A new strategy for the functionalization of aminofurazans: the synthesis of (3-R-furazan-4-yl)dichloroimines

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The reactions of 3-amino-4-R-furazans with CCl_4 in the presence of $AlCl_3$ or [bmim][$AlCl_4$] gave the corresponding (3-R-furazan-4-yl)dichloroimines in preparatively useful yields.

The development of synthetic methods for functionalised furazans is of considerable synthetic importance.[1] The introduction of functionality to the amino group at the furazan ring is an important but difficult operation. The furazan ring is highly π-deficient; as a result, usually the amino group at the ring is difficult to modify.

There is a wide variety of methods by which a valuable dichloroimine group can be generated and utilised in synthesis.[2] An attractive approach to the formation of the dichloroimine group involves the coupling of a primary amine with CCl_4 in the presence of a Lewis acid. However, there have been only a few reports on analogous syntheses of azinyl dichloroimines in the literature;[3] data on the synthesis of similar azolyl dichloroimine are absent. We undertook the present study as part of our investigation into the scope of dichloroimine formation from azolylamines promoted by $AlCl_3$.

A variety of reaction conditions similar to those employed previously have been examined on the model reaction of 3-amino-4-methylfurazan **1a** and CCl_4 in the presence of $AlCl_3$ (Method A).† The conversion of **1a** in a CCl_4 solution into desired dichloroimine **2a** was achieved by the addition of ~5 equiv. of $AlCl_3$ to the reaction mixture and refluxing (85 °C) for 2–3 h (Scheme 1). Gaseous HCl was evolved during the reaction. An equimolar amount of a Lewis acid required a longer reaction time and gave a lower yield. The reaction success was strongly dependent on the absence of water.

Similar conditions were successfully applied to the synthesis of other (3-R-furazan-4-yl)dichloroimines **2b**–**e**.† Electron-withdrawing substituents at the 3-position were explored with the result that no dramatic difference in yields was observed. In contrast to 3,4,5,6-tetrafluoro-1,2-diaminobenzene,[4] 3,4-diaminofurazan **1f** was transformed into bisdichloroimine **2f**, and the corresponding imidazo[4,5-*c*]furazan‡ was not formed. Diamines **1g** and **1h** also gave bisdichloroimines **2g** and **2h**. The results are summarised in Table 1. Compounds **2a**–**g**§ are oils that, in contrast to starting amines **1a**–**h**, are well soluble in nonpolar organic solvents.

One significant drawback to the use of $AlCl_3$, however, is the need for its hydrolysis at the end of the reaction. The standard workup procedure involves the addition of large quantities of water to remove the Lewis acid and so large-scale reactions would generate considerable amounts of aqueous waste. An alternative and more reliable route to these dichloroimines **2a**–**h** was therefore developed.

Table 1 Conditions and yields of dichloroimines **2a**–**h**.

Product	Yield (%)	
	Method A	Method B
2a	67	85
2b	72	84
2c	62	81
2d	77	87
2e	80	86
2f	69	71
2g	48	59
2h	56	70

† *General procedure for the preparation of dichloroimines* (Method A). $AlCl_3$ (0.03 mol per amino group) was added in a single portion to a solution or suspension of aminofurazan **1a**–**h** (0.01 mol) in CCl_4 (20 ml) with stirring under anhydrous conditions at room temperature. The reaction mixture was vigorously stirred at a reflux temperature for up to 5 h until the complete consumption of the starting amine (according to TLC and IR data). The mixture was cooled to room temperature and poured with stirring in 50 g of ice and water. The quenched mixture was extracted with CH_2Cl_2 (2×20 ml). The combined extracts were washed with cold water until neutral reaction and dried with $MgSO_4$. The solution was passed through a short SiO_2 pad and evaporated to give the product as a clear liquid: GLPC purity > 97%. These compounds can be additionally purified by sublimation onto a dry ice cooled cold finger when heated to 35–55 °C/1 Torr.

