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Metalated Nitrile and Enolate Chlorinations

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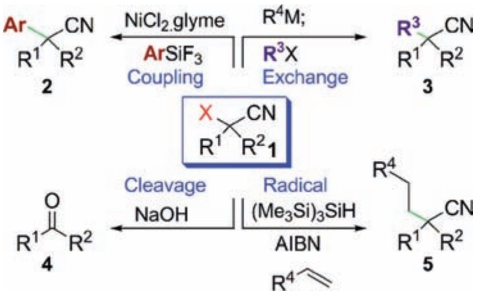
ABSTRACT

Metalated nitriles and enolates rapidly and efficiently abstract chlorine from 2-chloro-2-fluoro-2-phenylacetonitrile to afford a diverse range of chloronitriles and chloroesters. The method provides the first general anionic chlorination of alkylnitriles, tolerates numerous functional groups, and addresses the challenge of synthesizing α-chloronitriles under mild conditions.

α-Halonitriles are versatile synthetic precursors by virtue of having two orthogonal functionalities substituting the same carbon. The powerful inductive electron withdrawal[1] of the nitrile activates the C−X bond toward transition-metal insertion in cross-coupling reactions[2] (**1** → **2**). An analogous activation facilitates the halogen−metal exchange, even with chloronitriles, despite alkyl chlorides generally being unreactive in this type of exchange (**1** → **3**, Scheme 1).[3] The electron-withdrawing halogen also activates the nitrile group with the generally difficult nitrile hydrolysis[4] proceeding easily in a versatile hydrolysis−decarboxylation route to ketones (**1** → **4**, Scheme 1).[5] The synergistic effect of geminal halogen and nitrile substitution also facilitates radical reactions, with chloronitriles undergoing homolytic cleavage and radical addition in the presence of an initiator and a hydrogen atom donor (**1** → **5**, Scheme 1).[6]

Scheme 1. Representative Ractions of α-Halonitriles



Historically, the two most prevalent routes to halonitriles are through Diels−Alder cycloadditions with α-haloacrylonitriles[7] and by free-radical halogenation of alkanenitriles. Typically, these free-radical halogenations require rather

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(1) (a) Richard, J. P.; Williams, G.; Gao, J. *J. Am. Chem. Soc.* **1999**, *121*, 715. (b) Bradamante, S.; Pagani, G. A. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1035. (c) Dayal, S. K.; Ehrenson, S.; Taft, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 9113.

(2) Strotman, N. A.; Sommer, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3556. For an electrochemical variation, see: Cannes, C.; Condon, S.; Durandetti, M.; Perichon, J.; Nedelec, J.-Y. *J. Org. Chem.* **2000**, *65*, 4575.

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(4) Eglin, J. L. *Comments Inorg. Chem.* **2002**, *23*, 23.

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(6) (a) Schule, A.; Liang, H.; Vors, J.-P.; Ciufolini, M. A. *J. Org. Chem.* **2009**, *74*, 1587. (b) Miura, K.; Fujisawa, N.; Saito, H.; Wang, D.; Hosomi, A. *Org. Lett.* **2001**, *3*, 2591.

(7) For reviews see: (a) Aggarwal, V. K.; Ali, A.; Coogan, M. P. *Tetrahedron* **1999**, *55*, 293. (b) Ranganathan, S.; Ranganathan, D.; Mehrota, A. K. *Synthesis* **1977**, 289.

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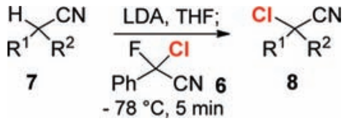
strong electrophilic halogen sources[8] such as chlorine[9] or bromine,[10] NBS,[11] PCl_5,[12] or PBr_5.[13] Sporadic iodinations of metalated nitriles[14] demonstrate the viability of developing a general electrophilic halogen source, although trapping with molecular iodine lacks generality.[15] In addition, iodonitriles are thermally labile[16] and have a limited reagent tolerance. The current challenge in synthesizing halonitriles lies in developing an efficient and reproducable halogenating agent with functional group tolerance.

