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Simple Reaction Conditions for the Formation of Ketonitrones from Ketones and Hydroxylamines

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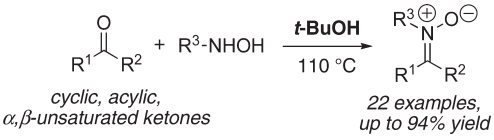

The condensation of ketones and hydroxylamines to form ketonitrones was reinvestigated by using thermal conditions previously found to minimize hydroxylamine decomposition (*t*-BuOH, 110 °C). This simple approach allows the formation of exocyclic, acyclic, and α,*β*-unsaturated ketonitrones with benzylic, linear, and branched nitrogen substituents in modest to excellent isolated yields.

Nitrones are valuable intermediates in synthetic organic chemistry.[1] Various methods have been developed for their formation,[2] including (1) condensation of a carbonyl precursor and a hydroxylamine, (2) oxidation of amines, hydroxylamines, or imines,[3] (3) *N*-alkylation of oximes and derivatives,[4] and (4) Cope-type hydroamination[5] of alkynes or allenes with hydroxylamines.[6] However, most of the nitrone literature relates to aldonitrones, and reports on the synthesis and reactivity of ketonitrones remain scarce and mostly limited to specific substrates such as *N*-methyl or *N*-benzyl substituted,[7] or endocyclic ketonitrones (which can be prepared by intramolecular reactions). With respect to the condensation approach, aldonitrones are prepared simply by mixing the aldehydes and *N*-alkylhydroxylamines, while ketonitrones are usually prepared by using Exner's two-step procedure (condensation of the ketone with RNHOH·HCl to afford the ketonitrone·HCl adduct, followed by neutralization with dry ammonia).[7n,8] In recent work on the intermolecular Cope-type hydroamination[5] reactivity of hydroxylamines,[9] we noted that the thermal stability of *N*-alkylhydroxylamines is highly solvent and substitution dependent, and that significant decomposition can occur upon heating in various common organic solvents.[10] However, heating is typically required in the scarce reports of ketonitrone formation from ketones and hydroxylamines.[2c,7n] Arguably, the scope of the direct condensation approach to ketonitrones would likely be extended if reaction conditions providing increased thermal stability for the hydroxylamines could be developed. Herein, we provide such procedures that allow the formation of exocyclic, acyclic,

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(2) (a) See ref 1a. (b) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1. (c) Tennant, G. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon Press: New York, 1979; Vol. 2, Part 8. (d) Delpierre, G. R.; Lamchen, M. *Q. Rev., Chem. Soc.* **1965**, *19*, 329. (e) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473.

(3) (a) Gella, C.; Ferrer, È.; Alibés, R.; Busqué, F.; de March, P.; Figueredo, M.; Font, J. *J. Org. Chem.* **2009**, *74*, 6365. (b) Saladino, R.; Neri, V.; Cardona, F.; Goti, A. *Adv. Synth. Catal.* **2004**, *346*, 639. (c) Soldaini, G.; Cardona, F.; Goti, A. *Org. Lett.* **2007**, *9*, 473 and references cited therein .

(4) (a) LeBel, N. A.; Balasubramanian, N. *Tetrahedron Lett.* **1985**, *26*, 4331 and references cited therein. For related reactivity of oximes with π-bonds, see [Alkynes]: (b) Pradharan, S. K.; Akamanchi, K. G.; Divakaran, P. P.; Pradhan, P. M. *Heterocycles* **1989**, *28*, 813. (c) Grigg, R.; Perrior, T. R.; Sexton, G. J.; Surendrakumar, S.; Suzuki, T. *J. Chem. Soc., Chem. Commun.* **1993**, 372. [Alkenes]: (d) Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 6929. (e) Grigg, R.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 10399. (f) Dondas, H. A.; Grigg, R.; Hadjisoteriou, M.; Markandu, J.; Thomas, W. A.; Kennewell, P. *Tetrahedron* **2000**, *56*, 10087. [Allenes]: (g) Shaw, R.; Lathbury, D.; Anderson, M.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 659 and references cited therein.

