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Pentafluorophenyltrifluorosilane in the silicon Mannich reaction

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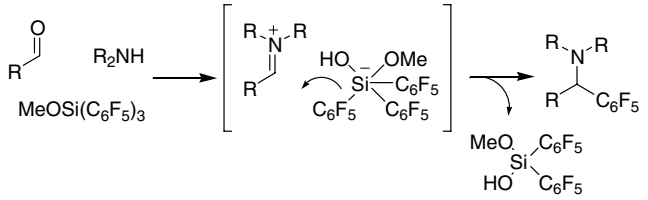
Abstract—The synthesis of α-C_6F_5-substituted amines by a three-component coupling reaction of $C_6F_5SiF_3$, aromatic aldehydes, and *N*-trimethylsilylamines has been elaborated. The optimized conditions include performing the reaction in dimethylformamide in the presence of stoichiometric amounts of lithium acetate.

Amines bearing, at the α-position, fluorinated substituents may serve as potential pharmaceutical and agrochemical agents.[1] Recently, we proposed a method for the synthesis of α-C_6F_5-substituted amines via Mannich-type coupling of aldehydes, amines and $(C_6F_5)_3SiOMe$ (Scheme 1).[2] The major disadvantage of this method is that from the rather expensive reagent $(C_6F_5)_3SiOMe$, only one C_6F_5-group can be used, since the resulting bis(pentafluorophenyl)silyl derivative is not reactive.[2a] Herein we report a solution to this problem.

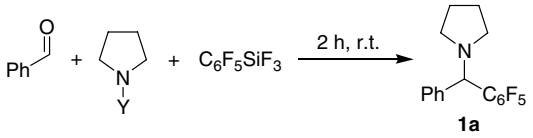
The key feature of the pentafluorophenylation reaction is the generation of a five-coordinate siliconate intermediate, which serves as a nucleophile towards the iminium cation. Based on the ability of fluorine to exert significant stabilization of hypercoordinate silicon species[3,4] we decided to study the applicability of pentafluorophenyltrifluorosilane[3] for the synthesis of C_6F_5-substituted amines.



Scheme 1.

Initial experiments employing benzaldehyde and pyrrolidine as model substrates and performing the reaction in acetonitrile for 2 h at room temperature were rather disappointing, affording the desired product **1a** in very low yield (Table 1, entry 1). The utilization of *N*-trimethylsilylated amine led to an increase in the yield of **1a** to 27% (entry 2). Since conducting the reaction for longer times had virtually no effect, it was surmised that the poor conversion was associated with the presence of $F_3SiOSiMe_3$, produced as a by-product of the reaction, which binds to benzaldehyde to form an inert acetal, $PhCH(OSiMe_3)(OSiF_3)$.

Table 1. Variation of conditions[a]



1a

Entry	Y	Solv.	Additive	Yield of **1a**,[b] %
1	H	MeCN	—	8
2	$SiMe_3$	MeCN	—	27
3	$SiMe_3$	MeCN	py	46
4	$SiMe_3$	MeCN	2,2′-bipy	55
5	$SiMe_3$	MeCN	py-*N*-oxide	65
6	$SiMe_3$	DMF	—	46
7	$SiMe_3$	DMF	AcOLi	78
8	H	DMF	AcOLi	20

[a] The ratio of reagents PhCHO/amine/$C_6F_5SiF_3$/additive = 1:1.2:1.2:1.1.
[b] Isolated yield.

Keywords: Fluorinated silanes; Hypervalent silicon; Mannich reaction.
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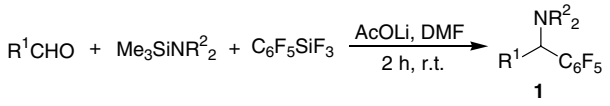
Rewardingly, a notable improvement was achieved by addition of stoichiometric amounts of a Lewis base such as pyridine, 2,2′-bipyridine, or pyridine-*N*-oxide which are capable of complexing $F_3SiOSiMe_3$ (entries 3–5). Further experimentation revealed that lithium acetate in dimethylformamide proved to be the best condition for the three-component coupling, furnishing amine **1a** in 78% isolated yield (entry 7).

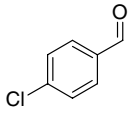
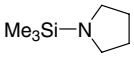
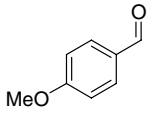
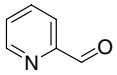
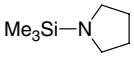
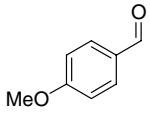
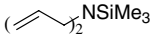
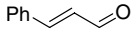
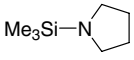
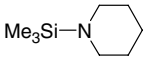
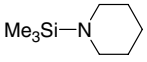
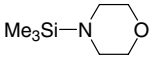
Under the optimized conditions, a series of aldehydes and *N*-silylamines were reacted with $C_6F_5SiF_3$ to give α-C_6F_5-substituted amines[5] (Table 2). Aromatic and heteroaromatic aldehydes gave good yields of products, whereas enolizable aliphatic aldehydes proved to be unsuitable substrates for this reaction. Silylated amines such as pyrrolidine, piperidine, diethylamine and diallylamine worked well. However, when the less nucleophilic *N*-silylmorpholine was used in combination with benzaldehyde, considerable amounts of pentafluorobenzhydrol were observed, resulting from addition of $C_6F_5SiF_3$ to benzaldehyde promoted by lithium acetate. Nevertheless, the target amine **1k** could be obtained in 71% yield by employing pyridine-*N*-oxide in acetonitrile (entry 10).

