Synthetic Communications®, 41: 2031–2035, 2011

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.491171

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RAPID ACCESS TO 1-BENZYL 2-SUBSTITUTED PIPERAZINES: APPLICATION TO THE SYNTHESIS OF 1-BENZYL-2-DIFLUOROMETHYL-PIPERAZINE

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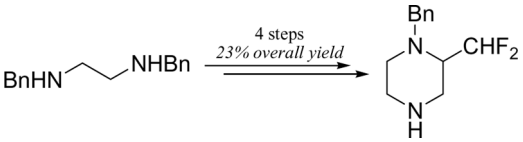
GRAPHICAL ABSTRACT



Abstract *A rapid and efficient synthesis of 1-benzyl-2-difluoromethyl-piperazine is herein described. The new pathway has the advantage of avoiding orthogonal protection at the two piperazine nitrogen atoms; therefore it is suitable for access to several 1-benzyl 2-substituted piperazines starting from the simple commercially available* N,N′*-dibenzylethylendiamine.*

Keywords Chemoselective deprotection; piperazines; privileged structures

INTRODUCTION

The piperazine ring is found in a number of biologically active compounds, including several marketed drugs,[1] and is considered to be a privileged structure in drug discovery.[2,3] The main feature that confers druglike properties is the constraint of the two nitrogen atoms in the six-membered ring, which enhances favorable interactions with macromolecules.

Whereas the synthesis of simple 1,4-disubstituted piperazines has received considerable attention, only a comparatively small number of C-substituted derivatives have been prepared and evaluated for their pharmacological properties.[4] C-Substituted piperazines are contained in several pharmacologically active compounds such as platelet activating factor (PAF) inhibitors,[5] soluble epoxide

Received December 26, 2009.

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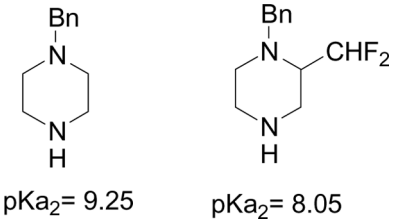


Figure 1. pKa_2 values of benzyl piperazine and 1-benzyl-2-difluoromethyl piperazine (**1**) (predicted with the ACD/labs software[9]).

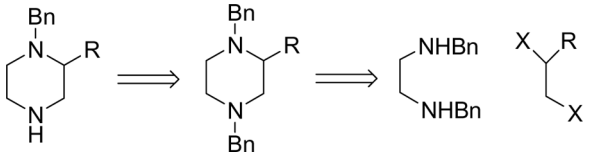
hydrolase (sEH) inhibitors,[6] farnesyl transferase inhibitors (i.e., L-745631),[7] and NK-1 antagonists (i.e., FK-355).[8]

As part of our efforts working toward the synthesis of novel scaffolds with high potential as building blocks in medicinal chemistry, we became interested in 1-benzyl-2-difluoromethyl-piperazine (**1**), hypothesizing that modulation of N-atom electronic as well as steric hindrance properties could be valuable strategies to modulate activity at the biological target and influence physicochemical properties (Fig. 1).

