JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
COMMUNICATION
pubs.acs.org/JACS

An Oxidative [2,3]-Sigmatropic Rearrangement of Allylic Hydrazides

Benjamin F. Strick, Devon A. Mundal, and Regan J. Thomson*

Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208, United States

S *Supporting Information*

ABSTRACT: The development of an efficient oxidative [2,3]-sigmatropic rearrangement of allylic hydrazides, via singlet *N*-nitrene intermediates, is reported. The requisite allylic hydrazide precursors are readily prepared and undergo smooth sigmatropic rearrangement upon exposure to iodosobenzene. The products of this novel transformation are shown to be useful precursors to a variety of compounds.

Hydrazine and hydrazine derivatives have proven to be useful reagents for a number of synthetically valuable transformations for at least a century. For example, hydrazine is widely employed in carbonyl deletions (Wolff–Kishner reduction, 1911),[1] and arylhydrazines are critical components in the venerable Fisher indole synthesis (1883).[2] Our interest in hydrazine derivatives stemmed from an exploration of [3,3]-sigmatropic rearrangements of *N*-allylhydrazones,[3] which has led to several useful carbon–carbon bond-forming transformations.[4] During the course of developing these reactions we prepared allylic hydrazides (i.e., **1**) as the precursors for condensation to the requisite hydrazones. Upon reflection, it occurred to us that such hydrazides might be useful precursors for a [2,3]-sigmatropic rearrangement (Figure 1). Thus, we anticipated that oxidation of hydrazide **1** would produce an intermediate nitrene (or related species) that would deliver the tertiary diazene **3** after sigmatropic bond reorganization.

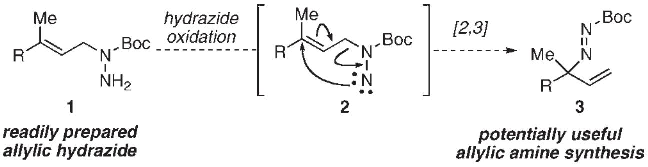


Figure 1. Oxidative [2,3]-sigmatropic rearrangement.

A related mercuric oxide-mediated sigmatropic rearrangement of alkyl and aryl substituted allylic hydrazines was reported by Baldwin and co-workers in 1971,[5] but has received little synthetic attention, probably due in large part to difficulties in substrate preparation and product manipulation. We viewed hydrazides such as **1** as ideal candidates for developing a synthetically useful variant of this underexplored sigmatropic rearrangement. They are readily prepared in two steps from the corresponding allylic alcohols or halides,[6] and moreover, the products of this rearrangement should be easily purified and lend themselves well to further transformations. In this communication, we detail the successful development of this new *N*-nitrene-based sigmatropic rearrangement.[7]

From the outset we were cognizant that secondary diazene products derived from 1,2-disubstituted alkenes might be problematic due to potential tautomerization. After preliminary explorations confirmed this suspicion, we targeted substrates that would generate tertiary diazene products. Accordingly, we prepared allylic hydrazide **4a**[6] and surveyed the effect of various hypervalent iodide reagents on their ability to promote the desired sigmatropic rearrangement to diazene **5a** (Table 1).

Our initial choice of hypervalent iodides stemmed from the established precedent from the group of Che who reported the aminoaziridination of alkenes using $PhI(OAc)_2$ and *N*-aminophthalimide.[8] Hypervalent iodides had also been shown to be effective oxidants of various amino precursors that engage in nitrene-type reactivity.[9] Exposure of **4a** to a selection of commercially available oxidants quickly established the validity of our general proposal, with diazene **5a** being produced with varying degrees of success depending upon reaction conditions. For instance, Dess–Martin periodinane (DMP) produced **5a** in only 23% yield when the reaction was conducted in CH_2Cl_2 (Table 1, entry 1), but afforded an enhanced 54% yield when THF was used as the solvent (Table 1, entry 2). Ultimately, we found that iodosobenzene produced the cleanest reaction mixtures, allowing isolation of **5a** in 77% yield (Table 1, entry 6). Next, we explored the use of Cbz and Boc derivatives **4b** and **4c**, respectively. Both substrates behaved well, but the Boc-derived allylic hydrazide **4c** gave the corresponding diazene (i.e., **5c**) in a greater yield (Table 1, entry 8).

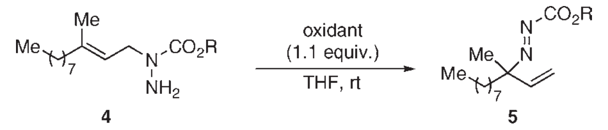
With suitable conditions established, we next explored the scope of substrates[6] that would participate in this new sigmatropic rearrangement (Table 2).

