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ω-Halonitriles: Domino Cyclizations to Oxa- and Carbocyclic Nitriles

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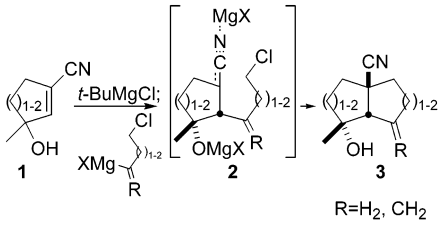
t-BuOK-induced deprotonation of *ω*-haloalkylnitriles generates remarkably stable potassiated nitriles. In situ deprotonation and alkylation of *ω*-chloroalkylnitriles with aldehyde electrophiles trigger sequential nucleophilic−electrophilic alkylations generating substituted tetrahydrofuranyl and tetrahydropyranyl nitriles. Redirecting the cyclization manifold with 5-iodopentanenitrile and a ketone causes a complementary electrophilic−nucleophilic cyclization to the corresponding carbonitrile. Collectively these cyclizations provide rapid assembly of five- and six-membered oxa- and carbocyclic nitriles demonstrating the utility of *ω*-halonitriles in domino alkylations.

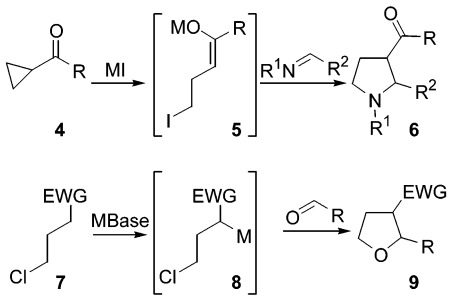
Haloalkyl organometallics are extremely versatile bifunctional reagents.[1] The value of haloalkyl organometallics stems from incorporating two reactive centers of opposite polarity within the same reagent, allowing sequential deployment of two reactive centers in domino reaction sequences[2] (Scheme 1). Sequential conjugate addition-alkylations of haloalkyl organometallics to Michael acceptors, such as alkenenitrile **1**,[3] trigger particularly efficient annulations[4] (Scheme 1) whereas addition-alkylations to imines, aldehydes, and ketones rapidly assembles diverse heterocycles[5] (Scheme 2).

Synthetically more attractive are the less common haloalkyl organometallics generated by deprotonation. The challenge lies in generating the haloalkyl organometallic while avoiding cyclization,[6] a requirement cleverly overcome in the metal iodide-induced cleavage of cyclopropanes[5] where ring opening reversibly generates homoenolates for in situ alkylation with imine and aldehyde electrophiles (**4** → **6**, Scheme 2). Alternatively, homologous chlorobutyl-substituted nitrile,[7] ester,[8] acylthiazolidine-2-thione,[9] acylsilane,[10] and aldehyde[11] functionalities are efficiently deprotonated and alkylated, although only recently have pioneering alkylation-cyclizations emerged as a viable domino alkylation strategy (Scheme 2, **7** → **9**).[12] Collectively these precedents establish the viability of generating haloalkyl organometallics and their potential in domino reactions.

