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Cyclic Alkenenitriles: Chemoselective Oxonitrile Cyclizations

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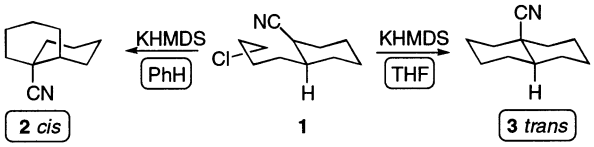
Potassium *tert*-butoxide triggers the chemoselective cyclization between nitrile anions and remote, enolizable carbonyl groups, despite the acidity difference favoring enolate formation and addition to the nitrile group. Domino deprotonation, cyclization, and dehydration efficiently transform a diverse array of ω-oxonitriles into carbocyclic and heterocyclic five- and six-membered alkenenitriles in a single synthetic operation.

Introduction

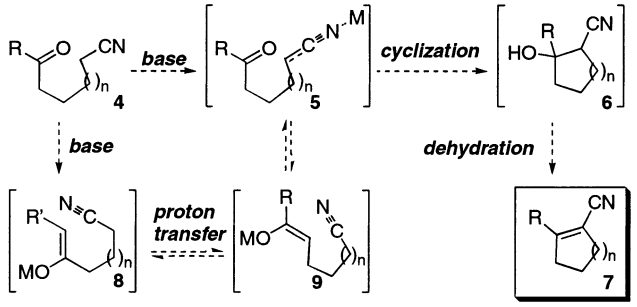
α,β-Alkenenitriles are versatile intermediates[1] to an array of heterocycles,[2] carbocycles,[3] and nitrile-containing natural products.[4] Cyclic alkenenitriles in particular are ideal precursors to substituted alkanenitriles that often exhibit unusual reactivity motifs that are inaccessible with the corresponding carbonyl compounds. For example, the cyclic nitrile **1** exhibits a unique solvent-dependent cyclization to *cis*- and *trans*-decalins **2** and **3**,[5] whereas ester enolates cyclize to *cis*-decalins regardless of the solvent[6] (Scheme 1).

SCHEME 1. Nitrile Anion Cyclizations



Despite the unique reactivity of cyclic nitriles, few are commercially available. Alternatively, synthesizing[7] cyclic alkenenitriles is attended by the inherent difficulty in sequentially performing an efficient cyclization−olefination sequence in a single synthetic operation.[8] A conceptually attractive solution[9] (**4**→**7**, Scheme 2) is the chemoselective condensation of a nitrile anion with a remote carbonyl group—chemoselective in cyclizing via a nitrile anion despite the presence of a more acidic carbonyl group ($\Delta pK_a = 5-10$)[10] favoring enolate formation and addition to the nitrile group (**8** or **9**, Scheme 2).

SCHEME 2. Chemoselective Oxonitrile Cyclizations



(1) Fatiadi, A. J. In *The Chemistry of Functional Groups, Supplement C*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1983; Chapter 26.

(2) Sharanin, Y. A.; Goncharenko, M. P.; Litvinov, V. P. *Russ. Chem. Rev.* **1998**, *67*, 393.

(3) Fleming, F. F.; Shook, B. C.; Jiang, T.; Steward O. W. *Org. Lett.* **1999**, *1*, 1547.

(4) Fleming, F. F. *Nat. Prod. Rep.* **1999**, *16*, 597.

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(6) Stork, G.; Gardner, J. O.; Boeckman, R. K., Jr.; Parker, K. A. *J. Am. Chem. Soc.* **1973**, *95*, 2014.

(7) For existing syntheses of cyclic alkenenitriles see: (a) Couthon, H.; Gourves, J.; Sturtz, G. *Eur. J. Org. Chem.* **1999**, 3489. (b) Bestmann, H. J.; Schmidt, M. *Angew. Chem.* **1987**, *26*, 79. (c) Flitsch, W.; Lerner, H.; Zimmermann, H. *Chem. Ber.* **1977**, *110*, 2765. (d) Oda, M.; Yamamuro, A.; Watabe, T. *Chem. Lett.* **1979**, 1427. (e) Grierson, D. S.; Sisti, N. J.; Zeller, E.; Fowler, F. W. *J. Org. Chem.* **1997**, *62*, 2093. (f) Henecka, H.; Aichinger, G.; Schubert, W. *Angew. Chem.* **1962**, *74*, 875.