‡ All earlier attempts to prepare of imidazo[4,5-*c*]furazans were unsuccessful.[5]

§ All spectroscopic and analytical data were consistent with the structures assigned. Selected data are given below.

For **2a**: oil. ^{1}H NMR ($CDCl_3$) δ: 2.28 (Me). ^{13}C NMR ($CDCl_3$) δ: 7.3 (Me), 138.5 (C^1), 147.1 (C^3), 154.6 (C^2). MS, *m*/*z*: 183 (1%), 181 (6.8%), 179 (11%) [M$^+$], 151, 149 [M$^+$ – NO], 140, 138, 112, 110, 108 (100%). Found (%): C, 26.74; H, 1.73; N, 23.27. Calc. for $C_4H_3Cl_2N_3O$ (%): C, 26.69; H, 1.68; N, 23.35.

For **2b**: oil. ^{1}H NMR ($CDCl_3$) δ: 3.72 (OMe). ^{13}C NMR ($CDCl_3$) δ: 32.5 (OMe), 142.9 (C^1), 151.0, 151.3 (C^2, C^3). MS, *m*/*z*: 199, 197, 195 [M$^+$], 167, 165 [M$^+$ – NO].

For **2c**: oil. ^{1}H NMR ($CDCl_3$) δ: 4.04 (OMe). ^{13}C NMR ($CDCl_3$) δ: 53.7 (OMe), 141.0 (C^1), 141.3 (C^3), 154.9 (C^2), 157.1 (*C*O$_2$Me). MS, *m*/*z*: 227, 225, 223 [M$^+$], 195, 193 [M$^+$ – NO].

For **2d**: oil. ^{13}C NMR ($CDCl_3$) δ: 115.5 (CF_3), 138.4 (C^3), 142.6 (C^1), 154.0 (C^2), 159.1 (*C*–C^3), 167.3 (*C*–CF_3). ^{19}F NMR ($CDCl_3$) δ: –64.8 (F). MS, *m*/*z*: 305, 303, 301 [M$^+$], 273, 271 [M$^+$ – NO].

For **2e**: oil. ^{13}C NMR ($CDCl_3$) δ: 144.3 (CCl_2), 149.4 (*C*–N=C), 153.5 (CNO_2). ^{14}N NMR ($CDCl_3$) δ: –38.1 (NO_2). MS, *m*/*z*: 212 (4%), 210 (6%) [M$^+$], 166, 164 [M$^+$ – NO_2], 138 (12%), 136 (63%), 134 (100%). IR (ν/cm^{-1}): 1664, 1580, 1536, 1448, 1344, 1184, 1032, 948, 832, 744.

For **2f**: oil. ^{13}C NMR ($CDCl_3$) δ: 140.8 (CCl_2), 150.1 (C–N). MS, *m*/*z*: 266 (1%), 264 (3%), 262 (7%), 260 (5%) [M$^+$], 227 (8%), 225 (8%) [M$^+$ – Cl], 112 (11%), 110 (62%), 108 (100%). IR (ν/cm^{-1}): 1656, 1460, 1236, 1024, 932, 792. Found (%): C, 18.27; N, 21.29; Cl, 54.22. Calc. for $C_4Cl_4N_4O$ (%): C, 18.35; N, 21.39; Cl, 54.15.

For **2g**: oil. ^{13}C NMR ($CDCl_3$) δ: 144.8 (C^1), 149.6 (C^2), 153.4 (C^3). Found (%): C, 20.12; N, 31.27; Cl, 39.65. Calc. for $C_6Cl_4N_8O_2$ (%): C, 20.13; N, 31.31; Cl, 39.62.

