ORGANIC LETTERS

2005
Vol. 7, No. 14
2913−2915

Synthesis of Pentafluorophenylmethylamines via Silicon Mannich Reaction

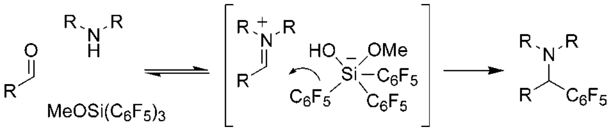
Alexander D. Dilman,*,[†] Pavel A. Belyakov,[†] Alexander A. Korlyukov,[‡] Marina I. Struchkova,[†] and Vladimir A. Tartakovsky[†]

N. D. Zelinsky Institute of Organic Chemistry, 119991 Moscow, Leninsky prosp. 47, Russian Federation, and A. N. Nesmeyanov Institute of Organoelement Compounds, 119991 Moscow, Vavilov str. 28, Russian Federation

adil25@mail.ru

Received April 18, 2005

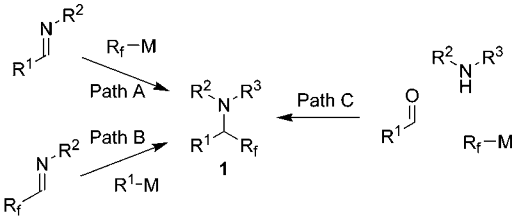
ABSTRACT



The three-component coupling of aldehydes, secondary amines, and methoxytris(pentafluorophenyl)silane, MeOSi(C_6F_5)$_3$, affording pentafluorophenylmethylamines has been described. The generation of the five-coordinate silicate intermediate is believed to be the key feature responsible for the efficiency of the reaction.

Amines containing, at the α-position, a perfluoroalkyl or perfluoroaryl substituent have garnered considerable attention from the synthetic community due to their ability to serve as potential pharmaceutical and agrochemical agents.[1−3] These compounds are usually produced from imines, with the fluorinated moiety coming either from the addition of an appropriate nucleophile[2] (path a) or from the imine itself[3] (path b) (Scheme 1). However, problems associated with the generation and reactivity of fluorinated nucleophiles, harsh reaction conditions, and the high cost of the starting material often limit the scope of this methodology. A more general and straightforward approach to amines such as **1** would be through three-component Mannich-type coupling of aldehydes, amines, and a nucleophile (path c). In the literature, only one such reaction has been described previously; it employed in situ generated titanium reagents $R_fTi(NEt_2)_3$ for the transfer of fluorinated and diethylamino groups on aromatic aldehydes.[4]

Scheme 1. Synthesis of Fluorinated Amines



We became interested in performing the Mannich reaction using silicon fluorinated nucleophiles R_3SiR_f since (a) these reagents are stable and easy-to-handle compounds, (b) nontoxic waste is produced on workup, and (c) their reactivity can be finely modulated by variation of the substituents.[5]

[†] N. D. Zelinsky Institute of Organic Chemistry.

[‡] A. N. Nesmeyanov Institute of Organoelement Compounds.

(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. (c) Faraci, W. S.; Walsh, C. T. *Biochemistry* **1989**, *28*, 431. (d) *Fluorine in Bioorganic Chemistry*; Welch, C. T., Eswarakrishnan, S., Eds.; John Wiley & Sons: New York, 1991.

(2) (a) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Synlett* **2001**, 77. (b) Petrov, V. A. *Tetrahedron Lett.* **2000**, *41*, 6959.

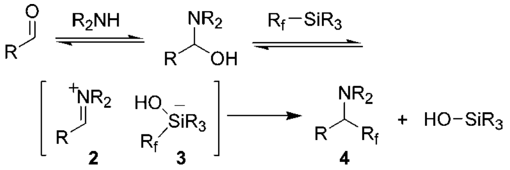
(3) (a) Magueur, G.; Crousse, B.; Bonnet-Delpon, D. *Tetrahedron Lett.* **2005**, *46*, 2219. (b) Funabiki, K.; Nagamori, M.; Goushi, S.; Matsui, M. *Chem. Commun.* **2004**, 1928.

