoallylamines **3** in good to high yields, regardless of the ring size or heteroatom identity, with all frameworks tested (including *N*-Boc-protected ketones) proving stable under the reaction conditions. The only exception was thietane-3-one, which proved to be a particularly challenging substrate. Literature suggests it behaves as a typical ketone [19], yet the imine formation has not been extensively reported, aside from Ti(O*i*Pr)$_4$-catalyzed reactions with *tert*-butylsulfinamide [20]. Using up to a 20-fold excess of ammonia (standard protocol) or 1.0 equiv. of benzylamine in methanol or toluene at 60°C led to complex mixtures (according to ^{1}H NMR) unsuitable for further purification. A stepwise approach involving the preliminary formation of benzylimine also failed.

We also tested our protocol on secondary amines, using cyclobutanone – a previously successful substrate in our earlier work [15]. However, neither morpholine nor dimethylamine yielded the expected homoallylamines (**3u** and **3w**).

These results suggest that the standard protocol is well-suited for most ketones without requiring activation to enhance electrophilicity as claimed previously.

Application to aldehydes

Compared to ketones, the Petasis reaction involving aldehydes is relatively well-studied. However, despite its practicality and versatility, it is rarely employed to construct amine-containing building blocks with a NH_2 group attached to a secondary carbon atom. For example, 2-aminopent-4-ene, which can be directly synthesized from bulk acetaldehyde, is typically prepared *via* indirect routes, such as the Gabriel synthesis [21] or azide-based strategy [22] exploiting the corresponding commercially available but expensive OH precursor. Recognizing this gap, we sought to demonstrate the general applicability of our method to aldehydes.

We selected acetaldehyde (**1o**), cyclopropanecarboxaldehyde (**1p**), and 2-*N*-Boc-aminoacetaldehyde (**1q**) as representative aldehydes. The latter was synthesized following the procedure of *Dilek et al.* [23] and used immediately without further purification due to its low stability. All three aldehydes performed similarly, yielding amines in the yield of 64–68% and up to 155 g scale.

Although previous Petasis reaction studies examined the competitive formation of alcohol by-products, our primary goal was to develop a robust preparative protocol rather than investigate mechanistic nuances. Nevertheless, analytical results confirmed that the isolated amines **3** contained negligible amounts of the alcohol side product, which was efficiently removed during work-up.

Isolation of homoallylamines

Finally, we would like to discuss protocols for the isolation of the homoallylamines synthesized. While all products could be purified *via* the acid-base extraction, we found that different approaches were optimal depending on the compound volatility and lipophilicity. Volatile amines (**3a,b, d,o,p**) were best isolated as hydrochloride salts (*Work-up Procedure B*). This protocol secures the removal of starting volatiles and possible

alcohol by-products. Another aspect for this group of amines concerns the amount of ammonia equivalents used in the reaction. The experiments indicated that the amount can be reduced twice (from ~5.8 to ~2.9 equiv.) without the loss of the reaction efficiency. This also conveniently reduces the quantity of the acid used for the neutralization of excessive ammonia, which is especially valuable for the large reagent loads. At the same time, amines with a high lipophilicity and a high boiling point (over 100 °C) can be isolated as free bases (*Work-up procedure A*) provided that all ketone is consumed in the reaction (TLC control). Although *Procedure B* is also applicable, this method stands as more convenient due to fewer operations, which again is crucial for the large-scale experiments. This way of isolation is proper for N-Boc ketones (**1j–l,n,q**) and ketones with a large hydrocarbon portion (**1c,f**). Notably, this method seems handier than reported previously for amine **3l** *via* the consecutive treatment of the reaction mixture with citric acid and NaOH [24]. The last group of amines **3** covers polar non-volatile compounds. Their polarity enabled them to be isolated as hydrochlorides from the dioxane solution (*Work-up procedure C*). Importantly, all the methods do not require a chromatography step. These approaches eliminate the need for chromatographic purification, streamlining the large-scale synthesis.

■ Conclusion

A highly efficient and scalable approach for the synthesis of homoallylic amines *via* α-aminoallylation of ketones, using an optimized protocol with allylboronic acid pinacol ester has been found. Key improvements include the reduction of excess reagents, enhanced reaction efficiency, and broad substrate compatibility. Additionally, the methodology extends to aldehydes, providing a streamlined and practical route to amine-containing building blocks. The optimized isolation procedures ensure easy purification without chromatography, providing suitability for the large-scale synthesis. Most of the compounds synthesized were previously unreported or had only been obtained through impractical methods on a mmol scale. Findings of this work contribute to advancing sustainable and practical synthetic strategies in amine chemistry, offering a valuable tool for future applications in pharmaceutical and material sciences.

■ Experimental part

This section contains protocols for the preparation of the compounds described in the paper. All starting compounds were obtained from commercial sources and used without additional purification unless otherwise stated. All solvents were purified according to the standard procedures. All compounds known from the literature are given appropriate references; experimental data comply with the referenced papers.

^{1}H NMR spectra were recorded on a Varian Unity Plus 400 (400 MHz) or a Bruker 170 AVANCE 500 (500 MHz) instrument; ^{13}C NMR spectra were recorded on a Varian Unity Plus 400 (100 MHz), a Bruker 170 AVANCE 500 (126 MHz), or an Agilent ProPulse 600 (151 MHz) spectrometer. The NMR chemical shifts are referenced using the solvent signals at 7.26 and 77.1 ppm for ^{1}H and ^{13}C nuclei, respectively, in $CDCl_3$, and 2.48 and 39.5 ppm for ^{1}H and ^{13}C nuclei, respectively, in DMSO-d_6. LCMS and GCMS analyses were performed using an Agilent LC/MSD SL 1100 instrument [atmospheric pressure electrospray ionization (ES-API)] or an Agilent 5890 Series II 5972 GCMS instrument [electron impact (EI) ionization (70 eV)], respectively. The results for the elemental analysis were obtained at the Analytical Laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine. The composition of hydrochloride salts was determined by the acid-base titration method. Melting points were determined on an MPA100 OptiMelt automated melting point system.

The general procedure for the preparation of homoallylamines

The starting ketone (0.50 mol, 1.0 equiv) was dissolved in a 10% ammonia in methanol solution (500 mL) at 0°C, and the resulting mixture was stirred for 10 min at this temperature (for substrates isolated *via* the *Work-up procedure B* the amount of the ammonia solution can be reduced to 250 mL without a loss of efficiency). Allylboronic acid pinacol ester (92.4 g, 0.55 mol, 1.1 equiv) was added to the reaction mixture in one portion at 0°C. The resulting mixture was warmed to 20°C and stirred at this temperature for 18-72 hours (until full consumption of all the starting ketone was shown by TLC or GCMS).

Work-up procedure A

The volatiles were removed *in vacuo*, and the residue was dissolved in a mixture of hexanes (900 mL) and MTBE (300 mL). The resulting solution was washed with 5% aqueous NaOH (500 mL)

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

and then with water (4×500 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the desired product.

Work-up procedure B

Aqueous HCl solution (12 M, 150 mL) was added to the reaction mixture. The volatiles were removed *in vacuo*, and the residue was dissolved in 10% aqueous NaOH solution (1.0 L). The resulting solution was extracted with the hexanes-MTBE mixture (1:1, 3×500 mL). Combined organic layers were stirred over anhydrous Na_2SO_4, and Na_2SO_4 was filtered off. 4 M HCl solution in dioxane was added to the resulting mixture until the amine solution turns acidic. The precipitate formed was collected *via* filtration, washed with an additional 300 mL of MTBE and dried in vacuum to obtain the desired product as a hydrochloric salt.

Work-up procedure C

The volatiles were removed *in vacuo*, and the residue was treated with 800 mL of MTBE. Solids were removed *via* filtration, and HCl solution in dioxane (4 M, 130 mL) was added to the resulting mixture. The precipitate was collected *via* filtration, washed with an additional 300 mL of MTBE and dried in vacuum, giving the product as a hydrochloric salt.

3-Methylhex-5-en-3-amine hydrochloride (3a) [25]

Synthesized according to the **General procedure** followed by **Work-up procedure B** starting from butan-2-one (**1a**) (40 g, 0.555 mol).

A white solid. Yield – 69% (57.1 g, 0.383 mol). M. p. 217–220ºC. Anal. Calcd for $C_7H_{16}ClN$, %: C 56.18, H 10.78, N 9.36. Found, %: C 56.32, H 10.70, N 9.53. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 0.86 (3H, t, J = 7.5 Hz), 1.16 (3H, s), 1.54 (2H, q, J = 7.7 Hz), 2.25–2.36 (2H, m), 5.12–5.20 (2H, m), 5.75–5.87 (1H, m), 8.09 (3H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 132.00, 119.60, 55.69, 41.30, 30.01, 22.56, 7.37. LCMS (ES-API), m/z: 114.2 $[M-Cl]^+$.

3-Ethylhex-5-en-3-amine hydrochloride (3b) [26]

Synthesized according to the **General procedure** followed by **Work-up procedure B** starting from pentan-3-one (**1b**) (25 g, 0.260 mol).

A white solid. Yield – 80% (37.8 g, 0.232 mol). M. p. >300ºC. Anal. Calcd for $C_8H_{18}ClN$, %: C 58.70, H 11.08, N 8.56. Found, %: C 58.78, H 11.12, N 8.41. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 0.85 (6H, td, J = 7.5, 2.1 Hz), 1.49–1.57 (4H, m), 2.29 (2H, d, J = 7.3 Hz), 5.12–5.22 (2H, m), 5.82 (1H, dddd, J = 17.3, 14.5, 7.3, 2.0 Hz), 8.02 (3H, s). ^{13}C NMR (151 MHz, DMSO-d_6), δ, ppm: 7.56, 28.22, 39.76, 58.62, 120.04, 132.37. LCMS (ES-API), m/z: 128.2 $[M-Cl]^+$.

3-Isopropyl-2-methylhex-5-en-3-amine (3c)

Synthesized according to the **General procedure** (The reaction mixture was stirred at 60 ºC for 72h in a closed vial) followed by **Work-up procedure A** starting from 2,4-dimethylpentan-3-one (**1c**) (11.4 g, 0.100 mol).

A colorless oil. Yield – 12% (1.9 g, 12.2 mmol). Anal. Calcd for $C_{10}H_{21}N$, %: C 77.35, H 13.63, N 9.02. Found, %: C 77.27, H 13.57, N 9.13. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.65–0.86 (2H, br. s), 0.9 (12H, t, J = 6.6 Hz), 1.72–1.87 (2H, m), 2.15 (2H, dd, J = 7.4, 1 Hz), 4.89–5.07 (2H, m), 5.79–5.92 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 17.35, 17.65, 34.10, 39.83, 57.04, 116.57, 136.07. LCMS (ES-API), m/z: 156.2 $[M+H]^+$.

1,1-Difluoro-2-methylpent-4-en-2-amine hydrochloride (3d)

Synthesized according to the **General procedure** followed by **Work-up procedure B** starting from 1,1-difluoropropan-2-one (**1d**) (40 g, 0.425 mol).

A white solid. Yield – 72% (52.4 g, 0.306 mol). M. p. 223–226 ºC. Anal. Calcd for $C_6H_{12}ClF_2N$, %: C 41.99, H 7.05, N 8.16. Found, %: C 42.08, H 7.10, N 8.29. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.26 (3H, s), 2.46 (2H, d, J = 3.1 Hz), 5.19–5.26 (2H, m), 5.77–5.89 (1H, m), 6.19 (1H, t, J = 54.2 Hz), 8.80 (3H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 16.92, 37.13, 56.35 (t, $^2J_{CF}$ = 21 Hz), 115.45 (t, $^1J_{CF}$ = 247 Hz), 120.85, 130.00. ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: -131.70 (d, J = 281.3 Hz), -130.73 (d, J = 281.5 Hz). LCMS (ES-API), m/z: 241.2 $[M-Cl]^+$.

2-Amino-2-methylpent-4-enamide hydrochloride (3e)

Synthesized according to the **General procedure** followed by **Work-up procedure C** starting from ethyl 2-oxopropanoate (**1e**) (11.6 g, 0.100 mol).

A white solid. Yield – 56% (9.2 g, 55.9 mmol). M. p. 106–110ºC. Anal. Calcd for $C_6H_{13}ClN_2O$, %: C 43.77, H 7.96, N 17.02. Found, %: C 43.84, H 7.89, N 17.14. ^{1}H NMR (400 MHz, DMSO), δ, ppm: 1.47 (3H, s), 2.54–2.72 (2H, m), 5.03–5.25 (2H, m), 5.86–5.60 (1H, m), 7.53 (1H, br. s), 7.90 (1H, br. s), 8.31 (3H, br. s). ^{13}C NMR (101 MHz, DMSO), δ, ppm: 22.33, 41.31, 59.68, 120.92, 131.30, 172.57. LCMS (ES-API), m/z: 129.2 $[M+H]^+$.

(1*r*,3*r*,5*r*,7*r*)-2-Allyladamantan-2-amine (3f)

Synthesized according to the **General procedure** followed by **Work-up procedure A** starting from (1*r*,3*r*,5*r*,7*r*)-adamantan-2-one (**1f**) (10.0 g, 66.7 mmol).

A colorless oil. Yield – 94% (12.0 g, 62.6 mmol). Anal. Calcd for $C_{13}H_{21}N$, %: C 81.61, H 11.06, N 7.32. Found, %: C 81.79, H 11.12, N 7.19. ^{1}H NMR (400 MHz, Chloroform-*d*), *δ*, ppm: 1.34 (2H, s), 1.51–1.62 (4H, m), 1.62–1.71 (4H, m), 1.82 (2H, q, *J* = 3.6 Hz), 1.96–2.04 (2H, m), 2.04–2.12 (2H, m), 2.36 (2H, d, *J* = 7.5 Hz), 5.07 – 5.15 (2H, m), 5.79–5.97 (1H, m). ^{13}C NMR (101 MHz, Chloroform-*d*), *δ*, ppm: 134.24, 117.96, 54.55, 43.11, 38.96, 37.37, 33.90, 33.00, 27.58, 27.32. LCMS (ES-API), m/z: 192.2 $[M+H]^+$.

3-(Prop-2-en-1-yl)oxetan-3-amine hydrochloride (3g)

Synthesized according to the **General procedure** followed by **Work-up procedure C** starting from oxetan-3-one (**1g**) (36.0 g, 0.50 mol).

A beige solid. Yield – 62% (46.2 g, 0.31 mol). M. p. 153–155ºC. Anal. Calcd for $C_6H_{12}ClNO$, %: C 48.17, H 8.08, N 9.36. Found, %: C 48.03, H 8.14, N 9.46. ^{1}H NMR (500 MHz, DMSO-d_6), *δ*, ppm: 2.61 (2H, d, *J* = 7.2 Hz), 4.41 (2H, d, *J* = 7.1 Hz), 4.62 (2H, d, *J* = 7.1 Hz), 5.21–5.31 (2H, m), 5.94 (1H, ddt, *J* = 17.4, 10.3, 7.2 Hz), 8.85 (3H, s). ^{13}C NMR (151 MHz, DMSO-d_6), *δ*, ppm: 38.73, 55.21, 76.91, 121.06, 131.54. LCMS (ES-API), m/z: 114.0 $[M-Cl]^+$.

3-(Prop-2-en-1-yl)oxolan-3-amine hydrochloride (3h) [27]

Synthesized according to the **General procedure** followed by **Work-up procedure C** starting from dihydrofuran-3(2*H*)-one (**1h**) (43.0 g, 0.50 mol).

A beige solid. Yield – 66% (53.8 g, 0.33 mol). M. p. 159–162ºC. Anal. Calcd for $C_7H_{14}ClNO$, %: C 51.38, H 8.62, N 8.56. Found, %: C 51.49, H 8.58, N 8.45. ^{1}H NMR (400 MHz, DMSO-d_6), *δ*, ppm: 2.01 (2H, t, *J* = 7.2 Hz), 2.52–2.57 (2H, m), 3.57 (1H, d, *J* = 9.8 Hz), 3.70–3.80 (2H, m), 3.93 (1H, q, *J* = 7.8 Hz), 5.15–5.26 (2H, m), 5.87 (1H, ddt, *J* = 17.2, 10.0, 7.2 Hz), 8.48 (3H, s). ^{13}C NMR (126 MHz, DMSO-d_6), *δ*, ppm: 131.85, 120.11, 73.76, 66.57, 61.86, 34.86. LCMS (ES-API), m/z: 128.2 $[M-Cl]^+$.

4-Allyl-4-aminotetrahydro-2*H*-thiopyran 1,1-dioxide hydrochloride (3i)

Synthesized according to the **General procedure** followed by **Work-up procedure C** starting from tetrahydro-4*H*-thiopyran-4-one 1,1-dioxide (**1i**) (50.0 g, 0.337 mol).

A white solid. Yield – 72% (54.6 g, 0.243 mol). M. p. 220–223ºC. Anal. Calcd for $C_8H_{16}ClNO_2S$, %: C 42.57, H 7.14, N 6.21. Found, %: C 42.70, H 7.04, N 6.26. ^{1}H NMR (400 MHz, DMSO-d_6), *δ*, ppm: 2.05–2.26 (4H, m), 2.53–2.59 (2H, m), 3.19 (2H, ddd, *J* = 14.0, 8.4, 3.6 Hz), 5.24 (1H, dd, *J* = 10.1, 2.2 Hz), 5.29 (1H, dd, *J* = 17.0, 2.2 Hz), 5.81–5.96 (1H, m), 8.56 (3H, s). ^{13}C NMR (126 MHz, DMSO-d_6), *δ*, ppm: 31.36, 45.52, 52.90, 121.02, 130.89. LCMS (ES-API), m/z: 190.2 $[M-Cl]^+$.

***tert*-Butyl 3-allyl-3-aminoazetidine-1-carboxylate (3j)**

Synthesized according to the **General procedure** followed by **Work-up procedure A** starting from *tert*-butyl 3-oxoazetidine-1-carboxylate (**1j**) (40 g, 0.234 mol).

A yellow oil. Yield – 89% (44.2 g, 0.208 mol). Anal. Calcd for $C_{11}H_{20}N_2O_2$, %: C 62.24, H 9.50, N 13.20. Found, %: C 62.08, H 9.61, N 13.34. ^{1}H NMR (400 MHz, Chloroform-*d*), *δ*, ppm: 1.45 (9H, d, *J* = 1.2 Hz), 1.73 (2H, s), 2.39–2.46 (2H, m), 3.64 (2H, d, *J* = 8.6 Hz), 3.82–3.89 (2H, m), 5.16–5.26 (2H, m), 5.74–5.89 (1H, m). ^{13}C NMR (126 MHz, Chloroform-*d*), *δ*, ppm: 27.86, 43.49, 50.42, 61.80, 78.94, 118.90, 131.96, 155.96. LCMS (ES-API), m/z: 157.2 $[M-C_4H_8+H]^+$.

***tert*-Butyl 3-allyl-3-aminopyrrolidine-1-carboxylate (3k)**

Synthesized according to the **General procedure** followed by **Work-up procedure A** starting from *tert*-butyl 3-oxopyrrolidine-1-carboxylate (**1k**) (40 g, 0.216 mol).

A yellow oil. Yield – 77% (37.6 g, 0.166 mol). Anal. Calcd for $C_{12}H_{22}N_2O_2$, %: C 63.69, H 9.80, N 12.38. Found, %: C 63.81, H 9.75, N 12.47. ^{1}H NMR (500 MHz, Chloroform-*d*), *δ*, ppm 1.45 (11H, s), 1.64–1.72 (1H, m), 1.84 (1H, dt, *J* = 12.2, 8.7 Hz), 2.27 (2H, d, *J* = 7.4 Hz), 3.08–3.31 (2H, m), 3.46 (2H, ddd, *J* = 20.9, 10.6, 4.4 Hz), 5.16 (2H, dd, *J* = 13.6, 9.1 Hz), 5.82 (1H, dd, *J* = 16.2, 8.8 Hz). ^{13}C NMR (126 MHz, Chloroform-*d*), *δ*, ppm: 27.99, 37.37, 37.89, 43.73, 44.01, 44.19, 44.33, 57.46, 57.84, 58.62, 78.67, 118.58, 132.97, 154.18. LCMS (ES-API), m/z: 171.2 $[M-C_4H_8+H]^+$.

