ORGANIC LETTERS

2012
Vol. 14, No. 4
988–991

Four-Component Assembly of Chiral N–B Heterocycles with a Natural Product-Like Framework

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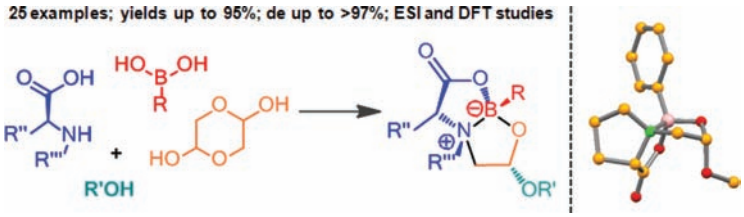
Received December 7, 2011

ABSTRACT



The dative N–B bond was used to simply assemble heterocycles with a skeleton akin to the 5-oxofuro[2,3-*b*]furan motif. Twenty-five new N–B heterocycles were prepared *via* a highly efficient one-pot four-component reaction in yields and diastereoselectivities up to 95% and >97%, respectively. Several reaction intermediates were discovered using electrospray ionization mass spectroscopy which set the basis for the mechanism elucidation using DFT calculations.

Modern medicinal chemistry continuously faces the problem of finding new lead compounds that deliver potency, specificity, and low toxicity. Therefore the quest for new therapeutically useful scaffolds is in the limelight of medicinal chemistry.[1] Natural products offer an invaluable source of structures with exciting biological properties.[2] Nevertheless, natural product chemical modification, with the objective of improving their biological profile, is a very demanding process which often requires the discovery of new and complex synthetic routes. Consequently, the synthesis of new compounds with natural product-like structures becomes an important approach for hit and lead identification, in early phase drug discovery.[3] A promising strategy to create such compounds is the use of a boron atom as an internal tether. Recently, this concept was elegantly used by Manheri et al. in the synthesis of a boron-containing tetracyclic framework in 45% yield, starting from the dipeptide BocAlaAlaOMe.[4] A scarcely explored alternative to create such architectures is the design of molecules based on the replacement of key C–C bonds of the natural product structure by isoelectronic N–B bonds

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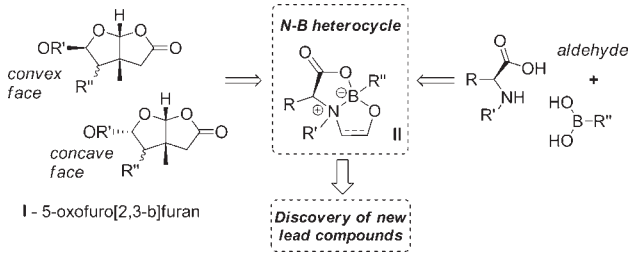
10.1021/ol203224n
Published on Web 02/08/2012

in the analogue.[5,6] In this manuscript we demonstrate the use of such an approach to prepare new scaffolds inspired by the 5-oxofuro[2,3-*b*]furan unit (**I**), a structural motif that is present in the framework of a relatively unexplored subgroup of spongiane diterpenoids such as the cheloviolene, macfarlandin C, or norrisolide (Scheme 1).[7]

Scheme 1. Natural Products with 5-Oxofuro[2,3-*b*]furan Motifs; One-Pot Assembly of N−B Heterocycles with a Natural Product-Like Structure

