An Approach to 1,1-Disubstituted Pyrazolylcyclopropane Building Blocks

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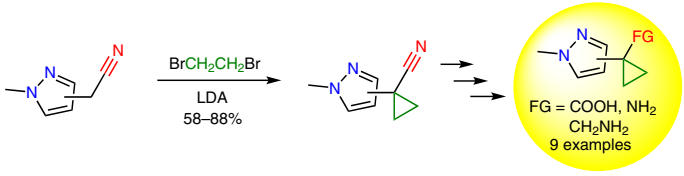

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Abstract An approach to isomeric 1,1-disubstituted pyrazolylcyclopropanes that relies on lithium diisopropylamide (LDA) mediated bis-alkylation of the corresponding pyrazolylacetonitriles is developed. The building blocks obtained can be considered as lead-like bioisosteres of arylpyrazole and pyrazolecarboxamide moieties and are thus useful for early drug discovery projects.

Key words cyclopropanes, pyrazoles, hetarylacetonitriles, nucleophilic substitution, lead-oriented synthesis

1,1-Disubstituted (het)arylcyclopropanes are important chemotypes for the discovery of biologically active compounds. Arylcyclopropane derivatives are found among marketed drugs and drug candidates, including Lumacaftor **1**, a drug for the treatment of cystic fibrosis approved by the FDA in 2015,[1] CHF5074 or CSP-1103 (**2**), which has recently completed phase II clinical trials for Alzheimer's disease treatment,[2] and MK-2894 (**3**), a potent and selective prostaglandin E2 subtype 4 receptor antagonist with potent anti-inflammatory activity that is currently in preclinical studies[3] (Figure 1). The corresponding hetarylcyclopropanes have also demonstrated significant potential in medicinal chemistry, with derivatives showing nanomolar-range activity as GPR142 agonists **4** (EC_{50} = 54 nM),[4] cannabinoid-1 (CB1) antagonists **5** (IC_{50} = 0.7 nM),[5] poly(ADP-ribose) polymerase (PARP) inhibitors **6** (IC_{50} = 25 nM),[6] and cathepsin S (Cat S) inhibitors **7** (IC_{50} = 0.5 nM).[7]

The 1,1-disubstituted cyclopropane motif has been considered as a bioisosteric replacement of the double bond, amide carbonyl group, and *ortho*-disubstituted phenylene ring or its hetero-analogues (Figure 2).[8] The latter idea was implemented into the design of highly potent inhibitors of Factor Xa (FXa).[9]

A general approach to the synthesis of 1,1-disubstituted (het)arylcyclopropanes relies on alkylation of (het)arylacetonitriles **8** with 1,2-dibromoethane or related bis-electro-

