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A mild and efficient method for aromatic chlorination of electron-rich arylalkyl amines

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Abstract—Sulfuryl chloride was used to chlorinate electron-rich arylalkyl amines in a mild and efficient one-pot transformation with simple product isolation via precipitation. Protection of the amines was not needed.

Application of sulfuryl chloride in chlorinating electron-rich aromatic compounds has been well documented.[1] These reactions are generally high yielding when the functionalities are compatible with this reagent. Despite the utility of sulfuryl chloride as a chlorinating reagent, there have been no reports in the literature on chlorinating arylalkyl amines using this reagent directly until our recent note describing the preparation of 3-chloro-4-methoxyphenylmethylamine.[2] This could be a result of the precedented reaction between sulfuryl chloride and amines which is known to form sulfonamide derivatives.[3] In this communication, we extend the scope of our earlier note[2] to report on the chlorination of a series of electron-rich arylalkyl amines using sulfuryl chloride directly, without the need for protection of the amine and with simple purification of the chlorinated product as its HCl salt via precipitation and filtration.

We required certain chloroarylalkyl amines, such as 3-chloro-4-methoxyphenyl methylamine,[2] to complete a structure–activity relationship study. Several methods for chlorinating arylalkyl amines had been reported in the literature, including the use of chlorine gas followed by distillation to procure the chlorinated product.[4] However, we found these routes to be cumbersome, and the yields of the chlorinated arylalkyl amines were not satisfactory. In searching for a more efficient and convenient chlorinating agent, we tested sulfuryl chloride. We reasoned that if the amine was protonated in a solvent such as acetic acid, it would not react with sulfuryl chloride. Chlorination of the aromatic ring could then proceed directly, releasing hydrogen chloride and forming the salt of the amine. We believed that these salts would be easily isolable solids. Our results using this methodology are summarized in Table 1.

The general procedure for the chlorination of electron rich arylalkyl amines was as follows. To a cooled, vigorously stirred reaction solution of the amine in glacial acetic acid (final concentration = 500 mM) was added sulfuryl chloride (1.5 equiv.) dropwise. The reaction temperature was maintained at <30°C during the sulfuryl chloride addition. The reaction solution initially changed to a suspension, but evolved back to a solution by the completion of the addition of sulfuryl chloride. The reaction was stirred at room temperature until all starting material was consumed as judged by HPLC (typically <2 h). Upon consumption of the starting amine, an equal volume of diethyl ether was added to the reaction mixture. The resulting suspension was then stirred at room temperature for 30 minutes. Filtration of the resulting mixture afforded the desired chloroarylalkyl amine as its hydrogen chloride salt, typically pure enough for direct use (>90% as judged by HPLC). If purification was needed, the chloroarylalkyl amine salt was recrystallized from methanol/diethyl ether to afford the chloroarylalkyl amine hydrochloride in >99% purity.

This procedure has been applied to other electron-rich arylalkyl amines (Table 1). The yields were good to excellent. The only side reaction we have observed has been di-chlorination if the reaction temperature

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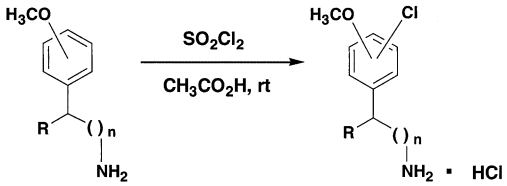
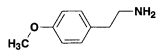
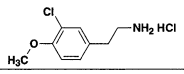
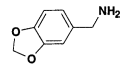
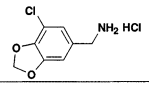
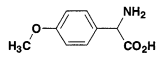
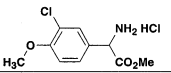
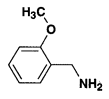
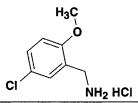
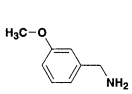
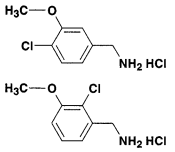
Table 1.[5]



Substrate	Product[3]	Entry	Isolated Yield (%)
		1	63
		2	75
		3*	60
		4	70
		5A 5B	80 (5A:5B = 9:1)

* Isolated as the methyl ester upon crystallization from methanol and ether.

exceeded 40°C during the addition of sulfuryl chloride. We continue to expand the scope of this methodology, specifically examining the range of functionality tolerated, and the chlorination of aromatic amino acids.