(5) Such reactions are also called reverse Cope cyclizations/eliminations. For a review, see: Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243.

(6) [Alkynes]: (a) Padwa, A.; Wong, G. S. K. *J. Org. Chem.* **1986**, *51*, 3125. (b) Davison, E. C.; Forbes, I. T.; Holmes, A. B.; Warner, J. A. *Tetrahedron* **1996**, *52*, 11601 and references cited therein. See also: (c) Nguyen, T. B.; Martel, A.; Dhal, R.; Dujardin, G. *Org. Lett.* **2008**, *10*, 4493. [Allenes]: (d) Dumez, E.; Dulcère, J.-P. *Chem. Commun.* **1998**, 479. (e) Schade, W.; Reissig, H.-U. *Synlett* **1999**, 632. See also: (f) Padwa, A.; Bullock, W. H.; Kline, D. N.; Perumattam, J. *J. Org. Chem.* **1989**, *54*, 2862.

(7) (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) Snider, B. B.; Lin, H.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 6442. (e) Hulsbos, E.; Marcus, J.; Brussee, J.; van der Gen, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1061. (f) Franco, S.; Merchán, F. L.; Merino, P.; Tejero, T. *Synth. Commun.* **1995**, *25*, 2275. (g) Funk, R. L.; Daggett, J. U. *Heterocycles* **1987**, *26*, 2175. (h) Mullen, G. B.; Swift, P. A.; St. Georgiev, V. *J. Pharm. Sci.* **1987**, *76*, 930. (i) Black, D. St. C.; Johnson, L. M.; Aust., J. *Chem.* **1984**, *37*, 117. (j) Robl, J. A.; Hwu, J. R. *J. Org. Chem.* **1985**, *50*, 5913. (k) Cummins, C. H.; Coates, R. M. *J. Org. Chem.* **1983**, *48*, 2070. (l) Abou-Gharbia, M.; Joullié, M. M. *Synthesis* **1977**, 318. (m) Pratt, R. N.; Stokes, D. P.; Taylor, G. A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 498. (n) Exner, O. *Collect. Czech. Chem. Commun.* **1951**, *16*, 258.

(8) A more recent, practical alternative has been reported by Merino et al. for BnNHOH and several ketones using equimolar amounts of $ZnCl_2$ and $MgSO_4$ in CH_2Cl_2. See ref 7f for details.

(9) (a) Beauchemin, A. M.; Moran, J.; Lebrun, M.-E.; 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. (c) Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A.-C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 874. (d) Moran, J.; Pfeiffer, J. Y.; Gorelsky, S. I.; Beauchemin, A. M. *Org. Lett.* **2009**, *11*, 1895.

(10) (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. Sueu.* **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.

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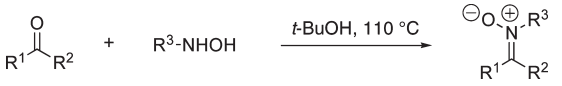
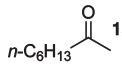
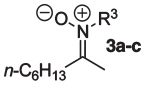
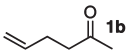
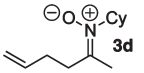
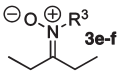
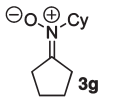
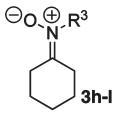
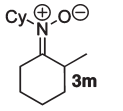
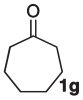
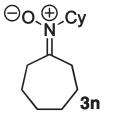
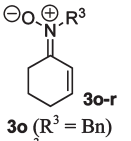
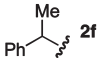
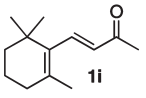
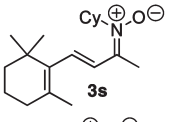
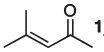
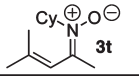
TABLE 1. Scope of Improved Conditions for Ketonitrone Formation[a]