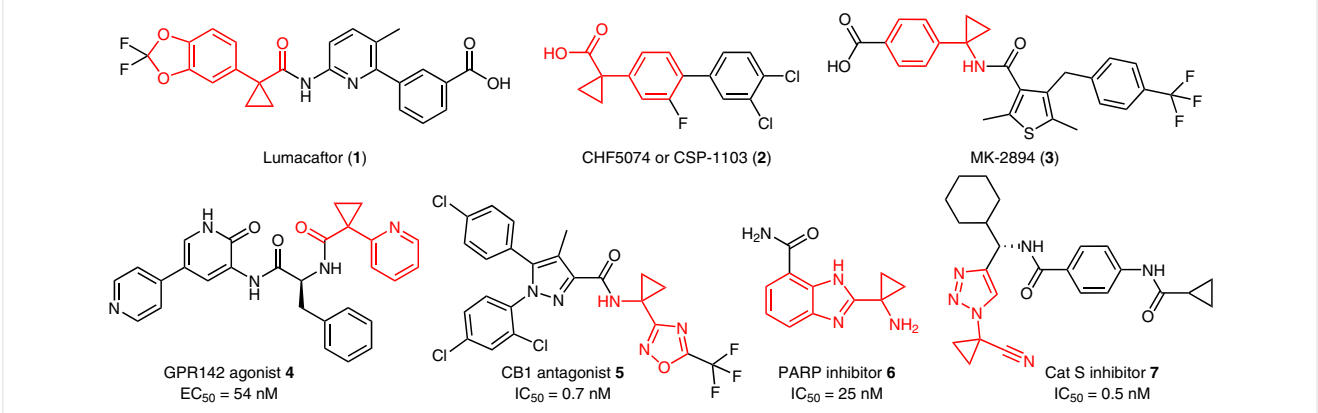


Figure 1 Biologically active 1,1-disubstituted (het)arylcyclopropanes

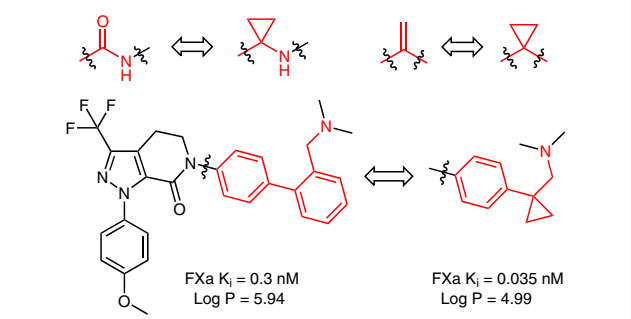
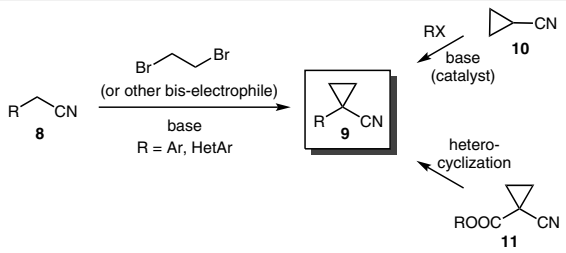


Figure 2 Bioisosteric replacements with 1,1-disubstituted cyclopropanes

philes in the presence of base (Scheme 1). The resulting 1-(het)arylcyclopropanecarbonitriles **9** are versatile key intermediates for the preparation of other building blocks, for example, carboxylic acids and amines, as well as for the construction of heterocyclic rings. Most of the reports on the synthesis of compounds of general formula **9** are related to the substituted benzene derivatives. Several reports on the development of general procedures for the preparation of 1-arylcyclopropanecarbonitriles **9** (R = Ar) from the corresponding arylacetonitriles **8** (R = Ar) have appeared;[10,11] however, their hetaryl-substituted counterparts are far less studied in analogous transformations. A number of isolated examples that have been reported involve pyrrole,[12] indole,[10,13] thiophene,[14] and pyridine[15] derivatives. In some cases, it has been reported that arylation of cyclopropylcarbonitrile **10**[16] or heterocyclizations involving 1-cyanocyclopropanecarboxylic acid or its derivatives **11**[17] were more convenient for the preparation of 1-hetarylcyclopropanecarbonitriles (**9**, R = HetAr).



Scheme 1 Selected general approaches to the preparation of 1-(het)arylcyclopropanecarbonitriles **9**

Recently, we[18] and others[19] have looked into the design and preparation of medicinal building blocks[20] that are compatible with the concept of lead-oriented synthesis.[21] As a part of this ongoing project, we became interested in the preparation of pyrazolyl-substituted building blocks **12**–**14** (Figure 3). Nitriles **9a**–**c** are obvious key precursors for the preparation of these compounds. Since the corresponding pyrazolylacetonitriles **8a**–**c** can be prepared from the known aldehydes **15a**–**c**,[22] we turned to their double alkylation as a possible method for the preparation of **9a**–**c**. It should be noted that, of the compounds **8a**–**c**, only **8b** was described previously.[23] This was prepared by reaction of aldehyde **15b** with TOSMIC in 65% yield. For the preparation of **8c**, we used the same procedure, which gave the target product in 63% yield. In the case of **8a**, the method did not work well, and the target compound was formed in less than 20% yield; therefore, an alternative three-step route was used.

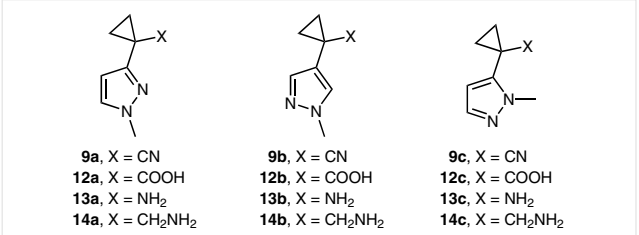


Figure 3 1,1-Disubstituted pyrazolylcyclopropane building blocks and precursors for their synthesis

To our knowledge, no examples of bis-alkylation of hetarylacetonitriles **8** having a basic nitrogen atom with 1,2-dibromoethane have been reported (the closest analogue contained an α-chloropyridine moiety,[15] which has low basicity). Typical conditions reported for alkylation of other substrates **8** with 1,2-dibromoethane are: (1) NaOH or KOH, phase-transfer catalyst, toluene or CH_2Cl_2–H_2O, r.t. to reflux; (2) NaH, DMF or DMSO, r.t. to 60 °C; (3) *t*-BuOK, DMSO, r.t. to 60 °C; (4) KHMDS, THF, –78 °C to r.t.

