

An Efficient Method for the Preparation of Carboxamides by Dehydration Condensation Using Tetrakis(1,1,1,3,3,3-hexafluoro-2-propoxy)silane

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The use of tetraalkoxysilanes, particularly tetrakis(perfluoroalkoxy)silanes, in dehydration condensation of carboxylic acids with amines was investigated. Tetrakis(1,1,1,3,3,3-hexafluoro-2-propoxy)silane, Si[OCH(CF₃)₂]₄, prepared easily from silicon tetrachloride and sodium 1,1,1,3,3,3-hexafluoro-2-propoxide, was found to be an effective dehydrating reagent for preparing various carboxamides in good to high yields from the corresponding carboxylic acids and amines.

A silicon-mediated dehydration reaction is one of the most convenient organic transformations and several useful methods have been developed by utilizing characteristic property of silicon, that is its strong affinity toward oxygen.¹ Recently, it was reported from our laboratory that novel types of silicon-containing dehydrating reagents such as tetrakis(2-methylimidazol-1-yl)silane [Si(2-Me-Im)₄]² and tetrakis(pyridin-2-yloxy)silane [Si(OPy)₄]³ were easily synthesized in almost quantitative yields by transsilylation between silicon tetrachloride (SiCl₄) and either 2-methyl-1-trimethylsilylimidazole [Me₃Si(2-Me-Im)] or trimethyl(pyridin-2-yloxy)silane (Me₃SiOPy). It was demonstrated there that these tetra-substituted silanes worked effectively as dehydrating reagents to form various carboxamides from carboxylic acids and amines under mild conditions. It is noted that the work-up procedures of the above mentioned methods are quite simple and the desired products are obtained in almost pure form just by removing co-products, 2-methylimidazole (or 2-hydroxypyridine) and silica [(SiO₂)_n] through extraction with water and filtration. In the course of our continuous studies on synthetic utilities of the silicon-based reagents, it was found that tetrakis(perfluoroalkoxy)silanes were also effective in the above condensation reaction. In this communication, we would like to report a mild and convenient synthetic method for the formation of carboxamides from the corresponding carboxylic acids and amines by using tetrakis(perfluoroalkoxy)silanes, particularly tetrakis(1,1,1,3,3,3-hexafluoro-2-propoxy)silane, as a dehydrating reagent.

In the first place, the reactivity of various tetraalkoxysilanes was screened by taking condensation reactions of 3-phenylpropanoic acid **1a** with benzylamine **2a** or 1-phenylmethylamine **2b** in THF at room temperature (Table 1). When tetramethoxysilane [Si(OMe)₄] and tetraethoxysilane [Si(OEt)₄] were used as dehydrating reagents, only a small amount of the desired carboxamide **3a** was formed (Entries 1 and 2). In order to increase the reactivity of tetraalkoxysilanes, the use of tetra-substituted silanes having fluoro-substituted alkoxy groups was tried next. Although several tetrakis(perfluoroalkoxy)silanes have already been isolated and characterized,⁴ their applications to organic syntheses have not yet been fully investigated. In the case when tetrakis(2,2,2-trifluoroethoxy)silane [Si(OCH₂CF₃)₄]^{4a}

and tetrakis(2,2,3,3,4,4,4-heptafluorobutoxy)silane [Si(OCH₂CF₂CF₂CF₃)₄]^{4a} were used, their reactivity was dramatically enhanced and the reactions of **1a** with benzylamine **2a** proceeded smoothly at room temperature to form the corresponding carboxamide **3a** in excellent yields (Entries 3 and 5). It is considered that, in the presence of amine **2a**, the in situ generated carboxylate reacted with tetrakis(perfluoroalkoxy)silanes to form silyl ester intermediates along with elimination of the corresponding perfluorinated alcohols, and then the reactive intermediates underwent the condensation with amine **2a** to afford the desired carboxamide **3a**. On the other hand, similar reactions that used more sterically-hindered 1-phenylmethylamine **2b** instead of benzylamine **2a** afforded the corresponding carboxamide **3b** together with the undesired formation of perfluoroalkyl esters because the two competitive nucleophilic attacks of amine **2b** and in situ liberated perfluorinated alcohols took place toward reactive silyl ester intermediates (Entries 4 and 6). Accordingly, the use of tetrakis(1,1,1,3,3,3-hexafluoro-2-propoxy)silane, Si[OCH(CF₃)₂]₄,⁵ was tried on the consideration that 1,1,1,3,3,3-hexafluoro-2-propanol was more weakly-nucleophilic. It was found then that Si[OCH(CF₃)₂]₄ worked effectively as a dehydrating reagent to form carboxamides **3** in high yields without

