Synthesis of 1-(pyrrolidin-2-ylmethyl)-1H-azoles and their piperidine-derived homologues

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Abstract: A convenient preparation of 1-(pyrrolidin-2-yl)-1H-pyrazoles, -imidazoles, and -1H-1,2,4-triazoles, 1-(piperidin-2-yl)-1H-pyrazoles and -1H-1,2,4-triazoles, and 1-(piperidin-3-yl)-1H-1,2,4-triazoles by alkylation of azoles (viz. pyrazoles, imidazoles, and triazoles) with N-Cbz-prolinol mesylate or its analogues and subsequent deprotection is reported. The two-step method allows for synthesis of the title compounds in 16–65% yields. The utility of the procedure has been demonstrated by multigram preparation of a 15-member building block mini-library for the lead-oriented synthesis of compound libraries. These building blocks perfectly fit the definition of low-molecular-weight hydrophilic three-dimensional templates, which leave much room for the lead-oriented synthesis of the compound libraries.

Keywords: Azoles • Saturated nitrogen heterocycles • Molecular rigidity • Lead-oriented synthesis • Alkylation

1. Introduction
Contemporary drug discovery relies heavily on the careful choice of chemotypes that can serve as the starting points for the design and synthesis of compound libraries. The so-called lead-likeness methodology for drug design, which relies on a number of concepts such as privileged structures, three-dimensional molecular shape, conformational restriction, and control of physicochemical properties of the potential lead compounds, have received much attention in the chemical literature recently [1–4]. The need for the “lead-oriented synthesis” [5] has guided the efforts of organic chemists towards novel low-molecular-weight hydrophilic three-dimensional scaffolds.

Among the numerous possible ways to design such structures we have turned our attention to the approach shown schematically in Fig. 1: a highly polar aromatic heterocycle is mounted onto a three-dimensional saturated template bearing an easily modifiable functional group (such as amino) [6–9]. The use of this approach is encountered among natural compounds (e.g. alkaloids nicotine 1 and anabasine 2, Fig. 2). Other examples comprise of synthesis of compounds of established biological activity, e.g. inhibitors of deacetylases (3) [10], tyrosine kinases (4) [11], or thrombin-activated fibrinolyse (5) [12]. In this work, we have focused on the scaffolds 6 – 11 obtained by linking theazole and pyrrolidine (or piperidine) heterocyclic rings by a single methylene unit (Table 1). Some examples of biologically relevant compounds derived from these templates are given in Fig. 2. Recently, derivatives of 7 have attracted additional attention as enantioselective catalysts [13,14] and chiral ionic liquids [15–19].

2. Experimental procedures
2.1. General
The solvents were purified according to the standard procedures. Compounds 13, 17, and 18 were prepared according to the methods reported in the literature [20]. All other starting materials were purchased from Acros, Merck, Fluka, and UkrOrgSyntez. All the chiral starting
materials were used as racemates. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. 1H and 13C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 499.9 MHz for Protons and 124.9 MHz for Carbon-13). Chemical shifts are reported (CH3Cl2 – MeOH – Et3N (9 : 1 : 0.1)) to give 6 – 11 (Table 1). To obtain the final compounds as dihydrochlorides, 6 – 11 (0.05 mol) were taken up in 10% HCl in dioxane (50 mL) and evaporated to dryness.

1-(Pyridolin-2-ylmethyl)-1H-pyrazole (6a): yield 58 g (44%). Yellowish liquid. 1H NMR (CDCl3), δ 7.47 (s, 1H), 7.42 (s, 1H), 6.20 (s, 1H), 4.15 (dd, J = 13.6 Hz and 4.8 Hz, 1H), 3.99 (dd, J = 13.6 Hz and 7.9 Hz, 1H), 3.49–3.56 (m, 1H), 2.91–2.96 (m, 1H), 2.83–2.89 (m, 1H), 2.14 (s, 1H), 1.79–1.90 (m, 1H), 1.64–1.79 (m, 2H), 1.36–1.44 (m, 1H). 13C NMR (CDCl3), δ 139.5, 129.7, 105.3, 58.6, 57.1, 46.4, 29.0, 25.2. Anal. calcd. for C11H10Cl2N3, C 47.50, H 7.74, Cl 27.89, N 16.38. MS (APCI): 180 (MH+).

4-Methyl-1-(pyridolin-2-ylmethyl)-1H-pyrazole (6b): yield 106 g (65%). Yellowish liquid. 1H NMR (CDCl3), δ 7.22 (s, 1H), 7.14 (s, 1H), 4.03 (dd, J = 13.6 Hz and 4.4 Hz, 1H), 3.87 (dd, J = 13.6 Hz and 7.7 Hz, 1H), 3.42–3.48 (m, 1H), 2.87–2.92 (m, 1H), 2.78–2.84 (m, 1H), 2.28 (s, 1H), 1.99 (s, 3H), 1.75–1.84 (m, 1H), 1.62–1.73 (m, 2H), 1.30–1.39 (m, 1H). 13C NMR (CDCl3), δ 139.7, 128.5, 115.7, 58.5, 56.8, 46.3, 28.9, 25.1, 8.8. Anal. calcd. for C11H13N3, C 47.50, H 8.30, N 27.96. MS (APCI): 152 (MH+).

