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A New Method for the Generation and Cyclization of Iminyl Radicals via the Hudson Reaction

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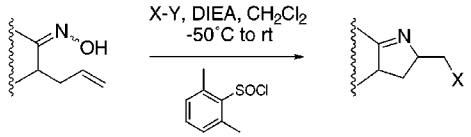
ABSTRACT



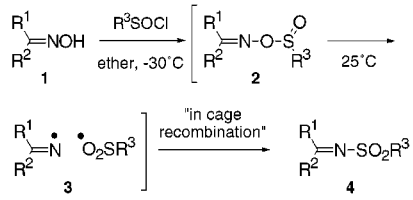
X-Y = Ph_2Se_2, Ph_2S_2, tempo, 1,4-cyclohexadiene

A mild new synthetic procedure has been developed for in situ generation and cyclization of iminyl radicals onto pendant alkenes, followed by functionalization of the resulting carbon radical by one of a variety of trapping reagents. The key process in the method involves production of the iminyl radical via treatment of an aldoxime or ketoxime with readily available 2,6-dimethylbenzenesulfinyl chloride at −50 °C to room temperature (Hudson reaction).

During the past several years, cyclizations of various types of nitrogen-based radicals onto pendant olefins have been recognized as a powerful method for construction of nitrogen heterocycles.[1,2] Iminyl radicals are especially useful in this regard since the cyclization products are functionally disposed for further elaboration into a variety of useful systems. In particular, Zard and co-workers have pioneered in the development of methodology for the generation and cyclization of iminyl radicals.[3,4]

In 1978, Hudson and co-workers described a general method for the mild generation of *N*-sulfonylimines **4** from ketoximes **1** and arylsulfinyl chlorides (Scheme 1).[5−7] Convincing evidence has been provided by EPR experiments

Scheme 1



that this transformation occurs via the homolytic fragmentation−recombination mechanism shown in the scheme, involving initial formation of a transient sulfinate ester **2**, which upon warming to room temperature leads to the "caged" diradical **3**. We were intrigued that an iminyl radical is postulated as an intermediate in this process and considered

(1) For an excellent review of nitrogen radicals, see: Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543.
(2) See also: Bowman, W. R.; Broadhurst, M. J.; Coghlan, D. R.; Lewis, K. A. *Tetrahedron Lett.* **1997**, *38*, 6301.
(3) (a) Boivin, J.; Fouquet, E.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron* **1994**, *50*, 1769. (b) Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1995**, *36*, 8791. (c) Boivin, J.; Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 6517. (d) 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. (e) Boivin, J.; Schiano, A.-M.; Zard, S. Z.; Zhang, H. *Tetrahedron Lett.* **1999**, *40*, 4531.
(4) See also: El Kaim, L.; Meyer, C. *J. Org. Chem.* **1996**, *61*, 1556.
(5) Brown, C.; Hudson, R. F.; Record, K. A. F. *J. Chem. Soc., Perkin Trans. 2* **1978**, 822.
(6) For related processes, see: (a) Bleeker, I. P.; Engberts, J. B. F. N. *Recl.: J. R. Neth. Chem. Soc.* **1979**, 121. (b) Bouma, W. J.; Engberts, J. B. F. N. *J. Org. Chem.* **1976**, *41*, 143. (c) Hovius, K.; Engberts, J. B. F. N. *Tetrahedron Lett.* **1972**, *13*, 181.
(7) For a comprehensive review of *N*-sulfonylimines, see: Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131.

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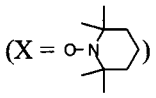
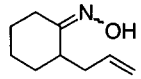
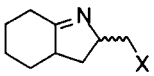
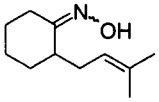
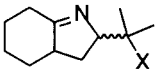
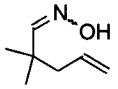
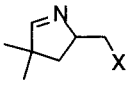
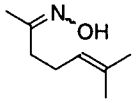
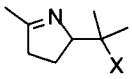
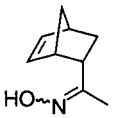
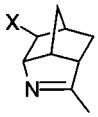
Table 1. Radical Cyclizations of Oxime Olefins Using 2,6-Dimethylbenzenesulfinyl Chloride[a,b]

