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Ketonitrones via Cope-Type Hydroamination of Allenes

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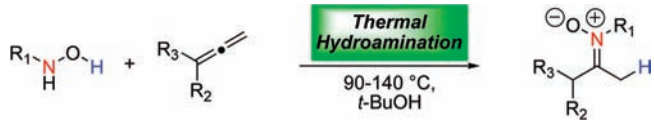
ABSTRACT



The synthesis of ketonitrones from *N*-alkylhydroxylamines and monosubstituted allenes is accomplished via a Cope-type hydroamination reaction in moderate to good yields. Allenes also undergo a similar reaction with aqueous hydroxylamine to give oximes in excellent yield. DFT calculations support a proposed concerted, five-membered hydroamination process, and calculated transition state energies are in excellent agreement with experimental observations.

Nitrones are highly useful intermediates in organic synthesis, and their reactivity has been studied extensively, particularly in the context of 1,3-dipolar cycloaddition chemistry.[1,2] The large bulk of this work focuses on aldonitrones, largely due to their ease of preparation via the condensation of an *N*-alkyhydroxylamine with an aldehyde. In contrast, the preparation of ketonitrones may not always be accomplished by simple condensation with a ketone, and occasional reports of synthetic routes to these compounds are typically of narrow scope and are rare for linear ketonitrones.[3] As such, the applications of ketonitrones as 1,3-dipoles and radical traps have been much less extensive than for their aldonitrone cousins.[2−4] Herein, we report a direct preparation of ketonitrones via an intermolecular Cope-type hydroamination reaction of *N*-alkylhydroxyalmines with allenes.[5]

The hydroamination reaction is a direct and atom-economical approach to the synthesis of nitrogen-containing molecules from unsaturated precursors.[6] The addition of amines to allenes has been particularly well studied because of the activated nature of their double bonds and their ability to give either imines or allylamines depending on the regiochemistry of the reaction.[7,8]

(1) (a) Grigor'ev, I. A. In *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; Feuer, H., Ed.; Wiley: Hoboken, 2008; Chapter 2. (b) Tufaniello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; VCH: New York, 1988; Vol. 2, pp 83−168.

(2) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473.

(3) (a) Fischer, R.; Hyrgova, E.; Fisera, L.; Hametner, C.; Cyranski, M. *Chem. Pap.* **2005**, *59*, 275. (b) Tomioka, Y.; Nagahiro, C.; Nomura, Y.; Maruoka, H. *J. Heterocycl. Chem.* **2003**, *40*, 121. (c) Torrente, S.; Noya, B.; Branchadell, V.; Alonso, R. *J. Org. Chem.* **2003**, *68*, 4772. (d) Hulsbos, E.; Marcus, J.; Brussee, J.; van der Gen, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1061. (e) Franco, S.; Merchán, F. L.; Merino, P.; Tejero, T. *Synth. Commun.* **1995**, *25*, 2275. (f) Black, D. St. C.; Johnson, L. M. *Aust. J. Chem.* **1984**, *37*, 117. (g) Exner, O. *Collect. Czech. Chem. Commun.* **1951**, *16*, 258.

(4) (a) Hassan, I. E.; Charles, L.; Lauricella, R.; Tuccio, B. *New J. Chem.* **2008**, *32*, 680. (b) Hassan, I. E.; Lauricella, R.; Tuccio, B. *Cent. Eur. J. Chem.* **2006**, *4*, 338.

(5) For intramolecular hydroaminations of *N*-allenylhydroxylamines, see: (a) Dumez, E.; Dulcère, J.-P. *Chem. Commun.* **1998**, 479. (b) Dumez, E.; Faure, R.; Dulcère, J.-P. *Eur. J. Org. Chem.* **2001**, 2577. (c) Schade, W.; Reissig, H.-U. *Synlett* **1999**, 632.

(6) For selected reviews including allene substrates, see: (a) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (b) Aillaud, I.; Collin, J.; Hannedouche, J.; Schulz, E. *Dalton Trans.* **2007**, 5105. (c) Hunt, P. A. *Dalton Trans.* **2007**, 1743. (d) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367–391. (e) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.

(7) For recent examples of intramolecular hydroaminations of allenes, see: (a) Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 14148. (b) Stubbert, B. D.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 4253. (c) Lalonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452. (d) Bender, C. F.; Widenhoefer, R. A. *Chem. Commun.* **2008**, 2741.