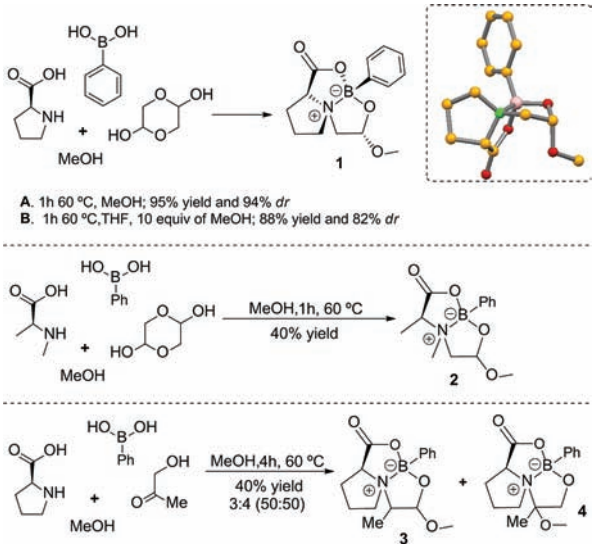


Aiming at the preparation of compounds with the structure depicted in Scheme 1 as **II**, we initiated our study by reacting different amino acids with phenyl boronic acid and glycolaldehyde dimer in MeOH. Very gratifyingly, L-proline after 1 h of reaction at 60 °C afforded the heterocyclic **1** in 95% yield and 94% diastereoselectivity while the *N*-methyl-L-alanine afforded product **2** in 40% isolated yield but as a complex mixture of diastereoisomers (Scheme 2). Using 1-hydroxyacetone instead of glycolaldehyde dimer the heterocycles **3** and **4** were obtained as a 1:1 mixture and as sole diastereoisomers. Surprisingly, instead of a three-component assembly, the tricyclic heterocycle **1** was obtained *via* a one-pot four-component condensation in which methanol entered at the concave face of the lactone−acetal byciclic system, as confirmed by the crystallographic analysis of **1** (Scheme 2). The unanticipated inclusion of MeOH increased the final product structural similarity with the 5-oxofuro[2,3-*b*]furan unit and occurred when using MeOH either as the solvent or as a reagent in THF, though, in this case, in lower yield and diastereoselectivity (Scheme 2).

Once the most efficient conditions to prepare these heterocycles were established, we evaluated the possibility of extending the protocol to different alcohols.

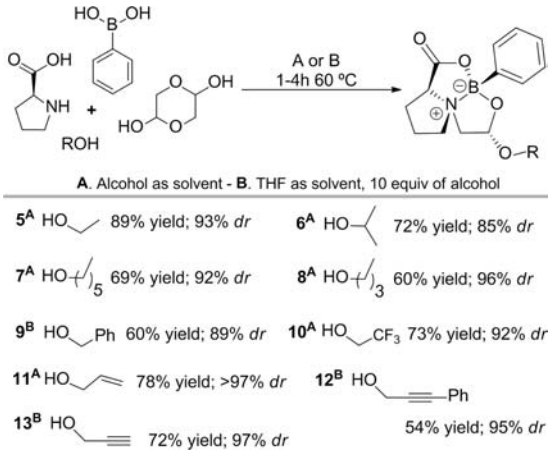
Using the same reaction conditions, several alcohols generated the tricyclic heterocyclic structures, though the reaction was quite sensitive to the alcohol steric effect (Scheme 3). A clear example of this was the fact that when

Scheme 2. Evaluation of the Four-Component Condensation[a]



[a] The configuration determined for **1** is as follows: $C_{proline}$ (*S*); C_{acetal} (*R*); B (***R***); N (*S*).

Scheme 3. One-Pot Four Component Condensation between L-Proline (2 equiv), Phenyl Boronic Acid (1 equiv), Glycolaldehyde Dimer (1.5 equiv), and Different Alcohols[a]



[a] Only the major diastereoisomers are represented.

using EtOH as solvent, compound **5** was obtained in 89%, while with the bulkier *i*PrOH the heterocycle **6** was isolated in 72% yield and with *t*BuOH no reaction was observed. Despite this, hexanol, butanol, trifluoroethanol, and benzyl alcohols all afforded the expected heterocycles in yields ranging from 60% to 78% and diastereoselectivities in between 89% and >97%. In addition, unsaturated alcohols such as allyl, phenyl propargyl, and propargyl alcohols all yielded the expected products in good yields and excellent diastereoselectivities (Scheme 3, **11**−**13**).

After the reaction tolerance toward a diverse set of alcohols was confirmed, the assembly reaction was evaluated

(6) Selected examples: (a) Bosdet, M. J. D.; Piers, W. E. *Can. J. Chem.* **2008**, *86*, 8. (b) Liu, Z.; Marder, T. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 242. (c) Liu, L.; Marwitz, A. J. V.; Matthews, B. W.; Liu, S.-Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 6817. (d) Abbey, E. R.; Zakharov, L. N.; Liu, S. Y. *J. Am. Chem. Soc.* **2011**, *133*, 11508.

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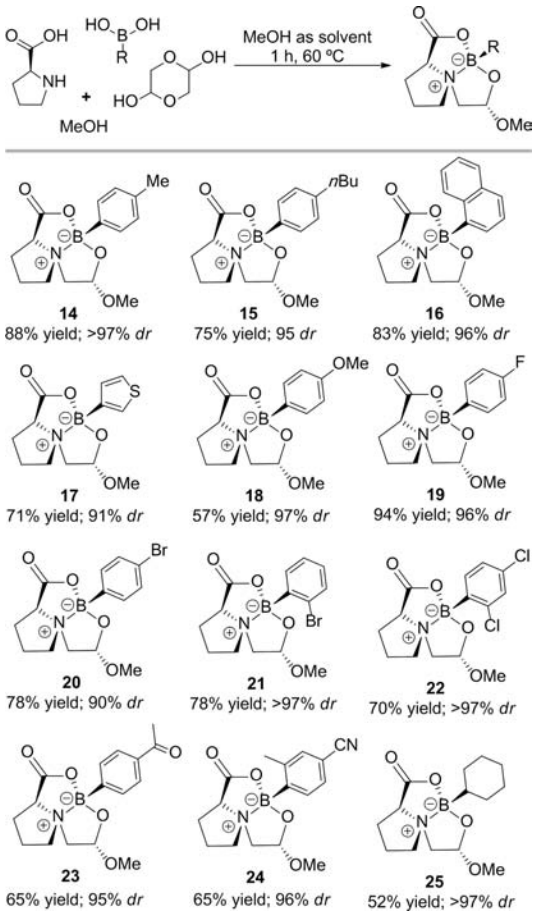
Scheme 4. One-Pot Four Component Condensation between L-Proline (2 equiv), Glycolaldehyde Dimer (1.5 equiv), and Different Boronic Acids (1 equiv)[a]



