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A Scalable Synthesis of 4-Functionalized Isoxazolidines and Pyrazolidines

Abstract

A practical and scalable cyclization method for the preparation of C4-functionalized isoxazolidine and pyrazolidine building blocks is described. The methodology is based on the use of commercially available 1,3-dihalide and protected hydroxylamine or hydrazine derivatives under unified NaH/DMF conditions, enabling direct assembly of both *N*,*O*- and *N*,*N*-heterocycles. The process is operationally robust and successfully implemented on an over 100 g scale. The oxidative conversion of exocyclic alkene intermediates made it possible to obtain isoxazolidin-4-one and pyrazolidin-4-one scaffolds. The resulting pyrazolidine derivatives demonstrate a broad tolerance to reductive and oxidative conditions, whereas isoxazolidines exhibit certain stability limitations. The combination of the modular C4 diversification, orthogonal nitrogen protection, and preparative scalability transforms these saturated heterocycles into practically accessible building blocks for medicinal chemistry applications.

Keywords: synthesis; isoxazolidine; pyrazolidine; scale-up; functionalization

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Масштабований синтез 4-функціоналізованих ізоксазолідинів та піразолідинів

Анотація

У статті описано практичний та масштабований метод одержання С4-функціоналізованих білдинг-блоків ізоксазолідину та піразолідину. Методологія базується на використанні комерційно доступних 1,3-дигалогеніду й захищених похідних гідроксиламіну або гідразину в уніфікованих умовах NaH/DMF, що забезпечує пряме утворення як *N*,*O*-, так і *N*,*N*-гетероциклів. Процес характеризується надійністю та масштабуванням понад 100 г. Окиснення проміжних продуктів з екзоциклічним алкеновим фрагментом дозволило одержати похідні ізоксазолідин-4-ону та піразолідин-4-ону. Отримані піразолідини демонструють стійкість до відновних та окиснювальних умов, тоді як ізоксазолідини характеризуються певними обмеженнями стабільності. Поєднання модульної С4-функціоналізації, ортогонального захисту атомів нітрогену та можливості масштабування перетворює ці насичені гетероцикли на доступні білдинг-блоки для застосування в медичній хімії.

Ключові слова: синтез; ізоксазолідин; піразолідин; масштабування; функціоналізація

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Introduction

In contemporary medicinal chemistry, it is virtually impossible to envision drug-like molecules devoid of cyclic frameworks. More than 90% of approved small-molecule drugs contain at least one ring system, and 67% of compounds currently in the clinical development rely on ring motifs already present in marketed drugs [1]. Among these, heterocycles play a particularly prominent role as the introduction of heteroatoms enables fine-tuning of the electronic distribution, hydrogen-bonding capacity, conformational preferences, and key physicochemical parameters, such as lipophilicity, solubility, and metabolic stability [2].

Nitrogen-containing heterocycles are especially dominant [3]. The analysis of 321 small-molecule drugs approved between 2013 and 2023 revealed that 82% of them incorporate at least one *N*-heterocyclic unit [4]. While aromatic systems are extensively represented in pharmaceutical chemistry, their saturated counterparts remain comparatively underexplored. Among them, there are isoxazolidines and pyrazolidines, fully hydrogenated analogs of isoxazoles and pyrazoles, which represent structurally intriguing yet underutilized five-membered heterocycles. Despite the prevalence of their aromatic congeners in approved drugs [1, 5], saturated isoxazolidine and pyrazolidine motifs are rarely encountered in medicinal chemistry programs (**Figure 1**A). This discrepancy likely stems not from intrinsic limitations of the scaffolds, but from the lack of general, practical, and scalable synthetic routes that enable structural diversification. Nevertheless, emerging examples suggest their untapped potential (**Figure 1**B). Cevidoplenib (SKI-O-703), an experimental SYK kinase inhibitor that received Orphan Drug designation from the FDA in 2024 for the treatment of immune thrombocytopenia, incorporates an isoxazolidine ring [6, 7]. Similarly, the pyrazolidine framework has appeared in drug discovery efforts, including the antiemetic candidate dazopride [8] and, more recently, in dual orexin receptor antagonist IDOR-1117-1680 [9]. Notably, these examples share the substitution in position C4 of the heterocycle, underscoring the synthetic and medicinal relevance of this diversification site.

Despite these precedents, synthetic access to C4-functionalized isoxazolidines (**Figure 1**C) and pyrazolidines (**Figure 1**D) remains limited. Most reported methodologies rely on the cyclization of protected hydroxylamines [10–14] or hydrazines [15–20] with 1,3-dielectrophiles. While efficient in selected cases, these approaches often focus on the *N*-functionalization, provide a limited carbon-centered diversification (particularly in C4), require the multi-step precursor preparation, or are demonstrated only on small scales. In the case of isoxazolidines, the 4-hydroxy derivative remains the most commonly accessible functionalized variant. Similar limitations apply to the pyrazolidine synthesis where examples of C4-functionalized derivatives are sporadic and frequently lack scalable or operationally simple protocols [21–25]. Thus, a practical, scalable synthetic platform that enables reliable access to structurally diverse C4-substituted isoxazolidine and pyrazolidine building blocks remains highly desirable.

Herein, we report a straightforward, robust, and multigram-scale method for the synthesis of C4-functionalized isoxazolidines and pyrazolidines bearing orthogonal *N*-protecting groups from inexpensive, commercially available starting materials (**Figure 1**E). In addition to developing an operationally simple synthetic route, we addressed the reactivity and stability profiles of the resulting heterocycles, thereby establishing their suitability as building blocks for medicinal chemistry and diversity-oriented synthesis. Collectively, this work expands the accessible chemical space of saturated *N*,*O*- and *N*,*N*-heterocycles and provides practical entry points to previously underrepresented scaffolds.

Results and discussion

For the synthesis of the targeted five-membered heterocycles, we adopted a strategy historically recognized for its reliability, involving the reaction of protected hydroxylamine or hydrazine derivatives with 1,3-dielectrophilic reagents. This approach enables a predictable ring closure and, importantly, the modular introduction of substituents in the future C4 position by varying the dihalide component.