Table 1. Effect of tetraalkoxysilanes

Entry	Tetraalkoxysilane	Amine	Yield ^a / %
1	Si(OMe) ₄	2a	9
2	Si(OEt) ₄	2a	8
3	Si(OCH ₂ CF ₃) ₄	2a	99
4	Si(OCH ₂ CF ₃) ₄	2b	69 ^b
5	Si(OCH ₂ CF ₂ CF ₂ CF ₃) ₄	2a	99
6	Si(OCH ₂ CF ₂ CF ₂ CF ₃) ₄	2b	83 ^c
7	Si[OCH(CF ₃) ₂] ₄	2a	92
8	Si[OCH(CF ₃) ₂] ₄	2a	82 ^d
9	Si[OCH(CF ₃) ₂] ₄	2a	49 ^e
10	Si[OCH(CF ₃) ₂] ₄	2b	86

^aIsolated yield. ^b2,2,2-Trifluoroethyl ester **4a** was afforded as a by-product (23% yield). ^c2,2,3,3,4,4,4-Heptafluorobutyl ester **4b** was afforded as a by-product (8% yield). ^dSi[OCH(CF₃)₂]₄ (0.5 equiv.) was used. ^eSi[OCH(CF₃)₂]₄ (0.25 equiv.) was used.

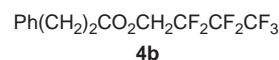
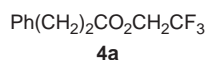


Table 2. Preparation of carboxamides by using Si[OCH(CF₃)₂]₄

Entry	Carboxylic acid	Amine	Yield ^a / %
1	Ph(CH ₂) ₂ CO ₂ H 1a	PhCH ₂ NH ₂ 2a	92
2	1a	PhCHMeNH ₂ 2b	86
3	1a	Ph(CH ₂) ₃ NH ₂ 2c	91
4	1a	PhCH ₂ NHMe 2d	83
5	1a	Piperidine 2e	92
6	1a	PhNH ₂ 2f	97
7	PhCHMeCO ₂ H 1b	2a	85
8	1b	2f	90
9	<i>c</i> -C ₆ H ₁₁ CO ₂ H 1c	2a	90
10	1c	2f	89
11	<i>t</i> -BuCO ₂ H 1d	2a	81
12	1d	2f	56 ^b
13	PhCO ₂ H 1e	2a	72
14	1e	2f	81

^aIsolated yield. ^bReaction was carried out at 50 °C for 10 h.

accompanying the undesired by-products, 1,1,1,3,3,3-hexafluoro-2-propyl esters, even when 1-phenylmethylamine **2b** was used (Entry 10).

Several examples of the formation of carboxamides **3** by using Si[OCH(CF₃)₂]₄ as a dehydrating reagent are listed in Table 2.⁶ In all cases, the undesired by-products, 1,1,1,3,3,3-hexafluoro-2-propyl esters, were not detected at all and the condensation reactions proceeded to form the corresponding carboxamides **3** in good to high yields at room temperature even when a weak nucleophile such as aniline **2f** was used (Entries 6, 8, 10, and 14).

