Mono-Chlorination of Electron-Rich Arylalkyl- and Heteroarylalkyl-amines and Amino Acids Using Sulfuryl Chloride

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Abstract: Sulfuryl chloride has been used to mono-chlorinate electron-rich arylalkyl- and heteroarylalkyl-amines and amino acids in a mild and efficient one-pot transformation with straightforward purification. Protection of the amines was not needed, and racemization of the chiral amino acids was minimal.

Key words: halogenation, chlorination, sulfuryl chloride, amino acids, amines

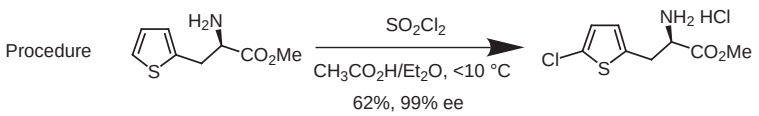
Chlorinated arylalkyl-amines and amino acids are common motifs in many natural products, such as vancomycin and teicoplanin.[1] In addition, they are attractive building blocks for biologically active compounds. Taken together, chlorinated arylalkyl- and heteroarylalkyl-amines and amino acids are generally desirable pharmacophores for medicinal chemistry.[2] There are numerous reported preparations for the chlorination of arylalkyl and heteroaryl compounds.[3] However, limited choices are available when a primary or secondary amine is present in the molecule. It usually takes multiple steps, including protecting-group transformations,[4] and/or utilizing chlorine gas as the chlorinating agent.[5] Since primary and secondary amines are important handles for analog preparation, it is desirable to have a simple procedure to obtain these types of molecules without protecting group transformations or the handling of chlorine gas.

Chlorinating electron-rich aromatic and heteroaromatic compounds using sulfuryl chloride has been well documented.[6] These reactions are generally high yielding when the functionalities are compatible with this reagent. However, until our recent communication,[7] there were no reports in the literature that sulfuryl chloride could be used to chlorinate electron-rich arylalkylamines directly, without the need for protection of the amino group. We have used this procedure to produce multi-kilogram quantities of 3-chloro-4-methoxyphenylmethylamine, which would otherwise have to be synthesized by either a multistep sequence with low overall yield,[4] or with the involvement of chlorine gas and the subsequent distillation of the product.[5] The ease and high efficiency of our new methodology prompted us to expand the scope of this reaction.

We found that sulfuryl chloride could be used directly to chlorinate a series of electron-rich arylalkyl- and heteroarylalkyl-amines and amino acids when the reactions were performed using glacial acetic acid as the reaction solvent (Scheme 1).[7] Protection of the amines was not needed as the acetic acid protonated them, masking their nucleophilicity. The resulting chlorinated products were purified as their hydrogen chloride salts via direct precipitation and filtration from the reaction mixtures.

This methodology has been applied to a number of electron-rich arylalkyl- and heteroarylalkyl-amines and amino acids (Tables 1 and 2). When needed, diethyl ether could be used as a co-solvent for dissolution of the amines. The yields of these reactions were generally good. The major side-reaction observed was dichlorination if the reaction temperature exceeded 40 °C during the addition of the sulfuryl chloride. Dichlorination was also observed even at lower temperature (< 25 °C) if the substrate was too reactive, as in the case of tyrosine methyl ester, and/or when sulfuryl chloride was used in excess. However, slow addition of one equivalent of SO_2Cl_2 generally circumvented the problem.

Application of this methodology to natural and unnatural amino acids effected the desired aromatic mono-chlorination. Integrity of the chiral centers in the optically pure amino acid methyl esters was examined using chiral HPLC analysis.[8] All of the enantiomeric pairs exhibited baseline separation under the applied HPLC conditions.



Scheme 1

Synthesis 2003, No. 3, Print: 28 02 2003.
Art Id.1437-210X,E;2003,0,03,0403,0407,ftx,en;M04402SS.pdf.