3,5-Dimethyl-1-(pyridolin-2-ylmethyl)-1H-pyrazole (6c) dihydrochloride: yield 29 g (19%). White powder. Mp 178–179 °C. 1H NMR (DMSO-d6), δ 10.59 (br s, 1H), 9.93 (br s, 1H), 9.83 (br s, 1H), 6.12 (s, 1H), 4.58 (dd, J = 14.7 Hz and 7.5 Hz, 1H), 4.44 (dd, J = 14.7 Hz and 5.7 Hz, 1H), 3.86–3.95 (m, 1H), 3.21–3.28 (m, 1H), 3.07–3.14 (m, 1H), 2.35 (s, 3H), 2.20 (s, 3H), 1.91–2.04 (m, 2H), 1.80–1.89 (m, 1H), 1.64–1.72 (m, 1H). 13C NMR (DMSO-d6), δ 146.4, 143.2, 106.7, 58.9, 47.9, 44.9, 28.0, 22.8, 12.6, 11.3. Anal. calcd. for C10H15Cl2N3, C 47.63, H 7.59, Cl 28.12, N 16.66. Found C 47.50, H 7.74, Cl 27.89, N 16.38. MS (APCI): 180 (MH+).

1-(Pyridolin-2-ylmethyl)-1H-imidazole (7a): yield 82 g (54%). White amorphous solid. 1H NMR (D2O), δ 7.83 (s, 1H), 7.29 (s, 1H), 7.14 (s, 1H), 4.49 (dd, J = 14.7 Hz and 4.5 Hz, 1H), 4.41 (dd, J = 14.7 Hz and 8.9 Hz, 1H), 4.00–4.07 (m, 1H), 3.41–3.46 (m, 1H), 3.32–3.38 (m, 1H), 2.24–2.30 (m, 1H), 2.03–2.18

Figure 1. Scaffolds for lead-oriented synthesis. By combining saturated and aromatic nitrogen heterocycles.

Figure 2. Biologically active derivatives of the scaffolds defined in Fig. 1 (the scaffolds are shown in red).
Table 1. Synthesis of 1-(pyrrolidinylmethyl)-1H-azoles and their piperidine-derived homologues 6 – 11. Conditions: (i) NaH (1 eq), DMF, 60°C or 100°C, 8 h; (ii) H₂, 10% Pd-C, MeOH, 1 atm, rt, monitored by NMR.

| Entry No. | Substrate | Azole | Product | Yield, % |
|-----------|-----------|-------|---------|----------|
| 1         | ![](13)   | ![](14a) | ![](6a)  | 44       |
| 2         | ![](14b)  |       | ![](6b)  | 65       |
| 3         | ![](14c)  |       | ![](6c)  | 19       |
| 4         | ![](15a)  |       | ![](7a)  | 54       |
| 5         | ![](15b)  |       | ![](7b)  | 43       |
| 6         | ![](15c)  |       | ![](7c)  | 16       |
| 7         | ![](15d)  |       | ![](7d)  | 17       |
| 8         | ![](16a)  |       | ![](8a)  | 56       |
| 9         | ![](16b)  |       | ![](8b)  | 23       |
| 10        | ![](17)   | ![](14a) | ![](9a)  | 22       |
| 11        | ![](14c)  |       | ![](9b)  | 26       |
Continued Table 1. Synthesis of 1-(pyrrolidinylmethyl)-1H-azoles and their piperidine-derived homologues 6–11. Conditions: (i) NaH (1 eq.), DMF, 60°C or 100°C, 8 h; (ii) H₂, 10% Pd-C, MeOH, 1 atm, rt, monitored by NMR.

| Entry No. | Substrate | Azole | Product | Yield, % |
|-----------|-----------|-------|---------|----------|
| 12        |          | ![16a](image) | ![10a](image) | 22       |
| 13        |          | ![16b](image) | ![10b](image) | 60       |
| 14        |          | ![16a](image) | ![11a](image) | 52       |
| 15        |          | ![16b](image) | ![11b](image) | 45       |

( Continued)
(s, 1H), 7.40 (s, 1H), 6.22 (s, 1H), 4.10 (dd, J = 13.6 Hz and 4.1 Hz, 1H), 3.94 (dd, J = 13.6 Hz and 8.7 Hz, 1H), 2.97–3.04 (m, 2H), 2.55 (td, J = 11.5 Hz and 2.5 Hz, 1H), 2.04 (br s, 1H), 1.79 (d, J = 11.5 Hz, 1H), 1.60 (t, J = 14.0 Hz, 2H), 1.27–1.46 (m, 2H), 1.14 (qd, J = 11.8 Hz and 3.4 Hz, 1H). 13C NMR (CDCl3), δ 139.8, 130.1, 105.2, 58.1, 56.5, 46.6, 30.1, 26.0, 24.3. Anal. calcd. for C9H15N3 C 65.42, H 9.15, N 25.43. Found C 65.73, H 9.06, N 25.43. Found C 65.73, H 9.06, N 25.62. MS (APCI): 166 (MH+).

