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Synthesis and computational analysis of conformationally restricted [3.2.2]- and [3.2.1]-3-azabicyclic diamines

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ABSTRACT

Conformational restriction is a useful approach for ligand design in organic and medicinal chemistry. This manuscript reports the facile synthesis and *in silico* conformational analysis of two new diastereomeric [3.2.2]-3-azabicyclic, two new [3.2.1]-3-aza-8-oxy-bicyclic and one new [3.2.1]-3-azabicyclic diamine scaffolds. A conformational analysis of these structures along with calculation of carbon–carbon/carbon–nitrogen bond angles was carried out and compared to those in the flexible 1,3-diaminopropane template upon which they were based. It is of particular importance that these scaffolds have bond lengths and angles that can overlap with low energy conformers of the flexible diamine. Such information is useful for ligand design in organic chemistry and for development of structure activity relationships and *in silico* screening in medicinal chemistry.

Introduction

Diamines are widely used in medicinal chemistry for the preparation of G-protein coupled receptor (GPCR) ligands and enzyme inhibitors and in organic chemistry as ligands in a range of chemical reactions.[1] In medicinal chemistry conformational restriction in a scaffold is valuable to probe specific regions of space in a protein in an attempt to optimize affinity.[2] Recent examples include the discovery of a potent, selective M1/M4 [3.2.1] bicyclic agonist **1a** which was superior to an analogous piperidine derivative **1b**[3] and Gosling et al. reported the synthesis and use of (±)-endo-3-azabicyclo[3.2.1]octane-6-amine **2**[4] to study adenosine receptor interactions (Fig. 1).

To extend the diversity of bicyclic diamines available in organic and medicinal chemistry, we now report the racemic synthesis and characterization of the unknown exo isomer (**3**) of **2**, the previously unknown 8-oxa-3-azabicyclo[3.2.1]octane amines **4** and **5** as well as the ring expanded [3.2.2]nonane amines **6** and **7** (Fig. 2). The oxygen-containing analogs represent conformationally restricted morpholine rings. Morpholine has been explored as a catalyst for a number of organic transformations.[5]

Furthermore, we carried out an *in silico* investigation of the conformational stability and rigidity of the scaffolds and their structural resemblance to low energy conformations of 1,3-diaminopropane. Here, we use Density Functional Theory (DFT) to investigate the relative stability of the boat-like conformation vs. the chair-like conformation of **2** and **3**–**7**. Overlaying the optimized structures for these compounds on low-energy conformations of 1,3-diaminopropane unit provides insight in the degree of distortion of the diamine unit in the scaffolds.

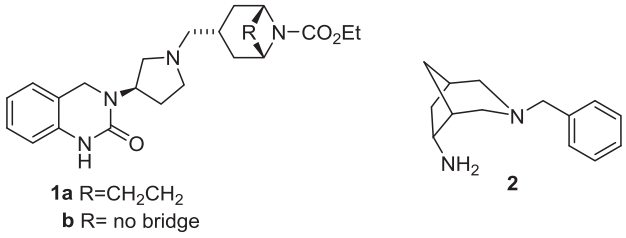

Fig. 1. Representative recent examples of conformationally restricted diamines.

Results and discussion

Our approach to the synthesis of these molecules is similar to that employed by Gosling (Scheme 1). Diels-Alder cycloaddition between ethyl acrylate and cyclopentadiene, furan and 1,3-cyclohexadiene provided known [3.2.1] and [3.2.2]-bicyclic esters as a separable mixture of exo and endo isomers, followed by saponification and stereospecific Curtius rearrangement.[4,6] Endo/exo stereochemistry in each ester intermediate was established by comparison to the NMR spectra of each compound in the literature