(8) (a) Kunesch, N.; Francois, D.; Poupon, E.; Lallemand, M.; Husson, H. *J. Org. Chem.* **2000**, *65*, 3209. (b) Tomoda, S.; Takeuchi, Y.; Nomura, Y. *J. Chem. Soc., Chem. Commun.* **1982**, 871. (c) Hoffmann, H. M. R.; Giesel, K.; Lies, R.; Ismal, Z. M. *Synthesis* **1986**, 548. (d) Kemp, D.S.; Carter, J. S. *Tetrahedron Lett.* **1987**, *28*, 4641. (e) Kemp, D. S.; Carter, J. S. *Tetrahedron Lett.* **1987**, *28*, 4645. (f) Merchant, J. R.; Dike, S. Y. *Proc. Indian. Acad. Sci.* **1978**, *87* (A8), 229. (g) Prajapati, D.; Lekhok, K. C.; Sandhu, J. S.; Ghosh, A. C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 959. (h) El Kaim, L.; Gacon, A. *Tetrahedron Lett.* **1997**, *38*, 3391.

(9) Deprotonation of β-ketonitriles,[a−d] β-cyanoesters,[e−g] β-cyanoamides,[h] and arylacetonitriles[i−n] permit analogous cyclizations although the more challenging cyclizations of alkanenitriles typically require two discreet synthetic operations.[o−p] (a) Fleming, F. F.; Guo, J.; Wang, Q.; Weaver, D. *J. Org. Chem.* **1999**, *64*, 8568. (b) Fleming, F. F.; Huang, A. Sharief, V.; Pu, Y. *J. Org. Chem.* **1999**, *64*, 2830 (c) Haase-Held, M.; Hatzis, M.; Mann, J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2907. (d) Haase-Held, M.; Hatzis, M.; Mann, J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2999. (e) Kulkarni, B. A.; Ganesan, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 2454. (f) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825. (g) Gorlitzer K. *Arch. Pharm.* **1975**, *308*, 700. (h) Ikeda, M.; Uchino, T.; Maruyama, K.; Sato, A. *Heterocycles* **1988**, *27*, 2349 (i) Bossio, R.; Marcaccini, S.; Pepino, R.; Torroba, T. *Synthesis* **1993**, 783. (j) Orlemans, E. O. M.; Schreuder, A. H.; Conti, P. G. M.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1987**, *43*, 3817 (k) Verboom, W.; Orlemans, E. O. M.; Berga, H. J.; Scheltinga, M. W.; Reinhoudt, D. N. *Tetrahedron* **1986**, *42*, 5053 (l) Verboom, W.; Berga, H. J.; Trompenaars, W. P.; Reinhoudt, D. N. *Tetrahedron Lett.* **1985**, 685. (m) Stefancich, G.; Artico, M.; Massa, S.; Vomero, S. *J. Heterocyclic Chem.* **1979**, *16*, 1443. (n) Flitsch, W.; Lerner, H.; Zimmermann, H. *Chem. Ber.* **1977**, *110*, 2765. (o) Nakashima, K.; Inoue, K.; Sono, M.; Tori, M. *J. Org. Chem.* **2002**, *67*, 6034. (p) For a similar one-step cyclization see: Elghamry, I.; Dopp, D.; Henkel, G. *Synthesis* **2001**, 1223.

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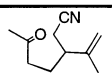
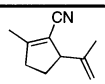
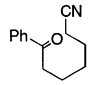
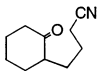
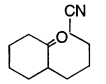
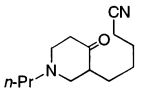
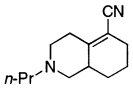
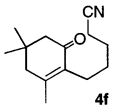
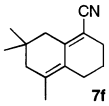
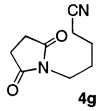
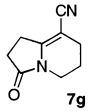
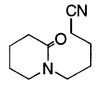
Conceptually, several competitive cyclizations exist for carbonyl-containing nitriles with only one mode leading to cyclic alkenenitriles. The cyclization chemoselectivity depends on the relative basicity and electrophilicity of the ketone and nitrile groups with the later being more critical.[11] Despite a perception to the contrary, nitriles are relatively poor electrophiles that often resist nucleophilic attack by organometallic reagents,[12] even allowing C≡N incorporation within organolithium[13] and Grignard reagents![14] Ketones, by contrast, are excellent electrophiles that condense rapidly with nitrile anions.[15] The combination of poor nitrile and high ketone electrophilicity favorably disposes carbonyl-containing nitriles toward nitrile anion cyclization.

Results and Discussion

Exploratory cyclizations with potassium *tert*-butoxide (*t*-BuOK) and commercially available ketonitrile **4a** established the viability of chemoselectively cyclizing oxonitriles (Table 1, entry 1). Base optimization revealed a minimum requirement for 2−3 equiv[16] of either *t*-BuOK[17] or *i*-BuOK, with 5 equiv permitting the complete conversion to the alkenenitrile **7a** within 5 h in refluxing tetrahydrofuran (THF).

