

Carbamate synthesis by solid-base catalyzed reaction of disubstituted ureas and carbonates

Sunil P. Gupte, Anand B. Shivarkar and Raghunath V. Chaudhari*

Homogeneous Catalysis Division, National Chemical Laboratory, Pune-411008, India.
E-mail: rvc@ems.ncl.res.in

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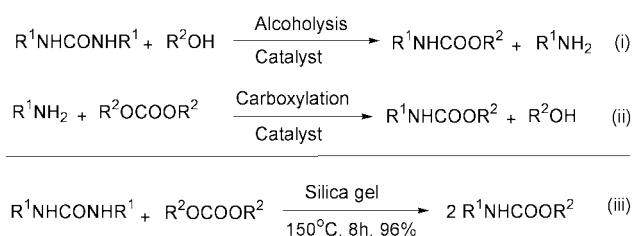
A simple and efficient methodology to prepare carbamates has been demonstrated for the first time from symmetrical ureas and organic carbonates in the presence of solid base catalysts.

Carbamates are compounds of growing interest because of their applications in the agrochemicals industry as herbicides, fungicides and pesticides, in the pharmaceuticals industry as drug intermediates and in the polymer industry, in the synthesis of polyurethane. The commercial production of urethane is almost exclusively based on phosgene technology, however, due to worldwide awareness of pollution hazards of phosgene and pollution prevention laws adopted by Governmental agencies it is most essential to substitute it by environmentally benign routes. Efforts have continuously been made for the replacement of the phosgene route with routes such as reductive carbonylation of nitro aromatics and oxidative carbonylation of amines which have shown some promise. However, the former route will suffer from a lack of economical viability in the near future¹ while the latter suffers from hazards in handling of carbon monoxide and oxygen under high pressures. Carbamate synthesis has also been accomplished by several-pot reaction methods such as Hofmann rearrangement from amides,² by reaction of chloroformates and amines catalyzed by zinc,³ and from alcohols to unsubstituted carbamates by treatment with trichloroacetyl isocyanate, followed by hydrolysis on Al₂O₃.⁴ Recently, the use of carbon dioxide to replace phosgene has been attracting attention of research workers mainly due to its non-hazardous nature and safety in handling under pressure. Usually powerful organic bases⁵ (e.g. *N*-cyclohexyl-*N,N,N'',N''*-tetramethylguanidine *etc.*) or additives such as crown ethers⁶ are required to stabilize carbamate anion generated during amine and CO₂ reaction. This difficulty was partly overcome by using tetraethylammonium hydrogen carbonates (TEAHC),⁷ and a combination of potassium carbonate and onium salts⁸ as catalysts for the synthesis of carbamates from alkyl halides and amines. However, these methods at present are not attractive for bulk production of carbamates as they utilize only stoichiometric quantities of reagents and generate salts as by-products, which are not easy to dispose.

Recently, two industrially very important methods have been reported for the synthesis of carbamates *viz.*, alcoholysis of ureas⁹ and carboxylation of amines.¹⁰ We were interested in developing methods for the synthesis of carbamates utilizing solid catalysts, as they are industrially important due to their potential in replacing conventional acid/base catalysts. The use of solid acid/base catalysts for synthesizing organic intermediates and fine chemicals is gaining increasing awareness and is a field of intense research activity.¹¹ While, working on reactions of alcoholysis of urea (i) and carboxylation of amines (ii) to carbamic acid esters (Scheme 1), we realized that, reactions (i) and (ii) both show poor atom economy and in each case alcohol or amine is produced as a byproduct reducing the functional group efficiency of the reagent. One way of improving the atom economy in reactions (i) and (ii) is to eliminate the use of alcohols and amines. Therefore, we were interested in effecting the conversion of disubstituted ureas and

carbonates to carbamates utilizing the total functionality of both the urea and the carbonate. In this communication, we report for the first time, a new methodology for the synthesis of carbamates from substituted ureas and organic carbonates using a highly efficient and simple catalyst system [Scheme 1, eqn. (iii)].[†] This novel protocol has 100% atom economy while using an environmentally benign reactant source.