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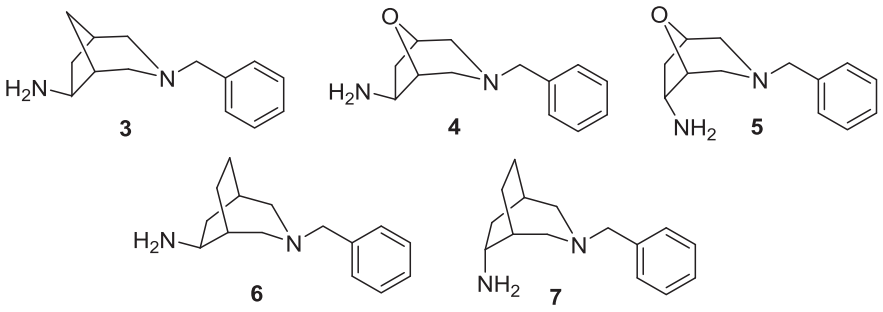
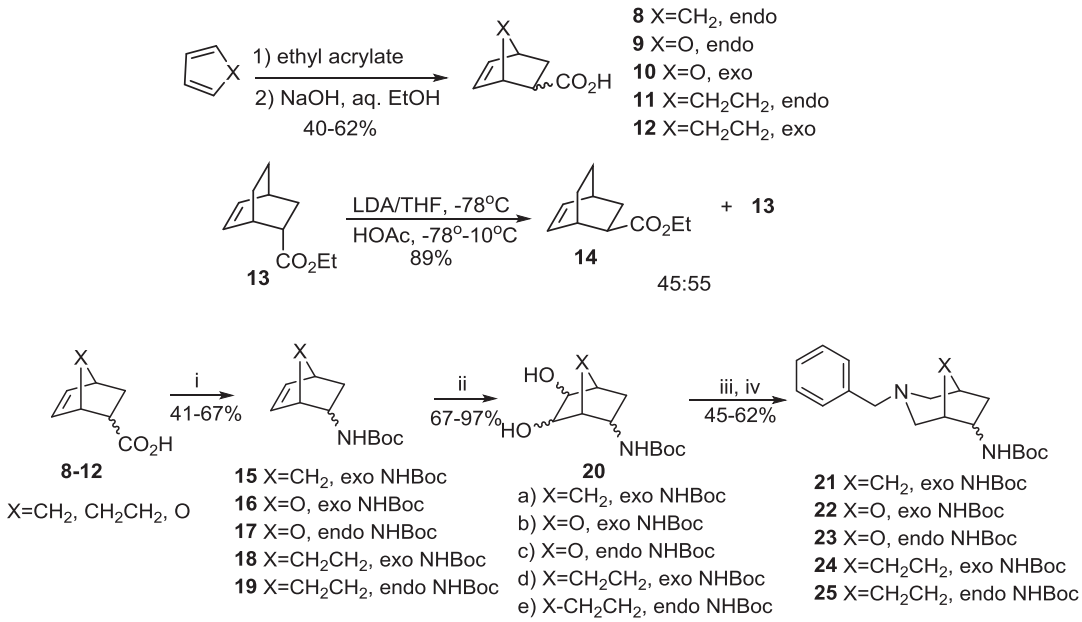


Fig. 2. Bicyclic diamine target molecules.



Scheme 1. Synthesis of [3.2.n]-bicyclodiamines.

and confirmed following base-mediated hydrolysis to known acids **9**–**12**.[6a,b] Acid **8** is commercially available. The Diels-Alder reaction between 1,3-cyclohexadiene and ethyl acrylate leading to bicyclo [2.2.2]-octene esters **13** and **14** proceeded in our hands with 9:1 endo:exo selectivity. To obtain sufficient quantities of the exo isomer **14**, **13** was epimerized (LDA/THF, -78 °C, acetic acid quench at 0 °C) leading to nearly a 1:1 mixture of that was efficiently separated by silica gel chromatography. The resulting Boc-protected bicycloalkenes (**15**–**19**) were efficiently converted to a diastereomeric mixture of diols (**20**a–e) using catalytic OsO_4 and *N*-methylmorpholine-*N*-oxide, followed by oxidative cleavage with sodium periodate to furnish bisaldehydes that were not purified. The crude bisaldehydes underwent reductive amination using benzylamine, catalytic acetic acid and sodium triacetoxyborohydride in dilute 1,2-dichloroethane solution at room temperature overnight leading to the desired Boc-protected bicyclic targets **21**–**25**.

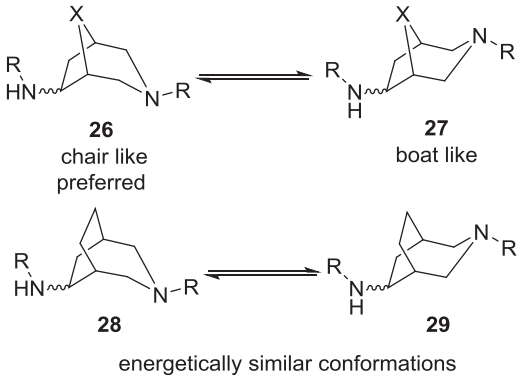


Fig. 3. Conformational mobility of bicyclic diamines.

Computational results

The relative energetics of templates **2–7** were studied to identify stable conformations and the energy barriers associated with transitions between chair-like and boat-like conformations – see Fig. 3. The benzyl group was replaced by hydrogen (R = H in Fig. 3) and results are shown in Table 1. (Structural parameters for all templates and data for oxabicycles **4** and **5** are included in the supplementary information.) Templates with the more flexible two-carbon bridge (**28** and **29**) show no significant difference in relative energy between the conformations shown in Fig. 3 (i.e. **13**–**14** and **15**–**16**).

