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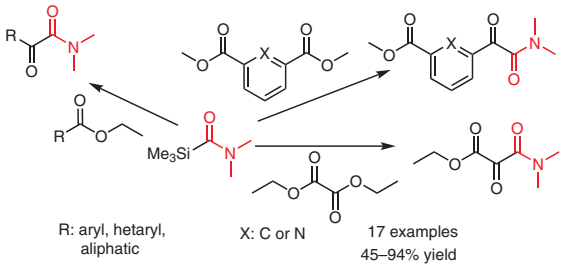
# Practical Approach for the Preparation of α-Keto Amides by Direct Aminocarbonylation of Carboxylic Esters with a Carbamoylsilane

**Yuling Han**[a]
**Shenghua Han**[b]
**Jiangwen Ma**[a]
**Weidong Li**[a]
**Jianxin Chen***[a]

[a] College of Chemistry and Materials Science, Shanxi Normal University, Linfen 041004, P. R. of China
jjxxcc2002@yahoo.com
[b] College of Chemistry and Engineering, Shanxi Datong University, Datong 037009, P. R. of China
hanshenghua@sina.com.cn

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**Abstract** A novel and practical method has been developed for the preparation of α-keto amides by a catalyst-free aminocarbonylation of carboxylic esters with *N*,*N*-dimethylcarbamoyl(trimethyl)silane under neutral conditions. A new protocol for the synthesis of vicinal tricarbonyl compounds was also developed by using this method. In the case of diesters, only one ester group reacted selectively with 1.2 equivalents of the carbamoylsilane, leading to the formation of a single α-keto amide. The reaction was suitable for aryl, hetaryl, or open-chain esters containing strongly electron-withdrawing groups.

**Keywords** keto amides, esters, carbamoylsilanes, aminocarbonylation, tricarbonyl compounds

α-Keto amides are an important class of organic synthetic intermediates in various functional-group transformations and in the elaboration of important heterocycles found in many natural products and drugs with various biological activities.[1] In addition, α-keto amides are also used in the development of inhibitors of peptidases, serine or cysteine proteases, peptidyl prolyl isomerases, cathepsin S, p38, or human cytosolic phospholipase $A_2$.[2] Consequently, various methods for the synthesis of α-keto amides have been developed. Earlier methods include the oxidation of α-amino amides,[3] α-hydroxy amides,[4] ynamines,[5] acyl cyanophosphoranes,[6] arylacetamides,[7] or α-cyano amides;[8] amidation of α-keto acids or α-keto acyl halides with amines;[9] transition-metal-catalyzed amino double carbonylation of organic halides;[10] Stetter reactions of glyoxamides;[11] reactions of isocyanides with aromatic acyl chlorides;[12] and nucleophilic addition of a Grignard reagents to Weinreb amides.[13] New protocols have continued to emerge.[12b,14] Although numerous, efficient approaches have been established, a review of the literature showed that most of these procedures suffer from such drawbacks as the use of toxic transition-metal salts as catalysts, the use of organic oxidants or an oxygen atmosphere, the use of hazardous carbon monoxide gas, the need for complicated experimental manipulations, low efficiencies, or the formation of toxic byproducts that must be disposed of. We previously discovered that the reaction of carbamoylsilanes with acid chlorides gives α-keto amides under mild conditions without the use of a catalyst.[15] In this reaction, an aminocarbonyl group was introduced into the substrates, leading to the formation of α-keto amides. This synthetic route is simple, practical, and overcomes the above-mentioned drawbacks. However, this method is limited by the nature of the precursors. Acid halide groups are unstable and their preparations require multistep operations in transformations of polyfunctional compounds. Carboxylic ester groups are more common in organic synthesis. They are readily available, bench stable, and easy to handle. Consequently, the development of a protocol for the direct conversion of a carboxylic ester group into an α-keto amide group is a significant and challenging research topic. We previously found that carbamoylsilanes add to the C=O bond of α-keto esters, α-keto amides, aldehydes, or ketones to give the corresponding α-hydroxy amides.[16] Cunico et al. found that a carbamoylsilane could react with diethyl oxalate to give an addition product.[17] Encouraged by these results, we tested the addition reaction between a carbamoylsilane and a range of esters. We were pleased to find that esters containing a strongly electron-withdrawing group reacted with the carbamoylsilane to give α-keto amides directly. To the best of our knowledge, this method for the preparation of α-keto amides has not previously been studied. Here, we present our recent studies on the use of *N*,*N*-dimethylcarbamoyl(trimethyl)silane as a source of the aminocarbonyl group in the reaction (Scheme 1).