***tert*-Butyl 3-allyl-3-aminopiperidine-1-carboxylate (3l)**

Synthesized according to the **General procedure** followed by **Work-up procedure A** starting from *tert*-butyl 3-oxopiperidine-1-carboxylate (**1l**) (40 g, 0.201 mol).

A yellow oil. Yield – 73% (35.3 g, 0.147 mol). Anal. Calcd for $C_{13}H_{24}N_2O_2$, %: C 64.97, H 10.07, N 11.66. Found, %: C 65.15, H 10.12, N 11.51. ^{1}H NMR (500 MHz, Chloroform-*d*), *δ*, ppm:

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

1.22–1.29 (1H, m), 1.45 (10H, s), 1.49–1.69 (4H, m), 2.11 (1H, dd, J = 13.7, 8.0 Hz), 2.17 (1H, dd, J = 13.8, 7.0 Hz), 3.01–3.63 (4H, m), 5.09–5.18 (2H, m), 5.80–5.92 (1H, m). ^{13}C NMR (151 MHz, $CDCl_3$), δ, ppm: 21.56, 24.60, 28.42, 36.79, 43.57, 50.27, 55.10, 79.54, 119.00, 133.13, 155.16. LCMS (ES-API), m/z: 241.2 $[M+H]^+$.

1-Methyl-4-(prop-2-en-1-yl)piperidin-4-amine dihydrochloride (3m)

Synthesized according to the **General procedure** followed by **Work-up procedure C** starting from 1-methylpiperidin-4-one (**1m**) (40.0 g, 0.354 mol).

A yellow solid. Yield – 83% (66.4 g, 0.294 mol). M. p. 192–195°C. Anal. Calcd for $C_9H_{20}Cl_2N_2$, %: C 47.58, H 8.87, N 12.33. Found, %: C 47.44, H 8.92, N 12.26. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.92–2.13 (4H, m), 2.72 (5H, s), 3.10 (2H, s), 3.61 (2H, s), 5.24 (2H, t, J = 12.3 Hz), 5.80–5.95 (1H, m), 8.64 (3H, s), 11.02 (1H, s). ^{13}C NMR (151 MHz, DMSO-d_6), δ, ppm: 30.16, 40.52, 42.26, 48.06, 52.08, 121.27, 131.28. LCMS (ES-API), m/z: 155.4 $[M-Cl]^+$.

***tert*-Butyl 3-allyl-3-amino-8-azabicyclo-[3.2.1]octane-8-carboxylate (3n)**

Synthesized according to the **General procedure** followed by **Work-up procedure A** starting from *tert*-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (**1n**) (30 g, 0.133 mol).

A white solid. Yield – 92% (32.6 g, 0.123 mol). M. p. 53–55°C. Anal. Calcd for $C_{15}H_{26}N_2O_2$, %: C 67.63, H 9.84, N 10.52. Found, %: C 67.48, H 10.01, N 10.39. ^{1}H NMR (400 MHz, Chloroform-*d*), δ, ppm: 1.00 (2H, s), 1.33 (2H, d, J = 14.0 Hz), 1.44 (9H, s), 1.82 (3H, d, J = 30.8 Hz), 1.93 (3H, d, J = 7.6 Hz), 2.13 (2H, d, J = 6.3 Hz), 4.10 (1H, s), 4.20 (1H, s), 4.97–5.07 (1H, m), 5.11 (1H, dd, J = 10.3, 2.3 Hz), 5.72 (1H, ddt, J = 17.4, 10.2, 7.4 Hz). ^{13}C NMR (126 MHz, Chloroform-*d*), δ, ppm: 24.33, 27.09, 27.76, 28.00, 41.42, 42.29, 49.59, 52.30, 53.09, 54.33, 78.40, 118.54, 132.93, 153.02. GCMS (EI, 70 eV), m/z: 267.2 $[M]^{+\cdot}$.

Pent-4-en-2-amine hydrochloride (3o) [21]

Synthesized according to the **General procedure** followed by **Work-up procedure B** starting from acetaldehyde (**1o**) (88.1 g, 2.00 mol).

A white solid. Yield – 64% (155 g, 1.28 mol). M. p. 86–88°C. Anal. Calcd for $C_5H_{12}ClN$, %: C 49.38, H 9.95, N 11.52. Found, %: C 49.53, H 10.08, N 11.36. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.16 (3H, d, J = 6.5 Hz), 2.21 (1H, dt, J = 14.7, 7.8 Hz), 2.41 (1H, ddd, J = 13.9, 6.7, 5.2 Hz), 3.20 (1H, p, J = 6.0 Hz), 5.09–5.20 (2H, m), 5.78 (1H, ddt, J = 17.2, 10.2, 7.1 Hz), 8.10 (3H, s). ^{13}C NMR (151 MHz, DMSO-d_6), δ, ppm: 18.11, 38.77, 46.65, 119.06, 133.82. LCMS (ES-API), m/z: 86.2 $[M-Cl]^+$.

1-Cyclopropylbut-3-en-1-amine hydrochloride (3p) [28]

Synthesized according to the **General procedure** followed by **Work-up procedure B** starting from cyclopropanecarboxaldehyde (**1p**) (60.0 g, 0.856 mol).

A white solid. Yield – 66% (83.1 g, 0.565 mol). M. p. 174–177°C. Anal. Calcd for $C_7H_{14}ClN$, %: C 56.94, H 9.56, N 9.49. Found, %: C 57.11, H 9.49, N 9.58. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 0.30 (1H, dq, J = 9.8, 4.8 Hz), 0.35–0.61 (3H, m), 0.90 (1H, qt, J = 8.8, 4.8 Hz), 2.43 (3H, tt, J = 10.5, 6.7 Hz), 5.07–5.22 (2H, m), 5.86 (1H, ddt, J = 17.1, 10.0, 6.8 Hz), 8.18 (3H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 3.28, 4.11, 13.32, 37.48, 55.48, 118.22, 133.36. LCMS (ES-API), m/z: 112.2 $[M-Cl]^+$.

***tert*-Butyl (2-aminopent-4-en-1-yl)carbamate (3q)** [29]

Synthesized according to the **General procedure** followed by **Work-up procedure A** starting from *tert*-butyl (2-oxoethyl)carbamate (**1q**) (30 g, 0.188 mol).

A colorless oil. Yield – 68% (25.7 g, 0.128 mol). Anal. Calcd for $C_{10}H_{20}N_2O_2$, %: C 59.97, H 10.07, N 13.99. Found, %: C 60.11, H 10.18, N 13.88. ^{1}H NMR (500 MHz, Chloroform-*d*), δ, ppm: 1.36 (2H, s), 1.43 (9H, s), 2.00 (1H, dt, J = 14.4, 7.4 Hz), 2.18–2.27 (1H, m), 2.90 (2H, pd, J = 7.9, 3.9 Hz), 3.23 (1H, dd, J = 16.8, 8.1 Hz), 4.96 (1H, s), 5.07–5.14 (2H, m), 5.71–5.83 (1H, m). ^{13}C NMR (151 MHz, Chloroform-*d*), δ, ppm: 28.38, 40.27, 46.65, 50.58, 79.19, 117.84, 134.88, 156.18. GCMS (EI, 70 eV), m/z: 127.0 $[M-C_4H_9O]^+$.

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

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Journal of Organic and Pharmaceutical Chemistry

Original Research

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UDC 54.057:547.812[547.315.2+547-316]

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Danishefsky's Diene *vs* Rawal's Diene in [4+2] *Hetero*-Diels-Alder Reactions with Aldehydes

Abstract

The Diels-Alder reaction remains one of the most versatile and widely employed cycloaddition strategies in synthetic organic chemistry. The development of functionalized dienes, particularly Danishefsky's diene (DD) and Rawal's diene (RD), has significantly expanded the synthetic potential of this reaction. A comparative analysis of these two dienes has been performed in this study; in particular their reactivity with aldehyde dienophiles, leading to pyran derivatives – key intermediates in the pharmaceutical synthesis, has been analyzed. The reactivity, scope, and reaction conditions for both dienes have been assessed. Although DD is well studied and widely used in synthetic protocols, RD exhibits higher reactivity, especially under mild thermal conditions, eliminating the need for the Lewis acid catalysis. Experimental results for eight aldehyde substrates have revealed key differences in their efficiency and scalability. The data obtained emphasize the complementary nature of DD and RD in synthetic applications, providing valuable recommendations for optimizing diene selection in complex organic transformations.

Keywords: Danishefsky's diene; Rawal's diene; Diels-Alder reaction; aldehyde; pyran

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Дієн Данішефського та дієн Раваля в реакціях [4+2] *гетеро*-Дільса-Альдера з альдегідами

Анотація

Реакція Дільса-Альдера залишається однією з найуніверсальніших і найширше застосовуваних стратегій циклоприєднання в синтетичній органічній хімії. Розвиток функціоналізованих дієнів, зокрема дієну Данішефського (DD) і дієну Раваля (RD), суттєво розширив синтетичний потенціал цієї реакції. У цьому дослідженні проведено порівняльний аналіз цих двох дієнів, зокрема їхньої реакційної здатності з альдегідними дієнофілами, що дозволяє одержати похідні піранів – ключові проміжні сполуки у фармацевтичному синтезі. Було оцінено реакційну здатність, сферу застосування та умови проведення реакцій для обох дієнів. Хоча DD добре вивчений і широко використовуваний у синтетичних протоколах, RD демонструє вищу реакційну здатність, особливо у м'яких термічних умовах, усуваючи потребу в каталізі кислотами Льюїса. Експериментальні результати для восьми альдегідних субстратів виявили ключові відмінності у їхній ефективності та масштабованості. Отримані дані підкреслюють взаємодоповняльний характер DD і RD у синтетичних застосуваннях, надаючи цінні рекомендації для оптимального вибору дієну в складних органічних перетвореннях.

Ключові слова: дієн Данішефського; дієн Раваля; реакція Дільса-Альдера; альдегід; піран

Citation: Shamrai, O. I.; Zarudnitskii, E. V. Danishefsky's Diene *vs* Rawal's Diene in [4+2] *Hetero*-Diels-Alder Reactions with Aldehydes. *Journal of Organic and Pharmaceutical Chemistry* **2025**, *23* (1), 21–29.
https://doi.org/10.24959/ophcj.25.324470
Supporting information: Copies of ^{1}H, ^{13}C NMR spectra of dihydropyranones and ^{1}H NMR spectra of crude mixtures.
Received: *4 January 2025*; **Revised:** *2 March 2025*; **Accepted:** *5 March 2025*

Funding: The author received no specific funding for this work.
Conflict of interests: The authors have no conflict of interests to declare.

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

Introduction

Since its discovery by Diels and Alder in 1928 [1], the synthetic potential of the Diels-Alder reaction has been significantly expanded through modifications of both the diene and dienophile components [2]. While a vast array of dienophiles has been explored, the key challenge often lies in selecting or designing a suitable diene that ensures the sufficient reactivity toward diverse dienophiles [3]. Early empirical observations, later supported by theoretical and computational studies, showed that incorporating lone-pair-containing heteroatoms into the diene framework increases the rate and regioselectivity of cycloaddition reactions [4, 5]. This understanding played an important role in the development of more reactive and functionally diverse dienes.

Among the first heteroatom-substituted dienes used in [4+2] cycloadditions were simple dialkoxy dienes, followed soon by monoalkoxy variants (**Figure**, *A*, upper row) [6]. However, the synthetic applications of these dienes were significantly limited, primarily due to the challenges associated with their preparation. A major breakthrough came with the discovery of efficient methods for converting carbonyl compounds into silyl enol ethers, which facilitated the synthesis of various siloxydienes – a class that ultimately surpassed simple alkoxy dienes in popularity.

One of the most significant advances in siloxy dienes was the development of 1-methoxy-3-trimethylsiloxy-1,3-butadiene in 1974 [6f], commonly known after its inventor as Danishefsky's diene. This diene gained the widespread use due to its high reactivity toward a variety of dienophiles, including heterodienophiles [7]. Its introduction marked a major milestone in *hetero*-Diels-Alder reactions, enabling the regioselective synthesis of pyrans and piperidines while allowing for further functional group manipulations. These advantages have led to extensive research efforts aimed at refining its reactivity profile.

Parallel to the development of alkoxy and siloxy dienes, researchers explored amino-substituted dienes (**Figure**, *A*, lower row), which also played a crucial role in the evolution of the Diels-Alder reaction. The first simple 1-amino-substituted diene, despite its relative instability, was found to be highly reactive toward various dienophiles [8]. The synthesis of 1-*N*-acylamino-1,3-butadienes provided a more stable alternative, enabling applications in the alkaloid synthesis [9]. Later, 2-aminodienes demonstrated promising results in asymmetric Diels-Alder reactions [10]. Despite their significance, the combination of siloxy and amino groups in a single diene received little attention. Rare examples included cyclopentene-containing diene [11] and cyclic *N*-acylamino dienes [12]. That was until 1997, when *Rawal* carefully investigated this approach to increasing the diene's reactivity [13]. The Rawal's subsequent studies emphasized unique structural features of the aminosiloxy molecular platform, its potential as a building block, and a promising alternative to Danishefsky-type dienes [14].

Over the decades of experiments, exactly two dienes – Danishefsky's diene and Rawal's diene – have emerged as the most prominent choices for the Diels-Alder type transformations due to their distinct reactivity patterns and broad synthetic utility. Despite their structural differences, both dienes efficiently interact with electron-deficient π-systems to yield diverse and functionally rich products. Nevertheless, there are three distinct points that make these two dienes unequal in terms of synthetic applicability – reactivity, substrate scope, and reaction conditions (**Figure**, *B*). The initial and follow-up evaluations of the relative reactivity of Rawal's and Danishefsky's dienes determined that the aminosiloxy diene was 25 to 3000 times more reactive than the 1-methoxy-3-siloxy diene in the reaction with alkenes activated with EWGs [14, 15]. Moreover, the presence of more nucleophilic amine group, and advantageous positioning of enamine and enol ether units in Rawal's diene enhances its reactivity in Diels-Alder reactions, enabling it to overcome synthetic challenges that Danishefsky's diene cannot address. One of such cases was reported by *Gagnon* and *Danishefsky* in the project aimed to reach a polycyclic alkaloid Xestocyclamine A isolated from a marine sponge *Xestospongia sp.* [16]. In this work, the dienes were found to have different activity toward the enone moiety. Less pronounced electron-rich nature of Danishefsky's diene compared to the Rawal's counterpart cut off some dienophile substrates from its scope. Thus, while both dienes are still viable options for alkene, alkyne, and aldehyde dienophiles, ketones are a tough nut to crack for Danishefsky's diene and remain a privilege option of the aminosiloxy diene. A direct consequence of the lower reactivity of the siloxy diene is the need for specific reaction conditions when engaging with aldehyde dienophiles and their *aza*-analogs. In these cases, a Lewis acid catalyst is essential to facilitate the effective interaction between the

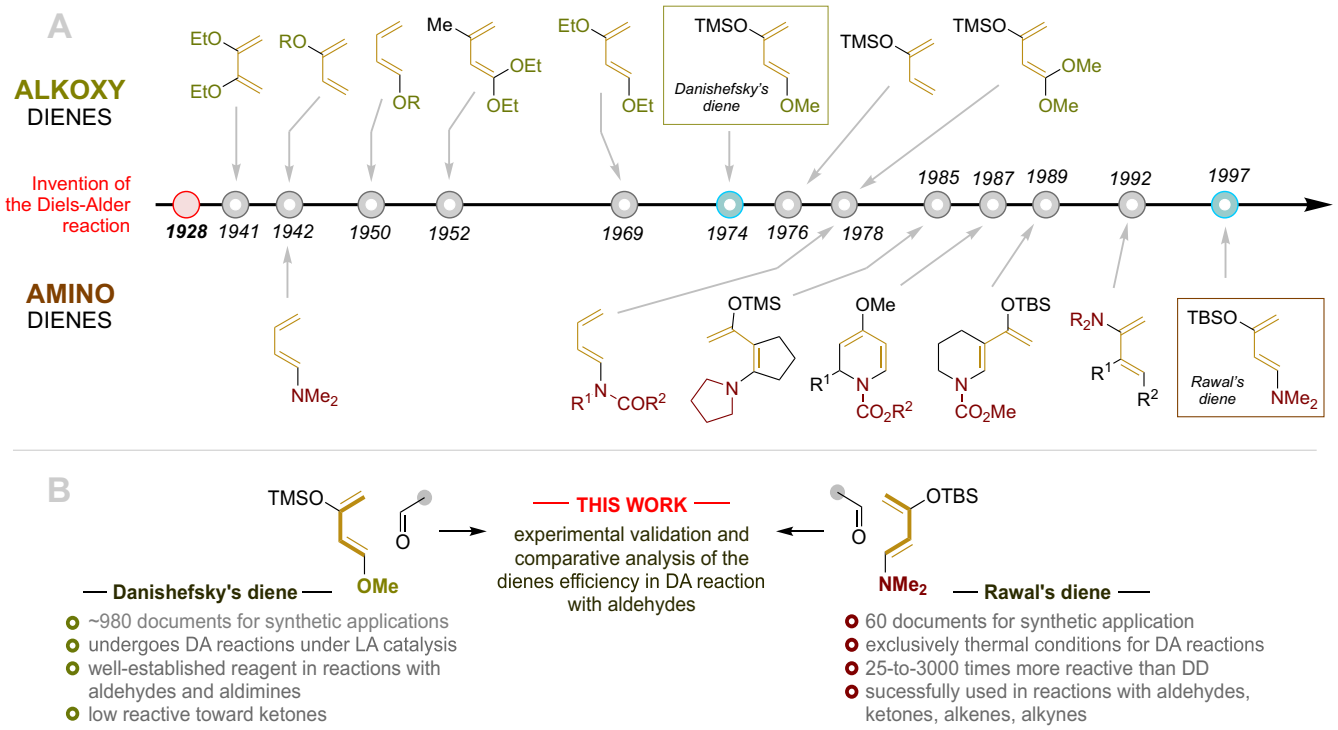


Figure. (**A**) The timeline of selected works related to electron-rich dienes used in the Diels-Alder reaction; (**B**) The synopsis of Danishefsky's and Rawal's dienes and the aim of the work

siloxy diene and the C=O(N) dienophile [7]. In contrast, Rawal's diene operates exclusively under thermal conditions, regardless of the dienophile, making it particularly advantageous for acid-sensitive substrates and challenging synthetic targets.

