Pergamon

Tetrahedron Letters, Vol. 36, No. 48, pp. 8791-8794, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01878-6

A New Source of Nitrogen Centered Radicals.

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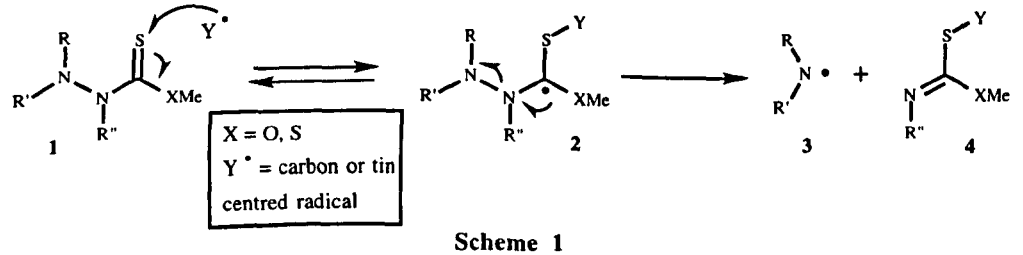
Abstract. Exposure of thiocarbazone derivatives **6b-10b**, **11c-13c**, and **14a-15a** to tributylstannane in the presence of AIBN leads to various nitrogen centered radicals which are easily captured by an internal olefin.

The past few years have witnessed an explosive surge in the use of radical reactions in organic synthesis, and this trend is showing no sign of abating. Most of the effort in this area has naturally focused on carbon centered radicals[1] but oxygen[2] and especially nitrogen radicals[3] are attracting an increasing attention since these species can provide access to a variety of important heterocyclic systems. We recently developed several processes to generate nitrogen radicals such as iminyls, amidyls and carbamyls.[4] Although these early methods allowed us to study the basic reactivity and synthetic potential of the hitherto little known iminyls, they suffer from several drawbacks such as fragile or difficult to prepare precursors and, in some cases, lack of generality. We now wish to report a new and apparently general approach to nitrogen centered radicals which overcomes essentially all of these limitations.

