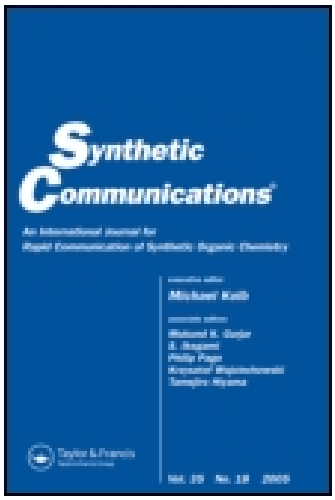

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Rajesh K. Pandey [a] , Sharda P. Dagade [b] , Mohan K. Dongare [b] & Pradeep Kumar [a]

[a] Division of Organic Chemistry: Technology , National Chemical Laboratory , Pune, India

[b] Catalysis Division , National Chemical Laboratory , Pune, India

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Synthesis of Carbamates Using Yttria-Zirconia Based Lewis Acid Catalyst

Rajesh K. Pandey,[1] Sharda P. Dagade,[2] Mohan K. Dongare,[2] and Pradeep Kumar[1,*]

[1]Division of Organic Chemistry: Technology and
[2]Catalysis Division, National Chemical Laboratory,
Pune, India

ABSTRACT

A variety of amines react with chloroformates in the presence of catalytic amount of yttria-zirconia based catalyst to afford the corresponding carbamates in excellent yields.

Key Words: Yttria-zirconia based Lewis acid; Heterogeneous catalysis; Carbamate; Chemoselectivity.

*Correspondence: Pradeep Kumar, Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune–411008, India; Fax: 0091-20-5893614; E-mail: tripathi@dalton.ncl.res.in.

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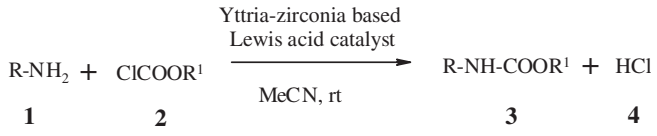
Carbamates are endowed with an array of biological activities.[1] They are known to have pesticide,[2a] insecticide,[2b] antibiotic,[2c] and other pharmacological properties.They also serve as useful protecting groups in organic synthesis, particularly in peptide synthesis.[3] Due to their high demand, there has been a considerable resurgence of interest in the synthesis and biological evaluation of carbamates.[4] The carbamate synthesis is generally performed by the reaction of an amine with chloroformate in the presence of bases such as sodium hydroxide, sodium bicarbonate, triethyl amine, or pyridine.[3a] A number of other methods employed to prepare carbamates are the reaction of diethyl carbonate with amine,[5] from amides,[6] reductive carbonylation of aromatic nitro compounds with $Ru_3(CO)_{12}$ or $Ru(CO)_3(PPh_3)_2$ and methanol,[7] enzymatic oxidative conversion of thio to oxo by Baker's yeast,[8] reaction of alcohol with trichloroacetyl isocyanate.[9] More recently, the reaction of amine with chloroformate using stoichiometric amount of activated zinc[10] and a three-component coupling reaction of amine, CO_2, and alkyl halide in the presence of cesium carbonate and tetrabutylammonium iodide[11] have been reported for carbamate synthesis. Although there has been several examples with regards to carbamate formation, the use of Lewis acid catalyst to effect the above transformation is rather scarce. One of the method reported by Porta and Cenini[12] used aliphatic amine with diethyl carbonate and catalyzed the transformation with different Lewis acids. However, this method could not be extended to the synthesis of *N*-arylcarbamate.

As part of our research program aimed at developing new catalyst and its subsequent application for various organic transformations, the yttria-zirconia based Lewis acid was found to be an extremely efficient catalyst for the Diels-Alder reaction,[13] transesterification of ß-keto esters[14] and acylation reaction.[15] This prompted us to use this catalyst for carbamate synthesis and herein we report that a yttria-zirconia based Lewis acid serves as an excellent catalyst for alkoxycarbonylation of amines (Sch. 1).