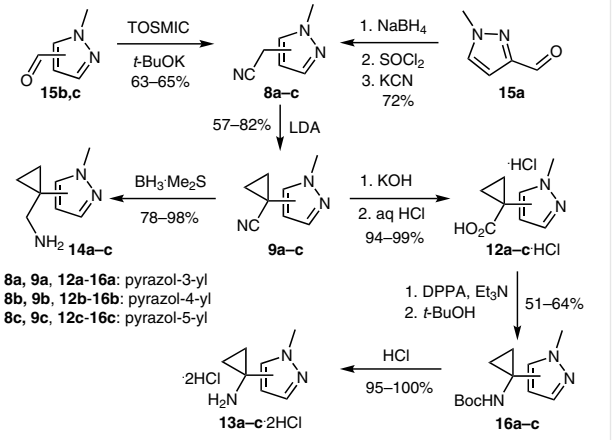
Surprisingly, these methods did not give satisfactory results for alkylation of the substrate **8b** (Table 1, entries 1–6). Therefore, we turned to screening of other bases, and found that the use of LDA in THF led to the formation of the target product **9b** in good yield (entry 8). Further experiments showed that the reaction could be performed without preliminary cooling to –78 °C. Hence, an operationally simple procedure was developed that allowed for the preparation of the target product in 69% yield (entry 9).

This simple and robust procedure for the transformation of **8** into **9** worked well with all three pyrazolylacetonitriles **8a**–**c**, with the corresponding cyclopropanes **9a**–**c** being obtained in up to 10 g amounts and 57–82% yields. The versatility of these synthetic intermediates was demonstrated by their transformation into our initial target building blocks **12**–**14** (Scheme 2). In particular, alkaline hydrolysis of **9a**–**c** gave carboxylic acids **12a**–**c** in 94–99% yields (isolated as hydrochlorides). A modified Curtius reaction of **12a**–**c**, followed by quenching of the intermediate isocyanate with *tert*-butanol, gave Boc derivatives **16a**–**c** (51–64% yields), which were transformed into amines **13a**–**c** (isolated as dihydrochlorides) in nearly quantitative yields. Alternatively, **9a**–**c** were reduced with borane–dimethylsulfoxide complex to give amines **14a**–**c** (78–98% yield).

Table 1 Alkylation of the Substrates **8b** with 1,2-Dibromoethane under Various Reaction Conditions

Entry	Conditions	Yield of **9b** (%)[a]
1	NaOH, benzyl thiethylammonium chloride, r.t.	0
2	NaOH, tetrabutylammonium bromide, 50 °C	0
3	NaH, DMF, r.t.	0
4	*t*-BuOK, DMSO, 60 °C	0
5	KHMDS, THF, –78 °C	0
6	KHMDS, THF, 0 °C to r.t.	40
7	LDA, THF, –78 °C	31
8	LDA, THF, –78 °C to r.t.	70[b]
9	LDA, THF, 0 °C to r.t.	69[b]

[a] Unless noted otherwise, yield was based on LCMS or ^{1}H NMR analysis.
[b] Isolated yield.



Scheme 2 Synthesis of pyrazolylcyclopropane building blocks **12–14**

In conclusion, a convenient approach to 1,1-disubstituted pyrazolylcyclopropane building blocks has been developed that is amendable for multigram-scale preparation. These products are promising building blocks for lead-oriented synthesis in medicinal chemistry, in particular as lead-like bioisosteric replacements of arylpyrazole or pyrazolecarboxamide moieties. They are low-molecular-weight (MW = 137–166), hydrophilic (cLog P = –0.16 to 1.06), have a limited number of polar atoms and rotatable bonds, and a reasonable fraction of sp^3 carbon atoms (Fsp^3 = 0.50–0.63) (Table 2).[24] Moreover, the pyrazolylcyclopropane scaffold complies with the 'biocore' concept for the scaffold design proposed by Kombarov and co-workers.[25] The procedure described can also be useful for the preparation of other 1,1-disubstituted (het)arylcyclopropanes, especially those containing basic nitrogen atoms.