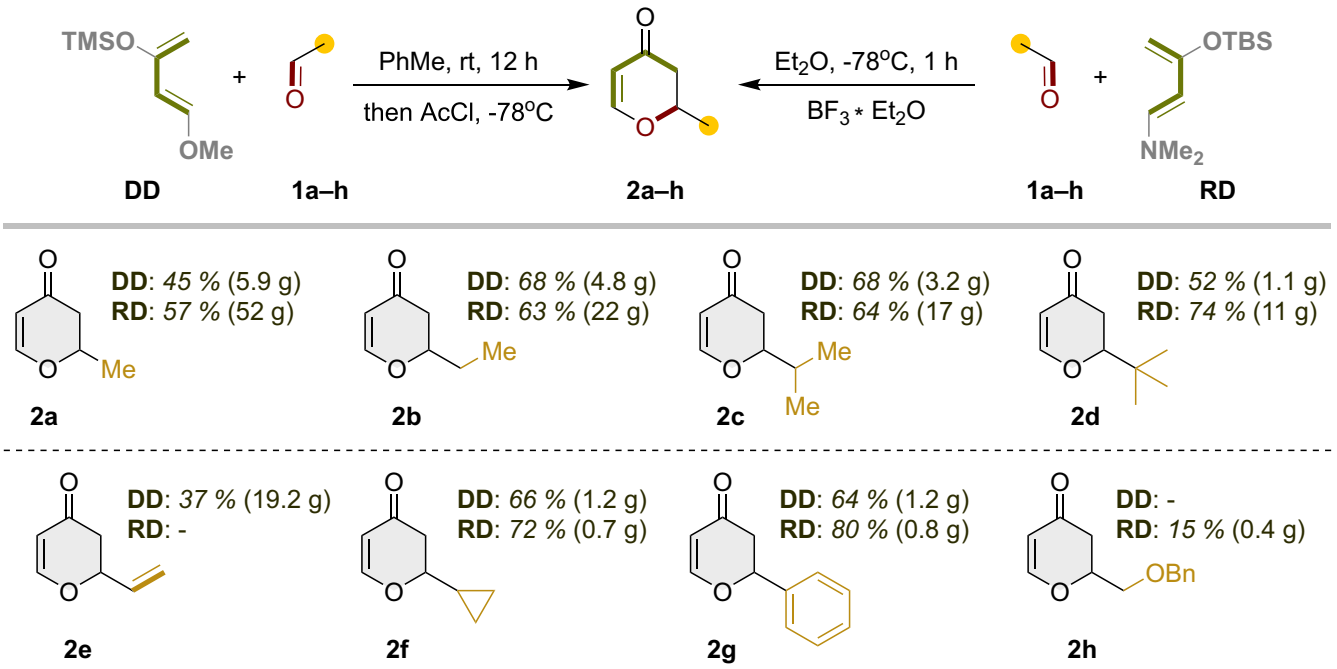
For borderline cases in synthetic organic chemistry, where several options are possible, choosing the optimal reagent for the reaction is crucial to achieve high yield, selectivity, and efficiency while minimizing side reactions and waste. The right choice ensures cost-effectiveness, scalability, and reproducibility, ultimately enhancing the success of synthetic methodologies in drug discovery, materials science, and industrial applications. From the discussion above, aldehydes are a typical substrate in hetero-Diels-Alder reactions posing a problem of choice of a diene counterpart. While Rawal's diene is seemingly a better variant owing to its higher reactivity, it must be acknowledged that Danishefsky's diene has been far more extensively studied, with over 15 times as many publications dedicated to its reactivity in Diels-Alder reactions (**Figure**, *B*). From years of experience of our synthetic group, most researchers tend to choose the more studied and reliable Danishefsky's diene rather than its powerful alternative. In this work, we are willing to present a comparative analysis of these two dienes, examining and re-evaluating their substrate scope, reaction conditions, yields, and selectivity in the *hetero*-Diels-Alder reaction with aldehydes. By evaluating their advantages and limitations, we aim to emphasize their complementary nature and give an idea of their optimal use in synthetic applications.

This work is further enriched by two key factors. First, to the best of our knowledge, there are currently no studies that specifically compare Danishefsky's diene (DD) and Rawal's diene (RD) in reactions with aldehydes. Second, the products of the transformation – 2,3-dihydro-4*H*-pyran-4-ones – are valuable intermediates for the synthesis of important pharmaceutical compounds [17].

■ Results and discussion

First and foremost, this paper aims to assess the convenience and efficiency of using dienes specifically for routine work. We did not seek to determine the most optimal reaction conditions, but instead employed the most commonly used ones (**Scheme**). For the reaction of aldehydes with the MeO-substituted siloxydiene, we followed the conditions reported by *Danishefsky* and *Kerwin* in one of their seminal works on the subject [18]. These conditions involve a low-temperature reaction in the presence of boron trifluoride etherate as a Lewis acid catalyst, followed by quenching with sodium bicarbonate. The aminosiloxy diene reacted with aldehydes in a two-step process under conditions we recently described in our work on the scaled synthesis of Rawal's diene [19].

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



Scheme. The results of *hetero*-DA reactions with Danishefsky's and Rawal's dienes

The first step proceeds under thermal control in a toluene solution at room temperature, without additives, using a 2–4-fold excess of aldehydes. The resulting cycloadduct was not isolated, but directly subjected to the "deprotection" step, efficiently performed with acetyl chloride at low temperature. Crude mixtures obtained from both protocols were analyzed by ^{1}H NMR (see *SI File*), and the final pure products were isolated *via* the column chromatography (see *Experimental Part*).

To ensure the broad substrate coverage and reinforce our conclusions, we selected eight structurally diverse aldehydes. These included simple linear and branched aliphatic aldehydes (**1a–d**), one containing a heteroatom in the carbon chain (**1h**), aromatic benzaldehyde (**1g**), alicyclic cyclopropanecarboxaldehyde (**1f**), and α,ß-unsaturated acrolein (**1e**). The latter was particularly intriguing due to its two electrophilic π-bonds, which could potentially undergo cycloaddition with dienes. Indeed, previous reports described such interactions with DD and RD. However, as stated earlier, our primary focus was on evaluating the practical convenience and efficiency of each diene for synthetic applications.

Our experiments showed that both dienes reacted with aliphatic aldehydes with a comparable efficiency on gram-to-multigram scales. The yields ranged from 45–68% for DD and 57–74% for RD. Notably, RD maintained the consistent efficiency even at a multigram scale, with yields slightly increasing for higher homologs. In contrast, DD exhibited the opposite trend, possibly due to the lower electrophilicity of higher homologs affecting DD more significantly than RD. Interestingly, for linear aliphatic aldehydes **1a,b** under DD conditions, we anticipated and observed substantial amounts of aldehyde trimers in the ^{1}H NMR spectra of crude mixtures. However, these trimers likely originated from the commercial aldehyde source rather than forming during the reaction as the RD crude mixture contained them in exactly the same relative amount as DD.

A surprising finding was that acrolein reacted exclusively with DD, yielding dihydropyranone **2e**. The ^{1}H NMR spectrum of the reaction mixture showed no evidence of an alternative cycloadduct involving the aldehyde's alkene moiety. In contrast, the reaction of RD with acrolein yielded a crude mixture dominated by TBS group signals, with no characteristic peaks corresponding to either the starting materials or expected products. This was unexpected, taking into account that previous reports describe a successful cycloaddition of RD with related substrates, such as methacrolein and acrylic acid derivatives, leading to high-yielding cyclohexene products [13].

Interestingly, cyclopropanecarboxaldehyde (**1f**) has not previously been reported to react with any of the dienes. However, we observed no unusual reaction behavior, and the final dihydropyranone **2f** was isolated with comparable yields on a gram scale for both dienes. Similarly, reactions with benzaldehyde proceeded smoothly, giving the corresponding 5-phenylpyranone in slightly higher yields for RD.

The introduction of an oxygen atom in the α-position of acetaldehyde was expected to

enhance the reactivity of aldehyde **1h** compared to **1a**. However, DD failed to yield the desired product **2h** as its ^{1}H NMR spectrum showed no characteristic pyranone signals. Literature precedents suggest that this failure could be attributed to the inefficiency of the catalyst used. Reports indicate that Zn-based promoters are more effective for this transformation than boron trifluoride [20]. Thus, when using DD, selecting an appropriate catalyst is crucial. Surprisingly, RD also exhibited low efficiency with **1h**, leading to significant tarring and yielding only 15% of **2h**.

While both dienes demonstrated comparable efficiency on a gram scale for aliphatic aldehydes, we identified several experimental factors favoring RD for scaled syntheses of dihydropyranone products. The use of DD requires careful temperature control during the Lewis acid addition. Even a single drop of etherate causes a significant temperature spike, and although larger reaction scales mitigate these fluctuations, the risk of exceeding the acceptable temperature range remains, potentially leading to extensive tarring. Maintaining -78°C throughout the reaction is also critical to prevent side reactions. In contrast, RD follows a straightforward, low-maintenance protocol requiring only reagent mixing at ambient temperature. It lacks an exothermic effect and other complicating factors, remaining unchanged regardless of the reaction scale. The second step of the RD protocol, involving the removal of dimethylamino and TBS groups, does require an exothermic reaction with acetyl chloride at low temperature, which presents some operational challenges. However, the temperature rise is more manageable compared to the boron trifluoride addition, and the exotherm is easily controlled. Additionally, the large-scale isolation of DD products can be cumbersome, requiring careful addition of the reaction mixture into a saturated sodium bicarbonate solution while maintaining a reaction temperature below -20°C to prevent the product decomposition in the acidic environment. The rate of addition must also be controlled to avoid excessive foaming and ensure that the aqueous layer remains slightly basic.

The chromatographic purification is necessary to purify the target pyranones in both diene cases.

Conclusion

The comparative analysis of Danishefsky's and Rawal's dienes in hetero-Diels-Alder reactions with aldehydes underscores their distinct reactivity profiles and practical implications in synthetic applications. Despite DD's historical prominence and extensive literature coverage, RD demonstrates clear advantages in reactivity, operational simplicity, and scalability. The RD's ability to engage aldehyde dienophiles under thermal conditions without Lewis acid catalysts makes it particularly suitable for acid-sensitive substrates and the large-scale synthesis. However, DD remains valuable for reactions requiring selective activation of specific dienophiles, as evidenced by its exclusive reactivity with acrolein. The results also highlight critical experimental factors, such as the temperature control and catalyst selection, that impact the reaction efficiency and the product isolation. This study not only refines our understanding of these two pivotal dienes, but also provides a framework for their strategic application in synthetic methodologies, particularly in pharmaceutical and materials chemistry. In future, additional functionalized dienophiles should be studied to further expand the scope and efficiency of Diels-Alder transformations.

Experimental part

This section contains protocols for the preparation of the compounds described in the paper. Unless otherwise stated, all starting compounds were obtained from commercial sources and used without additional purification. All solvents were purified according to the standard procedures. All compounds known from the literature are given appropriate references; experimental data comply with the referenced papers.

^{1}H NMR spectra were recorded on a Varian Unity Plus 400 (400 MHz) or a Bruker 170 AVANCE 500 (500 MHz) instrument; ^{13}C NMR spectra were recorded on a Bruker 170 AVANCE 500 (126 MHz) or an Agilent ProPulse 600 (151 MHz) spectrometer. The NMR chemical shifts are referenced using the solvent signals at 7.26 and 77.1 ppm for ^{1}H and ^{13}C nuclei, respectively, in $CDCl_3$. GCMS analyses were performed using an Agilent 5890 Series II 5972 GCMS instrument [electron impact (EI) ionization (70 eV)]. Results for the elemental analysis were obtained at the Analytical Laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine.

The general procedure for the reaction of Danishefsky's diene with aldehydes

To a solution of Danishefsky's diene (1.0 equiv.) in diethyl ether (25 mL for 1 mmol of the diene)

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

under argon at -78°C an aldehyde (1.1 equiv.) was added followed by the dropwise addition of boron trifluoride etherate (1.0 equiv.). In 1 hour at a temperature of -78°C the mixture was carefully added to the saturated solution of $NaHCO_3$ (~10 mL for 1 mmol of the diene). The organic phase was separated, the water fraction was additionally extracted with two more portions of diethyl ether. Combined organic fractions were dried over $MgSO_4$ and evaporated. The crude product obtained was purified by the flash-chromatography (hexane/methyl *tert*-butyl ether, 100:0→80:20→50:50). The presence of pyranones in the eluted fractions was controlled by TLC, hexane/methyl *tert*-butyl ether 4:1, the staining reagent was $KMnO_4$.

The general procedure for the reaction of Rawal's diene with aldehydes

An aldehyde (4.0 equiv. for **1a–d** and 2.0 equiv. for **1e–h**) was dissolved in toluene (550 mL for 1 mol of the aldehyde) under the argon atmosphere, followed by the Rawal's diene (1.0 equiv.) added dropwise at room temperature (water bath). The reaction mixture was allowed to stir overnight, then the volatiles were removed on a rotary evaporator under reduced pressure. The residue was dissolved in methyl *tert*-butyl ether (550 mL for 1 mol of the aldehyde), and the solution was cooled to -78°C under argon. Acetyl chloride (2.0 equiv.) was added to the solution slowly, keeping the temperature at -78°C. Then, the cooling bath was removed, and the mixture was allowed to cool to 0°C and poured into the saturated solution of $NaHCO_3$ (the resulting pH must be > 7). The organic layer was separated, and the water fraction was extracted with methyl *tert*-butyl ether again. The combined organic fraction was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product obtained was purified by the flash-chromatography (hexane/methyl *tert*-butyl ether, 100:0→80:20→50:50). The first eluted fraction (100:0) contained non-identified components, in the second fraction (80:20) there were TBS-containing by-products (^{1}H NMR), the target product was obtained with the most polar eluent (50:50). The presence of pyranones in the eluted fractions was controlled by TLC, hexane/methyl *tert*-butyl ether 4:1, the staining reagent was $KMnO_4$.

2-Methyl-2,3-dihydro-4*H*-pyran-4-one (**2a**) [19]

A light-brown oil. Yield: RD – 57% (52 g), DD – 45% (5.9 g). Anal. Calcd for $C_6H_8O_2$, %: C 64.27, H 7.19. Found, %: C 64.35, H 7.13. ^{1}H NMR (500 MHz, Chloroform-*d*), *δ*, ppm: 1.40–1.50 (3H, m), 2.38–2.57 (2H, m), 4.54 (1H, dp, *J* = 12.2, 6.0 Hz), 5.35–5.44 (1H, m), 7.30–7.39 (1H, m). ^{13}C NMR (151 MHz, Chloroform-*d*), *δ*, ppm: 20.31, 43.45, 75.96, 106.85, 163.25, 192.58. GCMS (EI), m/z: 112.1 $[M]^{+\cdot}$.

2-Ethyl-2,3-dihydro-4*H*-pyran-4-one (**2b**) [19]

A colorless oil. Yield: RD – 63% (22 g), DD – 68% (4.8 g). Anal. Calcd for $C_7H_{10}O_2$, %: C 66.65, H 7.99. Found, %: C 66.77, H 7.91. ^{1}H NMR (500 MHz, Chloroform-*d*), *δ*, ppm: 1.00 (3H, t, *J* = 7.5 Hz), 1.66–1.87 (2H, m), 2.41 (1H, ddd, *J* = 16.7, 3.7, 1.2 Hz), 2.50 (1H, dd, *J* = 16.8, 13.5 Hz), 4.32 (1H, dddd, *J* = 13.2, 7.3, 5.4, 3.7 Hz), 5.38 (1H, dd, *J* = 6.0, 1.2 Hz), 7.35 (1H, d, *J* = 6.0 Hz). ^{13}C NMR (151 MHz, Chloroform-*d*), *δ*, ppm: 9.12, 27.42, 41.38, 80.68, 106.89, 163.30, 192.75. GCMS (EI), m/z: 126.0 $[M]^{+\cdot}$.

2-Isopropyl-2,3-dihydro-4*H*-pyran-4-one (**2c**) [19]

A yellow oil. Yield: RD – 64% (17 g), DD – 68% (3.2 g). Anal. Calcd for $C_8H_{12}O_2$, %: C 68.55, H 8.63. Found, %: C 68.67, H 8.51. ^{1}H NMR (500 MHz, Chloroform-*d*), *δ*, ppm: 0.98 (3H, d, *J* = 6.9 Hz), 1.00 (3H, d, *J* = 6.8 Hz), 1.92–2.06 (1H, m, *J* = 7.2, 6.7 Hz), 2.37 (1H, ddd, *J* = 16.5, 3.4, 1.2 Hz), 2.52 (1H, dd, *J* = 16.7, 14.6 Hz), 4.14 (1H, ddd, *J* = 14.6, 5.9, 3.3 Hz), 5.38 (1H, dd, *J* = 6.0, 1.2 Hz), 7.37 (1H, d, *J* = 5.9 Hz). ^{13}C NMR (126 MHz, Chloroform-*d*), *δ*, ppm: 17.04, 17.26, 31.24, 38.44, 83.60, 106.30, 162.95, 192.51. GCMS (EI), m/z: 140.1 $[M]^{+\cdot}$.

2-*tert*-Butyl-2,3-dihydro-4*H*-pyran-4-one (**2d**) [19]

A light-yellow oil. Yield: RD – 74% (11 g), DD – 52% (1.1 g). Anal. Calcd for $C_9H_{14}O_2$, %: C 70.10, H 9.15. Found, %: C 69.97, H 9.24. ^{1}H NMR (400 MHz, Chloroform-*d*), *δ*, ppm: 1.01 (9H, s), 2.41 (1H, ddd, *J* = 16.6, 3.3, 1.3 Hz), 2.54 (1H, dd, *J* = 16.6, 15.1 Hz), 4.04 (1H, dd, *J* = 15.1, 3.3 Hz), 5.41 (1H, dd, *J* = 5.9, 1.3 Hz), 7.42 (1H, dd, *J* = 5.9, 0.8 Hz). ^{13}C NMR (151 MHz, $CDCl_3$), *δ*, ppm: 25.37, 33.78, 37.17, 86.89, 106.60, 163.89, 193.70. GCMS (EI), m/z: 154.1 $[M]^{+\cdot}$.

2-Vinyl-2,3-dihydro-4*H*-pyran-4-one (**2e**) [21]

A yellow liquid. Yield: DD – 37% (19.2 g). Anal. Calcd for $C_7H_8O_2$, %: C 67.73, H 6.50. Found, %: C 67.88, H 6.42. ^{1}H NMR (500 MHz, Chloroform-*d*), *δ*, ppm: 2.49–2.68 (2H, m), 4.90 (1H, dt, *J* = 12.8, 5.0 Hz), 5.33 (1H, dd, *J* = 10.7, 3.5 Hz), 5.37–5.45 (2H, m), 5.97 (1H, ddd, *J* = 16.9, 10.6, 5.7 Hz), 7.36 (1H, d, *J* = 5.9 Hz). ^{13}C NMR (126 MHz, Chloroform-*d*), *δ*, ppm: 41.47,

79.49, 107.26, 118.39, 134.33, 162.80, 191.81. GCMS (EI), m/z: 124.1 $[M]^{+\cdot}$.

2-Cyclopropyl-2,3-dihydro-4*H*-pyran-4-one (2f)

A yellow liquid. Yield: RD – 72% (0.7 g), DD – 66% (1.2 g). Anal. Calcd for $C_8H_{10}O_2$, %: C 69.55, H 7.30. Found, %: C 69.40, H 7.39. ^{1}H NMR (500 MHz, Chloroform-*d*), δ, pm: 0.29 (1H, dq, *J* = 10.3, 4.7 Hz), 0.47 (1H, dq, *J* = 8.8, 4.8 Hz), 0.57–0.70 (2H, m), 1.11–1.21 (1H, m), 2.53 (1H, ddd, *J* = 16.8, 3.7, 1.3 Hz), 2.65 (1H, dd, *J* = 16.8, 13.3 Hz), 3.67 (1H, ddd, *J* = 12.7, 8.6, 3.6 Hz), 5.37 (1H, dd, *J* = 6.0, 1.2 Hz), 7.34 (1H, d, *J* = 6.0 Hz). ^{13}C NMR (126 MHz, Chloroform-*d*), *δ*, ppm: 2.09, 3.37, 14.55, 41.90, 84.15, 106.94, 163.38, 192.73. GCMS (EI), m/z: 138.1 $[M]^{+\cdot}$.

2-Phenyl-2,3-dihydro-4*H*-pyran-4-one (2g) [22]

A brown oil. Yield: RD – 80% (0.8 g), DD – 64% (1.2 g). Anal. Calcd for $C_{11}H_{10}O_2$, %: C 75.84, H 5.79. Found, %: C 75.99, H 5.83. ^{1}H NMR (500 MHz, Chloroform-*d*), *δ*, ppm: 2.66 (1H, dd, *J* = 16.8, 3.6 Hz), 2.91 (1H, dd, *J* = 16.9, 14.4 Hz), 5.43 (1H, dd, *J* = 14.5, 3.5 Hz), 5.53 (1H, d, *J* = 6.0 Hz), 7.36–7.45 (5H, m), 7.48 (1H, d, *J* = 6.0 Hz). ^{13}C NMR (126 MHz, Chloroform-*d*), *δ*, ppm: 42.85, 80.58, 106.86, 125.58, 128.33, 128.41, 137.35, 162.63, 191.59. GCMS (EI), m/z: 174.0 $[M]^{+\cdot}$.