The alkoxide-promoted cyclization effectively assembles a diverse range of carbocyclic and heterocyclic alkenenitriles. Acyclic and cyclic ketonitriles (Table 1, entries 1−2 and 3−8, respectively) cyclize equally efficiently, generating a variety of monocyclic and bicyclic five- and six-membered alkenenitriles. Ketone electrophiles tolerate aliphatic, olefinic, and aromatic substituents (Table 1, entries 1 and 3−5, 6, and 2, respectively) with the cyclization being favored over a potentially competitive conjugate addition in the case of enone **4f** (Table 1, entry 6). The cyclization is not limited to ketones,[18] with imide **4g** and lactam **4h** readily cyclizing to the corresponding indolizidine **7g** and quinolizidine **7h**.[19] Cyclization of **4h** (Table 1, entry 8), obtained by alkylating δ-valerolactam with bromopentanenitrile, expediently provides a rapid entry to alkaloids through quinolizidine **7h**.[20]

TABLE 1. Chemoselective Oxonitrile Cyclizations

entry	nitrile	base	alkenenitrile	yield
1	 **4a**	*t*-BuOK[a]	 **7a**	60%
2	 **4b**	*t*-BuOK[b]	 **7b**	66%
3	 **4c**	*t*-BuOK	 **7c**	79%[c]
4	 **4d**	*t*-BuOK	 **7d**	67%
5	 **4e**	*t*-BuOK	 **7e**	61%[c]
6	 **4f**	*i*-BuOK	 **7f**	61%
7	 **4g**	*t*-BuOK	 **7g**	62%[d]
8	 **4h**	*t*-BuOK	 **7h**	60%

[a] Reaction performed at ambient temperature.[21] [b] A 1 equiv amount of *t*-BuOK was employed to prevent deleterious decyanation.[22] [c] Reaction time was 3 h. [d] Brief exposure to aqueous HCl was performed during workup to ensure complete dehydration of the carbinol amine intermediate.

Mechanistically the cyclization involves sequential anion equilibration,[23] cyclization, and elimination[24]

(10) The pK_a of acetone and acetonitrile are 20 and 25,[a] respectively, with the pK_a of acetonitrile being recently revised upward to ∼30.[b] (a) Bordwell, F. G.; Matthews, W. S. *J. Am. Chem. Soc.* **1974**, *96*, 1214. (b) Richard, J. P.; Williams, G.; Gao, J. *J. Am. Chem. Soc.* **1999**, *121*, 715.

(11) Nitriles appear to exhibit an inherent propensity to react with ketones or esters in the presence of base: Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1.

(12) Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1987**, *52*, 3901.

(13) (a) Parham, W. E.; Nelson, J. H. A. *J. Org. Chem.* **1982**, *15*, 300. (b) Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 1187. (c) Tucker, C. E.; Majid, T. M.; Knochel, P. *J. Am. Chem. Soc.* **1992**, *114*, 3983.

(14) (a) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333. (b) Lee, J.-S.; Valerde-Ortiz, R.; Guijarro, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428. (c) Abarbri, M.; Thibonnet, J.; Berillon, L.; Dehmel, F.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618. (d) Thibonnet, J.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 3319. (e) Kitagawa, K.; Ioue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem.* **2000**, *39*, 2481. (f) Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 3674.

(15) DiBiase, S. A.; Lipisko, B. A.; Haag, A.; Wolak, R. A.; Gokel, G. W. *J. Org. Chem.* **1979**, *44*, 4640.

(16) No observable reaction occurs with less than 2 equiv of *t*-BuOK.

(17) *t*-BuOK is estimated to have an acidity comparable to LiHMDS in THF: Hartwig, J. F. *Angew. Chem.* **1998**, *37*, 2046. For recent deprotonations of alkanenitriles with *t*-BuOK see: Bunlaksananusorn, T.; Rodriguez, A. L.; Knochel, P. *Chem. Commun.* **2001**, 745. For the extremely high basicity in DMSO see: Cram, D. J.; Rickborn, B.; Knox, G. R. *J. Am. Chem. Soc.* **1960**, *82*, 6412.

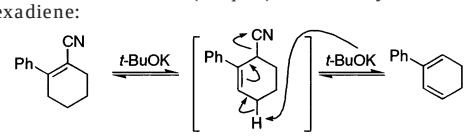
(18) Aldol condensation prevents the use of enolizable aldehydes. For an excellent intermolecular addition to aromatic aldehydes see: Kisanga, P. B.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 426.

(19) For a related enolate−thiolactam condensation see: Guarna, A.; Lombardi, E.; Machetti, F.; Occhiato, E. G.; Scarpi, D. *J. Org. Chem.* **2000**, *65*, 8093.

(20) Michael, J. P.; Jungmann, C. M. *Tetrahedron* **1992**, *48*, 10211.

(21) Performing the reaction at reflux causes partial nitrile hydrolysis to the corresponding amide.

