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A Practical Synthesis of Differentially Protected 2-(Hydroxymethyl)piperazines

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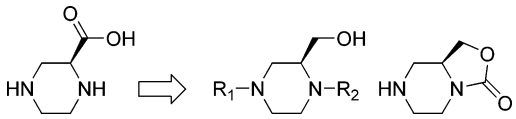

An efficient and scalable synthesis of three differentially protected 2-(hydroxymethyl)piperazines is presented, starting from optically active and commercially available (2*S*)-piperazine-2-carboxylic acid dihydrochloride. These synthetic building blocks are useful in the preparation of biologically active compounds and as chemical scaffolds for the construction of combinatorial libraries.

The piperazine ring is a favored structural element in medicinal chemistry and is often encountered in the structure of enzyme inhibitors and clinical therapeutics. Piperazine-2-carboxylic acid, for example, has been employed in the synthesis of novel peptides and peptidomimetics, including the HIV protease inhibitor indinavir.[2] Piperazine-2-carboxylic acid is traditionally prepared from pyrazinecarboxylic acid and may be resolved as the (*S*)-camphorsulfonic acid salt.[3,4] Bigge and co-workers reported an orthogonally protected derivative of piperazine-2-carboxylic acid bearing benzyloxycarbonyl and *tert*-butoxycarbonyl protecting groups.[5] This useful synthetic building block and related hydroxymethyl derivatives have since been employed in the preparation of a variety of biologically active compounds, including antibacterial,[6,7] antineoplastic,[8,9] and antinociceptive[10] agents.

In connection with one of our discovery programs, we required a practical route to 2-(hydroxymethyl)piperazine building blocks in which reaction at each of the heteroatoms could be achieved selectively. A recent report by Clark and Elbaum[11] on orthogonally protected 2-piperazines prompted us to report here our very similar (albeit independently arrived at) solution to this problem. In our laboratory, the methods reported herein have provided up to tens of grams of piperazines **1**−**3**[12] in excellent yields and with only a single chromatographic purification step required in the entire reaction sequence. The starting material, piperazine-2-carboxylic acid dihydrochloride, is available commercially at reasonable cost in either enantiomeric form.

The synthesis of piperazines **1**−**3** is illustrated in Scheme 1. The conversion of (2*S*)-piperazine-2-carboxylic acid dihydrochloride (**4**·2HCl) to **1** required the protection of both amino groups as *tert*-butyl carbamates (Boc) and reduction of the carboxylic acid function. First, the acid **4** was reacted with di-*tert*-butyl dicarbonate in aqueous Na_2CO_3 and tetrahydrofuran to provide the bis-carbamate intermediate **5**, which exhibited spectral properties consistent with those reported previously.[13] This material was obtained in excellent yield and was of sufficient purity for use in the next step without purification. A highly efficient reduction of **5** was achieved via initial conversion to the methyl ester (CH_3I, K_2CO_3, DMF) and subsequent reaction with sodium borohydride and calcium chloride.[14] Using this protocol, >30 g of alcohol **1**[11] was prepared in 95% overall isolated yield from **4**.

Our synthesis of **2** and **3** proceeds from alcohol **1** and involves the intermediacy of the oxazolopyrazinone **6**. Clark and Elbaum effected the cyclization of **1** to **6** by refluxing the corresponding sodium alkoxide (formed with NaH) in tetrahydrofuran.[11] We chose an alternate strategy involving activation of the hydroxyl function in **1** as a mesylate, thus setting the stage for intramolecular S_N2 displacement by the carbonyl oxygen of the neighboring carbamate function to form the oxazolidinone ring of **6** with concomitant loss of isobutene.[15] This activation−cyclization approach affords **6** in improved yield and without the need for a chromatographic purification step. Piperazine **2** was then prepared from **6** in essentially quantitative yield by heating with lithium hydroxide in ethanol−water. Piperazine **2** displayed spectroscopic properties (including optical rotation) identical to that of an authentic sample,[12] thus confirming the identity and stereochemical integrity of material prepared via this route. Finally, the oxazolopyrazinone **3** could be prepared in quantitative yield from **6** by reaction with HCl in dioxane.

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(12) Recently, the Boc-protected piperazine **2** has become available commercially, although its cost (ca. $300/g) is prohibitive for work on larger scales.

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(15) Cyclizations of this type are known; see: Benedetti, F.; Berti, F.; Norbedo, S. *J. Org. Chem.* **2002**, *67*, 8635−8643 and references cited therein.

