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[3,3]-Sigmatropic Rearrangement of Boronated Allylcyanates: A New Route to α-Aminoboronate Derivatives and Trisubstituted Tetrahydrofurans

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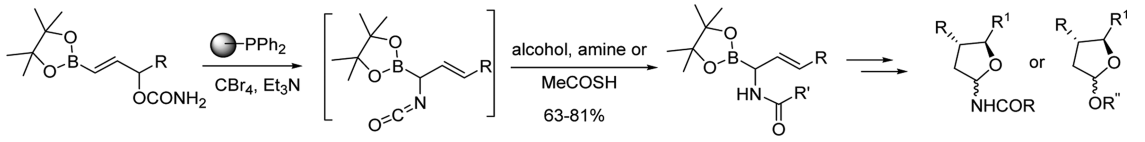
ABSTRACT



[3,3]-Sigmatropic cyanate−isocyanate rearrangement provides a powerful tool for the preparation of α-isocyanato allylboronic esters, which can be further trapped with a variety of nucleophiles. Hydrogenation gave the corresponding α-aminoboronates derivatives while addition of aldehydes afforded homoallylic alcohols, (tetrahydrofuran-2-yl)carbamate, ether, or urea derivatives.

Boronic acids have attracted considerable interest as versatile intermediates in organic synthesis.[1] Besides these numerous and important synthetic applications, this class of compounds has long been underevaluated in chemical biology and drug discovery programs. This situation has changed at the beginning of the 21th century. In May 2003, bortezomib (Velcade) was the first boron compound to be approved as a selective and reversible inhibitor of the 26S proteasome for advanced multiple myeloma treatment.[2] Another borodipeptide, Val-boroPro (Talabostat), has antitumor activity against colorectal cancer via the inhibition of postproline cleaving enzymes, a ubiquitous class of serine proteases (Figure 1).[3]

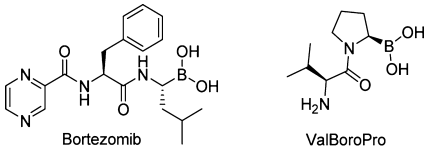


Figure 1. Some examples of bioactive boropeptides.

If α-aminoboronic acids and derivatives are widely represented within bioactive boron compounds, other boron derivatives have also shown interesting biological properties.[4]

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[‡] BoroChem SAS.

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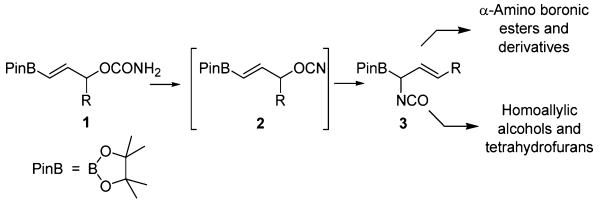
Only a few methods have been reported for the synthesis of α-aminoboronic esters. The most common approach is certainly the one developed by Matteson et al. α-Halogenoboronates are readily prepared by diastereoselective insertion of a CHCl group into a carbon−boron bond.[5] An S_N2 displacement of the halogen α to the boron atom with amines and derivatives as nucleophiles led to α-aminoboronic esters with high diastereomeric excesses. Borylation of organolithium or organomagnesium reagents with trialkyl borates has also found useful applications, especially in the highly enantioselective synthesis of boroproline.[6] Another elegant diastereoselective method was based on the addition of bis(pinacolato)diboron to *N*-*tert*-butanesulfinyl aldimines in the presence of a copper catalyst,[7] while enantioselective organocatalytic pinacolboryl addition to tosylaldimines was reported a few years later.[8] Other approaches of lower applicability include electrophilic amination,[9] Overman [3,3]-sigmatropic rearrangements,[10] and iridium-catalyzed amination of potassium allyltrifluoroborates.[11] Finally, more recently, the Yudin group disclosed a new attractive and efficient access to a wide range of α-amino *N*-methyliminodiacetyl (MIDA) boronates *via* the Curtius rearrangement of the corresponding carboxylic acids.[12]

In parallel, we sought to develop a new approach, which combines a versatile access to α-aminoboronic esters from the corresponding allylisocyanates and the rich chemistry of allylboronates[13] (Scheme 1).

