Tetrahedron Letters, Vol. 33, No. 46, pp. 6941-6944, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

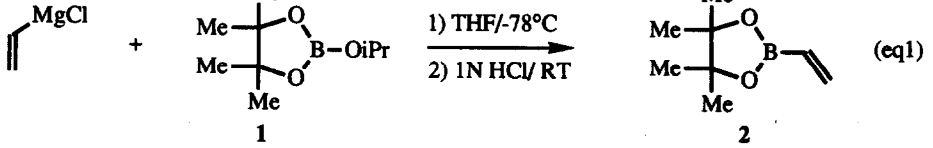
Preparation and 1-Carbon Homologation of Boronic Ester Substituted Δ^2-isoxazolines: The 1,3 Dipolar Cycloaddition of Nitrile Oxides to Vinyl Boronic Esters‡

Richard H. Wallace* and K. K. Zong
Department of Chemistry, University of Alabama, Tuscaloosa, AL 35487

Abstract: The dipolar cycloaddition of a variety of nitrile oxides to pinacol vinylboronate (2) is described. In addition, the 1-carbon homologation of the boronic ester substituted Δ^2-isoxazolines obtained from the cycloadditions has been carried out employing iodomethyllithium.

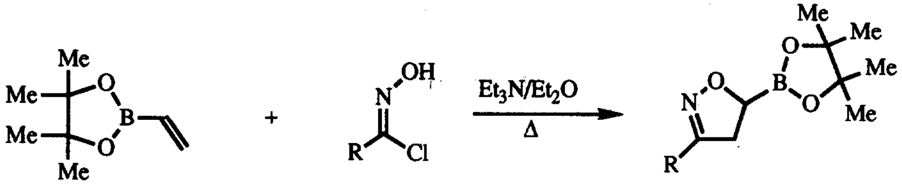
The Δ^2-isoxazolines produced by a 1,3-dipolar cycloaddition of a nitrile oxide to an alkene have proven to be extremely useful compounds in organic chemistry.[1a,b,c,d] Among the various classes of compounds which have been prepared from these cycloadducts are enones,[1a] 1,3 amino alcohols,[1e] β,γ-dihydroxy ketones,[1f] and β-hydroxy ketones.[1a] The boronic ester functionality has also enjoyed considerable use in organic synthesis.[2a,b] Procedures exist for the direct conversion of boronic esters into alcohols,[2b] aldehydes,[2b,c] carboxylic acids,[2b,c] and amines.[2b,c] It has also been shown that it is possible to homologate boronic esters by inserting a methylene into the carbon-boron bond.[3a,b,c,d] The ability to carry out the homologation of a boronic ester coupled with the large number of functional groups which it represents has resulted in the boronic ester becoming an extremely versatile functional group. We report in this letter our results which combine the usefulness of the Δ^2-isoxazoline with that of the boronic ester, by carrying out nitrile oxide cycloadditions on vinyl boronic esters to afford boronic ester substituted Δ^2-isoxazolines.[4a,b,c]

Pinacol vinylboronate (2) was chosen as the dipolarophile in our initial studies. This is a known compound previously prepared by Matteson by transesterification of dibutyl vinylboronate with pinacol.[5a] The route chosen for the synthesis of 2 (eq1) employs mixed borate 1[5b], and avoids the somewhat tedious isolation of dibutyl vinylboronate.[5c] The reaction of 1 with vinylmagnesium chloride in THF at -78°C, followed by quenching at room temperature with a mixture of 1N HCl (aq) and pentane,[5b] to which phenothiazine had been added,[5c] provided vinylboronate 2 in 68% yield after vacuum distillation.



[‡] Dedicated to Professor John W. Huffman on the occasion of his 60th birthday.

With the desired vinyl boronic ester **2** in hand, its use as a dipolarophile in 1,3-dipolar cycloadditions with nitrile oxides was explored. Our initial studies involved the use of nitrile oxides generated by treatment of the corresponding hydroxamic acid chlorides[6] with Et_3N in Et_2O in the presence of **2** (Huisgen Method).[7a] Benzonitrile oxide[7a] and 2,2-dimethylpropane nitrile oxide[7b,c] were explored, and both afford cycloadducts, **4a** & **4b** respectively, in good yield after filtration and Kugelrohr distillation.(eq2)

