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One-pot synthesis of *N*-substituted (3-oxobutanyl)carbamates from primary amines using modified zeolite Hβ at room temperature

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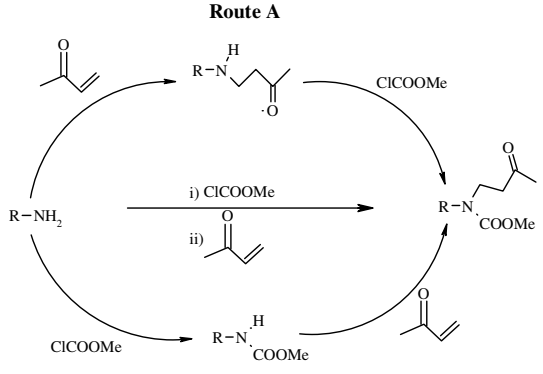
Abstract—The one-pot synthesis of *N*-substituted (3-oxobutanyl)carbamates via the tandem condensation of primary amines with methyl chloroformate, followed by the conjugate addition of the resulting carbamate with methyl vinyl ketone in the presence of Sn^{4+} modified zeolite Hβ (Hβ-SnA) at room temperature is described.

Multifunctional compounds are important synthons and the one-pot synthesis of such compounds is an ever challenging area in synthetic organic chemistry. The β-amino carbonyl unit is present in natural products such as alkaloids and polyketides.[1] Compounds with this unit also serve as intermediates for the synthesis of amino alcohols, β-amino acid derivatives and in the preparation of antibiotics.[2] Mannich type reactions are classically the best methods for the preparation of β-amino carbonyl compounds. However, due to harsh conditions and long reaction times, such methods, have serious disadvantages.[3] In contrast, the aza-Michael addition to α,β-unsaturated ketones of nitrogen containing nucleophiles is an atom economic and simple process for the preparation of β-amino carbonyl compounds. Recent studies in this area report various catalysts for the aza-Michael addition such as lanthanide triflates, $FeCl_3$, $InCl_3$, $CeCl_3$/NaI, platinum group metal complexes and other Lewis acids.[4] Due to the low basicity of nitrogen in a carbamate, the aza-Michael reaction of enones with carbamates is difficult. Only very recently have a few catalysts such as $FeCl_3{\cdot}6H_2O/Me_3SiCl$,[5a] arylphosphines/$Me_3SiCl$,[5b] Nafion®, SAC-13 perfluorinated resin sulfonic acid[6a] and some transition metal salts[6b] in their higher valency state been reported for this reaction.

Carbamates show biological activity as pesticides, insecticides and antibiotics.[7] They can also act as good protecting groups in peptide synthesis.[8] The preparation of a carbamate using a chloroformate is typically performed in the presence of base catalysts[8a] such as NaOH, Na_2CO_3, triethylamine and also Lewis acids.[9]

N-Aryl/alkyl (3-oxoalkyl)carbamates can be prepared from primary amines by two routes as shown in Scheme 1. As both the steps involved in these routes can be catalysed by suitable acidic reagents, we thought it worthwhile to attempt a one-pot synthesis of *N*-alkyl/aryl (3-oxobutanyl)carbamate using a solid acid



Scheme 1. Routes for the formation of *N*-substituted (3-oxoalkyl)-carbamates.

Keywords: aza-Michael addition; Hβ-zeolite; Ion-exchange; Carbamates.
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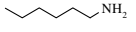
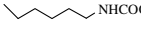
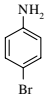
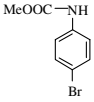
catalyst. Lewis acid catalysts are soft acids. In recent years, the importance of metals like Fe and Sn has been recognised possibly due to the low oxidation potentials of the respective cations. Zeolites have also emerged as good solid supports as well as promising heterogeneous catalysts.[10] We have been working in the area of supported solid acid catalysis since the last decade.[11] The efficacy of $SnCl_4$ has been reported for the Mukaiyama–Michael type reaction.[12] Therefore, we thought of exploring the synergistic effect of zeolite Hβ modified by $SnCl_4$ for the aza-Michael reaction.

In Scheme 1 two routes for the preparation of *N*-alkyl/aryl (3-oxobutanyl)carbamate are shown. Route A, which seems to be the simpler, involves the aza-Michael addition of amines with methyl vinyl ketone followed by reaction with methyl chloroformate. However, one disadvantage of the Michael addition of primary amines to methyl vinyl ketone is that it produces a mixture of two products, as a result of subsequent addition of methyl vinyl ketone to the initial adduct, leading to a low yield of the desired product. Hence, we preferred Route B, which involves carbamate formation followed by Michael addition to methyl vinyl ketone. This route gave good yields in spite of the fact that the aza-Michael addition of carbamates to methyl vinyl ketone was anticipated to be difficult.

The catalyst, Hβ-SnA, was prepared by modification of zeolite H with $SnCl_4$ in aqueous medium.[13] The preparation of the carbamate by addition of methyl chloroformate to the corresponding amines was carried out as in step (i) of Route B at room temperature. This gave yields of more than 90% of the carbamates for each amines (Table 1).

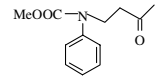
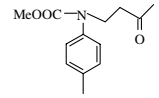
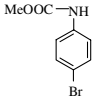
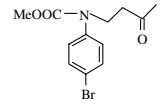
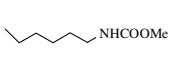
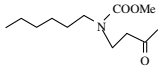
Step (ii) of Route B, the aza-Michael reaction of methyl vinyl ketone with various carbamates, was performed at room temperature, using acetonitrile as solvent (Table 2). All the substrates tested gave good yields ranging from 65% to 75%.

