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Extending the scope of Ruppert's reagent: trifluoromethylation of imines

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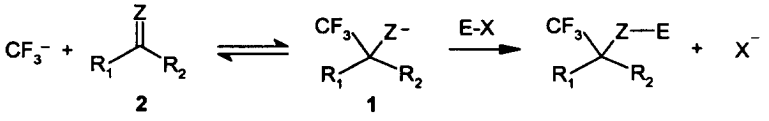
Abstract

The absence of reactivity of imines towards Ruppert's reagent (CF_3SiMe_3) could be overcome by the addition of an auxiliary silylating agent to the reaction medium. Under these conditions variously substituted α-trifluoromethylated amines are readily obtained from the corresponding imines. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Trifluoromethyltrimethylsilane (Ruppert's reagent) has found widespread use for the introduction of a trifluoromethyl group by nucleophilic reaction with a variety of substrates.[1,2] The usefulness of this versatile chemical intermediate is continuously growing: it has been shown recently that unactivated esters[3] as well as nitrones[4] could be trifluoromethylated by this reagent. However, it has been repeatedly stated that, except in the unique case of azirines,[5] imines are unreactive towards Ruppert's reagent.[1,2,4–6]

The proposed mechanism for the reaction of CF_3SiMe_3 with carbonyl compounds under fluoride anion catalysis is thought to involve initial formation of an alkoxide **1** (Scheme 1, Z=O) and fluorotrimethylsilane. The final addition product is formed in a subsequent catalytic cycle in which the alkoxide **1** is regenerated.



Scheme 1.

The lack of reactivity of imines has been ascribed to the lability and weakness of the nitrogen–silicon bond compared to the oxygen–silicon bond,[1,2] which prevents the intermediate **1** from entering the catalytic cycle. This argument explains quite well the observed absence of reactivity with a catalytic amount of initiator (F^-), but fails to explain why the reaction does not occur under stoichiometric conditions. One clue to this behaviour may be the instability of intermediate **1** (Z=N-R) which is

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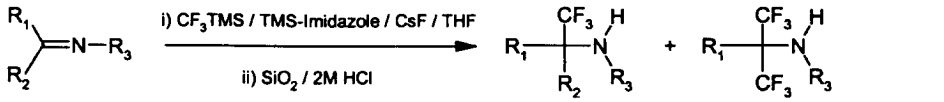
susceptible to revert to the starting material **2** and to highly reactive free trifluoromethide (Scheme 1, left part). The latter may either abstract a proton in the reaction medium or decompose to difluorocarbene, shifting the equilibrium to the left.

Based on this rather crude notion, we thought that the introduction into the reaction medium of a suitable electrophile (E-X) to trap the intermediate **1** once formed might prevent the decomposition of the latter (Scheme 1, right part), and push the reaction to completion. The requisite electrophile has to fulfil the following requirements: it must react with **1** but not (or at least more slowly) with fluoride or trifluoromethyl anions, and the released anion (X^-) must not interfere with the trifluoromethylation process. We show here that for imines derived from aromatic amines, *N*-trimethylsilylimidazole is one such reagent.

Upon adding trifluorotrimethylsilane to a stirred mixture of an imine **3** (Scheme 2), cesium fluoride and *N*-trimethylsilylimidazole in THF at room temperature, we were pleased to find that a smooth reaction ensued (24 h) leading, after hydrolytic work-up,[7] to a monotrifluoromethylated amine **4**, mixed (in the case of aldimines) with the bistrifluoromethylated amine derivative **5**. Results are gathered in Table 1.



3 **4** **5** (when R_2 = H)

a R_1 = Ph, R_2 = H, R_3 = Ph
b R_1 = 2-Naphthyl, R_2 = H, R_3 = Ph
c R_1 = 2-Furyl, R_2 = H, R_3 = Ph
d R_1 = 3-MeOC$_6$H$_4$, R_2 = H, R_3 = Ph
e R_1 = PhCH=CH, R_2 = H, R_3 = Ph
f R_1 = Ph, R_2 = H, R_3 = 3-CF$_3$C$_6$H$_4$
g R_1 = Ph, R_2 = CF$_3$, R_3 = Ph
h R_1 = Ph, R_2 = Me, R_3 = Ph
i R_1-R_2 = -(CH$_2$)$_5$-, R_3 = Ph
j R_1 = Ph, R_2 = H, R_3 = PhCH$_2$

Scheme 2.

As expected for this strongly basic medium, poor results were obtained with imines derived from enolizable ketones (Table 1, entries 8–9),[8] and the reaction succeeded only with *N*-aryl imines (entry 10).

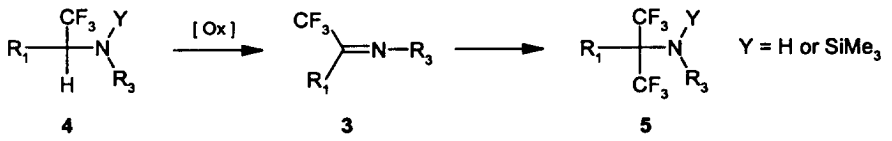
Table 1

Entry	imine [a]	products [b]
1	**3a**	**4a** 55 % (-74.5 ppm), **5a** 4 % (-70.0 ppm)
2	**3b**	**4b** 57 % (-74.2 ppm), **5b** 10% (-69.7 ppm)
3	**3c**	**4c** 54 % (-75.0 ppm), **5c** 2 % (-72.1 ppm)
4	**3d**	**4d** 42 % (-74.4 ppm), **5d** 4 % (-69.9 ppm)
5	**3e**	**5e** 19 % (-73.1 ppm)
6	**3f**	**4f** 26 % (-63.5 and -74.5 ppm), **5f** 4 % (-63.7 and -70.2 ppm)
7	**3g**	**4g** (= **5g** = **5a**) 64 % (-70.0 ppm)
8	**3h**	traces
9	**3i**	**4i** 2% (-79.8 ppm)
10	**3j**	traces

[a] imines were prepared by published procedures : **3a**—**f** and **3j**, [9] **3g**, [10] **3h** and **3i**. [11]

[b] isolated yields, ^{19}F n.m.r. chemical shifts in parentheses.