Surprisingly, the reaction between aromatic ureas and carbonates has not been studied¹² previously. A non-catalytic reaction between *N,N'*-diphenylurea and diphenyl carbonate gave only traces of *N*-phenyl phenyl carbamate after 24 h at 150 °C (see Table 1, entry 1). During the course of our investigations for screening of catalysts it was observed that basic catalysts such as triphenyl phosphine, sodium phenolate *etc.* were more effective than classical acid catalysts such as Lewis acids (FeCl₃, AlCl₃ *etc.*) and solid acid catalysts such as acidic Al₂O₃ (entry 4). However, heterogeneous basic catalysts *e.g.* Mg–Al hydrotalcite, Li–MgO, PbZrO₃, the Na form of zeolite ZSM-5 and amorphous catalyst grade silica gel were found to give excellent results amongst the catalysts examined, which are summarized in Table 1. Most of the catalyst screening and recycling of catalyst studies were carried out aiming for industrially important phenyl *N*-phenyl carbamate (PPC) as the product and for this purpose *N,N'*-diphenyl urea (DPU) and diphenyl carbonate (DPC) were chosen as model substrates (entries 2–9). From the catalysts screened, amorphous silica gel was found to be the most suitable catalyst because of its commercial availability, low cost and ease in recycling. Therefore, further studies were carried out using silica gel catalyst. The generalized applicability of the method is also verified and is evident from the range of carbamates synthesized from different ureas and carbonates (Table 1). Aromatic substituted ureas were also found to react smoothly with DPC giving the corresponding carbamates in excellent to high yields (entries 10–14). However, reaction between DPU and dimethyl carbonate (DMC) gave only a poor yield of *N*-phenyl methyl carbamate (entry 15). Interestingly, industrially important *N*-methyl methyl carbamate is produced in excellent yield from dimethyl urea and DMC (entry 16), while dimethyl urea and dibutyl carbonate require highly basic potassium supported silica gel catalyst for excellent yields of carbamate (entry 17). In general it was observed from screening of the substrates that, excellent yields of carbamates are obtained, when an aromatic urea was reacted with an aromatic carbonate and likewise for aliphatic derivatives. Catalyst screening experiments indicated that the basicity of the catalysts plays a vital role in their

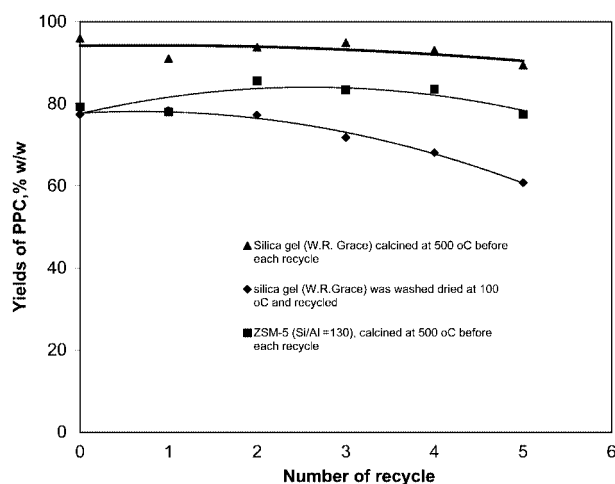


Scheme 1 Carbamate synthesis from urea and carbonate.

Table 1 Solid base catalysed carbamate synthesis from ureas and carbonates^a

Entry	R ¹ (urea)	R ² (carbonate)	Catalyst	Time/h	Yield ^b (%)
1	C ₆ H ₅	C ₆ H ₅	None	24	Trace
2	C ₆ H ₅	C ₆ H ₅	Silica gel ^c	3	81
3	C ₆ H ₅	C ₆ H ₅	Silica gel ^d	8	96
4	C ₆ H ₅	C ₆ H ₅	Al ₂ O ₃ (acidic) ^e	3	23
5	C ₆ H ₅	C ₆ H ₅	5% Pb on silica gel ^c	3	0
6	C ₆ H ₅	C ₆ H ₅	PbZrO ₃ ^f	3	18
7	C ₆ H ₅	C ₆ H ₅	Mg–Al hydrotalcite ^{g,h}	3	92
8	C ₆ H ₅	C ₆ H ₅	Na-ZSM-5 (Si/Al = 130) ^h	3	95
9	C ₆ H ₅	C ₆ H ₅	Li–MgO ⁱ	4	79
10	4-CH ₃ C ₆ H ₄	C ₆ H ₅	Silica gel ^c	3	90
11	2-ClC ₆ H ₄	C ₆ H ₅	Silica gel ^c	8	89
12	3-ClC ₆ H ₄	C ₆ H ₅	Silica gel ^c	8	73
13	4-ClC ₆ H ₄	C ₆ H ₅	Silica gel ^c	8	79
14	4-NO ₂ C ₆ H ₄	C ₆ H ₅	Silica gel ^c	8	89
15	C ₆ H ₅	CH ₃ ^j	Silica gel ^c	8	91
16	CH ₃	CH ₃ ^j	Silica gel ^c	8	18
17	CH ₃	C ₄ H ₉	Silica gel ^c	8	81
			5%K-Silica gel ^{c,k}	8	80

^a Reaction conditions: urea: 3.16 mmol; carbonate: 15.4 mmol; catalyst: 200 mg; solvent: carbonate; temperature: 150 °C; agitation: 1000 rpm. ^b Isolated. ^c Silica gel from W.R.Grace, USA. ^d Silica gel from Davisil, Aldrich. ^e Activated, Brockmann-1, Aldrich. ^f 0.9 mmol. ^g Mg/Al ratio: 3:1. ^h Synthesized in our laboratory using a standard procedure. ⁱ Prepared by wet impregnation of lithium acetate on magnesium acetate followed by calcination in air at 750 °C (Li/Mg = 0.1). ^j A 50 cm³ autoclave was used with 30 bar nitrogen pressure and 15 cm³ of dimethyl carbonate. ^k Wet impregnation of K₂CO₃ on silica gel followed by calcinations in air at 500 °C.