The more restricted [3.2.1] structures **26** and **27** (with X = CH_2) show a preference for the chair-like conformation (e.g., **26** in Fig. 3) of 5–8 kcal/mol. The barrier heights for forward and reverse conversions range between 3.5 and 9.8 kcal/mol. For all templates, the reverse barrier is higher than the forward barrier, though in case of the [3.2.2] scaffold the difference is insignificant. The position of the primary amine group (exo or endo) does not

Table 1
Relative energies (in kcal/mol) for the 8 studied template derivatives. DFT calculations[8] were at the B3-LYP/def2-TZVP level of theory. The RPA results were obtained using PBE input orbitals with the def2-QZVPP basis set. On all templates, the benzyl substituent was replaced by hydrogen (see Supporting Information for computational details).

Structure	Relative Energy (kcal/mol)	
[3.2.1]	DFT	RPA
2 chair-like	0.2	0.3
2 boat-like	5.5	5.7
3 chair-like	0	0
3 boat-like	7.9	8.5
[3.2.2]		
6 chair-like	1.3	1.3
6 boat-like	1.5	1.5
7 chair-like	0	0
7 boat-like	0.7	0.9

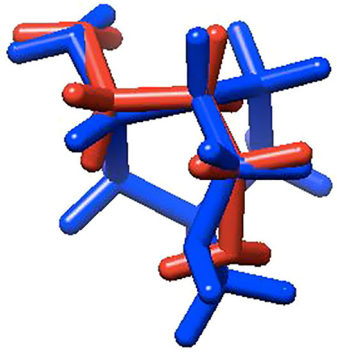


Fig. 4. Stick representations of **3** (blue, without benzyl substituent) and 1,3-diaminopropane (red) overlapped to show extent of deviation.

significantly affect the relative energies of these templates. Results from the random phase approximation (RPA) show no significant difference with the DFT/B3-LYP results indicating that non-covalent interactions do not play a significant role. The free energy barrier heights are very similar to the electronic energies with a maximum difference of about 1 kcal/mol. Inclusion of solvation effects changed the barrier heights by at most 1.3 kcal/mol (for the 9.0 kcal/mol reverse barrier of **2**) with no changes to the order of the relative energies (see Supporting Information for Results). Thus, finite temperature effects and solvation do not change the qualitative results.

The energetics of the templates are affected by addition of substituents to either the primary or secondary nitrogen (R in Fig. 3). Adding phenyl to the secondary, endocyclic nitrogen effectively removes the barrier between chair- and boat-like conformation due to the overlap of the π-system with the lone pair electrons on the nitrogen which stabilizes the transition state. On the other hand, using *t*-butyl as substituent has very little effect. The addition of *t*-butyl carbamate on the primary nitrogen results in only one type of minimum energy structure per template: boat-like for **7**, chair-like for **2**, **3**, **6**. For the more restricted [3.2.1] structures, this is in agreement with the findings in Table 1 where the chair-like structure was preferred. The substituent alters the potential energy surface in such a way that a local minimum for the boat-like conformation can no longer be found.

Finally, the optimized structure for 1,3-diaminopropane was mapped onto the propane diamine unit contained in the templates to investigate to what extent its structure is preserved the bicyclic units (Fig. 4). The energetically most stable structures display a gauche arrangement for the NCCC dihedral angles[7] and resemble the minimum-energy structure of 1,3-diaminopropane to a high degree. Addition of substituents on the primary (*t*-butyl carbamate) and nitrogen (benzyl or *t*-butyl) does not significantly change the structure of the propane diamine unit.

Conclusions

We synthesized and characterized five new racemic bicyclic diamines based on [3.2.1] and [3.2.2] templates using chemistry that is scalable and efficient. These structures are conformationally restricted 1,3-propanediamines that are of interest in organic and medicinal chemistry as building blocks for development of structure-activity relationships in enzyme inhibitors and receptor ligands. Calculations showed that there are two distinct orientations (chair-like and boat-like) of the ring containing the secondary nitrogen with a comparatively low energy barrier (<9 kcal/mol) between these conformations. Chair-like conformations are more stable for the [3.2.1] templates, whereas interestingly in the [3.2.2] templates the two orientations are very similar in energy. When adding *t*-butyl carbamate to the primary amine only the chair-like minimum is found for the [3.2.1] templates. Either the boat-like or chair-like orientation is found for the [3.2.2] templates. The effect of a substituent on the secondary amine depends on its electronic structure: phenyl removes the barrier between chair- and boat-like orientation, whereas *t*-butyl has no significant effect.

Both the [3.2.1] and [3.2.2] templates can be overlaid on low energy conformations of 1,3-diaminopropane with similar bond lengths and bond angles. This observation is an important one, highlighting the value of these scaffolds to mimic low energy conformations of the flexible diamine. In view of the wide use of conformationally restricted diamines in medicinal chemistry and the use of virtual screening as a starting point for hit identification, these results offer medicinal chemists new scaffolds for exploration. Given the comparative ease of synthesis, the ability to adapt this to obtain optically active versions with high enantiospecificity, their relative structural rigidity and similarity to low energy conformations of the flexible parent diamine, these scaffolds can be more readily explored in both organic and medicinal chemistry. Investigations toward these objectives are underway and will be reported in due course.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.09.033.

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