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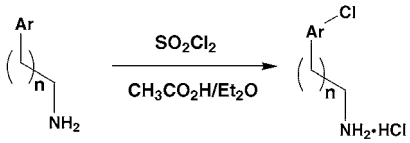
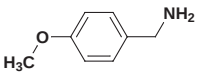
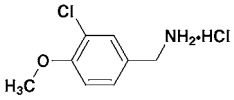
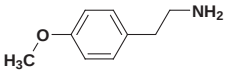
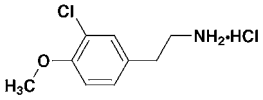
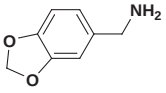
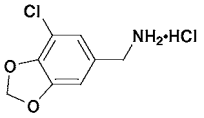
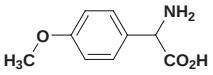
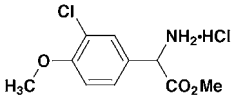
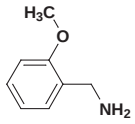
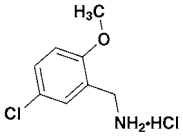
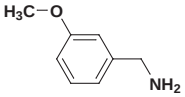
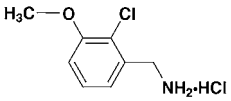
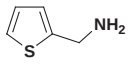
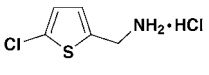
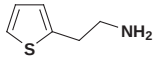
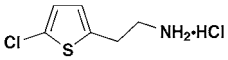
Table 1 Arylalkyl- and Heteroarylalkyl-amines



Substrate	Product[3]	Compd Number	Isolated Yield (%)
		**1**	80
		**2**	63
		**3**	75
 racemic		**4**[a]	60
		**5**	70
		**6a** **6b**	80 (**6a**–**6b** = 9:1)
		**7**	86
		**8**	60

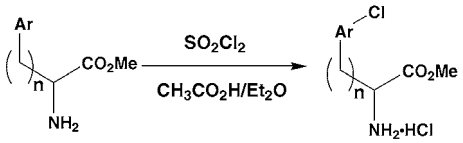
[a] Isolated as the methyl ester upon crystallization from methanol and diethyl ether.

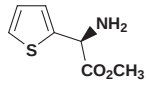
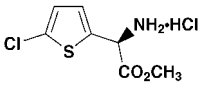
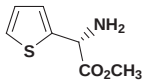
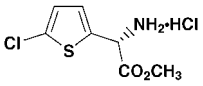
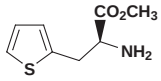
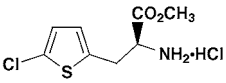
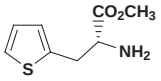
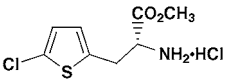
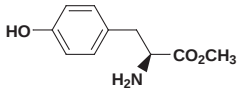
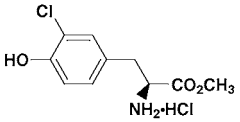
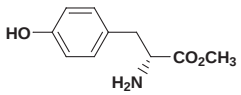
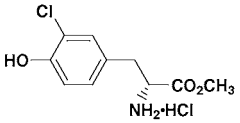
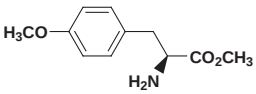
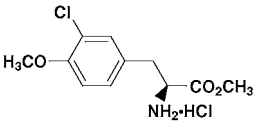
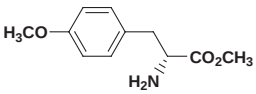
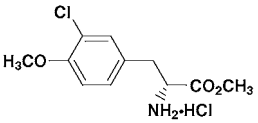
Loss of 10–20% enantiomeric excess was observed with the thiophenyl glycine methyl esters (**9** and **10**) under the current reaction conditions. Presumably, the observed racemization was due to the increased reactivity of the α position adjacent to the thiophene ring. These reactions were not optimized, as the effects of temperature, reaction time, and additional co-solvents on the degree of racemization were not investigated.