Byproduct of nitrogen extrusion from **6g**:

A range of acyclic allylic hydrazides (**6a**–**e**) produced the desired allylic diazene products (i.e., **7a**–**e**) in yields ranging from 77% to 88%. Cyclohexyl and phenyl substituted hydrazides **6f** and **6g**, respectively, afforded the corresponding diazenes **7f** and **7g** in good yield. We noted, however, that **7g** was produced along with a small quantity of ester **8** (see eq 1). We attributed formation of this byproduct to a favorable extrusion of nitrogen from **7g** to generate radical pair **I** and **II** that recombined at the less hindered end of the presumed allyl radical intermediate (**I**).[10,11] We also explored the use of branched secondary hydrazides and found that both **6h** (R_3 = Me) and **6i** (R_3 = *i*-Pr) afforded the corresponding diazenes **7h** and **7i** in excellent yield, as single alkene stereoisomers. Cyclic substrates **7k**–**m** preformed well under the reaction conditions in terms of chemical yield, but displayed variable levels of diastereoselectivity. For example, **7l** was generated as a 1:1 mixture of syn and

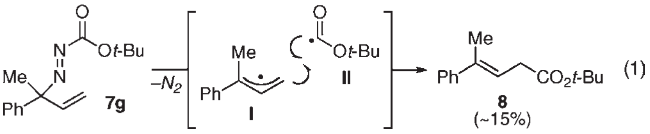
Received: July 15, 2011
Published: August 19, 2011

Table 1. Initial Development of [2,3]-Rearrangement[a]



entry	R	oxidant	time (h)	yield[c] 5 (%)
1[b]	Me (**4a**)	DMP	0.5	23 (**5a**)
2	Me (**4a**)	DMP	0.5	54 (**5a**)
3	Me (**4a**)	$PhI(OAc)_2$	24	48 (**5a**)
4	Me (**4a**)	$PhI(OTFA)_2$	4	0[d] (**5a**)
5	Me (**4a**)	$PhI(OPv)_2$	20	50 (**5a**)
6	Me (**4a**)	PhIO	2	77 (**5a**)
7	Bn (**4b**)	PhIO	2	75 (**5b**)
8	*t*-Bu(**4c**)	PhIO	2	86 (**5c**)

[a] Reactions conducted using **4** (0.16 mmol) in THF (0.2 M). [b] Reaction conducted in CH_2Cl_2. [c] Isolated yield after chromatography. [d] Rapid decomposition to multiple products.



anti stereoisomers, indicating there was no bias for equatorial bond formation as had been observed by Weinreb and coworkers in the [2,3]-sigmatropic rearrangement of the corresponding allylic sulfilimine.[12] On the other hand, α-substitution provided greater levels of stereocontrol, with the C–N bond forming opposite the adjacent substituent, as one would expect (i.e., **7m**).

To gain insight into the reaction mechanism we prepared hydrazide **9** and exposed it to iodosobenzene in the presence of either *cis*- or *trans*-stilbene. While not synthetically efficient, the aziridinations were stereospecific in nature. Under our reaction conditions for the [2,3]-rearrangement, hydrazide **9** produced only the *cis*-aziridine **11** when exposed to *cis*-stilbene (eq 2, path A) and only *trans*-aziridine **12** when exposed to *trans*-stilbene (eq 3, path B).[13] Although most nitrenes are ground-state triplets, the stereospecificity observed here provides evidence of a singlet nitrene intermediate.[14,15]