(4) Chen, Q.-Y.; Wu, J.-P. *J. Chem. Res., Synop.* **1990**, 268.

10.1021/ol050845l CCC: $30.25

The three-component Mannich reaction involving moderately nucleophilic allylic silanes has recently been reported and prescribed utilization of a Lewis acid for generation of iminium cation electrophiles.[6] However, fluorinated silanes, R_3SiR_f, cannot be used in this process owing to their very low nucleophilicity. According to Mayr's reactivity scale, the iminium ions (e.g., $R_2N^+{=}CH_2$) have electrophilicity parameters E from -5 to -8.[7] At the same time, based on the data of Eaborn that protodesilylation of $C_6F_5SiMe_3$ occurs ca. 10^5 times slower than that of $C_6H_5SiMe_3$,[8] the nucleophilicity parameter N of $C_6F_5SiMe_3$ can be expected to be well below -4. Therefore, the rate constant for direct coupling between the iminium cation and $C_6F_5SiMe_3$ will be less than 10^{-9} L mol^{-1} s^{-1}. To render the silicon species more reactive an additional nucleophilic activator is required[5a,9] that must be compatible with iminium carbocations. The general mechanistic scenario for base-assisted silicon Mannich reaction is presented in Scheme 2.

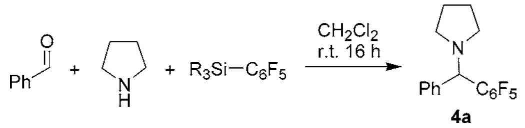
Scheme 2. Silicon Mannich Reaction



The combination of aldehyde and amine first affords a hemiaminal, which interacts with silane generating iminium ion **2** and pentacoordinate silicon intermediate **3**. Subsequent transfer of a fluorinated group from **3** to **2** effects C,C-bond formation providing amine **4**.

We began our investigations with variation of pentafluorophenylsilane nucleophile using benzaldehyde and pyrrolidine as model substrates, performing the reaction in dichloromethane (Table 1). Among the different reagents tested,[10] methoxytris(pentafluorophenyl)silane (**5**) turned out to be the most reactive, presumably owing to the presence of several electron-withdrawing substituents stabilizing the five-coordindate intermediate **3**.[11,12] Silane **5** can transfer only one C_6F_5 group, which may be rationalized by the low activity of the dioxy species $(C_6F_5)_2Si(OMe)OH$ formed after the first transfer step (cf. Table 1, entry 6). The structure of **5**, established by X-ray diffraction analysis (Figure 1), features a short Si−O bond distance of 1.60 Å that may reflect enhanced electron deficiency of the silicon atom.

Table 1. Variation of Silane Reagent[a]



entry	$R_3SiC_6F_5$	yield of **4a**,[b] %
1	$Me_3SiC_6F_5$	–
2	$Me_2Si(C_6F_5)_2$	–
3	$MeSi(C_6F_5)_3$	trace
4	$Si(C_6F_5)_4$	12
5	$(EtO)_3SiC_6F_5$	–
6	$(EtO)_2Si(C_6F_5)_2$	trace
7	$MeOSi(C_6F_5)_3$	86

[a] The ratio of reagents PhCHO/pyrrolidine/$R_3SiC_6F_5$ = 1:1.1:1. [b] Isolated yield.

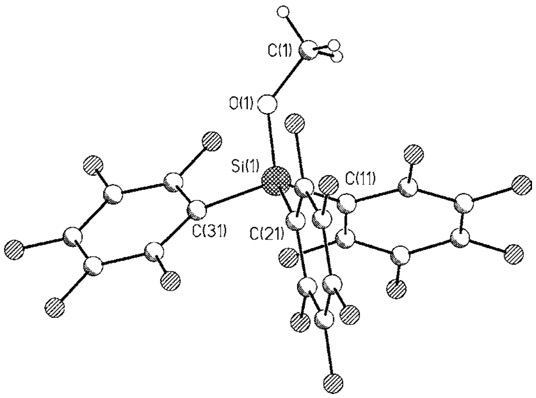


Figure 1. X-ray structure of $MeOSi(C_6F_5)_3$ (**5**).

