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Synthesis of novel piperazine based building blocks: 3,7,9-triazabicyclo[3.3.1]nonane, 3,6,8-triazabicyclo[3.2.2]-nonane, 3-oxa-7,9-diazabicyclo[3.3.1]nonane and 3-oxa-6,8-diazabicyclo[3.2.2]nonane

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Abstract—The preparation of four novel bridged piperazine building blocks is described: 3,7,9-triazabicyclo[3.3.1]nonane **1**, 3-oxa-7,9-diazabicyclo[3.3.1]nonane **2**, 3,6,8-triazabicyclo[3.2.2]nonane **3** and 3-oxa-6,8-diazabicyclo[3.2.2]nonane **4**. The scaffold of **1** was synthesized from *N*,*N*′-dibromobenzenesulfonamide and ethyl acrylate. Compound **2** may be prepared from identical starting materials or alternatively from α,α′-diglycerol. Compounds **3** and **4** were identified as side products from possible aziridinium intermediates.
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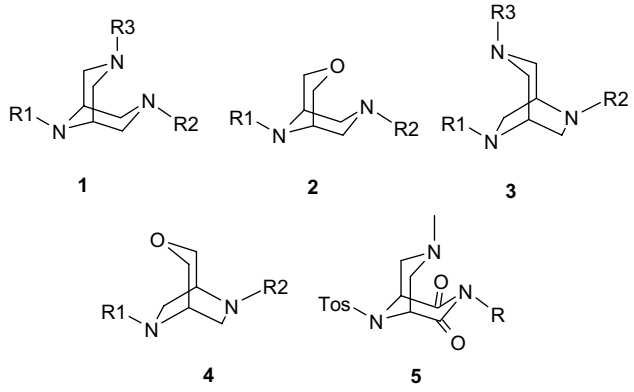
Piperazine and its derivatives are popular building blocks and have been successfully applied for drug design and synthesis in the past. Among the 1729 marketed drugs, 71[1] contain a piperazine fragment. Some of the newest blockbusters are piperazine derivatives, for example, Viagra®,[2] Ciprofloxacine®[3] or Glivec®.[4] The choice of readily available piperazine derivatives is however rather limited and therefore offers a wide field for chemical and commercial activities, considering, for example, scaffold hopping strategies with novel piperazines as building blocks resulting in novel chemical entities with pharmacologically useful properties. Here, we report on the synthesis of hitherto unknown bridged piperazines **1**–**4**, which may find use in target-oriented or diversity-oriented synthesis.[5]



3,8-Diazabicyclo[3.2.1]octane[6–8] and 3,9-diazabicyclo-[3.3.1]nonane[9–11] systems have been prepared before as building blocks for medicinal chemistry. In contrast, the seemingly simple structures of 3-oxa-7,9-diazabicyclo[3.3.1]nonane **2**, 3,6,8-triazabicyclo[3.2.2]nonane **3** and 3-oxa-6,8-diazabicyclo[3.2.2]nonane **4** represent unknown frameworks. Piperazine analogue **5**[12]—a potential precursor of 3,7,9-triazabicyclo[3.3.1]nonane **1**—has been described previously; but the author failed to convert **5** into **1**. In view of the expected difficulties to reduce the imide functionality of **5**, our synthesis of **1** followed a different synthetic route and started with the light-induced addition of *N*,*N*-dibromobenzenesulfonamide **6** to ethyl acrylate, generating the desired *meso*-addition product **7**[13] and its racemic isomer in ~60% total yield (Scheme 1).

The crystalline *meso*-dibromide **7** was obtained in ~25% yield and was easily separated from its oily racemic