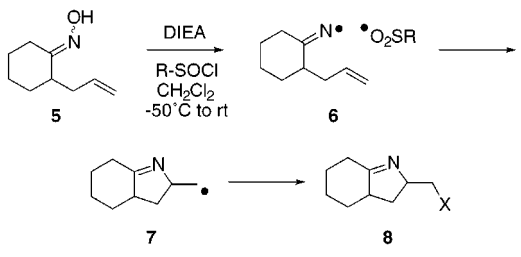
			Radical Traps			
			TEMPO (X = )	PhSeSePh (X = SePh)	PhSSPh (X = SPh)	(X = H)
Starting Oxime		Product				
	**5**		**8a** (61%)	**8b** (61%)	**8c** (70%)	
	**9**		**10a** (62%)	**10b** (65%)	**10c** (75%)	**10d** (60%)
	**11**		--[c]	**12b** (49%)	**12c** (56%)	
	**13**		**14a** (49%)	**14b** (51%)	**14c** (60%)	
	**15**		**16a** (58%)	**16b** (55%)	**16c** (67%)	

a) Standard reaction conditions: to a solution of the oxime (0.3 mmol) and radical trap (TEMPO: 0.45 mmol, diphenyl diselenide: 0.6 mmol, diphenyl disulfide: 6 mmol or cyclohexadiene: 30 mmol) in methylene chloride (7.5 mL) at -50°C were added successively *N,N*-diisopropylethylamine (0.6 mmol) and 2,6-dimethylbenzenesulfinyl chloride (0.6 mmol). The mixture was warmed slowly to rt, and then stirred for 5 h. The resulting solution was concentrated and the cyclization product was isolated by flash chromatography; b) Compounds **8** and **10** were mixtures of stereoisomers which were not separated; c) Inexplicably, no cyclization product could be isolated in this case.

the possibility that the Hudson reaction might provide a synthetically useful source of such radicals for intramolecular cyclizations onto olefins.

For our initial exploratory work in this area, 2-allylcyclohexanone oxime (**5**) was chosen as the substrate. Treatment of this compound with *p*-toluenesulfinyl chloride[8] as described by Hudson indeed led to some of the desired bicyclic sulfone imine **8a**, but only in low yield (Scheme 2).[9] In the presence of diphenyl diselenide as a trapping agent, a similarly poor yield of selenide cyclization product **8b** was produced. It appeared most likely that recombination of the diradical **6** to the corresponding *N*-sulfonylimine was responsible for the low yields of the desired cyclization products. Although we could in fact detect by TLC what we believed to be the *N*-tosylimine derived from oxime **5**, it was too hydrolytically unstable to be isolated.

Scheme 2



a: R = *p*-tol	X = Ts	19%
b: R = *p*-tol/Ph_2Se_2	X = SePh	22%
c: R = Bn/Ph_2Se_2	"	41%
d: R = cinnamyl/Ph_2Se_2	"	27%
e: R = *t*-Bu/Ph_2Se_2	"	47%
f: R = 2,6-dimethylphenyl/Ph_2Se_2	"	61%
g: R = 2,4,6-triisopropylphenyl/Ph_2Se_2	"	23%

We thus reasoned that if we could suppress recombination of diradical **6**, it should be possible to intercept the iminyl radical more efficiently to produce the requisite bicyclic radical **7**.

Two different strategies toward solving this problem have been explored which are based upon the sulfinyl chloride reagent. Therefore, reagents that lead to unstable sulfonyl radicals (i.e. radicals which can rapidly lose SO_2[10]) and preclude recombination (cf. entries c−e, Scheme 2) were investigated, and/or more hindered sulfinyl chlorides were utilized to slow the recombination step by steric effects (cf. entries e−g, Scheme 2).

Thus, replacing *p*-toluenesulfinyl chloride with the benzyl derivative led to a significantly improved yield of the bicyclic seleno imine (cf. **8c**). It was found that benzyl phenyl selenide was also produced in this reaction in about 24%

(8) Kurzer, F. *Organic Syntheses*; Wiley: New York; Collect. Vol. IV, 1967; p 937.