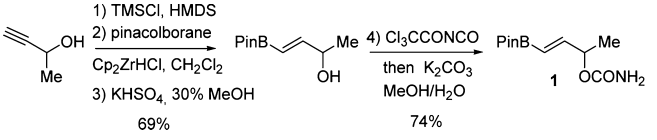
The rearrangement of allylcyanates, prepared from 5-(2-alkenyloxy)-1,2,3,4-thiatriazoles, to allylisocyanates was discovered by Holm in 1970.[14] Eight years later, Overman proposed another route based on the reaction of allylic alkoxides with cyanogen chloride.[15] But it was only with the work of Ichikawa in 1991, who prepared allylcyanates by dehydration of the corresponding allylcarbamates, that this method proved to be a powerful tool in organic synthesis.[16] The [3,3]-sigmatropic rearrangement occurred at room temperature, and the use of various nucleophiles to trap the resulting isocyanate gave access to a large variety of derivatives.[17] Spino et al. also successfully used this approach for the stereocontrolled synthesis of amino acids and *N*-heterocycles bearing a quaternary chiral carbon.[18]

Scheme 1. [3,3]-Sigmatropic Rearrangement of Boronated Allyl Cyanates **2** and Further Transformations



On the basis of these results, we planned to study the [3,3]-sigmatropic rearrangement of the allylcyanate **2** generated from the carbamate **1** (R = Me), chosen as a model compound, and the reactivity of the resulting allylisocyanate **3** (Scheme 1). Compound **1** was efficiently synthesized in a stereochemically pure (*E*)-form from 3-butyn-2-ol (Scheme 2). Protection as its trimethylsilyl ether was followed by hydroboration with pinacolborane to afford the corresponding alkenylboronate.[19] Finally, after deprotection with $KHSO_4$ in $MeOH/H_2O$, the boronated allylic alcohol was converted to the allylcarbamate **1** according to the procedure described by Ichikawa et al.[20] (51% overall yield, four steps).

Scheme 2. Synthesis of Allylcarbamate **1**



Several conditions were screened to optimize the formation of the isocyanate **3** from **1**: triflic anhydride, diisopropylethylamine;[16] pivaloyl chloride, pyridine;[21] trifluoroacetic anhydride, triethylamine;[18] oxalyl chloride, 2,6-lutidine.[22] Best results were obtained with carbon tetrabromide,

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(15) Overman, L. E.; Kakimoto, M. *J. Org. Chem.* **1978**, *43*, 4564.

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(17) (a) Ichikawa, Y.; Yamazaki, M.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2429. (b) Ichikawa, Y.; Kobayashi, C.; Isobe, M. *Synlett* **1994**, 919. (c) Ichikawa, Y.; Osada, M.; Ohtani, I. I.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1449. (d) Ichikawa, Y.; Yamauchi, E.; Isobe, M. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 939. (e) Ichikawa, Y. *Synlett* **2007**, 2927.

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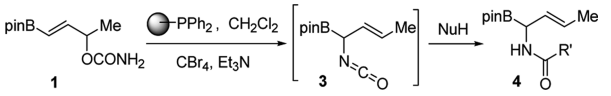
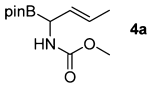
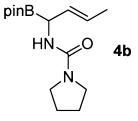
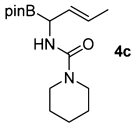
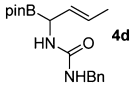
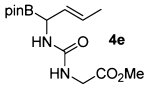
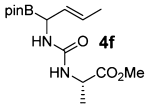
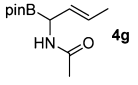
triphenylphosphine, and triethylamine in methylene chloride.[17] The use of a polymer-supported phosphine to simplify the purification step was finally selected despite a longer reaction time. Although the expected isocyanate **3** was observed in the crude ^{1}H NMR spectrum, we were unable to isolate it with satisfactory yield and purity and therefore chose to add methanol to the crude mixture. The allylboronate **4a** was then obtained in 81% yield. A single *E*-isomer (^{1}H NMR, $J_{HC=CH}$ = 15.4 Hz) was detected in agreement with a chair transition state with the boronate and methyl groups in pseudoequatorial positions, as previously reported.[17e]

Table 1. Preparation of *a*-Boryl Allyl Ureas, Carbamates, and Amides **4a**–**g**



entry	NuH	product	δ ^{11}B (ppm)	yield(%)[a]
1	Methanol	 **4a**	22.5	81
2	Pyrrolidine	 **4b**	12.7	80
3	Piperidine	 **4c**	12.4	76
4	Benzylamine	 **4d**	12.4 and 22.4	78
5	Glycine methyl ester HCl[c]	 **4e**	12.3 and 22.5	70
6	L-alanine methyl ester HCl[c]	 **4f**	12.3 and 22.7	60[b]
7	Thioacetic acid	 **4g**	14.7	63

[a] Isolated yields after column chromatography. [b] Mixture of two diastereomers (50/50). [c] In the presence of a supplementary equivalent of NEt_3