 
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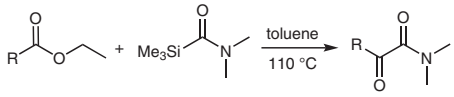
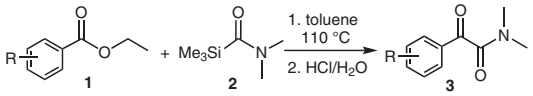


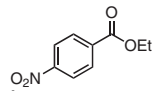
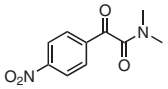
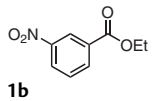
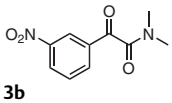
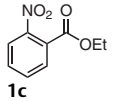
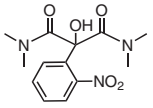
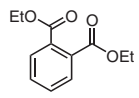
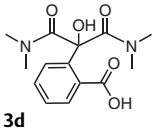
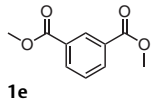
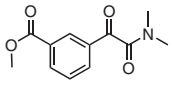
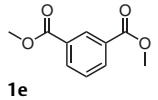
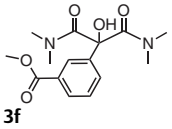

**Scheme 1** α-Keto amides from esters and *N*,*N*-dimethylcarbamoyl(trimethyl)silane

In our initial studies, we investigated the reaction of common esters, such as ethyl benzoate, ethyl *p*-methylbenzoate, or ethyl *p*-methoxybenzoate, with *N*,*N*-dimethylcarbamoyl(trimethyl)silane in toluene at 110 °C, and we found that these esters were unreactive under these conditions. We next tested the reactivity of carboxylic esters containing a strongly electron-withdrawing group, such as ethyl *p*-nitrobenzoate. The reaction was typically conducted in toluene and was allowed to continue until all the carbamoylsilane **2** was consumed (Table 1). We found that a mixture of unreacted **1**, small amounts of DMF, and the addition product of the carboxylic ester with carbamoylsilane **2** was formed. The addition product was hydrolyzed in hydrochloric acid solution and then isolated to afford the α-keto amide **3a** in 69% yield (Table 1, entry 1).

To explore the scope of this reaction, we screened several carboxylic esters bearing electron-withdrawing groups in the reaction with carbamoylsilane **2** (Table 1) Ethyl benzoates containing a nitro group in the *meta*- or *ortho*-position afforded corresponding products **3b** and **3c** (Table 1, entries 2 and 3). A comparison of the results of the reactions for the three isomeric ethyl nitrobenzoates **1a–c** showed that the reactivity of the ethyl nitrobenzoate increased with decreasing distance between the nitro group and the ester group. Compound **1c** was the most reactive and required the shortest reaction time; moreover, the reaction gave the bisadduct through in situ reaction of the monoaddition product with an additional equivalent of carbamoylsilane **2**; the α-hydroxymalonamide derivative **3c** was generated by hydrolysis. This result demonstrates that the reaction is highly sensitive to inductive effects. The yield of bisadduct **3c** increased on using an excess of the carbamoylsilane **2**. Turning to diethyl phthalate (**1d**), a similar phenomenon was also observed, and the reaction afforded product **3d**, which corresponds to the bisadduct, whereas dimethyl isophthalate (**1e**) reacted with 1.2 equivalents of the carbamoylsilane **2** to afford desired product **3e** in 56% yield; this was the product from addition to only one ester group. When 2.4 equivalents of **2** were used, the reaction afforded **3f**, corresponding to the bisadduct formed in situ from one ester group. The reaction did not occur on both ester groups. The use of diethyl terephthalate, which has *para*-ester groups with opposing inductive effects resulted in less than a 5% yield of the corresponding α-keto amide. We conclude that, in general, the inductive effect of an electron-withdrawing group on the aryl ring is a key factor in this reaction.