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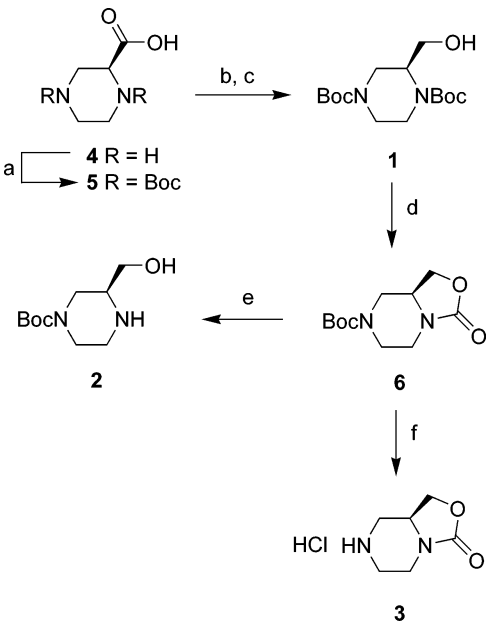
SCHEME 1. Synthesis of Differentially Protected Piperazines 1−3[a]



[a] Reagents and conditions: (a) Boc_2O, Na_2CO_3, THF, H_2O, rt; (b) CH_3I, K_2CO_3, DMF, rt; (c) $NaBH_4$, $CaCl_2$, EtOH, (95% overall from **4**); (d) Ms_2O, DIEA, $ClCH_2CH_2Cl$, reflux; (e) LiOH, EtOH, H_2O, reflux (98% overall from **1**); (f) HCl, dioxane, rt (99% overall from **1**).

In summary, multigram quantities of differentially protected piperazine building blocks were prepared in excellent yields from commercially available 2(*S*)-piperazine-2-carboxylic acid dihydrochloride. Compounds **1**−**3** and **6** should prove useful for the selective elaboration of the 2-(hydroxymethyl)piperazine scaffold, facilitating the preparation of a variety of substituted piperazines.

Experimental Section

(2*S*)-1,4-Bis(*tert*-butoxycarbonyl)piperazine-2-carboxylic Acid (5).[13] To an aqueous solution of Na_2CO_3 (103 g, 0.974 mol, in 500 mL of water) at 23 °C was added (*S*)-piperazine-2-carboxylic acid dihydrochloride (26 g, 0.129 mol), followed by di-*tert*-butyl dicarbonate (107 g, 0.49 mol) and tetrahydrofuran (250 mL). The reaction mixture was stirred at 23 °C for 20 h and then concentrated in vacuo to remove tetrahydrofuran. The resulting solution was then extracted with diethyl ether (3 × 200 mL) to remove nonpolar species. The aqueous phase was treated with 3.0 M HCl until it was slightly acidic (pH = 4) and then extracted with ethyl acetate (4 × 400 mL). The combined ethyl acetate extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated to afford (2*S*)-1,4-bis(*tert*-butoxycarbonyl)piperazine-2-carboxylic acid (42 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (bs, 18H), 2.83 (m, 1H), 3.08−3.18 (m, 2H), 3.83 (q, J = 13.2 Hz, 1H), 3.99 (br, 1H), 4.51−4.76 (m, 2H), 7.61 (br, 1H).

Di-*tert*-butyl (2*S*)-2-(Hydroxymethyl)piperazine-1,4-dicarboxylate (1).[11] A solid mixture of (2*S*)-1,4-bis(*tert*-butoxycarbonyl)-piperazine-2-carboxylic acid (**5**) (37.5 g, 0.114 mol) and potassium carbonate (16.4 g, 0.119 mol) was suspended in DMF (300 mL). The resulting mixture was cooled to 0 °C and treated with iodomethane (15 mL, 0.241 mol) via syringe over 1 min. The reaction mixture was allowed to warm to 23 °C, stirred for 6 h, and then poured into water (1400 mL). The solution was extracted with ethyl acetate (4 × 400 mL), and the combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated to afford 1,4-di-*tert*-butyl 2-methyl (2*S*)-piperazine-1,2,4-tricarboxylate (39 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (bs, 18H), 2.83 (bs, 1H), 3.08−3.22 (m, 2H), 3.74 (s, 3H), 3.74−3.98 (m, 2H), 4.48−4.72 (m, 2H). To a cold (0 °C) solution of 1,4-di-*tert*-butyl 2-methyl (2*S*)-piperazine-1,2,4-tricarboxylate (39 g, 0.113 mol) in ethanol (500 mL) was added $CaCl_2$ (25 g, 0.225 mol), followed by $NaBH_4$ (17.2 g, 0.455 mol) in two portions. The reaction mixture was allowed to warm to room temperature and stirred for 1.5 h. The reaction mixture was then recooled to 0 °C and quenched with aqueous citric acid solution (100 g citric acid in 1 L of water). The resulting solution was then extracted with ethyl acetate (4 × 300 mL), and the combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by silica gel flash chromatography (eluting with 25% to 50% ethyl acetate in hexanes) to afford di-*tert*-butyl (2*S*)-2-(hydroxymethyl)piperazine-1,4-dicarboxylate (**1**): yield 34.3 g (95% over three steps); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (br, 18H), 2.95 (br, 4H), 3.61 (br, 2H), 3.8−4.0 (m, 2H), 4.17 (br, 2H); ESI-MS (*m*/*z*) $[M + Na]^+ = 339$.

