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Metalated Nitriles: Halogen–Metal Exchange with α-Halonitriles

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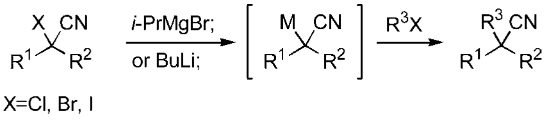
ABSTRACT



α-Halonitriles react with organometallic reagents in a facile halogen–metal exchange. The halogen–metal exchange is extremely fast with Grignard and alkyllithium reagents, generating metalated nitriles in situ with aldehyde, ketone, acid chloride, and acyl cyanide electrophiles. Sequential halogen–metal exchange and methylation of conformationally constrained nitriles is highly stereoselective and consistent with a retentive alkylation of a C-magnesiated nitrile.

α-Metalated nitriles are particularly versatile synthetic intermediates.[1] The versatility stems from the high carbon nucleophilicity of metalated nitriles[1] and the ease of converting the nitrile group into a plethora of functional derivatives.[2] These synthetically valuable traits have led to metalated nitriles being featured in numerous sterically demanding alkylations.[1]

Metalated nitriles are typically generated by deprotonation with metal amide bases.[1b] Seminal X-ray structures of metalated nitriles,[3] generated with excess amide bases,[4] reveal a preference for coordination of the metal with the nitrile nitrogen that is consistent with solution NMR and IR analyses[5] (Figure 1, **1**). Coordination of the metal at carbon is only observed with lithiated cyclopropylnitriles where N- and C-coordination exist, with the latter C-lithiated nitrile being favored by the hybridization of the cyclopropane ring (Figure 1, **2**).[6] Conceptually, the metal coordination site in metalated nitriles could potentially relay into reactivity differences, as implied by intriguing stereoselectivity differences exhibited by metalated nitriles generated in the absence of amines.[7]

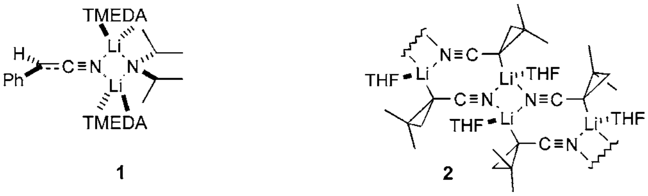


Figure 1. X-ray structures of metalated nitriles.

Historically, probing the reactivity of metalated nitriles in the absence of amines has been complicated by the difficulty in generating metalated nitriles without recourse to metal amides for deprotonation. Density functional

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[†] Duquesne University.

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(1) (a) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1. (b) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React.* **1984**, *31*, 1.

(2) Fatiadi, A. J. In *The Chemistry of Triple-Bonded Functional Groups. Supplement C*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1983; pp 1157−1190.

(3) Boche, G. *Angew. Chem., Int. Ed.* **1989**, *28*, 277.

(4) Zarges, W.; Marsch, M.; Harms, K.; Boche, G. *Angew. Chem., Int. Ed.* **1989**, *28*, 1392.

(5) For leading references, see: (a) Corset, J.; Castellà-Ventura, M.; Froment, F.; Strzalko, T.; Wartski, L. *J. Org. Chem.* **2003**, *68*, 3902. (b) Carlier, P. R.; Lo, C. W.-S. *J. Am. Chem. Soc.* **2000**, *122*, 12819. (c) Carlier, P. R.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 11602.

(6) (a) For a crystal structure, see: Boche, G.; Harms, K.; Marsch, M. *J. Am. Chem. Soc.* **1988**, *110*, 6925. (b) For solution alkylations, see: Walborsky, H. M.; Motes, J. M. *J. Am. Chem. Soc.* **1970**, *92*, 2445.

(7) Fleming, F. F.; Shook, B. C. *J. Org. Chem.* **2002**, *67*, 2885.

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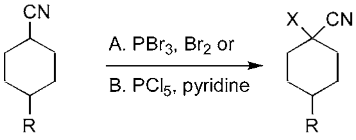
calculations[8] reveal that deprotonation with lithium amide bases leads directly to N-metalated nitriles, precluding their use for kinetically accessing C-metalated nitriles. Alternatively, the metal hydrides NaH and KH are generally ineffective for deprotonating aliphatic nitriles,[1b] whereas *t*-BuOK, while excellent for deprotonating nitriles,[9] has the complication of establishing rapid prototropic equilibria.[10]

A potentially general route for generating metalated nitriles, without recourse to amide bases, is through halogen−metal exchange.[11] Halogen−metal exchange of related α-iodoketones[12] permits facile enolate formation, though the analogous formation of metalated nitriles is unknown, despite the opportunity for selectively generating elusive C-metalated nitriles. The opportunity for accessing C-metalated nitriles, with the added attraction of potentially generating metalated nitriles in the presence of more acidic functionality, stimulated the development of a halogen−metal exchange with α-halonitriles.