Our design was inspired by our previous work on the reaction of 3-chloro-2-(chloromethyl)prop-1-ene with *N*-Boc-2-aminoethanol, which provided access to functionalized 1,4-oxazepanes *via* a robust multigram protocol [26]. In that study, careful control of the reagent order, concentration, and temperature proved essential for ensuring reproducibility and scalability, while also enabling safe handling of NaH/DMF systems. The successful diversification of 6-methylene and

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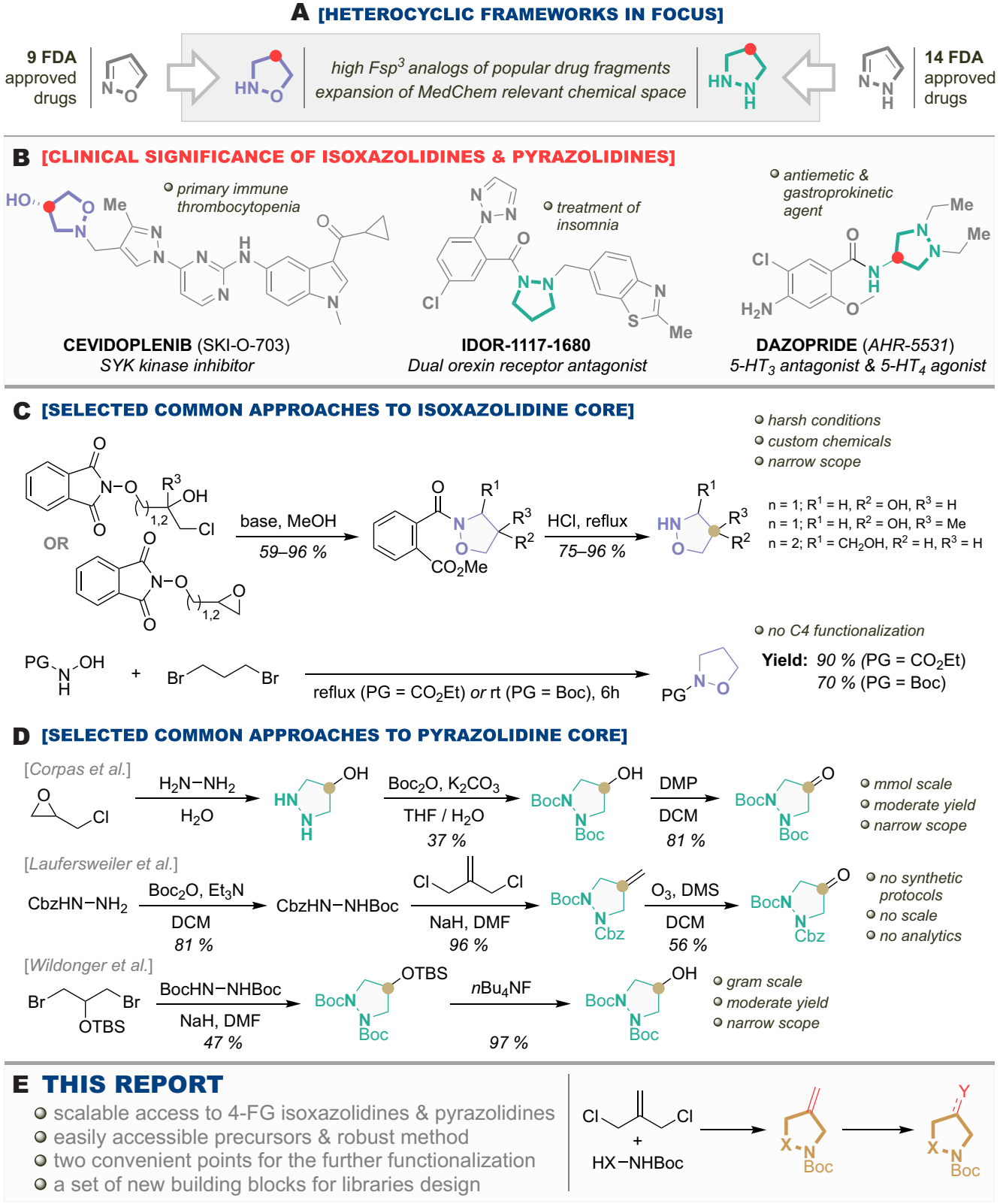
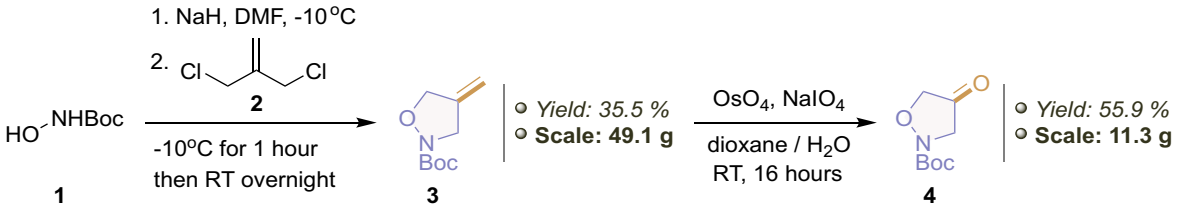


Figure 1. The hallmarks of the work

6-oxo oxazepane cores demonstrated the synthetic flexibility of this platform and encouraged us to extend the methodology to insufficiently explored five-membered heterocycles. We therefore sought to adapt this operationally simple strategy to the preparation of 4-functionalized isoxazolidines and pyrazolidines.

Isoxazolidin-4-one **4** was envisioned as a versatile intermediate for further structural diversification. However, no practical protocol for its scalable preparation has been described. Alkene **3** was obtained *via* the nucleophilic substitution of *N*-Boc-protected hydroxylamine (**1**) with 3-chloro-2-(chloromethyl)prop-1-ene (**2**) in the presence of



Scheme 1. The synthesis and functionalization of the oxazolidine core

NaH in DMF (**Scheme 1**), following the optimized protocol developed in our previous work to suppress undesired excessive foaming. In particular, deviations from the procedure described in the *Experimental Section*, especially with respect to the reaction time and temperature, may result in uncontrolled foaming, which ultimately leads to the reaction mixture solidification and subsequent complications during the alkylation step. Surprisingly, despite the favorable formation of five-membered rings, alkene **3** was obtained with an isolated yield of only about 35%, even after extensive optimization efforts. Nevertheless, the operational simplicity of the transformation and the use of inexpensive, commercially available reagents allowed the process to be implemented reproducibly on a scale of about 50 g without significant complications. The purification of product **3** was achieved without chromatographic techniques by the vacuum distillation, which proved convenient for the multigram-scale synthesis. However, the spontaneous ignition of the hot residue in the distillation flask upon exposure to air may occur, likely due to residual *N*-Boc-hydroxylamine (see the *Experimental Section*).