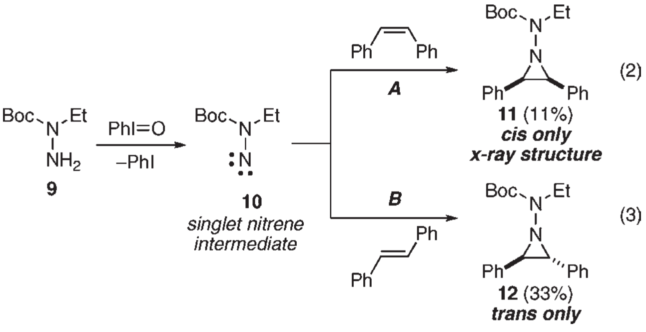
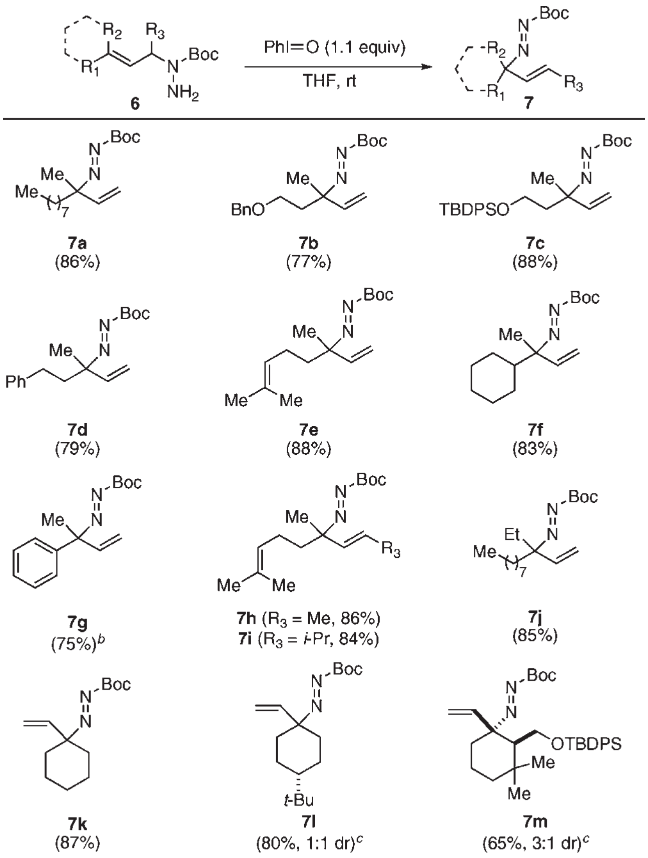


Table 2. Substrate Scope of Oxidative [2,3]-Rearrangement[a]



[a] Reactions conducted using **6** (0.5 mmol) in THF (0.2 M). Yields reported after chromatography. [b] Isolated as a 5:1 mixture of **7g** and ester **8** (see eq 1). [c] Diastereomer ratio determined by ^{1}H NMR spectroscopy.

We also conducted the reaction using enantioenriched hydrazide **6h** and observed complete stereochemical transfer to the product **7h** (Figure 2).[13] This result, in conjunction with our investigations using hydrazide **9**, supports a mechanism whereby oxidation of the allylic hydrazide with iodosobenzene produces a reactive singlet *N*-nitrene that undergoes a highly stereoselective [2,3]-sigmatropic shift. Presumably, reaction of hydrazide **6h** with iodosobenzene initially generates aminoiodinane **A**, which loses iodobenzene to produce the free singlet *N*-nitrene **B**. The barrier for loss of iodobenzene from **A** to form **B** is probably extremely low; the related decomposition of *N*-aminoiminoiodanes has been calculated to be activationless.[9d] The generation of **7h** as a single trans alkene isomer with complete stereochemical transfer implies that the transition state for the sigmatropic rearrangement places the methyl substituent in a pseudoequatorial disposition to minimize allylic strain, as shown by **B**.

The utility of the diazene products generated through this oxidative sigmatropic rearrangement is outlined in Scheme 1. Reduction of the diazene **7k** to the hydrazide **13** took place under mild conditions using Zn/AcOH (93%). Formation of acetamide **14** was achieved from diazene **7k** by initial reduction to hydrazide **13**, followed by Boc-cleavage and hydrogenolysis of the resultant crude hydrazine salt over PtO_2.[16] Acylation of the thus formed residue afforded acetamide **17** (78% yield from **7k**, one purification). Recognizing that the diazene N–N double bond is polarized, we showed that Grignard reagents add with complete regiocontrol to **7k** to yield substituted hydrazides **15** and **16** in excellent yield.[17] Application of this type of general transformation might be particularly useful for the generation of molecular libraries or as a fragment coupling reaction in total synthesis. Finally, we demonstrated that the thermal extrusion of nitrogen from **7k** proceeded