Using these optimized conditions, we then assessed the scope and limitations of this reaction using various other nucleophiles (Table 1). Primary and secondary amines also reacted with **3** to afford the corresponding urea in good yields. When α-aminoester hydrochlorides were used in the presence of a supplementary equivalent of triethylamine, comparable results were obtained, thus opening a valuable route to hitherto unknown boron analogues of urea peptidomimetics. The condensation of **3** with thioacetic acid resulted in the formation of the amide **4g** with loss of a carbon oxysulfide as byproduct.[23] The NMR data are in full agreement with the proposed structures, the ^{11}B chemical shifts varying from 12.3 to 22.7 ppm, which is consistent with intramolecular B–O dative bonds as previously demonstrated in the literature.[24] Furthermore, evidence for the tetrahedral structure of **4b** in the solid state is given by X-ray crystallographic analysis, which revealed that the carbonyl oxygen atom of the urea moiety is close to the boron (B9–O10 distance 1.60 Å) (Figure 2).[25] In addition, the torsional angles between O14–B9–O18–C19 and O18–B9–O14–C15 are, respectively, 2.9° and 20.8°, which shows a distortion of the five-membered 1,3,2-dioxaborolane ring due to the coordination between the oxygen and boron atoms. It is also worth noting that, in the case of compounds **4d**–**f**, a second peak was observed at 22.4–22.7 ppm in ^{11}B NMR, which suggests a possible competitive chelation with the nitrogen atom.

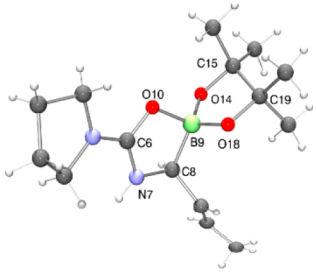


Figure 2. X-ray crystallographic structure of urea **4b**.

The transformation of these α-aminoboronate derivatives into the corresponding boronic acids was evaluated using **4c** as a model substrate (Scheme 3). We were unable to obtain the desired unsaturated product in good yield under various conditions due to a facile deborylation reaction. This failure was attributed to the presence of an allylic moiety that weakens the B–C bond. Indeed, hydrogenation of the double bond gave **5** and treatment with 2-methylpropylboronic acid in a biphasic mixture of methanol/hexane afforded the acid **6**.

Besides the presence of a boronic ester and a carbamate, urea, or amide functional group in the same core, **4a**–**g** present the interesting feature of also having an allylic moiety. Allylboronic esters have been proven to be highly

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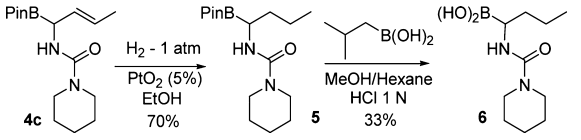
(24) (a) Matteson, D. S.; Michnick, T. J.; Willett, R. D.; Patterson, C. D. *Organometallics* **1989**, *8*, 726. (b) Biedrzycki, M.; Scouten, W. H.; Biedrzycka, Z. *J. Organomet. Chem.* **1992**, *431*, 255. (c) Besong, G.; Jarowicki, K.; Kocienski, P. J.; Sliwinski, E.; Boyle, F. T. *Org. Biomol. Chem.* **2006**, *4*, 2193. (d) Lai, J. H.; Liu, Y.; Wu, W.; Zhou, Y.; Maw, H. H.; Bachovchin, W. W.; Bhat, K. L.; Bock, C. W. *J. Org. Chem.* **2006**, *71*, 512. (e) Ohmura, T.; Awano, T.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 13191. (f) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894.

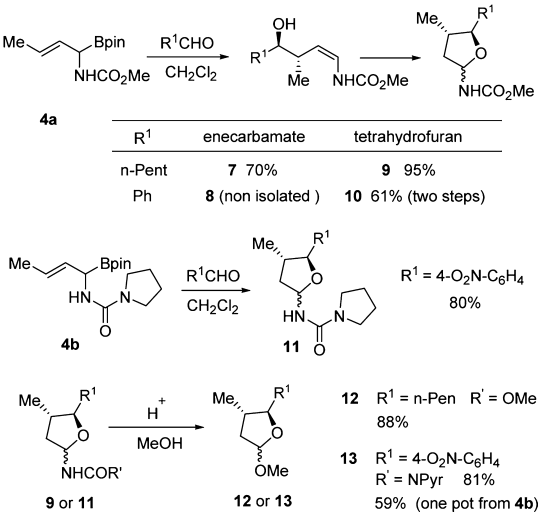
(25) CCDC 927328 contains the supplementary crystallographic data for compound **4b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 3. Synthesis of Ureidoboronic Acid **6**



