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A mild new procedure for production, cyclization and trapping of amidyl radicals: application to a formal total synthesis of peduncularine

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Abstract

Treatment of an olefinic hydroxamic acid with *tert*-butylsulfinyl chloride and Hunig's base from −50°C to room temperature in the presence of a radical trap such as diphenyl diselenide, diphenyl disulfide or TEMPO affords a functionalized product derived from an amidyl radical cyclization. The methodology has been used in a formal total synthesis of the 6-azabicyclo[3.2.1]octane-containing indole alkaloid peduncularine.

Keywords: cyclization; radicals and radical reactions; nitrogen heterocycles; hydroxamic acids and derivatives; alkaloids.

Recent work from these laboratories has demonstrated that iminyl radicals **2** generated from an oxime **1** and a sulfinyl chloride (Hudson reaction) can be intercepted intramolecularly by a pendant olefin to produce an intermediate cyclization product such as **3**, which can then be trapped in situ by a number of reagents to afford a functionalized imine **4** (Scheme 1).[1,2] It was found that the key to making this process synthetically useful is to slow the recombination of the caged radical pair **2** to the corresponding *N*-sulfonylimine.[3] We discovered that the most effective way to minimize this problem is to use a bulky sulfinyl compound, and it proved that 2,6-dimethylphenylsulfinyl chloride was the optimum reagent to effect the chemistry in Scheme 1.

In order to extend the scope of the methodology, we considered the possibility of applying this same strategy to the formation and cyclization of other types of nitrogen-centered radicals.[2] In fact, in a series of papers Engberts et al.[4] have convincingly demonstrated that upon treatment with *tert*-butylsulfinyl chloride *N*-hydroxyureas and *N*-hydroxycarbamates do indeed form the corresponding *N*-sulfonylureas and carbamates, respectively, via a mechanism involving nitrogen radicals. Subsequently, using CIDNP and isotope labelling methods, Heesing et al.[5] showed that hydroxamic acids produce amidyl radicals on exposure to sulfinyl chlorides. Further mechanistic studies by Hudson and Banks[6] confirmed this observation. Since there was good precedent for the desired transformation, we therefore focused on

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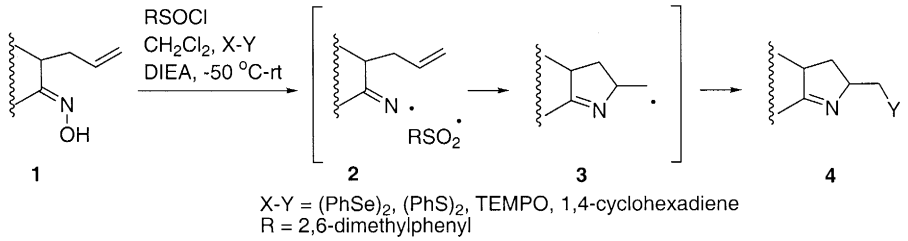
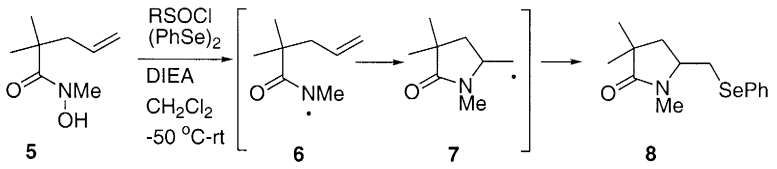


Scheme 1.

developing a synthetically viable method for producing amidyl radicals from hydroxamic acids via this chemistry, and we now report some of our preliminary results.[7,8]

Initial feasibility studies were carried out with hydroxamic acid **5** using diphenyl diselenide as the radical trap under the reaction conditions shown in Scheme 2. It was found that 2,6-dimethylphenylsulfinyl chloride and 2,4,6-triisopropylsulfinyl chloride produced only mediocre yields of the desired cyclization product **8**. With benzylsulfinyl chloride the yield of lactam selenide **8** improved somewhat. However, the best yield of the cyclization product (64%) could be obtained with readily available *tert*-butylsulfinyl chloride.[9,10] Careful isolation of the other products of this reaction also indicated the presence of small amounts of the uncyclized *N*-*tert*-butylsulfonylamide (14%) derived from radical pair recombination, the secondary amide resulting from hydrogen abstraction by intermediate amidyl radical **6** (6%), probably from solvent, and 10% of the starting hydroxamic acid **5**. The reaction can also be successfully run with diphenyl disulfide or TEMPO as the trapping agent to give other functionalized lactam analogs of **8** as shown in Table 1. Moreover, the reaction has been applied to the additional hydroxamic acid substrates listed in Table 1 to give good to moderate yields of cyclization products.

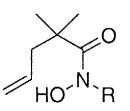
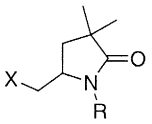
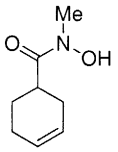
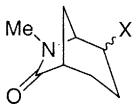
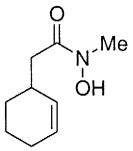
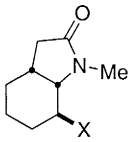
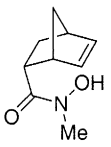
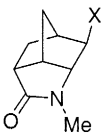


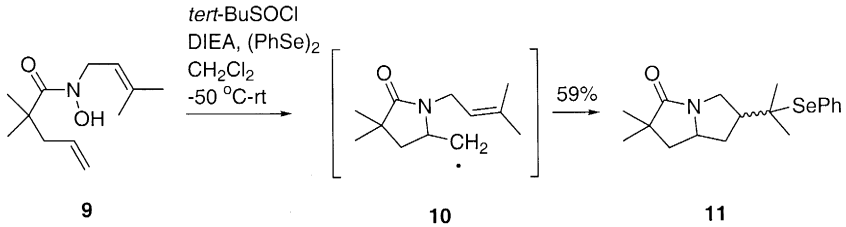
Scheme 2.

