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Chloride ion promoted nucleophilic pentafluorophenylation of imines

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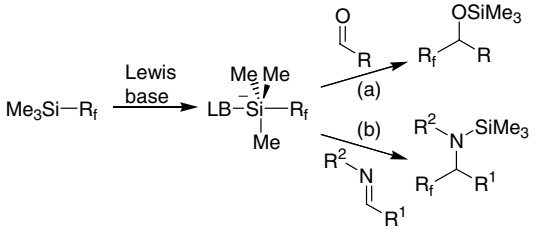
Abstract—Nucleophilic addition of the pentafluorophenyl group from $(C_6F_5)_3SiF$ to non-activated imines affording α-C_6F_5-substituted secondary amines in high yield has been described. The reaction proceeds via simultaneous activation of imines and the silane reagent by means of a proton and chloride ion, respectively.

Organofluorine compounds have found widespread applications in the pharmaceutical industry and agrochemistry.[1] Among many approaches developed for the introduction of a fluorinated fragment into an organic substrate,[1,2] the methodology based on the employment of fluorinated silanes has received particular attention in recent years.[3] In the presence of a Lewis base, silanes form hypercoordinate species, which serve as a source of fluorinated carbanions in reaction with electrophiles.

This method was elaborated by Prakash and co-workers and was most efficiently exploited for the trifluoromethylation of carbonyl compounds[3] (Scheme 1, path a). At the same time, addition of fluorinated group to imines (path b) was problematic owing to the lower electrophilicity of the C=N double bond and possible reversibility of the C–C bond forming event. Correspondingly, only strongly biased substrates such as azirines,[4] imines of perfluorinated ketones,[5] or *N*-tosylated or sulfinylated[6] imines worked well in this process. The direct addition to imines bearing an aryl group at nitrogen has been reported, but proceeds in only moderate yields.[7,8] Reactions of *N*-alkyl substituted substrates with fluorinated silanes have not been described.



Scheme 1.

Herein, we report a different approach for the transfer of a fluorinated fragment from silicon to non-activated imines. Our investigation was performed using pentafluorophenylsilanes, since many of these reagents can be readily obtained by conventional organometallic synthesis.[9]

Recently, we showed that the introduction of three C_6F_5-groups to a silicon atom greatly increases the sensitivity of silicon reagents towards activation by Lewis bases.[10,11] Thus, even non-nucleophilic chloride anions may serve as competent Lewis bases to mediate transfer of the C_6F_5-group from the silicon to *N*,*N*-dialkyliminium carbocations.[11] Based on the latter observation we proposed that iminium cations, generated by protonation of imines with hydrochloric acid, could also be involved in a nucleophilic pentafluorophenylation reaction.

The general mechanism of the process is given in Scheme 2. The iminium chloride is produced from the imine **1**

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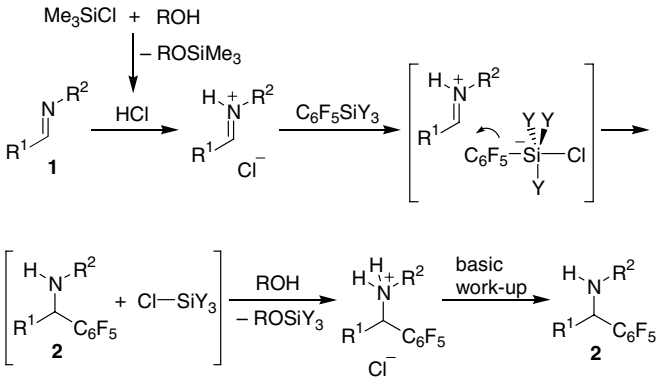


Scheme 2.

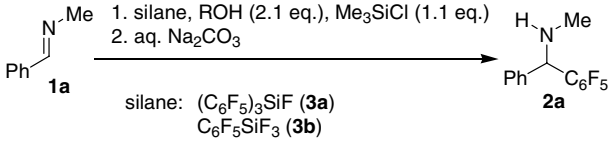
and anhydrous HCl, which is conveniently obtained by mixing chlorotrimethylsilane and an alcohol. The interaction of the chloride ion with the silane generates a five-coordinate siliconate complex, which transfers the C_6F_5-group from the silicon to the iminium electrophile. However, the resulting amine **2** is expected to be more basic than the starting imine **1**, and, therefore, has to be protonated by a second equivalent of acid. The latter step can be easily achieved simply by using one extra equivalent of alcohol to generate HCl from the chlorosilane produced during the C–C bond forming event. At the end of the reaction, a mildly basic aqueous work-up has to be performed in order to isolate the free amine **2**.

