Pergamon

Tetrahedron Letters 40 (1999) 4531–4534

TETRAHEDRON
LETTERS

A New Method for the Generation and Capture of Iminyl Radicals

Jean Boivin,[a] Anne-Marie Schiano,[a] Samir Z. Zard,[a,b]*# and Haiwen Zhang[b]

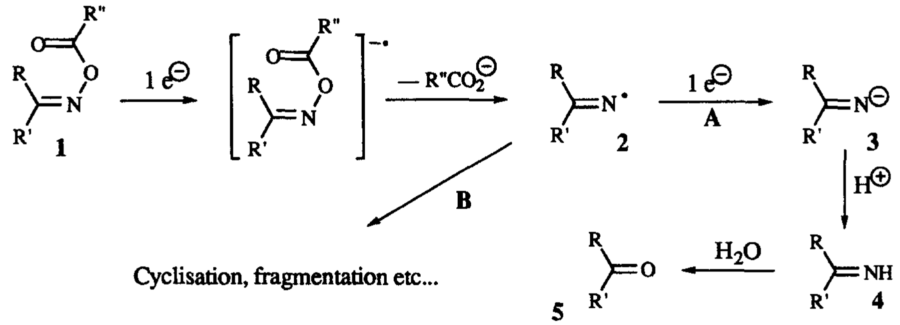
a) Laboratoire de Synthèse Organique associé au CNRS
Ecole Polytechnique, 91128 Palaiseau, France

b) Institut de Chimie des Substances Naturelles, C. N. R. S.,
91198 Gif-Sur-Yvette, France

Received 29 March 1999; accepted 7 April 1999

Abstract : Iminyl radicals can be generated from ketoxime esters and captured by an internal olefin; the sequence may be terminated in a variety of ways depending on the nature of the ensuing carbon radical and the added external trap. © 1999 Elsevier Science Ltd. All rights reserved.

The synthetic potential of iminyl radicals has hardly been exploited by organic chemists partly because of their reputation as rather stabilised and unreactive, but mostly because of a lack of convenient methods for generating them.[1] We have, over the past few years, described several new processes for creating these species (and nitrogen centered radicals in general) and shown that, in contrast to previous claims, they were endowed with sufficient reactivity to undergo many useful transformations.[2] Recent kinetic measurements performed by Newcomb and his co-workers have revealed that iminyl radicals undergo 5-*exo*-cyclisations about one order of magnitude slower than a saturated carbon radical.[3]



Scheme 1

It is possible to generate iminyls by cleaving the N—O bond in oxime esters using stannyl radicals, produced by the usual stannane methodology.[2,4] Another route is to cleave the same weak bond by a single electron transfer as outlined in Scheme 1. The radical anion thus created rapidly collapses into a carboxylate anion and iminyl radical **2** which can undergo further electron transfer to the level of anion **3** (path A). Most reducing agents (usually metals or low valent metal salts) deliver the two electrons too rapidly to allow useful capture of the intermediate radical **2**. What is therefore observed is chemistry derived from iminyl anion **3**: protonation and hydrolysis in a wet medium provides ketone **5**,[5] whereas under anhydrous conditions imine

