# A Convenient Method for Preparations of 1-Acylimidazoles and Carboxamides by Using Novel Imidazolylsilane Derivatives

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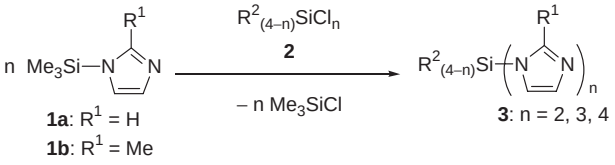
Various imidazolylsilane derivatives were synthesized by a trans-silylation procedure between 1-(trimethylsilyl)imidazoles and chlorosilanes. Among them, tris- and tetrakis(imidazol-1-yl)silane compounds reacted smoothly with free carboxylic acids to form the corresponding 1-acylimidazoles, which subsequently underwent condensation with amines to afford carboxamides in good to high yields. These results indicate that novel reagents containing silicon–imidazole linkage are effectively utilized as dehydrating reagents to form carboxylic acid derivatives from free carboxylic acids and nucleophiles under mild conditions.

Silicon is widely used in the chemistry of inorganic, organic, organometallic, and polymeric compounds, and preparations and reactions of novel types of organosilicon species have recently been studied intensively.[1] Among them, a silicon-mediated dehydrating reaction is one of the most important and fundamental synthetic reactions because silicon has a strong affinity for oxygen.[2] Accordingly, many condensation reactions of free carboxylic acids with amines by using silicon-containing dehydrating reagents have been reported; namely, the use of hexamethyldisilazane (HMDS),[3] silicon tetrachloride ($SiCl_4$),[4] dichlorodimethylsilane ($Me_2SiCl_2$),[5] etc.[6] These conventional reagents, however, have the following synthetic limitations: (i) high reaction temperature and long reaction time are required in the reaction by using HMDS; (ii) in the case when chlorosilanes such as $SiCl_4$ or $Me_2SiCl_2$ are used, the reactions are carried out in pyridine as a solvent to neutralize the liberated hydrogen chloride. Therefore, it is still an important topic to develop more efficient silicon-containing dehydrating reagents for the synthesis of carboxylic acid derivatives under mild conditions. On the other hand, 1,1′-carbonyldiimidazole (CDI) and its analogues have been frequently used as condensation reagents in preparing amides, dipeptides, esters, etc;[7] however, their analogues having silicon–imidazole linkage have not yet been explored. In this communication, we would like to report the use of novel types of imidazol-1-ylsilane derivatives, effective dehydrating reagents, in the condensation of free carboxylic acids with amines via the formation of active 1-acylimidazole intermediates under mild conditions.

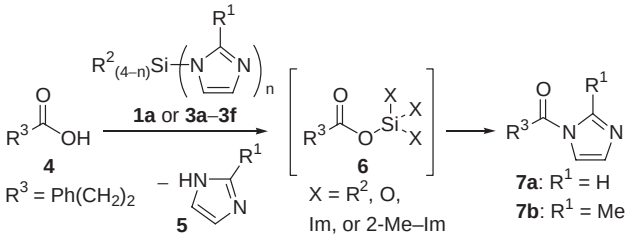
Commercially available 1-(trimethylsilyl)imidazole ($Me_3$-SiIm) **1a**, a monoimidazolylsilane, has been generally employed as a silylating reagent for the protection of hydroxyl groups,[8] but bis-, tris-, and tetrakis(imidazol-1-yl)silane compounds are scarcely known. Among few, Klingebiel et al. reported the method for the preparation of bis(imidazol-1-yl)dimethylsilane [$Me_2Si(Im)_2$] from the sodium salt of imidazole and $Me_2SiCl_2$, but the yield was poor (21%).[9] In order to improve the yield and to apply to synthesis of other analogues, a trans-silylation procedure employed in preparing tris(3,5-dimethylpyrazol-1-yl)-methylsilane[10] was tried (Scheme 1). As a result, various imidazol-1-ylsilane derivatives **3** were easily synthesized in almost quantitive yield by an exchange reaction between 1-(trimethylsilyl)imidazoles **1** and appropriate chlorosilanes **2** along with the evolution of chlorotrimethylsilane ($Me_3SiCl$).[11] Most of the derivatives were not previously reported in the literature despite their simple structures.




**Scheme 1.**

Next, the reactivities of these imidazol-1-ylsilanes, **1a** and **3**, were screened by taking the reactions with 3-phenylpropanoic acid **4** as shown in Table 1. It was thought that the reactions of imidazol-1-ylsilanes with **4** would proceed smoothly to afford the silyl ester intermediates **6**, which would successively afford the corresponding 1-acylimidazoles **7** by either intramolecular rearrangement of **6** or nucleophilic attack of liberated imidazoles **5** on the carbonyl carbon. In the reaction of **1a** with **4**, a small