[a] Only the major diastereoisomers are represented.

using different boronic acids. As shown in Scheme 4, the reaction afforded compounds **14**–**25** in good to excellent yields using aryl, heteroaryl, and alkyl boronic acids and diastereoselectivities ranging from 90% to >97%. Regarding the substitution profile on the aromatic ring, alkyl substituents afforded the desired products **14** and **15** in 88% and 75% yield and >97% and 95% *dr* respectively, while the 2-naphthyl boronic acid yielded the heterocycle **16** in 83% yield and 96% *dr*. The reaction was slightly more sensitive toward the electronic profile of the aryl substituent. The substitution of the electron-donating *para*-methoxide in compound **18** by the electron-withdrawing *para*-fluoride in compound **19** increased the yield from 57% to 94% maintaining the high levels of diastereoselectivity. Finally, the *ortho*-substitution versus the *para*-substitution had an almost negligible effect in the reaction efficiency as the same isolated yield was obtained when using the *para*- and the *ortho*-bromo aryl boronic acids (Scheme 4, **20**, **21**, and **22**). Very gratifyingly, despite the possible reaction with proline, the method was tolerant to the presence of the ketone functionality as the 4-acetylphenylboronic acid afforded product **23** in 65% yield and 95% *dr*. Finally, the 4-cyano-2-methylphenylboronic acid and the cyclohexyl boronic acid afforded heterocycles **24** and **25** in 65% yield, 96% *dr* and 52% yield, >97% *dr* respectively (Scheme 4).

Intrigued by the excellent level of diastereoselectivity observed in this four-component assembly, we studied the reaction mechanism using electrospray ionization mass spectroscopy (ESI-MS). Therefore, we performed the reaction between L-proline (2 equiv), phenyl boronic acid (1 equiv), glycolaldehyde dimer (1.5 equiv), and MeOH (10 equiv) in 2 mL of THF at 60 °C. Aliquots of the reaction mixture, corresponding to the moment immediatly after the addition of all reactants and after 10 min at 60 °C, were collected and analyzed by ESI-MS. Very interestingly, the spectra obtained after the addition of all reactants show an increased concentration of intermediates **A** and **B** formed between the proline and the phenyl boronic acid (Figure 1), while analysis of the spectra obtained after 10 min at 60 °C revealed the formation of a new tricyclic intermediate **C** which then disapears to afford product **1**. Based on these results, the reaction mechanism was studied by means of DFT calculations,[8] and the resulting highlights are shown in Figure 1. The complete energy profile is presented as Supporting Information.

The calculated mechanism starts with a complex of proline and boronic acid (**B**), and with its solvent adduct (**A**), both detected by ESI-MS data (Figure 1) in the initial aliquot. Addition of glycolaldehyde to **B** results in intermediate **C**. This step is assisted by OH coordination to the B-atom, first, and then by proton transfer from the alcohol to the O-atom in C=O activating the carbonyl group to the nucleophilic atom from the nitrogen.

Protonation of **C** leads to **D** with the corresponding activation of the B–O bond. Then, the exchange between the two B–O bonds, from **D** to **E**, allows the activation of the C–O bond involving the C-atom α to the nitrogen and gives rise to the breaking of that bond and to the formation of the iminium ion that occurs in the following step, from **E** to **F**.

Next, from **F** to **G**, there is abstraction of one proton by the OH group coordinated to boron, with the corresponding breaking of one C–H bond in the side chain. In **G**, there is regeneration of a neutral N-atom and formation of an enol (NCH=CHOH) that finaly coordinates the boron through its O-atom (in **G**).

From **G** to **H**, there is a nucleophilic attack from the N-atom to boron with the consequent loss of one water molecule. The coordinated enol (**H**) tautomerizes to the corresponding aldehyde, from **H** to **I**. The carbonyl group in **I** is activated by coordination to the B-atom and, thus, suffers nucleophilic attack from the solvent (methanol) yielding the final product of the reaction, **J**.

It should be noticed that solvent plays an active and important role in the entire reaction path, through its assistance in all proton transfer steps, as expected for a protic

(8) (a) Parr, R. G.; Yang, W. In *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989. (b) The DFT calculations were perfomed with the PBE1PBE functional using the Gaussian 03 package. A complete account of the computational details and the corresponding list of references are provided as Supporting Information.

