An Effective Method for the Synthesis of Carboxamides by Using Tetrakis(pyridine-2-yloxy)silane as a Mild Coupling Reagent

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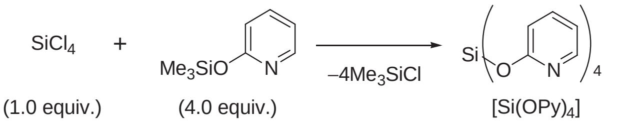
Tetrakis(pyridin-2-yloxy)silane [Si(OPy)$_4$] is easily prepared by trans-silylation between silicon tetrachloride and trimethyl(pyridin-2-yloxy)silane in the molar ratio of 1:4. This novel reagent is effectively employed as a mild dehydrating reagent in forming various carboxamides from the corresponding carboxylic acids and amines that involve secondary or tertiary alkyl substituted ones in good to high yields without using any basic promoters such as tertiary amines or 4-(dimethylamino)pyridine.

In our preceding paper, it was reported that various imidazolylsilane derivatives were easily synthesized by trans-silylation between 1-(trimethylsilyl)imidazoles and chlorosilanes.[1] It was revealed there that the novel reagents having silicon–imidazole linkage were effectively utilized as dehydrating reagents to form carboxamides from free carboxylic acids and amines via the formation of active 1-acylimidazole intermediates under mild conditions. While a classical azolide method by using 1,1′-carbonyldiimidazole (CDI) as a condensation reagent requires a strict stepwise operation so as to prevent the side reaction of forming undesired urea,[2] a new method with novel dehydrating reagents having silicon–imidazole linkage successfully proceeds just by mixing carboxylic acids, amines, and imidazolylsilanes at a time. The desired carboxamides are afforded then in good yields without accompanying any side-products even when an excess amount of the dehydrating reagent is used. Further, it is noted that the work-up procedure is quite simple and carboxamides are obtained in almost pure form if tetrakis(2-methylimidazol-1-yl)silane [Si(2-Me-Im)$_4$] is used since the co-products of the reaction are 2-methylimidazole and silica [(SiO$_2$)$_n$]. 2-Methylimidazole can be removed by washing with dilute acid and the silica thus formed is removed easily just by filtration since it is insoluble in any common solvents.

In the meantime, dehydrating reagents having 2-oxypyridine moiety have been studied intensively, and it was demonstrated that a convenient method for the synthesis of carboxamides or dipeptides was attained in high yields from the corresponding carboxylic acids and amines or α-amino acids by using di(2-pyridyl) carbonate (DPC) or *O*,*O*-di(2-pyridyl) thiocarbonate (DPTC) in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP).[3,4] Further, a still more efficient method by employing 1,1′-carbonyldioxydi[2(1*H*)-pyridone] (CDOP) has also been accomplished in the absence of basic promoters such as DMAP.[5] These reactions by using reactive carbonates as condensation reagents require a strict stepwise procedure since the unreacted carbonates react directly with amines to form undesired by-products such as ureas, carbamates, or isothiocyanates that are often difficult to remove from the reaction mixture.

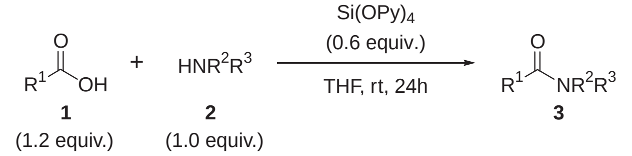


Scheme 1.

In the course of our continuous investigations on the preparation of silicon-containing heterocycles and their application to dehydration reactions, the use of pyridin-2-yloxysilane was focused upon. Now, we would like to report a mild and convenient procedure for the synthesis of carboxamides from the corresponding carboxylic acids and amines that involve secondary or tertiary alkyl substituted ones by using tetrakis(pyridin-2-yloxy)silane [Si(OPy)$_4$], a novel dehydrating reagent.

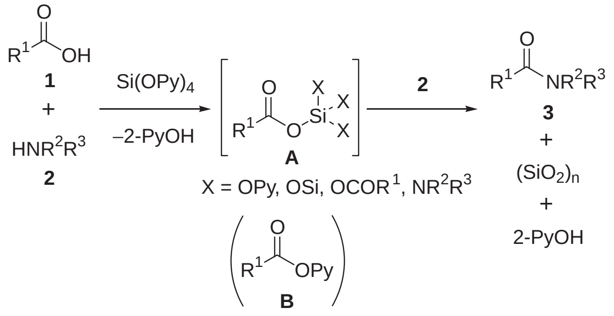
Based on our previously reported procedure employed for the preparation of Si(2-Me-Im)$_4$,[1] tetrakis(pyridin-2-yloxy)silane [Si(OPy)$_4$] was synthesized in almost quantitative yield

Table 1. Preparation of various carboxamides by using Si(OPy)$_4$



Entry	Carboxylic acid		Amine		Yield[a]/%
1	Ph(CH$_2$)$_2$CO$_2$H	**1a**	Ph(CH$_2$)$_3$NH$_2$	**2a**	98
2	**1a**		**2a**		95[b]
3	**1a**		**2a**		61[c]
4	**1a**		**2a**		trace[d]
5	**1a**		PhCH$_2$NH$_2$	**2b**	96
6	**1a**		Ph$_2$CHNH$_2$	**2c**	89
7	**1a**		PhCHMeNH$_2$	**2d**	95
8	**1a**		PhCH$_2$NHMe	**2e**	93
9	**1a**		Piperidine	**2f**	97
10	**1a**		PhNH$_2$	**2g**	86[e]
11	**1a**		*t*-BuNH$_2$	**2h**	62[e]
12	*c*-C$_6$H$_{11}$CO$_2$H	**1b**	**2a**		90
13	**1b**		**2f**		85
14	*t*-BuCO$_2$H	**1c**	**2a**		80[e]
15	**1c**		**2b**		86[e]
16	PhCO$_2$H	**1d**	**2a**		84
17	**1d**		**2f**		73
18	(*E*)-MeCH=CHCO$_2$H	**1e**	**2a**		86
19	(*Z*)-MeCH=CMeCO$_2$H	**1f**	**2a**		74