SCHEME 1. *ω*-Haloalkyl Organometallic Annulations



SCHEME 2. *ω*-Haloalkyl Organometallic Cyclizations



(1) Piers, E. *Pure Appl. Chem*. **1988**, *60*, 107.
(2) Ho, T.-L. In *Tandem Organic Reagents*; Wiley: New York, 1992.
(3) Fleming, F. F.; Zhang, Z.; Wang, Q.; Steward. *Org. Lett.* **2002**, *4*, 2493.
(4) (a) Piers, E.; Karunaratne, V. *Tetrahedron* **1989**, *45*, 1089. (b) Piers, E.; Chong, J. M. *Can. J. Chem*. **1988**, *66*, 1425. (c) Piers, E.; Marais, P. C. *J. Chem. Soc., Chem. Commun*. **1989**, 1222. (d) Piers, E.; Friesen, R. W.; Keay, B. A. *Tetrahedron* **1991**, *47*, 4555. (e) Piers, E.; Yeung, B. W. A.; Fleming, F. F. *Can. J. Chem*. **1993**, *71*, 280. (f) Piers, E.; Lemieux, R. *J. Chem. Soc., Perkin. Trans. 1* **1995**, 3. (g) Brown, I. D. *J. Am. Chem. Soc*. **1980**, *102*, 2113. (h) Rozema, M. J.; Rajagopal, D.; Tucker, E. C.; Knochel, P. *J. Organomet. Chem*. **1992**, *438*, 11. (i) Knochel, P.; Singer, R. D. *Chem. Rev*. **1993**, *93*, 2117.
(5) (a) Lautens, M.; Han, W. *J. Am. Chem. Soc*. **2002**, *124*, 6312. (b) Bertozzi, F.; Gustafsson, M.; Olsson, R. *Org. Lett*. **2002**, *4*, 3147. (c) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed*. **1999**, *38*, 3186. (d) Han, Z.; Uehira, S.; Tsuritani, T.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2001**, *57*, 987.
(6) For nitrile cyclizations see: (a) Fleming, F. F.; Shook, B. C.; *Tetrahedron* **2002**, *58*, 1. (b) Diez-Barra, E.; de la Hoz, A.; Moreno, A.; Sánchez-Verdu, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2593. For cyclizations of carbonyl compounds see: (c) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589.
(7) (a) Park, D. J.; Lee, J. K.; Kim, D. H. *Bioorg. Med. Chem*. **2001**, *9*, 237. (b) Reference 6b.
(8) (a) Molander, G. A.; Harris, C. R. *J. Org. Chem*. **1998**, *63*, 4374. (b) Cooke, M. P., Jr. *J. Org. Chem*. **1993**, *58*, 2910. (c) Cooke, M. P., Jr. *J. Org. Chem*. **1992**, *57*, 1495. (d) Comins, D. L.; Brown. J. D. *Tetrahedron Lett*. **1986**, *27*, 2219.
(9) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc*. **1988**, *110*, 289.
(10) Bonini, B. F.; Franchini, M. C.; Mazzanti, A.; Mazzanti, G.; Ricci, A.; Zani, P. *Synthesis* **1995**, 261.
(11) Kuehne, M. E.; Seaton, P. J. *J. Org. Chem*. **1985**, *50*, 4790.

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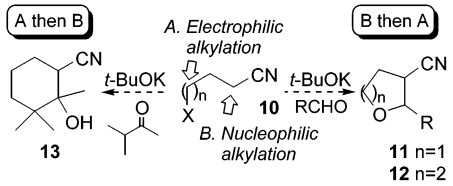
SCHEME 3. Halonitrile Anion Alkylation Strategies

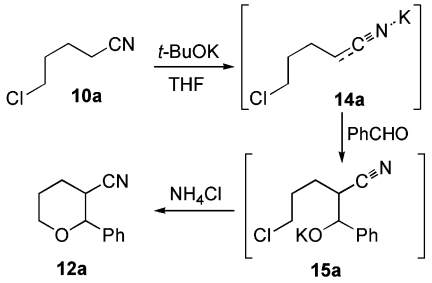


Haloalkyl organometallics have two reactive centers that can potentially be deployed in two complementary bond-forming sequences: nucleophilic-electrophilic alkylations, or electrophilic-nucleophilic alkylations (Scheme 3). Conceptually, interchanging the alkylation order provides complementary strategies to heterocycles and carbocycles from the same haloalkyl organometallic reagent. Independent alkylations of ω-halonitriles[12a,b] achieve these two objectives, providing an array of nitrile-substituted oxa- and carbocyclic nitriles in a single synthetic operation.