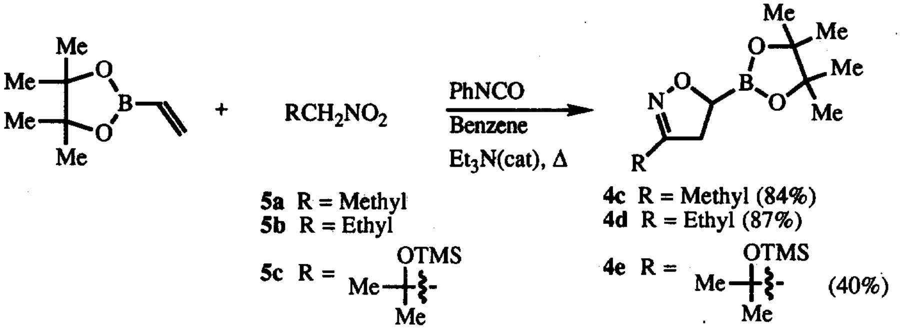


(eq2)

3a R= Ph
3b R= *t*-butyl

4a R=Ph (85%)
4b R=*t*-butyl (88%)

The possibility of carrying out the cycloaddition with nitrile oxides generated by the Mukaiyama method (1° nitroalkane, PhNCO, and Et_3N (cat),[8a] was also explored. We were delighted to find that treatment of a benzene solution of **2**, nitroethane, and phenyl isocyanate with a catalytic amount of Et_3N provided cycloadduct **4c** in 84% yield after Kugelrohr distillation. The cycloadducts were also obtained in good yield when the cycloaddition was carried out employing nitropropane (**5b**), and in moderate yield with the functionalized nitroalkane **5c**,[8b] previously utilized by Curran and coworkers.(eq3)



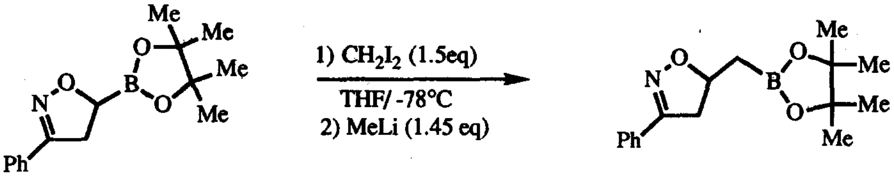
(eq3)

5a R = Methyl
5b R = Ethyl
5c R =

4c R = Methyl (84%)
4d R = Ethyl (87%)
4e R = (40%)

After it was established that it was possible to carry out the cycloadditions in good yield with nitrile oxides generated by either of the two methods described above, we turned our attention to the task of carrying out the 1-carbon homologation of the boronic ester substituted Δ^2-isoxazolines. This reaction is clearly of great importance if the full synthetic potential of these cycloadducts is to be realized.

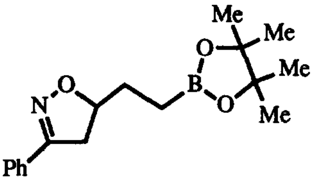
In 1985 Matteson and Sadhu had described a 1-carbon homologation of boronic esters by treatment with chloromethyllithium (generated by the addition of *n*-butyllithium to iodochloromethane in the presence of the boronic ester).[3a] This reaction, which occurs with retention of stereochemistry in the alkyl group bonded to boron, proceeds by first formation of the "ate" complex, migration of the alkyl group from boron, and loss of chloride. When the substituted cycloadduct **4a** was subjected to these conditions, none of the desired homologated compound **6** was obtained. We also observed no change in the reaction upon the addition of anhydrous $ZnCl_2$.[3e] In 1991 Matteson and Michnick reported the use of bromomethyllithium for the homologation of boronic esters.[3b] When this procedure was applied to cycloadduct **4a** the homologated product **6** was obtained as the only product in 40% yield; however, attempts to further optimize this reaction were unsuccessful. Since bromide is a better leaving group than chloride, and a higher yield is obtained with $BrCH_2Li$ than with $ClCH_2Li$, the use of ICH_2Li[9] appeared promising. We were extremely pleased to find that this was indeed the case. When **4a** was subjected to treatment with ICH_2Li at -78°C, (generated in situ from CH_2I_2 and MeLi),[10] **6** was obtained in an isolated yield of 69% after Kugelrohr distillation.(eq4) This appears to be the first reported homologation of a boronic ester using iodomethyllithium.[11a,b]



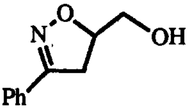
(eq4)

6

In an effort to explore the further functionalization of Δ^2-isoxazoline **6**, it was subjected to treatment with $LiCH_2Br$ at -78°C,[3b] to provide the homologated Δ^2-isoxazoline **7** in 90% yield. To explore possible functional group interconversions of the boronic ester functionality and the Δ^2-isoxazoline, (and to confirm the structure of **6**), the oxidation (H_2O_2, NaOH, THF, RT)[12] of boronic ester **6** was carried out. This afforded Δ^2-isoxazoline **8** in 75% isolated yield. This compound is identical, (^1H NMR, ^{13}C NMR, MS and mp), to the cycloadduct obtained by treatment of allyl alcohol with phenyl hydroxamic acid chloride (**3a**) with Et_3N in Et_2O.[1f]



7



8

In summary, we have shown that the vinyl boronic ester functionality is compatible with both methods of nitrile oxide generation described above, and affords the desired cycloadducts in high yield. We have also shown that iodomethyllithium is an effective reagent for the 1-carbon homologation of the resulting boronic ester substituted Δ^2-isoxazolines.[13] Further studies in this area are currently underway.