Table 1. Preparation of carbamate from amines

	Amine	Product	Time (min)	Yield[a] (%)
1			60	95
2			10	96
3			90	94
4			45	95

Reaction conditions: amine = 5 mmol, methyl chloroformate = 5 mmol, catalyst (Hβ-SnA) = 0.2 g, temperature = 30 °C, acetonitrile (solvent) = 10 mL.
[a] Isolated yields, after purification by column chromatography.

Table 2. Michael addition of carbamates to methyl vinyl ketone

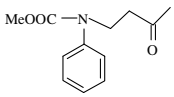
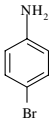
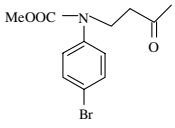
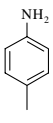
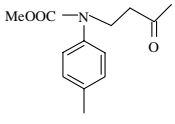
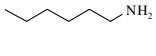
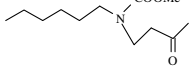
	Carbamate	Product	Time (h)	Yield[a] (%)
1			24	75
2			24	74
3			24	70
4			24	65

Reaction conditions: carbamate = 5 mmol, acetonitrile (solvent) = 10 mL methyl vinyl ketone = 5 mmol, catalyst (Hβ-SnA) = 0.2 g, temperature = 30 °C.
[a] Isolated yields, after purification by column chromatography.

Encouraged by these results, we considered whether it would be possible to carry out a one-pot synthesis of *N*-substituted (3-oxoalkyl)carbamates, by successive reactions of methyl chloroformate with the respective amines, followed by aza-Michael reaction of the resulting carbamates with methyl vinyl ketone (Table 3).[14] The substituents have no significant effects on the yields of the reaction as shown in Table 3. However, the aliphatic substrate gives lower yields.

The Sn content in the catalyst Hβ-SnA was found to be 6.77% (ICP analysis). In order to prepare *N*-aryl (3-oxoalkyl)carbamates we chose aromatic amines with electron donating and electron withdrawing groups. The reaction was also performed under similar conditions but using unmodified Hβ-zeolite, 10% product.

Table 3. One-pot reactions of amines with methyl chloroformate and methyl vinyl ketone

	Amine	Product	Time (h)	Yield[a] (%)
1			24	72
2			24	68
3			24	71
4			24	64

Reaction conditions: amine = 5 mmol, methyl chloroformate = 5 mmol, methyl vinyl ketone = 6 mmol, acetonitrile (solvent) = 10 mL, catalyst (Hβ-SnA) = 0.2 g, temperature = 30 °C.
[a] Isolated yield, after purification by column chromatography.

These examples clearly indicate that *N*-aryl or *N*-alkyl (3-oxoalkyl)carbamates can be easily synthesised using Sn modified zeolite Hβ. The quenching experiment (terminating the reaction half way through, separation of the catalyst, allowing the reaction to continue in the filtrate) showed that leaching was not significant, as the reaction did not proceed once the catalyst had been separated from the reaction mixture.

In summary, we have developed an environmentally friendly and reusable catalyst for the one-pot aza-Michael reaction to produce *N*-aryl as well as *N*-alkyl (3-oxoalkyl)carbamate from the corresponding amines.[15] The procedure is clean operationally and simple. To our knowledge this is the first reported Lewis acid supported zeolite (Hβ-SnA) for aza-Michael reactions.

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13. *Typical procedure for catalyst preparation*: to anhydrous $SnCl_4$ (15 g) dissolved in deionised water (60 mL), Hβ-zeolite (10 g) was added over a period of 10 min. The resultant slurry was stirred at room temperature (30 °C) for 5 h. The resultant catalyst was filtered and washed with deionised water until free from Cl^- ions (tested by silver nitrate). The catalysts were dried at 80 °C to obtain Hβ-SnA.
14. *General procedure for one-pot synthesis*: to a mixture of Hβ-SnA (0.2 g, 0.27 mmol of Sn) and methyl chloroformate (5 mmol) in 5 mL of acetonitrile, amine (5 mmol) dissolved in 5 mL of acetonitrile added dropwise. The reaction mixture was stirred at room temperature until the completion of the reaction as indicated by TLC. To the resulting mixture, methyl vinyl ketone (6 mmol) was added and the reaction was stirred until the completion as indicated by TLC. The reaction mixture was filtered and evaporated. The crude product was purified by column chromatography.
15. All compounds were characterised by ^1H NMR, IR and CHN analysis.
Spectral data for *methyl N-(4-bromophenyl)-N-(3-oxobutan-1-yl)carbamate*: IR (neat): cm^{-1} 3036, 2974, 1707, 1466, 1378, 1018, ^1H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, $J = 8.7$ Hz, 2H), 7.05 (d, $J = 8.7$ Hz, 2H), 3.9 (t, $J = 7.2$ Hz, 2H), 3.68 (s, 3H), 2.75 (t, $J = 7.5$ Hz, 2H), 2.18 (s, 3H), Anal. Calcd for $C_{12}H_{14}BrNO_3$: C, 48.02; H, 4.68; Br, 26.51; N, 4.64. Found: C, 48.19; H, 4.65; Br, 26.49; N, 4.63%.