Tetrahedron Letters, Vol 32, No 31, pp 3783-3786, 1991
Printed in Great Britain

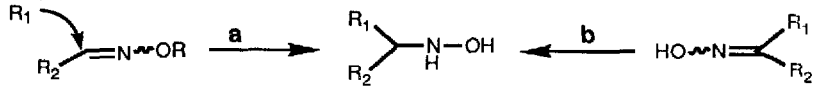
0040-4039/91 $3.00 + 00
Pergamon Press plc

ADDITION OF ORGANOLITHIUM COMPOUNDS TO N-THP PROTECTED NITRONE

Anwer Basha*, James D. Ratajczyk and Dee W. Brooks
Abbott Laboratories,
D-47K AP10, Abbott Park, IL 60064-3500

Abstract: *A novel synthesis of a-branched primary hydroxylamines by addition of organolithium reagents to N-THP protected nitrone is described.*

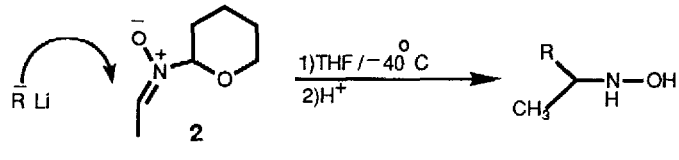
As a part of our medicinal chemistry program, we required a-branched primary hydroxylamines of the type 1, in which R_1 and R_2 could be either or both alkyl or aryl groups. In the literature, this type of hydroxylamine could be prepared in either of the following methods.:



1

First method (a) involves the addition of an organolithium to O-protected oximes in presence of BF_3:OEt_2.[1] Organometallic addition preferentially reacts with the Z-isomer of the mixture of E and Z oximes and provides modest to low yields of desired adduct. The second method (b) involves reduction of the oximes of the corresponding ketones.[2] This sometimes poses a problem of over reduction and some oximes are not readily reduced to hydroxylamines. Organometallic additions to nitrones have been reported, which provide N-substituted hydroxylamines.[3]

In this report we describe the first isolation of the N-THP nitrone **2** and addition of organolithium compounds to this nitrone as a method to provide a-branched primary hydroxylamines (eq. 1).



2 Eq 1

The nitrone **2** has previously been inferred as an intermediate in [2+3] cycloaddition reactions but organometallic additions have not been reported.[4]

When 5-hydroxypentanal oxime was treated with acetaldehyde in chloroform or CH_2Cl_2 solution in presence of a water scavenger such as anhydrous calcium chloride, after 6 h at 0°C, TLC showed a single spot faster moving than starting oxime. However, attempts to isolate this produce resulted in considerable decomposition. NMR spectroscopy at -2°C showed characteristic signals for the nitrone vinyl proton at 7.25 (q, J = 7 Hz). After evaporation of chloroform *in vacuo* at low temperature (0 - 5°C) this nitrone was taken up in anhydrous THF and treated with various organo metallic compounds at low temperature, which after aqueous acidic hydrolysis afforded the desired a-branched primary hydroxylamines.

In some cases the hydroxylamines were quite unstable. In order to purify these compounds, they were converted into the corresponding hydroxyureas by treatment with TMSNCO in (24 - 36% overall yields).

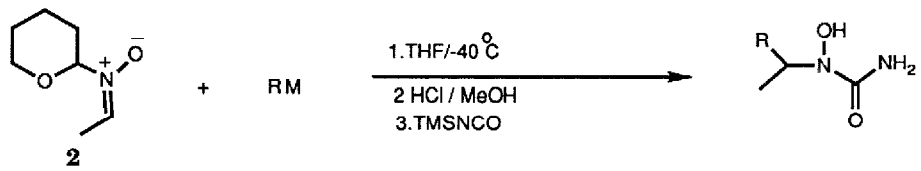
This method provides a direct synthesis of α-branched primary hydroxylamines from a readily prepared nitrone intermediate. A major side reaction seems to be hydrogen abstraction from the α-methyl group of the nitrone **2**, thus providing the starting compound and accounting for the low conversion to product.

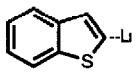
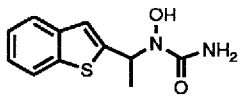
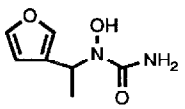
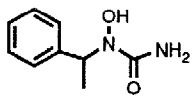
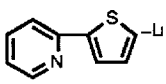
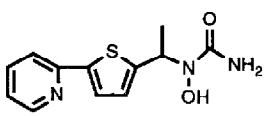
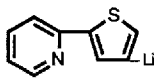
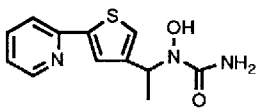
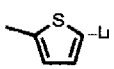
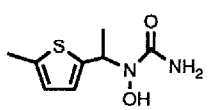
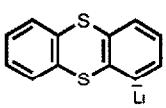
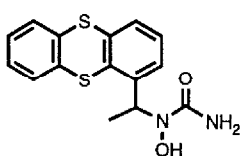
Representative examples of the addition of organolithium compounds to nitrone **2** are shown in Table I. The addition consistently works between the range of 24 - 36% overall yield for three steps, and have not been optimized. In the case of thiopyridine, (entries 4 and 5) when dry THF was employed as a solvent at -30C, lithiation occurs at 5-position, whereas in dry ether 3-position was metallated.[5]

A representative example for synthesis of N-hydroxy-N-(1-(2-benzothienyl)ethyl)urea is illustrated as follows: 5-hydroxy pentanal oxime (1.64 g, 14.05 mmol) was allowed to react with acetaldehyde (0.9 ml, 16 mmol) in the presence of anhydrous calcium chloride (8 g) in chloroform or methylene chloride (10 ml) at 0 - 5°C for 6 h. The $CaCl_2$ was filtered off and the filtrate was evaporated *in vacuo* at 0 - 5°C, kept under high vacuum for 10 min at 0 - 5°C and then the viscous oil was used without further purification. (TLC showed one major spot faster moving then the starting oxime with CH_2Cl_2:MeOH; 9:1).