The oxidation of the exocyclic double bond proved more challenging than anticipated. In contrast to our earlier oxazepane study, the $RuCl_3$-mediated oxidation resulted in unidentifiable resinous by-products. Improved results were achieved using OsO_4 with periodate as the stoichiometric oxidant, giving ketone **4** in the yield of 56% on a gram scale. Further functional diversification of alkene **3** and ketone **4** was explored, but did not yield satisfactory results. In particular, the hydroboration/oxidation of alkene **3** proved impractical due to low yields and poor purity of the corresponding hydroxymethyl derivative. Attempts to obtain the corresponding carboxylic acid *via* the crude hydroxymethyl intermediate oxidation using the $RuCl_3/NaIO_4$ system were likewise unsuccessful.

The next step was to extend the strategy to the pyrazolidine synthesis. *N*,*N*′-*di*-Boc-protected hydrazine **5** was reacted with 3-chloro-2-(chloromethyl)prop-1-ene (**2**) under similar conditions to obtain alkene **6**, which was subsequently oxidized using $OsO_4/NaIO_4$ to give pyrazolidin-4-one **7** (**Scheme 2**A). One worth noting that compounds **6** and **7** were previously described [27]. Although the reported protocols demonstrate the feasibility of accessing these structures, they do not address key experimental aspects of such transformations as discussed in our previous work [26] likely because they were implemented on a small scale.

In contrast to the isoxazolidine system, the pyrazolidin-4-one core demonstrated greater tolerance toward the downstream functionalization. Exocyclic alkene **6** underwent the hydroboration/oxidation to give alcohol **8**, which was further oxidized to acid **9** using the $RuCl_3/NaIO_4$ system (**Scheme 2**B). Additionally, the carbonyl group reduction with sodium borohydride furnished alcohol **10**, which was smoothly converted to bromide **11** *via* the Appel reaction. The carbonyl functionality was also transformed into an amino group *via* oxime intermediate **12**, followed by the Raney Ni-mediated hydrogenation. Collectively, these transformations demonstrate the versatility of the C4-functionalized pyrazolidine scaffold as a synthetic intermediate.

A defining feature of the pyrazolidine core is the presence of two endocyclic nitrogen atoms, offering multiple points for the selective modification. To enable the controlled functionalization, an orthogonally Boc- and Cbz-protected alkene **15** was prepared in a similar way (**Scheme 3**A). Subsequent transformations confirmed the practical value of this design. The downstream hydroboration/oxidation of the double bond, followed by the oxidation to the corresponding acid and the methylation with methyl iodide, provided a series of crude pyrazolidine derivatives that could further be transformed into mono-*N*-deprotected building blocks. Thus, the Cbz group was removed selectively by the hydrogenolysis, cleanly providing access to alcohol **19** and ester **20** (**Scheme 3**B). If needed, the Boc deprotection could be achieved independently under standard acidic conditions. In this way, the orthogonal protection strategy enables the stepwise and predictable functionalization of the pyrazolidine framework, significantly enhancing its synthetic utility.