R = alkyl, aryl, amino acid; R^1 = methyl, ethyl, benzyl

Scheme 1.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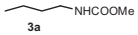
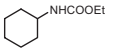
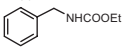
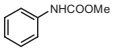
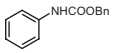
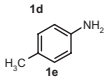
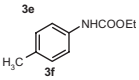
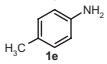
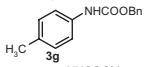
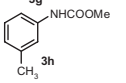
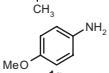
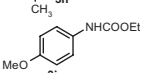
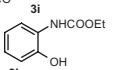
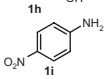
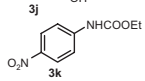
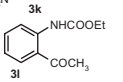
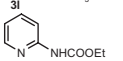
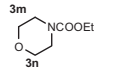
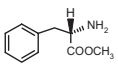
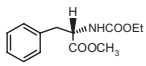
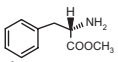
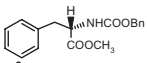
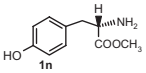
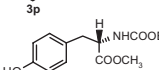
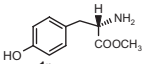
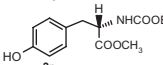
RESULTS AND DISCUSSION

Thus, when a variety of amines were treated with chloroformates in the presence of catalytic amount of the new yttria-zirconia based catalyst, the corresponding carbamates were obtained in excellent yields. The substrates examined in our studies and the results obtained are summarized in Table 1. Thus, the present procedure for carbamate synthesis is quite general as a wide range of structurally varied amines such as open chain, cyclic, aromatic, heteroaromatic, amino acid underwent reaction smoothly with chloroformates. The reaction is remarkably fast and leads to high yields of the products. As summarized in Table 1, aromatic amines underwent facile carbamation with a variety of chloroformates in excellent yields. Subsequently, with the introduction of an electron withdrawing substituent on the aromatic ring (i.e., carbonyl or nitro group), the amine was rendered less nucleophilic; hence the reactions were sluggish; however, an excellent yields of product were obtained (Table 1, Entries 11–12). Similarly the reaction of various amines with benzyl chloroformate was found to be relatively slow and hence a little longer time was required to complete the reaction; affording excellent yields of the products (Table 1, Entries 5, 7, 16, 18). It is noteworthy that the reaction is chemoselective in case of 2-aminophenol as the amine, being more nucleophilic than alcohol, underwent reaction faster giving the corresponding *N*-carbamate product in excellent yield (Table 1, Entry 10). Another notable feature of the reaction is that even a secondary amine reacted smoothly to afford the carbamate in high yield (Table 1, Entry 14). Mention must be made here that amino group in amino acid could be protected easily demonstrating the practical utility of this protocol particularly in peptide synthesis. Thus L-phenylalanine ester was smoothly converted to the corresponding carbamate in excellent yield (Table 1, Entry 15). Similarly in case of L-tyrosine ester, the amino group is protected selectively in the presence of hydroxyl group (Table 1, Entries 17, 18). Under the reaction conditions employed, the ester groups remain unaffected and there is no racemization of the chiral substrate encompassing amino acid. So this protocol could be useful and further be extended to the peptidomimetic synthesis.

A time dependent study of carbamation of aniline with methyl chloroformate in the absence and in the presence of varying concentration of yttria-zirconia catalyst indicated that even small amount of catalyst (10 wt%) can catalyse and accelarate the reaction, however, high yields of carbamates and high efficiency of the reaction are found only using catalyst (20 wt%). In the absence of the catalyst, the limited carbamation occurred very slowly even when the reaction was continued for 20 h. The reaction was performed even on large scale in the presence

Table 1. Preparation of carbamates by yttria-zirconia based Lewis acid catalyst.