Results and Discussion

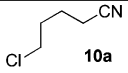
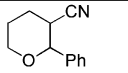
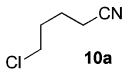
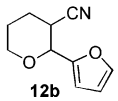
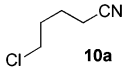
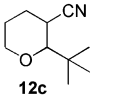
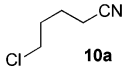
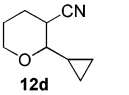
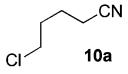
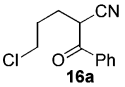
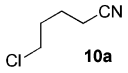
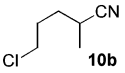
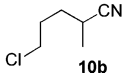
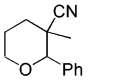
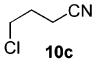
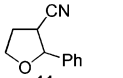
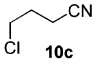
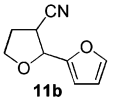
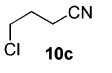
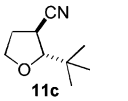
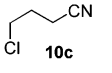
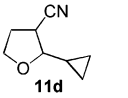
Exploratory deprotonations employed chloronitrile **10a** as a prototype since the potentially deleterious internal cyclization of **14a** to a cyclobutane is significantly slower than that for other medium-sized rings (Scheme 4).[13] Deprotonating the chloronitrile **10a** with *t*-BuOK,[14] in the presence of benzaldehyde, rapidly generates the tetrahydropyranyl nitrile **12a**. Presumably the transient potassiated nitrile **14a** rapidly intercepts benzaldehyde generating **15a** with the nucleophilic potassium alkoxide ideally predisposed for internal displacement to the tetrahydropyranyl nitrile **12a**.

SCHEME 4. Nucleophilic−Electrophilic Alkylation of 10a



The facile cyclization of **10a** with benzaldehyde is typical of the reactivity exhibited with a range of electrophiles (Table 1). Aromatic and aliphatic aldehydes generate tetrahydropyrans equally efficiently, even with the potentially enolizable cyclopropanecarboxaldehyde (Table 1, entry 4). Alkylating potassiated chloropentanecarbonitrile is not limited to aldehyde electrophiles with ethyl benzoate generating the corresponding chloroketonitrile **16a** and MeI alkylation[15] affording the substituted chloropentanenitrile **10b** (Table 1, entries 5 and 6, respectively). The modest diastereoselectivity[16] arises

TABLE 1. *t*-BuOK Alkylations of ω-Chloroalkylnitriles

entry	halonitrile	electrophile	nitrile	yield[a]
1	 **10a**	PhCHO	 **12a**	88% (1:1)
2	 **10a**		 **12b**	75% (1.5:1)
3	 **10a**	*t*-BuCHO	 **12c**	88% (2.5:1)
4	 **10a**		 **12d**	85% (1:1)
5	 **10a**		 **16a**	58%
6	 **10a**	MeI	 **10b**	93%
7	 **10b**	PhCHO	 **12e**	72% (1:1)
8	 **10c**	PhCHO	 **11a**	75% (2.5:1)
9	 **10c**		 **11b**	81% (2:1)
10	 **10c**	*t*-BuCHO	 **11c**	93%
11	 **10c**		 **11d**	72% (1:1)

[a] Isolated yields with diastereomeric ratios in parentheses.

(12) (a) Makosza, M.; Judka, M. *Chem. Eur. J.* **2002**, *8*, 4234. (b) Makosza, M.; Przybrorwski, J.; Klajn, R.; Lwast, A. *Synlett* **2000**, 1773. (c) Shibata, I.; Yamasaki, H.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1992**, *57*, 6909.

(13) Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 678−681.

(14) *t*-BuOK is estimated to have an acidity comparible to that of 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 of *t*-BuOK in DMSO see: Cram, D. J.; Rickborn, B.; Knox, G. R. *J. Am. Chem. Soc.* **1960**, *82*, 6412.

(15) Alkylation was performed with excess *t*-BuOK (10 equiv) and MeI (10 equiv) since formation of *t*-BuOMe competes with the alkylation.