**Table 1.** Effect of various imidazol-1-ylsilanes




| Entry | Imidazol-1-ylsilane/equiv. | | Conditions[a] | Yield[b]/% |
|---|---|---|---|---|
| 1 | $Me_3SiIm$ (2.0) | **1a** | toluene, reflux, 10 h | 8 |
| 2 | $Me_2Si(Im)_2$ (1.2) | **3a** | THF, reflux, 6 h | 40 |
| 3 | $Me_2Si(Im)_2$ (1.2) | | toluene, reflux, 10 h | 67 |
| 4 | $MeSi(Im)_3$ (1.2) | **3b** | $CH_2Cl_2$, rt, 6 h | 81 |
| 5 | $MeSi(2\text{-Me–Im})_3$ (1.2) | **3c** | $CH_2Cl_2$, rt, 6 h | 92 |
| 6 | $BuSi(Im)_3$ (1.2) | **3d** | $CH_2Cl_2$, rt, 6 h | 91 |
| 7 | $BuSi(Im)_3$ (1.2) | | THF, rt, 6 h | 94 |
| 8 | $Si(Im)_4$ (1.0) | **3e** | $CH_2Cl_2$, rt, 10 h | trace |
| 9 | $Si(2\text{-Me–Im})_4$ (1.0) | | $CH_2Cl_2$, rt, 1 h | quant. |
| 10 | $Si(2\text{-Me–Im})_4$ (0.5) | **3f** | $CH_2Cl_2$, rt, 1 h | 90 |
| 11 | $Si(2\text{-Me–Im})_4$ (0.5) | | THF, rt, 1 h | 89 |

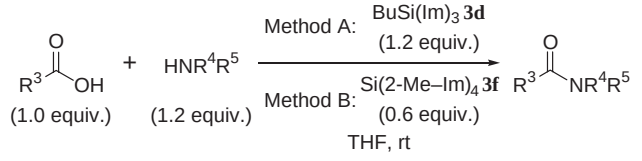
[a]Reactions were carried out using **4** (0.5 mmol) in solvent (1 mL). [b]Yield was determined by $^1$H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

amount of 1-acylimidazole **7a** was detected when the reaction temperature was raised up to the refluxing temperature of toluene (Entry 1). The use of $Me_2Si(Im)_2$ **3a** prepared from a 2:1 molar ratio of **1a** and $Me_2SiCl_2$ led to an increase in the yield of **7a** although higher reaction temperature was still required (Entries 2 and 3). On the other hand, several tris(imidazol-1-yl)alkylsilane derivatives **3b**–**3d** prepared from a 3:1 molar ratio of **1** and alkyltrichlorosilanes ($R^2SiCl_3$) smoothly reacted with **4** at room temperature to afford the corresponding **7** in good yields (Entries 4–7). The reaction by using tetrakis(imidazol-1-yl)silane [$Si(Im)_4$] **3e** prepared from a 4:1 molar ratio of **1a** and $SiCl_4$ hardly afforded **7a** because of its extremely low solubility (Entry 8). However, tetrakis(2-methylimidazol-1-yl)silane [$Si(2\text{-}Me\text{–}Im)_4$] **3f** prepared from a 4:1 molar ratio of 2-methyl-1-trimethylsilylimidazole [$Me_3Si(2\text{-}Me\text{–}Im)$] **1b** and $SiCl_4$ readily reacted with **4** at room temperature to give the corresponding 1-acyl-2-methylimidazole **7b** in good yields even when the amount of **3f** was reduced to 0.5 equivalents (Entries 9–11).

Then, the condensation of free carboxylic acids with various amines was further tried by using $BuSi(Im)_3$ **3d** or $Si(2\text{-}Me\text{–}Im)_4$ **3f** as condensation reagents in THF (Table 2).[12] In most cases, the reactions proceeded smoothly under mild conditions to provide the corresponding carboxamides in good to high yields. It is noted that the work-up procedure is quite simple and almost pure carboxamides are obtained when **3f** is used since the by-product of the reaction is silica [$(SiO_2)_n$], which is insoluble in all common solvents and thereby can be removed easily by filtration.

Thus, novel types of imidazol-1-ylsilanes, particularly tris- and tetrakis(imidazol-1-yl)silane derivatives, reacted readily with free carboxylic acids to give the corresponding 1-acylimidazoles, which smoothly underwent the subsequent condensation with amines to form carboxamides in good to high yields. Further investigations on the preparation of silicon-containing heterocycles and their application to various dehydration reactions are now in progress.

**Table 2.** Preparation of various carboxamides using **3d** or **3f**




| Entry | Carboxylic acid | Amine | Method | Yield[a]/% |
|---|---|---|---|---|
| 1 | $Ph(CH_2)_2CO_2H$ | $Ph(CH_2)_3NH_2$ | A | 88 |
| 2 | | | B | 90 |
| 3 | | $PhCHMeNH_2$ | A | 70 |
| 4 | | | B | 73 |
| 5 | | $PhCH_2NHMe$ | A | 96 |
| 6 | | | B | 92 |
| 7 | | Piperidine | A | 96 |
| 8 | | | B | 96 |
| 9 | | $PhNH_2$ | A | 53[b] |
| 10 | | | B | 71[b] |
| 11 | $PhCO_2H$ | $Ph(CH_2)_3NH_2$ | A | 71 |
| 12 | | | B | 76 |
| 13 | | Piperidine | A | 82 |
| 14 | | | B | 87 |

[a]Isolated yield. [b]Reaction was carried out at 50 °C for 6 h.