Entry	Amines	Reaction times (min)	Products	Yields[a]
1	 1a	5	 3a	94
2	 1b	5	 3b	88
3	 1c	8	 3c	90
4	 1d	7	 3d	96
5	 1d	15	 3e	95
6	 1e	7	 3f	90
7	 1e	15	 3g	95
8	 1f	8	 3h	90
9	 1g	5	 3i	94
10	 1h	5	 3j	94
11	 1i	360	 3k	90
12	 1j	355	 3l	90
13	 1k	15	 3m	94
14	 1l	10	 3n	91
15	 1m	12	 3o	93
16	 1m	18	 3p	92
17	 1n	15	 3q	92
18	 1n	20	 3r	91

[a]All the product exhibited physical and spectral (NMR and IR) properties in accord with the assigned structure.

of catalyst and the results could be reproduced. The anhydrous HCl generated during reaction evolves in the form of gas which has been experimentally detected by trapping it into the ammonia solution. Thus, the HCl gas evolved was driven away in order to avoid the formation of any amine hydrochloride.

The heterogenous catalytic method described here is profitable as it provides high yields of the product and does not involve the use of stoichiometric amount of reagent such as base for carbamate synthesis. Thus, the present protocol could be useful particularly for those substrates containing base sensitive functionalities. In addition, the reaction conditions are particularly mild and the work-up procedure is exceedingly simple and reduced to a mere filtration. Another significant advantage of the present method lies in the simplicity involved in the preparation of the catalyst. The recovered catalyst can be reactivated for reuse by heating it at 500°C in the presence of air. The same catalyst was recycled for all the reactions without loss of activity and selectivity.

In summary, a facile heterogeneous catalytic method for the preparation of a variety of carbamates employing a novel yttria-zirconia based Lewis acid catalyst has been developed. To the best of our knowledge this is the first report of use of Lewis acid catalyst for carbamate synthesis from amine using chloroformate. Furthermore, the present protocol offers mild reaction conditions, selectivity, and short reaction times. The noteworthy feature of this methodology is that chiral substrate is resistant to racemization and labile functionalities such as an ester is compatible with the reaction condition. In addition, the heterogeneous catalytic method is advantageous in respect of easy separation, higher and consistent yield, and recyclability of the catalyst. Thus the present catalytic method should offer a general synthetic method for various carbamates offering a wide variety of application.

EXPERIMENTAL

Solvents were purified and dried by standard procedures before use according to reported procedure; petroleum ether of boiling range 60–80°C was used. The amines and chloroformates were obtained from commercial sources and were purified by distillation/recrystallization before the experiment. Infrared spectra were recorded with ATI MATT-SON RS-1 FT-IR spectrometer. Proton NMR spectra were recorded on Bruker AC-200 machine in $CDCl_3$ with TMS as internal standard. The diffractogram of X-ray powder diffraction pattern was recorded on a Rigaku diffractometer model D/Max. IIIVC with

Ni-filtered Cu-Kα radiation. FTIR spectrum of pyridine adsorbed on the yttrium-based catalyst was recorded on a Nicolet 60 SXB FTIR spectrometer. TPD profile (ammonia) of the yttrium-based catalyst was recorded on a Sorbstar apparatus. Determination of specific surface area was carried out by BET (Brunner-Emmett-Teller) N_2 adsorption using a Omnisorp 100 CX apparatus.

Procedure for the Preparation of Catalyst

The catalyst was prepared by mixing aq. solutions of yttrium nitrate and zirconyl nitrate in the mole ratio 16:84, to which aqueous ammonia (28%) was added under vigorous stirring until a pH of 8.5 was achieved and a precipitate was formed. Washing with deionized water, drying at 110°C for 24 h, treating with sulfuric acid (4 M), drying at 120°C, and subsequent programmed calcination at 500°C for 3 h at a heating rate of $2^{\circ}C\,min^{-1}$ resulted in a highly acidic material. The chemical composition of the final catalyst (determined by XRF technique) was found to be 82.6 mol% Zr, 15.6 mol% Y, and 1.8 mol% S. The physicochemical characterization of the catalyst was carried out by titrations, temperature programmed desorption (TPD), scanning electron microscopy (SEM), and N_2 adsorption techniques.