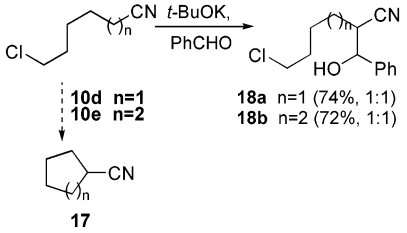
(16) X-ray crystallography permitted unequivocal stereochemical assignments for **12e** (CCDC 201175), (±)-(*R*,*R*)-**18b** (CCDC 201178), **13**-*cis* (CCDC 201177), and **13**-*trans* (CCDC 201178). The supplementary crystallographic data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK (fax +44 1223 336033; or deposit@ccdc.cam.ac.uk.)

from epimerization of the cyclic nitriles[12a] with no facial discrimination occurring for the attack of **10b** on benzaldehyde where formation of the quaternary center prevents subsequent equilibration (Table 1, entry 7).[17]

Remarkably, 4-chlorocyclobutanenitrile (**10c**) triggers an analogous cyclization to tetrahydrofuranyl nitriles (Table 1, entries 8−11) despite the seemingly increased propensity of the intermediate nitrile anion toward internal cyclization to a cyclopropane.[13] *t*-BuOK-initiated deprotonation of **10c**, with in situ trapping, generates tetrahydrofuranyl nitriles with aryl- and alkyl-substituted aldehydes, with pivaldehyde affording **11c** as a single geometric isomer (Table 1, entry 10).

Control experiments at 0 °C indicate that, in the absence of an electrophile, complete cyclization of **10a** occurs within 3 h whereas **10c** cyclizes in less than 10 min.[18] The viability of deprotonating ω-chloronitriles **10a**, **10b**, and **10c** prompted analogous in situ alkylations with ω-chlorohexane- and ω-chloroheptanenitriles, **10d** and **10e**, that can potentially cyclize to five- and six-membered carbonitriles **17** (Scheme 5). Remarkably, no observable *intramolecular* cyclization to five- or six-membered carbonitriles occurs on deprotonating **10d** or **10e** in the presence of benzaldehyde. Exclusive *intermolecular* alkylation generates intermediate alkoxides without forming oxacycles, reflecting the increased steric demands required for cyclizations to medium-sized rings.[13]

SCHEME 5. Alkylations of Homologous ω-Haloalkylnitriles



Collectively the sequential nucleophilic−electrophilic alkylations of **10a**−**e** demonstrate the viability and utility of metalated ω-halonitriles. The remaining challenge of a reversed electrophilic−nucleophilic alkylation sequence was probed with the more electrophilic bromopentanenitrile **10f** (Scheme 6).[19] Addition of the nitrile **10f** to an excess of *t*-BuOK and ketone **19** triggers the desired enolate alkylation-cyclization[20] generating **13** in a modest 32% yield, in addition to the tetrahydropyranyl nitrile **12f** (8%), and the alkenenitrile **22** (20%). Formation of the alkenenitrile **22** arises by a *t*-BuOK-initiated ring opening of the first-formed nitrile **12f** as implied by resubjecting **12f** to *t*-BuOK, which affords **22**.[21] Consistent with this mechanism is the substitution of the less electrophilic chloropentanenitrile (**10a**) for bromopentanenitrile (**10f**) that diverts the cascade sequence entirely toward formation of **12f** and **22** with no detectable formation of the carbonitrile **13**.

Formation of the nitriles **12f** and **22** provided key mechanistic insight for optimizing the electrophilic−nucleophilic alkylation sequence. Formation of nitriles **12f** and **22** requires facile proton transfer[22] between the ketone enolate **20** and nitrile **10f** ($\Delta pK_a = 5-10$),[23] followed by preferential nitrile anion−ketone condensation (**14f** + **19** → **15f**).[22] Whereas moderating the proton transfer is difficult, redirecting the cascade manifold in favor of carbonitrile **13** simply requires a more reactive electrophile. Indeed, repeating the electrophilic−nucleophilic alkylation cascade with the more electrophilic iodopentanenitrile **10g** (**10f**, Br = I) redirects the cyclization cascade to exclusively[24] afford carbonitrile **13** in 63% yield.[25] Mechanistically the reaction is remarkably efficient given the series of proton transfers required during the sequential alkylations leading to installation of the two new bonds.