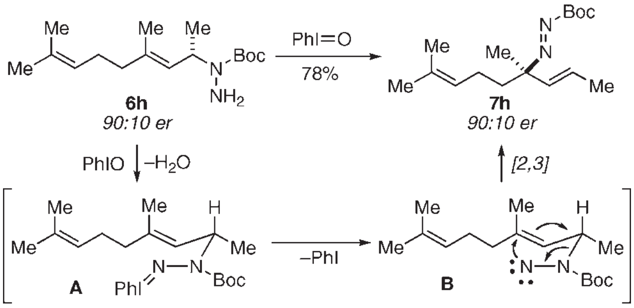
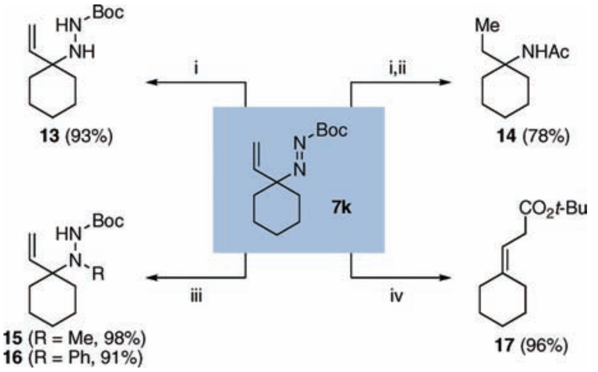


Figure 2. Plausible mechanism for oxidative rearrangement.

Scheme 1. Utility of Products from [2,3]-Rearrangement[a]



[a] Conditions: (i) Zn, AcOH; (ii) HCl, dioxanes; PtO_2, H_2; AcCl, Et_3N, DMAP; (iii) MeMgCl or PhMgCl, THF; (iv) toluene, reflux.

readily upon mild heating in toluene to afford β,γ-unsaturated ester **17** in 96% yield.

In summary, we have developed an efficient and high yielding oxidative [2,3]-sigmatropic rearrangement of allylic hydrazides, and demonstrated the utility of the diazene products obtained. Complete stereochemical transfer when an enantioenriched hydrazide was used provides a new method to access nonracemic tertiary carbinamine derivatives. In recent years there have been many significant advances in enantioselective nitrene-type transformations,[18] and although our oxidative [2,3]-rearrangement does not require transition-metal additives, it still seems reasonable to suggest that a catalytic enantioselective variant may be developed in the future.[19]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Detailed experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

r-thomson@northwestern.edu

■ ACKNOWLEDGMENT

We gratefully acknowledge support from the National Science Foundation (CHE0845063 and CHE0923236), Amgen Inc., Dow Chemical Company and Northwestern University. We thank Reed Larson (NU) for X-ray analysis of compound **11**.

■ REFERENCES

(1) Kishner, N. *J. Russ. Chem. Soc.* **1911**, *43*, 582. For a review, see:Hutchins, R. O. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8. For recent advances, see: Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 5436–5445.

(2) Fischer, E.; Jourdan, F. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241–2245.

(3) Stevens, R. V.; McEntire, E. E.; Barnett, W. E.; Wenkert, E. *J. Chem. Soc., Chem. Commun.* **1973**, 662–663.

(4) (a) Mundal, D. A.; Lee, J. J.; Thomson, R. J. *J. Am. Chem. Soc.* **2008**, *130*, 1148–1149. (b) Mundal, D. A.; Lutz, K. E.; Thomson, R. J. *Org. Lett.* **2009**, *11*, 465–468. (c) Mundal, D A.; Avetta, C. A., Jr.; Thomson, R. J. *Nat. Chem.* **2010**, *2*, 294–297. (d) Kutz, K. E.; Thomson, R. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 4437–4440.

(5) Baldwin, J. E.; Brown, J. E.; Höfle, G. *J. Am. Chem. Soc.* **1971**, *93*, 788–789. For related literature, see: (a) Ollis, W. D.; Sutherland, I. O.; Thebtaranonth, Y. *Chem. Commum.* **1970**, 1199–1200. (b) Bellamy, A. J.; Maclean, L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 204–210.

(6) The allylic hydrazides utilized in this study were synthesized using procedures originally reported by Jamart-Gregoire and coworkers, see: (a) Pinto, M. F.; Brosse, N.; Jamart-Gregoire, B. *Synth. Commun.* **2002**, *32*, 3603–3610. (b) Brosse, N.; Pinto, M. F.; Jamart-Grégoire, B. *Eur. J. Org. Chem.* **2003**, 4757–4764. (c) Brosse, N.; Pinto, M. F.; Jamart-Grégoire, B. *J. Org. Chem.* **2000**, *65*, 4370–4374. (d) Brosse, N.; Pinto, M. F.; Jamart-Grégoire, B. *Tetrahedron Lett.* **2000**, *41*, 205–207(full experimental details may be found in the Supporting Information and ref 4).