**Table 1** α-Keto Amides **3** from Arylcarboxylic Esters **1** and Carbamoylsilane **2**

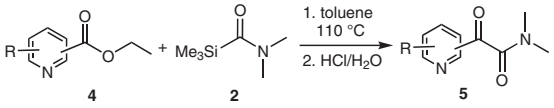



| Entry | Ester | Product | Time[a] (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1[c] |  **1a** |  **3a** | 42 | 69 |
| 2[c] |  **1b** |  **3b** | 34 | 75 |
| 3[c] |  **1c** |  **3c** | 25 | 52 |
| 4[c] |  **1d** |  **3d** | 30 | 51 |
| 5[c] |  **1e** |  **3e** | 34 | 56 |
| 6[d] |  **1e** |  **3f** | 30 | 70 |

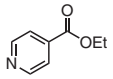
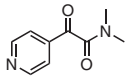
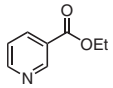
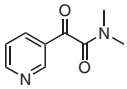
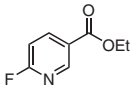
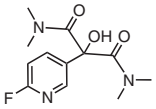
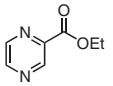
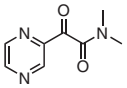
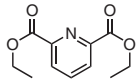
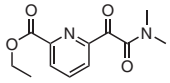
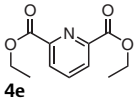
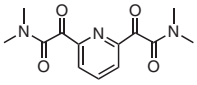
[a] Time to complete consumption of carbamoylsilane **2** in toluene at 110 °C.
[b] Isolated yield based on ester **1**.
[c] 1:1.2 molar ratio of ester **1** to carbamoylsilane **2**.
[d] 1:2.4 molar ratio of ester **1** to carbamoylsilane **2**.

To explore the synthetic potential of this process further, we examined the reactions of electron-deficient hetaryl carboxylate esters, such as pyridyl or pyrazinyl derivatives, with carbamoylsilane **2** (Table 2). We were pleased to find that all the tested esters **4a–e** gave moderate yields of the corresponding α-keto amides. Ethyl pyrazine-2-carboxylate (**4d**) afforded a higher yield than that from **4a** or **4b** due to the strong electron-withdrawing effect of its two nitrogen atoms. Picolinate **4c**, containing a fluoro group at the C6-position, was investigated in the hope that it would produce an increased yield; however, this reaction gave the α-hydroxy malonamide derivative **5c**, corresponding to the bisadduct, due to the effect of the strongly electron-withdrawing substituents. Diethyl 2,6-pyridinedicarboxylate (**4e**) reacted with 1.2 equivalents of carbamoylsilane **2** to give the single-addition product **5e** in good yield, whereas

**Table 2** α-Keto Amides **5** from Arylcarboxylic Esters **4** and the Carbamoylsilane **2**




4 2 5

| Entry | Ester | Product | Time[a] (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1[c] |  **4a** |  **5a** | 28 | 55 |
| 2[c] |  **4b** |  **5b** | 26 | 52 |
| 3[c] |  **4c** |  **5c** | 24 | 45 |
| 4[c] |  **4d** |  **5d** | 3 | 68 |
| 5[c] |  **4e** |  **5e** | 6 | 71 |
| 6[d] |  **4e** |  **5f** | 4.5 | 94 (**5e**/**5f** = 1:2) |

