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# The efficient synthesis of 3-hydroxyoxetane-3-carboxamides by the reaction of carbamoylsilanes with oxetan-3-one

**Pengpeng Zhang,[a] Shenghua Han[b] and Jianxin Chen*[a]**

[a] *College of Chemistry and Materials Science, Shanxi Normal University, Lin fen 041004, P. R. China. E-mail: jjxxcc2002@yahoo.com*

[b] *College of Chemistry and Engineering, Shanxi Datong University, Datong 037009, P. R. China. E-mail: hanshenghua@sina.com.cn*

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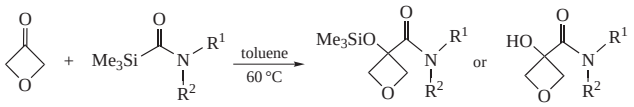
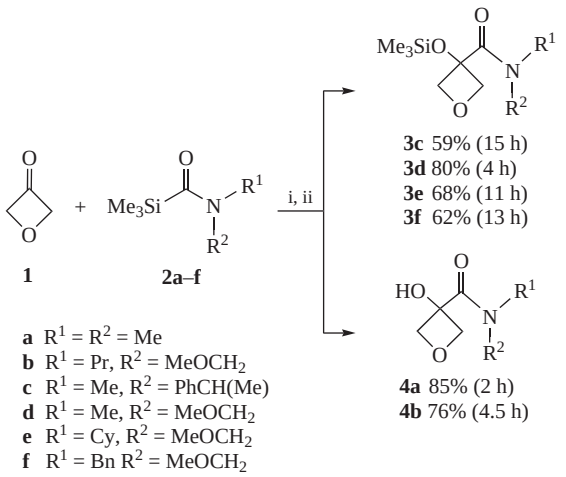
**The reaction of carbamoylsilanes with oxetan-3-one under anhydrous conditions in toluene at 60 °C affords 3-silyloxy- or 3-hydroxyoxetane-3-carboxamides in good yields.**




Oxetanes, four-membered oxygen heterocycles, have attracted attention due to their increasing application in medicinal chemistry.[1–3] They are used in the synthesis of biologically active compounds and as bioisosteric substitutes for common functional groups such as gem-dimethyl or carbonyl groups in drug molecules.[4–6] Oxetane moiety can be found in some drugs, which can induce beneficial effects on the lipophilicity, aqueous solubility, metabolic stability and conformational preference of drug molecules.[7–9] 3,3-Difunctional oxetanes do not have additional stereocentres, which makes them preferential when they are used as the molecular scaffolds.[2,8,10] The common accesses toward 3-substituted oxetanes involve the multi-step routes[2,10,11] and multi-component reactions.[12] In previous work, we discovered a simple and practical method for the preparation of α-hydroxy amides by the addition of various carbamoylsilanes at C=O group of α-keto esters, α-keto amides, ketones or aldehydes.[13–16] α-Hydroxy amides are important intermediates in organic synthesis and also serve as valuable agents in medicinal chemistry.[17] However, in the case of ketones, the scope was limited to aryl ketones and aryl enones, while cyclic ketones reacted poorly. Here, we report that oxetan-3-one **1** can readily react with carbamoylsilanes[18] **2** under mild conditions to provide good yields of new 3-silyloxyoxetane-3-carboxamides **3** or 3-hydroxyoxetane-3-carboxamides **4** under mild conditions (Scheme 1). To the best of our knowledge, such a combination of reactants has not previously been studied. Our study was initiated by examining the influence of solvents and temperature using *N*,*N*-dimethylcarbamoyl(trimethyl)silane **2a** as the model reactant (Table 1). The reaction did not proceed in polar solvents such as dichloromethane, THF and acetonitrile (entries 1–3), in distinction to nonpolar benzene and toluene (entries 4–7). The product turned to be desilylated derivative **4a**, the hydrolysis having took place in the course of chromatography purification on $SiO_2$. The temperature variation showed that at 60 °C the yield of the product was higher (entry 5), decrease in reaction temperature having led to a drop in the yield (entry 6).