2-[(3,5-Dimethyl-1H-pyrazol-1-yl) methyl] piperidine (9b): yield 12 g (26%). Yellowish liquid. 1H NMR (CDCl3), δ 5.73 (s, 1H), 3.78–3.88 (m, 2H), 2.97–3.06 (m, 2H), 2.56 (td, J = 11.8 Hz and 2.5 Hz, 1H), 2.48 (br s, 1H), 2.20 (s, 3H), 2.18 (s, 3H), 1.72–1.80 (m, 1H), 1.53–1.60 (m, 2H), 1.25–1.47 (m, 2H), 1.10–1.20 (m, 1H). 13C NMR (CDCl3), δ 147.7, 139.5, 104.7, 56.7, 54.1, 46.6, 30.2, 26.0, 24.4, 13.5, 11.2. Anal. calcd. for C9H16Cl2N4 C 40.18, H 6.74, N 23.43. Found C 39.87, H 6.51, N 23.62. MS (APCI): 167 (MH+).

3-[(3,5-Dimethyl-1H-1,2,4-triazol-1-yl)methyl] piperidine (11b): yield 87.6 g (45%). Yellowish liquid. 1H NMR (CDCl3), δ 3.70–3.82 (m, 2H), 2.86 (t, J = 13.6 Hz, 2H), 2.50 (td, J = 11.8 Hz and 2.1 Hz), 2.30 (s, 3H), 2.22 (s, 3H), 1.97 (br s, 1H), 1.56–1.71 (m, 3H), 1.31–1.40 (m, 1H), 1.04–1.13 (m, 1H). 13C NMR (CDCl3), δ 159.2, 152.1, 51.4, 50.2, 46.8, 37.6, 28.8, 25.5, 13.7, 11.9. Anal. calcd. for C9H11N3 C 61.82, H 9.34, N 28.84. Found C 61.64, H 9.48, N 29.08. MS (APCI): 195 (MH+).

3. Results and discussion

Only a few reports on the synthesis of compounds 6 – 11 can be found in the literature: namely, the preparation of compounds 6a [13] and 7a [14,18] has been documented (Scheme 1). Both compounds were obtained by alkylation of the corresponding azole anions with N-Boc-prolinol tosylate (12). For the preparation of compounds 6 – 8, we have used an analogous method commencing from N-Cbz-prolinol mesylate (13) (Table 1), which is more reactive than N-Boc-prolinol tosylate, is shelf-stable and can be easily obtained on a hundred gram scale [20]. Azoles 14 – 16 were used to generate anions for the reaction with 13 (Table 1, Entries 1–9).

It was found that anions of pyrazoles 14a–c were more reactive towards alkylation with 13 than anions of imidazoles 15a–d or 1,2,4-triazoles 16a,b. Whereas 13 and anions of 14a–c reacted smoothly in DMF already at 60°C, in the case of 15a–d or 16a,b, the reaction was successful only at 100°C. It should be noted that in the case of 16, the alkylation proceeded regioselectively at N-1 atom of the heterocycle. The corresponding Cbz derivatives were not characterized but subjected to catalytic hydrogenation (10% Pd-C, MeOH, 1 atm, rt) to give pure 6 – 8 in 16–65% overall yields.
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As was described previously by our group [20], the mesylate of benzyl 2-(hydroxymethyl)piperidine-1-carboxylate is not stable enough to be isolated. Therefore the corresponding chloride [17] was used in the reaction with the azole anions (Table 1, Entries 10–13). This change did not affect the outcome of the reaction sequence described above: the corresponding products 9a,b and 10a,b were obtained in 22–60% yields. The method was equally efficient for the preparation of 1-(pyrrolidin-2-yl)-1H-1,2,4-triazoles 11a,b (45–52% yields) starting from mesylate 18 [20] and anions of 16a,b (Table 1, Entries 14 and 15).

Compounds 6 – 11 were obtained as rather hygroscopic liquids or oils, therefore any aqueous work-up should be avoided during their isolation and/or purification. In some cases, the compounds were isolated as dihydrochlorides; 10% HCl in dioxane was used for that purpose. Although the synthetic scheme included chromatographic purifications, it was easily scaled up for the preparation of 100 g of the final products in a single run.

Analysis of the physicochemical properties of the simplest (N-methyl) derivatives of the amines 6 – 11 (Table 2) showed that these building blocks perfectly fit the definition of low-molecular-weight hydrophilic three-dimensional templates [21]. They provide an opportunity for the lead-oriented synthesis of the compound libraries even if the strictest current criteria of lead-likeness are considered [5] (Fig. 3).

4. Conclusions

A convenient approach to multigram synthesis of 1-(pyrrolidin-2-yl)-1H-pyrazoles, -imidazoles, and -1H-1,2,4-triazoles, 1-(piperidin-2-yl)-1H-pyrazoles and -1H-1,2,4-triazoles, and 1-(piperidin-3-yl)-1H-1,2,4-triazoles was developed. The method allowed for the preparation of the target compounds in 16–65% yields. The building blocks obtained comply with the strictest definitions of templates for lead-oriented synthesis of the compound libraries.

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