For **2h**: mp 97–99 °C. ^{13}C NMR ($CDCl_3$) δ: 141.7, 144.0 (CCl_2), 149.3, 149.4, 152.2, 152.8 (C–N→O). ^{14}N NMR ($CDCl_3$) δ: –70.0 (N→O). MS, *m*/*z*: 260 (3%), 258 (12%), 256 (27%), 254 (25%) [M$^+$ – O]. Found (%): C, 19.24; N, 29.91; Cl, 38.00. Calc. for $C_6Cl_4N_8O_3$ (%): C, 19.27; N, 29.97; Cl, 37.92.

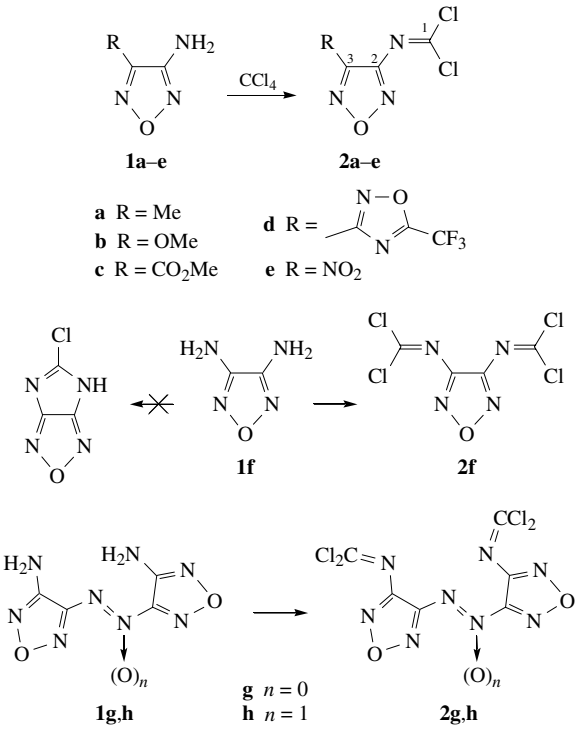
For **3**: oil. MS, *m*/*z*: 446 [M$^+$], 400 [M$^+$ – NO_2], 354 [M$^+$ – 2NO_2], 308 [M$^+$ – 3NO_2]. Calc. for $C_7H_4F_2N_8O_{13}$ (446.15).

For **4**: mp 156–158 °C. MS, *m*/*z*: 198 [M$^+$], 168 [M$^+$ – NO]. Calc. for $C_5H_6N_6O_3$ (198.14).

For **5**: oil. MS, *m*/*z*: 301 [M$^+$], 271 [M$^+$ – NO]. Found (%): C, 31.88; H, 2.69; N, 32.47. Calc. for $C_8H_8ClN_7O_4$ (%): C, 31.85; H, 2.67; N, 32.50.

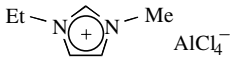
For **6**: mp 112–114 °C. MS, *m*/*z*: 204 [M$^+$], 186 [M$^+$ – H_2O], 172 [M$^+$ – NH_2O], 158 [M$^+$ – NO_2], 142, 130, 112, 95. Calc. for $C_3H_4N_6O_5$ (204.10).

For **7**: mp 123–125 °C. MS, *m*/*z*: 460 [M$^+$], 150 [M$^+$ – NO]. Calc. for $C_{17}H_{10}F_6N_6O_3$ (460.30). IR (ν/cm^{-1}): 3440, 3296, 1640, 1616, 1576, 1460, 1420, 1336, 1328, 1320, 1284, 1176, 1128, 1032.