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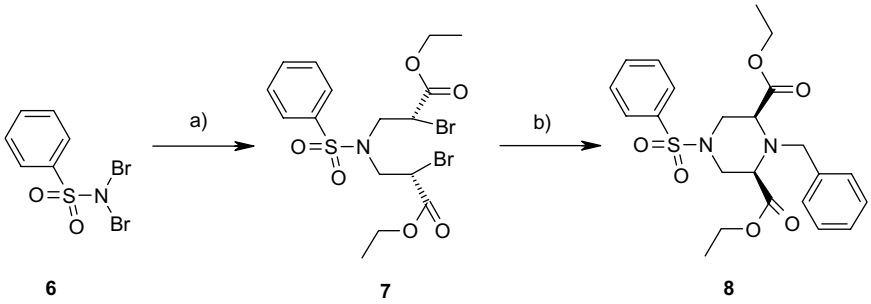
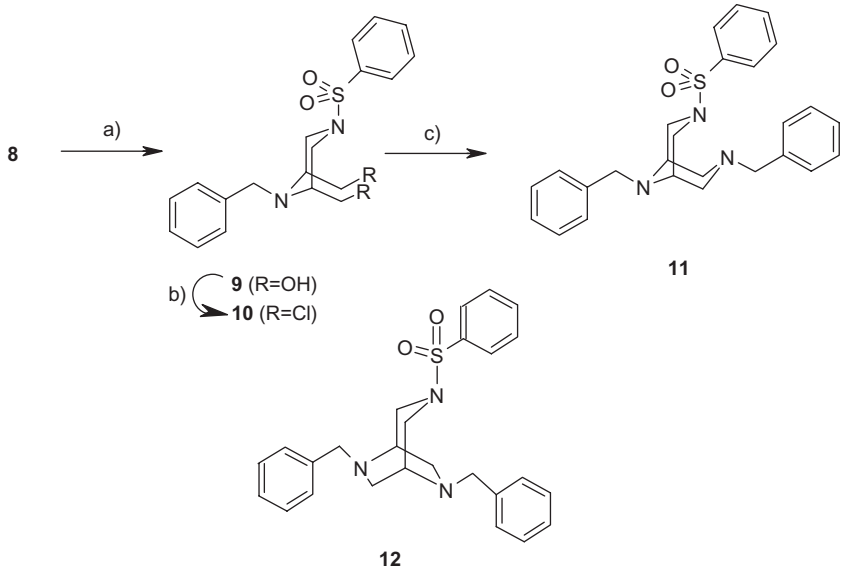


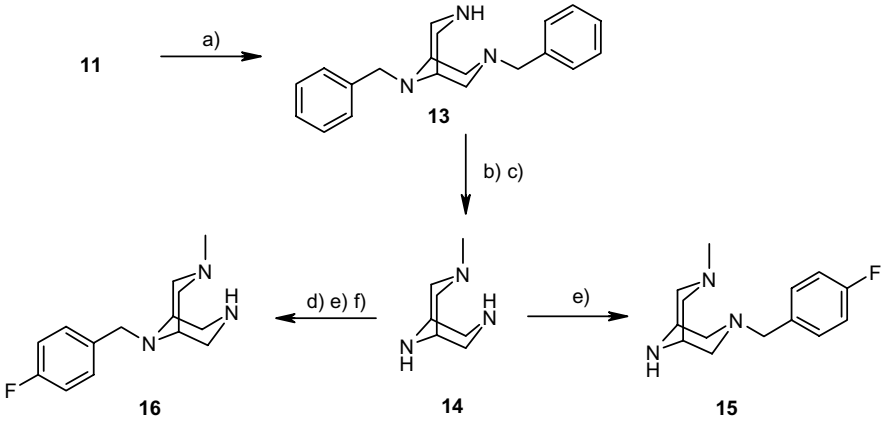
Scheme 1. Reagents and conditions: (a) ethyl acrylate (5 equiv), CH_2Cl_2, light, reflux, 4 h, 25%; (b) benzylamine (3 equiv), toluene, 85 °C, 2 h, 60%.

isomer by filtering the crude reaction mixture through a bed of silica gel, followed by slow crystallization from toluene/hexanes. When treated with benzylamine, only *meso*-**7** yielded the desired piperazine **8** (60%); the racemic isomer of **7** resulted in decomposition. Selective reduction of the diester **8** by $LiAlH_4$ generated *cis*-diol **9** in 80% yield (Scheme 2).

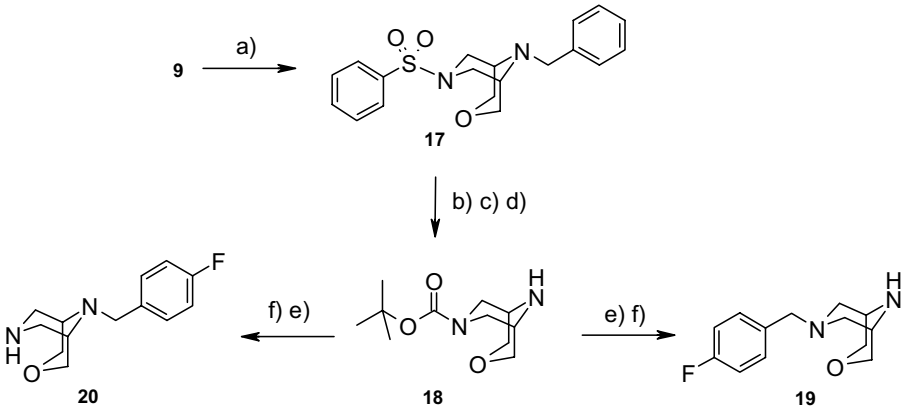
cis-Dichloride **10** was obtained in 77% yield by treating **9** with 5 equiv of thionylchloride in DMF at 0 °C to



Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF, reflux, 4 h, 80%; (b) $SOCl_2$ (5 equiv), DMF, 0 °C to rt, basic workup, 77%; (c) xylene, benzylamine (4 equiv), reflux, 12 h, 75%.