***tert*-Butyl (8a*S*)-3-Oxotetrahydro-1,3-oxazolo[3,4-*a*]pyrazine-7(1*H*)-carboxylate (6).**[11] Diisopropylethylamine (60 mL, 0.345 mol) and then methanesulfonic anhydride (22 g, 0.126 mol) were added to a solution of di-*tert*-butyl (2*S*)-2-(hydroxymethyl)piperazine-1,4-dicarboxylate (**1**) (35.3 g, 0.112 mol) in 1,2-dichloroethane (800 mL) at 23 °C. The reaction mixture was heated at reflux for 1 h and then cooled to 23 °C and diluted with 400 mL of chloroform. The resulting solution was washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated to afford *tert*-butyl (8a*S*)-3-oxotetrahydro-1,3-oxazolo[3,4-*a*]pyrazine-7(1*H*)-carboxylate (**6**): yield 27 g; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.65 (br, 1H), 2.80 (m, 1H), 3.00 (dt, J = 3.6 Hz, J = 12.6 Hz, 1H), 3.74−3.84 (m, 2H), 3.95 (dd, J = 5.7 Hz, J = 9.0 Hz, 1H), 4.07 (br, 1H), 4.22 (br, 1H), 4.44 (t, J = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.0, 40.2, 42.3 (br), 46.8 (br), 52.0, 65.0, 79.4, 153.4, 155.9; ESI-MS (*m*/*z*) $[M + Na]^+ = 265$.

***tert*-Butyl (3*S*)-3-(Hydroxymethyl)piperazine-1-carboxylate (2).** A solution of *tert*-butyl (8a*S*)-3-oxotetrahydro-1,3-oxazolo[3,4-*a*]pyrazine-7(1*H*)-carboxylate (**6**) (24 g, 0.099 mol) in ethanol (400 mL) was heated to reflux and treated with lithium hydroxide solution (41 g of $LiOH\cdot H_2O$ in 300 mL of water, 0.98 mol). The reaction mixture was heated at reflux for 1.5 h, cooled to 0 °C, and then neutralized to pH = 8 by slow addition of 3.0 M aqueous HCl solution. The resulting solution was extracted with chloroform (3 × 300 mL), and the combined organic layers were washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated to afford *tert*-butyl (3*S*)-3-(hydroxymethyl)piperazine-1-carboxylate (**2**): yield 21 g (98% overall from **1**); $[\alpha]^{25}_D$ +18.7 (EtOH, c = 2.0); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 2.23 (br, 2H), 2.67−3.02 (m, 5H), 3.49 (dd, J = 6.9 Hz, J = 10.8 Hz, 1H), 3.64 (dd, J = 3.9 Hz, J = 10.8 Hz, 1H), 3.87 (br, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.1, 43.9 (br), 44.8, 46.5 (br), 56.5, 62.9, 78.4, 153.7; ESI-MS (*m*/*z*) $[M + H]^+ = 217$.

(8a*S*)-Hexahydro-1,3-oxazolo[3,4-*a*]pyrazin-3-one (3). To a solution of *tert*-butyl (8a*S*)-3-oxotetrahydro-1,3-oxazolo[3,4-*a*]-pyrazine-7(1*H*)-carboxylate (**6**) (3.5 g, 14.5 mmol) in methanol (25 mL) at 23 °C was added HCl solution (25 mL, 4.0 M in dioxane, 100 mmol). The reaction mixture was stirred for 1.5 h at 23 °C and then concentrated to afford (8a*S*)-hexahydro-1,3-oxazolo[3,4-a]pyrazin-3-one (**3**) as the hydrochloride salt: yield 2.6 g (99% overall from **1**); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.89 (m, 2H), 3.15−3.37 (m, 3H), 3.72 (dd, J = 3.9, 13.8 Hz, 1H), 4.00 (m, 1H), 4.11−4.21 (m, 1H), 4.40 (t, J = 8.7 Hz, 1H), 9.62 (bs, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 37.2, 41.4, 44.7, 49.3, 64.9, 155.7; ESI-MS (*m*/*z*) $[M + H]^+ = 143$.

Supporting Information Available: Copies of ^{1}H NMR spectra for compounds **2**, **3**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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