Scheme 1

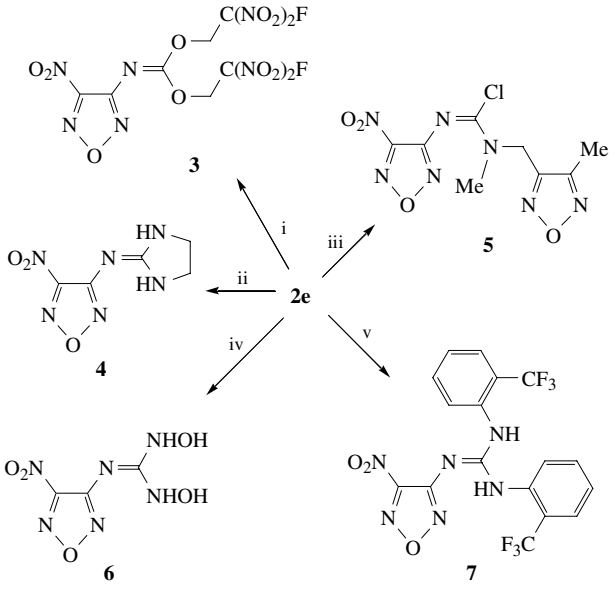
We have investigated the new use of a room temperature ionic liquid in the Lewis acid-mediated reaction. These liquids have recently been found to be excellent environmentally benign solvents for a variety of reactions.[6] Ionic liquids offer an attractive alternative to usual organic solvents because they are easy to recycle and are involatile and non-combustible. We considered that the ionic liquid 1-ethyl-3-methylimidazolium chloroaluminate ([emim][$AlCl_4$])[7] could be used for the reaction of **1a**–**h** with CCl_4 as the solvent and catalyst. According to published data, [emim][$AlCl_4$] exhibits excellent catalytic activity in Friedel–Crafts reactions.[8]



[emim][$AlCl_4$]

Indeed, we found that dichloroimines **2a**–**h** could be isolated in good yields when 3-amino-4-R-furazans **1a**–**h** and CCl_4 reacted in a mixed [emim][$AlCl_4$]–CCl_4 solvent¶ (Method B, Table 1). Thus, the heating of 3-amino-4-methylfurazan **1a** (1 equiv.) in a mixture of [emim][$AlCl_4$]–CCl_4 (1/4 equiv.) under anhydrous conditions produced dichloroimine **2a** in 85% yield. Similar yields of **2a** were obtained using different ratios between starting materials and different amounts of the ionic liquid and CCl_4. This showed that only small amounts of the ionic liquid are required for the reaction to proceed. At the end of the reaction, the ionic liquid can be easily recovered by distillation of cosolvent and the product at reduced pressure. Note that the recovered ionic liquid can be reused without any detriment to the product yield.

The prepared products are versatile precursors to guanidine furazans, which are difficult to prepare,[9] and to new carbamates and carbonate imines.[10] Thus, dichloroimine **2** reacted smoothly with nucleophiles at 0–25 °C. Displacement of both of chlorine atoms usually occurred. A few examples of nucleophilic reactions are depicted in Scheme 2.



Scheme 2 *Reagents and conditions*: i, $HOCH_2C(NO_2)_2F$/pyridine/CH_2Cl_2; ii, $(CH_2NH_2)_2$/NEt_3/THF; iii, 3-(methylaminomethyl)-4-methylfurazan/NEt_3/$(CH_2Cl)_2$; iv, NH_2OH/EtOH/CH_2Cl_2; v, *o*-CF_3-aniline/$(CH_2Cl)_2$.

We found that a variety of (3-R-furazan-4-yl)dichloroimines can be readily prepared from aminofurazans and CCl_4 in the presence of a Lewis acid. Moreover, the synthesis of dichloroimines can be carried out in an alternative solvent such as the ionic liquid [emim][$AlCl_4$].

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¶ *General procedure for the preparation of dichloroimines* (Method B). Aminofurazan **1a**–**h** (1 mmol) was added to a mixture of [emim][$AlCl_4$] (1 ml) and CCl_4 (5 ml) under anhydrous conditions in an atmosphere of argon. The reaction mixture was then heated at 80 °C with stirring until the starting amine was completely consumed (3–5 h, according to TLC). CCl_4 was removed under reduced pressure. The product was separated from the residue by sublimation onto a dry ice cooled cold finger when heated to 35–55 °C/0.1 Torr.