Diverse α-halonitriles are available by free-radical halogenation[13] and from α-haloacrylonitriles by Diels−Alder cycloaddition[14] and organomercurial conjugate additions.[15] Direct halogenation is particularly robust, providing α-bromonitriles with PBr_3/Br_2[16] and α-chloronitriles with PCl_5/pyridine[17] (Scheme 1). Collectively, these halogenations provide a range of α-halonitriles for probing the halogen−metal exchange.

Scheme 1. Synthesis of α-Halonitriles

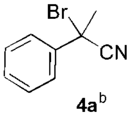
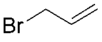
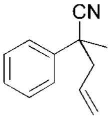
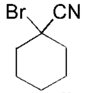
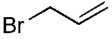
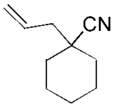
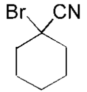
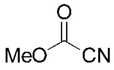
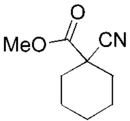
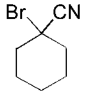
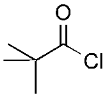
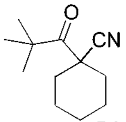
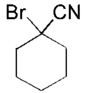
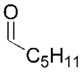
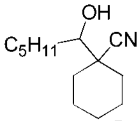
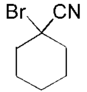
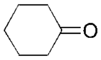
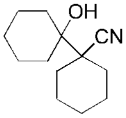
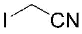
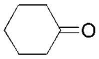
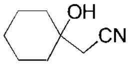
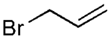
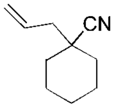
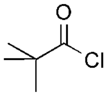
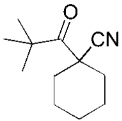


3

4b X=Br, R=H (90%)
4c X=Br, R=*t*-Bu (73%)
4d X=Cl, R=H (81%)

Halogen−metal exchange of α-halonitriles is extremely rapid. Exploratory exchange reactions with **4a** and *i*-PrMgBr caused an immediate yellow coloration that correlated with the virtually instantaneous exchange at −78 °C. Intercepting the metalated nitrile derived from **4a** with allyl bromide affords the corresponding quaternary nitrile **5a** (Table 1, entry 1). The generality of the halogen−metal exchange was probed with **4b** and a range of electrophiles that affords a variety of alkylated nitriles (Table 1, entries 2−6).

Table 1. Halogen−Metal Exchange of α-Halonitriles

entry	α-halonitrile	conditions	nitrile	yield[a]	
				a	b
1	 **4a**[b]	*i*-PrMgBr 	 **5a**	72%	
2	 **4b**	*i*-PrMgBr 	 **5b**	62%	82%
3	 **4b**	*i*-PrMgBr 	 **5c**	58%	80%
4	 **4b**	*i*-PrMgBr 	 **5d**	52%	70%
5	 **4b**	*i*-PrMgBr 	 **5e**		65%
6	 **4b**	*i*-PrMgBr 	 **5f**		73%
7	 **4e**	*i*-PrMgBr 	 **5g**		79%
8	 **4d**	BuLi 	 **5b**	72%	
9	 **4d**	BuLi 	 **5c**	54%	

[a] Isolated yields for sequential metalation−alkylation, column a, and with an in situ metalation−alkylation, column b. [b] Prepared by free-radical bromination with NBS.[18]

The extremely rapid halogen−metal exchange suggested performing the exchange with the electrophile in situ.[19]

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(8) Carlier, P. R. *Chirality* **2003**, *15*, 340.

(9) For recent examples, see: (a) Fleming, F. F.; Gudipati, V.; Steward, O. W. *J. Org. Chem.* **2003**, *68*, 3943. (b) Bunlaksananusorn, T.; Rodriguez, A. L.; Knochel, P. *Chem. Commun.* **2001**, 745. (c) Makosza, M.; Judka, M. *Chem. Eur. J.* **2002**, *8*, 4234.

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

(11) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4415.

(12) (a) William, A. D.; Kobayashi, Y. *J. Org. Chem.* **2002**, *67*, 8771. (b) Aoki, Y.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1995**, 463.

(13) (a) Hartzler, H. D. In *The Chemistry of the Cyano Group*; Rappoport, Z., Ed.; Wiley-Interscience: New York, 1970; Chapter 11, pp 671−716. (b) For a novel photochemical conjugate addition−halogenation, see: Mitani, M.; Kato, I.; Koyama, K. *J. Am. Chem. Soc.* **1983**, *105*, 6719.

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

(15) (a) Russel, G. A.; Shi, B. Z. *Synlett* **1993**, 701. (b) Giese, B.; González-Gómez, J.-A. *Chem. Ber.* **1986**, *119*, 1291.