In summary, we have successfully utilized sulfuryl chloride to directly mono-chlorinate electron-rich arylalkyl- and heteroarylalkyl-amines and amino acids in a mild and efficient one-pot reaction. Use of acetic acid as the reaction solvent was successful at masking the nucleophilicity of the amino groups, and their protection was not needed. The chlorinated products were easily purified by simple, direct filtration of the HCl salt of the amines. In comparison with reported procedures in preparing similar compounds, our methodology using sulfuryl chloride in acetic acid should prove to be more convenient and efficient.[9]

All reagents were commercially available and used directly as received. Some of the amino acid methyl esters were prepared using one equivalent of trimethylsilyl chloride in methanol in the cases they were not commercially available, and their chiral integrity were intact as judged by Chiral HPLC. ^{1}H NMR spectra were recorded in a JOEL at 500 MHz; ^{13}C NMR spectra were recorded in the same instrument at 125 MHz.

Table 2 Arylalkyl- and Heteroarylalkyl Amino Acid Methyl Esters



Substrate	Product[3]	Compd Number	Isolated Yield (%)	ee (%) of Product[5]
 (99%ee)		**9**	78	90
 (97%ee)		**10**	75	83
		**11**	66	>99
		**12**	62	>99
		**13**	87	>95
		**14**	82	>95
		**15**	89	>99
		**16**	86	>99

Caution should be exercised when handling sulfuryl chloride.

Mono-Chlorination of Arylalkyl- And Heteroarylalkyl-amines and Amino Acids; General Procedure

To an ice cooled (5–20 °C) and vigorously stirred reaction solution of the amine (final concentration = 500 mM) in glacial HOAc or HOAc–Et_2O (9:1) was added sulfuryl chloride (1.0–1.5 equiv) dropwise. The reaction temperature was maintained below 25 °C during the sulfuryl chloride addition. The reaction was then stirred at r.t. until all starting material was consumed (typically < 1 h). Upon completion of the reaction, Et_2O was added to the reaction mixture (enough to double the reaction volume). The resulting white suspension was then stirred at r.t. for 30 min. Filtration of the resulting white solid afforded the desired chlorinated amine as its hydrogen chloride salt. These products were typically pure enough (> 90% as judged by HPLC). If higher purity material was needed, the products could be recrystallized from MeOH– Et_2O to afford the pure amines and amino acids in >99% purity as their hydrochloride salts.

3-Chloro-4-methoxyphenylmethylamine Hydrogen Chloride (1)

^{1}H NMR (500 MHz, CD_3OD): δ = 3.9 (s, 3 H), 4.1 (s, 2 H), 7.1 (d, 1 H), 7.4 (dd, 1 H), 7.5 (s, 1 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 43.4, 56.8, 113.8, 123.9, 127.3, 130.2, 132.0, 157.2.

HRMS: *m*/*z* calcd for $C_9H_{12}NClO$: 186.0685; found: 186.0688.

2-(3-Chloro-4-methoxyphenyl)ethylamine Hydrogen Chloride (2)

^{1}H NMR (500 MHz, CD_3OD): δ = 2.9 (t, 2 H), 3.1 (t, 2 H), 3.8 (s, 3 H), 7.0 (d, 1 H), 7.2 (dd, 1 H), 7.3 (m, 1 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 33.2, 41.9, 56.7, 113.8, 123.6, 129.4, 131.05, 131.33, 155.6.

HRMS: *m*/*z* calcd for $C_9H_{12}NClO$: 186.0685; found: 186.0688.

C-Benzo[1,3]dioxol-5-ylmethylamine Hydrogen Chloride (3)
^{1}H NMR (500 MHz, CD_3OD): δ = 4.2 (s, 2 H), 6.1 (s, 2 H), 7.0 (s, 1 H), 7.1 (s, 1H).