[a] Time to complete consumption of carbamoylsilane **2** in toluene at 110 °C.
[b] Isolated yield based on carboxylic ester **4** after chromatography (silica gel).
[c] 1:1.2 molar ratio of ester **4** and carbamoylsilane **2**.
[d] 1:2.4 based on carboxylic esters **4**

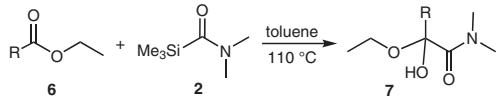
the reaction with 2.4 equivalents of **2** afforded a mixture of products **5e** and **5f** in high yield; **5f** was the product of addition to both carboxylic ester groups, and the ratio of **5e** and **5f** was 1:2.

Next, we explored the reaction of aliphatic esters containing a strongly electron-withdrawing group (Table 3). Ethyl trifluoroacetate (**6a**), methyl trifluoroacetate (**6b**), and phenyl trifluoroacetate (**6c**) were each treated with carbamoylsilane **2**, and the reaction mixtures were then purified by Kugelrohr distillation to give product **7a**, which corresponds to the bisadduct, in good yields; the structure of product **7a** was similar to those of **3c** and **3d**. The reactions of **6a–c** gave similar yields and required similar reaction times, indicating that the nature of the ester group did not affect the reactivity or the yield of the reaction. Ethyl trichloroacetate (**6d**) reacted to give addition product **7d**, containing an ethoxy group, which confirmed that an addition process occurs in this transformation. As expected, the reaction was slower and gave lower yield than that of **6a** due to the weaker electron-withdrawing effect of chlorine compared with fluorine. Product **7d** can be converted into an α-keto amide by acid hydrolysis or by heating under vacuum.[18]

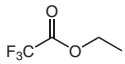
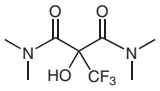
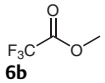
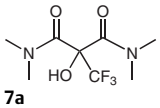
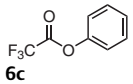
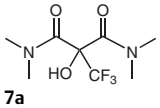
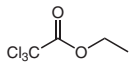
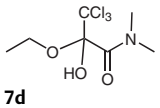
Diethyl oxalate (**8**) reacted with 1.2 equivalents of carbamoylsilane **2** to give the vicinal tricarbonyl compounds **9** directly in good yield (Scheme 2); this product corresponds to the single-addition product. Vicinal tricarbonyl compounds have been widely used in syntheses of heterocyclic compounds or biologically active compounds such as antibiotics and protease inhibitors, and they are key structural units in many biologically active natural products.[19] Methods for their synthesis and studies on their reactivity have been important areas of research since the first review article was published in 1975.[18,20] We have therefore developed a simple and practical new procedure for the synthesis of vicinal tricarbonyl compounds.

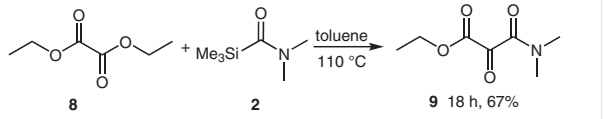
**Table 3** Compounds **7** from Carboxylic Esters **6** and Carbamoylsilane **2**




6 2 7

| Entry | Ester | Product | Time[a] (h) | Yield[b,c] (%) |
|---|---|---|---|---|
| 1 |  **6a** |  **7a** | 18 | 47[d] |
| 2 |  **6b** |  **7a** | 18 | 48[d] |
| 3 |  **6c** |  **7a** | 20 | 46 |
| 4 |  **6d** |  **7d** | 23 | 51 |

[a] Time to complete consumption of carbamoylsilane **2** in toluene at 110 °C.
[b] Isolated yield based on carboxylic ester **6** after chromatography (silica gel).
[c] 1:1.2 molar ratio of ester **6** to carbamoylsilane **2**.
[d] Reaction in toluene at 40 °C.