2-((Benzyloxy)methyl)-2,3-dihydro-4*H*-pyran-4-one (2h) [20]

A yellow oil. Yield: RD – 15% (0.4 g). Anal. Calcd for $C_{13}H_{14}O_3$, %: C 71.54, H 6.47. Found, %: C 71.71, H 6.38. ^{1}H NMR (500 MHz, Chloroform-*d*), *δ*, ppm: 2.40 (1H, dd, *J* = 16.8, 3.5 Hz), 2.74 (1H, dd, *J* = 16.9, 14.2 Hz), 3.64–3.76 (2H, m), 4.53–4.68 (3H, m), 5.41 (1H, d, *J* = 5.9 Hz), 7.28–7.43 (6H, m). ^{13}C NMR (126 MHz, Chloroform-*d*), *δ*, ppm: 38.34, 70.58, 73.58, 78.29, 107.11, 127.75, 127.98, 128.55, 137.40, 162.90, 192.01. GCMS (EI), m/z: 218.1 $[M]^{+\cdot}$.

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Journal of Organic and Pharmaceutical Chemistry

Original Research

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UDC 54.057:547.718:547.72

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The Synthesis of 2,5-Dioxaspiro[3.4]octane Building Blocks: Three-Dimensional Spirocyclic Analogs of 1,4-Dioxanes

Abstract

A ring-closing metathesis (RCM) strategy was employed for the synthesis of spirooxetane compounds with a tetrahydrofuran (THF) core. The approach proposed relied on the preparation of an unsaturated spirooxetane from vinyl oxetanol. The reaction sequence involved the NaH-mediated *O*-alkylation with methyl 2-(bromomethyl)acrylate in the presence of TBAI. The subsequent RCM reaction using the Grubbs' II catalyst gave the dihydrofuran carboxylate with a yield of 70 %. The hydrogenation under high-pressure conditions using a Pearlman's catalyst made it possible to obtain the saturated THF-derived carboxylate, which was then subjected to alkaline hydrolysis to give a stable lithium carboxylate. The corresponding alcohol obtained *via* $LiAlH_4$-mediated reduction of the ester was oxidized to the corresponding aldehyde using DMP. The alcohol was further converted into a mesylate serving as a precursor for the corresponding amine and bromide. The set of dioxane analogs proposed can serve as promising building blocks readily available on a multigram scale for the scientific community.

Keywords: oxetanes; dioxanes; spirocycles; building blocks

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Синтез 2,5-діоксаспіро[3.4]октанових будівельних блоків як тривимірних спіроциклічних аналогів 1,4-діоксанів

Анотація

Для синтезу спірооксетанових сполук із тетрагідрофурановим (ТГФ) фрагментом було застосовано реакцію метатезу із замиканням циклу. Запропонований підхід ґрунтувався на одержанні ненасиченого спірооксетану з вінілоксетанолу. Послідовність реакції передбачала NaH-опосередковане *O*-алкілування метил-2-(бромметил)акрилатом у присутності TBAI. Подальша побудова спіроциклічного каркаса у випадку використання каталізатора Граббса II дала дигідрофуранкарбоксилат із виходом 70 %. Гідрування під високим тиском за допомогою каталізатора Перлмана дозволило одержати насичений ТГФ-карбоксилат, який піддавали лужному гідролізу для утворення стабільного карбоксилату літію. Відповідний спирт, отриманий відновленням естеру під дією $LiAlH_4$, окиснювали за допомогою DMP до відповідного альдегіду. Спирт також перетворювали на мезилат, який слугував вихідною сполукою для синтезу відповідного аміну та броміду. Одержані аналоги діоксану постають перспективними будівельними блоками, відтепер доступними в багатограмових кількостях для наукової спільноти.

Ключові слова: оксетани; діоксани; спіроцикли; будівельні блоки

Citation: Litskan, E. V.; Vashchenko, B. V. The Synthesis of 2,5-Dioxaspiro[3.4]octane Building Blocks: Three-Dimensional Spirocyclic Analogs of 1,4-Dioxanes. *Journal of Organic and Pharmaceutical Chemistry* **2025**, *23* (1), 30–35.
https://doi.org/10.24959/ophcj.25.324901
Received: *16 November 2024*; **Revised:** *26 February 2025*; **Accepted:** *5 March 2025*

Funding: The work was funded by the internal Enamine grant.
Conflict of interests: The authors are employees or consulting scientists at Enamine Ltd, which offers the title compounds from the company's catalog.

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

Introduction

Oxetane is an emerging motif in medicinal chemistry due to its distinctive structural and physicochemical characteristics [1–4]. With an intrinsic ring strain comparable to that of epoxides, oxetanes have a nearly planar structure that minimizes strain and gauche interactions, which, in turn, is attributed to the presence of the oxygen atom [5, 6]. Nowadays, the incorporation of the oxetane moiety into molecules can significantly enhance physicochemical properties, i.e., aqueous solubility, lipophilicity, metabolic stability, acidity/basicity, and ADMET parameters (absorption, distribution, metabolism, excretion, and toxicity) [1, 2, 7, 8]. *Ziresovir* serves as a prominent example of hit optimization through the inclusion of an oxetane fragment (**Figure 1**, *A*) [9, 10].

Other noticeable examples of pharmaceutically relevant oxetanes have a bicyclic structure (**Figure 1**, *B*) [11]. Intriguingly, some oxetanes from the group, particularly bicyclic analogs of 1,4-dioxane, i.e. 2,5-dioxaspiro[3.4]octanes, have been largely overlooked in the scientific literature despite their potential as promising fragments for drug discovery. Therefore, in this study, we aim to synthesize spirocyclic oxetanes, specifically three-dimensional analogs of 1,4-dioxanes (**Figure 1**, *C*). These analogs are expected to provide a range of novel building blocks on a multigram scale, i.e., carboxylates, alcohols, amines, halides, etc.

Results and discussion

The ring-closing metathesis (RCM) reaction was considered as an effective approach for the synthesis of spirooxetane compounds with a tetrahydrofuran (THF) core. For this purpose, we used a bulk reagent, oxetanone **1**, which could be functionalized in optimized conditions, as recently disclosed [12]. The optimized Grignard reaction of **1** provided vinyl oxetanol **2** with a yield of 83% after the distillation *in vacuo* on over a 300 g scale in a single run (**Scheme 1**). The subsequent step included the NaH-mediated alkylation with methyl 2-(bromomethyl)acrylate in the presence of TBAI giving *bis*-allyl ether **3** with a yield of 49%, which was subjected to the RCM reaction. The second-generation Grubbs' catalyst was suitable for the latter reaction and gave the target dihydrofuran carboxylate **4** with a yield of

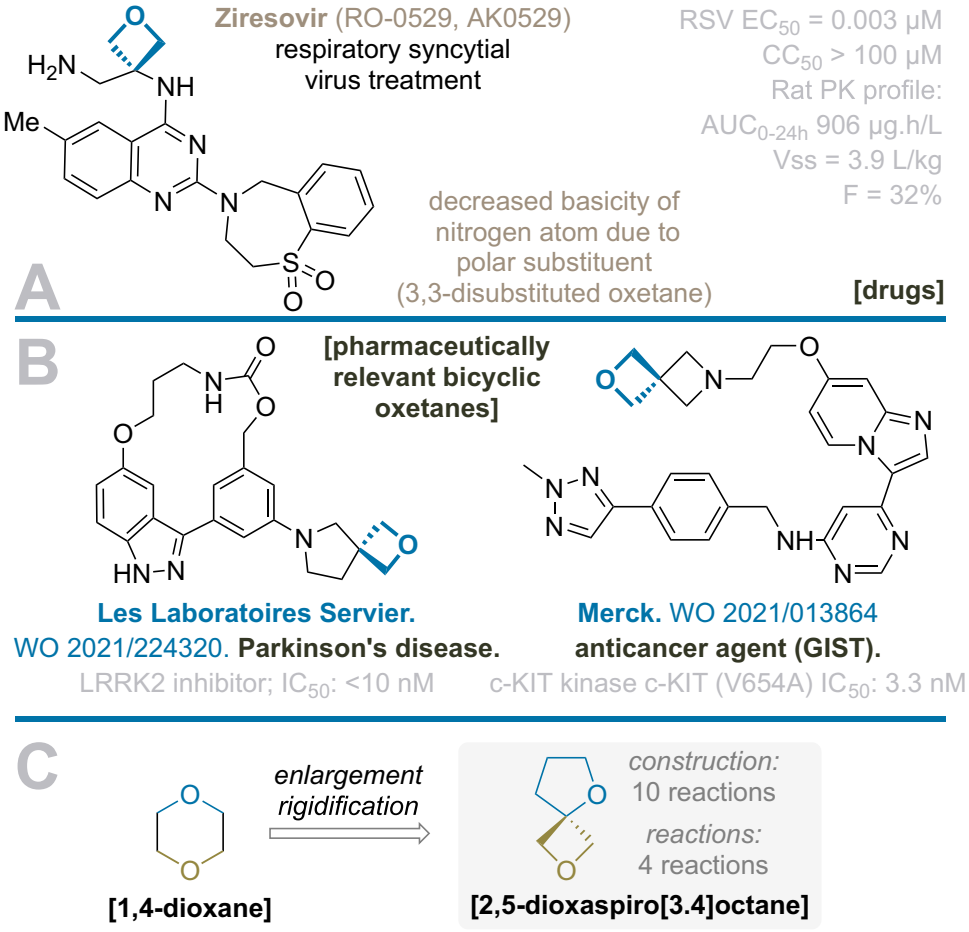
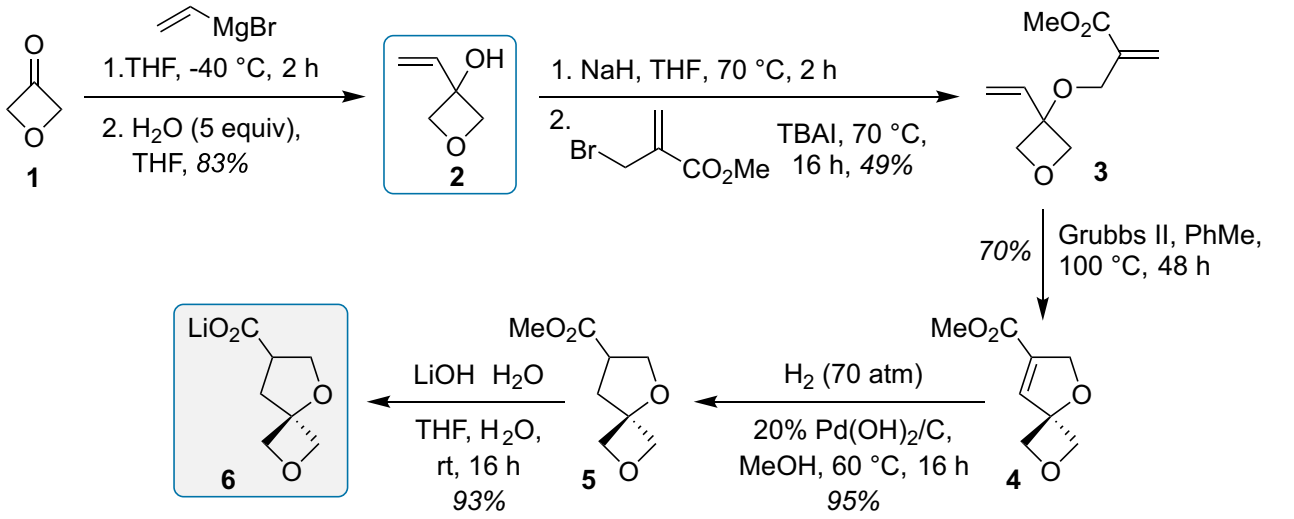


Figure 1. Prominent examples of oxetanes in drug discovery programs (*A*, *B*), and the target fragment of this study (*C*)



Scheme 1. The synthesis of lithium 2,5-dioxaspiro[3.4]octane-7-carboxylate (**6**)

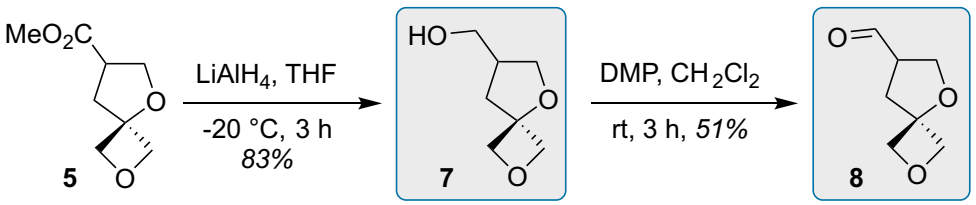
70% on over a 200 g scale. The subsequent catalytic hydrogenation of acrylate **4** in an autoclave (70 atm pressure of H_2) in the presence of Pearlman's catalyst gave a bicyclic THF scaffold **5**, which was subjected to the alkaline hydrolysis to give lithium carboxylate **6** with a yield of 93% (20 g scale). It should be noted that the acidification of **6** or attempted synthesis of the corresponding carboxylic acid were unfruitful due to instability of the oxetane core.

Alcohol **7** was obtained with a yield of 83% from ester **5** by the robust reduction with $LiAlH_4$ (**Scheme 2**). Notably, this approach allowed for the preparation of **7** on a 90 g scale in a single run. Then, the alcohol obtained was oxidized to aldehyde **8** using DMP (Dess-Martin periodinane) in CH_2Cl_2 (30 g scale, 51% yield).

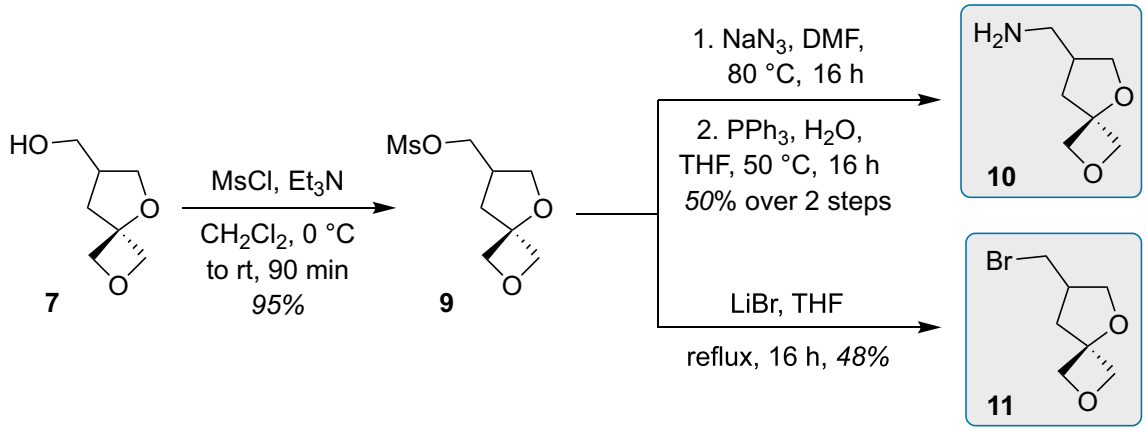
Alcohol **5** was transformed into mesylate **9** (**Scheme 3**), which was used as a precursor for the synthesis of amine **10** with a yield of 50% on up to a 25 g scale *via* the nucleophilic substitution with NaN_3 followed by the Staudinger reaction. Finally, the promising alkylating agent, e.g., bromide **11**, was obtained using the nucleophilic substitution with LiBr in THF (48% yield).

Conclusions

This study demonstrates the successful synthesis of spirocyclic oxetanes as three-dimensional



Scheme 2. The synthesis of 2,5-dioxaspiro[3.4]octane-derived alcohol **7** and aldehyde **8**



Scheme 3. The synthesis of 2,5-dioxaspiro[3.4]octane-derived amine **9** and bromide **10**

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

bicyclic analogs of 1,4-dioxanes, expanding the range of available building blocks for medicinal chemistry. The key ring-closing metathesis (RCM) reaction proved to be an effective approach for constructing spiro-oxetane compounds with a THF core. The synthetic sequence developed enabled the preparation of key intermediates on a scale of more than 200 g through the NaH-mediated alkylation, metathesis of *bis*-allyl ether thus obtained, the catalytic hydrogenation of the acrylate fragment, and the functional group subsequent transformations. The ability to convert these intermediates into diverse derivatives, including aldehydes, amines, and bromides, highlights the synthetic versatility of the methodology proposed. Taking into account the significance of oxetane-containing motifs in drug discovery, the structures obtained may serve as valuable scaffolds for further development in medicinal chemistry and related applications.

■ Experimental part

The solvents were purified according to the standard procedures [13]. All starting compounds were available from Enamine Ltd or purchased from other commercial sources. Melting points were measured on the MPA100 OptiMelt automated melting point system. ^{1}H and $^{13}C\{^{1}H\}$ spectra were recorded on an Agilent ProPulse 600 spectrometer (at 151 MHz for ^{13}C NMR), a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, and 126 MHz for $^{13}C\{^{1}H\}$ NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and $^{13}C\{^{1}H\}$ in $CDCl_3$, 7.13 and 127.60 ppm for ^{1}H and $^{13}C\{^{1}H\}$ in C_6D_6, 2.48 and 39.50 ppm for ^{1}H and $^{13}C\{^{1}H\}$ in DMSO-d_6. Coupling constants (J) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), integration, multiplicity, and coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. LCMS and GCMS analyses were performed using an Agilent LC/MSD SL 1100 instrument [atmospheric pressure electrospray ionization (ES-API)] or an Agilent 5890 Series II 5972 GCMS instrument [electron impact (EI) ionization (70 eV)], respectively. High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

3-Vinyloxetan-3-ol (2)

An oven-dried round-bottomed flask filled with 2 M vinylmagnesium bromide solution in THF (2.07 L, 4.14 mol) was cooled to –40 °C. To the above-precooled solution 3-oxetanone (336 g, 3.72 mol) in THF (3 L) was added dropwise under Ar atmosphere, maintaining the temperature below –40 °C and stirred at –40 °C for 1 h. Upon completion, the reaction was quenched with careful addition of THF–H_2O mixture (240 mL, 1:1, *v*/*v*, 2 equiv. of H_2O). Then, H_2O (300 mL) was added in portions. The resulting suspension was filtered, and the filter cake was washed with THF (2 × 1 L). The combined filtrates were dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by distillation in *vacuo* (0.3 mmHg, 44–47 °C) to obtain alcohol **2**.

A colorless liquid. Yield – 83% (311 g). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.16 (1H, br. s), 4.64 (2H, d, J = 6.8 Hz), 4.66 (2H, d, J = 6.8 Hz), 5.24 (1H, d, J = 10.8 Hz), 5.39 (1H, d, J = 17.4 Hz), 6.25 (1H, dd, J = 17.4, 10.8 Hz). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$), δ, ppm: 74.5, 83.8, 114.3, 139.0. HRMS (ESI–TOF), m/z: $[M–H_2O+H]^+$ calcd for C_6H_7O 83.0497, found 83.0551; $[M+H]^+$ calcd for $C_5H_9O_2$ 101.0603, found 101.0604; $[M+NH_4]^+$ calcd for $C_5H_{12}NO_2$ 118.0868, found 118.0863.

Methyl 2,5-dioxaspiro[3.4]oct-7-ene-7-carboxylate (4)

NaH (2.5 equiv, 5.84 mol) was added in portions to a solution of compound **2** (292 g, 2.92 mol) in THF (5 L) under Ar atmosphere, and the resulting mixture was stirred at 70 °C for 2 h. Then, the reaction mixture was cooled to 0 °C, and methyl 2-(bromomethyl)prop-2-enoate (902 g, 4.67 mol) followed by TBAI (1 mol%) were added, and the resulting mixture was stirred at 70 °C for 16 h. After that, the resulting mixture was poured into saturated aq. NH_4Cl (388 g, 7.26 mol), and then extracted with EtOAc (3×1 L). Combined organic layers were washed with brine (1 L), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product obtained was purified by the flash column chromatography using hexanes–EtOAc (4:1, *v*/*v*) as an eluent. The resulting diene **3** (1.44 mol) in toluene (8 L) was degassed 3 times and refilled with Ar. Then, Grubbs II catalyst (14.5 g, 17.1 mmol, 1.5 mol%) was added, and the resulting mixture was stirred at 100 °C for 48 h. Then, the reaction mixture was concentrated *in vacuo*. The product obtained was purified by the flash column chromatography using hexanes–EtOAc (4:1, *v*/*v*) as an eluent.

Fusible brownish crystals. Yield – 70% (172 g). Anal. Calcd for $C_8H_{10}O_4$, %: C 56.47, H 5.92.