(7) This chemistry differs from the related [2,3]-sigmatropic rearrangements of imino-ylides commonly derived from allylic sulfides. For relevant examples of this type of reactivity, see: (a) Ash, A. S. F.; Challenger, F.; Greenwood, D. *J. Chem.Soc.* **1951**, 1877–1882. (b) Johnson, C. R.; Mori, K.; Nakanishi, A. *J. Org. Chem.* **1979**, *44*, 2065–2067. Schönberger, N.; Kresze, G. *Liebigs Ann. Chem.* **1975**, 1725–1731. (c) Sharpless, K. B.; Hori, T. *J. Org. Chem.* **1976**, *41*, 176–177. (d) Sharpless, K. B.; Hori, T.; Truesdale, L. K.; Dietrich, C. O. *J. Am. Chem. Soc.* **1976**, *98*, 269–271. (e) Bach, T.; Körber, C. *J. Org. Chem.* **2000**, *65*, 2358–2367.

(8) Li, J.; Liang, J.-L.; Chan, P. W. H.; Che, C.-M. *Tetrahedron Lett.* **2004**, *45*, 2685–2688.

(9) For leading references on the use of hypervalent iodides in nitrene-type reactions, see: (a) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233–2236. (b) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935–6936. (c) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598–600. (d) Richardson, R. D.; Desaize, M.; Wirth, T. *Chem.—Eur. J.* **2007**, *13*, 6745–6754. (e) Moriarty, R. M.; Tyagi, S. *Org. Lett.* **2009**, *12*, 364–366. (f) Zibinsky, M.; Stewart, T.; Surya Prakash, G. K.; Kuznetsov, M. A. *Eur. J. Org. Chem.* **2009**, *21*, 3635–3642.

(10) Similar reactions of related diazenes have been reported in the literature. For examples, see: (a) Wieland, H.; von Hove, H.; Borner, K. *Justus Liebigs Ann. Chem.* **1925**, *446*, 31–48. (b) Ford, M. C.; Rust, R. A. *J. Chem. Soc.* **1958**, 1297–1298. (c) Tsuji, T.; Kosower, E. M. *J. Am. Chem. Soc.* **1971**, *93*, 1992–1999. (d) Barton, D. H. R.; McCombie, S. W. *J. Chem Soc., Perkin Trans. 1* **1975**, 1574–1585.

(11) For a review on the decomposition of azoalkanes, see:Engel, P. S. *Chem. Rev.* **1980**, *80*, 99–150.

(12) Natsugari, H.; Turos, E.; Weinreb, S. M.; Cvetovich, R. J. *Heterocycles* **1987**, *25*, 19–24. For related studies of [2,3]-sigmatropic rearrangements forming carbon−carbon bonds, see: (a) G. Andrews, G.; Evans, D. A. *Tetrahedron Lett.* **1972**, 5121. (b) Mander, L. N.; Turner, J. V. *J. Org. Chem.* **1973**, *38*, 2915–2916. (c) Evans, D. A.; Sims, C. L.; Andrews, G. C. *J. Am. Chem. Soc.* **1977**, *99*, 5453–5461.

(13) Full experimental details may be found in the Supporting Information.

(14) Alkyl, aryl and carbonyl nitrenes are known to have triplet ground states, while *N*-aminonitrenes have singlet ground states, see: (a) Berry, R. S. In *Nitrenes*; Lwowski, W., Ed.; Interscience: New York,

NY, 1970; Chapter 2. (b) Lernal, D. M. In *Nitrenes*; Lwowski, W., Ed.; Interscience: New York, NY, 1970; Chapter 10.

(15) Singlet nitrenes were invoked to rationalize the stereospecificity of aziridination using *N*-aminophthalimide:Anderson, D. J.; Gilchrist, T. L.; Horwell, D. C.; Rees, C. W. *J. Chem. Soc. C* **1970**, 576–582.

(16) Errasti, G.; Koundé, C.; Mirguet, O.; Lecourt, T.; Micouin, L. *Org. Lett.* **2009**, *11*, 2912–2915.

(17) Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 897–900.

(18) For formative reviews on this topic, see: (a) Collet, F.; Lescot, C.; Dauban, P. *Chem. Soc. Rev.* **2011**, *40*, 1926–1936. (b) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905–2920. For recent examples, see: (c) Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 9220–9221. (d) Milczek, E.; Boudet, N.; Blakey, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6825–6828.

(19) A catalytic enantioselective variant of the [2,3]-Meisenheimer rearrangement, a reaction that proceeds thermally in the absence of a catalyst, was recently reported, see:Bao, H.; Qi, X.; Tambar, U. K. *J. Am. Chem. Soc.* **2011**, *133*, 1206–1208.