Tetrahedron Letters 53 (2012) 6332–6334

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Concise synthesis of N^3- and N^6-monoprotected 3,6-diazabicyclo[3.1.1]heptanes; useful intermediates for the preparation of novel bridged bicyclic piperazines

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ARTICLE INFO

Article history:
Received 16 August 2012
Revised 30 August 2012
Accepted 31 August 2012
Available online 19 September 2012

Keywords:
3,6-Diazabicyclo[3.1.1]heptane
Piperazine
Bicyclic
Heterocycle
Azetidine

ABSTRACT

Bridged bicyclic piperazines are important building blocks in medicinal chemistry research. The bicyclic piperazine 3,6-diazabicylo[3.1.1]heptane is of particular interest as a piperazine isostere because it is achiral and shows similar lipophilicity to that of piperazine based on the *c*Log*P* of a derived analog. A concise synthesis of N^3- and N^6-monoprotected 3,6-diazabicyclo[3.1.1]heptanes **2d** and **2e**, respectively, is described. The seven step sequence begins with inexpensive starting materials and uses straightforward chemistry.

Introduction

Piperazines are used extensively in drug discovery research. Numerous drugs approved by the FDA and other regulatory agencies for the treatment of human diseases contain a piperazine ring. Some examples are shown in Figure 1, including ciprofloxacin (**1**, Cipro®),[1] sildenafil (Viagra®),[2] ziprasidone (Geodone®),[3] and dasatinib (Sprycel®).[4] Over the years, several types of bridged bicyclic piperazines have been developed as piperazine isosteres (Fig. 2); many of these piperazine isosteres have shown desirable biological activities for a number of pharmacological targets.[5] In some instances, the bicyclic analog showed enhanced biological activity and/or selectivity compared to the corresponding piperazine analog.[5b,c,e,f]

Of the parent bicyclic piperazines shown in Figure 2, 3,6-diazabicyclo[3.1.1]heptane (**2a**) shows particular promise of becoming a useful piperazine isostere due to its similarity in structure and properties to piperazine. For example, *c*Log*P* calculations on fluoroquinolones **1** and **2b** suggest the lipophilicity of **2a** is comparable to that of piperazine. In addition, **2a** is achiral, which eliminates the need to separate and test the individual enantiomers. Of the remaining piperazines in Figure 2, **3a** is also achiral, and a number of reports have shown its utility as an effective piperazine isostere.[5a,c] However, *c*Log*P* calculations on a derived fluoroquinolone-containing analog (**3b**) suggest that **3a** increases lipophilicity compared to piperazine. The remaining two bicyclic piperazines in Figure 2, **4a** and **5a**, have also been utilized successfully as piperazine surrogates;[5a–f] however, both of these piperazines are chiral.

Syntheses of the parent bridged bicyclic piperazines **3a**,[7] **4a**,[8] and **5a**,[9] illustrated in Figure 2, have been previously described, and some mono-*N*-protected versions of these bicyclic piperazines

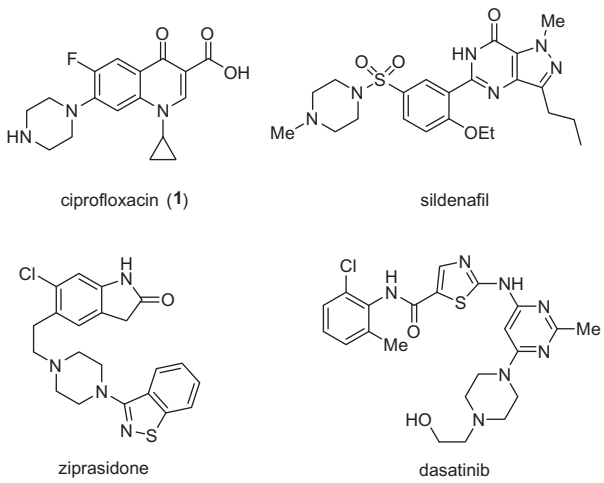

Figure 1. Marketed drugs possessing a piperazine ring.