Other reagents have been tried in place of *N*-trimethylsilylimidazole, which is known to silylate only weakly basic amines,[12] but without success. For example, Ruppert's reagent was recovered mainly unchanged upon attempted reactions using chlorotrimethylsilane[13] or pentafluorobenzyl bromide.[14] In both cases, immonium formation was evident,[13] perhaps preventing complexation of the imine with the fluorinating agent.[15–17] On the other hand, an exothermic reaction was observed with *N*-methyl-*N*-trimethylsilylacetamide[18] with rapid darkening of the mixture and complete consumption of **1**, but no trifluoromethylation occured. Formation of the bistrifluoromethylated by-products **5**, in the case of aldimines, is not fully understood. We consider that they could arise from further trifluoromethylation of the trifluoromethylated imines **3** (Scheme 3). Some support for the potential intermediacy of fluorinated imines **3** comes from the facile trifluoromethylation of imine **3g** (Table 1, entry 7).



Scheme 3.

The imines **3** may in turn arise by oxidation, in the reaction medium, of amines **4** (or their *N*-silyl derivatives),[19] although the exact nature of the oxidizing agent is not yet known.

Typical experimental procedure: trimethylsilylimidazole (1 ml, 7.5 mmol) was added to a stirred mixture of imine **3a** (500 mg, 2.8 mmol) and cesium fluoride (1.3 g, 8.6 mmol) in THF (25 ml) under a stream of argon. The argon source was disconnected and trifluoromethyltrimethylsilane (1.4 ml, 10 mmol) added via a syringe. The mixture was stirred for 24 h before the addition of silica gel (4 g) and hydrochloric acid (2 M, 10 drops). Stirring was continued for 4 h. After filtration, the filtrate and washings (diethyl ether) were concentrated and eluted on a silica gel column using 5–10% diethyl ether in pentane as eluent to afford, in the order of elution, the bistrifluoromethyl compound **5a**† (40 mg, 0.12 mmol, 4%) and the amine **4a**‡ (383 mg, 1.52 mmol, 55%).

Acknowledgements

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† Data for **5a**: oil, b.p. 248°C (Siwoloboff); HRMS found 319.0790 $C_{15}H_{11}F_6N$ requires 319.0796; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49 (s, 1H, N*H*), 6.45 (d, 2H, *J* 8.0 Hz, Ar*H*), 6.82 (t, 1H, *J* 7.4 Hz, Ar*H*), 7.06 (t, 2H, *J* 8.0 Hz, Ar*H*), 7.42–7.55 (m, 3H, Ar*H*), 7.76 (d, 2H, *J* 7.6 Hz, Ar*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ –70.0 (s); ^{13}C NMR (85 MHz, $CDCl_3$) δ 70.1 (sept, $^2J_{CF}$ 27 Hz, *C*$(CF_3)_2$), 117.2 (NArC_2), 120.5 (NArC_4), 126.7 (q, $^1J_{CF}$ 294 Hz, *C*F_3), 128.0 (ArC_2), 128.7 (2C, ArC_4 and ArC_3), 129.1 (NArC_3), 130.1 (ArC_1), 142.1 (NArC_1); IR (CCl_4, cm^{-1}) 3428, 1609 and 1491; *m/z* (EI) 319 ($M^{+\cdot}$, 42%) and 250 (M–CF_3, 100%).

‡ Data for **4a**: oil, b.p. 272°C (Siwoloboff); HRMS found 251.0923 $C_{14}H_{12}F_3N$ requires 251.0922; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.2 (br s, 0.5H, NH), 4.94 (q, 1H, $^3J_{HF}$ 7.3 Hz, *C*HCF_3), 6.67 (d, 2H, *J* 8.0 Hz, Ar*H*), 6.80 (t, 1H, *J* 7.3Hz), 7.19 (t, 2H, *J* 7.9 Hz, Ar*H*), 7.36–7.52 (m, 5H, Ar*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ –74.5 (d, $^3J_{FH}$ 7.3 Hz); ^{13}C NMR (85 MHz, $CDCl_3$) δ 60.6 (q, $^2J_{CF}$ 30 Hz, *C*HCF_3), 113.9 (NArC_2), 119.2 (NArC_4), 125.0 (q, $^1J_{CF}$ 282 Hz, *C*F_3), 127.9, 128.9 and 129.1 (ArC_2, ArC_3 and ArC_4), 129.3 (NArC_3), 134.0 (ArC_1), 145.5 (NArC_1); IR (CCl_4, cm^{-1}) 3433, 1609 and 1507; *m/z* (EI) 251 ($M^{+\cdot}$, 70%) and 182 (M–CF_3, 100%).

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