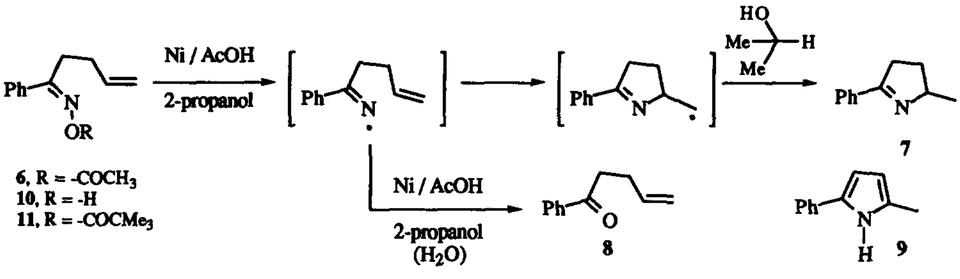
---

#*Fax: +33 (0)1 69 33 30 10; e-mail : sam.zard@icsn.cnrs-gif.fr*

0040-4039/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(99)00720-0

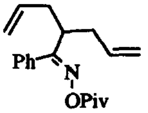
4 can be acylated to give enamides;[6] if the reducing system is sufficiently powerful, further reduction to the amine can take place.[5a,7] We have found in contrast that if *plain* nickel powder, in conjunction with a weak carboxylic acid, is used as the reducing agent, then the second formal electron transfer is slow enough to allow a radical process to intervene. In this way, 13-*epi*-17-ketosteroids were prepared by opening and closing ring D *via* the corresponding 17-iminyl radical.[8] We have now found that under these conditions, the intermediate iminyl radicals are sufficiently long-lived to add to an internal olefin in a 5-*exo* mode, providing a convenient, versatile route to various dihydropyrroles.

Heating oxime acetate **6** with nickel powder and acetic acid in isopropanol gave pyrrolenine **7** in good yield (67 %). The isopropanol acts as the source of hydrogen atom for the primary carbon radical resulting from the cyclisation step. In addition, a small amount of ketone **8** (2%), arising from premature reduction of the iminyl radical (cf. path A in Scheme 1), as well as pyrrole **9** (3%) and oxime **10** (8%), were isolated. The oxime is almost certainly produced by hydrolysis (or alcoholysis) of the starting oxime acetate. The formation of the oxime could be avoided and a slightly better yield of **7** (82%) secured by using the more robust pivalate **11**. These preliminary results are summarised in Scheme 2.

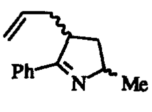


Scheme 2

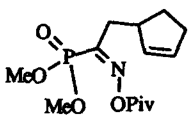
This process was successfully applied to more functionalised substrates as illustrated by the three examples displayed below (Piv = -COCMe$_3$). The obtention of the highly complex cyclisation product **17** is noteworthy. Precursor **16** is easily derived from thevinone, the Diels-Alder product of thebain and methyl vinyl ketone.[9]



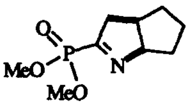
12



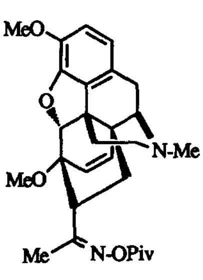
13 (60%) (*trans:cis* 4:1)



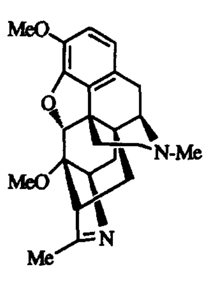
14



15 (53%)

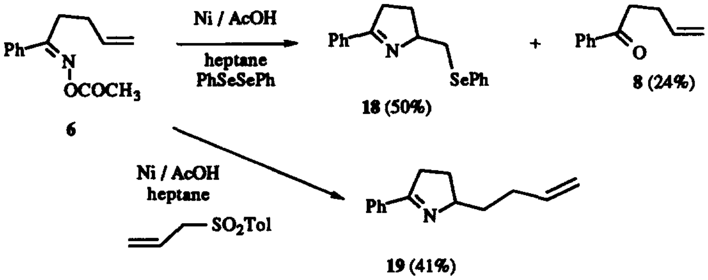


16

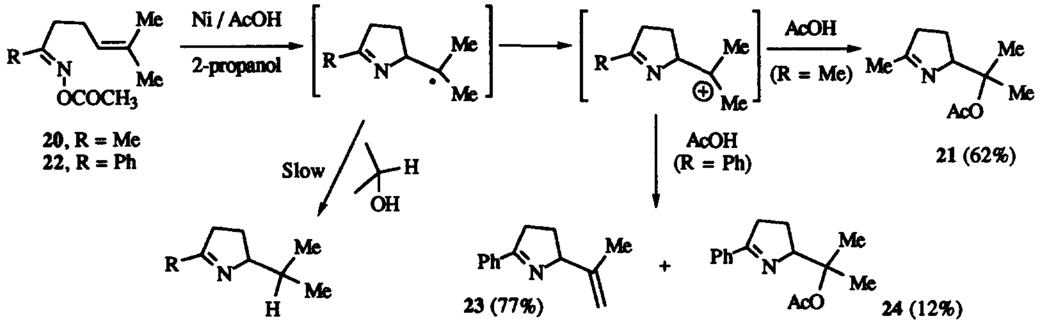


17 (52%)

