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Nucleophilic fluoroalkylation of iminium salts

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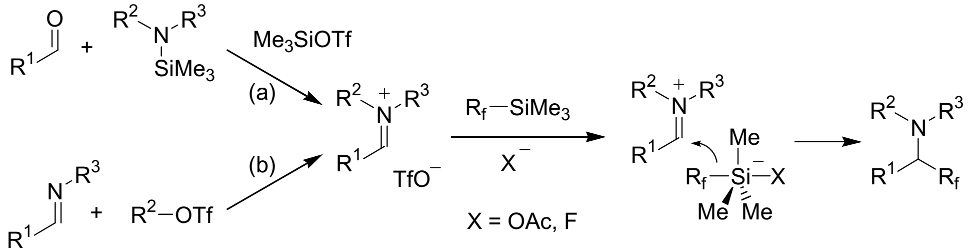
Abstract

Iminium cations generated by the coupling of aldehydes, *N*-trimethylsilylamines and TMSOTf or by the methylation of imines with MeOTf smoothly react with silanes of a general formula Me_3SiR_f ($R_f = CF_3$, CCl_2F, C_6F_5) to afford the corresponding tertiary amines having a fluorinated substituent. The key step, involving C–C bond formation, is promoted by NaOAc or KF in DMF as a solvent.

Keywords: Iminium ions; Imines; Fluorinated silanes; Lewis bases

Amines containing a trifluoromethyl group[1] or another fluorinated substituent[2] at the α-position have attracted significant attention due to their diverse biological activity. Recently, we proposed a new approach for the synthesis of C_6F_5-substituted amines based on the transfer of a C_6F_5 group from silicon to iminium cations.[3] This methodology requires the use of sophisticated silanes (e.g., $(C_6F_5)_3SiX$,[3a–g] $C_6F_5SiF_3$[3h]) in combination with mild Lewis bases. However, the same approach cannot conveniently be used for transferring trifluoromethyl or other fluorinated groups owing to the difficulties in synthesizing the corresponding silicon reagents.

At the same time, trifluoromethyltrimethylsilane, Me_3SiCF_3, has found numerous applications[4] for the trifluoromethylation of carbonyl compounds[5] and imines.[6] During our studies of the reactions of enamines with different silanes, we noted that reagents such as Me_3SiCF_3 and $Me_3SiC_6F_5$ were able to serve as a source of fluorinated groups for the iminium cations, though the yields of the desired products were moderate.[7] Herein, we report a



Scheme 1.

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convenient method for the transfer of CF_3, C_6F_5 and CCl_2F groups from the readily available trimethylsilyl reagents to iminium cations.[8]

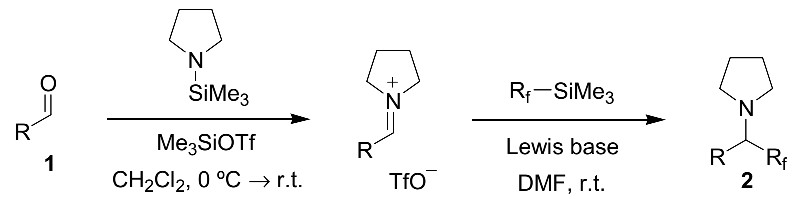
For the generation of iminium salts, two procedures were exploited: the reaction of aldehydes with *N*-trimethylsilylamines in the presence of Me_3SiOTf (path a)[9] and the alkylation of imines with a strong alkylating agent (path b) (Scheme 1). For the activation of fluorinated silanes, acetate and fluoride ions were used.[10] The C–C bond forming event is likely to occur in a tight ion pair consisting of the iminium cation and a five-coordinate siliconate anion.[3b]

The selection of Lewis base deserves special comment. Fluoride is the most efficient activator, which is frequently used in the form of Bu_4NF, Me_4NF or $Bu_4NPh_3SiF_2$.[4,6] Since for the interaction of silanes with iminium ions a stoichiometric amount of fluoride is required, we sought conditions that made use of cheaper and more convenient fluoride sources, such as alkali fluorides. Recently, for the reaction of quinolinium and pyridinium salts with Me_3SiCF_3, Makosza and co-workers reported the application of potassium fluoride in dichloromethane in the presence of 0.3 equiv of Ph_3SnF as a phase transfer catalyst.[11] The applicability of acetate anions for the activation of fluorinated silanes was first disclosed by Mukaiyama in 2005, and it was demonstrated that acetate anions may work in the form of alkali salts (lithium, sodium and potassium) only if DMF is used as a solvent.[12] Consequently, for the reaction of iminium salts with silanes we decided to test alkali fluorides and acetates in DMF.

The generation of iminium triflates from aldehydes **1** and *N*-trimethylsilylpyrrolidine proceeded smoothly in the presence of Me_3SiOTf in dichloromethane.[13] Next, a change of solvent to DMF and the addition of the silane and Lewis base afforded amines **2** (Table 1).

