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A practical carbamoylsilane-based synthesis of β-arylidene *N*-methoxymethyl α-siloxy carboxamides from α,β-enones

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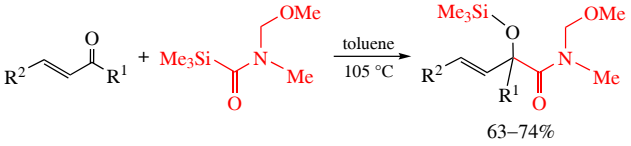
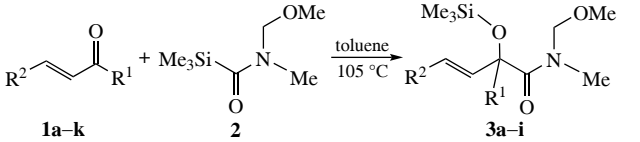
Using *N*-methoxymethyl-*N*-methylcarbamoylsilane as potent secondary amide source, the direct transformation of β-aryl-α,β-enones into the corresponding *N*,*N*-disubstituted β-arylidene α-siloxy carboxamides *via* the aminocarbonylation reaction is described. The reactions provide good yields of the products under simple and catalyst-free conditions.



Keywords: β-arylidene α-siloxy carboxamides, carbamoylsilanes, unsaturated ketones, aminocarbonylation.

α-Hydroxy carboxamides are widely used in the synthesis of bioactive peptide products;[1–3] they also possess biological activities.[4,5] β-Arylidene α-hydroxy amides were used as precursors in the construction of angiotensin-converting enzyme inhibitors such as ramipril and benazepril.[6,7] The commonly used method for their preparation is the aldol condensation between aromatic aldehydes and compounds with MeC(O)C(O) fragment followed by reduction of the keto group.[8,9] Carbamoyllithium reagents have also been used to introduce carbamoyl groups by the nucleophilic addition to α,β-unsaturated aldehydes or ketones,[10] however, this reaction is accompanied by formation of by-products.[11] We have previously reported that the reaction between *N*,*N*-dimethylcarbamoylsilane and aldehydes provided direct route to α-hydroxy amides.[12] Recently, He reported that the catalytic reaction between *N*,*N*-dimethylcarbamoylsilane and ketones gave α-hydroxy amides.[13] Although that synthetic route was simple and effective in generating α-hydroxy amides, however, the reaction scope was limited only to tertiary amides. Meantime, for practical applications secondary α-hydroxy amides are strongly desired.[14,15] Taking this into account, carbamoylsilane bearing *N*-methoxymethyl substituent as the protecting group may be a solution to the problem.

In this study, we have accomplished the reaction of α,β-enones **1** with carbamoylsilane **2** containing *N*-methoxymethyl group to afford β-arylidene α-siloxy amides **3** under non-catalysis conditions (Scheme 1). The reaction of α,β-enones **1** was performed under anhydrous conditions with 1.2 equiv. of *N*-methoxymethyl-*N*-methylcarbamoylsilane **2**[16] in toluene. Trimethylsilyl group in products **3** may be regarded as a hydroxy protecting group and can be eliminated. *N*-Methoxymethyl group in compounds **3** can be easily hydrolyzed in a mixture of concentrated hydrochloric acid and dichloromethane at room temperature[17,18] thus affording the target secondary amides. To our knowledge, there are currently no reports on the direct synthesis of secondary β-arylidene α-hydroxy amides from α,β-unsaturated ketones and carbamoylsilanes.