(8) For recent examples of intermolecular hydroamination of allenes, see: (a) Lavallo, V.; Frey, G. D.; Donnadieu, B.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5224. (b) Nishina, N.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3314. (c) Kinder, R. E.; Zhang, Z.; Widenhoefer, R. A. *Org. Lett.* **2008**, *10*, 3157.

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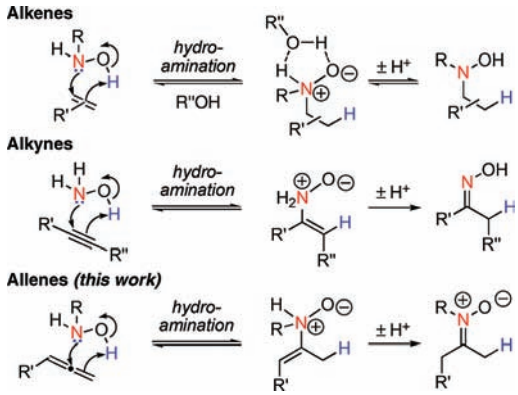
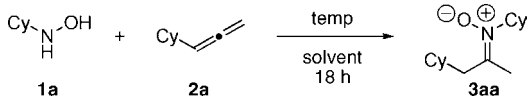
Recently, we reported that the intermolecular addition of aqueous hydroxylamine and *N*-alkylhydroxylamines to alkenes and alkynes can be accomplished simply by heating, via a mechanistic pathway analogous to the reverse of the Cope elimination (Scheme 1).[9,10] Although most intermolecular hydroaminations have a high thermal activation energy and thus require catalysis or stoichiometric additives to occur, this "Cope-type hydroamination" strategy is a thermal concerted process occurring at temperatures around 100 °C. Addition of an *N*-alkylhydroxylamine to an unsaturated precursor generates an *N*-oxide intermediate, which undergoes proton transfer to give the more stable final products. As reported herein, analogous intermolecular reactivity of allenes is also possible.

Scheme 1. Cope-Type Hydroamination with Hydroxylamines



Gratifyingly, exposure of cyclohexylallene (**2a**) to the conditions previously reported to effect additions of *N*-alkylhydroxylamines to strained alkenes resulted in the formation of ketonitrone **3aa** in acceptable yield (Table 1, entry 3). Optimization was undertaken to maximize the rate of addition while minimizing the amount of unwanted thermal decomposition of hydroxylamine **1a**.[9b,11] The reaction was found to occur in various protic and aprotic solvents. Although little change in the rate of the reaction was observed between the various solvents, *tert*-butanol was found to be most effective at minimizing this decomposition. Increasing the temperature and performing the reaction at 0.50 M in **1a** resulted in an efficient and clean reaction in 87% conversion (entry 8). The reaction still proceeded in 67% conversion if only 1 equiv of allene was employed (entry 9).

Table 1. Optimization of Reaction of **1a** with **2a**[a]

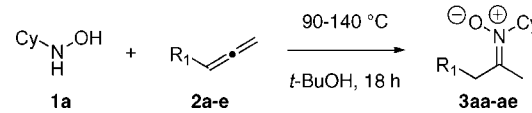


entry	solvent	temp (°C)	concn (M)	NMR yield[b] (%)
1	C_6H_6	110	0.50	62
2	$CHCl_3$	110	0.50	63
3	*n*-PrOH	110	0.50	62
4	*i*-PrOH	110	0.50	~65
5	*t*-BuOH	110	0.50	61
7	*t*-BuOH	140	0.25	65
8	*t*-BuOH	140	0.50	87
9	*t*-BuOH	140	0.50	67[c]
10	*t*-BuOH	140	1.0	75

[a] Conditions: 2 equiv of allene, 1 equiv of **1a**, sealed tube, 18 h. [b] Determined by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard. [c] Only 1 equiv of allene.

The scope of the reaction with respect to the allene partner was then investigated. The reaction was found to be compatible with a variety of alkyl-substituted allenes, whereas aryl-substituted allenes were more challenging (Table 2). The ketonitrone products were easily purified by silica gel chromatography, and no regioisomeric products were observed in all cases. Unfortunately, reactions with disubstituted terminal and nonterminal allenes did not result in synthetically useful yields.