Using methylbenzylideneamine (**1a**) as a model substrate we screened the reaction conditions (Table 1). Fluorotris(pentafluorophenyl)silane (**3a**, 1 equiv relative to **1a**) was first tested as a source of the C_6F_5-group, since this compound was found to be the most efficient reagent for the chloride ion mediated reactions.[11] Utilization of methanol as a proton source and carrying out the reaction in refluxing acetonitrile for 1 h afforded amine **2a** in 70% yield (entry 1). When trifluoroethanol was employed instead of methanol, the yield of amine **2a** increased to 93%. It should be pointed out that chloride ions rather than the alcohol play the role of nucleophilic activator, since upon substituting TMSCl with TMSOTf, no reaction was observed.

Lowering the reaction temperature significantly retarded the reaction, affording poor yields even over prolonged periods of time (entry 3). This effect may be associated with the low solubility of iminium chloride in acetonitrile. However, performing the reaction in dimethylformamide for 20 h at room temperature provided amine **2a** in 72% yield (entry 4).

Though good yields of the product were obtained with a stoichiometric amount of $(C_6F_5)_3SiF$, we attempted to reduce the quantity of the silicon reagent. Unfortunately, with 0.51 or 0.34 equiv of $(C_6F_5)_3SiF$ only modest yields were achieved under all conditions examined (entries 5–8). In a different approach to solve the efficiency problem we tested pentafluorophenyltrifluorosilane (**3b**), possessing only one C_6F_5-group.[11] Despite considerable experimentation we could not increase the yield higher than 54% (entries 9–11). The poor performance of **3b** may be tentatively ascribed to its competitive interaction with trifluoroethanol to give pentafluorobenzene.[12]

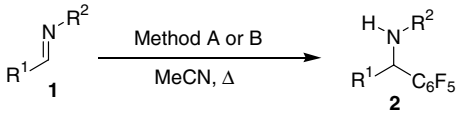
Table 1. Optimization of reaction conditions



Entry	3	Equivalent of 3	ROH	Solvent	Conditions	Yield of 2a, %[a]
1	**3a**	1	MeOH	MeCN	1 h, 82 °C	70
2	**3a**	1	CF_3CH_2OH	MeCN	1 h, 82 °C	93
3	**3a**	1	CF_3CH_2OH	MeCN	20 h, rt	18
4	**3a**	1	CF_3CH_2OH	DMF	20 h, rt	72
5	**3a**	0.51	CF_3CH_2OH	MeCN	1 h, 82 °C	61
6	**3a**	0.34	CF_3CH_2OH	MeCN	1 h, 82 °C	40
7	**3a**	0.51	*i*-PrOH	MeCN	1 h, 82 °C	45
8	**3a**	0.51	AcOH	MeCN	1 h, 82 °C	41
9	**3b**	1.1	CF_3CH_2OH	MeCN	1 h, 82 °C	27
10	**3b**	1.1	CF_3CH_2OH	DMF	1 h, 82 °C	41
11	**3b**	1.1	AcOH	DMF	1 h, 82 °C	54

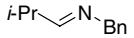
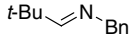
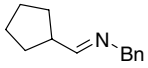
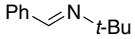
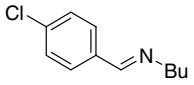
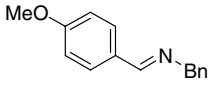
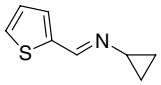
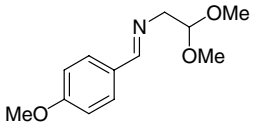
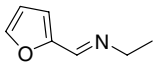
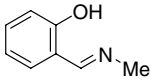
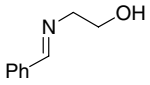
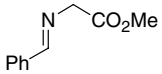
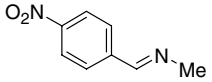
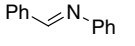
[a] Isolated yield.

Table 2. Pentafluorophenylation of imines



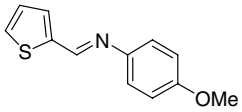
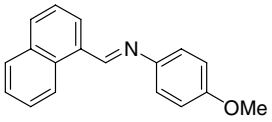
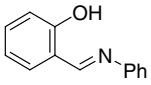
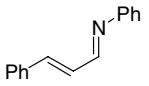
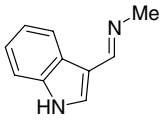
1 **2**

A: $(C_6F_5)_3SiF$ (1 eq.), CF_3CH_2OH (2.1 eq.), Me_3SiCl (1.1 eq.)
B: $(C_6F_5)_3SiF$ (1 eq.), CF_3CH_2OH (2.1 eq.), Me_3SiCl (1.1 eq.), $BnNEt_3Cl$ (1 eq.)