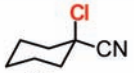
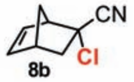
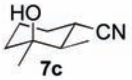
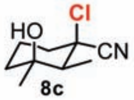
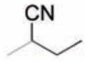
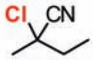
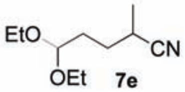
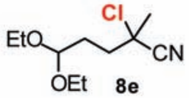
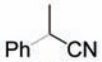
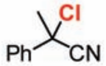
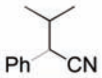
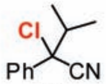
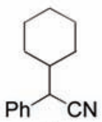
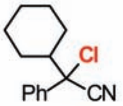
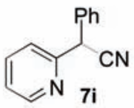
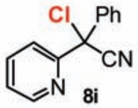
Exploratory alkylations of metalated nitriles with 2-chloro-2-fluoro-2-phenylacetonitrile (**6**)[17] serendipitously revealed this reagent to be an excellent chlorinating agent (Table 1).[18] Optimizations with cyclohexanecarbonitrile (**7a**) revealed the need to *rapidly* add a slight excess of **6** to the lithiated nitrile to prevent dimerization (Table 1, entry 1).[19] This simple expedient minimizes the attack of the lithiated nitrile, derived from **7**, on the electrophilic chloronitrile **8**, efficiently providing the chloronitrile in less than 5 min at −78 °C.

LDA-induced deprotonation and rapid addition of **6** efficiently halogenates a range of alkylnitriles (Table 1). Cyclic and acyclic alkylnitriles (Table 1, entries 1−5) are readily chlorinated as are several significantly more acidic[20] arylacetonitriles (Table 1, entries 6−9). The chlorination method is ideal for nitriles bearing functionality that would otherwise react with radical-based halogenating agents: nitriles **7b**, **7c**, **7e**, and **7i**,[21] containing alkene, alcohol, acetal, and pyridine functionalities, respectively. The only limitation lies in the substitution of the alkylnitriles which must be tertiary.[22]

Encouraged by the effective chlorination of nitriles, the analogous chlorination of enolates was explored. The attraction lies in expanding the limited number of electrophilic halogenating agents available for intercepting ester enolates.[23] Using the same deprotonation−chlorination protocol with a series of ester enolates and 2-chloro-2-fluoro-2-phenylacetonitrile (**6**) readily provides the corresponding chloroesters (Table 2, entries 1−7). Aliphatic, acyclic, and cyclic esters are efficiently chlorinated as is the benzylic ester **9g** (Table 2, entry 7). Alkenes are tolerated within the acyl skeleton (Table 2, entries 1 and 4) and in the alkyl chain (Table 2, entry 2). Analogous chlorinations of ketone and lactone enolates smoothly afford the corresponding chloroketone and

Table 1. Metalated Nitrile Chlorinations



entry	nitrile	chloronitrile	yield (%)
1	 **7a**	 **8a**	93
2	 **7b**	 **8b**	93[a]
3	 **7c**	 **8c**	76[b]
4	 **7d**	 **8d**	85
5	 **7e**	 **8e**	94
6	 **7f**	 **8f**	92
7	 **7g**	 **8g**	93
8	 **7h**	 **8h**	79
9	 **7i**	 **8i**	76

[a] 14.3:1 ratio of diastereomers at the nitrile-bearing carbon. [b] 9:1 ratio of diastereomers at the nitrile-bearing carbon.

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(8) Halonitriles are also generated by halogenating cyanohydrins: (a) Matveeva, E. D.; Podrugina, T. A.; Tishkovskaya, E. V.; Zefirov, N. S. *Mendeleev Commun.* **2003**, 260–262. (b) Gassman, P. G.; Guggenheim, T. L. *J. Org. Chem.* **1982**, *47*, 3023.

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(12) Freeman, P. K.; Balls, D. M.; Brown, D. J. *J. Org. Chem.* **1968**, *33*, 2211.

(13) Stevens, C. L.; Coffield, T. H. *J. Am. Chem. Soc.* **1951**, *73*, 103.

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(15) Sequential silylketenimine formation and iodination is currently the most general route to iodonitriles but is limited to arylacetonitriles: Watt, D. S. *J. Org. Chem.* **1974**, *39*, 2799.

(16) Mori, M.; Kubo, Y.; Ban, Y. *Heterocycles* **1990**, *31*, 433.

(17) Commercially available from SynQuest Fluorochemicals.

(18) In an extensive screening of halogenating agents no electrophilic halogen source was as effective as 2-chloro-2-fluoro-2-phenylacetonitrile (**6**).

(19) Li, X.; Jain, N.; Russell, R. K.; Ma, R.; Branum, S.; Xu, J.; Sui, Z. *Org. Process Res. Dev.* **2006**, *10*, 354.