Found, %: C 56.33, H 5.84. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.78 (3H, s), 4.70 (2H, d, J = 7.0 Hz), 4.79 (2H, d, J = 2.4 Hz), 4.88 (2H, d, J = 7.0 Hz), 7.01 (1H, t, J = 2.4 Hz). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$), δ, ppm: 52.1, 74.3, 83.0, 90.4, 134.2, 138.1, 162.7. GCMS (EI), m/z: 140 $[M-CH_2O]^+$.

Methyl 2,5-dioxaspiro[3.4]octane-7-carboxylate (5)

20% $Pd(OH)_2$/C (25.0 g) was added to the compound **4** (207 g) solution in MeOH (2 L), and the resulting solution was stirred at H_2 (70 atm; in autoclave), 50 °C for 48 h. After that, the catalyst was filtered thought a pad of silica gel, and the filtrate obtained was concentrated in *vacuo*, and immediately used in the next step. Yield – 95% (194 g).

Lithium 2,5-dioxaspiro[3.4]octane-7-carboxylate (6)

$LiOH\times H_2O$ (6.50 g, 0.155 mol) was added to a solution of compound **5** (26.7 g, 0.155 mol) obtained in THF/H_2O (100 mL/100 mL), and the resulting mixture was stirred at rt for 16 h. After that, the reaction mixture was concentrated *in vacuo* until it became solid. The title product was obtained after trituration with acetone (2×50 mL) and Et_2O (2×50 mL) resulting in the target product.

A colorless solid. Yield – 93% (23.7 g). M. p. 94–96 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 2.15 (1H, dd, J = 12.5, 8.2 Hz), 2.33 (1H, dd, J = 12.5, 6.9 Hz), 2.71 (1H, p, J = 7.4 Hz), 3.81 (2H, d, J = 7.4 Hz), 4.34 – 4.62 (4H, m). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6), δ, ppm: 176.4, 83.1, 82.9, 82.4, 71.2, 46.4, 39.0. HRMS (ESI-TOF), m/z: $[M-Li]^-$ calcd for $C_7H_9O_4$ 157.0501, found 157.0509.

(2,5-Dioxaspiro[3.4]octan-7-yl)methanol (7)

$LiAlH_4$ (29.9 g, 0.788 mol) was added to THF (2 L), and the mixture was cooled to –20 °C. Then, ester **5** (135 g, 0.788 mol) in THF (200 mL) was added dropwise at –20 °C. The mixture was stirred at –20 °C for 3 h, then 30 % aq. KOH (65 mL) was added at –20 °C. The mixture was warmed up to rt, stirred for an additional 2 h, then filtered and evaporated *in vacuo*.

A colorless oil. Yield – 83% (94.2 g). ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.89 (1H, dd, J = 12.8, 6.3 Hz), 2.19 (1H, dd, J = 12.8, 7.8 Hz), 2.25–2.36 (1H, m), 3.21–3.32 (2H, m), 3.53 (1H, dd, J = 8.4, 5.8 Hz), 3.77 (1H, t, J = 7.8 Hz), 4.37–4.60 (4H, m), 4.66 (1H, t, J = 5.1 Hz). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6), δ, ppm: 37.2, 41.2, 62.1, 69.9, 82.0, 82.7, 83.1. HRMS (ESI-TOF), m/z: $[M+H]^+$ calcd for $C_7H_{13}O_3$ 145.0865, found 145.0860.

2,5-Dioxaspiro[3.4]octane-7-carbaldehyde (8)

DMP (240 g, 0.566 mol) was added in portions to a solution of **7** (62.0 g, 0.431 mol) in CH_2Cl_2 (800 mL) at rt, and the resulting mixture was stirred at rt for 3 h. Then, the reaction mixture was poured into saturated aq. $NaHCO_3$ (145 g, 2.72 mol) and saturated aq. $Na_2S_2O_3\cdot 5H_2O$ (321 g, 1.29 mol), and the resulting mixture was stirred at rt for 1 h. Then, the organic layer was separated, washed with H_2O (700 mL), brine (700 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product obtained was purified by the flash column chromatography using hexanes–EtOAc (7:3, *v*/*v*) as an eluent.

A colorless oil. Yield – 51% (31.2 g). ^{1}H NMR (500 MHz, C_6D_6), δ, ppm: 1.49 (1H, dd, J = 13.2, 8.6 Hz), 1.93 (1H, dd, J = 13.2, 5.1 Hz), 2.02–2.10 (1H, m), 3.22–3.28 (1H, m), 3.61 (1H, dd, J = 9.1, 4.5 Hz), 4.16 (1H, d, J = 6.6 Hz), 4.34 (1H, d, J = 6.6 Hz), 4.59 (1H, d, J = 6.6 Hz), 4.65 (1H, d, J = 6.6 Hz), 8.94 (1H, s). ^{13}C{^{1}H} NMR (151 MHz, C_6D_6), δ, ppm: 34.8, 51.1, 66.7, 82.8, 82.9, 83.2, 198.8. HRMS (ESI-TOF), m/z: $[M+H]^+$ calcd for $C_7H_{11}O_3$ 143.0708, found 143.0702.

(2,5-Dioxaspiro[3.4]octan-7-yl)methyl methanesulfonate (9)

MsCl (81.1 g, 0.708 mol) was added dropwise to a solution of compound **7** (51.0 g, 0.354 mol) and Et_3N (71.7 g, 0.708 mol) in CH_2Cl_2 (500 mL) at 0 °C, and the resulting solution was stirred at rt for 90 min. Then, the reaction mixture was washed with 1 M $NaHCO_3$ (2×200 mL), brine (200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. After that, the residue obtained was dissolved in *t*BuOMe (300 mL), concentrated *in vacuo* twice, and immediately used in the next steps. Yield – 95% (74.6 g).

(2,5-Dioxaspiro[3.4]octan-7-yl)methanamine (10)

NaN_3 (45.8 g, 0.705 mol) was added to a solution of compound **9** (78.0 g, 0.351 mol) in DMF (400 mL), and the resulting mixture was stirred at 80 °C for 16 . After that, the reaction mixture was poured into H_2O (1.2 L), and it was extracted with *t*BuOMe (4×350 mL). Combined organic layers were washed with H_2O (300 mL), brine (300 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Then, Ph_3P (123 g, 0.469 mol) followed by H_2O (17.0 mL, 0.944 mol) were added to a solution of the crude azide obtained (ca. 0.310 mol) in THF (500 mL), and the resulting mixture was stirred at 50 °C for 16 h. After that, the reaction mixture was cooled to rt and concentrated

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

in vacuo. The product obtained was purified by the flash column chromatography using hexanes–EtOAc (4:1, *v*/*v*) as an eluent.

A yellowish solid. Yield – 50% over two steps (25.0 g). M. p. 100–101 °C. Anal. Calcd for $C_7H_{13}NO_2$, %: C 58.72, H 9.15, N 9.78. Found, %: C 58.81, H 9.20, N 9.63. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.56 (1H, d, J = 10.7 Hz), 1.67–1.76 (1H, m), 2.19–2.27 (1H, m), 2.41–2.47 (2H, m), 2.60 (1H, d, J = 12.8 Hz), 2.64–2.70 (1H, m), 3.27 (1H, d, J = 11.4 Hz), 3.33 (1H, d, J = 11.4 Hz), 3.39 (2H, s), 3.70 (1H, dd, J = 7.5, 4.5 Hz), 3.92 (1H, d, J = 7.5 Hz). LCMS (ESI), m/z: 144 $[M+H]^+$.

7-(Bromomethyl)-2,5-dioxaspiro[3.4]octane (11)

LiBr (31.4 g, 0.362 mol) was added to a solution of compound **9** (26.8 g, 0.121 mol) in THF (250 mL), and the resulting mixture was refluxed for 16 . After that, the reaction mixture was concentrated *in vacuo*, and the residue obtained was dissolved in H_2O (100 mL) and extracted with CH_2Cl_2 (3×100 mL). Combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product obtained was purified by the flash column chromatography using hexanes–EtOAc (4:1, *v*/*v*) as an eluent.

A dark oil. Yield – 48% (12.0 g). Anal. Calcd for $C_7H_{11}BrO_2$, %: C 40.60, H 5.35. Found, %: C 40.48, H 5.41. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 4.79 (1H, d, J = 6.7 Hz), 4.74 (1H, d, J = 6.7 Hz), 4.60 (1H, d, J = 6.7 Hz), 4.53 (1H, d, J = 6.7 Hz), 3.98 (1H, dd, J = 9.0, 7.0 Hz), 3.64 (1H, dd, J = 9.0, 6.4 Hz), 3.40–3.27 (2H, m), 2.76–2.63 (1H, m), 2.46 (1H, dd, J = 13.2, 7.7 Hz), 2.03 (1H, dd, J = 13.2, 7.0 Hz). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$), δ, ppm: 34.2, 40.7, 41.7, 72.1, 82.8, 83.5, 84.5. GCMS (EI), m/z: 176/178 (intensity ration 1:1) $[M–CH_2O]^+$.

■ Acknowledgements

The authors thank Mr. Bohdan Sosunovych for his help with the manuscript preparation, Prof. Dr. Serhii Ryabukhin for helpful discussions, and Prof. Dr. A. O. Tolmachov for his encouragement and support, and all the brave defenders of Ukraine for making this publication possible.

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Journal of Organic and Pharmaceutical Chemistry

Original Research

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UDC 547-302+547-316

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Hydrolysis of Difluorocyclopropenes: the Role of the Cyclopropenyl Cation and the Effects of Substituents

Abstract

Monosubstituted *gem*-difluorocyclopropenes undergo hydrolysis yielding cyclopropenones and acrylic acid derivatives. Herein, we investigate the reaction routes of hydrolysis for both aromatic and alkyl derivatives. The study supports the idea that the formation of a cyclopropenyl cation controls the reactivity of *gem*-difluorocyclopropenes, and aromatic substituents accelerate the hydrolysis *via* the resonance stabilization. Reaction conditions, including the solvent composition and temperature, significantly affect the conversion and the product selectivity. This information facilitates the preparative synthesis and improves understanding of the fluorinated cyclopropene reactivity.

Keywords: difluorocyclopropenes; cyclopropenyl cation; hydrolysis

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Гідроліз дифтороциклопропенів: роль циклопропенільного катіона та ефекти замісників

Анотація

Монозаміщені *гем*-дифтороциклопропени піддаються гідролізу з утворенням циклопропенонів і похідних акрилової кислоти. У цій роботі ми досліджуємо реакційні шляхи гідролізу як ароматичних, так і алкільних похідних. Дослідження підтверджує ідею про те, що реакційною здатністю *гем*-дифтороциклопропенів керує утворення циклопропенільного катіона, а ароматичні замісники прискорюють гідроліз через резонансну стабілізацію. Умови реакції, зокрема склад розчинника та температура, значно впливають на конверсію і вибірковість утворення продукту. Ці відомості полегшують препаративний синтез і покращують розуміння реакційної здатності фторованого циклопропену.

Ключові слова: дифтороциклопропени; циклопропеніл-катіон; гідроліз

Citation: Pashko, M. O.; Ryabukhin, S. V. Hydrolysis of Difluorocyclopropenes: the Role of the Cyclopropenyl Cation and the Effects of Substituents. *Journal of Organic and Pharmaceutical Chemistry* **2025**, *23* (1), 36–42.
https://doi.org/10.24959/ophcj.25.324913
Supporting information: The SI contains details of experiments and synthesis; spectral and analytical data for the compounds synthetized.
Received: *27 December 2024;* **Revised:** *11 March 2025;* **Accepted:** *16 March 2025*

Funding: The work was funded by the internal Enamine grant and the grant of the Ministry of Education and Science of Ukraine (grant number 0123U102102).
Conflict of interests: The authors have no conflict of interests to declare.

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

Introduction

Difluorocyclopropenes, particularly 3,3-difluorocyclopropenes, are compact, strained, three-membered cyclic compounds bearing two fluorine atoms on a single carbon atom of an unsaturated cyclopropene framework. Their unique electronic and steric properties render them valuable building blocks for organic synthesis in a broad range of transformations [1–3]. The recent studies have shown that many compounds of this class can be viewed as bench-stable reagents [4], which enhanced the overall interest to *gem*-difluorocyclopropenes and facilitated further research.

Upon exposure to water, difluorocyclopropenes undergo a rapid hydrolysis, leading predominantly to the formation of cyclopropenones and, under certain conditions, to acrylic acid derivatives [5]. The hydrolytic instability is particularly marked in aromatic monosubstituted derivatives where the presence of aromatic rings appears to accelerate the process. This enhanced reactivity is attributed to electronic effects that promote the formation of a cyclopropenyl cation intermediate [6], which is a highly stabilized, aromatic species characterized by the 2π electron system [7].

The mechanistic pathway is hypothesized to involve the nucleophilic attack of water at the cyclopropene ring, leading to the elimination of fluoride ions and the transient formation of the cyclopropenyl cation [8]. The subsequent reaction steps yield cyclopropenones [9] as the primary hydrolysis products, although further transformation to acrylic acid derivatives can occur, particularly under conditions that favor ring opening [5]. The precise nature of this pathway remains a subject of further research, with yet no direct experimental evidence that would clarify whether the cationic species is a discrete intermediate or part of a more complex reaction cascade.

Substituent effects play a critical role in modulating the hydrolysis rate of *gem*-difluorocyclopropenes. Aromatic substituents appear to facilitate the reaction by stabilizing the cyclopropenyl cation *via* the resonance delocalization, thereby lowering the activation energy for the hydrolysis. In contrast, alkyl substituents offer significantly less stabilization, resulting in slower reaction rates [4]. Understanding these substituent-dependent reactivity patterns is essential not only for elucidating the mechanistic details of the *gem*-difluorocyclopropenes hydrolysis process, but also for the potential optimization of preparative approaches to the synthesis of cyclopropenone and acrylic acid derivatives.

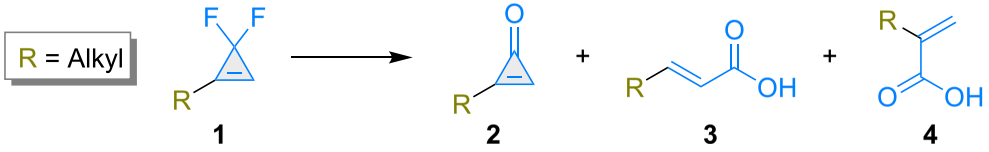
In this study, we systematically investigate the hydrolysis of monosubstituted *gem*-difluorocyclopropenes containing both aromatic and alkyl substituents. Our research focuses on identifying the scope and limitations of these hydrolytic reactions while assessing the potential of substrates for practically valuable preparative transformations.

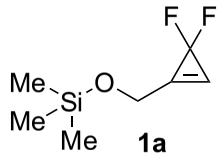
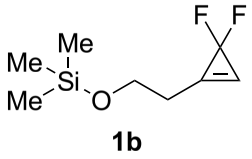
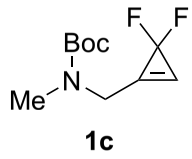
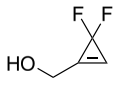
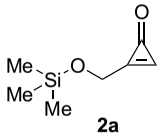
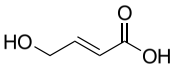
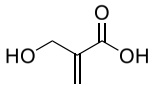
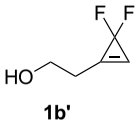
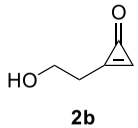
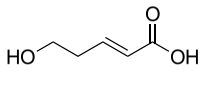
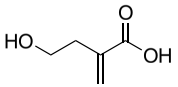
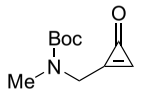
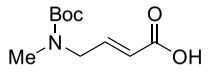
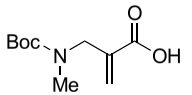
Results and discussion

The hydrolysis of 1-alkyl-3,3-difluorocyclopropenes was evaluated under several reaction conditions (**Table 1**). Under mild conditions (**Table 1**, *entry 1*: DCM/SiO_2 on air, 18 h), the substrates remained largely unchanged, affording primarily the starting materials (**1a, 1b, 1c, Table 1**). When the controlled amount of water was introduced (**Table 1**, *entry 2*: DCM/SiO_2/H_2O, 5 equiv., 18 h), a partial conversion occurred, yielding mixtures of products (e.g., **1a/1a′** and **1b/1b′**, **Table 1**), while substrate **1c** showed the minimal conversion. A similar outcome was observed with a DCM/MeOH (2:1) mixture on SiO_2 (**Table 1**, *entry 3*). In contrast, the application of the MeOH/H_2O (10:1) solvent system on SiO_2 for 18 h (**Table 1**, *entry 4*) led to a more complex distribution: intermediate products appeared alongside nascent hydrolysis products (e.g., **1a′**, **2a**, **3a** for substrate **a**; similar profiles were seen for substrates **b** and **c**, **Table 1**). Increasing the reaction time to 72 h in the same solvent system (**Table 1**, *entry 5*), or carrying out the reaction at a higher water ratio (MeOH/H_2O, 5:1) at 60 °C for 18 h (**Table 1**, *entry 6*) led to the fact that the conversion was almost completed, resulting in mainly the final products of hydrolysis (**3a/4a**, **3b/4b**, **3c/4c**, **Table 1**). Notably, basic conditions (using MeOH/K_2CO_3 or MeOH/NaOH, **Table 1**, *entries 7* and *8*) led to degradation of the substrates to unidentifiable mixtures, emphasizing that silica gel played a crucial role in binding the eliminating HF and stabilizing the reaction environment. These results highlight the significant effect of the solvent composition, reaction time, and temperature on the efficiency and selectivity of the hydrolysis process.

The MeOH/H_2O solvent system on SiO_2, particularly with either extended reaction times or a higher water ratio at moderate temperatures emerged as the most promising preparative approach for efficiently converting alkyl *gem*-difluorocyclopropenes into acrylic acid derivatives.

Table 1. The hydrolysis of 1-alkyl *gem*-difluorocyclopropenes **1a–c** under different reaction conditions



Reaction Conditions	Substrates, products, and product ratio		
	 **1a**	 **1b**	 **1c**
	 **1a'**  **2a**  **3a**  **4a**	 **1b'**  **2b**  **3b**  **4b**	 **2c**  **3c**  **4c**
1. DCM/SiO_2/Air, 18 h	**1a**	**1b**	**1c**
2. DCM/SiO_2/H_2O (5 equiv.), 18 h	**1a**(70%) + **1a'** (30%)[a]	**1b**(75%) + **1b'** (25%)[a]	1c
3. DCM/MeOH (2:1) SiO_2, 18 h	**1a**	**1b**	**1c**
4. MeOH/H_2O (10:1) SiO_2, 18 h	**1a'** (60%), **2a** (25%), **3a** (15%)	**1b'** (40%), **2b** (45%), **3b** (12%), **4b** (3%)	**1c** (55%), **2c** (35%), **3c** (20%)
5. MeOH/H_2O (10:1) SiO_2, 72 h	**3a** (95%), **4a** (5%)	**3b** (72%), **4b** (28%)	**3c** (84%), **4c** (16%)
6. MeOH/H_2O (5:1) SiO_2, 60C 18 h	**3a** (95%), **4a** (5%)	**3b** (72%), **4b** (28%)	**3c** (85%), **4c** (15%)
7. MeOH/K_2CO_3	complex mixture	complex mixture	complex mixture
8. MeOH/NaOH	complex mixture	complex mixture	complex mixture

Note: [a]**1a'**, **1b'** – products where the CF_2 moiety remains unchanged, while the $SiMe_3$ protection group degrades

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

In the case of 1-aryl-3,3-difluorocyclopropenes (**Table 2**), the hydrolysis proceeded under considerably milder conditions compared to their alkyl counterparts. Under ambient conditions (DCM/SiO_2/Air, 18 h, **Table 2**, *entry 1*) even slight exposure to the atmospheric moisture initiated hydrolysis, as evidenced by the formation of hydrolysis products (**2e** (80%) and **3e** (20%), **Table 2**, *entry 1*) in case of the substrate containing the strongest donating aromatic group in the series (**1e**, **Table 2**). Notably, the electron-donating 4-methoxyphenyl fragment of the substrate **1e** (**Table 2**) had the most significant potential to effectively stabilize the cyclopropenyl cation intermediate, which was an indirect indication of the key role that the cyclopropenyl cation formation had for the *gem*-difluorocyclopropene hydrolysis rate and course. In contrast, such substrates as **1d**, **1f**, and **1g** (**Table 2**) showed lower reactivity under these conditions, with **1d** remaining largely unconverted. When the reaction medium was changed to a DCM/MeOH (1:1) mixture (**Table 2**, *entry 2*), the conversion of substrate **1d** improved (yielding 40% of **2d** and 60% of **3d**), while substrate **1e** further progressed to yield predominantly **3e** (82%) alongside a minor quantity of **4e** (16%) (**Table 2**, *entry 2*). For substrates **1f** and **1g**, the DCM/MeOH conditions resulted only in a partial conversion, forming small amounts of the "first stage" hydrolysis product – cyclopropenones **2f** (25%) and **2g** (20%), respectively (**Table 2**, *entry 2*).

