Published in final edited form as:

Tetrahedron Lett. 2012 August 22; 53(34): 4536–4537. doi:10.1016/j.tetlet.2012.06.046.

A Simple, General Synthesis of Carbonimidic Dichlorides

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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.

Keywords

Carbonimidic Dichlorides; Isonitrile Dichlorides; Isonitriles

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.ⁱ

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,ⁱⁱ but also as building blocks for more complex molecular architectures.ⁱⁱⁱ Carbonimidic dibromides can usually be prepared by simple addition of elemental bromine to the isonitrile. However, as noted in a seminal review,^{iv} the comparable addition of elemental chlorine (Cl₂) 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** (Eqn 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.

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SUPPLEMENTARY DATA: Full ¹H-NMR, ¹³C-NMR, infrared and mass spectra are provided for all compounds reported in the Table (25 pages). Supplementary data can be found online at ScienceDirect.

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Sulfuryl chloride has long been known as both an excellent chlorinating and sulfonylating agent for aromatic compounds, depending on the choice of experimental conditions.^v 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,^{vi} has led to a resurgence of interest in sulfuryl chloride on the part of academic and industrial researchers.^{vii}

Using cyclohexylisonitrile as a test case, neat SO_2Cl_2 (1 equiv) was added dropwise to a stirred CH_2Cl_2 solution (1.0 *M*) of the isonitrile at $-20\text{ }^\circ\text{C}$ 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 $-45\text{ }^\circ\text{C}$ and pre-diluting the SO_2Cl_2 with CH_2Cl_2 , the product *n*- $\text{C}_4\text{H}_9\text{N}=\text{CCl}_2$ was obtained ca 95% pure.

Chlorinations of representative isonitriles **1a–1f** using SO_2Cl_2 at $-45\text{ }^\circ\text{C}$ are summarized in the Table and illustrate the broad scope and efficiency of the method. Both aliphatic and aromatic isonitriles are readily converted to the corresponding dichlorides in excellent yield. Although carbonimidic dichlorides **2a–2e** have previously been synthesized (as referenced in the Table), very little spectroscopic or physical characterization (other than IR and mp) data was provided in earlier publications. All products **2a–2f** were fully characterized by ^1H -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 $-20\text{ }^\circ\text{C}$ for up to 4–5 days without appreciable 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. However a strong signal at *m/z* 57 was observed, which likely arose from the fragmentation shown in Eqn 2. By contrast, analysis of **2c** using EIMS did reveal the expected *M*, *M*+2 and *M*+4 pattern of parent ions as well as characteristic fragment ions arising from both α -cleavage and inductive cleavage pathways.

Eqn 2

Data in the Table 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. $\text{CH}_3\text{--Ar}$ in **1d**; $\text{--SO}_2\text{CH}_2\text{--}$ in **1e**; $\text{--CH}_2\text{CO}_2\text{Et}$ in **1f**).

EXPERIMENTAL^{xii}

Representative Procedure for the Chlorination of Isonitriles Using SO₂Cl₂

A magnetically-stirred CHCl₃ solution of isonitrile (0.7–1.0 mmol) under N₂ in an oven-dried 25 mL RBF was cooled in a Dry Ice-CHCl₃ bath to –45°C. A solution of freshly distilled SO₂Cl₂ (1 equiv) in CHCl₃ (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)

¹H-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); ¹³C-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)

¹H-NMR δ 3.52–3.58 (m, 1 H), 1.22–1.88 (m, 10 H); ¹³C-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)

¹H-NMR δ 1.39 (s, 9 H); ¹³C-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 CH₃); 57 (base peak).

(2-Methylphenyl)carbonimidic dichloride (2d)

¹H-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); ¹³C 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)

¹H-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); ¹³C-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)

¹H-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); ¹³C-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).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding for HVL was provided by the NIH (GM 008500 Training Grant). Support of the Cornell NMR Facility has been provided by NSF (CHE 7904825; PGM 8018643) and NIH (RR02002).

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- xii. ¹H-NMR spectra (400 MHz) were taken using CDCl₃ with 0.05% v/v TMS as solvent. Spectra were recorded in δ (ppm) and referenced to TMS (0.00 ppm). ¹³C-NMR spectra (100 MHz) were taken using CDCl₃ with 0.05% v/v TMS as solvent. Spectra were recorded in δ (ppm) and referenced to CDCl₃ (77.16 ppm for ¹³C NMR). IR spectra were recorded using an FT-IR spectrometer and recorded in wavenumbers. Mass spectra were taken using acetonitrile (for electron impact) or cyclohexane (for chemical ionization) solutions. NOTE: Most isonitriles have extremely unpleasant odors; therefore, all operations should be conducted in a well-ventilated hood.

Table

Synthesis of Isonitrile Dichlorides Using Sulfuryl Chloride

Isonitrile	Isonitrile Dichlorides (% Yield)	Lit. Reference
1a R= <i>n</i> -butyl	2a (80)	viii
1b R= cyclohexyl	2b (99)	ix
1c R= <i>t</i> -butyl	2c (90)	9b
1d R= <i>o</i> -tolyl	2d (98)	9a, 9b, x
1e R= TsCH ₂	2e (97)	xi
1f R= CH ₂ CO ₂ Et	2f (98)	