A solution of benzothiophene (1.23 g, 9.2 mmol) at -20°C in dry ether (10 ml) was treated with one equivalent of n-BuLi (3.6 ml of 2.5 M in hexane, 9.2 mmol) and the mixture was stirred for 1 h. A solution of freshly prepared nitrone **2**, as above (2.0 g 14.05 mmol) in ether (10 ml) was added to the cold mixture (-40°C) and stirred for 20 min. Ethanol (20 ml) was added followed by dilute HCl (6 N, 8 ml) and the mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo*. Aqueous Na_2CO_3 (20 ml) and dichloromethane 50 ml was added to the residue and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 30 ml) and the combined organic extract was washed with brine and evaporated to provide the hydroxylamine. This hydroxylamine was dissolved in tetrahydrofuran (20 ml) and treated with trimethylsilylisocyanate (1.5 g, 13 mmol) and stirred at room temperature for 6 h. The solvent was evaporated *in vacuo* and a solution of dichloromethane and pentane was added to induce crystallization. The desired product was collected by filtration and recrystallization to provide the N-hydroxy urea 700 mg (36% yield). m.p. 149 - 151°C. (entry 1).

Table 1. Addition of organolithium compounds to nitrone **2**



Entry	RM	Product[a]	Yield(%)[b]
1.			36
2.			25
3.			28
4.			30
5.			34
6.			24
7.			25

[a]All compounds were characterized by elemental analysis, mass and nmr spectroscopy (300 MHz).

[b]Overall yield in three steps after purification.

Zileuton is a 5-lipoxygenase inhibitor, currently in clinical trials for treating human diseases involving leukotrienes as mediators.[6,7]

References.

1. Rodriques, K. E.; Basha, A.; Summers, J. B.; Brooks, D. W.; *Tetrahedron Lett.* **1988**, 29, 3455.

2. (a) Kawase, M.; Kikugawa, Y.; *Chem. Lett.* **1977**, 1279; *J. Chem. Soc. Perkin Trans. I*, **1979**, 643; (b) Herscheid, J. D. M.; Ottenheigm, H. C. J.; *Tetrahedron Lett.* **1978**, 5143; (c) Gribble, G. W.; Leiby, R. W.; Sheehan, M. N.; *Synthesis* **1977**, 856; (d) Fener, H.; Braunstein, D. M.; *J. Org. Chem.* **1969**, 34, 1817; (e) Brown, H. C.; Bigley, D. B.; Arora, S. K.; Yoon, N M. *J. Am. Chem. Soc.* **1970**, 92, 7161.

3. (a) Randel W.; in Houlein-Weyl: Methoden der organischen Chemie, **1968**, 10:4 309, (E. Muller, Ed.) G. Thieme Verleg, Stuttgart; (b) Tafforiello, J. J.; In "1,3-Dipolar Cycloaddition Chemistry) (A. Padwa, Ed;) Wiley, New York, **1984**, 2, 83; (c) Cowling, M. P.; Jenkins, P. R.; Cooper, K.; *J. Chem Soc. Chem. Commun.* **1988**, 1503; (d) Chang, Z. Y.; Coates, M. R.; *J. Org. Chem.* **1990**, 55, 3464 and references cited therein.

4. (a) Huber, R.; Knierzinger, A.; Obrecht J. P.; Vasella, A.; *Helv. Chim. Acta* **1985**, 68, 1730; (b) Bernet, B.; Krawczyk, E.; Vasella, A.; *Helv. Chim. Acta* **1985**, 68, 2299; (c) Mzengeza, S; Whitney, R. A.; *J. Chem. Soc., Chem Commun.* **1984**, 606.

5. Kauffmann, T.; Mitschker, A.; Woltermann, A.; *Ber.* **1983**, 116, 992.

6. Carter, G. W.; Young, P. R.; Albert, D. H.; Bouska, J. B.; Dyer, R. D.; Bell, R. L.; Summers, J. B.; Brooks, D. W.; Gunn, B. P.; Rubin, P.; Kesterson, J.; *Leukotrienes and Prostanoids in Health and Disease, New Trends in Lipid Mediators Research* U. Zor, z. Naor, A Danon, eds., Karger, Basel **1989**, 50.

7. Brooks, D. W.; Summers, J. B.; Gunn, B. P.; Dellaria, J. F.; Holms, J. H.; Maki, R. G.; Martin, M. B.; Moore, J. L.; Rodriques, K. E.; Stewart, A. O.; Albert, D. H.; Bell, R. L.; Bouska, J. B.; Dyer, R. D.; Malo, P. E.; Young, P. R.; Rubin, P.; Kesterson, J.; Carter, G. W.; *Abstracts of the American Chemical Society Meeting* Boston, MA **1990**, Abstract 148.

(Received in USA 18 March 1991)