Acknowledgements: We thank the Research Grants Committee of The University of Alabama for financial support of this work.

References and Footnotes:

1. For reviews of nitrile oxide cycloadditions, see: (a) Curran, D. P. *Advances in Cycloaddition*; JAI Press, Greenwich, CT, Curran, D. P. ed.; 1988, 1, 280. (b) Grünanger, P.; Vita-Finzi, P. *Isoxazoles, Part I*; John Wiley and Sons; Taylor, E. C. ed.; 1991, 417. (c) Caramella, P.; Grünanger, P. *1,3-Dipolar Cycloaddition Chemistry*, Wiley-Interscience, Vol. I.; Padwa, A. ed.; 1984, 1, 291. (d) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. (e) Jäger, V.; Müller, I. *Tetrahedron* **1985**, *41*, 3519. (f) Curran, D. P.; Zhang, J. *J. Chem. Soc. Perkin. Trans. I.* **1991**, 2613.

2. (a) For a recent review of boronic ester chemistry, see: Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859. (b) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*, Academic Press, New York, 1988. (c) For a recent paper which summarizes some of the functional group interconversions possible with boronic esters, see: Rangaishenvi, M. V.; Singaram, B.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 3286.

3. (a) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687. (b) Michnick, T. J.; Matteson, D. S. *Syn. Lett.* **1991**, 631. (c) Brown, H. C.; Singh, S. M.; Rangaishenvi, M. V. *J. Org. Chem.* **1986**, *51*, 3150. (d) For a recently published report which details a new method for the 3-carbon homologation of boronic esters, see: Brown, H. C.; Rangaishenvi, M. V.; Jayaraman, S. *Organometallics* **1992**, *11*, 1948. (e) It has been reported that in many cases the addition of $ZnCl_2$ has an advantageous effect on reactions of this type, see refs. 2a, 2c, 3b and references therein.

4. (a) For a paper dealing with the use of dibutyl vinylboronate as a dipolarophile with ethyl diazoacetate and diphenyldiazomethane, see: Matteson, D. S. *J. Org. Chem.* **1962**, *27*, 4293. (b) For another report dealing with the use of ethyl diazoacetate as a 1,3-dipole in a cycloaddition with a vinyl boronic ester, see: Woods, W. G.; Bengelsdorf, I. S. *J. Org. Chem.* **1966**, *31*, 2769. (c) For papers dealing with the 1,3-dipolar cycloaddition between dibutyl vinylboronate and 3 aromatic nitrile oxides, see: Bianchi, G.; Cogoli, A.; Grünanger, P. *J.Organometal. Chem.* **1966**, *6*, 598. and Bianchi, G.; Cogoli, A.; Grünanger, P. *Ric. Sci.* **1966**, 132.

5. (a) Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 1529. (b) Andersen, M. W.; Hildebrandt, B.; Köster, G.; Hoffmann, R. W. *Chem. Ber.* **1989**, *122*, 1777. (c) Matteson, D.S. *J. Am. Chem. Soc.* **1960**, *82*, 4228.

6. Liu, K.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916.

7. (a) Bast, K.; Christl, M.; Huisgen, R.; Mack, W.; Sustmann, R. *Chem. Ber.* **1973**, *106*, 3258. (b) Curran, D. P.; Scanga, S. A.; Fenk, C. J. *J. Org. Chem.* **1984**, *49*, 3474. (c) Zinner, G.; Günther, H. *Chem Ber.* **1965**, *98*, 1353.

8. (a) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339. (b) Curran, D. P.; Fenk, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 6023.

9. For the initial report on the preparation of ICH_2Li, see: Koebrich, G.; Von Nagel, R. *Chem.-Ztg., Chem. App*, **1970**, *94*, 984.

10. The procedure employed is essentially the same as that described in ref. 3b with the exception that CH_2I_2 was employed in place of CH_2Br_2 and MeLi (Aldrich) was used instead of *n*-butyllithium.

11. For two other papers dealing with the preparation and use of ICH_2Li, see: (a) van Eikema Hommes, N. J. R.; Bickelhaupt, F.; Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 514. (b) Kobayashi, T.; Pannell, K. H. *Organometallics* **1991**, *10*, 1960.

12. Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426.

13. All yields shown are isolated yields, and all new compounds gave satisfactory spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, and HRMS).

(Received in USA 15 July 1992; accepted 18 August 1992)