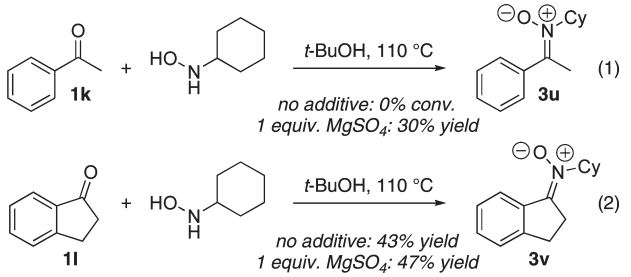
				
1	"	*c*-C_6H_{11} (**2a**)	**3a** (R^3 = *c*-C_6H_{11})	85 / 81
2	"	*n*-C_6H_{13} (**2b**)	**3b** (R^3 = *n*-C_6H_{13})	79 / 70
3	"	Bn (**2c**)	**3c** (R^3 = Bn)	90 / 82
4		*c*-C_6H_{11} (**2a**)		65 / 60
				
5[c]	"	*c*-C_6H_{11} (**2a**)	**3e** (R^3 = *c*-C_6H_{11})	59 / 41
6	"	Bn (**2c**)	**3f** (R^3 = Bn)	60 / 50
7[c]	"	Bn (**2c**)	**3f** (R^3 = Bn)	71 / 71
8		*c*-C_6H_{11} (**2a**)		99 /83
				
9	"	Bn (**2c**)	**3h** (R^3 = Bn)	81 / 61
10	"	*n*-C_6H_{13} (**2b**)	**3i** (R^3 = *n*-C_6H_{13})	78 / 78
11	"	*c*-C_5H_9 (**2d**)	**3j** (R^3 = *c*-C_5H_9)	91 / 82
12	"	*c*-C_6H_{11} (**2a**)	**3k** (R^3 = *c*-C_6H_{11})	99 / 94
13	"	*c*-C_7H_{13} (**2e**)	**3l** (R^3 = *c*-C_7H_{13})	88 / 88
14		*c*-C_6H_{11} (**2a**)		36 / 26
15		*c*-C_6H_{11} (**2a**)		95 / 83
				
16	"	Bn (**2c**)	**3o** (R^3 = Bn)	83 / 71
17	"	*n*-C_6H_{13} (**2b**)	**3p** (R^3 = *n*-C_6H_{13})	70 / 63
18	"	*c*-C_6H_{11} (**2a**)	**3q** (R^3 = *c*-C_6H_{11})	99 / 91
19	"		**3r** (R^3=CHMePh)	84 / 63
20		*c*-C_6H_{11} (**2a**)		89 / 80
21		*c*-C_6H_{11} (**2a**)		53 / 44

[a]Conditions: Ketone (2 equiv), R^3NHOH (1 equiv), *t*-BuOH (0.5 M), 110 °C, 18 h, under Ar. [b]Typically *E*/*Z* mixtures of ketonitrone isomers were isolated with unsymmetrical ketones. See the Supporting Information for ratios and stereochemical assignment. [c]Performed with 5 equiv of ketone.

and α,β-unsaturated ketonitrones bearing various nitrogen substituents.

Recently, we reported that ketonitrones can directly be accessed from allenes and *N*-alkylhydroxylamines upon heating in *tert*-butanol at 90−140 °C.[9d] Remarkably, these conditions were even appropriate for linear *N*-alkylhydroxylamines and provided in general modest to good yields, suggesting that little hydroxylamine and/or ketonitrone decomposition occurred under the reaction conditions. Encouragingly, initial condensation attempts with 2-octanone (**1a**) and *N*-cyclohexylhydroxylamine (**2a**) under similar reaction conditions provided the ketonitrone **3a** in 81% isolated yield. Reaction of 2-octanone (**1a**) with the more labile *n*-hexylhydroxylamine (**2b**) also provided the desired ketonitrone **3b** effectively (70% yield), which prompted the determination of the substrate scope (Table 1).