Table 2. Reaction of **1a** with Allenes[a12]



entry	R_1	product	NMR yield[b] (%)	yield[c] (%)
1	Cy	**3aa**	91	91
2	*n*-C_6H_{13}	**3ab**	85	81
3	$BnO(CH_2)_2$	**3ac**	81	75
4	$TBDPSO(CH_2)_3$	**3ad**	85	73
5[d]	Ph	**3ae**	52	40

[a] Conditions: 2 equiv of allene, 1 equiv of **1a**, *t*-BuOH (0.5M), 140 °C, sealed tube, 18 h. [b] Determined by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard. [c] Isolated yield after column chromatography. [d] Heated to 90 °C.

Investigation of the reaction scope with respect to hydroxylamine substitution revealed that a variety of *N*-

(9) (a) Beauchemin, A.; Moran, J.; Lebrun, M.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem., Int. Ed.* **2008**, *47*, 1410. (b) Moran, J.; Gorelsky, S. I.; Dimitrijevic, E.; Lebrun, M.-E.; Bédard, A.-C.; Séguin, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 17893.

(10) For an excellent review of the reverse Cope cyclization, see: Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243.

(11) (a) Horiyama, S.; Suwa, K.; Yamaki, M.; Kataoka, H.; Katagi, T.; Takayama, M.; Takeuchi, T. *Chem. Pharm. Bull.* **2002**, *50*, 996. (b) Beckett, A. H.; Rashid Purkaystha, A.; Morgan, P. H. *J. Pharm. Pharmacol.* **1977**, *29*, 15. (c) Lindeke, B.; Anderson, E. *Acta Pharm. Suec.* **1975**, *12*, 183. (d) Posner, T. *Ann. Chim.* **1912**, *389*, 1. (e) Fischer, E.; Scheibler, H.; Groh, R. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 2020. (f) Posner, T. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 2316.

(12) Typical experimental procedure. A 5 mL sealed vial (Biotage microwave vial 0.5−2 mL) was charged with a stir bar, *N*-alkylhydroxylamine (0.81 mmol, 1.0 equiv), *tert*-butanol (1.6 mL, 0.50 M in *N*-alkylhydroxylamine), and allene (1.6 mmol, 2.0 equiv). The vial was sealed using a cap with a resealable septum and purged through the septum with argon and an outlet for 5 min with stirring. The vial was then heated while stirring in a wax bath at 140 °C for 18 h and analyzed by TLC (7% MeOH/CH_2Cl_2). The tube was cooled to ambient temperature, concentrated under reduced pressure, and analyzed by ^{1}H NMR ($CDCl_3$) using 1,4-dimethoxybenzene as an internal standard, then again concentrated under reduced pressure and purified by silica gel chromatography (4% MeOH/CH_2Cl_2) to give the corresponding nitrone.

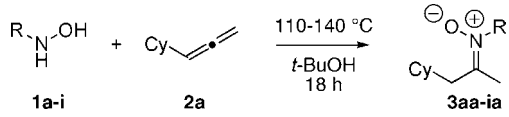
alkylhydroxylamines afford Cope-type hydroamination products in moderate to good yields (Table 3). Hydroxylamines possessing bulky alkyl substituents such as neopentyl and norbornyl groups performed well under the reaction conditions. Although hydroxylamines possessing linear alkyl groups decomposed under our conditions optimized for alkenes,[9b] *n*-hexylhydroxylamine gave the ketonitrone **3fa** in good yield.

Additions of aqueous hydroxylamine to allenes to give oximes were then carried out under the optimal conditions for addition of NH_2OH to alkenes (Table 4).[9] The reaction times, temperature, and reaction scope were similar to those observed with *N*-alkylhydroxylamines, and the higher yields were likely due to the superior thermal stability of aqueous hydroxylamine. Although monosubstituted allenes afforded the desired oximes efficiently (entries 1−5), disubstituted allenes proved rather unreactive (entries 6 and 7).