The less nucleophilic morpholine reacted much slower giving only traces of product. Variation of solvent (Table 2) showed that polar aprotic solvents significantly accelerated the reaction, and in addition induced the formation of pentafluorobenzhydrol **6**. The latter byproduct arises from the transfer of C_6F_5 group on benzaldehyde, and contribution of this process is most pronounced in strongly donating DMSO and DMF. Acetonitrile, which serves as a polar and weakly coordinating medium, was found to be the solvent of choice for the three component coupling allowing for high **4b**/**6** ratio (entry 5).

---

(5) (a) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757. (b) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer: New York, 1983.

(6) (a) Ella-Menye, J.-R.; Dobbs, W.; Billet, M.; Klotz, P.; Mann A. *Tetrahedron Lett.* **2005**, *46*, 1897. (b) Veenstra, S. J.; Schmid, P. *Tetrahedron Lett.* **1997**, *38*, 997. (c) Billet, M.; Schoenfelder, A.; Klotz, P.; Mann, A. *Tetrahedron Lett.* **2002**, *43*, 1453.

(7) (a) Mayr, H.; Ofial, A. R. *Tetrahedron Lett.* **1997**, *38*, 3503. (b) For general description of Mayr's scale, see: Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.

(8) Eaborn, C.; Treverton, J. A.; Walton, D. R. M. *J. Organomet. Chem.* **1967**, *9*, 259.

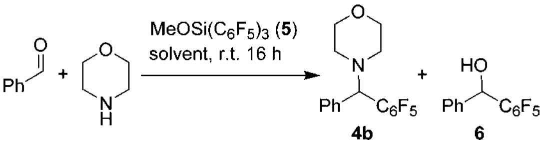
(9) (a) Furin, G. G.; Vyazankina, O. A.; Gostevsky, B. A.; Vyazankin, N. S. *Tetrahedron* **1988**, *44*, 2675. (b) Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2001**, *112*, 123.

(10) Silanes from entries 1−6 can easily be obtained starting from C_6F_5-MgBr and chloro- or ethoxysilanes, see: (a) Whittingham, A.; Jarvie, A. W. P. *J. Organomet. Chem.* **1968**, *13*, 125. (b) Wall, L. A.; Donadio, R. E.; Pummer, W. J. *J. Am. Chem. Soc.* **1960**, *82*, 4846. (c) For the synthesis of silane **5** see Supporting Information.

(11) (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, U.K., 1998; Vol. 2, p 1339.

(12) Formation of **2** and **3** can be considered as abstraction of hydroxide group from the hemiaminal by the Lewis acidic silane; see: Dilman, A. D.; Ioffe, S. L *Chem. Rev.* **2003**, *103*, 733.

Table 2. Optimization of Solvent[a]

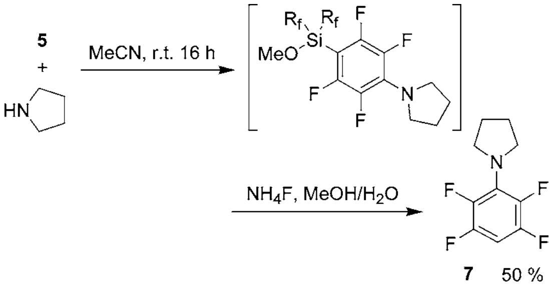


entry	solvent	**4b**/**6**[b]	yield of **4b**,[c] %
1	CH_2Cl_2		trace
2	MeOH		–
3	DMSO	1:6	*d*
4	DMF	6.5:1	36
5	MeCN	20:1	58

[a] The ratio of reagents PhCHO/morpholine/**5** = 1:1.1:1. [b] Determined by ^{1}H NMR analysis of crude product. [c] Isolated yield. [d] Alcohol **6** was isolated in 12% yield.