We have found that it is also possible to effect tandem amidyl radical cyclizations using this methodology. Thus, when hydroxamic acid **9** is treated with *tert*-butylsulfinyl chloride and diphenyl diselenide under our standard conditions,[10] pyrrolizidinone **11** is formed (~2:1 mixture of diastereomers), presumably via intermediate radical **10** (Scheme 3).[11]

The methodology has also been applied to a formal total synthesis of peduncularine (**18**), a major alkaloid from the Tasmanian shrub *Aristotelia peduncularis*.[12] To date, two syntheses of this interesting indole alkaloid have appeared.[13] It was our intention to use the amidyl radical cyclization strategy in a short, direct approach to the interesting 6-azabicyclo[3.2.1]octane array of this molecule. It was possible to effect a Diels–Alder reaction of acrylate-derived hydroxamic acid dienophile **13** with commercially available 1-methoxybutadiene **12** under high pressure (12 Kbar) to afford cycloadduct **14** (Scheme 4). Exposure of hydroxamic acid **14** to *tert*-butylsulfinyl chloride/diphenyl diselenide under the usual conditions led to the desired azabicyclooctane system **15** (30%) as a single diastereomer (probably the *exo* selenide). Oxidation of this selenide with hydrogen peroxide then afforded the requisite alkene **16**

Table 1
Radical cyclizations of hydroxyamic acids using *tert*-butylsulfinyl chloride[10]

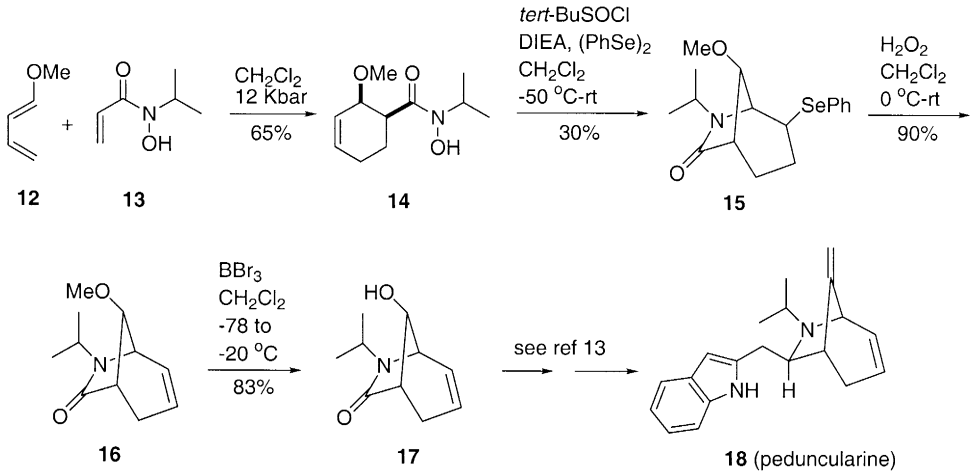
Starting Material	Product(s)	X = SePh	X = SPh	X = O–N
		R = Me 64%	58%	60%
		R = Bn 70%	74%	78%
		58%	61%	57%
		59%	56%	56%
		65%	64%	62%



Scheme 3.

in high yield.[14] Finally, mild cleavage of the methyl ether group of **16** with boron tribromide led to the known bicyclic lactam alcohol **17**, which has previously been converted to peduncularine **18**.[13a] Despite the modest yield in the amidyl radical cyclization step, we believe this route to the alkaloid is competitive with the others due to the simplicity and conciseness of the synthetic sequence.

In summary, we have devised efficient methodology to generate and cyclize amidyl radicals formed from a variety of hydroxamic acids under mild reaction conditions (−50°C to room temperature). The procedure also leads to cyclization products which are highly functionalized, and thus more amenable



Scheme 4.

to further manipulation than those produced by the more common tributylstannane-mediated methods.[2,7] Work is currently in progress to refine and extend this chemistry.

Acknowledgements

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7. For some recent notable examples of generating amidyl radicals from hydroxamic acid derivatives, see: (a) Boivin, J.; Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 6517. (b) Clark, A. J.; Filik, R. P.; Peacock, J. L.; Thomas, G. H. *Synlett.* **1999**, 441. (c) Clark, A. J.; Deeth, R. J.; Samuel, C. J.; Wongtap, H. *Synlett.* **1999**, 444, and references cited therein.
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10. General procedure for amidyl radical cyclizations: To a solution of the hydroxamic acid (0.3 mmol) and the radical trap (TEMPO: 0.45 mmol; diphenyl diselenide: 0.6 mmol; diphenyl disulfide: 12 mmol) in methylene chloride (15 mL) at

−50°C was added *N*,*N*-diisopropylethylamine (0.75 mmol) and *tert*-butylsulfinyl chloride (0.45 mmol). The mixture was then warmed slowly to room temperature, and stirred for about 5 h. The solution was concentrated and the residue was purified by flash column chromatography on silica gel (hexanes:ethyl acetate, 80:20–50:50) to give the cyclization product.

11. For another example of a tandem amidyl radical cyclization see Ref. 7a.
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