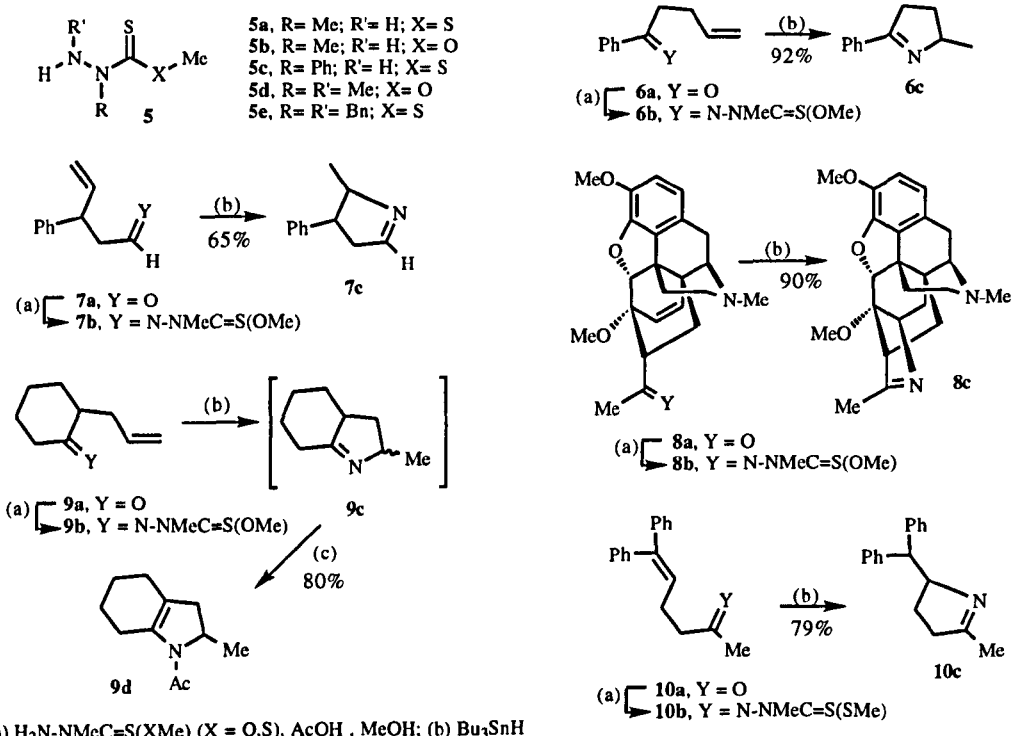


Scheme 1

The present process exploits the relative weakness of a nitrogen-nitrogen bond. With the special exception of α-azido radicals[5] which undergo loss of nitrogen and the pyrolysis of certain hydrazine derivatives,[6] a process quite limited in scope, cleavage of such a bond does not appear to have been employed to generate nitrogen centered radicals for use in synthesis. Thiocarbazone derivatives **1**, contain a highly radicophilic thiocarbonyl group which allows the creation of an intermediate radical **2** capable of undergoing the desired β-scission as summarized in scheme 1.

For the generation of iminyls, the required hydrazones (for example **6b-10b**) are easily prepared by condensation of a ketone with hydrazide **5a**, a nicely crystalline compound made in one step by reaction of methylhydrazine with carbon disulfide and methyl iodide,[7] or with hydrazide **5b**, also a readily available substance.[7] In most cases, derivatives of the latter have been used since, for reactions involving tributyl

stannane ($Y^{\bullet}$= $Bu_3Sn^{\bullet}$ in scheme 1), the logical tin containing co-product (**4**, Y= Bu_3Sn-; R"= Me; X= S) decomposes partially on silica to generate the obnoxious methanethiol. Slow addition of tributylstannane and a small amount of AIBN to a refluxing solution of either type of thiocarbazone precursors **6b-10b** in cyclohexane provided smoothly and efficiently the expected pyrrolines **6c-10c** in the yields shown in scheme 2. Iminyls derived either from ketones or aldehydes are thus readily accessible. In the case of **9b**, the reaction gave **9c** as a mixture of two diastereomers which upon heating with acetic anhydride were converted to the same enamide **9d** in good overall yield.

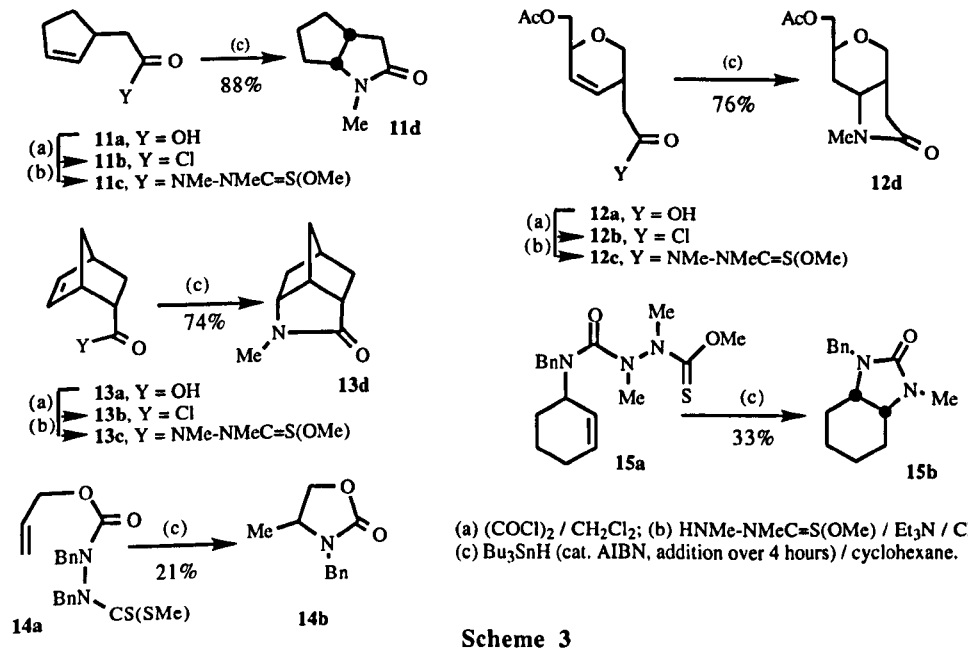


(a) H_2N-NMeC=S(XMe) (X = O,S), AcOH , MeOH; (b) Bu_3SnH (cat. AIBN, addition over 4 hours) / cyclohexane; (c) Ac_2O / cyclohexane.