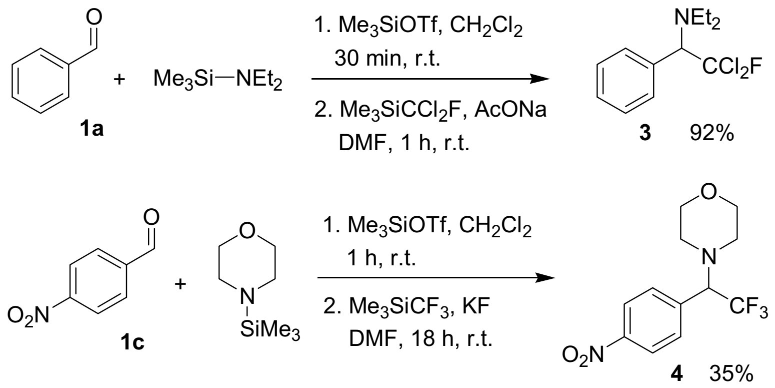
Sodium acetate and potassium fluoride appeared to be equally effective Lewis bases, though fluoride provided higher yields for more reactive electrophilic iminium ions. Thus, in the case of *p*-nitrobenzaldehyde, which forms a

Table 1
Interaction of aldehydes, *N*-trimethylsilylpyrrolidine and fluorinated silanes[a]



Entry	R		R_f	Time[b] (h)	Lewis base[c]	2	Yield of **2**[d] (%)
1	Ph	**1a**	CF_3	1	NaOAc	**2a**	78
2	Ph	**1a**	CF_3	1	KF	**2a**	76
3	Ph	**1a**	CF_3	1	NaF	**2a**	—
4	Ph	**1a**	C_6F_5	1	NaOAc	**2b**	62
5	Ph	**1a**	CCl_2F	1	NaOAc	**2c**	90
6	Ph	**1a**	CCl_3	1	NaOAc	**2d**	72
7	*p*-$MeOC_6H_4$	**1b**	CF_3	1	NaOAc	**2e**	70
8[e]	*p*-$O_2NC_6H_4$	**1c**	CF_3	18	NaOAc	**2f**	28
9[e]	*p*-$O_2NC_6H_4$	**1c**	CF_3	18	KF	**2f**	68

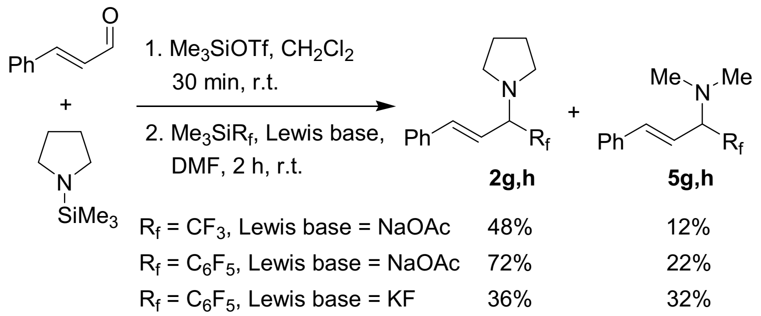
[a] Unless stated otherwise, the generation of iminium ions was performed for 30 min, the ratio of reagents **1**:amine:Me_3SiOTf:R_fSiMe_3 = 1:1.2:1.2:1.5.
[b] Time for the reaction of the iminium salt with the fluorinated silane.
[c] For NaOAc, 2 equiv; for KF or NaF, 1.5 equiv.
[d] Isolated yield.
[e] Time for the generation of the iminium ion was 2 h.



Scheme 2.

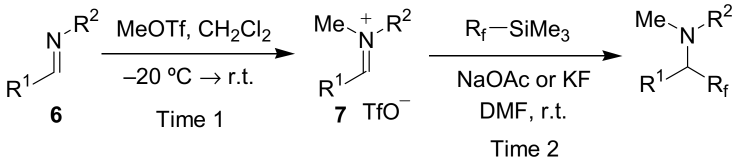
less stable cation, NaOAc and KF gave the desired amine in 28% and 68% yields, respectively (entries 8 and 9). The latter phenomenon may be associated with the stronger affinity of fluorine to silicon. This method can be applied for the synthesis of amines bearing CF_3, C_6F_5, CCl_2F and CCl_3 groups.[14]

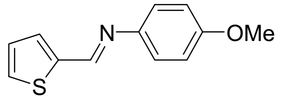
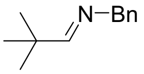
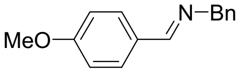
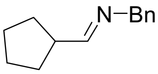
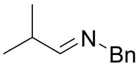
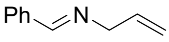
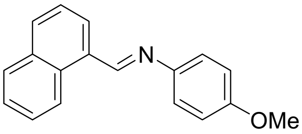
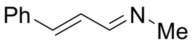
N-Trimethylsilyl derivatives of diethylamine and morpholine can also be used in the reaction with aldehydes and fluorinated silanes (Scheme 2). The diminished yield (35%) of product **4** obtained from *p*-nitrobenzaldehyde and *N*-silylmorpholine is, apparently, due to the significant electrophilicity of the intermediate iminium cation, which



Scheme 3.