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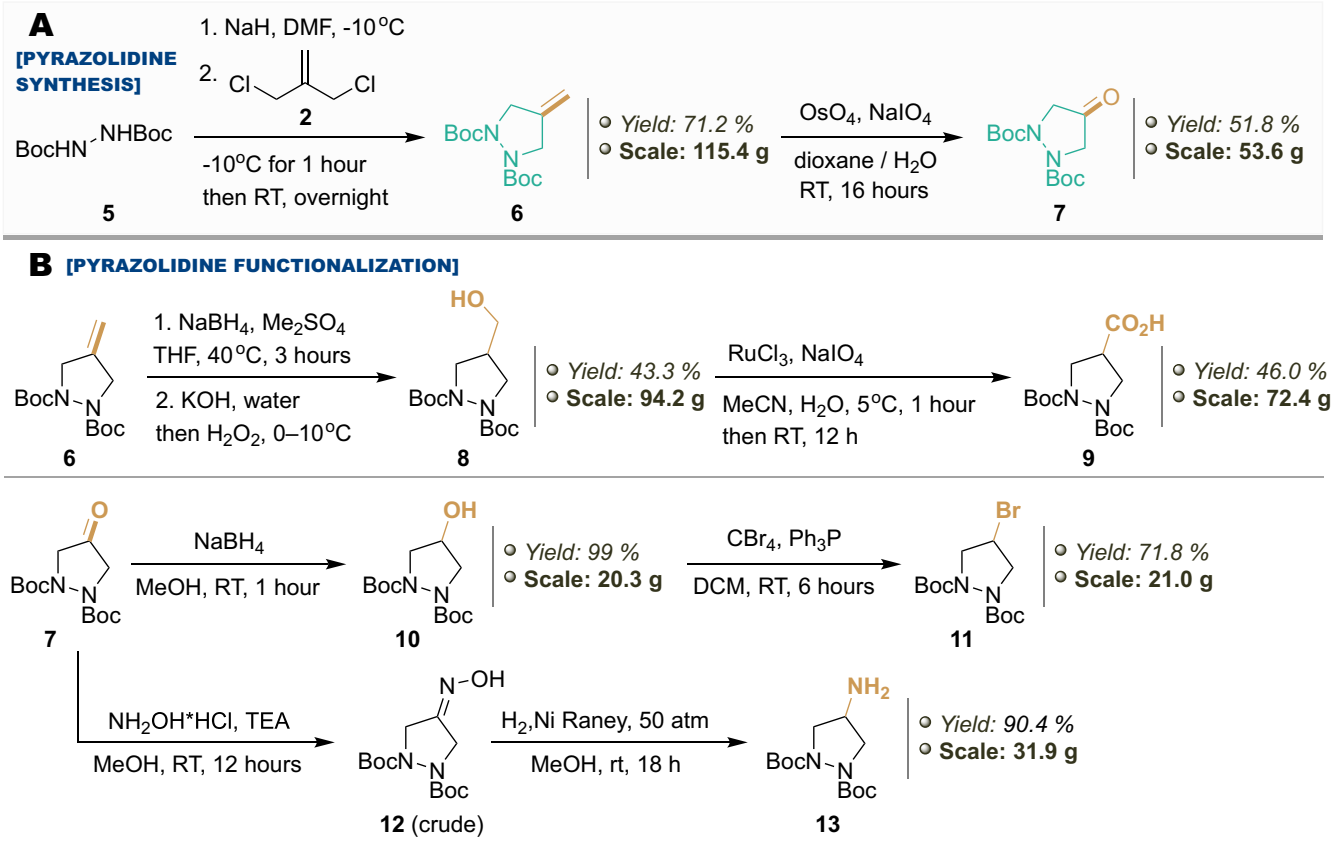
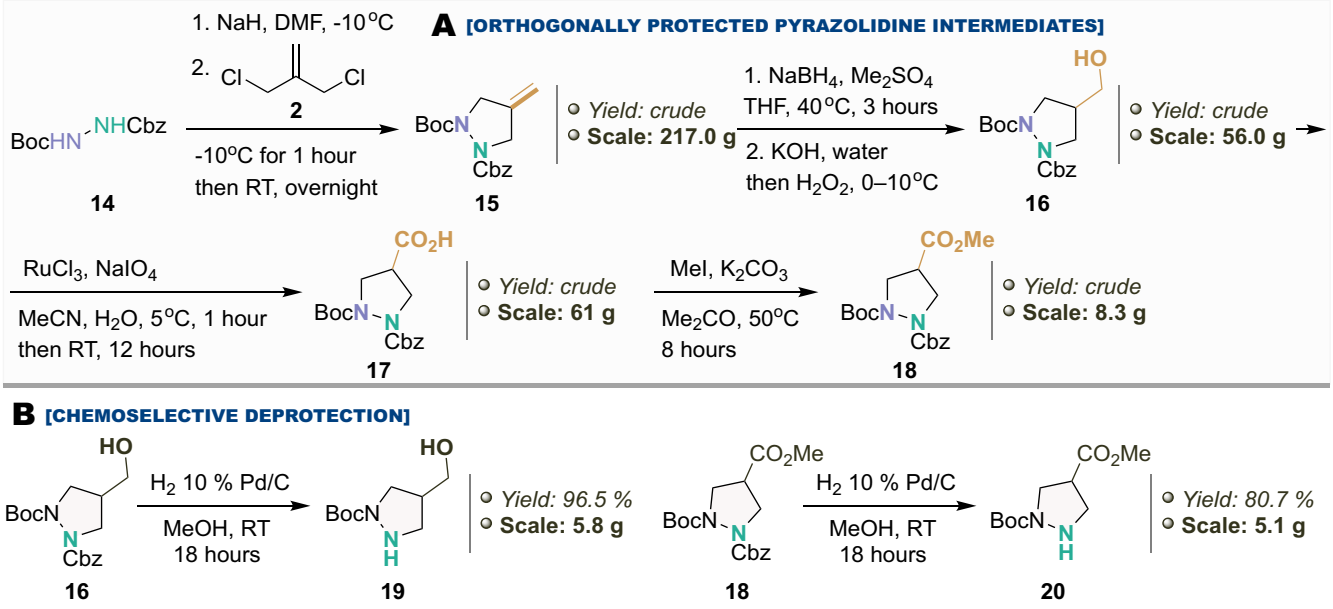


Scheme 2. The synthesis (A) and functionalization (B) of the pyrazolidine core



Scheme 3. The synthesis of orthogonally protected pyrazolidines

Conclusion

Thus, we have developed a practical and scalable cyclization method that allows us to obtain C4-functionalized isoxazolidine and pyrazolidine building blocks from commercially available materials. It has been found that a single set of reaction conditions is applicable to both *N*,*O*- and *N*,*N*-heterocycles, simplifying the experimental workflow. The protocol has been demonstrated to be operationally robust, including its implementation at an over 100 g scale. Systematic downstream transformations have confirmed the synthetic versatility of the pyrazolidine scaffold and defined stability limitations of the isoxazolidine core under reductive conditions. The combination of the modular C4 functionalization, orthogonal nitrogen protection, and preparative

scalability transforms these previously underutilized heterocycles into practically accessible building blocks for medicinal chemistry applications.

■ Experimental part

All starting compounds were obtained from commercial sources and used without additional purification. All solvents were purified according to standard procedures. ^{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 (101 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 elemental analysis results were obtained at the Analytical Laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine. Melting points were determined on an MPA100 OptiMelt automated melting point system.

***Tert*-butyl 4-methyleneisoxazolidine-2-carboxylate (3)**

tert-Butyl hydroxycarbamate (**1**) (100 g, 0.75 mol) was dissolved in DMF (1 L), and the resulting solution was cooled to -10 °C. Sodium hydride (60% dispersion in mineral oil, 63.1 g, 1.58 mol) was added in one portion, and the suspension was stirred at -10 °C for 40 min. The solution of 3-chloro-2-(chloromethyl)prop-1-ene (**2**) (104.3 mL, 0.90 mol) was then added dropwise, maintaining the internal temperature between -5 and -10 °C. After the completion of the addition, the reaction mixture was stirred at -10 °C for 1 h, then warmed to room temperature and stirred overnight. The reaction was carefully quenched by the dropwise addition of water (1 L). The resulting mixture was extracted with MTBE (2 × 1 L). The combined organic layers were washed with water (3 × 500 mL) and a brine (500 mL), dried over the anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by distillation under reduced pressure to give *tert*-butyl 4-methyleneisoxazolidine-2-carboxylate (**3**).

Caution: To avoid a potential ignition, the distillation flask must be cooled completely before the residue is exposed to air.