(9) In all cases, cyclization products **8** were ~3:2 mixtures of stereoisomers which were not separated.

(10) See: Bertrand, M. P. *Org. Prep. Proc. Int.* **1994**, *26*, 257, and references cited.

yield based on oxime, thereby supporting the presumption that loss of sulfur dioxide is of significance. Similarly, *tert*-butylsulfinyl chloride[11] gave an even higher yield of cyclization product along with some *tert*-butyl phenyl selenide (~14%). This latter system may work by a combination of the loss of SO_2 from the intermediate *tert*-butylsulfonyl radical and steric effects. It might be noted that in the cases involving alkylsulfinyl chlorides, only 1 equiv could be used since excess reagent destroys the imine product.

With hindered arylsulfinyl chlorides, the best yield of **8** (61%) was obtained using 2,6-dimethylbenzenesulfinyl chloride, which was easily synthesized in two steps from the corresponding commercially available aryl Grignard reagent (see Supporting Information).[12] It is also possible to use this arylsulfinyl chloride in excess in order to improve the yields of cyclization products. With the hindered triisopropylbenzenesulfinyl derivative, the yield of cyclization product **8** was low, probably reflecting the difficulty in the initial *O*-sulfinylation of the oxime. Therefore, 2,6-dimethylbenzenesulfinyl chloride was used for all further investigations.

Using this sulfinylating reagent, a variety of ketoximes and aldoximes were successfully cyclized to afford the desired imines in yields ranging from 49 to 75% (Table 1). To demonstrate the functional group versatility of the methodology, four different radical traps were explored in these reactions, including diphenyl diselenide, TEMPO, diphenyl disulfide, and 1,4-cyclohexadiene. It is noteworthy that the use of a less reactive radical scavenger must be compensated for by increasing its concentration (from 0.06 M with TEMPO ($k_{\text{termination}} \approx 10^9$ M^{-1} s^{-1})[13] to 2.9 M with cyclohexadiene ($k_{\text{termination}} \approx 6 \times 10^4$ M^{-1} s^{-1})[14]).[15] If the concentration of the less efficient trapping agents is not increased, a variety of unidentified side products are produced.

Noteworthy is the fact that 1,4-cyclohexadiene can be used as a source of a hydrogen atom, thus avoiding the use of toxic tributylstannane, along with the usual problems associated with removal of tin residues.

It is important to note that the reaction conditions employed here are exceptionally mild compared to many of the other current methods for the production and cyclization of iminyl radicals. In addition, radical traps can be used which lead to more highly functionalized products than those produced by tin hydride-induced processes. Thus, we have proven that it is possible to easily incorporate an oxygen-, selenium-, or sulfur-based substituent in the termination step. Indeed, one of the appealing features of this chemistry is the range of synthetically useful postcyclization manipulations that are potentially available from the various product imines.

In conclusion, we have demonstrated the utility of the Hudson reaction for the generation and cyclization of iminyl radicals generated at room temperature from olefinic oximes and 2,6-dimethylbenzenesulfinyl chloride. Further variations and synthetic applications of this new methodology will be reported in due course.

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Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990720E

(11) Richey, H. G., Jr.; Farkas, J., Jr. *J. Org. Chem.* **1987**, *52*, 479.

(12) 2,6-Dimethylbenzenesulfinyl chloride has been synthesized previously by a less convenient procedure: Cevasco, G.; Novi, M.; Petrillo, G.; Thea, S. *Gazz. Chim. Ital.* **1990**, *120*, 131.

(13) Rate constants are at room temperature: Claridge, R. F. C., Ed. *Landolt Bórnstein, New Series II, Vol. 18-A*; Springer-Verlag: Berlin, 1994; p 57.

(14) Claridge, R. F. C., Ed. *Landolt Bórnstein, New Series II, Vol. 18-A*; Springer-Verlag: Berlin, 1994; p 4.

(15) For the rate constants of radical trapping with diphenyl diselenide and diphenyl disulfide, see: Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.