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A simple, general synthesis of carbonimidic dichlorides

Claire M. Gober, Hoang V. Le, Bruce Ganem *

Department of Chemistry & Chemical Biology, Baker Laboratory, Cornell University, Ithaca, NY 14853-1301, USA

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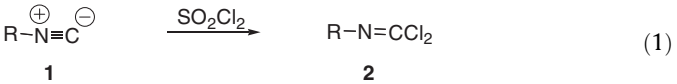
ABSTRACT

The reaction of aliphatic and aromatic isonitriles with sulfuryl chloride provides an efficient, general route to the corresponding dichlorides without byproducts of free-radical substitution.

Isonitriles, which have been known for over 150 years, embody the only stable functional group containing a divalent carbon atom. As one consequence of their unusual electronic structure, isonitriles display a broad range of chemical reactivity with both nucleophiles and electrophiles. For that reason, isonitriles have long played a central role in the design and development of multicomponent reactions.[1]

Carbonimidic dihalides (also known as isonitrile dihalides; typically dibromides or dichlorides) have recently attracted attention in their own right, not only as protecting groups for isonitriles,[2] but also as building blocks for more complex molecular architectures.[3] Carbonimidic dibromides can usually be prepared by simple addition of elemental bromine to the isonitrile. However, as noted in a seminal review,[4] the comparable addition of elemental chlorine (Cl_2) to isonitriles is not a generally useful reaction with alkylisonitriles, since free-radical processes generally produce alkyl chloride byproducts resulting from C–H substitution.

Here we report that the chlorination of isonitriles **1** using sulfuryl chloride rapidly and selectively furnishes the corresponding carbonimidic dichlorides **2** Eq. 1. Besides being readily available, inexpensive, and quite convenient to use, sulfuryl chloride is also easy to purify and manipulate in small quantities for benchtop experimentation.



1 **2** (1)

Sulfuryl chloride has long been known as both an excellent chlorinating and sulfonylating agent for aromatic compounds, depending on the choice of experimental conditions.[5] Aliphatic chlorination of hydrocarbons can also be achieved either under ionic conditions, using Lewis acid catalysts, or under free radical conditions in the presence of a suitable catalyst (peroxides) or light. However, in the absence of such free radical initiators, aliphatic chlorination can largely be suppressed at low temperatures. This exquisite control of product outcomes, as summarized in a recent review,[6] has led to a resurgence of interest in sulfuryl chloride on the part of academic and industrial researchers.[7]

Using cyclohexylisonitrile as a test case, neat SO_2Cl_2 (1 equiv) was added dropwise to a stirred $CHCl_3$ solution (1.0 M) of the isonitrile at −20 °C under nitrogen and the reaction mixture warmed to rt (15–30 min total reaction time). The desired carbonimidic dichloride was obtained in nearly quantitative yield and exhibited the expected 9:6:1 ratio of M:M+2:M+4 peaks characteristic of two chlorine atoms in the structure. Applying the same procedure to *n*-butylisonitrile led to product contaminated with 10–15% chain-chlorinated byproducts. However, by lowering the reaction temperature to −45 °C and pre-diluting the SO_2Cl_2 with $CHCl_3$, the product n-$C_4H_9N{=}CCl_2$ was obtained ca 95% pure.

Chlorinations of representative isonitriles **1a**–**1f** using SO_2Cl_2 at −45 °C are summarized in Table 1 and illustrate the broad scope and efficiency of the method. Both aliphatic and aromatic isonitriles are readily converted into the corresponding dichlorides in excellent yield. Although carbonimidic dichlorides **2a**–**2e** have previously been synthesized (as referenced in Table 1), very little spectroscopic or physical characterization (other than IR and mp) data were provided in earlier publications. All products **2a**–**2f** were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, and either chemical ionization mass spectrometry (CIMS) or electron impact mass spectrometry (EIMS). The product carbonimidic dichlorides could be stored neat at −20 °C for up to 4–5 days without appreciable

* Corresponding author.
E-mail address: bg18@cornell.edu (B. Ganem).

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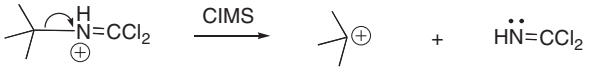
Table 1
Synthesis of isonitrile dichlorides using sulfuryl chloride

Isonitrile	Isonitrile dichlorides (% Yield)	Lit. reference
1a R = *n*-butyl	**2a** (80)	8
1b R = cyclohexyl	**2b** (99)	9
1c R = *t*-butyl	**2c** (90)	9b
1d R = *o*-tolyl	**2d** (98)	9a,b,10
1e R = $TsCH_2$	**2e** (97)	11
1f R = CH_2CO_2Et	**2f** (98)	

decomposition, but NMR samples deteriorated appreciably upon standing at rt after 1–2 d.