Based on the above results, tetrakis(perfluoroalkoxy)silanes were also applied to the direct transformation of carboxylic acid **1a** into the corresponding perfluoroalkyl esters (Table 3). When the reaction of **1a** with Si(OCH₂CF₃)₄ in THF at room temperature was carried out in the presence of bases such as triethylamine or 4-(dimethylamino)pyridine (DMAP), the desired 2,2,2-trifluoroethyl ester **4a** was obtained in high yield (Entries 2 and 3). Similarly, the reaction of **1a** with Si[OCH(CF₃)₂]₄ proceeded smoothly to form the corresponding 1,1,1,3,3,3-hexafluoro-2-propyl ester **4c** in 83% yield when DMAP was used as a base (Entry 5). On the other hand, it was shown that the simple tetraalkoxysilane such as Si(OMe)₄ was not reactive enough to promote the transformation of **1a** at room temperature (Entries 6 and 7).

Thus, an effective dehydrating reagent, Si[OCH(CF₃)₂]₄, was easily prepared from commercially available SiCl₄ and 1,1,1,3,3,3-hexafluoro-2-propanol, and was used conveniently for the preparation of various carboxamides from carboxylic acids and amines in good to high yields under mild conditions. It is noted that the simple work-up procedure is one of the advantages of the present reaction, and the desired carboxamides are obtained in almost pure form since the co-products of the reaction are silica [(SiO₂)_n] and 1,1,1,3,3,3-hexafluoro-2-propanol. Thus formed silica can be removed by filtration, and also

Table 3. Preparation of perfluoroalkyl esters

Entry	Tetraalkoxysilane	Base	Yield ^a / %
1	Si(OCH ₂ CF ₃) ₄	none	N.D.
2	Si(OCH ₂ CF ₃) ₄	Et ₃ N	93
3	Si(OCH ₂ CF ₃) ₄	DMAP	91
4	Si[OCH(CF ₃) ₂] ₄	Et ₃ N	N.D.
5	Si[OCH(CF ₃) ₂] ₄	DMAP	83
6	Si(OMe) ₄	Et ₃ N	N.D.
7	Si(OMe) ₄	DMAP	N.D.

^aIsolated yield.

1,1,1,3,3,3-hexafluoro-2-propanol (bp 58 °C) can be easily removed in vacuo.

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References and Notes

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- Si[OCH(CF₃)₂]₄ was prepared according to a slight modification of Mazdiyasi's procedure.^{4c} Sodium (4.0 g, 175 mmol) was dissolved carefully in 80 mL of 1,1,1,3,3,3-hexafluoro-2-propanol under argon with stirring. After the solution was cooled to 0 °C, SiCl₄ (5.0 mL, 43.7 mmol) was added slowly, then the precipitation of a white solid was observed. The mixture was kept 0.5 h at room temperature, and then was refluxed for 4 h. After cooling to room temperature, the mixture was allowed to stand overnight and filtered. The filtrate was evaporated and the crude product was purified by distillation (57–58 °C/15 mmHg) to give Si[OCH(CF₃)₂]₄ (16.0 g, 53%). This reagent can be stored for a long time within a sealed bottle at room temperature. ¹H NMR (270 MHz, neat) δ 4.68 (brs, 4H); ¹³C NMR (67.8 MHz, neat) δ 122.3 (q, ¹J(C, F) = 280 Hz), 73.4 (septet, ²J(C, F) = 36.3 Hz); Tetramethylsilane was used as an internal standard.
- General procedure for the preparation of carboxamides by using Si[OCH(CF₃)₂]₄ (Table 2); To a stirred solution of Si[OCH(CF₃)₂]₄ (0.5 mmol) in THF (0.6 mL) were successively added a carboxylic acid (0.5 mmol) and a solution of an amine (0.6 mmol) in THF (0.6 mL) at room temperature. The reaction mixture was stirred for 24 h at the same temperature, followed by the addition of water. Precipitated silica was filtered off and washed with EtOAc, and then the filtrate was extracted with EtOAc. The organic layer was washed with 1 M HCl aq, saturated NaHCO₃ aq, and brine, dried over anhydrous Na₂SO₄. After filtration, the solvent was removed under reduced pressure to give a carboxamide in almost pure form.