Table 2 Calculated Physicochemical Parameters of the Building Blocks **12–14** Prepared in this Work[a]

Compound	MW	cLog P	HAcc	HDon	RotB	TPSA (Å^2)	Fsp^3
12a	166	1.06	3	1	2	55.1	0.50
12b	166	0.56	3	1	2	55.1	0.50
12c	166	0.47	3	1	2	55.1	0.50
13a	137	0.30	2	1	1	43.8	0.57
13b	137	–0.08	2	1	1	43.8	0.57
13c	137	–0.16	2	1	1	43.8	0.57
14a	151	0.48	2	1	2	43.8	0.63
14b	151	0.09	2	1	2	43.8	0.63
14c	151	0.01	2	1	2	43.8	0.63

[a] MW: molecular weight; cLog P: calculated partitioning coefficient logarithm; HAcc: hydrogen-bond acceptor count; HDon: hydrogen-bond donor count; RotB: number of rotatable bonds; TPSA: total polar surface area; Fsp^3: fraction of sp^3 carbon atoms.

The solvents were purified according to standard procedures.[26] Compounds **15a**,[22a] **8b**,[23] and **15c**[22b] were prepared by using reported methods. All other starting materials were purchased from commercial sources. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini 2000 spectrometer (at 400 MHz for ^{1}H and 101 MHz for ^{13}C NMR). Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) as an internal standard. Mass spectra were recorded with an Agilent 1100 LCMSD SL instrument (electrospray ionization (APESI)).

(1-Methyl-1*H*-pyrazol-3-yl)methanol (17)

To a solution of aldehyde **15a** (58.3 g, 0.529 mol) in MeOH (750 mL), $NaBH_4$ (40.0 g, 1.06 mol) was added portionwise at 0 °C. The resulting mixture was stirred overnight at r.t., then evaporated, diluted with 10% aq NaOH (500 mL), and extracted with EtOAc (3 × 250 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuo to give **17**, which was pure enough for the next step. An analytically pure sample was obtained by vacuum distillation.

Yield: 49.5 g (84%); colorless oil; bp 70–72 °C/1 mbar.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.28 (d, *J* = 2.2 Hz, 1 H), 6.22 (d, *J* = 2.2 Hz, 1 H), 4.79 (br. s, 1 H), 4.64 (s, 2 H), 3.85 (s, 3 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 152.0, 130.6, 104.0, 57.9, 38.3.

MS (ESI): *m*/*z* = 113 [MH$^+$].

Anal. Calcd for $C_5H_8N_2O$: C, 53.56; H, 7.19; N, 24.98. Found: C, 53.47; H, 6.84; N, 24.75.

3-(Chloromethyl)-1-methyl-1*H*-pyrazole Hydrochloride (18)

To a solution of **17** (12.0 g, 0.107 mol) in anhydrous CH_2Cl_2 (150 mL), $SOCl_2$ (19.1 g, 0.16 mol) was added dropwise at 0 °C. The reaction mixture was stirred overnight at r.t., then evaporated in vacuo, and the solid was triturated with anhydrous Et_2O (200 mL), filtered, washed with anhydrous Et_2O (100 mL), and dried under reduced pressure to give **18**. An analytically pure sample was obtained by recrystallization from acetone.

Yield: 17.0 g (95%); white solid; mp 136–138 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.86 (br. s, 1 H), 7.64 (d, J = 2.1 Hz, 1 H), 6.27 (d, J = 2.1 Hz, 1 H), 4.64 (s, 2 H), 3.79 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 147.4, 131.9, 105.2, 39.2, 38.4.

MS (ESI): m/z = 131/133 [MH$^+$].

Anal. Calcd for $C_5H_8Cl_2N_2$: C, 35.95; H, 4.83; N, 16.77; Cl, 42.45. Found: C, 35.91; H, 4.72; N, 16.81; Cl, 42.70.

2-(1-Methyl-1*H*-pyrazol-3-yl)acetonitrile (8a)

Compound **18** (9.70 g, 58.1 mmol) was dissolved in DMSO (300 mL), KCN (15.1 g, 0.232 mol) was added, and the mixture was stirred at r.t. overnight, then diluted with H_2O (600 mL), and extracted with EtOAc (3 × 250 mL). The combined extracts were washed with brine (250 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give **8a**. An analytically pure sample was obtained by column chromatography (EtOAc–hexanes, 1:2).

Yield: 6.51 g (92%); reddish oil; R_f 0.62 (EtOAc–hexanes, 1:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, J = 2.2 Hz, 1 H), 6.20 (d, J = 2.2 Hz, 1 H), 3.82 (s, 3 H), 3.69 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.8, 131.3, 116.9, 104.5, 38.6, 17.2.

MS (ESI): m/z = 122 [MH$^+$].