These observations underscore that the electronic properties of aromatic substituents critically dictate the hydrolysis rate, with donor groups markedly enhancing the reaction *via* better stabilization of the cyclopropenyl cation, while substrates with less favorable (electron withdrawing) characteristics display the reduced reactivity.

■ Conclusion

Our study strongly supports the concept that the hydrolysis of *gem*-difluorocyclopropenes is controlled by the formation of a cyclopropenyl cation intermediate, which stability plays a central role in determining both the reaction rate and the product distribution. Our experimentations show that 1-aryl-*gem*-difluorocyclopropenes display divergent behavior depending on the electronic nature of the substituents attached to the aromatic ring. When electron-donating groups, such as methoxy or alkyl groups, are present, they engage in resonance with the cyclopropene framework, effectively delocalizing the positive charge of the cyclopropenyl cation. This stabilization presumably lowers the energy barrier for the hydrolysis reaction, leading to a faster conversion and a more efficient formation of cyclopropenones under milder conditions. Conversely, aromatic systems containing electron-withdrawing groups, such as fluorine or carboxyl functionalities, offer limited resonance stabilization for the cationic intermediate. The reduced stabilization leads to an increase in the activation energy, thereby slowing down the hydrolysis process and requiring more stringent conditions to achieve notable conversion.

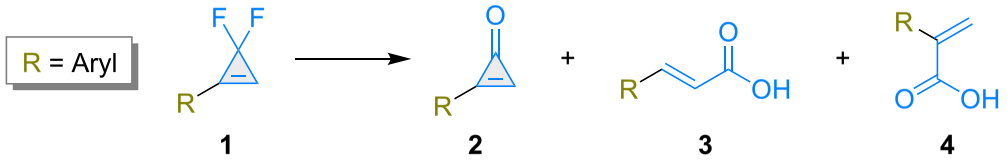
Furthermore, the use of silica gel to bind the evolving HF proves essential in both scenarios as it prevents degradation pathways and helps to maintain the integrity of the reaction environment. 1-Alkyl-*gem*-difluorocyclopropenes, lacking the conjugative effects of an aromatic ring, require more rigorous conditions, such as an increased water content or higher temperatures, to achieve an effective hydrolysis. Together, these findings not only provide a nuanced understanding of how the substituent effects modulate the stability of key intermediates, but also inform the optimization of the reaction conditions for the preparative synthesis of cyclopropenones, and acrylic acid derivatives using *gem*-difluorocyclopropenes as substrates, thereby advancing the scope of potentially valuable transformations of this accessible class of building blocks.

■ Experimental part

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. ^1H, ^{19}F, and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 500 MHz for ^1H, 470 MHz for ^{19}F, and 126 MHz for ^{13}C) and Varian Unity Plus 400 spectrometers (at 400 MHz for ^1H, 376 MHz for ^{19}F and 101 MHz for ^{13}C). The NMR chemical shifts are referenced using the solvent signals at 7.26 and 77.1 ppm for ^1H and ^{13}C nuclei, respectively, in $CDCl_3$ and 2.48 and 39.5 ppm for ^1H and ^{13}C nuclei, respectively, in DMSO-d_6; C_6F_6 was used as the internal standard for ^{19}F NMR spectra. HPLC analyses were done on an Agilent 1200 instrument. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)).

Table 2. The hydrolysis of 1-aryl *gem*-difluorocyclopropenes **1d–g** under different reaction conditions



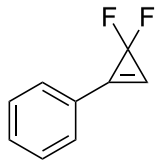
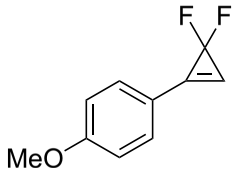
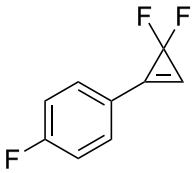
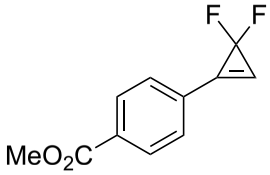
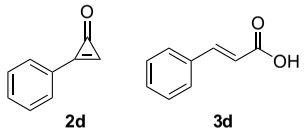
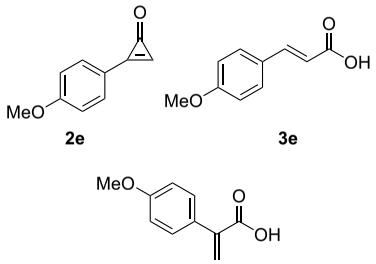
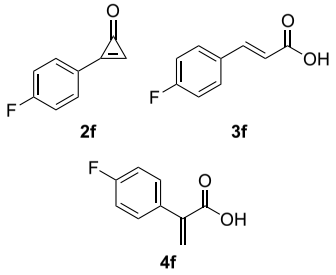
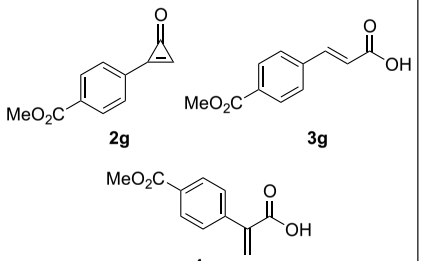
Reaction Conditions	Substrates, products, and product ratio			
	 **1d**	 **1e**	 **1f**	 **1g**
	 **2d** **3d** **4d**	 **2e** **3e** **4e**	 **2f** **3f** **4f**	 **2g** **3g** **4g**
1. DCM/SiO_2/Air, 18h	**1d**	**2e** (80%), **3e** (20%)	**1f**	**1g**
2. DCM/MeOH (1:1) SiO_2, 18h	**2d** (40%), **3d** (60%)	**3e** (82%), **4e** (16%)	**1f** (75%), **2f** (25%)	**1g** (80%), **2g** (20%)

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Table 3. Hydrolysis protocol details for the hydrolysis of 1-alkyl-*gem*-difluorocyclopropenes **1a–c**

Table 1 entries	Hydrolysis protocol details
1. DCM/SiO_2/Air, 18 h	A difluorocyclopropene (1 equiv.) was dissolved in dichloromethane (20 mL g^{-1}) and SiO_2 (5 equiv.) was added. The reaction mixture was stirred in an open flask for 18 hours at room temperature. The reaction mixture was then filtered and evaporated
2. DCM/SiO_2/H_2O (5 equiv), 18 h	A difluorocyclopropene (1 equiv.) was dissolved in dichloromethane (20 mL g^{-1}), SiO_2 (5 equiv.), and water (5 equiv.) were added. Then the reaction mixture was stirred for 18 hours at room temperature. The reaction mixture was then filtered, dried over sodium sulfate, and evaporated
3. DCM/MeOH (2:1), SiO_2, 18 h	A difluorocyclopropene (1 equiv.) was dissolved in a 2-to-1 dichloromethane/methanol mixture (20 mL g^{-1}), SiO_2 (5 equiv.) was added, and the reaction mixture was stirred for 18 hours at room temperature. Then water was added to the reaction mixture and extracted twice with dichloromethane, the organic layer was dried over sodium sulfate and evaporated
4. MeOH/H_2O (10:1), SiO_2, 18 h	A difluorocyclopropene (1 equiv.) was dissolved in a 10-to-1 methanol/water mixture (20 mL g^{-1}), SiO_2 (5 equiv.) was added, and the reaction mixture was stirred for 18 (entry 4) or 72 (entry 5) hours at room temperature. Then methanol was evaporated, water was added to the reaction mixture, and extracted twice with dichloromethane. The organic layer was dried over sodium sulfate and evaporated
5. MeOH/H_2O (10:1), SiO_2, 72 h	
6. MeOH/H_2O (5:1), SiO_2, 60°C 18 h	A difluorocyclopropene (1 equiv.) was dissolved in a 5-to-1 methanol/water mixture (20 mL g^{-1}), SiO_2 (5 equiv.) was added, and the reaction mixture was stirred for 18 hours at 60°C. Then, the reaction mixture was cooled, methanol was removed *in vacuo*, and water was added. The mixture was extracted twice with dichloromethane, the organic layer was dried over sodium sulfate and evaporated
7. MeOH/K_2CO_3	A difluorocyclopropene (1 equiv.) was dissolved in methanol (20 mL g^{-1}), K_2CO_3 (entry 7) or NaOH (entry 8) (2 equiv.) was added, and the reaction mixture was stirred for 18 hours at room temperature. Then, the methanol was evaporated, water was added, and the mixture was acidified with sodium hydrogen sulfate to pH 3 and extracted twice with dichloromethane. The organic layer was dried over sodium sulfate and evaporated
8. MeOH/NaOH	

Table 4. Hydrolysis protocol details for the hydrolysis of 1-aryl-*gem*-difluorocyclopropenes **1d–g**

Table 2 entries	Hydrolysis protocol details
1. DCM/SiO_2/Air, 18 h	Similarly to **Table 1**, conditions for **entry 1**
2. DCM/MeOH (1:1), SiO_2, 18 h	A difluorocyclopropene (1 equiv.) was dissolved in a 1-to-1 dichloromethane/methanol mixture (20 mL g^{-1}), SiO_2 (5 equiv.) was added, and the reaction mixture was stirred for 18 hours at room temperature. Then, water was added, and the mixture was extracted twice with dichloromethane, the organic layer was dried over sodium sulfate and evaporated

The column chromatography was performed with silica gel (200–300 mesh).

Tables 3 and **4** contain experimental protocols used during experimentation and reflect the results highlighted in **Tables 1** and **2**.

■ Acknowledgment

The authors thank Enamine Ltd for access to the building blocks stock, Prof. Andrey A. Tolmachev for his encouragement and support.

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

Journal of Organic and Pharmaceutical Chemistry

Original Research

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Freely available online on
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UDC 54.057:547.825

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An Efficient Synthesis of a Variety of Substituted Pyridine-3-Thiols

Abstract

A practical and convenient method for the synthesis of pyridine-3-thiols using substituted 3-iodopyridines as starting compounds has been developed. Based on the use of thiobenzoic acid as a sulfur donor in a two-step procedure, this approach made it possible to synthesize a number of pyridine-3-thiols with F, Cl, Br, CH_3, OCH_3 substituents in various positions of the pyridine ring. The procedure presented gives high yields of the target products with a purity of 95 % and is suitable for the synthesis in tens of grams.

Keywords: pyridine; thiols; thiobenzoic acid; chromatography; hydrolysis

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Ефективний метод синтезу різноманітних заміщених піридин-3-тіолів

Анотація

Розроблено практичний і зручний метод синтезу піридин-3-тіолів із використанням як вихідних сполук заміщених 3-йодопіридинів. Цей підхід, заснований на використанні тіобензойної кислоти як донора сульфуру в межах двостадійної процедури, надав можливість синтезувати ряд піридин-3-тіолів із F, Cl, Br, CH_3, OCH_3 замісниками в різноманітних положеннях піридинового циклу. Зазначена процедура дозволяє одержати цільові продукти на масштабі десятків грам із високими виходами й чистотою 95 %.

Ключові слова: піридин; тіоли; тіобензойна кислота; хроматографія; гідроліз

Citation: Bohdan, D. P.; Borysov, O. V. An Efficient Synthesis of a Variety of Substituted Pyridin-3-Thiols. *Journal of Organic and Pharmaceutical Chemistry* **2025**, *23* (1), 43–48.
https://doi.org/10.24959/ophcj.25.324523
Received: *24 January 2025*; **Revised:** *6 March 2025*; **Accepted:** *10 March 2025*

Funding: The authors received no specific funding for this work.
Conflict of interests: The authors have no conflict of interests to declare

■ Introduction

Pyridine is a part of the body's oxidation systems and, in the form of nicotinic acid (vitamin B3), is a component of NAD^+ and $NADP^+$ (**Figure 1**) [1–3]. Pyridines are found in plants, for example, in alkaloids, such as nicotine. The latter is an important biological component and activator of nicotinic acetylcholine receptors (nAChRs); it plays a significant role in the formation of tobacco addiction [4, 5]. Anabasine, an alkaloid related to nicotine, is the major toxin of the Pacific hoplonemertine *Paranemertes peregrina*, which presumably uses the alkaloid for defense or to paralyze its prey [6].

The pyridine cycle is a pharmacophore of dihydropyridine calcium channel blockers [7]. Many other biologically active compounds with a pyridine cycle are known [8]. For example, huperzine A, an active Lycopodium alkaloid extracted

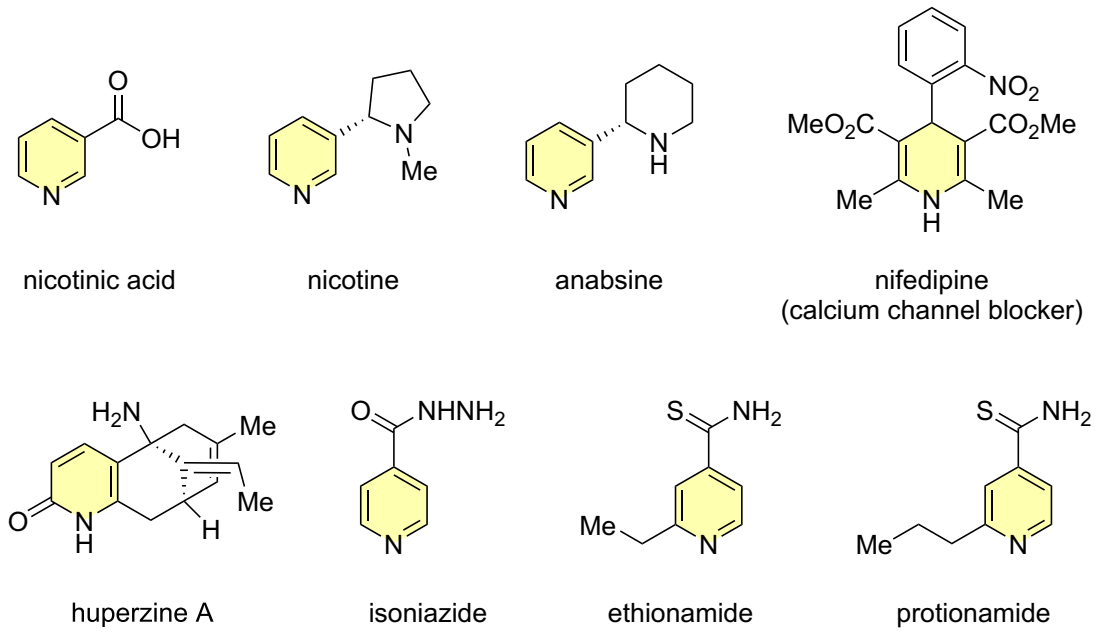


Figure 1. Natural pyridines and pyridine-containing medicines

from a traditional Chinese herb, is a potent, selective, and reversible acetylcholinesterase (AChE) inhibitor and has been widely used in China for the treatment of Alzheimer's disease [9].

Undoubtedly, pyridine derivatives play a crucial role in the therapy of tuberculosis as drugs like isoniazid [10], ethionamide, and protionamide [11] are the derivatives of pyridine.

Pyridinethiols are of great importance as the parts of biologically active compounds (**Figure 2**). The introduction of pyridine-4-thiol fragment helped to obtain an effective dual inhibitor of cancer-related cysteine isopeptidase human ubiquitin-specific proteases 7 (**USP7**) and 47 (**USP47**). This is considered to have the potential as a cancer therapeutic, owing to the ability to stabilize the tumor suppressor p53 and to decrease DNA polymerase ϐ (Polϐ). Both of them have potential antitumor effects [12].

Newly developed selective galectin-3 inhibitors combining high affinity (nM) with oral bioavailability, which reduce the profibrotic gene expression in liver myofibroblasts and display the antifibrotic activity in CCl_4-induced liver fibrosis and bleomycin-induced lung fibrosis mouse models, also have 5-bromopyridine-3-thiol galactoside in their structure. Compound **GB1211** was selected as the clinical candidate. It is currently in phase IIa clinical trials as a potential therapy for liver cirrhosis and cancer [13].

Pyridine-4-thione is also a part of the fused systems of the effective and potent BRAF inhibitors bearing a novel pyridoimidazolone hinge-binding group. They showed beneficial therapeutic efficacy in mutant BRAF tumors, including melanoma. A thiopyridine derivative was found to be 4-fold more potent than sorafenib in inhibiting WM266.4 melanoma cell growth [14].

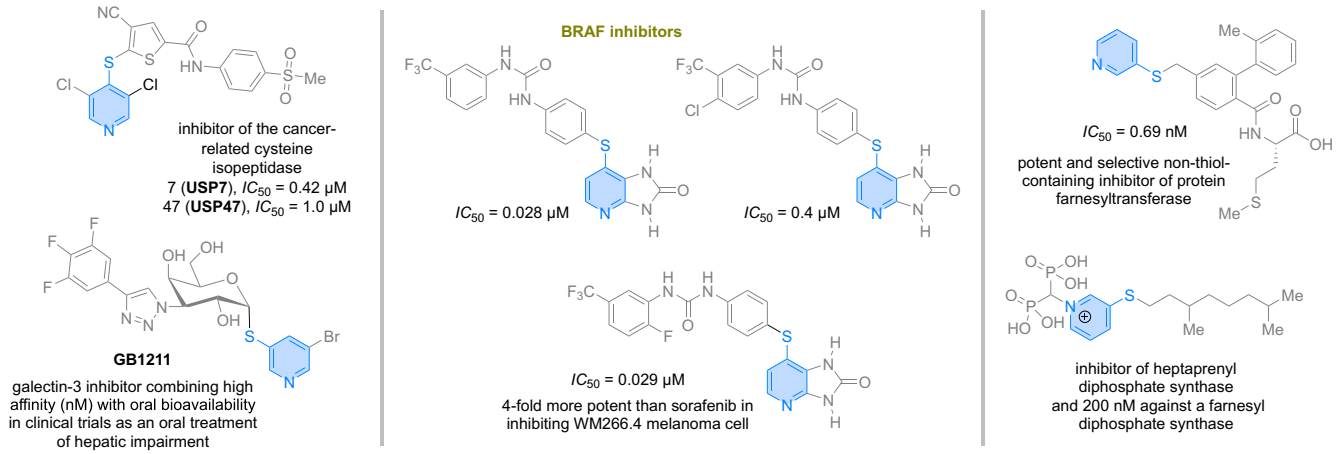


Figure 2. Biologically active compounds with a thiopyridine fragment

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

The *o*-tolyl biphenyl core dramatically and unexpectedly enhanced the potency of other compounds as exemplified the activity of potent and selective non-thiol-containing inhibitors of protein farnesyltransferase playing an important role for the Ras protein posttranslational modifications, such as the farnesylation of a cysteine residue near the C-terminus by the enzyme farnesyltransferase (FTase). The inhibition of this enzyme will render Ras inactive and block the uncontrolled mitogenic signaling pathway [15].

The compound with the antimicrobial activity against *Bacillus anthracis*, *Mycobacterium smegmatis*, *Bacillus subtilis,* and *Staphylococcus aureus* bearing pyridine-3-thione was reported. The compounds from this series target the biosynthesis of bacterial isoprenoids by inhibiting heptaprenyl diphosphate synthase and farnesyl diphosphate synthase at 200 nM [16].

Pyridine-2-thiol is a perfect ligand to stabilize the complexes with metals [17, 18].

The analysis of the screening compounds market revealed the urgent need for a variety of pyridine-3-thiols as building blocks. The analysis of the market using mathematical algorithms also clearly indicates a small number of blocks containing the SH group and the vacancy of this market segment [19].