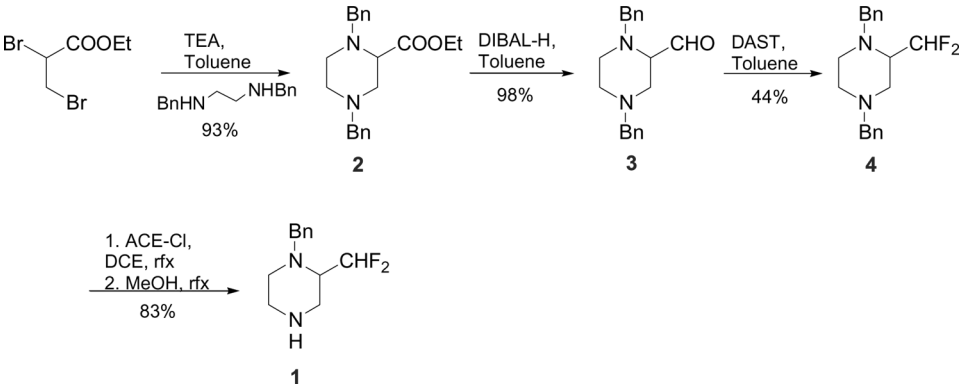
To the best of our knowledge, only one approach to the synthesis of 2-difluoromethyl-piperazine has been reported, and it involves the reaction of pyrazine-carboxaldehyde and diethylaminosulfur trifluoride (DAST) followed by catalytic reduction.[10] However, this synthetic pathway is unsuitable for a multigram scale because of its low efficiency (5% overall yield), and moreover it gives access to the full deprotected 2-difluoromethyl-piperazine, which can be converted into desired **1** only after protection/deprotection steps. Inspired by a paper of Gubert and collaborators in which regioselective debenzylation of (1,4-dibenzyl-piperazin-2-yl)-acetonitrile was described,[11] we have explored a general and efficient route for the preparation of **1** starting from commercially available *N,N′*-dibenzylethylendiamine (Scheme 1).

Double alkylation of *N,N′*-dibenzylethylendiamine with ethyl 2,3-dibromopropenoate afforded excellent yields of ester **2**, which was quantitatively converted into difluoro derivative **4** through controlled reduction with diisobutylaluminumhydride (DIBAL)–H at −78 °C followed by double fluorine substitution with DAST (43% yield over two steps). Both classical catalytic hydrogenation conditions and *N*-deprotection via carbamate [1-chloroethyl chloroformate (ACE-Cl), dimethylchloride (DCM), 2 h, reflux; then MeOH at reflux] gave access in excellent yield to the desired **1** (four steps, 23% overall yield, Scheme 2).

In conclusion, a rapid and efficient synthesis of 1-benzyl-2-difluoromethyl-piperazine is herein described. This pathway has the advantage of avoiding



Scheme 1. Retrosynthetic analysis.



Scheme 2. Synthesis of 1-benzyl-2-difluoromethyl piperazine (**1**).

orthogonal protection at the two piperazine nitrogen atoms and allows us to directly functionalize the piperazine ring at the less accessible *N*-position.

EXPERIMENTAL

All moisture-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. All chemicals and solvents were purchased from commercial sources and used without purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400-MHz instrument operating at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in ppm (δ) using the residual solvent line as internal standard. Reactions were monitored by thin-layer chromatography (TLC) (precoated silica-gel plate F254, Merck). Chromatography was carried out on silica gel (70–230 mesh) supplied by Merck AG Darmstadt, Germany. Combustion analyses were performed using a CHNO analyzer.

Ethyl 1,4-Dibenzylpiperazine-2-carboxylate (2)

A solution of N,N-diisopropylethylamine (DIPEA) (4.73 mL, 27.2 mmol) and *N,N′*-dibenzylethylendiamine (2 mL, 8.5 mmol) dissolved in 13.5 mL dry toluene was added to a solution of ethyl 2,3-dibromopropionate (2.48 mL, 17.0 mmol) in 20 mL dry toluene warmed to 50 °C. The mixture was heated to reflux for 21 h, cooled to room temperature, and filtered from the solid. The organic layer was evaporated under vacuum, and the crude residue was purified by chromatography over silica gel ($PE/Et_2O = 85:15$) to afford the pure ester **2** (2.68 g, 93%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.34 (m, 10H), 4.08–4.20 (m, 2H), 3.92 (d, $J = 13.6$ Hz, 1H), 3.48–3.62 (m, 2H), 3.38 (d, $J = 13.2$ Hz, 1H), 3.24–3.35 (m, 1H), 3.02–3.12 (m, 1H), 2.59–2.80 (m, 2H), 2.38–2.57 (m, 3H), 1.24 (t, $J = 7.2$ Hz, Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 49.0, 53.4, 55.9, 60.0, 60.8, 63.0, 63.2, 127.1, 127.4, 127.6, 128.0, 128.6, 128.8, 138.3, 138.5, 172.5. Elemental analysis calculated for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28; O, 9.45. Found: C, 74.49; H, 7.78; N, 8.23; O, 9.50.