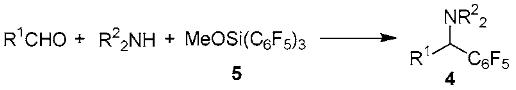
Under the optimized conditions, a variety of aldehydes and amines entered into the silicon Mannich reaction with $MeOSi(C_6F_5)_3$ affording pentafluorophenylmethylamines **4** (Table 3). Aromatic, heteroaromatic, and aliphatic α-branched aldehydes gave good yields of products, whereas linear aliphatic aldehydes were not suitable partners for this reaction, presumably due to competing aldolization. Ketones were unreactive even in the presence of strongly nucleophilic amines. For example, when acetophenone was used in combination with pyrrolidine no coupling product was detected; instead, the nucleophilic attack by the amine on the pentafluorophenyl ring of **5** occurred yielding compound **7** after desilylative workup (Scheme 3).

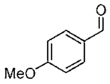
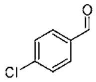
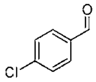
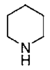
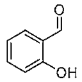
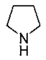
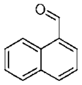
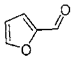
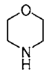
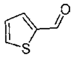
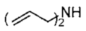
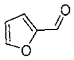
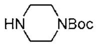
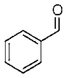
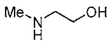
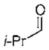
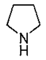
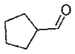
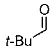
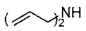
Scheme 3. Interaction of **5** with Amine



The coupling reaction is sensitive to the nature of the amine. Thus, while pyrrolidine, piperidine, and dialkylamines are suitable substrates, weakly nucleophilic amines such as *N*-Boc-protected piperazine and *N*-methylethanolamine led to moderate yields of the products. Primary amines are not effective at all, furnishing imines as the only observable compounds.[13] Nevertheless, successful involvement of diallyl and dibenzylamines opens up opportunities for the synthesis of primary and secondary fluorinated amines via a selective deprotection technique.[14]

Table 3. Three-Component Coupling[a]



entry	aldehyde	amine	condtns.	yield of **4**, %[b]
1		$(PhCH_2)_2NH$	0 °C, 16 h	72
2		Et_2NH	0 °C, 16 h	71
3			0 °C, 16 h	65
4[c]			r.t., 16 h	91
5		Et_2NH	0 °C, 16 h	87
6			r.t., 16 h	77
7			0 °C, 16 h	90
8[d]			r.t., 16 h	57
9			r.t., 67 h	28
10			0 °C, 16 h	81
11		$(PhCH_2)_2NH$	0 °C, 16 h	78
12			0 °C, 48 h	85

[a] The ratio of reagents RCHO/amine/**5** = 1:1.1:1, 0.4 M, in acetonitrile unless stated otherwise. [b] Isolated yield. [c] Performed in CH_2Cl_2 with RCHO/amine/**5** = 1:1.15:1.15. [d] AcOH was used as additive, RCHO/amine/**5**/AcOH = 1:1.1:1:1.

In summary, a new approach to fluorinated amines based on three component coupling of aldehydes, amines, and a fluorinated silane nucleophile has been described. The generation of pentacoordinate silicate species is believed to be responsible for the efficiency of the reaction. Our future efforts will be directed toward expanding the scope of the discovered process.

Acknowledgment. This work was supported by INTAS (Project No. 2003-55-1185). We also thank Prof. S. L. Ioffe for start-up funding.

Supporting Information Available: Experimental procedures; spectroscopic, analytical, and X-ray data (CIF) for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050845L

---

(13) At the same time, no reaction was observed between preformed imines and **5**. We thank the reviewer for suggesting this experiment.

(14) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535.