A colorless liquid. Yield – 49.1 g (35.5%). Anal. Calcd. for $C_9H_{15}NO_3$, %: C 58.36, H 8.16, N 7.56. Found, %: C 58.43, H 8.20, N 7.43. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.46 (9H, s), 4.14 (2H, s), 4.36 (2H, s), 5.04 (1H, t, J = 2.5 Hz), 5.07 (1H, t, J = 2.3 Hz). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 27.6, 51.8, 71.2, 81.8, 104.1, 145.0, 157.3. LC-MS, m/z (ES-API): 86.2 [M-C_4H_8-CO_2+H]$^+$.

***Tert*-butyl 4-oxoisoxazolidine-2-carboxylate (4)**

Osmium tetroxide (0.27 g, 10.8 mmol) was added to a stirred solution of *tert*-butyl 4-methyleneisoxazolidine-2-carboxylate (**3**, 20 g, 0.108 mol) and sodium periodate (57.7 g, 0.27 mol) in the mixture of dioxane (400 mL) and water (100 mL) precooled to 10 °C. The resulting reaction mixture was allowed to warm to room temperature and stirred for 16 h. The precipitated solids were removed by filtration and washed with MTBE (2 × 200 mL). The combined filtrates were diluted with water (500 mL) and extracted with MTBE (3 × 500 mL). The combined organic layers were washed successively with a brine (500 mL), 2 M aqueous Na_2SO_3 solution (2 × 500 mL), and water (500 mL), then dried over the anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by distillation under reduced pressure to give *tert*-butyl 4-oxoisoxazolidine-2-carboxylate **4**.

A colorless oil. Yield – 11.3 g (55.9%). Anal. Calcd. for $C_8H_{13}NO_4$, %: C 51.33, H 7.00, N 7.48. Found, %: C 51.45, H 6.91, N 7.59. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.52 (9H, s), 3.97 (2H, s), 4.08 (2H, s). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 28.1, 53.8, 70.9, 83.6, 156.8, 209.0. GC-MS, m/z (EI): 87.0 [M-C_4H_8-CO_2]$^+$.

Di-*tert*-butyl 4-methylenepyrazolidine-1,2-dicarboxylate (6) [27]

Di-*tert*-butyl hydrazine-1,2-dicarboxylate (**5**, 132.3 g, 0.57 mol) was dissolved in DMF (1.3 L), and the resulting solution was cooled to -10 °C. Sodium hydride (60% dispersion in mineral oil, 83.5 g, 2.1 mol) was added in one portion, and the suspension was stirred at -10 °C for 40 min. The solution of 3-chloro-2-(chloromethyl)prop-1-ene (**2**) (138.0 mL, 1.2 mol) was then added dropwise, maintaining the internal temperature between -5 and -10 °C. After the completion of the addition, the reaction mixture was stirred at -10 °C for 1 h, then warmed to room temperature and stirred overnight. The reaction mixture was carefully

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quenched by the dropwise addition of water (1.3 L). The resulting mixture was extracted with MTBE (2 × 1 L). The combined organic layers were washed with water (3 × 500 mL) and a brine (500 mL), dried over the anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by the flash column chromatography (EtOAc/hexane, gradient 0–40%) to give di-*tert*-butyl 4-methylenepyrazolidine-1,2-dicarboxylate (**6**).

A light-yellow solid. Yield – 115.4 g (71.2%). M. p. 88–90 °C. Anal. Calcd. for $C_{14}H_{24}N_2O_4$, %: C 59.14, H 8.51, N 9.85. Found, %: C 59.26, H 8.39, N 9.60. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.47 (18H, s), 3.83 (2H, d, J = 16.0 Hz), 4.43 (2H, d, J = 15.0 Hz), 5.04–5.09 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 28.2, 51.1, 81.3, 105.8, 143.5, 155.6. LC-MS, m/z (ES-API): 129.0 $[M\text{-}2C_4H_8\text{-}CO_2+H]^+$.

Di-*tert*-butyl 4-oxopyrazolidine-1,2-dicarboxylate (7) [27]

Osmium tetroxide (0.92 g, 36.1 mmol) was added to a stirred solution of di-*tert*-butyl 4-methylenepyrazolidine-1,2-dicarboxylate **6** (102.7 g, 0.36 mol) and sodium periodate (193.0 g, 0.90 mol) in the mixture of dioxane (1.2 L) and water (300 mL) pre-cooled to 10 °C. The resulting reaction mixture was allowed to warm to room temperature and stirred for 16 h. The precipitated solids were removed by filtration and washed with MTBE (2 × 400 mL). The combined filtrates were diluted with water (1.0 L) and extracted with MTBE (3 × 700 mL). The combined organic layers were washed successively with a brine (800 mL), 2 M aqueous Na_2SO_3 solution (2 × 800 mL), and water (900 mL), then dried over the anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give di-*tert*-butyl 4-oxopyrazolidine-1,2-dicarboxylate (**7**).

A white solid. Yield – 53.6 g (51.8%). M. p. 109–111 °C. Anal. Calcd. for $C_{13}H_{22}N_2O_5$, %: C 54.53, H 7.74, N 9.78. Found, %: C 54.40, H 7.70, N 9.67. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.49 (18H, s), 3.65 (2H, d, J = 18.1 Hz), 4.25 (2H, d, J = 18.1 Hz). ^{13}C NMR (151 MHz, $CDCl_3$), δ, ppm: 28.1, 53.2, 82.5, 155.0, 207.9. GC-MS, m/z (EI): 186.1 $[M\text{-}C_4H_8\text{-}CO_2]^+$.

Di-*tert*-butyl 4-(hydroxymethyl)pyrazolidine-1,2-dicarboxylate (8)

To the suspension of sodium borohydride (28.7 g, 0.76 mol) and di-*tert*-butyl 4-methylenepyrazolidine-1,2-dicarboxylate **6** (204.8 g, 0.72 mol) in THF (1.5 L), dimethyl sulfate (75.8 mL, 0.79 mol) was added dropwise under the argon atmosphere, while maintaining the internal temperature below 40 °C. After the completion of the addition, the reaction mixture was stirred for 3 h. The mixture was then cooled to 0 °C, and water (210 mL) was added slowly dropwise, followed by the addition of KOH (46.5 g, 0.83 mol) dissolved in water (210 mL). After stirring for 15 min, hydrogen peroxide (210 mL, 33 wt%) was added dropwise at 0-10 °C, and the reaction mixture was stirred for the additional 30 min after the addition was complete. MTBE (1.0 L) was added, and the organic phase was decanted from the inorganic precipitate. The organic layer was washed successively with water (700 mL), 2 M aqueous Na_2SO_3 solution (2 × 700 mL), and a brine (700 mL), then dried over the anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by the flash column chromatography (MeCN/$CHCl_3$, gradient 0–50%) to give di-*tert*-butyl 4-(hydroxymethyl)pyrazolidine-1,2-dicarboxylate (**8**).