1,4-Dibenzyl-2-(difluoromethyl)piperazine (4)

DIBAL-H solution (25% wt) in toluene (1.58 mL, 2.36 mmol) was added dropwise at −78 °C to a solution of ester **2** (400 mg, 1.18 mmol) in 10 mL dry toluene. The mixture was stirred at −78 °C for 15 min, and then saturated aqueous NH_4Cl solution and EtOAc were added. The layers were separated, and the organic phase was washed twice with saturated aqueous NH_4Cl solution, dried (Na_2SO_4), and filtered. Solvent removal under reduced pressure afforded aldehyde **3** (340 mg, 98%), which was used for the next step without purification. DAST (365 μL, 2.76 mmol) was added dropwise to a solution of **3** (340 mg, 1.15 mmol) in 17 mL dry toluene cooled to 0 °C. The mixture was gently warmed to reflux; after 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution. EtOAc was added. The layers were separated, and the organic phase was washed twice with brine, dried (Na_2SO_4), filtered, and concentrated under vacuum. Chromatography of the crude residue over silica gel (PE/Et_2O = 9:1) gave the pure difluoro derivative **4** (160 mg, 44%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.36 (m, 10H), 6.32 (dt, J = 6.0 Hz, J = 56.4 Hz, 1H), 3.91 (dd, J = 2.8 Hz, J = 13.6 Hz, 1H), 3.78 (d, J = 14.0 Hz, 1H), 3.52 (d, J = 13.2 Hz, 1H), 3.48 (d, J = 13.2 Hz, 1H), 2.80–2.98 (m, 2H), 2.67–2.78 (m, 1H), 2.44–2.60 (m, 3H), 2.34–2.40 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.6, 52.6, 52.9, 55.6, 56.7, 60.3, 121.0, 124.3, 127.1, 128.0, 128.6, 129.1, 130.4, 135.8, 139.7. Elemental analysis calculated for $C_{19}H_{22}F_2N_2$: C, 72.13; H, 7.01; N, 8.85. Found: C, 72.24; H, 7.00; N, 8.83.

1-Benzyl-2-(difluoromethyl)piperazine (1)

ACE-Cl (6.25 mL, 57.4 mmol) was added dropwise to a solution of piperazine **4** (13.9 g, 44.1 mmol) in 50 mL dry 1,2-dichloroethane cooled to 0 °C. The mixture was gently heated to reflux. After 2 h, volatiles were evaporated under vacuum; the crude residue was dissolved in 20 mL MeOH, and the resulting mixture was heated to reflux for 1 h. After cooling to rt, filtration from the precipitate and volatile evaporation afforded a brown oil. Crystallization from $CHCl_3$/MeOH (9:1) afforded amine **1** as hydrochloride salt (white solid, 9.59 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (bs, 1H), 9.86 (bs, 1H), 7.26–7.41 (m, 5H), 6.41 (t, J = 54.4 Hz, 1H), 4.10 (d, J = 13.2 Hz, 1H), 3.69 (d, J = 13.2 Hz, 1H), 3.12–3.56 (m, 5H), 3.07 (bd, J = 1.7 Hz, 1H), 2.82 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.1, 48.1, 49.5, 51.6, 60.4, 119.9, 124.4, 128.0, 130.4, 139.7. Elemental analysis calculated for $C_{12}H_{16}F_2N_2$: C, 63.70; H, 7.13; N, 12.38. Found: C, 63.65; H, 7.22; N, 12.33.

ACKNOWLEDGMENTS

The authors thank A. Casolari and E. Durini for careful assistance in NMR experiments and structure assignments.

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