In summary, we have successfully utilized sulfuryl chloride to monochlorinate electron-rich arylalkyl amines in a mild and efficient one-pot reaction with purification by simple filtration of the HCl salt of the amine. This procedure should be broadly useful for monochlorination of arylalkyl amines without the need for protection of the amine.

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5. All starting materials were commercially available and used without further purification. All products have been characterized by ^{1}H NMR, ^{13}C NMR, HRMS, and elemental analysis. **1**. ^{1}H NMR (500 MHz, CD_3OD): δ 2.9 (t, 2H), 3.1 (t, 2H), 3.8 (s, 3H), 7.0 (d, 1H), 7.2 (dd, 1H), 7.3 (m, 1H); ^{13}C NMR (500 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; anal. calcd for $C_9H_{12}NClO{\cdot}H_2O{\cdot}0.85HCl$: C, 46.07; H, 6.38; N, 5.97; Cl, 27.95. Found: C, 46.25; H, 5.76; N, 5.88; Cl, 27.75.
2. ^{1}H NMR (500 MHz, CD_3OD): δ 4.2 (s, 2H), 6.1 (s, 2H), 7.0 (s, 1H), 7.1 (s, 1H); ^{13}C NMR (500 MHz, CD_3OD): δ 42.0, 104.0, 111.0, 111.5, 124.8, 127.7, 148.9, 150.9; HRMS m/z for $C_8H_8NO_2Cl$: 186.0321, found: 186.0316; anal. calcd for $C_8H_8NO_2Cl{\cdot}0.5H_2O{\cdot}1.2HCl{\cdot}0.2CH_3COOH$: C, 40.30; H, 4.43; N, 5.59; Cl, 31.15. Found: C, 40.16; H, 3.89; N, 5.81; Cl, 30.81.
3. ^{1}H NMR (500 MHz, CD_3OD): δ 3.8 (s, 3H), 3.9 (s, 3H), 5.2 (s, 1H), 7.2 (s, 1H), 7.4 (s, 1H), 7.5 (s, 1H); ^{13}C NMR (500 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 for $C_{10}H_{12}NO_3Cl$: 230.0584, found: 230.0588; anal. calcd for $C_{10}H_{12}NO_3Cl{\cdot}1.1HCl$: C, 44.52; H, 4.89; N, 5.19; Cl, 27.60. Found: C, 44.27; H, 4.73; N, 5.16; Cl, 27.62.
4. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.8 (s, 3H), 3.9 (m, 2H), 7.1 (d, 1H), 7.4 (d, 1H), 7.5 (s, 1H); ^{13}C NMR (500

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; anal. calcd for $C_8H_{10}NClO{\cdot}0.75H_2O{\cdot}0.75HCl$: C, 45.22; H, 5.81; N, 6.59; Cl 29.2. Found: C, 45.01; H, 5.17; N, 6.14; Cl, 28.91.

5A and **5B**. ^1H NMR (500 MHz, CD_3OD): δ 3.8 (s, 3H), 4.2 (s, 2H), 7.0 (d, 1H), 7.1 (s, 1H), 7.4 (d, 1H); ^{13}C NMR (500 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; anal. calcd for $C_8H_{10}NClO{\cdot}0.2H_2O{\cdot}1.15HCl$: C, 44.25; H, 5.36; N, 6.45; Cl, 35.10. Found: C, 44.67; H, 5.22; N, 6.48; Cl, 35.13.