When dichloride **2c** was analyzed using CIMS, no parent ion could be detected, likely because of the facile fragmentation of protonated 2c shown in Eq. 2. However the EIMS spectrum of **2c** revealed the expected M, M+2 and M+4 pattern of parent ions, as well characteristic fragment ions resulting from both α-cleavage and inductive cleavage pathways.



(2)

2c (protonated)

Data in Table 1 confirm that the reaction is compatible with other functionality, including carboxylic esters. Moreover, no aromatic chlorination products were detected. In a competition experiment between cyclohexylisonitrile and 1-decene, dichloride **2b** was formed exclusively (94%) and 1-decene was returned unchanged, indicating high selectivity for chlorine addition to the isonitrile in the presence of an alkene. Furthermore, isonitriles **1d**–**1f** selectively underwent addition in preference to substitution, even in the presence of activated methyl and methylene groups (e.g., CH_3–Ar in **1d**; $–SO_2CH_2–$ in **1e**; $–CH_2CO_2Et$ in **1f**).

Experimental

Representative procedure for the chlorination of isonitriles using SO_2Cl_2

A magnetically-stirred $CHCl_3$ solution of isonitrile (0.7–1.0 mmol) under N_2 in an oven-dried 25 mL RBF was cooled in a dry ice-$CHCl_3$ bath to −45 °C. A solution of freshly distilled SO_2Cl_2 (1 equiv) in $CHCl_3$ (1 M) was added dropwise via microsyringe over 10 min and the resulting solution was stirred for 10 min, then allowed to warm to rt. The desired product was obtained by concentrating the solution on a rotary evaporator and briefly exposing the residual oil to a vacuum line (0.1–0.25 torr, 1–2 min) to remove last traces of solvent. The product carbonimidic dichlorides were characterized without further purification.

n-Butylcarbonimidic dichloride (2a)

^{1}H NMR δ 3.49 (t, 2 H, J = 6.9 Hz), 1.59–1.65 (m, 2 H), 1.36–1.40 (m, 2 H), 0.94 (t, 3 H, J = 7.4 Hz); ^{13}C NMR δ 123.4, 54.6, 31.3, 20.3, 13.6; IR 1654; CIMS m/z 154 (MH^+), 156 (MH^++2), 158 (MH^++4).

Cyclohexylcarbonimidic dichloride (2b)

^{1}H NMR δ 3.52–3.58 (m, 1 H), 1.22–1.88 (m, 10 H); ^{13}C NMR δ 121.7, 63.9, 32.2, 25.4, 24.2; IR 1644; CIMS m/z 180 (MH^+), 182 (MH^++2), 184 (MH^++4).

tert-Butylcarbonimidic dichloride (2c)

^{1}H NMR δ 1.39 (s, 9 H); ^{13}C NMR δ 116.4, 59.9, 28.5; IR 1648; EIMS m/z 153 (M^+), 155 (M^++2), 157 (M^++4); 138, 140, 142 (loss of CH_3); 57 (base peak).

(2-Methylphenyl)carbonimidic dichloride (2d)

^{1}H NMR δ 7.25–7.17 (m, 3 H), 7.13 (td, 1 H, J = 7.5, 1.4 Hz), 6.82 (dd, 1 H, J = 7.8, 1.3 Hz), 2.17 (s, 3H); ^{13}C NMR δ 144.5, 130.6, 128.4, 126.4, 125.9, 118.9, 17.6; IR (cm^{-1}) 1647; CIMS (electron impact, m/z): 188 (MH^+), 190 (MH^++2), 192 (MH^++4).

{[(4-Methylphenyl)sulfonyl]methyl}carbonimidic dichloride (2e)

^{1}H NMR δ 7.83 (d, 1 H, J = 8.3 Hz), 7.39 (d, 1 H, J = 8.0 Hz), 4.79 (s, 2 H), 2.47 (s, 3 H); ^{13}C NMR δ 145.7, 134.0, 129.9, 129.0, 128.8, 73.9, 21.7; IR 1650; CIMS m/z 266 (MH^+), 268 (MH^++2), 270 (MH^++4).

Ethyl [(dichloromethylidene)amino]acetate (2f)

^{1}H NMR δ 4.29 (s, 2 H), 4.26 (q, 2 H, J = 7.2 Hz), 1.30 (t, 3 H, J = 7.2 Hz); ^{13}C NMR δ 167.3, 129.9, 61.7, 55.6, 44.1, 14.1; IR 1662; CIMS m/z 184 (MH^+), 186 (MH^++2), 188 (MH^++4).

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Supplementary data

Supplementary data (Full ^{1}H NMR, ^{13}C NMR, infrared and mass spectra are provided for all compounds reported in the Table) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.046.

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