Scheme 2

Amidyl radicals are obtained from acyl derivatives such as **11c-13c** (scheme 3), which are produced by reacting the hydrazide **5d** [7] with the appropriate acid chloride, and cyclised to suitably located olefins using the same procedure. A variety of lactams **11d-13d** were thus prepared in generally high yield. A modification of the process allowed access to carbamyl and ureidyl radicals as shown by examples **14b** and **15b**. The corresponding precursors **14a** and **15a** were made by reacting allyl chloroformate and the cabamoyl chloride derived from N-benzyl-2-cyclohexenylamine with hydrazides **5e** and **5d** respectively. The cyclisation was not particularly efficient in these cases (the remainder being mostly uncyclised material) but it must be said that none of the reactions has been optimized. Very little is known about carbamyl radicals [8] and almost nothing about ureidyl radicals; it is quite possible that the rate of cyclisation will be influenced significantly by the substituents on the nitrogen atoms which can alter the population of rotamers. This aspect has not been investigated yet. Nevertheless, access to these radicals opens the way to the

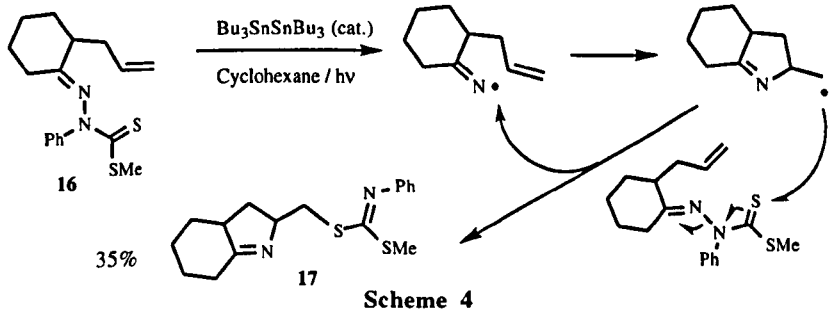
construction of vicinal amino alcohols and diamines with defined relative stereochemistry. Such a combination of functional groups is common in many natural products as for example aminocyclitols and conduramines.[9]



(a) $(COCl)_2$ / CH_2Cl_2; (b) HNMe-NMeC=S(OMe) / Et_3N / CH_2Cl_2; (c) Bu_3SnH (cat. AIBN, addition over 4 hours) / cyclohexane.

Scheme 3

Even though the above examples involved tributylstannane to mediate the desired transformation, the presence of a reactive thiocarbonyl group opens up the possibility of propagating the chain by direct reaction of the carbon radical on the sulfur of the thiocarbonyl. Thus, irradiation with visible light of a solution of **16**, a compound derived from 2-allylcyclohexanone and hydrazide **5c**) in cyclohexane in the presence of a small amount of hexabutylditin resulted in the formation of 35 % of functionalized pyrroline **17**, through the chain reaction depicted in scheme 4. The process still needs to be optimized to increase efficiency and chain length but nevertheless this experiment demonstrates its feasibility. Moreover the extra functionality thus introduced opens an entry into the the exceptionnally rich chemistry of sulfur.



Scheme 4

In conclusion, these preliminary results show the potential of this mild and fairly general approach for

generating nitrogen centered radicals, and hence for the synthesis of a variety of five-membered nitrogen heterocycles. This allows the conception of new synthetic strategies, especially in the field of alkaloids, where such rings are frequently found.

Acknowledgments: We wish to thank Rhône-Poulenc Rorer for generous financial support to one of us (ACC-D) and Drs G. Bashiardes and J. Boivin for many friendly discussions.

References.

1. For leading references see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986. (b) Curran, D. P. *Synthesis* **1988**, 417-439, 489-513. (c) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541-3676. (d) Hart, D. J. *Science* **1984**, *223*, 883. (e) Curran, D. P. in *Comprehensive Organic Synthesis* Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford, 1991, Vol 4, pp 715-831. (f) Two volumes in the Houben-Weyl series are solely dedicated to carbon radicals: *Houben-Weyl Methoden der Organischen Chemie;* Regitz, M.; Giese, B., Eds; Georg. Thieme Verlag: Stuttgart, 1989 (Band E19a).