Typical Experimental Procedure

In a typical experimental procedure, chloroformate (20 mmol) in dry acetonitrile (15 mL) was added dropwise to a solution of amine (20 mmol) in dry acetonitrile (25 mL) containing catalyst (20% by weight) with constant stirring and the mixture was stirred at room temperature for the indicated length of time (Table 1). The reaction was monitored by TLC. After completion of reaction, the catalyst was filtered and the solid was washed thoroughly with ether (100 mL). The combined filtrate was washed with 10% sodium bicarbonate solution, then water, brine, and dried over anhydrous sodium sulfate. Evaporation of solvent gave the crude product which was purified by silica gel chromatography using petroleum ether:ethyl acetate (97:03) as eluent to give the pure product.

Butylcarbamic acid methyl ester (3a). Yellow oil. IR ν_{max}/cm^{-1} (Neat): 3323, 2964, 1710, 1520, 1216. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.90 (t, $J = 6.5$, 3H), 1.25–1.50 (m, 4H), 1.75 (bs, 1H), 3.20 (t, $J = 6.5$, 2H), 3.15 (s, 3H).

Cyclohexylcarbamic acid ethyl ester (3b). White solid. M.p.: 60°C. IR ν_{max}/cm^{-1} (Neat): 3323, 2962, 1730, 1546, 1235. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.11 (t, $J = 7.5$, 3H), 1.15–2.25 (m, 10H), 3.15 (m, 1H), 3.45 (bs, 1H), 4.10 (q, $J = 5.6$, 2H).

Benzylcarbamic acid ethyl ester (3c). White solid. M.p.: 55°C. IR ν_{max}/cm^{-1} (Nujol): 3450, 3018, 1711, 1516, 1216. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.10 (t, $J = 7.5$, 3H), 3.90 (q, $J = 5.6$, 2H), 4.15 (d, $J = 5.3$, 2H), 7.05–7.50 (m, 5H), 8.50 (bs, 1H).

Phenylcarbamic acid methyl ester (3d). White solid. M.p.: 50°C. IR ν_{max}/cm^{-1} (Nujol): 3291, 2950, 1730, 1543, 1216. ^1H NMR (200 MHz, $CDCl_3$) δ: 3.50 (s, 3H), 6.70 (bs, 1H), 7.10–7.40 (m, 5H).

Phenylcarbamic acid benzyl ester (3e). White solid. M.p.: 80°C. IR ν_{max}/cm^{-1} (Nujol): 3431, 3019, 1731, 1525, 1214. ^1H NMR (200 MHz, $CDCl_3$) δ: 5.07 (s, 2H), 6.85–7.38 (m, 10H), 8.31 (bs, 1H).

***p*-Tolylcarbamic acid ethyl ester (3f).** White solid. M.p.: 63°C. IR ν_{max}/cm^{-1} (Nujol): 3318, 2981, 3019, 1706, 1529, 1229. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.25 (t, $J = 7.2$, 3H), 2.60 (s, 3H), 4.20 (q, $J = 5.6$, 2H), 6.60 (bs, 1H), 7.10 (d, $J = 5.45$, 2H), 7.25 (d, $J = 5.45$, 2H).

***p*-Tolylcarbamic acid benzyl ester (3g).** White solid. M.p.: 140°C. IR ν_{max}/cm^{-1} ($CHCl_3$): 3431, 3018, 1724, 1526, 1217. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 5.21 (s, 2H), 6.68 (bs, 1H), 7.1–7.5 (m, 9H).

***m*-Tolylcarbamic acid methyl ester (3h).** White solid. M.p.: 50°C. IR ν_{max}/cm^{-1} ($CHCl_3$): 3430, 2922, 1713, 1457, 1226. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.30 (s, 3H), 3.15 (s, 3H), 6.68 (bs, 1H), 7.10–7.80 (m, 4H).

(4-Methoxyphenyl)carbamic acid ethyl ester (3i). White solid. M.p.: 85–86°C. IR ν_{max}/cm^{-1} ($CHCl_3$): 3313, 2921, 1697, 1458, 1241. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.20 (t, $J = 7.25$, 3H), 3.60 (s, 3H), 4.10 (q, $J = 5.9$, 2H), 6.70 (bs, 1H), 6.91 (d, $J = 6$, 2H), 7.20 (d, $J = 6$, 2H).