^{13}C NMR (125 MHz, CD_3OD): δ = 42.0, 104.0, 111.0, 111.5, 124.8, 127.7, 148.9, 150.9.

HRMS: *m*/*z* calcd for $C_8H_8NO_2Cl$: 186.0321; found: 186.0316.

Amino-(3-chloro-4-methoxyphenyl)acetic Acid Methyl Ester Hydrogen Chloride (4)
^{1}H NMR (500 MHz, CD_3OD): δ = 3.8 (s, 3 H), 3.9 (s, 3 H), 5.2 (s, 1 H), 7.2 (s, 1 H), 7.4 (s, 1 H), 7.5 (s, 1 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 49.0, 56.6, 56.9, 114.0, 124.2, 126.6, 129.3, 130.8, 157.7, 170.5.

HRMS: *m*/*z* calcd for $C_{10}H_{12}NO_3Cl$: 230.0584; found: 230.0588.

5-Chloro-2-methoxyphenylmethylamine Hydrogen Chloride (5)
^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.8 (s, 3 H), 3.9 (m, 2 H), 7.1 (d, 1 H), 7.4 (d, 1 H), 7.5 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 37.5, 56.7, 113.4, 124.5, 124.6, 130.2, 130.5, 156.7.

HRMS: *m*/*z* for $C_8H_{10}NClO$: 172.0529; found: 172.0532.

4-Chloro-3-methoxyphenylmethylamine Hydrogen Chloride and 2-Chloro-3-methoxybenzylamine Hydrogen Chloride (6a and 6b)
^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.8 (s, 3 H), 4.2 (s, 2 H), 7.0 (d, 1 H), 7.1 (s, 1 H), 7.4 (d, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 39.4, 55.7, 115.7, 116.1, 123.63, 130.1, 132.6, 158.1.

HRMS: *m*/*z* for $C_8H_{10}NClO$: 172.0529; found: 172.0528.

(5-Chlorothiophen-2-yl)methylamine Hydrogen Chloride (7)
^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.18 (s, 2 H), 7.10 (d, 1 H), 7.13 (d, 1 H), 8.42(br s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 36.0, 126.7, 130.0, 129.4, 134.7.

HRMS: *m*/*z* calcd for C_5H_6ClNS [M + H + CH_3CN]$^+$: 189.0253; found: 189.0256.

2-(5-Chlorothiophen-2-yl)ethylamine Hydrogen Chloride (8)
^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.04 (s, 4 H), 6.87 (d, 1 H), 7.01 (d, 1 H), 8.10(br s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 28.4, 122.4, 127.0, 127.8, 132.6, 139.7.

HRMS: *m*/*z* calcd for C_6H_8ClNS [M + H]$^+$: 162.0144; found: 162.0140.

(*R*)-Amino-(5-chlorothiophen-2-yl)acetic Acid Methyl Ester Hydrogen Chloride (9)
^{1}H NMR (500 MHz, CD_3OD): δ = 3.85 (s, 3 H), 5.51 (s, 1 H), 7.01 (d, 1 H), 7.12 (d, 1 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 52.5, 54.2, 127.6, 130.1, 132.0, 133.5, 168.3.

HRMS: *m*/*z* calcd for $C_7H_8ClNO_2S$ [M + H]$^+$: 206.0043; found: 206.0035.

(*S*)-Amino-(5-chlorothiophen-2-yl)acetic Acid Methyl Ester Hydrogen Chloride (10)
^{1}H NMR (500 MHz, CD_3OD): δ = 3.85 (s, 3 H), 5.51 (s, 1 H), 7.01 (d, 1 H), 7.13(d, 1 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 52.5, 54.3, 127.8, 130.3, 132.3, 133.6, 168.4.

HRMS: *m*/*z* calcd for $C_7H_8ClNO_2S$ [M + H]$^+$: 206.0043; found: 206.0039.