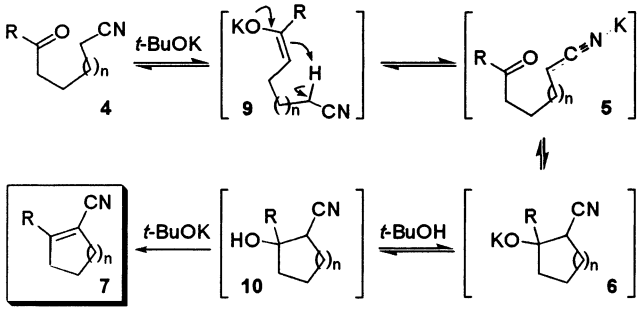
(22) Use of excess *t*-BuOK (5 equiv) causes decyanation to 2-phenylcyclohexadiene:



(23) A rapid proton transfer is observed with related ester enolate nitriles: Stetter, H.; Marten, K. *Liebigs Ann. Chem.* **1982**, 240.

(24) Cyclic β-hydroxynitriles are readily deprotonated adjacent to the nitrile group: Wade, P. A.; Bereznak, J. F. *J. Org. Chem.* **1987**, *52*, 2973.

SCHEME 3. Counterintuitive Cyclization Mechanism



(Scheme 3). Evidence for anion equilibration with *t*-BuOK emanates from the unusual cyclization of **4h** with excess KH (63% yield) that is anticipated to generate both the enolate **9** and the nitrile anion **5** (Scheme 3). Complete conversion to the cyclic alkenenitrile **7**, without recovery of **4**, implies a relatively efficient inter- or intramolecular proton transfer that converges the enolate **9** to the nitrile anion **5**. Cyclization (**5**→**6**), proton transfer (**6**→**10**), and dehydration (**10**→**7**)[25] then furnishes the respective cyclic alkenenitriles.

Consistent with the proposed mechanism is the cyclization of **4f** with *i*-BuOK rather than *t*-BuOK (Table 1, entry 6), which induces cyclization without concomitant dehydration. Presumably the intermediate alkoxide **6** (Scheme 3) is generated in each case, with the subsequent protonation being more favorable from *i*-BuOH than *t*-BuOH, allowing displacement of the equilibrium toward the alkenenitrile **7**.

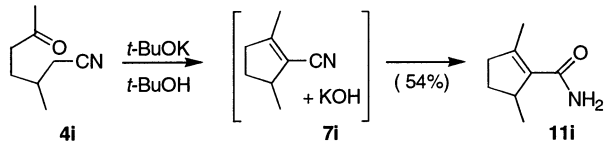
Ejection of hydroxide during the cyclization generates hydroxide ideally suited for nitrile hydrolysis. Performing the cyclization in *t*-BuOH enhances the hydroxide nucleophilicity,[26] triggering a domino sequence in which nitrile **4i** is transformed into the cyclic amide **11i**[27] (Scheme 4). The overall sequence of proton transfers is remarkably efficient for the deprotonation, cyclization, dehydration, and nitrile hydrolysis cascade.

(25) The alcohol **10d** is an observable intermediate in the cyclization of **4d** to **7d**.

(26) Hall, J. H.; Gisler, M. *J. Org. Chem.* **1976**, *41*, 3769.

(27) Cyclopentanecarbonitriles seem prone to hydrolysis: Jaroszewski, J. W.; Olafsdottir, E. S.; Cornett, C.; Schaumberg, K. *Acta Chem. Scand.* **1987**, *B41*, 410.

SCHEME 4. Domino Cyclization−Dehydration−Hydrolysis



Alkoxide-induced cyclizations of ω-oxonitriles smoothly generate cyclic α,β-alkenenitriles in a single synthetic operation. Selective nitrile anion formation triggers facile cyclization onto tethered ketone, enone, lactam, and imide carbonyls, generating cyclic five- and six-membered alkenenitriles. Performing the cyclization in *t*-BuOH, rather than THF, enhances the nucleophilicity of the ejected hydroxide, expediently triggering a cyclization, dehydration, hydrolysis cascade to the corresponding amide. Collectively, the chemoselective cyclizations afford a diverse array of carbocyclic and heterocyclic nitriles that are otherwise difficult to synthesize.

Experimental Section[28]

General Cyclization Procedure. Solid *t*-BuOK (5 equiv) was added to a refluxing, THF solution of the ketonitrile (1 equiv, 0.01−0.05 M). After 5 h the solution was cooled, saturated, aqueous NH_4Cl was added, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and then purified by radial chromatography (EtOAc/hexanes).

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Supporting Information Available: Experimental procedures and ^1H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026396+

(28) For general experimental procedures see: Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305. The high-resolution mass spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center.