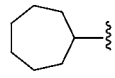
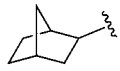
Pioneering work by Ciganek[13] and Oppolzer[14] on intramolecular Cope-type hydroaminations with alkenes provides strong evidence for a concerted process, and this mechanism appears consistent with the experimental regioselectivity and scope observed in this study. Calculations supporting this mechanism have previously been reported for the Cope-type hydroamination of alkynes and alkenes,[9] as well as the microscopic reverse of the latter reaction (the Cope elimination).[15]

Seeking to obtain more information, density functional theory (DFT) calculations were performed to obtain transition state structures and energies for the reaction of NH_2OH with allene and methylallene (Figure 1). The concerted hydroamination process occurs via a five-membered coplanar transition state, and amination on the central carbon of allene is favored by 5.7 kcal/mol (A vs B). For methylallene, the isomeric transition states for the addition to the terminal π bond (31.9 kcal/mol for C and 33.5 kcal/mol for D) were both found to be lower energy than for addition to the *internal* π bond (35.7 kcal/mol for E). The experimental observation that the reactions of *N*-alkylhydroxylamines with geminally disubstituted allenes are more difficult is thus explained by the

Table 3. Reaction of *N*-Alkylhydroxylamines with Cyclohexylallene[a]

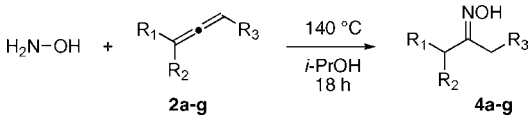


1a-i **2a** **3aa-ia**

entry	R	product	temp (° C)	NMR yield[b] (%)	yield[c] (%)
1	Cy	**3aa**	140	91	91
2	Bn	**3ba**	140	81	81
3	*i*-Pr	**3ca**	110	n.d.[d]	63
4	*sec*-Bu	**3da**	140	51	49
5	$CH_2C(CH_3)_3$	**3ea**	140	n.d.[d]	47
6	*n*-C_6H_{13}	**3fa**	140	54	51
7		**3ga**	140	62	58
8		**3ha**	140	n.d.[d]	71
9		**3ia**	140	40	38

[a] Conditions: 2 equiv of **2a**, 1 equiv of RNHOH, *t*-BuOH (0.5M), sealed tube, 18 h. [b] Determined by ^1H NMR using 1,4-dimethoxybenzene as an internal standard. [c] Isolated yield after column chromatography. [d] Not determined due to overlapping peak in ^1H NMR.

Table 4. Reaction of Aqueous Hydroxylamine with Allenes[a]



2a-g **4a-g**

entry	R_1	R_2	R_3	product	yield[b] (%)
1	Cy	H	H	**4a**	75
2	*n*-C_6H_{13}	H	H	**4b**	93
3	$BnO(CH_2)_2$	H	H	**4c**	99
4	$TBDPSO(CH_2)_3$	H	H	**4d**	88
5	Ph	H	H	**4e**	71
6	*n*-C_6H_{13}	*n*-Pr	H	**4f**	21[c]
7	*n*-Pr	H	*n*-Pr	**4g**	13

[a] Conditions: 1 equiv of allene (2.5 M), 2 equiv of aq NH_2OH, *i*-PrOH, sealed tube, 140 °C, 18 h. [b] Isolated yield after column chromatography. [c] Heated in a microwave reactor at 160 °C. See Supporting Information.

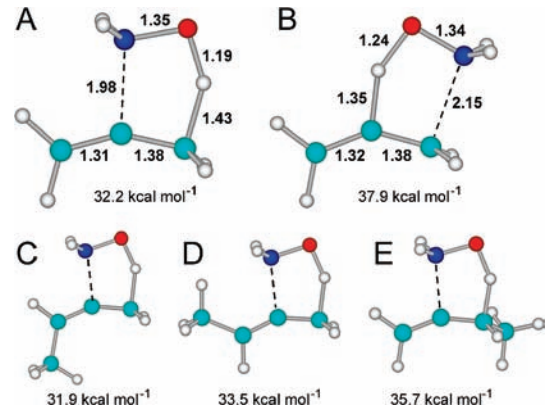


Figure 1. Transition state structures for the Cope-type hydroamination of NH_2OH with allene (A, B) and methylallene (C−E) at the B3LYP/TZVP level of theory. The internuclear distances (Å) are shown only for relevant chemical bonds.

(13) (a) Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007. (b) Ciganek, E.; Read, J. M., Jr.; Calabrese, J. C. *J. Org. Chem.* **1995**, *60*, 5795.

(14) Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139.

(15) (a) Komaroni, I.; Tronchet, J. M. J. *J. Phys. Chem. A* **1997**, *101*, 3554. (b) Acevedo, O.; Jorgensen, W. L. *J. Am. Chem. Soc.* **2006**, *128*, 6141.