[a]Isolated yield. [b]Si(OPy)$_4$ (1.0 equiv.) was used. [c]Si(OPy)$_4$ (0.3 equiv.) was used. [d]Me$_3$SiOPy (1.0 equiv.) was used instead of Si(OPy)$_4$. [e]Carboxylic acid (1.5 equiv.) was used.



Scheme 2.

by trans-silylation between silicon tetrachloride ($SiCl_4$) and trimethyl(pyridin-2-yloxy)silane (Me_3SiOPy)[6] in the molar ratio of 1:4 in dry toluene (Scheme 1). After removal of the solvent and thus formed chlorotrimethylsilane (Me_3SiCl), the resulting solid product that can be stored without decomposition for several weeks in a sealed bottle would be used directly for the next condensation reactions.[7]

As a preliminary experiment, the reaction of 3-phenylpropanoic acid **1a** (1.2 equiv.) and 3-phenylpropylamine **2a** (1.0 equiv.) was examined in THF by using $Si(OPy)_4$ (0.6 equiv.) at room temperature, and the corresponding carboxamide was obtained in 98% yield (Table 1, Entry 1). When Me_3SiOPy was used instead of $Si(OPy)_4$, on the other hand, only a trace amount of the desired carboxamide was formed (Entry 4). Several examples of carboxamides **3** obtained by using $Si(OPy)_4$ as a dehydrating reagent are listed in Table 1.[8] In most cases, the reactions proceeded smoothly at room temperature to form the corresponding carboxamides **3** in good to high yields even when highly hindered carboxylic acids or amines such as pivalic acid **1c** or *tert*-butylamine **2h** were used. In addition, it was found that no substantial isomerization took place either when base-sensitive substrates such as crotonic acid **1e** or angelic acid **1f** were used (Entries 18 and 19).[5] This is because the present reactions are carried out without using any bases such as tertiary amines or DMAP.

The proposed mechanism for the formation of carboxamides from free carboxylic acids and amines by using $Si(OPy)_4$ is as follows (Scheme 2). Free carboxylic acids **1** react readily with $Si(OPy)_4$ to form silyl ester intermediates **A** along with elimination of 2-hydroxypyridine [2(1*H*)-pyridone]. In the case when $Si(2\text{-Me-Im})_4$ is used as a dehydrating reagent, in situ formed silyl ester intermediates are smoothly transformed into the corresponding 1-acyl-2-methylimidazoles by nucleophilic attack of 2-methylimidazole to the carbonyl carbon.[1] In this reaction by using $Si(OPy)_4$, other active intermediates such as 2-pyridyl esters **B** are not detected at all because 2-hydroxypyridine [2-(1*H*)-pyridone] is a weakly nucleophilic substance. Therefore, it is considered that reactive silyl ester intermediates **A** directly undergo the subsequent condensation with amines **2** to afford the desired carboxamides **3**.

Thus, a novel dehydrating reagent, $Si(OPy)_4$, was easily prepared by trans-silylation between $SiCl_4$ and Me_3SiOPy, and was used conveniently for the preparation of various carboxamides from free carboxylic acids and amines that involve secondary or tertiary alkyl substituted ones in good to high yields under very mild conditions. Further, its experimental procedure is quite simple and the desired carboxamides are obtained in almost pure form just by removing co-products, 2-hydroxypyridine (2-PyOH) and silica [$(SiO_2)_n$], through extraction with water and filtration.

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7 Preparation of tetrakis(pyridin-2-yloxy)silane [$Si(OPy)_4$] (Scheme 1). To a solution of Me_3SiOPy (10.5 g, 62.8 mmol) in toluene (5 mL) was added slowly $SiCl_4$ (1.46 mL, 12.7 mmol) at room temperature under argon. The precipitation of a white solid was observed. After the mixture was stirred at 80 °C for 1 h, the generated Me_3SiCl and the solvent were removed under reduced pressure to give a white powder in almost quantitative yield (6.35 g). The reagent can be handled for brief periods in the air though it is sensitive to moisture. ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.02 (brs, 1H), 7.56 (brs, 1H), 6.99 (brs, 1H), 6.82 (brs, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 159.5, 147.1, 139.0, 118.2, 113.0.

8 General procedure for the preparation of carboxamides by using $Si(OPy)_4$ (Table 1); To a stirred suspension of $Si(OPy)_4$ (0.3 mmol) in THF (0.75 mL) was successively added a carboxylic acid (0.6 mmol) and a solution of an amine (0.5 mmol) in THF (0.75 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 and washed with EtOAc, and then the filtrate was extracted with EtOAc. The organic layer was washed with 1 M HCl aq, saturated $NaHCO_3$ aq, and brine, dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under reduced pressure to afford an almost pure (by ^{1}H NMR and TLC) carboxamide.

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