Scheme 3. Reagents and conditions: (a) Red-Al®, xylene, reflux, 1.5 h, 78%; (b) $NaBH_4$, CH_2O/H_2O, MeOH, 15 min, 45 °C, 98%; (c) Pd–C, H_2, EtOH, 76%; (d) THF, Boc_2O, room temperature, 2 h, 72%; (e) 1 equiv of 4-fluorobenzyl chloride, $NaHCO_3$, EtOH, reflux, 1.5 h, 49% for **15**; 74% for **16**; (f) EtOH, HCl concd, room temperature, 5 min, basic workup, 98%.



Scheme 4. Reagents and conditions: (a) $SOCl_2$ (1 equiv), DMF, room temperature, then reflux 75 min, basic workup, 47%; (b) Red-Al®, xylene, 1.5 h reflux, 84%; (c) Boc_2O, TBME, room temperature, 3 h, 90%; (d) EtOH, Pd–C, H_2, 1 h, quant; (e) EtOH, HCl concd, 5 min, room temperature, basic workup, quant; (f) 1 equiv of 4-fluorobenzyl chloride, $NaHCO_3$, EtOH, reflux, 1.5 h, 77% for **19**; 84% for **20**.

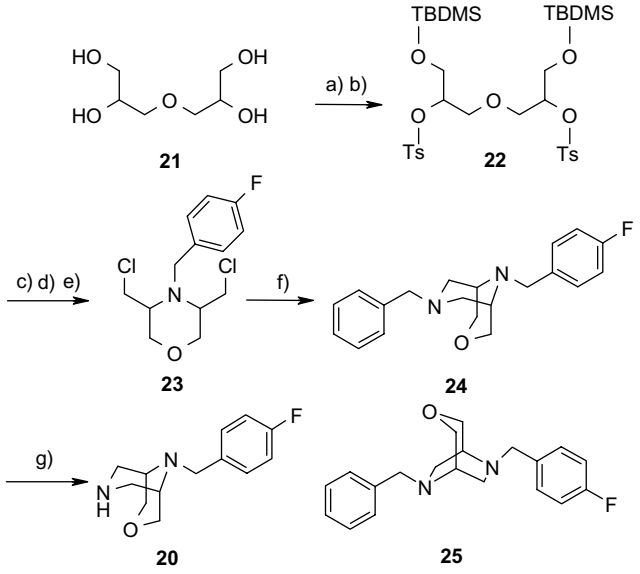
room temperature for 1 h. Refluxing **10** in xylene with 3 equiv of benzylamine resulted in the clean conversion to the triazabicyclo[3.3.1]nonane framework of **11**. When the above reaction was run in benzylamine as solvent at 180 °C for 15 min, **11** was isolated as the major product in 61% yield, accompanied by ~10% of **12**, a representative of the hitherto unknown 3,6,8-triazabicyclo[3.2.2]nonane scaffold. The sulfonamide-protecting group in **11** was removed by reduction with Red-Al®, delivering **13** in 78% yield (Scheme 3).

Reductive methylation of **13** followed by debenzylation delivered **14** in good yield. Compound **14** was selectively 4-fluorobenzylated at the less hindered N-atom to yield **15** (formation of **16** was not observed), or was treated with Boc_2O to deliver an intermediate, which permitted the more hindered N-atom to be 4-fluorobenzylated. Removal of the Boc-protecting group yielded **16**.

The 3-oxa-7,9-diazabicyclo[3.3.1]nonane scaffold **2** was prepared from **9** (Scheme 4).

Compound **9** was treated with 1 equiv of thionylchloride in DMF at room temperature and then refluxed for 75 min to yield **17** in 47% yield. As above, the sulfonamide group was removed by treatment with Red-Al® and replaced by the more convenient Boc-group, followed by hydrogenation to generate intermediate **18**. Removing the Boc-group of **18** and selective benzylation at the less hindered N-atom delivered **19** (formation of **20** was not observed), while the regioisomer **20** was produced by benzylation first, followed by removal of the Boc-group.