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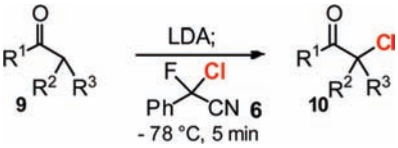
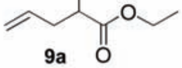
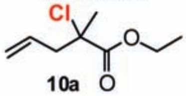
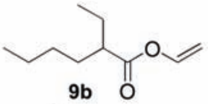
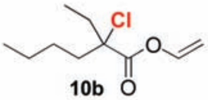
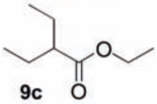
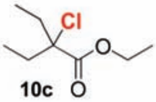
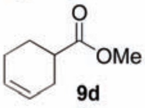
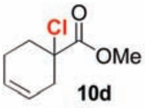
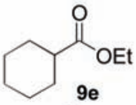
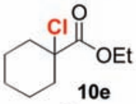
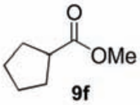
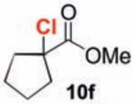
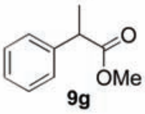
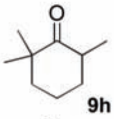
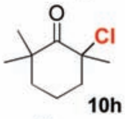
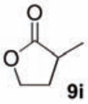
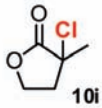
(21) Deutsch, H. M.; Shi, Q.; Gruszecka-Kowalik, E.; Schweri, M. M. *J. Med. Chem.* **1996**, *39*, 1201.

(22) The conversion with secondary nitriles is low and considerable dimerization is observed. A similar limitation exists for the iodination of aldehyde enolates: Groenewegen, P.; Kallenberg, H.; van der Gen, A. *Tetrahedron Lett.* **1979**, 2817.

(23) (a) Arnold, R. T.; Kulenovic, S. T. *J. Org. Chem.* **1978**, *43*, 3687. (b) Stotter, P. L.; Hill, K. A. *J. Org. Chem.* **1973**, *38*, 2576. (c) Rathke, M. W.; Lindert, A. *Tetrahedron Lett.* **1971**, 3995.

Table 2. Chlorination of Ester and Ketone Enolates

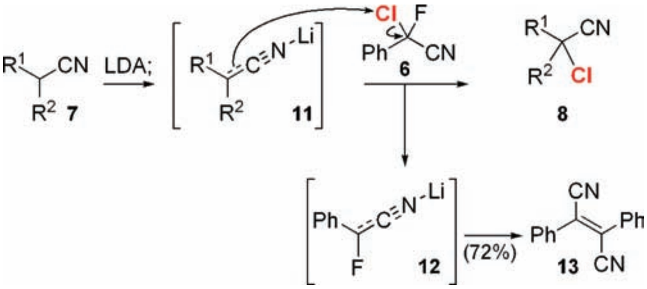


entry	carbonyl	chloronitrile	yield (%)
1	 9a	 10a	76
2	 9b	 10b	77
3	 9c	 10c	75
4	 9d	 10d	82
5	 9e	 10e	78
6	 9f	 10f	80
7	 9g	 10g	74
8	 9h	 10h	83
9	 9i	 10i	74

chlorolactone (Table 2, entries 8 and 9, respectively), hinting at the generality for chlorinating these carbonyl-containing functionalities.

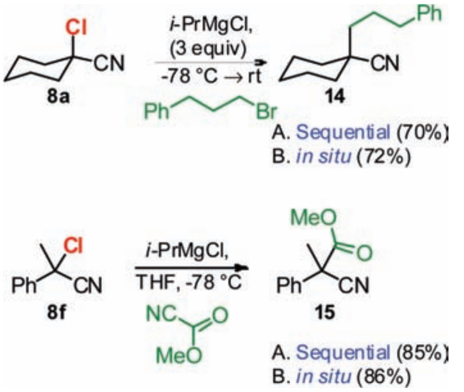
Chlorofluoronitrile **6** functions as an excellent electrophilic chlorine source,[24] probably because of the powerful electron withdrawal by the adjacent nitrile[1] and fluorine groups.[1c] Mechanistically, nucleophilic S_N2-type attack[24a,25] of the metalated nitrile, or enolate, on **6** might generate the chlorinated nitrile or carbonyl with simultaneous formation of lithiated fluorophenylacetonitrile (**12**).[26] Isolating fumaronitrile (**13**)[27] as the aromatic fragment is consistent with a nucleophilic displacement on **6** releasing the carbenoid **12**[28] which subsequently dimerizes to fumaronitrile (**13**) (Scheme 2).[29]

Scheme 2. Metalated Nitrile Chlorination Mechanism



Prior halogen−magnesium exchange reactions, primarily with bromonitriles, indicated that chloronitriles do not undergo chlorine−magnesium exchange.[3] Access to diverse chloronitriles allowed a reinvestigation which revealed that chloronitriles do exchange with *i*-PrMgCl, although at higher temperatures than for the corresponding bromonitrile.[30] Addition of 3 equiv of *i*-PrMgCl to **8a** and warming to room temperature effectively generates a nucleophilic magnesiated nitrile (Scheme 3). Intercepting the magnesiated nitrile with 3-phenylpropyl bromide affords the alkylated nitrile **14** in

Scheme 3. *i*-PrMgCl Exchange−Alkylation of Chloronitriles



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[24] For related halogenating agents, see: (a) Plaumann, H. P.; Rodrigo, R. *Pol. J. Chem.* **1979**, *53*, 201. (b) Hata, T. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 547.