Hydrogen transfer is not the only way of terminating the sequence. If the reduction is performed in the presence of diphenyl diselenide, transfer of a phenyl seleno group takes place. Using this modification, selenide **18** was prepared from oxime **6** in 50 % yield. Under these conditions, a more significant amount of ketone **8** (24%) was produced. The cause for this is not clear at the moment but could be due to the formation of a small amount of benzeneselenol (by reduction of the diselenide) which quenches the iminyl radical before it cyclises.[10] Another variation is to carry out the reduction in the presence of an allyl transfer agent such as allyl tolyl sulfone.[11] The carbon-nitrogen bond formation is now followed by the creation of a new carbon-carbon bond leading to **19** (41 %). In this case too, a similar amount of ketone **8** (24%) was isolated, perhaps due to the intervention of toluenesulfinic acid, the co-product in the allylation step. The elongation of the side chain in such a simple manner is noteworthy and could certainly be exploited for the construction of bicyclic structures found in indolizidine alkaloids.

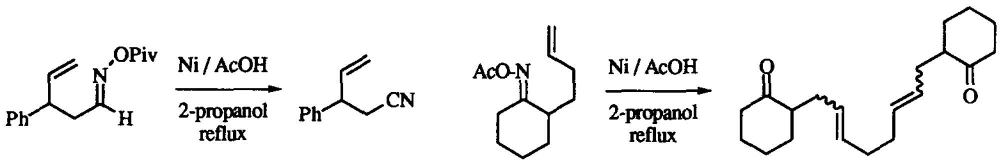


In all of the preceeding examples, the carbon radical ensuing from the cylisation is either primary or secondary. When we applied the iminyl cyclisation to a case where a tertiary carbon radical is formed, we were surprised to find that the reaction took another course. Instead of reduction by hydrogen transfer from 2-propanol, an oxidation occurred as illustrated by the conversion of compound **20** into acetate **21** (Scheme 3). Starting from oxime acetate **22**, the major product was olefin **23** (77%), whereas the expected acetate **24** (12%) turned out to be the minor product. Hydrogen abstraction from 2-propanol by the tertiary radical is perhaps too slow. Electron transfer to the oxime ester eventually leads to the formation of a cation equivalent which, depending of the structure of the substrate and exact experimental conditions, is quenched by acetic acid to give the tertiary ester and / or looses a proton to form the olefin. These are still speculations at this stage, even though some evidence may be found in the literature for electron transfer from a phenolate to oxime derivatives.[12] Further work is under way aimed at clarifying the mechanistic picture.



Scheme 3

Two limitations have emerged from this preliminary study. The first is that esters of aldoximes undergo elimination to give a nitrile under the normal reaction conditions. This is illustrated by the efficient conversion of pivalate **25** into nitrile **26** (Scheme 4). The second is our failure to construct a six-membered ring in a simple case: the reaction of oxime **27** was not very clean and, from the complex mixture, we isolated what appears to be dimer **28** in poor yield (NMR and GC-MS). This compound arises presumably from an internal allylic hydrogen abstraction followed by coupling of the ensuing allylic radicals. This limitation is inherent to the reactivity of the iminyl radical and not to the method itself.



25 **26** (81%) **27** **28** (15%)

Scheme 4

Despite the above shortcomings, this approach to iminyl radicals offers simplicity, mildness, and flexibility in terms of the way the radical sequence is terminated. It is also cheap and uses readily available precursors. Finally, the experimental procedure is particularly straightforward.[13] As for the mechanistic aspects, many questions still need to be answered but at least the intermediacy of iminyls has been established by the nature of the products obtained.