The product **1l**, derived from α-furaldehyde and *N*-silyldiallylamine, was isolated in 88% yield, but it turned out to be unstable. Although compound **1l** can be stored for at least five days at −25 °C, it undergoes isomerization into tricycle **2** at room temperature (15% conversion in 20 h in $CDCl_3$) (Scheme 2). On a preparative scale this intramolecular cycloaddition was effected by refluxing

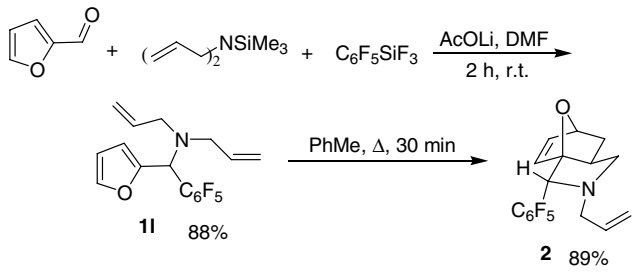
Table 2. Three-component coupling[a]



1

Entry	Aldehyde	Amine	1	Yield of 1,[b] %
1			**1b**	78
2		Me_3SiNEt_2	**1c**	70
3	PhCHO	Me_3SiNEt_2	**1d**	70
4		Me_3SiNEt_2	**1e**	79
5			**1f**	81
6			**1g**	89
7			**1h**	67
8			**1i**	62
9			**1j**	80
10[c]	PhCHO		**1k**	71

[a] The ratio of reagents PhCHO/amine/$C_6F_5SiF_3$/AcOLi = 1:1.2:1.2:1.1, 0.5 M in DMF, 2 h unless otherwise stated.
[b] Isolated yield.
[c] Reaction was performed in MeCN in the presence of pyridine-*N*-oxide for 28 h.



Scheme 2.

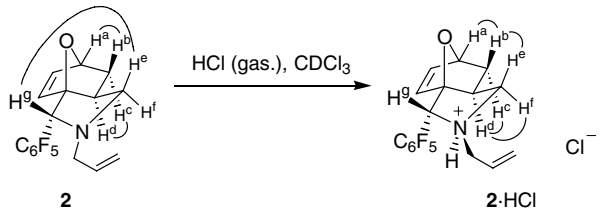


Figure 1. Summary of the NOE data based on NOE-difference and 2D-NOESY experiments.

in toluene for 30 min. Importantly, only one isomer of **2** corresponding to the *exo*-cycloaddition mode was produced.

The relative stereochemistry was established on the basis of extensive NMR measurements on compound **2** and its hydrochloride salt **2**·HCl in which the ^{1}H NMR signals were better resolved (Fig. 1). In particular, the observation of an NOE between H^a–H^b and H^c–H^d suggested that the proton H^d was located *trans* to the oxygen. The position of the C_6F_5-group was determined from the NOE between protons H^e and H^g.

An intramolecular cycloaddition for a similar substrate with an NO_2CH_2-group instead of pentafluorophenyl has recently been described[6] and required heating in THF for seven days. Probably, the accelerating effect of the C_6F_5-group is associated with its influence on the conformational population of the substrate.

In summary, we have demonstrated that pentafluorophenyltrifluorosilane can be conveniently employed in the Mannich-type coupling of aromatic aldehydes and *N*-silylamine, providing an efficient approach to α-C_6F_5-substituted amines.

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.2006.06.164.

References and notes

1. (a) Kim, C.-Y.; Chang, J. S.; Doyon, J. B.; Baird, T. T., Jr.; Fierke, C. A.; Jain, A.; Christianson, D. W. *J. Am. Chem. Soc.* **2000**, *122*, 12125; (b) Faraci, W. S.; Walsh, C. T. *Biochemistry* **1989**, *28*, 431; (c) Welch, C. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1991.
2. (a) Dilman, A. D.; Belyakov, P. A.; Korlyukov, A. A.; Struchkova, M. I.; Tartakovsky, V. A. *Org. Lett.* **2005**, *7*, 2913; For the use of other tris(pentafluorophenyl)silyl derivatives as a source of nucleophilic C_6F_5-group towards the iminium cation, see: (b) Dilman, A. D.; Levin, V. V.; Belyakov, P. A.; Struchkova, M. I.; Tartakovsky, V. A. *Synthesis* **2006**, 447; (c) Levin, V. V.; Dilman, A. D.; Belyakov, P. A.; Korlyukov, A. A.; Struchkova, M. I.; Antipin, M. Y.; Tartakovsky, V. A. *Synthesis* **2006**, 489.
3. Dilman, A. D.; Levin, V. V.; Karni, M.; Apeloig, Y. *J. Org. Chem.*, in press.
4. (a) Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371; (b) Kost, D.; Kalikhman, I. In *The Chemistry of Organic Silicon Compounds*; Apeloig, Y., Rappoport, Z., Eds.; Wiley: Chichester, UK, 1998; Vol. 2, p 1339.
5. General procedure: Under an argon atmosphere, to solid AcOLi (73 mg, 1.1 mmol) were successively added DMF (2 mL), aldehyde (1 mmol), and *N*-silylamine (1.2 mmol). The mixture was cooled to 0 °C and $C_6F_5SiF_3$ (302 mg, 1.2 mmol) was added via a syringe. After stirring for 2 h at room temperature the mixture was quenched with satd aq Na_2CO_3 (0.4 mL), and diluted with excess ether. The organic phase was decanted, washed with water (10 mL), and the aqueous phase was washed with ether (10 mL). The combined organic phase was dried ($MgSO_4$), concentrated under vacuum and purified by flash chromatography on silica gel using hexane/ethyl acetate (see Supplementary data for compound characterization data).
6. Namboothiri, I. N. N.; Ganesh, M.; Mobin, S. M.; Gojocaru, M. *J. Org. Chem.* **2005**, *70*, 2235.