To study the scope of this reaction, we screened a range of carbamoylsilanes bearing various groups on the amide nitrogen under optimal conditions (toluene, 60 °C, see Scheme 1).† For all the carbamoylsilanes, the yields were from good to excellent. When carbamoylsilane **2a** reacted with oxetan-3-one, a fast,




**Scheme 1** *Reagents and conditions*: i, toluene, 60 °C, 2–15 h; ii, column chromatography on silica gel.

**Table 1** Optimization of the reaction conditions between oxetan-3-one **1** and *N*,*N*-dimethylcarbamoyl(trimethyl)silane **2a**.

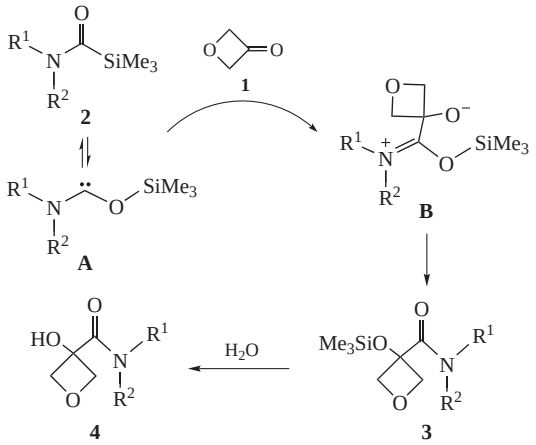
| Entry | Solvent | *T*/°C | Time[a]/h | Yield of **4a**[b] (%) |
|---|---|---|---|---|
| 1 | THF | 60 | 25 | 0 |
| 2 | $CH_2Cl_2$ | 30 | 24 | 0 |
| 3 | MeCN | 60 | 25 | 0 |
| 4 | PhH | 60 | 8 | 41 |
| 5 | PhMe | 60 | 2 | 85 |
| 6 | PhMe | 25 | 6 | 47 |
| 7 | PhMe | 80 | 1.5 | 79 |

[a] To complete consumption of **2a**. [b] Isolated yield based on **2a**, the **1** : **2a** molar ratio was 1 : 1.2.

† *General procedure for the synthesis of 3,3-disubstituted oxetanes* **3** *or* **4**. A Schlenk tube fitted with a Teflon vacuum stopcock and a micro stirring bar was flame-heated under vacuum and refilled with argon. Oxetan-3-one **1** (0.5 mmol), anhydrous toluene (1.5 ml) and carbamoylsilane **2** (1.2 equiv.) were added. The mixture was stirred at 60 °C until complete consumption of the carbamoylsilane (TLC). Volatiles were removed under vacuum and the residue was chromatographed using light petroleum–EtOAc as the eluent to obtain products **3** or **4**.

clean, and complete reaction occurred within 2 h, furnishing excellent yield of the corresponding product **4a**. When oxetan-3-one was reacted with carbamoylsilane **2c** bearing a large group on the amide nitrogen, the silyl ether bond was not hydrolyzed and product **3c** was obtained in 59% yield. This indicates that the reaction outcome is sensitive to steric factors.

Carbamoylsilanes **2b**,**d**,**e** containing methoxymethyl protective grouping were screened to react with oxetan-3-one, in hope to access further secondary amide derivatives (*cf.* ref. 19). The corresponding products **4b** (as free hydroxyl derivative) and **3d**,**e** (as silyl ethers) were obtained. A comparison of the results obtained with reactants **2b**,**d**,**e** indicates that placing a large group on the amide nitrogen causes steric impediment to reaction. The lesser the steric hindrance, the shorter the reaction time and the higher yield of the product. Oxetan-3-one reacted with carbamoylsilane **2f** containing two amine protecting groups simultaneously to afford the corresponding product **3f**. Hopefully, removal of methoxymethyl group and benzyl one (*cf.* ref. 20) should open access to primary amides of chemotype in question.