■ Results and discussion

There are a number of approaches to the preparation of aromatic thiols that have been shown to be promising for the synthesis of pyridinethiols. The first reported method for obtaining pyridine-3-thiols was the reduction of the corresponding sulfonyl chloride [20]. In subsequent publications, the authors used more modern reduction methods, which made it possible to preserve a number of functional groups, such as the double bond or Boc protected amine [21, 22]. A number of researchers used pyridin-3-ol as a starting compound, which, when treated with dimethylthiocarbamoyl chloride, gave an *S*-aryl thiocarbamate, that could be further thermally rearranged into the corresponding *S*-aryl thiocarbamate according to the Newman–Kwart rearrangement [23]. It was shown that the hydrolysis of 3-pyridyl *S*-aryl thiocarbamate was a good way for the preparation of sodium salts of pyridine-3-thiol [15, 16]. Copper (II) sulfate catalyzed the interaction of 3-bromo pyridine with 1,2-ethandithiol was also reported as the one for preparing pyridine-3-thiol, which was alkylated *in situ* [24]. Some less convenient methods where the formation of disulfides was one of the by-processes were also reported [25].

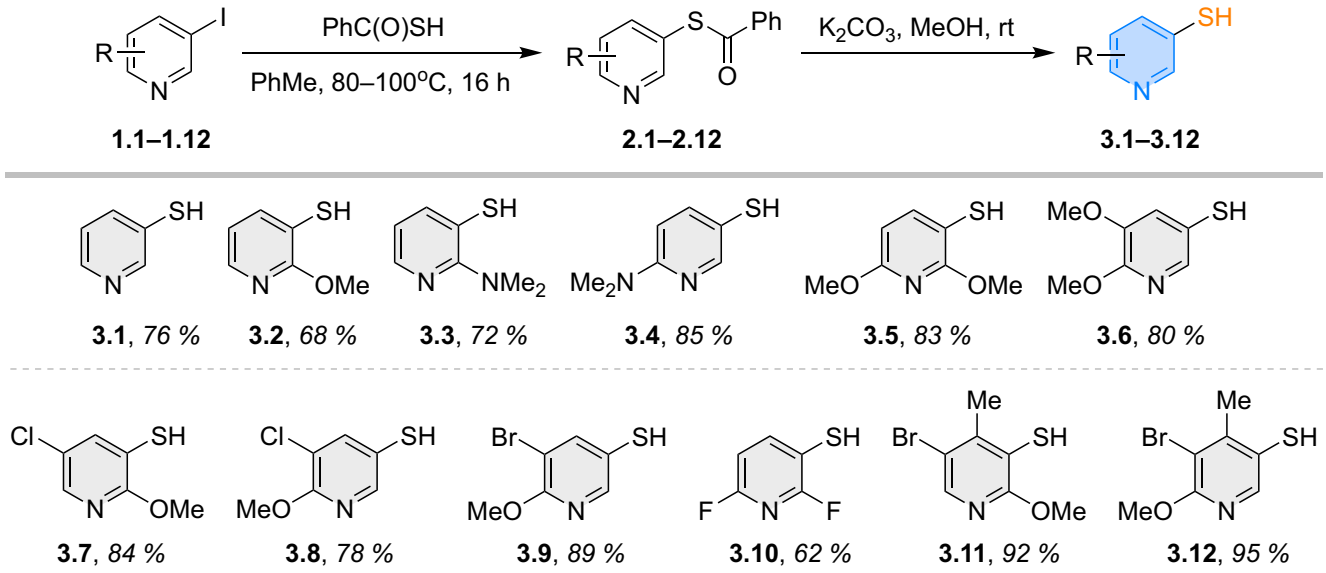
The analysis of the above methods has shown that most of them do not allow the isolation of pyridine-3-thiol with a purity of more than 95% and have not been studied on a wide variety of substituted pyridine derivatives. In recent years, the appearance of 3-iodopyridines in the market has led us to the idea of using them as starting compounds for the synthesis of corresponding thiols. Our attention was drawn to the possibility of the copper-catalyzed coupling of aryl iodides and thiobenzoic acid [26]. This reaction was previously carried out to form *S*-pyridin-3-yl benzenecarbothioate, which was subsequently used for the oxidative synthesis of the corresponding sulfochlorides [27].

The authors [26] also showed the possibility of *S*-phenyl benzenecarbothioate cleavage with the formation of thiophenol under mild conditions (K_2CO_3, MeOH, rt). Thus, we decided to apply this approach and investigate it on a number of substituted 3-iodopyridines as the starting compounds.

As a result, we have found that the reaction of a number of 3-iodopyrimidines with thiobenzoic acid in the presence of phenanthroline and DIPEA as an organic base readily produces the corresponding *S*-pyridin-3-yl benzenecarbothioate. For more thorough purification, the residue was subjected to the flash chromatography using a gradient (toluene/hexane 1:1 to 100% toluene) on silica gel. This procedure turned out to be important for a significant increase in the yield of thiols in the next step.

Further cleavage of thiobenzoate was carried out in a 10-fold volume of methanol and using a 40% excess of a dry potassium carbonate at room temperature. For the purification of the target pyridine-3-thiol, the salt was dissolved in water, and non-polar impurities were extracted with methylene chloride. To isolate the product, the aqueous layer was acidified to pH 5, and the product was extracted with methylene chloride. To remove residual acid, the organic layer was washed with saturated sodium bicarbonate solution, dried, and evaporated. This isolation procedure allows obtaining a pure product **3** without additional operations (**Scheme**). The use of this procedure enabled the preparation of a variety of substituted pyridine-3-thiols in high yields.

In the spectra of compounds **3** obtained, a clear signal of the SH group is observed in the range of 2.89–4.29 ppm in $CDCl_3$ and at 4.73 ppm



Scheme. The synthesis of substituted pyridine-3-thiols

in DMSO-d_6 for 2,6-dimethoxypyridine-3-thiol **3.5**, indicating, together with the HRMS spectral data, the formation of pure compound **3** with a thione group without disulfide impurities.

■ Conclusions

An effective and practical two-step procedure for the preparation of pyridine-3-thiol starting from 3-iodopyridines has been developed. The scope of the iodo derivatives that could be used for the reaction has been studied, and as a result, 12 substituted pyridine-3-thiols have been obtained with a high yield.

■ Experimental part

All of the regents were taken from "Enamine" Ltd stock. Analytical TLC was performed using Polychrom SI F254 plates. The column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H NMR spectra were recorded on a Varian Unity Plus 400 (400 MHz) or a Bruker 170 AVANCE 500 (500 MHz) instrument; ^{13}C NMR spectra were recorded on a Bruker 170 AVANCE 500 (126 MHz) or an Agilent ProPulse 600 (151 MHz) spectrometer; ^{19}F spectra were obtained on a Varian Unity Plus 400 (376 MHz) spectrometer. HRMS spectra were acquired with an Agilent 6200 Series TOF and 6500 Series Q-TOF LC/MS System.

The general procedure for the coupling step (compounds 2)

The reaction was carried out in a single-necked flask. To 0.1 mol of the corresponding 3-iodopyridine **1**, 150 mL of toluene was added, then 3.6 g of phenanthroline, 2 g of CuI, 30 mL of diisopropylethylamine and 14 mL of thiobenzoic acid were added while stirring. The flask was filled with argon. The reaction mixture was heated to 80–100 °C for 12–16 h. Then 150 ml of hexane was added to the cool reaction mixture. The reaction mixture was chromatographed on a 200 mL Schott funnel (50–60°C, 100–150 mL of silica gel) starting from the toluene/hexane 1:1 phase and pure toluene at the end furnishing thioesters **2**.

The general procedure for the hydrolysis step (thiols 3)

The resulting thiobenzoate **2** was added to methanol (1 g per 10 mL), then 40% excess of dry K_2CO_3 was added there. The hydrolysis took 1 h at 25°C. Then methanol was evaporated, and the residue was dissolved in the same amount of water. The amount of water was twice washed with dichloromethane, then acidified to pH 5 and extracted with dichloromethane. The dichloromethane extract was separated and washed with the aqueous sodium bicarbonate saturated solution. Then methylene chloride was evaporated leaving a residue of the pure product **3**.

Pyridine-3-thiol (**3.1**)

A yellow powder. Yield – 40 g (76%). M. p. 77–79°C dec. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.26 (1H, s, SH), 7.17 (1H, dd, J = 8.1, 4.7 Hz), 7.61 (1H, dt, J = 8.1, 2.0 Hz), 8.27–8.45 (1H, m), 8.52 (1H, d, J = 2.4 Hz). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 123.1, 127.8, 136.3, 146.3, 149.3. HRMS (ESI/TOF-Q), m/z: calcd for C_5H_5NS 111.0143, found 111.0143.

2-Methoxypyridine-3-thiol (**3.2**)

A yellow liquid. Yield – 25 g (68%). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.76 (1H, s, SH), 4.01

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

(3H, s), 6.79 (1H, dd, J = 7.4, 4.9 Hz), 7.51 (1H, dd, J = 7.4, 1.7 Hz), 7.95 (1H, dd, J = 5.0, 1.7 Hz). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 53.5, 115.6, 116.6, 136.6, 142.7, 158.8. HRMS (ESI/TOF-Q), m/z: calcd for C_6H_7NOS 141.0248, found 141.0246.

2-(Dimethylamino)pyridine-3-thiol (**3.3**)

A yellow liquid. Yield – 20.2 g (72%). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.89 (7H, m, $2NCH_3$ + SH), 4.30 (1H, s), 6.84 (1H, ddd, J = 7.6, 4.7, 2.0 Hz), 7.55 (1H, dd, J = 7.7, 1.8 Hz), 8.10 (1H, dd, J = 4.8, 1.8 Hz). ^{13}C NMR (151 MHz, $CDCl_3$), δ, ppm: 41.7, 118.1, 122.7, 138.1, 144.2, 160.1. HRMS (ESI/TOF-Q), m/z: calcd for $C_7H_{10}N_2S$ 154.0565, found 154.0563.

6-(dimethylamino)pyridine-3-thiol (**3.4**)

A yellow powder. Yield – 18 g (85%). M. p. 65–68°C. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.05 (7H, m, $2NCH_3$ + SH), 6.41 (1H, d, J = 8.8 Hz), 7.41–7.47 (1H, m), 8.18 (1H, d, J = 2.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 37.6, 105.4, 108.7, 141.3, 150.9, 157.9. HRMS (ESI/TOF-Q), m/z: calcd for $C_7H_{10}N_2S$ 154.0565, found 154.0562.

2,6-Dimethoxypyridine-3-thiol (**3.5**)

A yellow powder. Yield – 39 g (83%). M. p. 43–46°C (dec.). ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.82 (3H, d, J = 1.2 Hz), 3.90 (3H, d, J = 1.3 Hz), 4.73 (1H, s, SH), 6.35 (1H, dd, J = 8.1, 1.3 Hz), 7.62 (1H, dd, J = 8.1, 1.3 Hz). ^{13}C NMR (151 MHz, $CDCl_3$), δ, ppm: 53.4, 54.0, 101.5, 101.8, 102.8, 141.8, 158.9, 161.6. HRMS (ESI/TOF-Q), m/z: calcd for $C_7H_9NO_2S$ 171.0354, found 171.0350.

5,6-Dimethoxypyridine-3-thiol (**3.6**)

A white powder. Yield – 41 g (80%). M. p. 38–42°C. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.29 (1H, s, SH), 3.84 (3H, d, J = 2.5 Hz), 3.97 (3H, d, J = 2.5 Hz), 7.02 (1H, t, J = 2.3 Hz), 7.70 (1H, d, J = 2.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 53.2, 55.2, 116.7, 120.3, 138.3, 143.3, 153.2. HRMS (ESI/TOF-Q), m/z: calcd for $C_7H_9NO_2S$ 171.0354, found 171.0352.

5-Chloro-2-methoxypyridine-3-thiol (**3.7**)

A gray powder. Yield – 43.8 g (84%). M. p. 48–52°C (dec.). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.82 (1H, s, SH), 3.98 (3H, s), 7.48 (1H, d, J = 2.3 Hz), 7.86 (1H, t, J = 2.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 53.9, 117.4, 123.5, 135.7, 140.7, 157.2. HRMS (ESI/TOF-Q), m/z: calcd for C_6H_6ClNOS 174.9859, found 174.9856.

5-Chloro-6-methoxypyridine-3-thiol (**3.8**)

A white powder. Yield – 39.8 g (78%). M. p. 53–58°C (dec.). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.30 (1H, s, SH), 3.99 (3H, s), 7.65 (1H, d, J = 2.2 Hz), 8.02 (1H, d, J = 2.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 53.9, 117.6, 117.8, 140.6, 146.0, 158.0. HRMS (ESI/TOF-Q), m/z: calcd for C_6H_6ClNOS 174.9859, found 174.9858.

5-Bromo-6-methoxypyridine-3-thiol (**3.9**)

A white powder. Yield – 41.5 g (89%). M. p. 49–53°C (dec.). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.30 (1H, s, SH), 3.98 (3H, s), 7.82 (1H, d, J = 2.2 Hz), 8.06 (1H, d, J = 2.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 54.1, 106.4, 117.9, 143.9, 146.8, 158.7. HRMS (ESI/TOF-Q), m/z: calcd for C_6H_6BrNOS 218.9353, found 218.9353.

2,6-Difluoropyridine-3-thiol (**3.10**)

A yellow powder. Yield – 25 g (62%). M. p. 39–44°C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 3.56 (1H, s, SH), 6.80 (1H, dd, J = 8.2, 3.0 Hz), 7.69–7.85 (1H, m). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -72.31, -66.11. ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 106.3 (dd, J = 35.3, 5.9 Hz), 109.7 (dd, J = 34.1, 6.2 Hz), 144.6 (dd, J = 7.3, 3.2 Hz), 155.9 (dd, J = 14.0, 3.2 Hz), 158.8 (dd, J = 242.3, 13 Hz), 159.4 (dd, J = 246.3, 12 Hz). HRMS (ESI/TOF-Q) m/z: calcd for C_5H_3FNS 146.9954, found 146.9955.

5-Bromo-2-methoxy-4-methylpyridine-3-thiol (**3.11**)

A white powder. Yield – 45.3 g (92%). M. p. 63–65°C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.42 (3H, s), 4.02 (3H, s), 4.29 (1H, s, SH), 8.03 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 20.0, 54.0, 114.9, 117.5, 142.2, 143.5, 157.0. HRMS (ESI/TOF-Q), m/z: calcd for C_7H_8BrNOS 232.9510, found 232.9506.

6-methoxy-5-Bromo-4-methylpyridine-3-thiol (**3.12**)

A white powder. Yield – 44.5 g (90%). M. p. 65–67°C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.52 (3H, s), 3.16 (3H, s), 3.97 (1H, s, SH), 8.04 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 21.2, 54.1, 109.3, 118.9, 146.0, 149.0, 159.1. HRMS (ESI/TOF-Q), m/z: calcd for C_7H_8BrNOS 232.9510, found 232.9506.

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

Journal of Organic and Pharmaceutical Chemistry

Original Research

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UDC 547-304.4+547.538.141+ 547.775+519.688

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The Theoretical and Experimental Study of Diazomethane-Styrene [3+2]-Cycloadditions

Abstract

Pyrazolines are an important class of heterocyclic compounds known for their biological activities, making them attractive objects for medicinal chemistry. This study investigated the regioselective [3+2]-cycloaddition of diazomethane with *para*-substituted styrenes featuring electron-withdrawing (EWG) and electron-donating (EDG) groups. Experimental results have demonstrated that the electronic properties of substituents significantly affect the reaction efficiency and regioselectivity, as well as the product stability. At the same time, EWG provided lower activation barriers and higher reaction yields. Calculations performed by the density functional theory (DFT) method confirmed the experimental data allowing us to understand in detail the reaction mechanism, activation energy values, and thermodynamic parameters. This integrated experimental and theoretical approach improves understanding of the effects of substituents, contributing to the rational design of substituted pyrazolines.

Keywords: diazomethane; styrene; pyrazoline; cycloaddition; DFT calculations

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Теоретичне та експериментальне дослідження реакції [3+2]-циклоприєднання діазометану до стиренів

Анотація

Піразоліни є важливим класом гетероциклічних сполук та відомі своєю біологічною активністю, що робить їх привабливими об'єктами для медичної хімії. У цій роботі досліджено регіоселективне [3+2]-циклоприєднання діазометану до *пара*-заміщених стиренів, які містять електроноакцепторні (EWG) та електронодонорні (EDG) групи. Експериментальні результати продемонстрували, що електронні властивості замісників помітно впливають на ефективність і регіоселективність реакції, а також стабільність продукту. Із цим EWG забезпечували нижчі бар'єри активації та вищі виходи реакції. Розрахунки, виконані методом теорії функціоналу густини (DFT), підтвердили експериментальні дані, давши змогу детально зрозуміти механізм реакції, значення енергії активації і термодинамічні параметри взаємодії. Інтегрований експериментально-теоретичний підхід покращує розуміння впливу замісників, сприяючи раціональному дизайну заміщених піразолінів.

Ключові слова: діазометан; стирен; піразолін; циклоприєднання; теорія функціоналу густини

Citation: Ivonin, S. P.; Shuvakin, S. I. The Theoretical and Experimental Study of Diazomethane-Styrene [3+2]-Cycloadditions. *Journal of Organic and Pharmaceutical Chemistry* **2025**, *23* (1), 49–55.
https://doi.org/10.24959/ophcj.25.326552
Supporting information: Details of experiments and synthesis; spectral and analytical data for the compounds synthetized; copies of ^{1}H, ^{19}F, and ^{13}C NMR spectra. Details of calculations.
Received: *29 December 2024*; **Revised:** *24 March 2025*; **Accepted:** *25 March 2025*

Funding: The work was supported by the National Reseach Foundation of Ukraine (grant No. 0124U003838).
Conflict of interests: The authors have no conflict of interests to declare.

Introduction

Pyrazolines, five-membered nitrogen-containing heterocycles, are widely recognized for their significant biological activities, including antimicrobial, anti-inflammatory, analgesic, antidepressant, and anticancer properties, making them valuable scaffolds in medicinal chemistry [1].

The regioselective [3+2] cycloaddition between diazomethane (CH_2N_2) and styrene derivatives is an important synthetic method for preparing substituted pyrazolines [2]. Despite its established importance, practical applications have historically been limited due to safety and operational challenges associated with diazomethane handling [3, 4]. However, recent advancements, particularly through flow chemistry techniques, have improved the safety and reproducibility of these reactions [5].

Previous studies have shown that substituents in styrene significantly affect the reaction efficiency, regioselectivity, and stability of the products. Electron-withdrawing groups generally enhance reactivity, while electron-donating groups reduce it [6]. However, isolation and thorough characterization of intermediate Δ^1-pyrazolines remain scarce despite their synthetic potential as precursors for various valuable derivatives [7].

In this study, using flow chemistry for safer handling of diazomethane, we investigated the regioselective cycloaddition of diazomethane with *para*-substituted styrenes featuring different electronic properties. By integrating experimental results and calculations based on density functional theory (DFT), we aim to gain an understanding of the effect of substituents and increase the practical synthetic utility of pyrazoline derivatives for medicinal chemistry applications.

Results and discussion

Styrenes containing substituents of different electronic nature in position 4 of the benzene ring were introduced into the reaction with diazomethane (**Figure 1**). By doing so, we found that 1-fluoro-4-vinylbenzene (**1a**), methyl 4-vinylbenzoate (**1b**), and 4-vinylbenzonitrile (**1c**) reacted regioselectively with diazomethane, forming the corresponding Δ^1-pyrazolines (**Figure 1**). Analysing crude reaction mixtures by ^{1}H NMR method evidenced that the reaction of **1b,c** with an excess of diazomethane (3 equiv.) led to 60% conversion of products **2b,c**, while the conversion of **1a** to **2a** was only 30%. After purification by chromatography on silica gel, pure products **2a–c** were isolated with the yields of 24–47%. It is worth noting that the use of a larger amount of diazomethane or increased reaction time (more than 2 days) did not improve the conversion to pyrazoline **2a–c**.

