Pergamon

Tetrahedron Letters, Vol. 35, No. 41, pp. 7493-7496, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01149-4

A Facile Method For The Preparation of 4-Hydroxy-Δ^2-isoxazolines *Via* a Cycloaddition/Oxidation Procedure Employing Nitrile Oxides and Vinylboronic Esters

Richard H. Wallace* and Jinchu Liu

Department of Chemistry, University of Alabama, Tuscaloosa, AL 35487

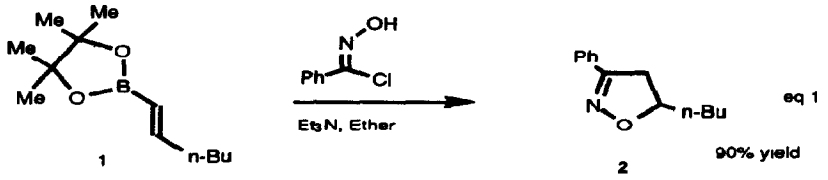
Abstract: The 1,3-dipolar cycloaddition of aromatic nitrile oxides with *trans*-1,2-disubstituted vinylboronic esters affords the 4-boronic ester substituted Δ^2-isoxazoline as the major regioisomer. If the reaction mixture is treated with t-BuOOH the corresponding 4-hydroxy-Δ^2-isoxazolines are obtained in good yield.

Jäger and others have shown 4-hydroxy-Δ^2-isoxazolines to be versatile intermediates for the synthesis of amino sugars and other biologically important molecules. [1, 2] We report in this letter a new method for the synthesis of this versatile class of compounds based upon oxidation of the cycloadducts obtained from nitrile oxide cycloaddition to vinylboronic esters. One reason why 4-hydroxy-Δ^2-isoxazolines have proven to be such valuable molecules centers around their conversion into amino-diols of defined stereochemistry by reduction with lithium aluminum hydride. The stereochemistry of the reduction is determined by the nature of the hydroxyl group on the 4-position. LAH reduction of a 4-hydroxy-Δ^2-isoxazoline with an unprotected hydroxyl group at the 4-position affords the amino-diol with *anti* stereochemistry between the amino and hydroxy group. The reduction occurs by complexation of LAH with the oxygen followed by intramolecular delivery of hydride from the same face of the molecule as the hydroxyl group. If LAH reduction is carried out on a 4-hydroxy-Δ^2-isoxazoline which has a protected hydroxyl group at the 4-position, reduction occurs opposite to the protected hydroxyl group to afford the corresponding *syn* isomer. [1, 2]

A variety of methods have been reported for the preparation of 4-hydroxy-Δ^2-isoxazolines. Jäger and coworkers have prepared 4-hydroxy-Δ^2-isoxazolines via deprotonation of a Δ^2-isoxazoline with LDA followed by reaction with trimethyl borate, and oxidative workup. [3] This procedure affords the hydroxy-isoxazoline in moderate yield, along with significant amounts of the unhydroxylated starting isoxazoline.[3] It was later reported by Auricchio and Ricca that better yields can be obtained by treatment of the isoxazoline anion with either dry air or oxygen. [4] Davis and Wade [5] recently reported that by employing optically active N-sulfonyloxaziridines as the oxidant it is possible to prepare optically active 4-hydroxy-isoxazolines from the isoxazoline anion. Another procedure for the synthesis of 4-hydroxy-Δ^2-isoxazolines involves the intramolecular ring opening of α,β-epoxy oximes. [6] Rosini and coworkers have reported a procedure for the preparation of 4-hydroxy-isoxazoline-N-oxides which can then be then converted into the 4-hydroxy-isoxazolines. [7] Wade and Price have also reported a method for preparation of this class of compounds via nitrosative cycloaddition. [8]

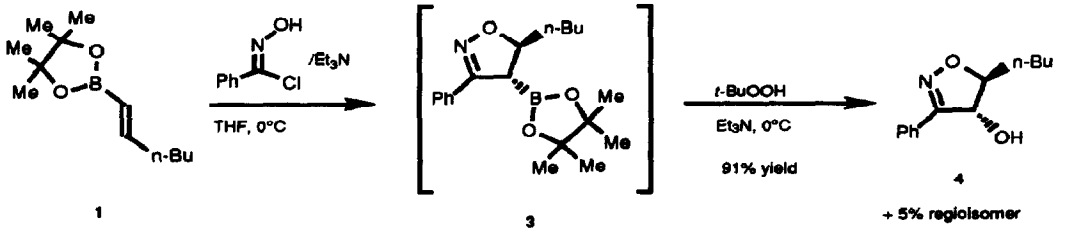
In continuation of our studies[9] into the use of vinylboronic esters as dipolarophiles in 1,3-cycloadditions, we carried out the 1,3-dipolar cycloaddition of benzonitrile oxide to the hexyne

derived pinacol vinylboronic ester (1). [10] This reaction afforded Δ^2-isoxazoline (2) in 90% yield, which was devoid of the boronic ester. (eq 1)