Anal. Calcd for $C_6H_7N_3$: C, 59.49; H 5.82; N, 34.69. Found: C, 59.49; H 5.82; N, 34.69.

2-(1-Methyl-1*H*-pyrazol-5-yl)acetonitrile (8c)

Potassium *tert*-butoxide (23.5 g, 95%, 0.199 mol) was suspended in anhydrous 1,2-dimethoxyethane (90 mL), and the mixture was cooled to –60 °C. TosMIC (23.8 g, 0.122 mol) was dissolved in anhydrous 1,2-dimethoxyethane (75 mL), and the resulting solution was added dropwise to the potassium *tert*-butoxide solution over 20 min. After stirring for 20 min at –60 to –55 °C, aldehyde **15c** (9.00 g, 0.0816 mol) in anhydrous 1,2-dimethoxyethane (55 mL) was added over 23 min. The mixture was stirred at –55 to –50 °C for 1 h to yield a thick suspension. MeOH (90 mL) was then added, which gave a clear brown solution. The cooling bath was removed and, after stirring at r.t. for 5 min, the reaction flask was placed into an oil bath preheated to 85 °C. The reaction mixture was stirred for 1 h, then cooled and concentrated in vacuo. The residue was dissolved in H_2O (180 mL) and AcOH (9 mL). The mixture was extracted with EtOAc (3 × 250 mL), and the combined extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a brown oil. The crude product was distilled under reduced pressure to give **8c**.

Yield: 6.22 g (63%); reddish oil; bp 65–66 °C / 0.1 mbar.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, J = 1.9 Hz, 1 H), 6.22 (d, J = 1.9 Hz, 1 H), 3.80 (s, 3 H), 3.72 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.2, 130.2, 114.8, 106.3, 36.3, 15.1.

MS (ESI): m/z = 122 [MH$^+$].

Anal. Calcd for $C_6H_7N_3$: C, 59.49; H 5.82; N, 34.69. Found: C, 59.61; H, 6.18; N, 34.77.

Preparation of Nitriles 9; General Procedure

To a solution of diisopropylamine (30.4 g, 0.300 mol) in THF (150 mL), *n*-BuLi (78.8 mL, 0.260 mol, 3.3 M in hexanes) was added at –30 °C, and the mixture was stirred at r.t. for 1 h. Nitrile **8a–c** (12.1 g, 0.100 mol) in THF (50 mL) was added at 0 °C, and the resulting mixture was stirred at r.t. for 1 h. 1,2-Dibromoethane (9.48 mL, 0.110 mol) was added at 0 °C, and the reaction mixture was stirred for an additional 1 h, then quenched with saturated aq NH_4Cl (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by column chromatography (hexanes–EtOAc, 4:1).

1-(1-Methyl-1*H*-pyrazol-3-yl)cyclopropanecarbonitrile (9a)

Yield: 5.62 g (57%); reddish oil; R_f 0.70 (hexanes–EtOAc, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, J = 2.2 Hz, 1 H), 6.24 (d, J = 2.2 Hz, 1 H), 3.81 (s, 3 H), 1.65–1.59 (m, 2 H), 1.52–1.47 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.3, 130.8, 121.9, 103.3, 38.7, 17.8, 9.0.

MS (ESI): m/z = 148 [MH$^+$], 121 [M$^+$–CN].

Anal. Calcd for $C_8H_9N_3$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.07; H, 5.79; N, 28.67.

1-(1-Methyl-1*H*-pyrazol-4-yl)cyclopropanecarbonitrile (9b)

Yield: 6.80 g (69%); yellowish oil; R_f 0.68 (hexanes–EtOAc, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (s, 1 H), 7.31 (s, 1 H), 3.86 (s, 3 H), 1.64–1.59 (m, 2 H), 1.24–1.20 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.6, 128.7, 122.6, 118.5, 39.3, 17.8, 5.6.

MS (ESI): m/z = 148 [MH$^+$].

Anal. Calcd for $C_8H_9N_3$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.31; H, 6.12; N, 28.45.

1-(1-Methyl-1*H*-pyrazol-5-yl)cyclopropanecarbonitrile (9c)

Yield: 8.09 g (82%); colorless oil; R_f 0.73 (hexanes–EtOAc, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, J = 1.9 Hz, 1 H), 6.07 (d, J = 1.9 Hz, 1 H), 3.99 (s, 3 H), 1.70 (dd, J = 7.6, 4.9 Hz, 2 H), 1.34 (dd, J = 7.6, 4.9 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.8, 136.5, 119.9, 105.9, 36.8, 15.9, 5.0.