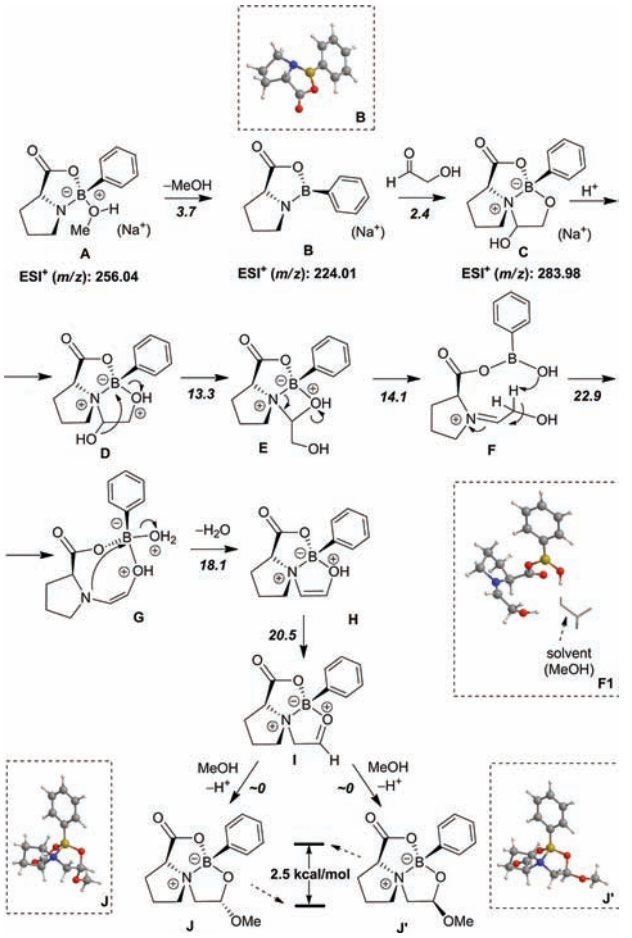


Figure 1. Schematic representation of reaction mechanism, obtained by DFT calculations. Selected optimized structures are shown, and the numbers in italics represent the maximum energy barrier (kcal mol^{-1}) calculated for each section of the mechanism.

solvent. Thus, in the calculated mechanism there was explicit consideration of one methanol that establishes an H-bond network with the various intermediates. In addition, in the section of the mechanism corresponding to enol formation from the iminium ion (**F** to **G**), a second methanol molecule was used in the calculations. The second solvent molecule coordinates the boron, allowing a tetrahedral environment around that atom that would otherwise remain trivalent as in **F**. The coordination of methanol enhances the electronic density in the B-atom and increases the basicity of the OH group that abstracts the proton from the C–H bond giving rise to the enol in **G**. In fact, the barrier calculated for this step without the $B-O_{MeOH}$ coordination is 6.6 kcal mol^{-1} higher than the one obtained considering methanol coordination. This indicates an active participation of the solvent along the reaction mechanism, and, in particular, in the enol formation step, the one with the highest calculated barrier: 22.9 kcal mol^{-1}.

Another interesting aspect of the reaction is the high diastereoselectivity found experimentally, especially taking into consideration the existence of four asymmetric centers in the product: the carbon from the proline, the N- and the B-atoms, and the acetal C-atom. On the other hand, the configuration observed for the N- and the B-atoms can be understood by the geometry of the intermediate **B** (Figure 1). In fact, the conformation of the amine five-membered ring, dictated by the configuration of the asymmetric C-atom and by the pyramidal geometry around the nitrogen, leaves only one side of the molecule available for the reaction with glycolaldehyde and determines the final configuration of both nitrogen and boron. Finally, the configuration on the acetal C-atom results from the relative stability of the two epimers. The last step is under thermodynamic control with negligible barriers calculated for the addition of methanol.

In summary we developed a new one-pot four-component assembly of N–B heterocycles with a natural product-like framework. The reaction displayed a broad scope regarding the alcohol and boronic acid components. The N–B heterocycles were obtained in yields up to 95% and excellent diastereoselectivities (up to >97%). All of these results indicate that the dative N–B bond may be exploited to simply assemble small libraries of compounds with discrete molecular surfaces similar to those found in natural product frameworks.

Acknowledgment. Fundação para a Ciência e Tecnologia (PTDC/QUI-QUI/118315/2010; PTDC/QUI-QUI/099389/2008; FRH/BPD/46589/2008;/48219/2008; Pest-OE/SAU/UI4013/2011; PEst-OE/QUI/UI0100/2011) are acknowledged for financial support.

Supporting Information Available. Experimental procedures, DFT and crystallographic details, full DFT reference list, atomic coordinates for the optimized species, spectral data for all compounds, and biological assays. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.