Entry	Imine		Method	Time, h	Yield of **2**, %[a]
1		**1b**	A	1	90
2		**1c**	A	1	95
3		**1d**	A	1	90
4		**1e**	A	1	96
5		**1f**	A	1	88
6		**1g**	A	0.5	93
7		**1h**	A	1	70
8		**1i**	A	1	90
9		**1j**	A	1	92
10		**1k**	A	1	74
11		**1l**	A	1	71
12		**1m**	A	1.5	68
13			B	0.5	75
14		**1n**	A	3	73
15			B	0.5	95
16		**1o**	B	1	91

(*continued on next page*)

Table 2 (*continued*)

Entry	Imine		Method	Time, h	Yield of **2**, %[a]
17		**1p**	B	1	96
18		**1q**	B	0.5	96
19		**1r**	B	0.5	77
20		**1s**	B	1	88
21		**1t**	B	1.5	38

[a] Isolated yield.

As follows from the above discussion, the optimal conditions for the pentafluorophenylation of imines include employment of silane **3a** in refluxing acetonitrile along with 1.1 equiv of Me_3SiCl and 2.1 equiv of trifluoroethanol (method A). As shown in Table 2, different imines can be used for this coupling, with reaction times being usually within 1 h (entries 1–11). Imines derived from aryl- and α-branched aldehydes and alkylamines afforded amines **2** in high yields. Acid sensitive functions such as an acetal group (entry 8) or a furan ring (entry 9) were tolerated. Of note is that substrates bearing unprotected hydroxyl groups could be employed leading to the corresponding amino alcohol products (entries 10 and 11).

On the other hand, reactions with diaryl imines were quite sluggish. For example, only 50% conversion was noted for the pentafluorophenylation of benzylideneaniline (**1o**) after 3 h. We reasoned that the slow rate may be associated with tight binding of the chloride ion with the iminium cation.[13] To overcome this problem it was necessary to increase the concentration of chloride ions. It was rewarding to find that addition of 1 equiv of benzyltriethylammonium chloride (method B) significantly accelerated the reaction and provided amines from several diarylimines in high yields (entries 16–19). In some cases the yields from the reactions of poorly reactive *N*-alkylimines could also be improved (entries 13 and 15).

The only substrate, for which we obtained poor results, was the indole derivative **1t**. After 1.5 h, NMR analysis of the crude product indicated a large amount of starting imine; column chromatography furnished amine **2t** in 38% yield. Increasing either the reaction time or loading of $(C_6F_5)_3SiF$ did not increase the conversion. The diminished reactivity of imine **1t** may be due to the strong electron-donating influence of the indole ring.

In summary, we have demonstrated that pentafluorophenyl groups can be efficiently transferred from silicon reagents to a wide variety of non-activated imines, providing C_6F_5-substituted secondary amines.[14] Simultaneous activation of the imine by means of a proton, and the silicon reagent by means of chloride ions, constitute the key features of the described process.

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.2006.10.019.

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7. The trifluoromethylation of *N*-aryl imines with Me_3SiCF_3 catalyzed by Bu_4N Ph_3SiF_2 or Me_4NF is accompanied by elimination of HF from the initial products, see: Prakash, G. K. S.; Mogi, R.; Olah, G. A. *Org. Lett.* **2006**, *8*, 3589.
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13. Mayr, H.; Ofial, A. R.; Würthwein, E.-U.; Aust, N. C. *J. Am. Chem. Soc.* **1997**, *119*, 12727.
14. General procedure. Method A. Me_3SiCl (141 μL, 1.1 mmol), imine **1** (1 mmol) and CF_3CH_2OH (153 μL, 2.1 mmol) were successively added to a suspension of $(C_6F_5)_3SiF$ (548 mg, 1 mmol) in acetonitrile (2 mL) at room temperature and the mixture was refluxed for the time given in Table 2. After cooling to room temperature, the solvent was evaporated under vacuum, the residue was dissolved in 96% ethanol (2 mL), and satd aq Na_2CO_3 (0.5 mL) was added. After stirring for an additional 3 min, the mixture was diluted with 15 mL of ether/hexane (1:1), filtered through Na_2SO_4, concentrated and the residue was chromatographed on silica gel with hexane/EtOAc. Method B. The same as above, but with the addition of $BnNEt_3Cl$ (228 mg, 1 mmol) before the addition of trifluoroethanol (see Supplementary data for compound characterization data).