MS (ESI): m/z = 148 [MH$^+$], 121 [M$^+$–CN].

Anal. Calcd for $C_8H_9N_3$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.48; H, 6.33; N, 28.39.

Preparation of Carboxylic Acids 12; General Procedure

A suspension of nitrile **9** (3.50 g, 0.0238 mol) in 10% aq NaOH (100 mL) was heated at reflux overnight (until NH_3 evolution ceased). The homogeneous solution was washed with Et_2O (50 mL), the aqueous layer was acidified with 6 M aq HCl to pH 3, and evaporated to dryness. The residue was triturated with *i*-PrOH (100 mL), the solid was filtered off, washed with *i*-PrOH (50 mL), and the combined filtrates were evaporated in vacuo. The residue was triturated with acetone (50 mL), filtered, and dried under reduced pressure to give **12**. An analytically pure sample was obtained by recrystallization from acetone–EtOH.

1-(1-Methyl-1*H*-pyrazol-3-yl)cyclopropanecarboxylic Acid (12a)

Yield: 4.62 g (96%); white solid; mp 182–183 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.60 (d, J = 1.8 Hz, 1 H), 6.32 (d, J = 2.0 Hz, 1 H), 3.77 (s, 3 H), 1.41 (dd, J = 6.7, 3.4 Hz, 2 H), 1.24 (dd, J = 6.7, 3.5 Hz, 2 H), COO*H* is exchanged with HDO.

^{13}C NMR (101 MHz, DMSO-d_6): δ = 174.2, 149.3, 131.3, 105.8, 38.2, 21.9, 17.1.

MS (ESI): m/z = 167 [MH$^+$], 149 [M$^+$–OH], 121 [M$^+$–COOH].

Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 58.20; H, 5.81; N, 17.20.

1-(1-Methyl-1*H*-pyrazol-4-yl)cyclopropanecarboxylic Acid (12b)

Yield: 4.50 g (94%) ;white solid; mp 168–170 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.72 (s, 1 H), 7.43 (s, 1 H), 3.79 (s, 3 H), 1.48–1.39 (m, 2 H), 1.10–1.05 (m, 2 H), COO*H* is exchanged with HDO.

^{13}C NMR (101 MHz, DMSO-d_6): δ = 175.4, 138.1, 130.9, 121.0, 38.7, 19.4, 18.1.

MS (ESI): *m*/*z* = 167 [MH$^+$], 121 [M$^+$–COOH].

Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.83; H, 5.8; N, 16.95.

1-(1-Methyl-1*H*-pyrazol-5-yl)cyclopropanecarboxylic Acid (12c)

Yield: 4.81 g (99%); white solid; mp 177–179 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.42 (s, 1 H), 6.20 (s, 1 H), 3.77 (s, 3 H), 1.53 (dd, *J* = 7.0, 3.9 Hz, 2 H), 1.23 (dd, *J* = 7.1, 3.9 Hz, 2 H), COO*H* is exchanged with HDO.

^{13}C NMR (101 MHz, DMSO-d_6): δ = 173.1, 141.6, 136.4, 106.3, 36.3, 19.3, 16.2.

MS (ESI): *m*/*z* = 167 [MH$^+$], 121 [M$^+$–COOH].

Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 58.08; H, 6.18; N, 16.53.

Preparation of 16; General Procedure

To a solution of carboxylic acid **12** (1.60 g, 9.58 mmol) in toluene (20 mL), NEt_3 (2.96 mL, 0.0213 mol) was added, followed by DPPA (3.25 g, 0.0118 mol) in toluene (5 mL) dropwise at 40 °C. The resulting mixture was heated at reflux for 3 h. *tert*-Butanol (5.90 g, 0.0797 mol) was added, and the resulting mixture was heated at reflux overnight. The solvent was evaporated and the residue was dissolved in EtOAc (50 mL), washed with H_2O (20 mL), 15% aq citric acid (20 mL), and saturated aq $NaHCO_3$ (20 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by column chromatography (EtOAc–hexanes, 1:1).

***tert*-Butyl 1-(1-Methyl-1*H*-pyrazol-3-yl)cyclopropylcarbamate (16a)**

Yield: 0.953 g (51%); yellowish oil; R_f 0.43 (EtOAc–hexanes, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 2.2 Hz, 1 H), 6.10 (br. s, 1 H), 5.34 (br. s, 1 H), 3.80 (s, 3 H), 1.45 (s, 9 H), 1.33–1.26 (m, 2 H), 1.21–1.14 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (two rotamers) = 155.4 and 154.6, 130.3, 129.3 and 124.7, 102.4, 79.0, 38.4, 30.9 and 29.4, 28.1, 17.2.