References and notes:

1. For a recent review, see: Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543-17594.
2. For a brief review of our work, see: Zard, S. Z. *Synlett* **1996**, 1148-1155.
3. Le Tadic-Biadatti, M.-H.; Callier-Dublanchet, A.-C.; Horner, J. H.; Quiclet-Sire, B.; Zard, S. Z.; Newcomb, M. *J. Org. Chem.* **1997**, *62*, 559-577.
4. (a) Boivin, J.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron Letters* **1994**, *35*, 249-252. (b) Boivin, J.; Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 6517-6528.
5. (a) Ho, T.-L *Synthesis* **1979**, 1-20. (b) Hanson, J. *Synthesis* **1974**, 1-8. (c) Corey, E. J.; Richman, J. E. *J. Am. Chem. Soc.* **1970**, *92*, 5276-5277 (d) Hanson, J.; Premuzic, E. *Angew. Chem. Internat. Ed. Engl.* **1968**, *7*, 247-252. (e) Timms, G. H.; Wildsmith, E. *Tetrahedron Lett.* **1971**, 191-194.
6. (a) Boar, R. B.; McGhie, J. F.; Robinson, M.; Barton, D. H. R.; Horwell, D. C.; Stick, D. C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1237-1241. (b) Boar, R. B.; McGhie, J. F.; Robinson, M.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1242-1244. (c) Barton, D. H. R.; Zard, S. Z. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2191-2192. (d) D. H. R. Barton, T. Bowles, S. Husinec, J. E. Forbes, A. E. A. Porter, S. Z. Zard, *Tetrahedron Lett.* **1988**, *29*, 3343-3346. (e) Laso, N. M.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 1605-1608.
7. Wagner-Jauregg, T.; Roth, M. *Helv. Chim. Acta* **1962**, *45*, 771-774.
8. Boivin, J.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron Letters* **1992**, *33*, 7849-7852.
9. Bentley, K. W.; Hardy, D. G. *J. Am. Chem. Soc.* **1967**, *89*, 3267-3273.
10. Crich, D.; Yao, Q. *J. Org. Chem.* **1995**, *60*, 84-88.
11. (a) Bertrand, M. *Org. Prep. Proc. Int.* **1994**, *26*, 257-290. (b) Pontén, F.; Magnusson, G. *J. Org. Chem.* **1996**, *61*, 7463-7466. (c) Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **1996**, *118*, 1209-1210. (d) Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 2864-2867. (e) Le Guyader, F.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *J. Am. Chem. Soc.* **1997**, *119*, 7410-7411 and references there cited.
12. Uchiyama, K.; Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1998**, 1261-1262.
13. Typical experimental procedure: a solution of oxime ester (1 mmole) in 2-propanol is added over one hour to a refluxing suspension of nickel powder (1.9g; 30eq.) in a mixture of 2-propanol (7.7 ml) and acetic acid (3.3 ml). Refluxing under an inert atmosphere was continued until thin layer chromatograghic analysis indicated essentially complete reaction (2-3 hours). For the synthesis of compounds **18** and **19**, diphenyl diselenide (2 eq.) and allyl tolylsulfone (10 eq.) were respectively added with the nickel at the beginning of the experiment. The reaction mixture was then filtered through Celite, diluted with water (20ml), neutralised with sodium bicarbonate, and finally extracted with ether. The organic layer was dried, concentrated, and the residue purified by flash chromatography. Compounds **7**, **15**, **17** were identical to authentic samples prepared previously by another route to iminyl radicals (ref. 4). Compound **21** is known in the literature (Gawley, R. E.; Termine, E. J.; Onan, K. D. *J. Chem. Soc., Chem. Commun.* **1981**, 568-569); as for the others (**13**, **18**, **19**, **23**, **24**, **26**), their relatively simple structure was easily established by the usual spectroscopic techniques and gave correct microanalyses or high resolution MS.