Larger amounts of **19** and **20** had to be prepared by a different route due to the instability of dibromide **6**, which tended to release bromine at room temperature and had to be used immediately for the next step. The alternative synthesis of **20** (Scheme 5) started from α,α′-diglycerol **21**, commercially available as a 1:1 mixture of racemate and mesoform. The primary alcohols of **21** were protected with TBDMSCl, while the secondary alcohols were subsequently tosylated to generate intermediate



Scheme 5. Reagents and conditions: (a) TBDMSCl, imidazole, DMF, room temperature, 5 h, 65%; (b) TsCl, NEt_3, DMAP, room temperature, 12–24 h, 70%; (c) *p*-fluorobenzylamine (5 equiv), 1.2 h, 60%; (d) EtOH, HCl concd, 2.5 h, 80 °C, basic workup, 95%; (e) $SOCl_2$ (5 equiv), DMF, 0–40 °C, 45 min, basic workup, 89%; (f) benzylamine (10 equiv) 180 °C, 2 h, 35%; (g) EtOAc/HOAc (150:1), Pd–C, H_2, 1 h, 82%.

22. *p*-Fluorobenzylamine and **22** were heated to 160 °C for 1.2 h to provide the morpholine scaffold.[14] Both primary alcohols of the latter were deprotected and converted to the dichloride **23**, which was obtained as a 1:1 cis/trans mixture. Heating the mixture **23** with benzylamine for 2 h at 180 °C gave rise to **24** in 35% yield accompanied by **25** (5%). **24** was easily isolated from the reaction mixture due to its highly crystalline properties. With the starting material **21** being a 1:1 mixture, the theoretical yield of **24** was limited to 50%. Only *cis*-**23** gave **24** and **25**, while *trans*-**23** decomposed upon heating with benzylamine. **25** is a 3-oxa-6,8-diazabicyclo[3.2.2]-nonane derivative, representing a hitherto unknown compound class. **25** and **12** (Scheme 1) were possibly

both generated from an aziridinium intermediate when heating **10** or *cis*-**23** with benzylamine. Compound **20** was finally obtained by selective debenzylation of **24**. Modification of the synthetic sequence in Scheme 5 by reacting **22** first with benzylamine followed by *p*-fluorobenzylamine resulted in isomer **19**.

In summary, we have developed methods for the preparation of four novel bridged piperazine based building blocks[15]—3,7,9-triazabicyclo[3.3.1]nonane **1**, 3-oxa-7,9-diazabicyclo[3.3.1]nonane **2**, 3,6,8-triazabicyclo[3.2.2]-nonane **3** and 3-oxa-6,8-diazabicyclo[3.2.2]nonane **4**—which may find useful application in target-oriented and diversity-oriented organic synthesis directed to drug discovery.

Acknowledgements

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15. All new compounds gave satisfactory elemental analysis and spectral data. Selected data for compounds **12**, **15**, **16**, **19** and **20** are shown below. Compound **12**: ^{1}H NMR (400 MHz; DMSO-d_6), δ (ppm): 2.71 (d, 2H); 2.98 (dd, 2H); 3.08 (m, 2H); 3.21 (dd, 2H); 3.43 (dd, 2H); 3.72 (dd, 4H); 7.17–7.30 (m, 10H); 7.53 (t, 2H); 7.71 (m, 1H); 7.28 (d, 2H). MS (*m*/*z*) ES+: 448.2 (MH+). Compound **15**: ^{1}H NMR (400 MHz; DMSO-d_6), δ (ppm): 2.17 (s, 3H); 2.25–2.35 (m, 4H); 2.58–2.65 (br d, 4H); 2.91 (br s, 2H); 3.39 (s, 2H); 4.35 (br s, 1H); 7.10 (t, 2H); 7.35 (dd, 2H). MS (*m*/*z*) ES+: 250.1 (MH+). Compound **16**: ^{1}H NMR (400 MHz; DMSO-d_6), δ (ppm): 2.10 (s, 3H); 2.40 (br s, 2H); 2.53 (br d, 3H); 2.69 (br d, 2H); 2.75 (br d, 2H); 3.03 (br d, 2H); 3.83 (s, 2H); 7.10 (t, 2H); 7.36 (dd, 2H). MS (*m*/*z*) ES+: 250 (MH+). Compound **19**: ^{1}H NMR (400 MHz; DMSO-d_6), δ (ppm): 2.33 (br d, 2H); 2.72 (br s, 2H); 2.80 (d, 2H); 3.47 (s, 2H); 3.63–3.74 (m, 4H); 7.13 (t, 2H); 7.38 (dd, 2H). The ROESY spectrum is in agreement with the structure. MS (*m*/*z*) ES+: 237.2 (MH+, 100). Compound **20**: ^{1}H NMR (400 MHz; DMSO-d_6), δ (ppm): 2.27 (s, 2H); 2.84 (d, 2H); 3.16 (br d, 2H); 3.79 (d, 2H); 3.98 (s, 2H); 4.03 (d, 2H); 7.13–7.40 (m, 5H). MS (*m*/*z*) ES+: 219.1 (MH+, 100).