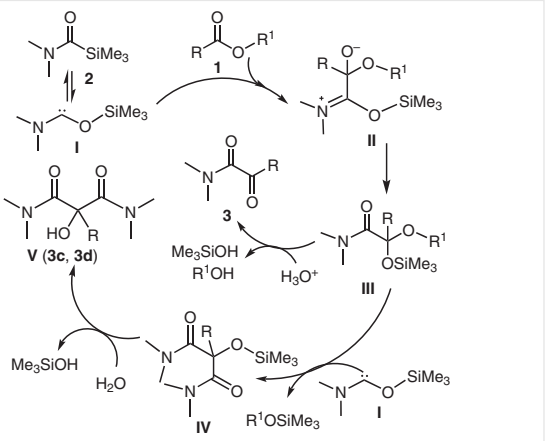



8 2

**Scheme 2** The reaction of carbamoylsilane **2** with diethyl oxalate

On the basis of our observations, a plausible mechanism for our reaction is shown in Scheme 3. Carbamoylsilane **2** rearranges to its nucleophilic carbene form **I**,[21] which attacks the carbonyl group of carboxylic ester **1** to produce unstable intermediate **II**. Subsequent 1,4-migration of the silyl group gives the α-ethoxy α-siloxy *N*,*N*-dimethyl amide **III**. Intermediate **III** is readily hydrolyzed under acidic conditions, with elimination of ethanol, to form the α-keto amide **3**. If the reactivity of the central carbon is increased by a strong electron-withdrawing effect of the R group, intermediate **III** can be attacked by a second equivalent of **I**, and subsequent 1,4-migration of the silyl group gives **IV**. Compound **IV** is hydrolyzed by residual moisture in the solvent or air during the isolation processes to give **V** (**3c**, **3d**).

In summary, we have developed a novel and practical method for the preparation of α-keto amides by direct aminocarbonylation of carboxylic esters with *N*,*N*-dimethylcarbamoyl(trimethyl)silane under neutral conditions.[22] By using this reaction, we also developed a new protocol for the




**Scheme 3** A plausible mechanism for the reaction of carbamoylsilane **2** with esters **1**

synthesis of vicinal tricarbonyl compounds. This method is more practicable than the previously reported methods for the introduction of α-keto amide groups into polyfunctionalized substrates. The protocol tolerates esters containing strongly electron-withdrawing groups, and is suitable for aryl, hetaryl, or open-chain esters, affording good yields of the corresponding α-keto amides under mild conditions. In the transformation of esters containing two carboxylate ester groups, the reaction occurred at only on one of the ester groups, leading to the formation of single α-keto amide. We believe that our method will find applications in medicinal and organic chemistry.

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691737.

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(22) **Aminocarbonylation of Carboxylic Esters with *N*,*N*-Dimethylcarbamoyl(trimethyl)silane (2); General Procedure**

A Schlenk tube equipped with a Teflon vacuum stopcock and micro-stirrer bar was flame-heated under vacuum and refilled with Ar. The appropriate ester (0.5 mmol) and anhyd toluene (1.5 mL) were added at ice-bath temperature. After 20 min, carbamoylsilane **2** (0.6 mmol) was added and the tube was sealed. The mixture was stirred at 110 °C until no carbamoylsilane **2** could be detected by TLC. For the reactions shown in Tables 1 and 2, $CH_2Cl_2$ (5 mL), $H_2O$ (2 mL), and concd HCl (0.5 mL) were added, and the mixture was stirred for 2 h at r.t. The organic layer was then decanted and the aqueous phase was extracted with $CH_2Cl_2$ (2 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to afford the crude product, which was purified by column chromatography (silica gel) to afford α-keto amides **3** or **5**. For the reactions shown in Table 3, entries 1–3, the residue was directly isolated by Kugelrohr distillation to give product **7a**. For the reactions shown in Table 3, entry 4 and Scheme 2, volatiles were removed under vacuum, and the residue was purified by chromatography (silica gel, PE–EtOAc) to yield products **7d** and **9**, respectively.