We felt that there were two possibilities to explain the loss of the boronic ester functionality. The first was that the boronic ester was lost prior to cyclization in a protonolysis reaction[11] followed by reaction of the resulting alkene with benzonitrile oxide. The second possibility was that the cyclization occurred with very high regioselectivity to afford the 4-boronic ester substituted Δ^2-isoxazoline which underwent loss of the boronic ester functionality. The second possibility seemed more plausible in light of the work of Jäger and coworkers in which they found that 4-boronic ester substituted isoxazolines generated by reaction of the isoxazoline anion and trimethyl borate proved to be quite labile towards protonolysis. [3] We have subsequently found that by careful manipulation of the reaction mixture we can observe the boronic ester containing nitrile oxide cycloadduct (3) by NMR. Drawing from the work of Jäger and coworkers[3], we rationalized that if we subjected the nitrile oxide cycloadduct (3) to oxidation this should provide the corresponding 4-hydroxy isoxazoline.

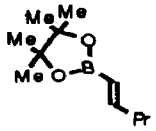
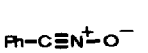
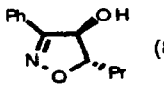
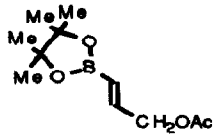
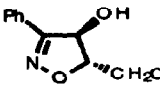
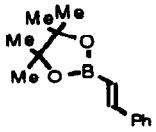
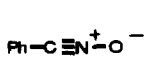
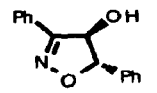
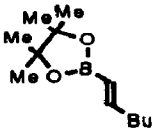
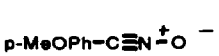
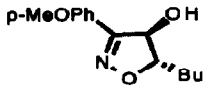
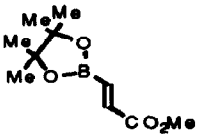
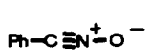
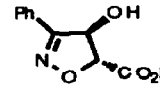
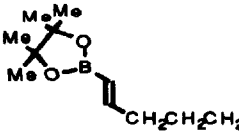
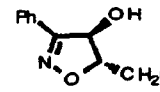
We were delighted to find that treatment of the hexyne derived vinylboronic ester (1) with benzonitrile oxide (1.1 eq) at 0° C for 30 minutes followed by treatment with *t*-BuOOH (*CAUTION*!) afforded the *trans*-4-hydroxy-5-butyl-Δ^2-iosxazoline (4)[5] in 91% yield, along with 5% of the regioisomeric hydroxy-isoxazoline. To confirm the structure of Δ^2-isoxazoline 4 we have prepared it from 2 via the procedure of Jäger [3] {1) LDA, HMPA, THF, -78°C; 2) $(MeO)_3B$, -78°C; 3) *t*-BuOOH, Et_3N}. This procedure afforded Δ^2-isoxazoline 4 (43%) along with recovered 2 (51%). The hydroxy-isoxazoline obtained from this procedure was identical to that obtained from the cycloaddition/oxidation route. We have subsequently investigated the reaction of a variety of vinylboronic esters and aromatic nitrile oxides in the cycloaddition/oxidation route described above. Some of the 4-hydroxy-Δ^2-isoxazolines which have been prepared via this procedure are shown in Table I.



It is interesting to note the high degree of regioselectivity displayed by the vinylboronic ester in these nitrile oxide cycloadditions. It is known that the regioselectivity of nitrile oxide cycloadditions to 1,2-disubstituted alkenes is usually very low. [2, 12] When the alkene bears an electron withdrawing group there is a small preference for the electron withdrawing group to

occupy the 4-position in the cycloadduct. When the alkene contains an electron donating substituent the regioselectivity is much better, affording the cycloadduct with the electron donating substituent on the 5-position of the isoxazoline. [2] The high degree of regioselectivity displayed by vinylboronic esters in nitrile oxide cycloadditions is currently under further investigation.