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http://dx.doi.org/10.1016/j.tetlet.2012.08.156

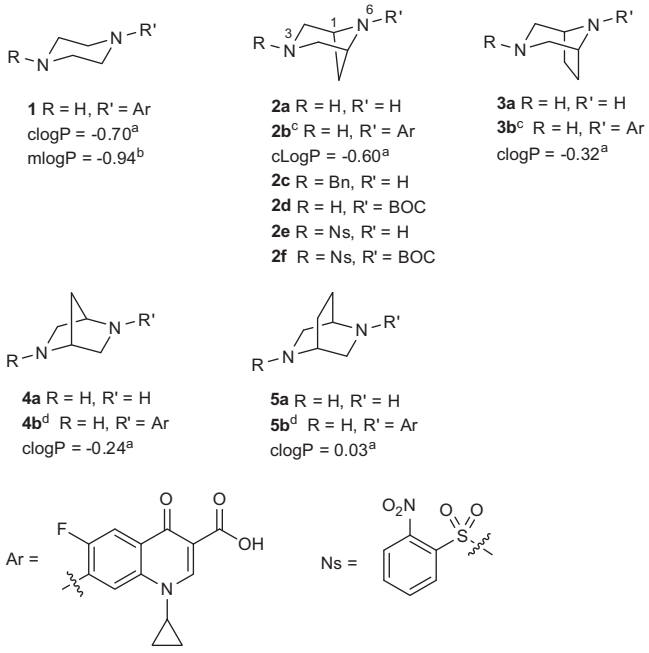
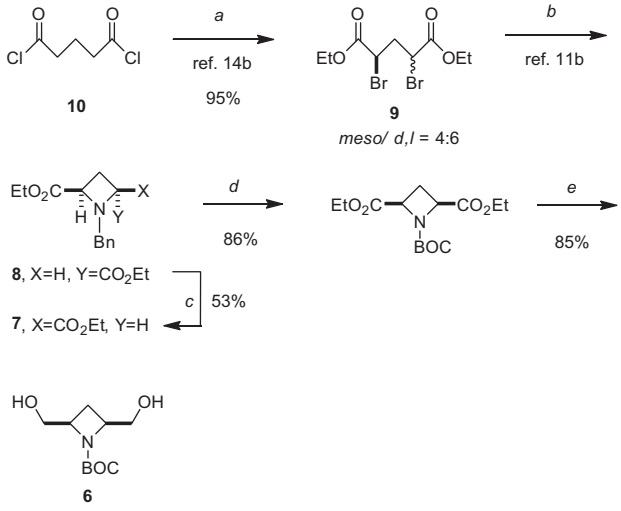
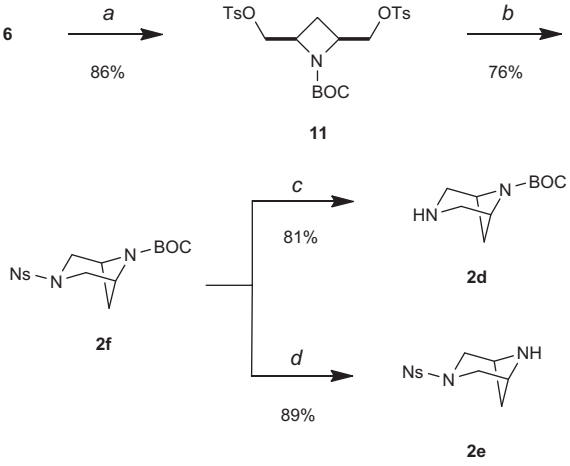


Figure 2. Synthetic targets **2d**–**f** and selected bridged bicyclic piperazine isosteres (**2a**–**5a**) utilized in medicinal chemistry. [a]Lipophilicity ($Log P_{o/w}$) values were calculated based on Molinspiration program predictions (Molinspiration Cheminformatics, Bratislava, Slovak Republic, http://www.molinspiration.com/cgi-bin/properties). [b]Measured Log*P*, see Ref. 6. [c]Analogs **2b** and **3b** are virtual compounds created to illustrate how their lipophilicities compare to ciprofloxacin (**1**). [d]For the preparation of analogs **4b** and **5b**, see Ref. 5b.



Scheme 1. Preparation of diol **6**. Reagents and conditions: (a) Br_2, *hv*, 80 °C, 6 h; EtOH, 0 °C → rt, 24 h; (b) $BnNH_2$, DMF, 80 °C, 10 h; (c) NaH, toluene–DMF, 80 °C, 24 h; (d) H_2, 20% $Pd(OH)_2$/C, Boc_2O, EtOH, 60 psi, 24 h; (e) $NaBH_4$ (3.0 equiv), $CaCl_2$ (3.0 equiv), MeOH, 0 → 10 °C, 5 h.