***N*,*N*-Dimethyl-2-(4-nitrophenyl)-2-oxoacetamide** (**3a**)

Yellowish solid; yield: 76.8 mg (69.1%, 0.5 mmol); mp 137.0–138.0 °C. IR (KBr): 1698, 1650, 1512 $cm^{-1}$. $^1H$ NMR (600 MHz, $CDCl_3$): δ = 8.38–8.16 (m, 4 H), 3.17 (s, 3 H), 3.03 (s, 3 H). $^{13}C$ NMR (150.8 MHz, $CDCl_3$): δ = 189.3, 165.6, 151.1, 137.5, 130.8, 124.1, 37.1, 34.3. Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54;

 

N, 12.61. Found: C, 54.19; H, 4.58; N, 12.55.

**2-Hydroxy-*N*,*N*,*N*′,*N*′-tetramethyl-2-(trifluoromethyl)malonamide (7a)**

Purified by Kugelrohr distillation to give a colorless solid; yield: 56.9 mg (47.0%, 0.5 mmol); mp 118.0–120.0 °C. IR (KBr): 3278, 1658, 1414 $cm^{-1}$. $^1H$ NMR (600 MHz, $CDCl_3$): δ = 5.64 (s, 1 H,), 3.09 (s, 6 H), 3.01 (s, 6 H). $^{13}C$ NMR (150.8 MHz, $CDCl_3$): δ = 164.4, 123.6, 121.7, 37.8, 37.2. $^{19}F$ NMR (564 MHz, $CDCl_3$): δ = –74.4. Anal. Calcd for $C_8H_{13}F_3N_2O_3$: C, 39.67; H, 5.41; N, 11.57. Found: C, 39.79; H, 5.38; N, 11.36.

**3,3,3-Trichloro-2-ethoxy-2-hydroxy-*N*,*N*-dimethylpropanamide (7d)**

Directly purified by flash chromatography (silica gel) to give a slightly brown liquid; yield: 67.7 mg (51.2%, 0.5 mmol). IR (KBr): 3368, 1768, 1535 $cm^{-1}$. $^1H$ NMR (600 MHz, $CDCl_3$): δ = 4.43–4.39 (m, 2 H), 3.21 (s, 3 H), 3.07 (s, 3 H), 1.62 (s, 1 H), 1.42–1.36 (m, 3 H). $^{13}C$ NMR (150.8 MHz, $CDCl_3$): δ = 163.6, 161.8, 79.7, 64.6, 38.5, 37.9, 13.7. Anal. Calcd for $C_7H_{12}Cl_3NO_3$: C, 31.78; H, 4.57; N, 5.29. Found: C, 31.81; H, 4.49; N, 5.56.

**Ethyl 3-(Dimethylamino)-2,3-dioxopropanoate (9)**

Colorless liquid; yield: 58.1 mg (67.1%, 0.5 mmol). IR (KBr): 1768, 1735, 1654, 1455 $cm^{-1}$. $^1H$ NMR (600 MHz, $CDCl_3$): δ = 4.40 (q, *J* = 7.2 Hz, 2 H), 3.07 (s, 3 H), 3.06 (s, 3 H), 1.39 (t, *J* = 7.2 Hz, 3 H). $^{13}C$ NMR (150.8 MHz, $CDCl_3$): δ = 180.8, 164.0, 160.5, 63.3, 36.8, 34.6, 14.0. Anal. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.68; H, 6.60; N, 7.90.