A yellow oil. Yield – 94.2 g (43.3%). Anal. Calcd. for $C_{14}H_{26}N_2O_5$, %: C 55.61, H 8.67, N 9.26. Found, %: C 55.42, H 8.55, N 9.07. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.39 (18H, s), 2.90 (1H, dd, J = 10.2, 5.4 Hz), 3.16 (1H, t, J = 9.5 Hz), 3.27 (2H, t, J = 5.9 Hz), 3.62 (1H, dd, J = 11.0, 3.7 Hz), 3.76 (1H, t, J = 9.5 Hz), 4.82 (1H, t, J = 5.0 Hz). GC-MS, m/z (EI): 302.1 $[M]^+$. LC-MS, m/z (ES-API): 147.0 $[M\text{-}2C_4H_8\text{-}CO_2+H]^+$.

1,2-*bis*(*tert*-Butoxycarbonyl)pyrazolidine-4-carboxylic acid (9)

Sodium periodate (467.2 g, 2.17 mol) was dissolved in the mixture of water (1.0 L) and MeCN (1.0 L), and the resulting solution was cooled to 5 °C. Ruthenium(III) chloride hydrate (5.9 g, 27.3 mmol) was then added, followed by the dropwise addition of the solution of di-*tert*-butyl 4-(hydroxymethyl)pyrazolidine-1,2-dicarboxylate (**8**) (180 g, 0.53 mol) in MeCN (300 mL), while maintaining the internal temperature between 0 and 10 °C. After the completion of the addition, the reaction mixture was stirred at 5 °C for 1 h, then warmed to room temperature and stirred for the additional 12 h. The precipitated solids were removed by filtration and washed with MTBE (2 × 700 mL). The combined filtrates were diluted with water (700 mL) and extracted with MTBE (3 × 50 mL). The combined organic layers were washed successively with a brine (700 mL) and water (700 mL), then dried over the anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 1,2-*bis*(*tert*-butoxycarbonyl)pyrazolidine-4-carboxylic acid (**9**).

A white solid. Yield – 72.4 g (46%). M. p. 130–132 °C. Anal. Calcd. for $C_{14}H_{24}N_2O_6$, %: C 53.15, H 7.65, N 8.86. Found, %: C 53.29, H 7.81, N 8.75. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.48 (18H, s), 3.25–3.32 (1H, m), 3.43 (1H, t, *J* = 10.1 Hz), 3.53 (1H, dd, *J* = 11.5, 5.9 Hz), 3.89–3.98 (1H, m), 4.12 (1H, t, *J* = 10.0 Hz), 4.25 (1H, dd, *J* = 11.7, 3.7 Hz), 9.16 (1H, s). ^{13}C NMR (101 MHz, $CDCl_3$), *δ*, ppm: 28.0, 28.1, 41.1, 43.9, 48.7, 49.4, 76.7, 77.0, 77.3, 81.8, 155.4, 155.8, 176.7. LC-MS, *m*/*z* (ES-API): 117.2 $[M\text{-}2C_4H_8\text{-}2CO_2+H]^+$.

Di-*tert*-butyl 4-hydroxypyrazolidine-1,2-dicarboxylate (10) [22, 24]

Sodium borohydride (1.6 g, 42 mmol) was added portionwise to the stirred solution of di-*tert*-butyl 4-oxopyrazolidine-1,2-dicarboxylate (**7**, 20.0 g, 0.070 mol) in MeOH (250 mL) at room temperature. The resulting reaction mixture was stirred at room temperature for 1 h. The solvent was then removed under reduced pressure, and the residue was diluted with water (200 mL) and MTBE (200 mL). The organic layer was separated, washed with a brine (100 mL), dried over the anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give di-*tert*-butyl 4-hydroxypyrazolidine-1,2-dicarboxylate (**10**).

A white solid. Yield – 20.3 g (99%). Anal. Calcd. for $C_{13}H_{24}N_2O_5$, %: C 54.15, H 8.39, N 9.72. Found, %: C 54.36, H 8.57, N 9.81. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.39 (18H, s), 3.04 (2H, t, *J* = 12.9 Hz), 3.63–3.76 (2H, m), 4.38 (1H, s), 5.11 (1H, d, *J* = 2.4 Hz). ^{13}C NMR (101 MHz, DMSO-d_6), δ, ppm: 28.2 and 28.3 (rotamers), 55.2, 70.1, 80.2 and 80.5 (rotamers), 154.9 and 157.0 (rotamers). LC-MS, *m*/*z* (ES-API): 133.2 $[M\text{-}2C_4H_8\text{-}CO_2+H]^+$.

Di-*tert*-butyl 4-bromopyrazolidine-1,2-dicarboxylate (11)

To the stirred solution of di-*tert*-butyl 4-hydroxypyrazolidine-1,2-dicarboxylate (**10**, 24.0 g, 83.2 mmol) in DCM (400 mL), triphenylphosphine (32.8 g, 0.125 mol) was added in one portion, followed by the portionwise addition of tetrabromomethane (41.4 g, 0.125 mol). The resulting reaction mixture was stirred at room temperature for 6 h. The solvent was removed under reduced pressure, and the resulting residue was purified by flash column chromatography (EtOAc/hexane, gradient 0–30%) to give di-*tert*-butyl 4-bromopyrazolidine-1,2-dicarboxylate (**11**).