1a–k **2** **3a–i**

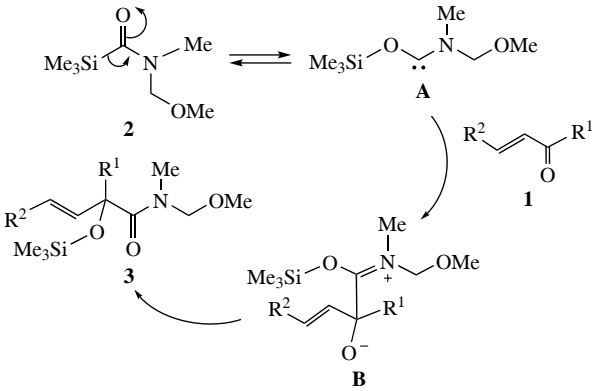
a $R^1 = R^2$ = Ph (67%)
b R^1 = Ph, R^2 = 4-MeC_6H_4 (63%)
c R^1 = Ph, R^2 = 4-$MeOC_6H_4$ (68%)
d R^1 = Ph, R^2 = 4-ClC_6H_4 (71%)
e R^1 = Ph, R^2 = 4-$O_2NC_6H_4$ (73%)
f R^1 = Ph, R^2 = PhCH=CH (74%)
g R^1 = PhCH=CH, R^2 = Ph (73%)
h R^1 = Ph, R^2 = 2-furyl (66%)
i R^1 = Ph, R^2 = 2-thienyl (64%)
j R^1 = Me, R^2 = Ph: no reaction
k $R^1 = Me_2C$=CH, R^2 = Ph: no reaction

Scheme 1

Our investigation was initiated by examining the effects of different reaction parameters on the reaction to optimize the conditions. A series of solvents, THF, benzene, toluene and acetonitrile, were screened using the reaction of *N*-methoxymethyl-*N*-methylcarbamoylsilane **2** with chalcone **1a** as a model. The reaction proceeded with all tested solvents, however, the highest yield of product **3a** was achieved in toluene at 105 °C. Lowering the temperature led to significant decrease in the yield and prolongation of the reaction time. Raising the temperature would reduce the conversion efficiency and cause formation of by-products (*e.g.*, *N*-methoxymethyl-*N*-methylformamide).

Under optimized conditions, we examined some other α,β-enones to explore the reaction scope and limitations (see Scheme 1).† A comparison of the results obtained with enones **3a**–**e** indicates that the electronic property of substituents is an important factor: electron-withdrawing groups accelerate the reaction while with electron-donating groups the reactions were slower. Anyway, the product yields in all these cases were at

† *General procedure for the aminocarbonylation of α,β-unsaturated ketones* **1** *with carbamoylsilane* **2**. A Schlenk tube fitted with a Teflon vacuum stopcock and micro stirring bar was flame heated under vacuum and refilled with argon. *α,β*-Unsaturated ketone **1a**–**i** (0.5 mmol) and anhydrous toluene (1.5 ml) were added at ice bath temperature. After 15 min, *N*-methoxymethyl-*N*-methylcarbamoylsilane **2** (0.6 mmol) was added. The sealed reaction mixture was stirred at 105 °C until no carbamoylsilane **2** could be detected by TLC. The volatiles were removed *in vacuo* to give crude products, which were purified by column chromatography on silica gel using light petroleum–ethyl acetate as eluent to yield products **3a**–**i**.



Scheme 2

the level of 70%. Chalcone 'vinylogs' **2f**,**g** as well as hetaryl analogs **2h**,**i** were similarly transformed into the corresponding products **3f**–**i** in good yields. However, enones with aliphatic substituents **2j**,**k** did not react with carbamoylsilane **2** even upon lengthening the reaction time to 150 h. Similar phenomenon was previously observed for alkyl ketones when nothing of the products was obtained.[19]

On the basis of the structure of products **3** and the literature reports,[20,21] a plausible mechanism of the reaction may be proposed (Scheme 2). Carbamoylsilane **2** would rearrange into its nucleophilic carbene form **A**,[22,23] which possesses a nucleophilic lone electron pair and can attack the positively charged C=O group in ketones **1** to produce unstable zwitterion intermediate **B**. The silyl group in **B** is prone to 1,4 migration from one oxygen atom to another negatively charged oxygen atom thus generating final products **3**.

To conclude, a practical synthesis toward β-arylidene α-siloxy carboxamides has been successfully developed based on *N*-methoxymethyl-*N*-methylcarbamoylsilane. The *N*-methoxymethyl group in the products may be regarded as a protecting group at amido function while Me_3Si group may be considered as the protection of the hydroxy group. The removal of these protections opens a way to secondary β-arylidiene α-hydroxycarboxamides, valuable substrates for the synthesis of biologically active compounds.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7707.

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