versatile carbon nucleophiles, usually showing very good levels of chemo-, regio-, and stereocontrol in various reactions with electrophiles.[26] Exposure of the carbamate **4a** to an aldehyde effectively afforded the *anti* (*Z*)-homoallylic alcohols **7** and **8**,[27] which, in the presence of HCl for **7** or spontaneously for **8**, cyclized respectively to the (tetrahydrofuran-2-yl)carbamates **9** and **10** (Scheme 4).[28] Regarding the mechanism of this process, we assume, in agreement with previous reports,[29] that the acid activation of the enecarbamate was followed by an intramolecular addition of the alcohol to afford **9** and **10** as 1/1 mixtures of epimers at C2.[30] A similar behavior was observed with the urea derivative **4b**. The corresponding tetrahydrofuran **11** was obtained in a 80% yield as a 65:35 diastereomeric mixture. Further treatment of **9** or **11** with HCl in dioxane in the presence of an excess of methanol gave, respectively, the (tetrahydrofuran-2-yl)ethers **12** or **13**,[31,32] some representative examples of a useful class of intermediates for natural products synthesis.[33] This transformation was also achieved in a one-pot process from **4b** to **13**, albeit in a slightly lower isolated yield.

Scheme 4. Reaction of Allylboronates **4a**,**b** with Aldehydes



In conclusion, we have developed a new route to α-isocyanato allylboronic esters via a [3,3]-sigmatropic cyanate−isocyanate rearrangement that enables the preparation of α-aminoboronic derivatives. Furthermore, their addition to aldehydes, followed by the intramolecular cyclization of the corresponding homoallylic alcohols, gave access to variously trisubstituted tetrahydrofurans. Further studies directed to the transposition of these results in a nonracemic series as well as the use of the enecarbamate or eneurea intermediates in natural product synthesis are under investigation.

Acknowledgment. We are indebted to BoroChem and ANRT for financial support for S.T. (CIFRE scholarship). This work was also supported by the CNRS and the University of Rennes 1.

Supporting Information Available. Experimental procedures and characterizations of new compounds as well as crystallographic data for **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

(26) (a) Kennedy, J. W.; Hall, D. G. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH:Weinheim, 2005; pp 241−277. (b) Lachance, H.; Hall, D. G. *Org. React.* **2008**, *73*, 1. (c) Elford, T. G.; Hall, D. G. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH:Weinheim, 2011; pp 393−426.

(27) The stereochemical course of the allylation step resulted from a preferred transition state where the carbamate or urea group adopts a pseudoaxial position, as mentioned in the literature for polar α-substituents. (a) Hoffmann, R. W. *Pure Appl. Chem.* **1988**, *60*, 123. (b) Hoffmann, R. W.; Wolff, J. J. *Chem. Ber.* **1991**, *124*, 563.

(28) For synthesis and Lewis acid catalyzed ring-opening reactions of this type of semicyclic *N*,*O*-acetals possessing an exocyclic nitrogen atom, see: Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510.

(29) For recent reviews on the enecarbamate chemistry, see: (a) Matsubara, R.; Kobayashi, S. *Acc. Chem. Res.* **2008**, *41*, 292. (b) Kovuru, G.; Kagan, H. *Chem. Rev.* **2011**, *111*, 4599.

(30) We never succeeded to isolate **8** free of **10**. The spontaneous cyclization of this enecarbamate can be attributed to the presence of traces of a boron compound resulting from the hydrolysis of the allylic O-Bpin, the first intermediate produced in the allylation step. In the case of **7**, without being able to explain this difference, the ene carbamate can be isolated and acid addition is necessary to achieve its complete conversion to **9**.

(31) The conversion of **9** to **12** required only 30 min while it is necessary to wait for 24 h to observe a complete transformation for **11**.

(32) For similar transformations, see, for example: (a) Gaul, C.; Seebach, D. *Helv. Chim. Acta* **2002**, *85*, 772. Whisler, M. C.; Vaillancourt, L.; Beak, P. *Org. Lett.* **2000**, *2*, 2655.

(33) For some recent references, see: (a) Enev, V. S.; Felzmann, W.; Gromov, A.; Marchart, S.; Mulzer, J. *Chem.—Eur. J.* **2012**, *18*, 965. (b) Yadav, J. S.; Venkateshwar Rao, C.; Prasad, A. R.; Al Khazim Al Ghamdib, A. *Synthesis* **2011**, 3894. (c) Kong, K.; Moussa, Z.; Lee, C.; Romo, D. *J. Am. Chem. Soc.* **2011**, *133*, 19844. (d) Yadav, J. S.; Srinivas Reddy, A.; Suresh Reddy, Ch.; Subba Reddy, B. V.; Saddanapu, V.; Addlagatta, A. *Eur. J. Org. Chem.* **2011**, 696. (e) Yadav, J. S.; Reddy, Ch. S. *Org. Lett.* **2009**, *11*, 1705. (f) Yadav, J. S.; Bhaskar Reddy, K.; Prasad, A. R.; Ur Rehman, H. *Tetrahedron* **2008**, *64*, 2063.

The authors declare no competing financial interest.