Table 1. 4-Hydroxy-Δ^2-isoxazolines From The Cycloaddition/Oxidation Route

Exp.	Vinylboronic Ester	Nitrile Oxide	Cycloadduct (% yield)
1			 (88%)
2			 (87%)
3			 (86%)
4			 (84%)
5			 (79%)
6			 (75%)

The stereochemistry of the products in Table 1 has been assigned by examining the coupling constant between the C-4 proton and the C-5 proton of the hydroxy-isoxazolines. It is known that the coupling constants between these two protons is ~2.5 Hz in the trans isomer. [13] The *trans*-1,2-disubstituted vinylboronic esters employed in these reactions were prepared via literature procedures by hydroboration of the corresponding alkyne with Br_2BH-Me_2S[10], pinacolborane[14], cyclohexyl borane[15], or Ipc_2BH. [16] The hydroximic acid chlorides required for preparation of the nitrile oxides were prepared from the corresponding oximes by chlorination with N-chlorosuccinimde.[17] The 4-hydroxy-isoxazolines obtained in experiments 1 and 3 are known compounds and displayed spectral data in agreement with those previously reported. [4,6]

As can be seen from the data in Table 1 this procedure is compatible with the presence of various functional groups and provides the hydroxy-isoxazolines in good isolated yields. We have shown vinylboronic esters to be very reactive dipolarophiles in 1,3-dipolar cycloadditions with nitrile oxides. [18] This high reactivity undoubtedly plays a role in the good yields obtained in the cycloaddition/oxidation route to 4-hydroxy-Δ^2-isoxazolines described above. Further studies including the development of an asymmetric variation on this reaction and the employment of the amino-diols produced by LAH reduction of the hydroxy isoxazolines in the synthesis of natural products are currently underway. [19]

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

References and Footnotes:

1. (a) Jäger, V.; Müller, I.; Schohe, R.; Frey, M.; Ehrler, R.; Häfele, B.; Schröter, D. *Lect. Heter. Chem.* **1985**, *6*, 79, and references therein. (b) Yin, H.; Franck, R. W.; Chen, S.; Quigley, G. J.; Todaro, L. *J. Org. Chem.* **1992**, *57*, 644. (c) Panek, J. S.; Beresis, R. T. *J. Am. Chem. Soc.* **1993**, *115*, 7898.
2. Grünanger, P.; Vita-Finzi, P. "Isoxazoles" John Wiley & Sons, Inc., New York, **1991**, p. 417.
3. Schwab, W.; Jäger, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 603.
4. Auricchio, S.; Ricca, A. *Heterocycles* **1988**, *27*, 2395.
5. Davis, F. A.; Kumar, A.; Reddy, R. E.; Chen, B.; Wade, P. A.; Shah, S. W. *J. Org. Chem.* **1993**, *58*, 7591.
6. Ito, S.; Sato, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2739.
7. Rosini, G.; Marotta, E.; Righi, P.; Seerden, J. P. *J. Org. Chem.* **1991**, *56*, 6258.
8. Wade, P. A.; Price, D. T. *Tetrahedron Lett.* **1989**, *30*, 1185.
9. Wallace, R. H.; Zong, K. K. *Tetrahedron Lett.* **1992**, *33*, 6941.
10. Brown, H. C.; Campbell, J. B. *J. Org. Chem.*, **1980**, *45*, 389.
11. Pelter, A.; Smith, K.; Brown, H. C. "Borane Reagents", Academic Press, New York, **1988**.
12. For other reports dealing with controlling the regioselectivity of nitrile oxide cycloadditions, see: (a) Curran, D. P.; Choi, S.; Gothe, S. A.; Lin, F. *J. Org. Chem.* **1990**, *55*, 3710. (b) Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324, and references therein.
13. Jäger, V.; Schröter, D. *Synthesis* **1990**, 556.
14. Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482.
15. Hoffman, R. W.; Dresely, S. *Synthesis*, **1988**, 103.
16. Rasset-Deloge, C.; Martinez-Fresneda, P.; Vaultier, M. *Bull. Soc. Chim. Fr.* **1992**, *129*, 285.
17. Liu, K.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916.
18. Wallace, R. H.; Zong, K. K.; Schoene, M. "Current Topics in the Chemistry of Boron" Royal Society of Chemistry, in press.
19. 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* 12 *April* 1994; *accepted* 10 *June* 1994)