The interaction of **1d** with diazomethane occurred almost quantitatively, as evidenced by the absence of the olefin proton signals in the ^{1}H NMR spectrum of the crude reaction mixture and the TLC data of the reaction mixture. However, it was not possible to isolate the product of the [3+2]-cycloaddition **2d** due to the polymerization of the reaction mixture content upon the evaporation of the solvent at temperatures below 0°C.

The interaction of alkenes **1e–f** with diazomethane under the standard conditions did not lead to the formation of pyrazolines, and the starting alkenes were isolated unchanged from the reaction mixture (**Figure 1**). For **1f**, we observed the formation of a small amount (5–7% according to ^{1}H NMR data) of the cyclopropanation product – 1-cyclopropyl-4-methylbenzene (**4f**). Diazomethane ntroduced into the reaction mostly formed a polymer. Additionally, using 4-vinylpyridine (**1g**) as a substrate in the reaction with diazomethane resulted in only the polymerization of **1g**.

The treatment of ethereal solutions of pyrazolines **2a,b** with HCl in a dry diethyl ether led to the isomerization into the corresponding Δ^2-pyrazolines **3a,b** (**Figure 1**).

A cursory analysis of the experimental data suggests that the introduction of an acceptor substituent into the aromatic fragment increases the activity of styrene in the reaction, while a donor substituent causes the opposite effect. Therefore, it became necessary to investigate this reaction by quantum-chemical calculations in the DFT approximation. As the study objects, we chose parent styrene undergoing a [3+2]-cycloaddition reaction with CH_2N_2, as well as *p*-F, *p*-CO_2Me-substituted derivatives, and, additionally, we employed three styrenes that did not react with diazomethane.

The reaction of styrenes **1** with diazomethane proceeded as a typical [3+2]-cycloaddition (**Figure 2**, *A*). In the structure of the transition state **TS-1h** (**Figure 2**, *B*), the interatomic distances C···C and C···N preceding the formation of the corresponding bonds in the cyclic product **2h** were 2.144 and 2.342 Å, respectively, therefore the process was quite synchronous. As shown by quantum chemical calculations, the values of the Gibbs free energies of activation of the cyclization

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

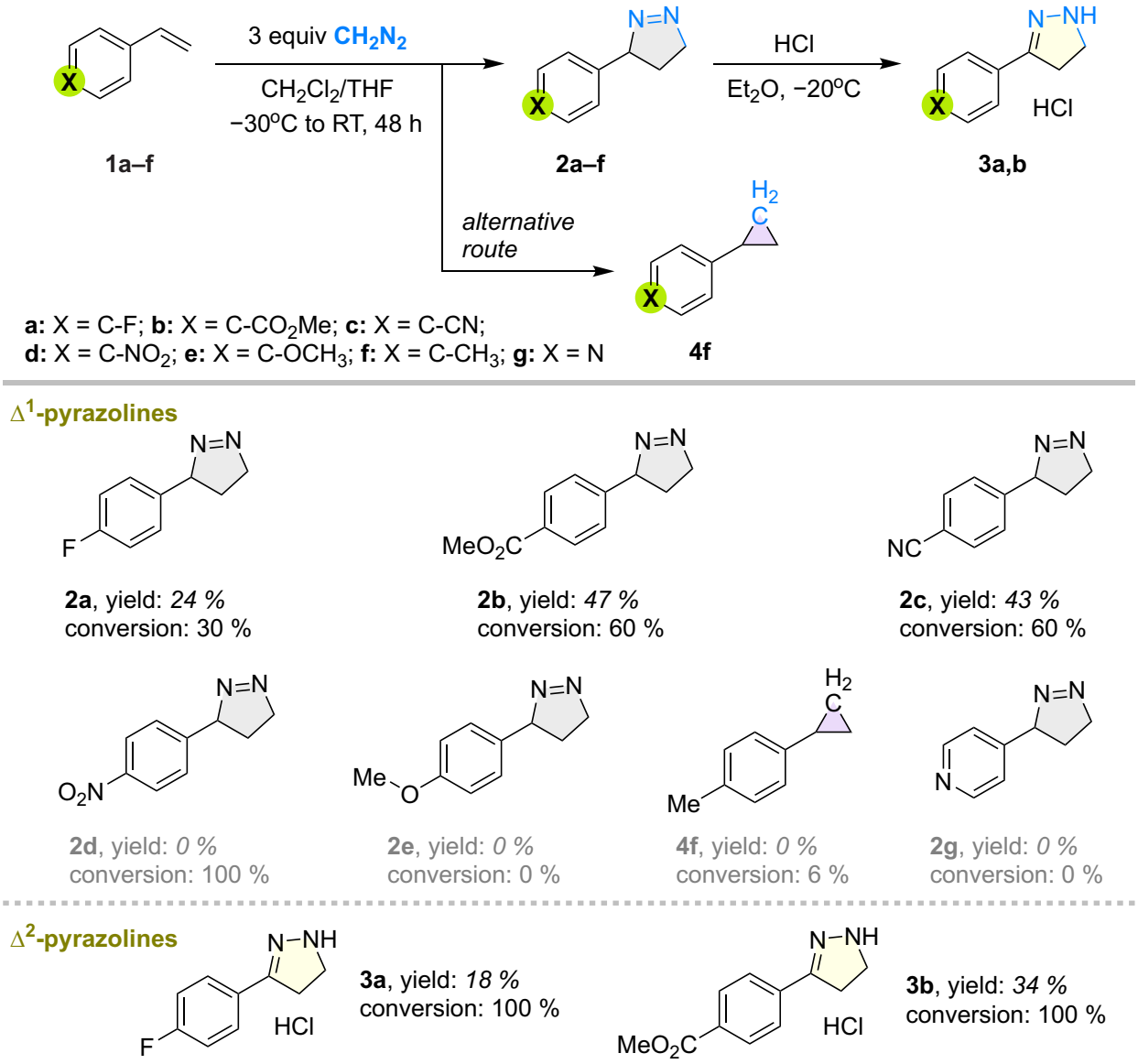
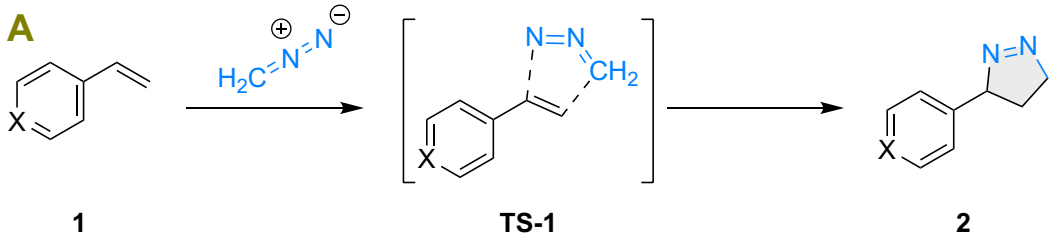


Figure 1. The synthesis of Δ¹-/Δ²-pyrazolines from *p*-substituted styrenes: scope and limitations

process (**Table 1**, $DG^{\neq}$) significantly exceeded the corresponding values of the thermally corrected energy and enthalpy values ($DE^{\neq}$ and $DH^{\neq}$); it was the result of the entropic component effect in the addition reaction. All the values were slightly dependent on the nature of the substitution in the benzene ring. However, in the case of styrenes with electron-withdrawing substituents in the aromatic moiety (**1b** and **1g**), the activation barrier values were somewhat lower than in the remaining compounds. However, there was no clear correlation between the results of calculations and the experiment. The cycloaddition products **2a,b,f–h** were significantly more favorable than the sum of the energies of the starting compounds **1a,b,f–h** and diazomethane, i.e., in all cases considered, the reaction was exothermic and exergonic. Therefore, the possibility of occurring a reverse reaction could be excluded.

■ Conclusions

This work presents an experimental and theoretical analysis of the regioselective [3+2]-cycloaddition of diazomethane with *para*-substituted styrenes. The application of the flow chemical approach made it possible to ensure safe handling of hazardous diazomethane and its controlled use, offering reproducible access to substituted pyrazolines. Experimental results have clearly demonstrated how substituent electronic effects significantly affect the reaction efficiency and regioselectivity, as well as the product stability, with electron-withdrawing groups facilitating cycloaddition. Calculations performed by the density functional theory (DFT) method confirmed these observations, providing valuable mechanistic insights and clarifying the energetic and structural aspects of reaction intermediates and transition states.



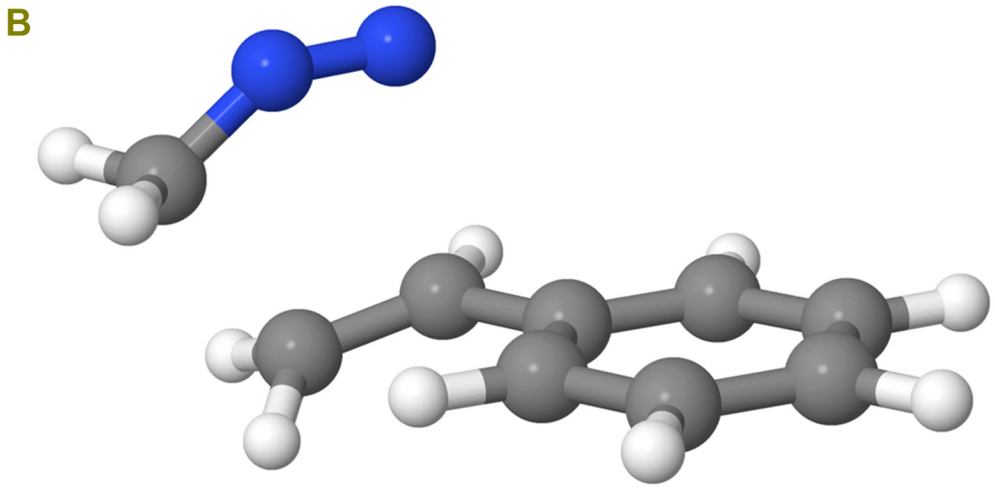


Figure 2. The model reaction used for quantum chemical studies (*A*); Jmol [8, 9] graphical representation of the transition state structure of **TS-1h** optimized in the M06-2X/def2-TZVP level of approximation (*B*)

Table 1. Calculated values of thermally corrected energies, enthalpies and Gibbs free energies of activation ($\Delta E^{\neq}$, $\Delta H^{\neq}$ та $\Delta G^{\neq}$, respectively, kcal mol^{-1}), corresponding to the transition state structures **TS-1a,b,f–h**, and energies, enthalpies and Gibbs free energies of forming **2a,b,f–h** (ΔE, ΔH and ΔG, respectively, kcal mol^{-1}) calculated in the CPCM(CH_2Cl_2)//M06-2X/def2-TZVP approximation

Structure	$\Delta E^{\neq}$	$\Delta H^{\neq}$	$\Delta G^{\neq}$	ΔE	ΔH	ΔG
TS-1h	14.2	13.6	26.6	-32.9	-33.5	-19.6
TS-1f	14.7	14.1	27.1	-33.3	-33.9	-20.5
TS-1a	14.4	13.8	26.8	-33.1	-33.6	-19.8
TS-1b	12.5	11.9	24.6	-33.1	-33.7	-19.8
TS-1g	12.0	11.5	24.8	-32.9	-33.5	-19.3

This integrated experimental and theoretical study improves understanding of the effects of substituents in diazomethane-based cycloadditions, contributing to the rational design and synthesis of structurally diverse pyrazolines for further applications in medicinal chemistry and organic synthesis.

■ Experimental part

All starting compounds and solvents were obtained from Enamine Ltd. and used without additional purification. Diazomethane was generated in-flow as it was reported previously [5]. The composition of hydrochloride salts was determined by the acid-base titration method. NMR experiments were performed on a Bruker Avance III (at 302 MHz for ^{1}H NMR, 188 MHz for ^{19}F NMR, and 76 MHz for ^{13}C NMR) in the DMSO-d_6 or D_2O solution. NMR chemical shifts are reported in ppm units with the use of the δ scale and referenced using the residual solvent peaks. Mass spectra were taken on an Agilent LC/MSD SL 1100 instrument (atmospheric pressure electrospray ionization (ES-API)). Elemental analyses were performed at the Analytical Laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine.

Details of calculations

All calculations were carried out using the ORCA (version 5.03) [10, 11] program package. First, the geometry optimization was performed using the BP86/TZVP level of approximation [12, 13] in combination with the Resolution of

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the Identity (RI) [14–17] routine. Then the structures were re-optimized using the same program at the M06-2X/def2-TZVP level of theory [18]. The TZVP and def2-TZVP basis sets were the TZV triple-zeta basis sets [19] extended by adding polarization functions, as implemented in the ORCA program. The RI – "chain of spheres" approximation (RIJCOSX) [20] was utilized in the case of the M06-2X functional to increase the calculation speed and efficiency. The solvent effects were taken into account, calculating the single-point energy values using the empirical CPCM procedure developed by Cammi and Tomasi [21]. In order to find the best approximation to transition state structures, the relaxed scanning of potential energy surfaces was performed at the RI-BP86/SV(P) level of approximation using the ORCA program package. The SV(P) basis sets were Ahlrichs split-valence basis sets [22] with one set of polarization d-functions for non-hydrogen atoms. Vibration frequencies and corrections for calculation of relative energies (ΔE) and relative free Gibbs energies (ΔG) were derived analytically at the BP86/TZVP level of theory and numerically for the M06-2X/def2-TZVP approach. For the structures corresponding to local energy minima, no imaginary frequencies were detected by the vibration analysis. The Jmol [8, 9] program was used for the graphical presentation of **TS-1h**.

The general procedure for the synthesis of pyrazolines 2a–c

0.01 mol of 4-substituted styrene was dissolved in 20 mL of a dry methylene chloride. A solution of diazomethane (0.03 mol, 3 equiv.) generated by a flow reactor at a rate of 0.40 mol h^{-1} was added dropwise to the styrene solution cooled to -30 °C over 4.5 min. The reaction mixture was left to stir in an ice bath for 4 h and allowed to stir for two days at ambient temperature in the darkness. The reaction mixture was evaporated under reduced pressure, redissolved in 50 mL of MTBE and filtered through cotton wool to remove the polymer formed by decomposition of diazomethane. The filtrate was evaporated, and chromatography on silica gel (hexane-MTBE, 70:30) gave the pyrazolines **2a–c**.

The general procedure for the synthesis of pyrazolines 3a,b

0.01 mol of 4-substituted styrene was dissolved in 20 mL of a dry methylene chloride. A solution of diazomethane (0.03 mol, 3 equiv.) generated by a flow reactor at a rate of 0.40 mol h^{-1} was added dropwise to the styrene solution cooled to -30 °C over 4.5 min. The reaction mixture was left to stir in an ice bath for 4 h and allowed to stir for two days at ambient temperature in the darkness. The reaction mixture was evaporated under reduced pressure, redissolved in 50 mL of a dry diethyl ether and filtered through a layer of cotton wool. The filtrate was cooled to -20 °C, and 5 mL of a saturated solution of HCl in diethyl ether was added dropwise. The reaction mixture was stirred vigorously for 10 min, and the precipitate formed was filtered off. The precipitate was collected and further dried in an oil pump vacuum, giving pyrazolines **3a,b**.

3-(4-Fluorophenyl)-4,5-dihydro-3H-pyrazole (**2a**)

A yellow oil. Yield – 390 mg (24%). Anal. Calcd for $C_9H_9FN_2$, %: C 65.84, H 5.53, N 17.06. Found, %: C 65.99, H 5.41, N 17.11. ^{1}H NMR (302 MHz, DMSO-d_6), δ, ppm: 1.23–1.44 (1H, m), 2.00–2.26 (1H, m), 4.16–4.38 (1H, m), 4.72–4.88 (1H, m), 5.29–5.46 (1H, m), 7.12–7.25 (2H, m), 7.25–7.35 (2H, m). ^{13}C NMR (76 MHz, DMSO-d_6), δ, ppm: 25.63, 76.66, 89.55, 115.48 (d, J = 21.3 Hz), 129.41 (d, J = 8.2 Hz), 135.88, 161.62 (d, J = 243.5 Hz). ^{19}F NMR (188 MHz, DMSO-d_6), δ, ppm: -114.96. MS (ES-API), m/z: 165 $[M+H]^+$.

Methyl 4-(4,5-dihydro-3H-pyrazol-3-yl)benzoate (**2b**)

An easily fusible solid. Yield – 960 mg (47%). Anal. Calcd for $C_{11}H_{12}N_2O_2$, %: C 64.69, H 5.92, N 13.72. Found, %: C 64.78, H 5.87, N 13.64. ^{1}H NMR (302 MHz, DMSO-d_6), δ, ppm: 1.44–1.31 (1H, m), 2.14–2.26 (1H, m), 3.86 (3H, s), 4.26–4.38 (1H, m), 4.79–4.90 (1H, m), 5.49 (1H, t, J = 9.0 Hz), 7.43 (2H, d, J = 8.1 Hz), 7.99 (2H, d, J = 8.1 Hz). ^{13}C NMR (76 MHz, DMSO-d_6), δ, ppm: 25.48, 52.20, 76.92, 89.91, 127.76, 128.82, 129.62, 144.94, 166.04. MS (ES-API), m/z: 205 $[M+H]^+$.

4-(4,5-Dihydro-3H-pyrazol-3-yl)benzonitrile (**2c**)

A yellow oil. Yield – 736 mg (43%). Anal. Calcd for $C_{10}H_9N_3$, %: C 70.16, H 5.30, N 24.54. Found, %: C 70.02, H 5.38, N 24.50. ^{1}H NMR (302 MHz, DMSO-d_6), δ, ppm: 1.20–1.54 (1H, m), 2.03–2.36 (1H, m), 4.15–4.46 (1H, m), 4.65–5.03 (1H, m), 5.48 (1H, t, J = 9.0 Hz), 7.48 (2H, d, J = 8.4 Hz), 7.85 (2H, d, J = 8.2 Hz). ^{13}C NMR (76 MHz, DMSO-d_6), δ, ppm: 25.38, 77.03, 89.77, 110.47, 118.77, 128.44, 132.70, 145.03. MS (ES-API), m/z: 172 $[M+H]^+$.

3-(4-Fluorophenyl)-4,5-dihydro-1H-pyrazole hydrochloride (**3a**)

A brown solid. Yield – 360 mg (18%). Anal. Calcd for $C_9H_{10}ClFN_2$, %: C 53.88, H 5.02, N 13.96. Found, %: C 53.81, H 5.10, N 14.04. ^{1}H NMR

(302 MHz, DMSO-d_6), δ, ppm: 3.46–3.68 (4H, m), 7.34–7.46 (2H, m), 7.90–8.02 (2H, m), 12.20–12.88 (1H, br. s). ^{13}C NMR (76 MHz, DMSO-d_6), δ, ppm: 35.26, 42.42, 116.31 (d, J_{C-F} = 22.1 Hz), 125.37, 131.27 (d, J_{C-F} = 9.2 Hz), 164.66 (d, J_{C-F} = 251.3 Hz), 173.26. ^{19}F NMR (188 MHz, DMSO-d_6) δ, ppm: -106.52. MS (ES-API), *m/z:* 165 $[M+H]^+$.

Methyl 4-(4,5-dihydro-1H-pyrazol-3-yl)benzoate hydrochloride (**3b**)

A yellow solid. Yield – 818 mg (34%). Anal. Calcd for $C_{11}H_{13}ClN_2O_2$, %: C 54.89, H 5.44, N 11.64. Found, %: C 55.05, H 5.37, N 11.56. ^{1}H NMR (302 MHz, D_2O), δ, ppm: 3.55–3.71 (2H, m), 3.84 (5H, s + m), 7.82 (2H, d, J = 8.2 Hz), 7.89 (2H, d, J = 8.5 Hz). ^{13}C NMR (76 MHz, D_2O), δ, ppm: 36.43, 43.75, 53.49, 129.35, 130.40, 132.50, 134.78, 168.50, 177.84. MS (ES-API), *m/z:* 205 $[M+H]^+$.

Aknowledgments

The work would not be possible without the National Reseach Foundation of Ukraine, which kindly provided funding for creating a computer cluster at the Taras Shevchenko National University of Kyiv used for the quantum-chemical calculations in this work. The authors also thank Prof. Dr. Alexander B. Rozhenko, Institute of Organic Chemistry, NAS of Ukraine, for performing the DFT calculations.

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