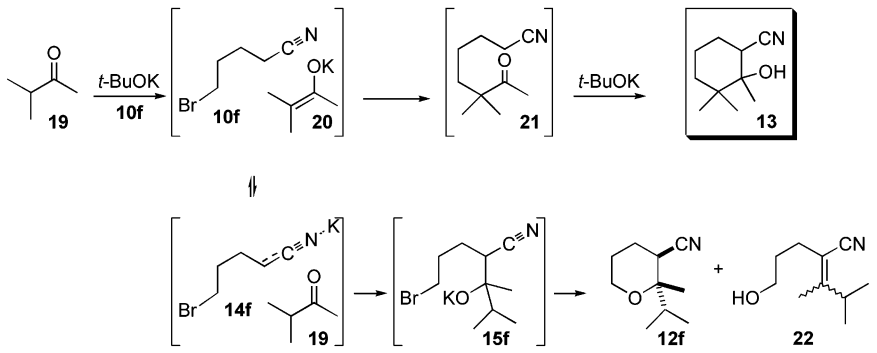
Conclusion

t-BuOK readily deprotonates ω-haloalkylnitriles to generate remarkably stable potassiated nitriles. Intercepting the potassiated nitriles with ester and alkyl halide electrophiles generates substituted ω-halonitriles whereas aldehyde electrophiles trigger sequential nucleophilic−electrophilic alkylations affording tetrahydrofuranyl and tetrahydropyranyl nitriles. Redirecting the cyclization manifold with the corresponding iodonitrile permits a reversed electrophilic−nucleophilic alkylation sequence where in situ enolate alkylation, deprotonation, and cyclization generates the corresponding carbonitrile. The complementary cyclization manifolds provide rapid assembly of five- and six-membered oxa- and carbocyclic nitriles demonstrating the utility of metalated ω-halonitriles in domino alkylation-cyclizations.

Experimental Section

General Procedure for Alkylations of Chloronitriles 10a−c. Addition of the electrophile (1 equiv, neat) to a 0 °C,

SCHEME 6. Electrophilic−Nucleophilic Alkylation Cascade to Carbonitrile 13



THF solution of *t*-BuOK (1 equiv) was followed immediately by the addition of the *ω*-chloronitrile. After 3 h, the reaction mixture was allowed to warm to room temperature and saturated, aqueous NH_4Cl was then added. The crude reaction mixture was then separated, the aqueous fraction extracted with EtOAc, and the combined crude product passed through a short plug of silica, concentrated, and purified by radial chromatography.

Acknowledgment. Financial support from NIH is gratefully acknowledged.

Supporting Information Available: Experimental procedures, ^1H NMR and ^{13}C NMR spectra for all new compounds, and ORTEP's for **12e**, **18**, **10**-*trans*, and **10**-*cis*. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For an extensive survey of factors controlling the stereoselectivity of "nitrile-aldol" reactions see: Carlier, P. R.; Lo, K. M.; Lo, M. M.-C.; Lo, P. C.-K.; Lo. C. W.-S. *J. Org. Chem.* **1997**, *62*, 6316.

(18) Rapid internal cyclization of **10c** occurs at −30 °C.[12a]

(19) For a related two-step malonate cyclization see: Meyer, W. L.; Goodwin, T. E.; Hoff, R. J.; Sigel, C. W. *J. Org. Chem.* **1977**, *42*, 2761.

(20) Walkup, R. D.; Boatman, P. D., Jr.; Kane, R. R.; Cunningham, R. T. *Tetrahedron Lett.* **1991**, *32*, 3937.

(21) Exposure of **12f** to *t*-BuOK in THF generates the alkenenitrile **22** accompanied by considerable polymeric material. Formation of **12f** as a single diastereomer, coupled with the modest conversion of **12f** to **22**, suggests that the diastereomer of **12f** is also generated and more efficiently converted to the alkenenitrile **22**.

(22) Fleming, F. F.; Funk, L. A.; Altundas, R.; Sharief, V. *J. Org. Chem.* **2002**, *67*, 9414.

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

(24) No tetrahydropyranyl nitrile **11f** or alkenenitrile **22** was evident by ^1H NMR analysis of the crude reaction mixture.

(25) Analogous alkylations of **20** with iodobutanenitrile were unsuccessful, presumably due to rapid formation of the corresponding nitrile anion and subsequent cyclization to a cyclopropane.[12a]