2-(*S*)-Amino-3-(5-chlorothiophen-2-yl)propionic Acid Methyl Ester Hydrogen Chloride (11)
^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.35 (q, 2 H), 3.75 (s, 3 H), 4.34 (t, 1 H), 6.88 (d, 1 H), 7.02 (d, 1 H), 8.67 (br s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 29.9, 52.7, 52.8, 126.9, 127.1, 128.3, 135.2, 168.8.

HRMS: *m*/*z* calcd for $C_8H_{10}ClNO_2S$ [M + H]$^+$: 220.0199; found: 220.0191.

2-(*R*)-Amino-3-(5-chlorothiophen-2-yl)propionic Acid Methyl Ester Hydrogen Chloride (12)
^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.33 (q, 2 H), 3.74 (s, 3 H), 4.32 (t, 1 H), 6.87 (d, 1 H), 7.01 (d, 1 H), 8.68 (br s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 29.9, 52.7, 52.8, 126.9, 127.1, 128.3, 135.2, 168.8.

HRMS: *m*/*z* calcd for $C_8H_{10}ClNO_2S$ [M + H]$^+$: 220.0199; found: 220.0201.

2-(*S*)-Amino-3-(3-chloro-4-hydroxyphenyl)propionic Acid Methyl Ester Hydrogen Chloride (13)
^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.02 (d, 2 H), 3.70 (s, 3 H), 4.26 (t, 1 H), 6.95 (q, 2 H), 7.22 (s, 1 H), 8.51 (br s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 34.5, 52.6, 53.2, 116.8, 119.5, 126.0, 129.0, 130.7, 152.4, 169.3.

HRMS: *m*/*z* calcd for $C_{10}H_{12}ClNO_3$ [M + H]$^+$: 230.0584; found: 230.0582.

2-(*R*)-Amino-3-(3-chloro-4-hydroxyphenyl)propionic Acid Methyl Ester Hydrogen Chloride (14)
^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.02 (d, 2 H), 3.71 (s, 3 H), 4.25 (t, 1 H), 6.97 (q, 2 H), 7.22 (s, 1 H), 8.50 (br s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6) : δ = 34.5, 52.6, 53.3, 115.5, 116.8, 126.0, 129.0, 130.7, 152.5, 169.3.

HRMS: *m*/*z* calcd for $C_{10}H_{12}ClNO_3$ [M + H]$^+$: 230.0584; found: 230.0586.

2-(*S*)-Amino-3-(3-chloro-4-methoxyphenyl)propionic Acid Methyl Ester Hydrogen Chloride (15)
^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.13 (d, 2 H), 3.68 (s, 3 H), 3.83 (s, 3 H), 4.23 (t, 1 H), 7.09 (d, 1 H), 7.17 (q, 1 H), 7.35 (d, 1 H), 8.80 (br s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 34.5, 52.5, 53.1, 56.1, 112.8, 120.9, 127.8, 129.4, 130.8, 153.7, 169.2.

HRMS: *m*/*z* calcd for $C_{11}H_{14}ClNO_3$ [M + H]$^+$: 244.0740; found: 244.0743.

2-(*R*)-Amino-3-(3-chloro-4-methoxyphenyl)propionic Acid Methyl Ester Hydrogen Chloride (16)
^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.08 (d, 2 H), 3.71 (s, 3 H), 3.84 (s, 3 H), 4.30(t, 1 H), 7.12 (d, 1 H), 7.16 (q, 1 H), 7.34 (d, 1 H), 8.52 (br s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 34.0, 52.6, 53.1, 56.1, 112.8, 120.8, 127.8, 129.4, 130.8, 153.7, 169.2.

HRMS: *m*/*z* calcd for $C_{11}H_{14}ClNO_3$ [M + H]$^+$: 244.0740; found: 244.0742.

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