MS (ESI): *m*/*z* = 260 [MNa$^+$], 238 [MH$^+$], 182 [MH$^+$–C_4H_9], 138 [MH$^+$–CO_2–C_4H_8].

Anal. Calcd for $C_{12}H_{19}N_3O_2$: C, 60.74; H, 8.07; N, 17.71. Found: C, 60.82; H, 7.81; N, 17.55.

***tert*-Butyl 1-(1-Methyl-1*H*-pyrazol-4-yl)cyclopropylcarbamate (16b)**

Yield: 1.10 g (59%); white solid; mp 112–114 °C; R_f 0.38 (EtOAc–hexanes, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (s, 1 H), 7.27 (s, 1 H), 5.23 (s, 1 H), 3.83 (s, 3 H), 1.44 (s, 9 H), 1.17–1.11 (m, 2 H), 1.04–0.97 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (two rotamers) = 156.6 and 155.6, 136.8, 128.7 and 127.9, 125.8 and 124.1, 79.4, 38.8, 28.3, 16.9, 16.3.

MS (ESI): *m*/*z* = 238 [MH$^+$], 182 [MH$^+$–C_4H_9].

Anal. Calcd for $C_{12}H_{19}N_3O_2$: C, 60.74; H, 8.07; N, 17.71. Found: C, 60.73; H, 8.47; N, 17.48.

***tert*-Butyl 1-(1-Methyl-1*H*-pyrazol-5-yl)cyclopropylcarbamate (16c)**

Yield: 1.17 g (64%); white solid; mp 97–99 °C; R_f 0.40 (EtOAc–hexanes, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 0.9 Hz, 1 H), 6.18 (br. s, 1 H), 5.24 (br s, 1 H), 4.00 (s, 3 H), 1.39 (s, 9 H), 1.31–1.21 (m, 2 H), 1.20–1.05 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.4, 143.0, 137.4, 106.0, 79.4, 36.9, 28.0, 26.9, 15.0.

MS (ESI): *m*/*z* = 238 [MH$^+$], 182 [MH$^+$–C_4H_9], 138 [MH$^+$–CO_2–C_4H_8], 121 [M$^+$ – NHBoc].

Anal. Calcd for $C_{12}H_{19}N_3O_2$: C, 60.74; H, 8.07; N, 17.71. Found: C, 61.14; H, 7.89; N, 17.91.

Preparation of 13·2HCl; General Procedure

To a solution of **16** (0.500 g, 2.11 mmol) in Et_2O (10 mL), saturated HCl in Et_2O (20 mL) was added, and the reaction mixture was stirred at r.t. overnight. The precipitate was filtered, washed with Et_2O (10 mL), and dried under reduced pressure. An analytically pure sample was obtained by recrystallization from acetone.

1-(1-Methyl-1*H*-pyrazol-3-yl)cyclopropanamine Dihydrochloride (13a·2HCl)

Yield: 0.424 g (95%); white solid; mp 184–186 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.99 (br. s, 3 H), 7.68 (d, *J* = 2.1 Hz, 1 H), 6.25 (d, *J* = 2.1 Hz, 1 H), 3.80 (s, 3 H), 1.49–1.34 (m, 2 H), 1.15–1.07 (m, 2 H), 1 H is exchanged with HDO.

^{13}C NMR (101 MHz, DMSO-d_6): δ = 149.3, 132.2, 101.8, 38.4, 31.6, 12.8.

MS (ESI): *m*/*z* = 138 [MH$^+$], 121 [MH$^+$–NH_3].

Anal. Calcd for $C_7H_{13}Cl_2N_3$: C, 40.02; H, 6.24; N, 20.00; Cl, 33.75. Found: C, 40.27; H, 6.36; N, 19.92; Cl, 33.70.

1-(1-Methyl-1*H*-pyrazol-4-yl)cyclopropanamine Dihydrochloride (13b·2HCl)

Yield: 0.440 g (100%); white solid; mp 170–172 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.30 (br. s, 1 H), 9.00 (br. s, 3 H), 7.82 (s, 1 H), 7.56 (s, 1 H), 3.78 (s, 3 H), 1.32 (dd, *J* = 6.7, 5.4 Hz, 2 H), 0.96 (dd, *J* = 6.7, 5.4 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 137.0, 130.0, 119.8, 38.6, 28.8, 12.2.