(16) In analogy to the parent reactions of alkynes, the proton transfer step of the *N*-oxide intermediate could likely be facilitated by *t*-BuOH, the hydroxylamine, or H_2O under the reaction conditions. For computational and experimental results highlighting the importance of this proton transfer step for Cope-type hydroaminations, see ref 9.

developing A(1,3) interactions that arise in the terminal transition states between the alkyl groups on the hydroxylamine and on the allene. Overall, the potential energy surface is consistent with product distribution being under kinetic control (Figure 2).[16]

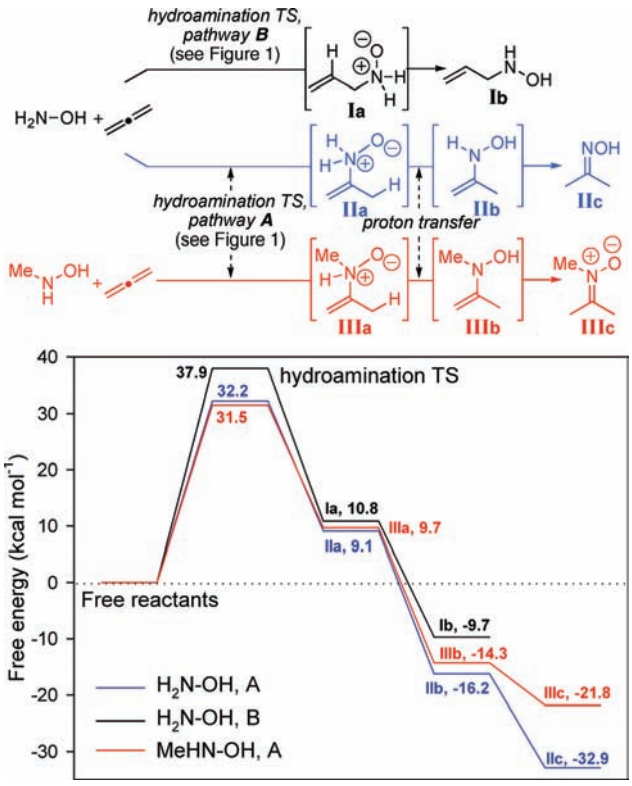
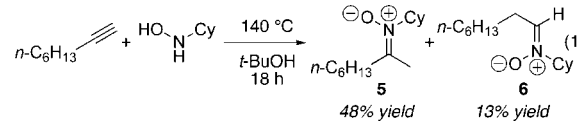


Figure 2. Gibbs free energy (in kcal/mol, 298K, 1 atm) profiles for the Cope-type hydroamination of allene using H_2NOH (**A** and **B**) and MeHNOH (**A**). Pathways **A** and **B** correspond to amination of the central and terminal carbons of allene, respectively.

The calculated hydroamination transition state structures shown in Figure 1 also provide insight on the diminished reactivity of *N*-alkylhydroxylamines toward alkynes (relative to allenes) observed experimentally in related ongoing work.[17] For example, the fact that 1-octyne affords the branched, Markovnikov nitrone **5** in lower yield and regioselectivity (eq 1) under similar conditions is likely due to destabilizing interactions between the *n*-C_6H_{13} and Cy substituents of the reacting partners in the Markovnikov hydroamination transition state.



In summary, simple, atom-efficient syntheses of ketonitrones (from allenes and *N*-alkylhydroxylamines) and of ketoximes (from allenes and NH_2OH) have been developed using an intermolecular Cope-type hydroamination approach. All reactions can be carried out in concentrated alcoholic solvents and do not require rigorous exclusion of water. DFT calculations provide insight into the reactivity and suggest that the reaction proceeds via a concerted, planar, and terminal transition state. Extensions and applications of this reactivity are underway and will be reported in due course.

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Supporting Information Available: Complete experimental procedures, full spectroscopic data for all new compounds, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Examples of intermolecular reactions of *N*-alkylhydroxylamines with electron-rich alkynes are rare. For an example with ethoxyacetylene, see: (a) Winterfeld, E.; Krohn, W. *Chem. Ber.* **1969**, *102*, 2336. For examples with aryl acetylenes and MeNHOH, see: (b) Padwa, A.; Wong, G. S. K *J. Org. Chem.* **1986**, *51*, 3125. For an example with phenyl acetylene and *c*-$C_6H_{11}NHOH$, see ref 9a.