Scheme 2. Preparation of bicyclic piperazines **2d** and **2e**. Reagents and conditions: (a) Ts_2O (2.2 equiv), pyridine, 0 °C → rt, 24 h; (b) 2-nitrobenzenesulfonamide (2.0 equiv), DBU (3.0 equiv), CH_3CN, reflux, 6 h; (c) $C_{12}H_{25}SH$ (2.0 equiv), $LiOH{\cdot}H_2O$ (2.0 equiv), DMF, rt, 2 h; (d) $TsOH{\cdot}H_2O$ (2.0 equiv), EtOH, reflux, 1 h.

are commercially available. Pinna et al. recently described the preparation of bicyclic piperazines **2c** and **2d**, which are N^3- and N^6-monoprotected analogs of bicyclic piperazine **2a**.[10] While Pinna et al. reported good yields for the preparation of piperazines **2c** and **2d**,[10] the synthetic route is somewhat lengthy, requiring eight-steps to prepare N^3-substituted piperazine **2c** and 10-steps to prepare N^6-substituted piperazine **2d** from commercial material. In connection with our on-going efforts to prepare isosteres of saturated heterocycles as useful building blocks for medicinal chemistry,[11] we became interested in developing a more concise synthesis of N^3- and N^6-monoprotected analogs of bicyclic piperazine **2a**. We detail below a seven-step synthesis of N^3- and N^6-monoprotected bicyclic piperazines **2e** and **2d** in which either compound is derived from a common intermediate (**2f**, Fig. 2).

Results and discussion

Our synthesis of N^3- and N^6-monoprotected bicyclic piperazines **2e** and **2d** commenced from the known azetidinediol **6** (Scheme 1),[11b] which was originally prepared by Evans et al.[12] In our hands, azetidine **6** was synthesized in 2-steps from *cis*-azetidine diester **7** using a modified protocol from what Evans originally reported.[11b] Employing conditions originally disclosed by Kozikowski et al. on a related substrate,[13] a separable 1:1 mixture of *cis*/*trans*-azetidine diesters **7** and **8** was synthesized in 75% yield from dibromide **9**. The overall yield of the *cis*-isomer (**7**) could be increased from 37% to 58% by equilibrating the undesired *trans*-isomer (**8**).[11b] Dibromide **9** was conveniently prepared in 95% yield from commercial glutaryl chloride (**10**) using Guanti and Riva's procedure.[14]

With the availability of azetidinediol **6**, efforts were directed at piperazine ring formation. Toward this end, exposure of diol **6** to *p*-toluenesulfonic anhydride gave rise (86%) to bis(tosylate) **11** (Scheme 2). In a prior study, we described a method for the formation of a pyrrolidine ring via a single pot, double *N*-alkylation of nitrobenzenesulfonamide.[15] We were pleased to find that methodology could be extended to the present substrate. Thus, treatment of bis(tosylate) **11** with 2-nitrobenzenesulfonamide in the presence of DBU afforded a 76% yield of bicyclic piperazine **2f**. With orthogonally protected bicyclic piperazine **2f** in hand, treatment of **2f** with lithium hydroxide and dodecanethiol,[16] a low cost and near-odorless mercaptan, afforded an 81% yield of N^6-monoprotected piperazine **2d**. Fortunately, no by-product resulting from thiolate addition to the carbon bearing the nitro group could be detected. This result is consistent with observations made by Wuts et al. who noted that the *o*-nosyl group is less likely to produce the nitro group-displacement by-product than the *p*-nosyl group.[17] The spectral properties of our **2d** were identical to those reported in the literature.[10] Alternatively, subjection of **2f** to *p*-toluenesulfonic acid led to an 89% yield of N^3-monoprotected piperazine **2e**. The spectral properties of **2e** were in complete agreement with the desired structure.

In summary, we have developed a concise synthesis of N^3- and N^6-monoprotected 3,6-diazabicyclo[3.1.1]heptanes **2e** and **2d**. The seven step synthesis features straightforward chemistry starting from inexpensive glutaryl chloride. The overall yields of **2d** and **2e** were 14% and 15%, respectively.[18] Given the similarities in structure and predicted lipophilicity between bicyclic piperazine **2a** and piperazine, it is anticipated that monoprotected bicyclic piperazines **2d** and **2e** will become useful building blocks in medicinal chemistry research.

Acknowledgment

We thank Greg Cavey of the Southwest Michigan Innovation Center Core Lab for accurate mass measurement, which is supported, in part, by the Michigan Economic Development Corporation (MEDC).

Supplementary data

Supplementary data (experimental procedures and characterization data for all new compounds (**11**, **2d**–**f**) and copies of NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.156.

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18. By subjecting the undesired *trans*-isomer **8** to one iteration of *cis*/*trans* equilibration (see: Ref. 11b), the overall yields of **2d** and **2e** increased to 20% and 22%, respectively.