MS (ESI): *m*/*z* = 138 [MH$^+$].

Anal. Calcd for $C_7H_{13}Cl_2N_3$: C, 40.02; H, 6.24; N, 20.00; Cl, 33.75. Found: C, 39.94; H, 6.16; N, 20.23; Cl, 33.84.

1-(1-Methyl-1*H*-pyrazol-5-yl)cyclopropanamine Dihydrochloride (13c·2HCl)

Yield: 0.446 g (100%); white solid; mp 161–163 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.10 (s, 3 H), 7.39 (d, J = 1.9 Hz, 1 H), 6.38 (d, J = 1.9 Hz, 1 H), 3.97 (s, 3 H), 1.50 (dd, J = 7.0, 5.7 Hz, 2 H), 1.15 (dd, J = 7.0, 5.7 Hz, 2 H), 1 H is exchanged with HDO.

^{13}C NMR (101 MHz, DMSO-d_6): δ = 138.5, 137.3, 108.4, 37.4, 26.8, 11.1.

MS (ESI): m/z = 138 [MH$^+$], 121 [MH$^+$–NH$_3$].

Anal. Calcd for $C_7H_{13}Cl_2N_3$: C, 40.02; H, 6.24; N, 20.00; Cl, 33.75. Found: C, 39.85; H, 6.63; N, 20.31; Cl, 33.97.

Preparation of Amines 14; General Procedure

To the solution of nitrile **9** (0.500 g, 3.40 mmol) in anhydrous THF (20 mL), BH_3·Me_2S (1.70 mL, 1.36 g, 0.0179 mol) was added. This mixture was stirred under reflux overnight, and then cooled to r.t. MeOH (20 mL) was added and the solution was stirred at r.t. for 0.5 h. The solvent was evaporated, and the residue was dissolved in saturated methanolic HCl (20 mL). The mixture was heated at reflux for 1 h to destroy the intermediate complex. After cooling, the solvent was evaporated, 10% aq NaOH was added to the residue to pH 8, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated in vacuo to give **14**. An analytical sample was obtained by column chromatography ($CHCl_3$–MeOH–NEt_3, 24:1:0.2).

(1-(1-Methyl-1*H*-pyrazol-3-yl)cyclopropyl)methanamine (14a)

Yield: 0.453 g (88%); yellowish oil; R_f 0.35 ($CHCl_3$–MeOH–NEt_3, 24:1:0.2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, J = 2.1 Hz, 1 H), 5.89 (d, J = 2.1 Hz, 1 H), 3.78 (s, 3 H), 2.82 (s, 2 H), 2.51 (br. s, 2 H), 0.89–0.82 (m, 2 H), 0.75–0.71 (m, 2 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 154.7, 130.2, 102.0, 49.2, 38.4, 22.3, 13.2.

MS (ESI): m/z = 152 [MH$^+$], 135 [MH$^+$–NH$_3$].

Anal. Calcd for $C_8H_{13}N_3$: C, 63.55; H, 8.67; N, 27.79. Found: C, 63.87; H, 8.42; N, 27.66.

(1-(1-Methyl-1*H*-pyrazol-3-yl)cyclopropyl)methanamine (14b)

Yield: 0.407 g (78 %); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, J = 0.7 Hz, 1 H), 7.28 (s, 1 H), 3.85 (s, 3 H), 2.77 (s, 2 H), 2.67 (br. s, 2 H), 0.75 (s, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.7, 130.2, 121.9, 49.2, 39.1, 15.6, 13.5.

MS (ESI): m/z = 152 [MH$^+$], 135 [MH$^+$–NH$_3$].

Anal. Calcd for $C_8H_{13}N_3$: C, 63.55; H, 8.67; N, 27.79. Found: C, 63.47; H, 9.04; N, 27.43.

(1-(1-Methyl-1*H*-pyrazol-3-yl)cyclopropyl)methanamine (14c)

Yield: 0.502 g (98%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, J = 1.9 Hz, 1 H), 6.08 (d, J = 1.8 Hz, 1 H), 3.90 (s, 3 H), 2.68 (s, 2 H), 1.67 (br. s, 2 H), 0.85–0.82 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.1, 137.6, 107.0, 49.3, 36.5, 20.3, 11.0.

MS (ESI): m/z = 152 [MH$^+$], 135 [MH$^+$–NH$_3$].

Anal. Calcd for $C_8H_{13}N_3$: C, 63.55; H, 8.67; N, 27.79. Found: C, 63.86; H, 8.36; N, 27.84.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588544.

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