(2-Hydroxyphenyl)carbamic acid ethyl ester (3j). White solid. M.p.: 80°C. IR ν_{max}/cm^{-1} ($CHCl_3$): 3224, 2921, 1700, 1456, 1231. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.35 (t, $J = 7.16$, 3H), 4.28 (q, $J = 5.9$, 2H), 6.80 (bs, 2H), 6.90–7.25 (m, 4H).

(4-Nitrophenyl)carbamic acid ethyl ester (3k). Yellow solid. IR ν_{max}/cm^{-1} ($CHCl_3$): 3221, 2921, 1730, 1458, 1230. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.34 (t, $J = 7.2$, 3H), 4.28 (q, $J = 5.9$, 2H), 7.06 (s, 1H), 7.80 (d, $J = 8.9$, 2H), 8.20 (d, $J = 8.9$, 2H).

(2-Acetoxyphenyl)carbamic acid ethyl ester (3l). Yellow oil. IR ν_{max}/cm^{-1} ($CHCl_3$): 3446, 3018, 1726, 1705, 1582, 1220. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.34 (t, $J = 7.25$, 3H), 2.64 (s, 3H), 4.28 (q, $J = 5.9$, 2H), 6.80 (bs, 1H), 7.10–7.88 (m, 4H).

Pyridin-2-yl-carbamic acid ethyl ester (3m). White solid. M.p.: 100°C. IR ν_{max}/cm^{-1} ($CHCl_3$): 3446, 3220, 3019, 1726, 1705, 1585, 1217.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.35 (t, $J = 7.25$, 3H), 4.25 (q, $J = 5.9$, 2H), 6.60 (bs, 1H), 7.0 (t, $J = 6.6$, 1H), 7.75 (t, $J = 6.6$, 1H), 8.05 (d, $J = 6.8$, 1H), 8.5 (d, $J = 5.3$, 1H).

Morpholine-4-carboxylic acid ethyl ester (3n). Colorless oil. IR ν_{max}/cm^{-1} ($CHCl_3$): 2927, 1695, 1454, 1103. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.2 (t, $J = 7.25$, 3H), 3.25 (m, 4H) 3.5 (m, 4H), 4.25 (q, $J = 5.9$, 2H).

2-Ethoxycabonylamino-3-phenylpropionic acid methyl ester (3o). White solid. M.p. 110°C. IR ν_{max}/cm^{-1} ($CHCl_3$): 3381, 2954, 1742, 1708, 1526, 1225. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.25 (t, $J = 7.25$, 3H), 3.10 (m, 2H), 3.75 (s, 3H), 4.20 (q, $J = 5.9$, 2H), 4.74 (s, 1H), 5.20 (m, 1H), 7.05–7.50 (m, 5H).

2-Benzyloxycabonylamino-3-phenylpropionic acid methyl ester (3p). White solid. M.p.: 190°C. IR ν_{max}/cm^{-1} ($CHCl_3$): 3381, 2954, 1742, 1708, 1526, 1225. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.10 (m, 2H) 3.75 (s, 3H), 4.74 (s, 1H), 5.20 (s, 2H), 5.25 (m, 1H), 7.05–7.50 (m, 10H).

2-Ethoxycarbonylamino-3-(4-hydroxyphenyl)propionic acid methyl ester (3q). White solid. IR ν_{max}/cm^{-1} ($CHCl_3$): 3381, 2954, 1745, 1708, 1528, 1220. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.25 (t, $J = 7.25$, 3H), 3.10 (m, 2H) 3.75 (s, 3H), 4.20 (q, $J = 5.9$, 2H), 4.74 (s, 1H), 5.20 (m, 1H), 6.90 (s, 1H), 7.01–7.50 (m, 4H).

2-Benzyloxycabonylamino-3-(4-hydroxyphenyl)propionic acid methyl ester (3r). White solid. M.p.: 200°C. IR ν_{max}/cm^{-1} ($CHCl_3$): 3380, 2950, 1740, 1702, 1522, 1220. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.10 (m, 2H) 3.75 (s, 3H), 4.74 (m, 1H), 5.22 (s, 2H), 5.25–5.56 (m, 1H), 7.10–7.53 (m, 10H).

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