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Efficient synthesis of β-nitro amides by aminocarbonylation of ethoxycarbonyl-containing nitroalkenes with carbamoylsilane

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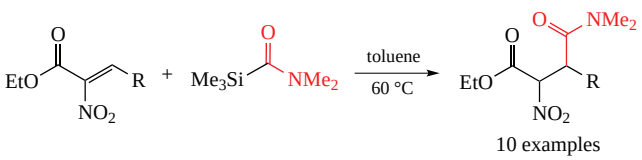
Direct aminocarbonylation of β-nitroalkenes bearing β-positioned ethoxycarbonyl group using carbamoylsilane as an amide source afforded β-nitro amide derivatives under mild conditions without use of catalysts.



Keywords: carbamoylsilanes, aminocarbonylation, nitro compounds, amides, β-nitroalkenes, organosilicon compounds.

Amides have a widespread application in polymer, pharmaceutical, cosmetic, dye and natural product syntheses.[1–5] Amides bearing α-hydroxy and α-amino groups are of significant interest for pharmacy due to their strong biological activity.[6–9] A large number of their syntheses have been developed.[10–14] Previously, we accomplished a practical preparation of various carbamoylsilanes[15] which could add at C=O bond of aldehydes and α-keto esters to form α-hydroxy amides.[16–19] They also added at the C=N bond of sulfonyl imines and Boc-imines to afford α-amino amides,[20–22] and added to electron-deficient aromatics to form amides.[23] Cunico *et al.* found that carbamoylsilanes could add to the C=C bond of alkenes bearing electron-withdrawing groups.[24] However, alkenes with conjugated aryl group were difficult to react, although such alkenes containing two cyano or two ethoxycarbonyl groups gave products in low yields. Recently, Asahara *et al*. reported that β-nitrostyrenes bearing ethoxycarbonyl group could react with KCN easily to yield addition products.[25]

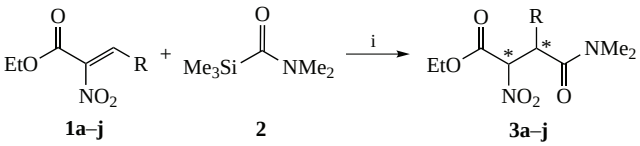
In this study, we tried β-nitroalkenes **1a–j** bearing ethoxycarbonyl group to react with carbamoylsilane **2**, and were pleased to find that this direct aminocarbonylation could proceed smoothly to give β-nitro amides **3a–j** in high yields under catalyst-free conditions (Scheme 1).† To the best of our knowledge, this reaction has not been studied so far. The thus obtained β-nitro amides look promising as they can be easily transformed into β-amino amides. β-Amino amides, in turn, are the components of bioactive natural products, *viz.* biological metabolism products, and have been broadly utilized for approach to peptide based pharmaceutical compounds.[26–29]

The starting ethoxycarbonyl-containing nitroalkenes **1a–j** were readily prepared by the condensation of aldehydes with ethyl nitroacetate.[30,31] Optimization (effects of solvent and temperature) was carried out with model ethyl 2-nitrophenylacrylate **1d** and *N*,*N*-dimethylcarbamoyl(trimethyl)silane **2** (1.2 equiv.). In all solvents such as dichloromethane, toluene, acetonitrile, benzene and THF, the reaction proceeded smoothly within several hours, however in toluene the reaction required shorter time and provided higher yields of product **3d**. The optimal temperature was found to be 60 °C as upon more heating the by-products would form.

Substrate screening (see Scheme 1) showed that products **3a–j** were obtained from good to excellent yields, although for reactants **1a–c** with electron-donating substituents in aryl groups the yields were somewhat lower (64–76%). Hetaryl and styryl analogues **1g–j** also underwent the transformation very efficiently. In all cases, two diastereomers (apparently, each of them being racemic mixture of two enantiomers) were formed, which conformed to the presence of two sets of characteristic peaks in the ^{13}C NMR spectra.

A possible reaction route is presented in Scheme 2. Carbamoylsilane **2** can rearrange into its nucleophilic carbene form **A**,[32] which would attack nitroalkenes **1** to produce unstable intermediate **B**. The following silyl 1,6-migration shloud give silyloxy ketene acetal **C** which can be hydrolyzed by residual moisture to form 3-nitro-4-hydroxy-3-butenamide derivatives **D**, which are enol tautomers of final products **3**.

To conclude, we have developed a straightforward and practical method for the synthesis of β-nitro amide derivatives



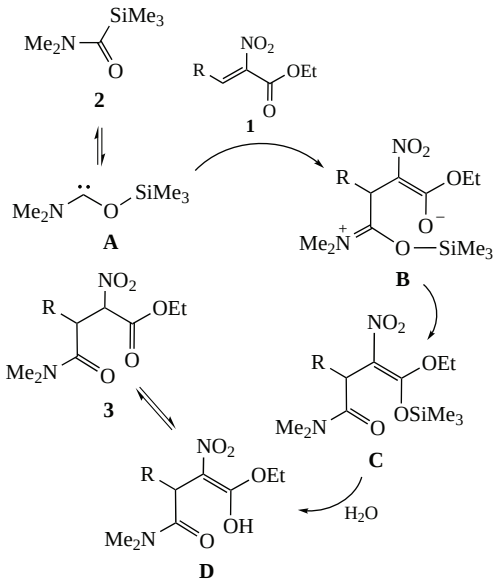
1a–j **2** **3a–j**

a R = 4-$Me_2NC_6H_4$, 64%
b R = 4-$MeOC_6H_4$, 76%
c R = 4-MeC_6H_4, 75%
d R = Ph, 85%
e R = 4-ClC_6H_4, 95%
f R = 3-$O_2NC_6H_4$, 96%
g R = 2-furyl, 80%
h R = 2-thienyl, 79%
i R = 2-pyridyl, 82%
j R = PhCH=CH, 85%

Scheme 1 *Reagents and conditions*: i, toluene, 60 °C, 6–27 h.

† *General procedure for the reaction of carbamoylsilane with nitroalkenes.* A Schlenk tube fitted with a Teflon vacuum stopcock and a micro stirring bar was flame-heated under vacuum and refilled with argon. Nitroalkenes **1** (0.5 mmol) and anhydrous toluene (2.0 ml) were added at ice bath temperature. After 20 min, carbamoylsilane **2** (0.6 mmol) was added. The tube was sealed, and the mixture was stirred at 60 °C until no carbamoylsilane could be detected by TLC. The volatiles were removed in vacuum to leave the crude product which was purified by column chromatography on silica gel (light petroleum/ethyl acetate combination) to afford β-nitro amide derivatives **3**.

For details and characterization of products **3a–j**, see Online Supplementary Materials.



Scheme 2

by direct aminocarbonylation of β-nitroalkenes bearing β-positioned ethoxycarbonyl group using carbamoylsilane as an amide source. The protocol tolerated a broad range of nitro alkenes bearing different groups on the C=C bond such as aryl, heteroaryl and styryl, and provided good to excellent yields of the corresponding β-nitro amide derivatives under catalyst-free conditions. We believe that the present protocol will be a useful contribution to the development of synthetic methodologies and will find applications in medicinal and organic chemistry.

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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.2021.01.041.

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