[25] Blay, G.; Cardona, L.; Garcia, B.; Lahoz, L.; Pedro, J. R. *Tetrahedron* **1996**, *52*, 8611.

(26) Current mechanistic experiments do not exclude a single electron transfer (SET) process. Small quantities of fluorophenylacetonitrile (**i**) are occasionally isolated in the chlorinations which could be accounted for by SET or S_N2 mechanisms. (a) Jonczyk, A.; Kwast, A.; Makosza, M. *J. Org. Chem.* **1979**, *44*, 1192.

(27) Spectrally indistinguishable to previously reported material: Yeh, H.-C.; Wu, W.-C.; Wen, Y.-S.; Dai, D.-C.; Wang, J.-K.; Chen, C.-T. *J. Org. Chem.* **2004**, *69*, 6455.

(28) Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697.

(29) (a) Maryanoff, C. A.; Sorgi, K. L.; Zientek, A. M. *J. Org. Chem.* **1994**, *59*, 237. (b) Makosza, M.; Serafin, B.; Gajos, I. *Rocz. Chem.* **1969**, *43*, 671.

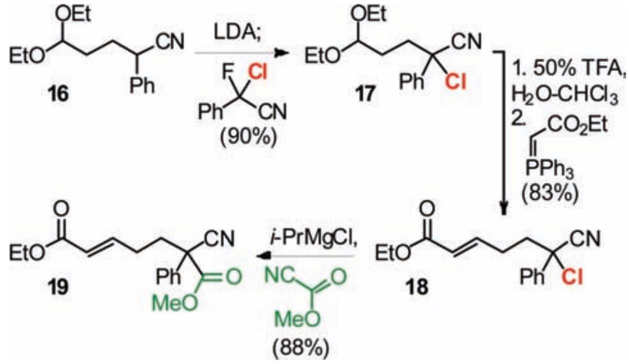
(30) The chloronitrile **8a** requires room temperature, whereas the corresponding bromonitrile exchanges with *i*-PrMgCl virtually instantaneously at − 78 °C.[3]

70% yield. Essentially the same efficiency is realized by adding *i*-PrMgCl to a solution containing the chloronitrile and the electrophile.

The analogous chlorine−magnesium exchange of the arylacetonitrile **8f** is significantly more facile. Activation of the carbon-chlorine bond by the aromatic ring likely facilitates the exchange which proceeds at −78 °C.[31] Sequentially adding *i*-PrMgCl and methyl cyanoformate to **8f** affords the ester nitrile **15** in 85% yield (Scheme 3). Essentially the same efficiency is achieved with an in situ procedure in which *i*-PrMgCl is added to a −78 °C THF solution containing **8f** and methyl cyanoformate.

The potential of chloronitriles as synthetic intermediates is illustrated in the synthesis and chlorine−magnesium exchange of the functionalized chloronitrile **18** (Scheme 4). Chlorination of the acetal-containing nitrile **16** efficiently provides the chloronitrile **17**. Subsequent acid-catalyzed hydrolysis and Wittig olefination **17** → **18** proceed without interference of the chloronitrile functionality. In fact α-chloronitriles readily tolerate acid,[32] ozone,[33] oxidants,[34] hydride reducing agents,[35] and hydrogenation.[36] The in situ chlorine−magnesium exchange and alkylation of **18** with methyl cyanoformate tolerates the enoate to efficiently generate the ester nitrile **19**. The selective formation of the magnesiated nitrile from **18** represents one of the few examples of selectively forming a metalated nitrile in the presence of an enolizable carbonyl functionality.[37]

Scheme 4. Reagent Tolerance of Chloronitriles



α-Chloronitriles are readily prepared by deprotonating tertiary nitriles and rapidly adding the highly unusual electrophilic chlorine source 2-chloro-2-fluoro-2-phenylacetonitrile (**6**). The method overcomes the long-standing difficulty of preparing functionalized halonitriles that were typically accessed under vigorous free radical conditions. Ester, lactone, and ketone enolates react analogously, efficiently providing the corresponding α-chloro ester, α-chloro lactone, and α-chloro ketone functionalities. The viability of a chlorine−magnesium exchange with α-chloronitriles is demonstrated, and their use as robust, latent metalated nitriles is illustrated in the synthesis of a functionalized ester nitrile. The high yields and the functional group tolerance make this an ideal method for preparing chloronitriles.

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Supporting Information Available: Experimental procedures and ^{1}H 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.

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