Table 2
The synthesis of amines **7** from imines[a]



Entry	Imine	6	R_f	Time 1	Time 2 (h)	Lewis base[b]	Product	Yield[c] (%)
1		**6a**	CF_3	15 min	2	NaOAc	**7a**	64
2		**6b**	CF_3	30 min	2	NaOAc	**7b**	67
3		**6b**	CF_3	30 min	2	KF	**7b**	81
4		**6b**	C_6F_5	15 min	1.5	NaOAc	**7c**	80
5		**6c**	CF_3	15 min	1	NaOAc	**7d**	73
6		**6c**	CCl_2F	15 min	1	NaOAc	**7e**	89
7		**6c**	C_6F_5	15 min	1.5	NaOAc	**7f**	85
8		**6d**	CF_3	30 min	1	NaOAc	**7g**	34
9		**6d**	CF_3	30 min	1	KF	**7g**	62
10		**6e**	CF_3	30 min	1	KF	**7h**	77
11		**6f**	CF_3	30 min	1	NaOAc	**7i**	51
12		**6f**	CF_3	30 min	1	KF	**7i**	58
13		**6g**	CF_3	18 h	2	KF	**7j**	67
14		**6h**	CF_3	15 min	1	NaOAc	**5g**	89
15		**6h**	C_6F_5	15 min	1	NaOAc	**5h**	94

[a] Ratio of reagents **6**:MeOTf:R_fSiMe_3 = 1:1.2:1.5.

[b] For NaOAc, 2 equiv; for KF, 1.5 equiv.

[c] Isolated yield.

may strongly bind fluoride anions in the form of fluoroaminal.

An unexpected result was observed for the iminium cation derived from cinnamaldehyde and *N*-trimethylsilylpyrrolidine (Scheme 3). In this case, besides the desired amines **2g**,**h**, dimethylamino derivatives **5g**,**h** were obtained in 12–32% yields. It is noteworthy that by using KF as the Lewis base, the yield of the byproduct was nearly equal to that of the desired pyrrolidine derivative.

In another approach to iminium salts, imines **6** were treated with methyl triflate in dichloromethane. Subsequent change of the solvent to DMF and the addition of the silane and Lewis base furnished fluorinated amines **7** (Table 2). As a rule, the products containing CF_3, C_6F_5 and CCl_2F groups were obtained in reasonable yields.[15]

Sodium acetate and potassium fluoride are effective activators for the reactions of non-enolizable substrates, such as those derived from the aromatic and heteroaromatic aldehydes, as well as pivalaldehyde. On the other hand, for imines possessing a hydrogen atom adjacent to a C=N bond, the use of potassium fluoride is preferable (for example, compare entries 8 and 9).

In summary, we have reported a convenient method for the synthesis of amines, bearing different fluorinated groups at the α-carbon atom. The method is based on the coupling of iminium salts with the readily available fluorinated silicon reagents under mild conditions.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.043.

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14. *General procedure for the synthesis of amines* **2**: *N*-Trimethylsilylpyrrolidine (209 μL, 1.2 mmol) and TMSOTf (220 μL, 1.2 mmol) were added successively to a solution of aldehyde **1** (1 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The cooling bath was removed, the solution was stirred for 30 min (for **1a**,**b**) or 2 h (for **1c**), and the solvent was removed under vacuum. The residual salt was dissolved in DMF (2 mL) followed by the successive addition of silane (1.5 mmol) and Lewis base (NaOAc, 164 mg, 2.0 mmol or KF, 82 mg, 1.5 mmol). The resulting suspension was stirred for the time indicated in Table 1. For the work-up, saturated aqueous Na_2CO_3 (1 mL) was added dropwise, the mixture was stirred for an additional two minutes, diluted with water (10 mL) and extracted with ether/hexane (1:1, 3 × 5 mL). The combined organic phase was filtered through Na_2SO_4, concentrated under vacuum, and the crude product was chromatographed on a silica gel eluting with hexanes/ethyl acetate.
15. *General procedure for the synthesis of amines* **7**: Methyl triflate (1.2 mmol, 136 μL) was added to a solution of imine **6** (1 mmol) in CH_2Cl_2 (2 mL) at −20 °C. The cooling bath was removed, the solution was stirred for the time indicated in Table 2, and the solvent was removed under vacuum. The residual salt was dissolved in DMF (2 mL) followed by the successive addition of silane (1.5 mmol) and Lewis base (NaOAc, 164 mg, 2.0 mmol or KF, 82 mg, 1.5 mmol). The resulting suspension was stirred for the time indicated in Table 2. For the work-up, saturated aqueous Na_2CO_3 (1 mL) was added dropwise, the mixture was stirred for an additional 2 min, then diluted with water (10 mL) and extracted with ether/hexane (1:1, 3 × 5 mL). The combined organic phase was filtered through Na_2SO_4, concentrated under vacuum, and the crude product was chromatographed on a silica gel eluting with hexanes/ethyl acetate.