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**References and Notes**

1 M. A. Brook, "Silicon in Organic, Organometallic, and Polymer Chemistry," John Wiley & Sons, New York (2000).
2 H. Vorbruggen, "Silicon-mediated Transformations of Functional Groups," Wiley-VCH, Weinheim (2004).
3 a) W.-C. Chou, M. C. Chou, Y.-Y. Lu, and S.-F. Chen, *Tetrahedron Lett.*, **40**, 3419 (1999). b) R. Peelegata, M. Pinza, and G. Pifferi, *Synthesis*, **1978**, 614. c) B. D. Harris, K. L. Bhat, and M. M. Joullie, *Synth. Commun.*, **16**, 1815 (1986). d) J. W. Lampe, P. F. Hughes, C. K. Biggers, S. H. Smith, and H. Hu, *J. Org. Chem.*, **59**, 5147 (1994).
4 a) T. H. Chan and L. T. L. Wong, *J. Org. Chem.*, **34**, 2766 (1969). b) I. Azumaya, H. Kagechika, K. Yamaguchi, and K. Shudo, *Tetrahedron Lett.*, **37**, 5003 (1996).
5 S. H. van Leeuwen, P. J. L. M. Quaedflieg, Q. B. Broxterman, and R. J. J. Liskamp, *Tetrahedron Lett.*, **43**, 9203 (2002).
6 E. P. Krysin, V. N. Karel'skii, A. A. Antonov, and G. E. Rostovskaya, *Khim. Prir. Soedin.*, **1979**, 684.
7 a) H. A. Staab, H. Bauer, and K. M. Schneider, "Azolides in Organic Synthesis and Biochemistry," Wiley-VCH, Weinheim (2004), pp 129–208. b) H. A. Staab, *Angew. Chem., Int. Ed. Engl.*, **1**, 351 (1962). c) T. Kitagawa, H. Kuroda, H. Sasaki, and K. Kawasaki, *Chem. Pharm. Bull.*, **35**, 4294 (1987). d) A. K. Saha, P. Schultz, and H. Rapoport, *J. Am. Chem. Soc.*, **111**, 4856 (1989).
8 a) L. D. Rowe, R. C. Beier, M. H. Elissalde, L. H. Stanker, and R. D. Stipanovic, *Synth. Commun.*, **23**, 2191 (1993). b) Y. Tanabe, M. Murakami, K. Kitaichi, and Y. Yoshida, *Tetrahedron Lett.*, **35**, 8409 (1994).
9 A. Frenzel, M. Gluth, R. Herbst-Irmer, and U. Klingebiel, *J. Organomet. Chem.*, **514**, 281 (1996).
10 S. Vepachedu, R. T. Stibrany, S. Knapp, J. A. Potenza, and H. J. Schugar, *Acta Crystallogr.*, **C51**, 423 (1995).
11 Typical procedure for the preparation of tetrakis-, tris-, and bis(imidazol-1-yl)silane derivatives by a trans-silylation technique is as follows: a) $Si(2\text{-}Me\text{–}Im)_4$ **3f**; To a solution of **1b** (7.85 g, 50.9 mmol) in toluene (5 mL) (or without using any solvent) 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. The reagent can be handled for brief periods in the air though it is sensitive to moisture. $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 2.09 (s, 12H), 6.84 (s, 4H), 7.18 (s, 4H); $^{13}$C NMR (67.8 MHz, $CDCl_3$) $\delta$ 15.4, 120.9, 132.3, 149.7; HRMS ($EI^+$) calcd for $C_{16}H_{20}N_8Si$ $[M]^+$ 352.1580, found $m/z$ 352.1582. b) $MeSi(2\text{-}Me\text{–}Im)_3$ **3c**; Following the procedure used to prepare **3f**, reaction was performed between **1b** and $MeSiCl_3$ in a 3:1 molar ratio. $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 1.38 (s, 3H), 2.29 (s, 9H), 6.50 (s, 3H), 7.07 (s, 3H); $^{13}$C NMR (67.8 MHz, $CDCl_3$) $\delta$ 0.1, 15.7, 120.8, 131.1, 149.4. c) $Me_2Si(Im)_2$ **3a**;[9] Following the procedure used to prepare **3f**, reaction was performed between **1a** and $Me_2SiCl_2$ in a 2:1 molar ratio. $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.95 (s, 6H), 6.95 (s, 2H), 7.23 (s, 2H), 7.61 (s, 2H); $^{13}$C NMR (67.8 MHz, $CDCl_3$) $\delta$ −1.8, 119.5, 131.7, 139.7.
12 General procedure for the preparation of carboxamides using **3f** (Table 2, Method B); To a stirred suspension of **3f** (0.3 mmol) in THF (1.0 mL) was successively added a carboxylic acid (0.5 mmol) and a solution of an amine (0.6 mmol) in THF (0.5 mL) at room temperature. The reaction mixture was stirred for 8–24 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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