2. (a) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1988**, *110*, 4415-4416; **1989**, *111*, 230-234 and references there cited. (b) Newcomb, M.; Udaya Kumar, M.; Boivin, J.; Crépon, E.; Zard, S. Z. *Tetrahedron Lett.* **1991**, *32*, 45-48. (c) Beckwith, A. L. J.; Davison, I. G. E. *Tetrahedron Lett.* **1991**, *32*, 49-52.

3. (a) Forrester, A. R., in *International Review of Science, Organic Chemistry Series Two: Free Radical Reactions* Butterworths: London, 1975, Vol. 10, Chap. 5. (b) Stella, L. *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 337-350. (c) Minisci, F. *Synthesis* **1973**, 1-24.(d) Furstoss, R.; Mackiewicz, P. *Tetrahedron* **1978**, *34*, 3241-3260. (e) Neale, R. S. *Synthesis* **1971**, 1-15. (f) Hudson, R. F.; Record, K. A. F. *J. Chem. Soc., Chem. Commun.* **1976**, 539-540. (g) Hasebe, M.; Kogawa, K.; Tsuchiya *Tetrahedron Lett.* **1984**, *25*, 3887-3890. (h) Forrester, A. R.; Gill, M.; Meyer, C. J.; Sadd, J. S.; Thomson, R. H. *J. Chem. Soc. Perkin Trans. 1* **1979**, 606-611. (i) Esker, J. L.; Newcomb, M. *Tetrahedron Lett.* **1993**, *34*, 6877-6880. (j) Esker, J. L.; Newcomb, M. *Tetrahedron Lett.* **1992**, *33*, 5913-5916. (k) Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1993**, *58*, 4933-4940. (l) Esker, J. L.; Newcomb, M. in *Adv. in Heterocyclic Chem., Vol 58;* Katritzky, A. R., Ed.; Academic Press: New York, 1993; pp 1-45. (m) Beckwith, A. L. J.; Maxwell, B. J.; Tsanaktsidis, J. *Aust. J. Chem.* **1991**, *44*, 1809-1812. (n) Russell Bowman, W.; Stephenson, P. T.; Young, A. R. *Tetrahedron Lett.* **1995**, *36*, 5623-5626 and references there cited.

4. (a) Boivin, J.; Fouquet E.; Zard S. Z. *Tetrahedron* **1994**, *50*, 1745-1756. (b) Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron* **1994**, *50*, 1757-1768. (c) Boivin, J.; Fouquet, E.; Schiano, A-M.; Zard, S.Z. *Tetrahedron* **1994**, *50*, 1769-1776. (d) Boivin, J.; Schiano, A.-M; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 249-252. (e) Boivin, J.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron Lett.* **1992**, *33*, 7849-7852. (f) Callier, A-C; Quiclet-Sire, B; Zard, S. Z. *Tetrahedron Lett.* **1994**, *33*, 6109-6112. (g) Boivin, J.; Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 6517-6528.

5. Roberts, B. P.; Winter, J. N. *J. Chem. Soc. Perkin Trans. 2* **1979**, 1353-1391.

6. (a) Crow, W. D.; Khan, A. N. *Aust. J. Chem.* **1976**, *29*, 2289-2297. (b) McNab, H. *J. Chem. Soc., Chem. Commun.* **1980**, 422-423. (c) idem. *J. Chem. Soc. Perkin Trans. 1* **1982**, 1941-1945.

7. Jensen, K. A.; Anthoni, U.; Holm, A. *Acta Chem. Scand.* **1969**, *23*, 1916-1934.

8. Caron, G.; Lessard, J. *Tetrahedron* **1993**, *49*, 8039-8058, and references there cited.

9. (a) Balci, M.; Sutbeyaz, Y.; Seçen, H. *Tetrahedron* **1990**, *46*, 3715-3742. (b) Posternak, T. *The Cyclitols* Holden-Day Inc.: San Francisco, 1965. (c) Trost, B. M.; Van Vranken, D. L., *J. Am. Chem. Soc.* **1993**, *115*, 444-458, and references therein.

(*Received in France* 30 *August* 1995; *accepted* 4 *October* 1995)