**Scheme 2**

*3-Hydroxy*-N,N-*dimethyloxetane-3-carboxamide* **4a**: colourless solid, yield 85%, mp 70–71 °C. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 5.02 (br. s, 1H), 4.98, 4.70 (dd, 4H, *J* 7.2 Hz), 3.14 (s, 3H), 3.02 (s, 3H). $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$: 170.7, 81.0, 74.7, 36.9, 36.6. IR (KBr, $\nu$/cm$^{-1}$): 3274, 1617, 1516, 1386, 1329, 1191. Found (%): C, 49.60; H, 7.43; N, 9.41. Calc. for $C_6H_{11}NO_3$ (%): C, 49.65; H, 7.64; N, 9.65.

N-*Methoxymethyl*-N-*methyl-3-silyloxyoxetane-3-carboxamide* **3d**: colourless liquid, yield 80%. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 5.09, 5.05 (dd, 2H, *J* 6.6 Hz), 4.68, 4.64 (dd, 2H, *J* 6.6 Hz), 4.82, 4.51 (ss, 2H), 3.35, 3.30 (ss, 3H), 3.00, 2.91 (ss, 3H), 0.15, 0.12 (ss, 9H). $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$: 171.4, 171.2, 81.0, 80.9, 78.7, 56.2, 55.7, 33.2, 33.1, 0.9, 0.8. IR (KBr, $\nu$/cm$^{-1}$): 1658, 1459, 1394, 1252, 1098. Found (%): C, 48.32; H, 8.29; N, 5.48. Calc. for $C_{10}H_{21}NO_4Si$ (%): C, 48.55; H, 8.56; N, 5.66.

N-*Benzyl*-N-*methoxymethyl-3-silyloxyoxetane-3-carboxamide* **3f**: colourless liquid, yield 62%. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.38–7.22 (m, 5H), 5.14, 5.10 (dd, 2H, *J* 7.2 Hz), 4.80–4.67 (m, 4H), 4.51, 4.48 (ss, 2H), 3.36, 3.26 (ss, 3H), 0.21, 0.11 (ss, 9H). $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$: 171.1, 136.8, 128.7, 128.5, 127.5, 127.3, 80.9, 80.7, 78.4, 55.5, 48.7, 47.9, 1.3, 1.0. IR (KBr, $\nu$/cm$^{-1}$): 1642, 1597, 1516, 1414, 1252, 1077. Found (%): C, 59.65; H, 7.56; N, 4.30. Calc. for $C_{16}H_{25}NO_4Si$ (%): C, 59.41; H, 7.79; N, 4.33.

For characteristics of compounds **3c**,**e** and **4b**, see Online Supplementary Materials.

A possible route to products **3** or **4** is presented in Scheme 2. Carbamoylsilane **2** can rearrange to its nucleophilic carbene form **A**[13] which would attack carbonyl of oxetan-3-one to produce an unstable intermediate **B**, followed by 1,4-migration of silyl group to give 3-siloxy-3-carbamoyl oxetane **3**. The latter can be easily hydrolyzed to form 3-hydroxy-3-carbamoyl oxetane **4**.

In conslusion, we have developed a novel, simple, direct route to the pharmaceutically important 3,3-disubstituted oxetane scaffold by the aminocarbonylation of oxetan-3-one with carbamoylsilanes as the carbamoyl group source. The reaction tolerates a broad range of substituents on the amide nitrogen of carbamoylsilanes (including protective groups) and provides good yields of the products; preparation of primary or secondary α-hydroxy amides with the removal of the protections may be anticipated. Ongoing work is focused on the development of addition reaction of other oxetane nucleus, and their application to drug discovery.

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*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.05.029.

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