A white solid. Yield – 21.0 g (71.8%). M. p. 98–100 °C. Anal. Calcd. for $C_{13}H_{23}BrN_2O_4$, %: C 44.45, H 6.60, N 7.98. Found, %: C 44.29, H 6.79, N 7.81. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.39 and 1.41 (18H, s, rotamers), 3.54 (1H, d, *J* = 13.4 Hz), 3.59 (1H, d, *J* = 12.6 Hz), 4.07 (1H, d, *J* = 13.4 Hz), 4.13 (1H, dd, *J* = 12.7, 5.8 Hz), 4.87 (1H, t, *J* = 5.0 Hz). ^{13}C NMR (101 MHz, DMSO-d_6), δ, ppm: 28.1 and 28.3 (rotamers), 48.3, 57.1, 80.9 and 81.2 (rotamers), 154.9 and 156.5 (rotamers). LC-MS, *m*/*z* (ES-API): 195.0 $[M\text{-}2C_4H_8\text{-}CO_2+H]^+$.

Di-*tert*-butyl 4-(hydroxyimino)pyrazolidine-1,2-dicarboxylate (12)

Triethylamine (7.3 mL, 52.4 mmol) was added to the stirred solution of di-*tert*-butyl 4-oxopyrazolidine-1,2-dicarboxylate (**7**, 10.0 g, 0.035 mol) in the appropriate solvent, followed by the addition of hydroxylamine hydrochloride (3.6 g, 52.4 mmol). The resulting reaction mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, and the residue was diluted with DCM (100 mL) and washed with water (2 × 50 mL). The organic layer was dried over the anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give di-*tert*-butyl 4-(hydroxyimino)pyrazolidine-1,2-dicarboxylate (**12**, 10.1 g, crude), which was used directly in the next step without further purification.

Di-*tert*-butyl 4-aminopyrazolidine-1,2-dicarboxylate (13)

The mixture of di-*tert*-butyl 4-(hydroxyimino)pyrazolidine-1,2-dicarboxylate (**12**, 37.1 g, 122.4 mmol) and freshly prepared Raney Ni (17 g) in methanol (500 mL) was hydrogenated at 50 atm and 20 °C for 18 h. After the completion, the catalyst was filtered off and washed with methanol (100 mL). The combined filtrates were concentrated under reduced pressure. Water (200 mL) was added to the residue, and the aqueous phase was acidified to pH 3 using sodium hydrogen sulfate. The mixture was washed with DCM (2 × 100 mL), then basified to pH 12 with aqueous KOH and extracted with DCM (2 × 200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give di-*tert*-butyl 4-aminopyrazolidine-1,2-dicarboxylate (**13**).

A white solid. Yield – 31.9 g (90.4%). M. p. 98–100 °C. Anal. Calcd. for $C_{13}H_{25}N_3O_4$, %: C 54.34, H 8.77, N 14.62. Found, %: C 54.49, H 8.56, N 14.83. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.38 (18H, s), 2.84 (1H, d, *J* = 10.5 Hz), 3.08 (1H, dd, *J* = 11.1, 5.2 Hz), 3.44 (1H, d, *J* = 11.1 Hz), 3.58 (1H, tq, *J* = 5.7, 2.6 Hz), 3.64 (1H, dd, *J* = 10.6, 6.0 Hz). ^{13}C NMR (101 MHz, DMSO-d_6), δ, ppm: 28.27 and 28.31 (rotamers), 51.8, 54.9 and 55.9 (rotamers), 80.2, 155.1 and 156.7 (rotamers). LC-MS, *m*/*z* (ES-API): 88.4 $[M\text{-}2C_4H_8\text{-}2CO_2+H]^+$.

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1-Benzyl 2-(*tert*-butyl) 4-methylenepyrazolidine-1,2-dicarboxylate (15)

1-Benzyl 2-(*tert*-butyl) hydrazine-1,2-dicarboxylate (**14**, 200 g, 1.65 mol) was dissolved in DMF (2 L), and the resulting solution was cooled to -10 °C. Sodium hydride (60% dispersion in mineral oil, 66.1 g, 1.65 mol) was added in one portion, and the suspension was stirred at -10 °C for 40 min. The solution of 3-chloro-2-(chloromethyl)-prop-1-ene (**2**, 104.3 mL, 0.90 mol) was then added dropwise, maintaining the internal temperature between -5 and -10 °C. After the completion of the addition, the reaction mixture was stirred at -10 °C for 1 h, then warmed to room temperature and stirred overnight. The reaction was carefully quenched by the dropwise addition of water (1 L). The resulting mixture was extracted with MTBE (2 × 1 L). The combined organic layers were washed with water (3 × 500 mL) and a brine (500 mL), dried over the anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by the flash column chromatography (EtOAc/hexane, gradient 0–40%) to give 1-benzyl 2-(*tert*-butyl) 4-methylenepyrazolidine-1,2-dicarboxylate (**15**, 217 g, crude) as a light-yellow oil, which was used directly in the next step without further purification.

1-Benzyl 2-(*tert*-butyl) 4-(hydroxymethyl)-pyrazolidine-1,2-dicarboxylate (16)

To the suspension of sodium borohydride (6.23 g, 165 mmol) and 1-benzyl 2-(*tert*-butyl) 4-methylenepyrazolidine-1,2-dicarboxylate (**15**, 50.0 g, 157 mmol) in THF (100 mL), dimethyl sulfate (16.38 mL, 173 mmol) was added dropwise under the argon atmosphere, while maintaining the internal temperature below 40 °C. After the completion of the addition, the reaction mixture was stirred for 3 h. The mixture was then cooled to 0 °C, and water (50 mL) was added slowly dropwise, followed by the addition of KOH (10.1 g, 180 mmol) dissolved in water (50 mL). After stirring for 15 min, hydrogen peroxide (50 mL, 33 wt%) was added dropwise at 0–10 °C, and the reaction mixture was stirred for the additional 30 min after the addition was complete. MTBE (500 mL) was added, and the organic phase was decanted from the inorganic precipitate. The organic layer was washed successively with water (300 mL), 2 M aqueous Na_2SO_3 solution (2 × 200 mL), and a brine (200 mL), then dried over the anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 1-benzyl 2-(*tert*-butyl) 4-(hydroxymethyl)-pyrazolidine-1,2-dicarboxylate **16** (56 g, crude), which was used directly in the next step without further purification.