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

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

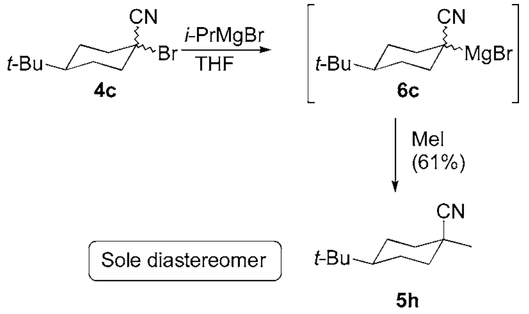
(18) Rouz-Schmitt, M.-C.; Petit, A.; Sevin, A.; Seyden-Penne, J.; Anh, N. T. *Tetrahedron* **1990**, *46*, 1263.

Remarkably, the in situ electrophilic alkylation is successful with acyl cyanide, acid chloride, ketone, and even aldehyde electrophiles (Table 1, entries 3−6).[20] In no instance was prior addition of the organometallic to the electrophile observed; in fact, the yield of reactions with in situ electrophilic alkylation was consistently 20% higher (Table 1, column b). Significantly, the successful in situ metalation−alkylation of iodoacetonitrile with *i*-PrMgBr indicates that the metal halogen exchange is even faster than the potentially competitive deprotonation (entry 7).[21]

α-Chloronitriles are successfully metalated despite the difficulty generally observed in chlorine−metal exchange reactions.[22] Metal−halogen exchange of chloronitriles is best achieved with BuLi rather than *i*-PrMgBr, allowing sequential lithiation−alkylation (Table 1, entries 8 and 9). Formation of lithiated nitriles from α-chloronitriles is particularly significant since numerous α-chloronitriles are readily available from Diels−Alder cycloadditions.[14]

Mechanistically, halogen−metal exchange likely generates a C-metalated nitrile.[23] The configurational stability of the putative C-metalated nitrile was probed through the in situ methylation of a diastereomeric mixture[24] of nitriles **4c** (Scheme 2). Formation of a single methylated nitrile **5h** indicates that the equilibration of the C-metalated nitriles is rapid, relative to methylation, presumably through a conducted tour mechanism.[8] Exclusive[25] formation of the equatorially oriented methyl group is consistent with formation of an equatorial, C-magnesiated nitrile that alkylates methyl iodide with retention of configuration.[26]

Scheme 2. Stereoselective Alkylation



Grignard and alkyllithium reagents trigger the rapid metal−halogen exchange of α-halonitriles. The resulting metalated nitriles alkylate a variety of electrophiles that are most efficiently intercepted in situ, preferentially allowing halogen−metal exchange with *i*-PrMgBr or BuLi even in the presence of reactive electrophiles. *i*-PrMgBr-induced exchange and alkylation with diastereomeric bromonitriles causes a rapid equilibration of the initial C-magnesiated nitriles that converge to a single methylated nitrile upon alkylation. Collectively, the metal−halogen exchange provides a general route to metalated nitriles for probing the stereo- and regiochemical dependence in diverse metalated nitrile alkylations.

Acknowledgment. Financial support of this research and travel funds from NSF are gratefully acknowledged.

Supporting Information Available: ^{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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(19) For an excellent survey of halogen−metal exchange reactions in the presence of electrophiles, see: Clayden, J. In *Organolithiums: Selectivity for Synthesis*; Pergamon: Amsterdam, 2002; pp 116 and 284−287.

(20) **Representative Procedure.** A THF solution of *i*-PrMgBr (1.05 equiv) was added to a −78 °C THF (1 mmol) solution of **4b** and the electrophile (1.05 equiv). After 2 h, saturated, aqueous NH_4Cl solution was added, and the crude product was extracted with EtOAc, concentrated, and purified by radial chromatography to afford analytically pure material by HRMS and ^{1}H and ^{13}C NMR.

(21) Only a trace of the iodo alcohol arising from the deprotonation of **4e** and addition of the resulting anion to cyclohexenone was detected.

(22) Reference 19, Chapter 3.

(23) Halogen−metal exchange through an ate complex leads to C-metalation, although progression to an *N*-metalated nitrile is conceivable: (a) Hoffmann, R. W.; Brönstrup, M.; Müller, M. *Org. Lett*. **2003**, *5*, 313. (b) Schulze, V.; Brönstrup, M.; Böhm, V. P. W.; Schwerdtfeger, P.; Schimeczek, M.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 824. (c) Reich, H. J.; Green, D. P.; Phillips, N. H.; Borst, J. P.; Reich, I. L. *Phosphorus, Sulfur, Silicon* **1992**, *67*, 83.

(24) A 2:1 ratio of diastereomers was employed.

(25) ^{1}H NMR analysis of the crude reaction mixture failed to identify any of the independently prepared diastereomeric nitrile.

(26) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 717.