Overall, the reaction conditions allow ketonitrone formation with various ketones and hydroxylamines. Both acyclic (entries 1−7) and cyclic (entries 8−15) ketones yield the desired adducts under the reaction conditions.[11] The condensation is most efficient for cyclic and acyclic methyl ketones (entries 8−13, 15, and 1−4, respectively), and shows some sensitivity to substitution α to the carbonyl (entries 5−7 and 14). Interestingly, α,β-unsaturated ketones react to form exclusively the condensation products over the possible[12] 1,4-addition products (entries 16−21). Various primary hydroxylamines are also compatible with the reaction conditions (entries 9−13 and 19), and the reactivity appears to be minimally affected by the nature of the ketones as surveyed with three representative hydroxylamines (entries 1−3 vs. 9−10, 12 vs. 16−18). In general, most ketonitrones could be purified by chromatography, with some nitrones being somewhat labile.



In contrast, acetophenone (**1k**) did not yield any product under the reaction conditions (eq 1). Speculating that this observation was due to unfavorable reaction thermodynamics, various dessicants were surveyed and a modest 30% yield of the desired aromatic ketonitrone **3u** could be obtained with $MgSO_4$.[13] In contrast, indanone (**1*l***) reacted

(11) To provide calibration on the importance of using *t*-BuOH as solvent to minimize hydroxylamine decomposition, the condensation shown in entry 6 with 3-pentanone and BnNHOH (which is typically moderately sensitive to thermolysis) was explored in other solvents, under identical reaction conditions and scale. Ketonitrone **3f** was formed in 12%, 12%, and 18% NMR yields in toluene, dioxane, and $CHCl_3$, respectively.

(12) (a) Niu, D.; Zhao, K. *J. Am. Chem. Soc.* **1999**, *121*, 2456. See also: (b) Moglioni, A. G.; Muray, E.; Castillo, J. A.; Álvarez-Larena, Á .; Moltrasio, G. Y.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2002**, *67*, 2402.

(13) See the Supporting Information for details.

(14) A solution of ketonitrone **3u** was heated under the usual reaction conditions (*t*-BuOH [1.0 M], 110 °C, 18 h, under Ar) in the presence of 10 equiv of H_2O. TLC and ^1H NMR analysis of the unpurified reaction mixture with an internal standard showed that partial hydrolysis of the ketonitrone had occurred. See the Supporting Information for details.

under the standard reaction conditions to afford the desired ketonitrone **3v**, and no improvement was observed in the presence of $MgSO_4$ (eq 2). The fact that ketonitrone **3u** was partially hydrolyzed by water under similar reaction conditions[14] suggests that the condensation to form ketonitrones is close to thermoneutrality, and that the position of the equilibrium depends on the stability of the ketone used and on the extent of steric destabilization of the ketonitrone product (dependent on the size of the hydroxylamine).[15]

In summary, various primary hydroxylamines and ketones are efficiently condensed simply upon heating in *t*-BuOH at 110 °C. These conditions are compatible with linear, benzylic, and cyclic hydroxylamines, as well as cyclic, acyclic, and α,β-unsaturated ketones, thus providing a general route to ketonitrones.

Experimental Section

Procedure for the Condensation of *N*-Alkylhydroxylamines with Ketones. A flame-dried 2 mL sealed vial was charged with a stir bar, *N*-alkylhydroxylamine (1.3 mmol, 1.0 equiv), *tert*-butanol (2.6 mL, 0.5 M to hydroxylamine), and ketone (2.6 mmol, 2.0 equiv). The vial was sealed with a septum and purged with argon and outlet for 5 min while stirring. The vial was sealed by using a cap with a resealable septum and was then heated while stirring in an oil bath at 110 °C for 18 h. The tube was cooled to ambient temperature, concentrated under reduced pressure, and analyzed by ^{1}H NMR ($CDCl_3$) with 1,4-dimethoxybenzene as an internal standard, then again concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding nitrone.

(15) A known strategy to overcome this issue involves the use of dialkylketals, as their reaction is entropically more favorable: see ref 7n.

Acknowledgment. We thank the University of Ottawa, the Canadian Foundation for Innovation, the Ontario Ministry of Research and Innovation, and NSERC for their support. A postgraduate scholarship to J.Y.P. (FQRNT) is also acknowledged. Joseph Moran is also thanked for helpful discussions.

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