A white oil. Yield – 56 g (crude). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.43 (9H, s), 1.98 (1H, d, *J* = 33.0 Hz), 2.59–2.70 (1H, m), 3.02–3.45 (2H, m), 3.55 (2H, s), 3.83–3.94 (1H, m), 4.05 (1H, d, *J* = 12.4 Hz), 5.11 (1H, d, *J* = 12.5 Hz), 5.26 (1H, d, *J* = 11.8 Hz), 7.26 – 7.42 (5H, m). LC-MS, *m*/*z* (ES-API): 337.2 $[M+H]^+$.

1-((Benzyloxy)carbonyl)-2-(*tert*-butoxycarbonyl)pyrazolidine-4-carboxylic acid (17)

Sodium periodate (127.2 g, 0.59 mol) was dissolved in the mixture of water (500 mL) and MeCN (500 mL), and the resulting solution was cooled to 5 °C. Ruthenium(III) chloride hydrate (1.66 g, 7.4 mmol) was then added, followed by the dropwise addition of the solution of 1-benzyl 2-(*tert*-butyl) 4-(hydroxymethyl)pyrazolidine-1,2-dicarboxylate (**16**, 50.0 g, 149 mmol) in MeCN (100 mL), while maintaining the internal temperature between 0 and 10 °C. After the completion of the addition, the reaction mixture was stirred at 5 °C for 1 h, then allowed to warm to room temperature and stirred for the additional 12 h. The precipitated solids were removed by filtration and washed with MTBE (2 × 500 mL). The combined filtrates were diluted with water (500 mL) and extracted with MTBE (3 × 400 mL). The combined organic layers were washed successively with a brine (500 mL) and water (500 mL), then dried over the anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 1-((benzyloxy)carbonyl)-2-(*tert*-butoxycarbonyl)pyrazolidine-4-carboxylic acid (**17**, 61 g, crude), which was used directly in the next step without further purification.

1-Benzyl 2-(*tert*-butyl) 4-methyl pyrazolidine-1,2,4-tricarboxylate (18)

The mixture of 1-((benzyloxy)carbonyl)-2-(*tert*-butoxycarbonyl)pyrazolidine-4-carboxylic acid **17** (25 g, 71.3 mmol), potassium carbonate (19.7 g, 143 mmol), and methyl iodide (8.88 mL, 143 mmol) in acetone (250 mL) was heated at 50 °C for 8 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with EtOAc (200 mL) and washed with water (2 × 200 mL). The crude product was purified by the flash column chromatography (EtOAc/hexane, gradient 20–40%) to give 1-benzyl 2-(*tert*-butyl) 4-methyl pyrazolidine-1,2,4-tricarboxylate (**18**).

A yellow oil. Yield – 8.3 g (crude). Anal. Calcd. for $C_{18}H_{24}N_2O_6$, %: C 59.33, H 6.64, N 7.69.

Found, %: C 59.25, H 6.80, N 7.50. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.43 (9H, s), 3.20–3.30 (1H, m), 3.36–3.63 (2H, m), 3.64–3.75 (3H, m), 4.09–4.28 (2H, m), 5.07–5.32 (2H, m), 7.28–7.40 (5H, m). LC-MS, *m/z* (ES-API): 265.1 $[M\text{-}C_4H_8\text{-}CO_2+H]^+$.

***tert*-Butyl 4-(hydroxymethyl)pyrazolidine-1-carboxylate (19)**

The mixture of 1-benzyl 2-(*tert*-butyl) 4-(hydroxymethyl)pyrazolidine-1,2-dicarboxylate **16** (10 g, 29.7 mmol) and 10% Pd/C (1 g) in methanol (100 mL) was hydrogenated at 50 atm and 20 °C for 18 h. After the completion, the catalyst was removed by filtration and washed with methanol (30 mL). The combined filtrates were concentrated under reduced pressure to give tert-butyl 4-(hydroxymethyl)pyrazolidine-1-carboxylate **19**.

A white solid. Yield – 5.8 g (96.5%). M. p. 60–63 °C. Anal. Calcd. for $C_9H_{18}N_2O_3$, %: C 53.45, H 8.97, N 13.85. Found, %: C 53.61, H 9.12, N 13.98. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.43 (s, 9H), 2.51–2.64 (1H, m), 2.99 (1H, dd, *J* = 11.6, 4.9 Hz), 3.10 (1H, dd, *J* = 11.6, 6.8 Hz), 3.21 (1H, dd, *J* = 10.8, 5.0 Hz), 3.52 – 3.67 (3H, m), 4.02 (2H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.4, 42.9, 48.7, 50.3, 63.0, 80.5, 154.9. LC-MS, *m/z* (ES-API): 147.2 $[M\text{-}C_4H_8+H]^+$.

1-(*tert*-Butyl) 4-methyl pyrazolidine-1,4-dicarboxylate (20)

The mixture of 1-benzyl 2-(*tert*-butyl) 4-methyl pyrazolidine-1,2,4-tricarboxylate (**18**, 10.0 g, 27.4 mmol) and 10% Pd/C (1 g) in methanol (100 mL) was hydrogenated at 50 atm and 20 °C for 18 h. After the completion, the catalyst was filtered off and washed with methanol (30 mL). The combined filtrates were concentrated under reduced pressure. Water (50 mL) was added to the residue, and the aqueous phase was acidified to pH 3 using sodium hydrogen sulfate. The mixture was washed with DCM (2 × 40 mL), then basified to pH 12 with the aqueous KOH and extracted with DCM (2 × 50 mL). The combined organic layers were dried over the anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 1-(*tert*-butyl) 4-methyl pyrazolidine-1,4-dicarboxylate (**20**).

A yellow oil. Yield – 5.1 g (80.7%). Anal. Calcd. for $C_{10}H_{18}N_2O_4$, %: C 52.16, H 7.88, N 12.17. Found, %: C 52.29, H 7.69, N 12.01. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.48 (9H, s), 3.14 (1H, dd, *J* = 11.5, 6.5 Hz), 3.21–3.31 (2H, m), 3.63 (1H, dd, *J* = 11.1, 4.3 Hz), 3.72 (3H, s), 3.76 (1H, dd, *J* = 11.1, 8.4 Hz), 4.14 (1H, s). LC-MS, *m/z* (ES-API): 231.2 $[M+H]^+$.

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