**Fig. 1** Catalyst recycle runs.

activity. Also, from the earlier literature, it is known that basic catalysts are highly efficient for reactions involving carbonates (e.g. carbomethoxylation, *trans*-esterification and methylation).¹³ The solid-base catalysts tested were all found to give excellent yields of carbamates, however, we believe that for exceptional activity, dual acid/base sites on the solid support are necessary. For catalysts having only basic sites (e.g. PPh₃, K₂CO₃, NaOH) only moderate yields of carbamates could be realised.¹⁴ The activity of silica gel catalyst can be attributed to the interactions of organic urea and carbonate with silanol groups on the silica gel surface.¹⁵ The variation in activity of silica gel catalysts procured from two different sources *viz.* W.R.Grace & Co., and Davisil (entries 2 and 3 of Table 1) is thought to be due to the difference in distribution of silanol groups in these two silica gels. Na-ZSM-5 catalysts with Si/Al ratio of 130 essentially behaved like SiO₂ since at these high ratios of Si/Al, Al atoms no longer contribute to a major extent to the framework structure of the zeolite. The activity in these zeolites is likely to be due to basic sites created by oxygen atoms while Al contributes to the Lewis acid sites.¹⁶ Common urea and *N*-methyl urea were also examined for carbamate synthesis from DPC, however, the carbamates formed were unstable and at the end of the reaction ill characterized white solids could only be isolated.

The reusability of catalysts was tested for silica gel and Na-ZSM-5 catalyst and the results are shown in Fig. 1. The results

show excellent reusability of both the catalysts for up to five recycles. Calcination for silica gel considerably improves the catalyst activity over simply drying and recycling of the catalyst.

In summary the protocol presented here is environmentally benign, simple and involves inexpensive reagents and can be effectively applied to large-scale synthesis of carbamates in high yield.

Notes and references

† *Experimental procedure:* A symmetrical urea (3.16 mmol), aromatic dicarbonate (155.6 mmol) and W.R.Grace silica gel catalyst (200 mg) were added to a well flushed and dried reaction vessel (50 cm³) equipped with a stirrer and reflux condenser. The contents were heated under stirring up to 150 °C and kept for 8 h while an inert atmosphere was maintained. After cooling to room temperature, the solid mass was dissolved in acetone, filtered to separate the catalyst and the carbamate isolated in pure form by column chromatography (silica gel, ethyl acetate–chloroform 0.2:9.8). All the products were fully characterized by elemental analysis, ¹H NMR, ¹³C NMR, IR, GC–IR and comparison with authentic samples whenever possible. Recycling of catalyst was carried out by filtration of catalyst from the crude reaction mixture in acetone followed by drying of catalyst and calcination 500 °C for 3 h.

- 1 F. Paul, *Coord. Chem. Rev.*, 2000, **203**, 310.
- 2 Y. Matsumura, T. Maki and Y. Satoh, *Tetrahedron Lett.*, 1997, **38**, 8879.
- 3 J. Yadav, G. Reddy, M. Reddy and H. Meshram, *Tetrahedron Lett.*, 1998, **39**, 3259.
- 4 P. Kocovsky, *Tetrahedron Lett.*, 1986, **27**, 5521.
- 5 W. D. McGhee, Y. Pan and D. P. Riley, *J. Chem. Soc., Chem. Commun.*, 1994, 699.
- 6 M. Aresta and E. Quaranta, *Tetrahedron*, 1992, **48**, 1515.
- 7 A. Inesi, V. Mucciante and L. Rossi, *J. Org. Chem.*, 1998, **63**, 1337.
- 8 M. Yoshida, N. Hara and S. Okuyama, *J. Chem. Soc., Chem. Commun.*, 2000, 151.
- 9 K. Kongen, C. Arihito, S. Kashun and R. Akyasu, *Jpn. Kokai Tokkyo Koho*, JP 08198815 A2 6th Aug, 1996.
- 10 A. E. Gurgiolo, *US Pat.*, 4 268 683, 1981; Z. H. Fu and Y. Ono, *J. Mol. Catal.*, 1994, **91**, 399; I. Vauthey, F. Valot, C. Gozzi and M. Lemaire, *Tetrahedron Lett.*, 2000, **41**, 6347.
- 11 K. Tanabe and W. F. Holderich, *Appl. Catal. A*, 1999, **181**, 399.
- 12 P. Molina and A. Tarraga, *Comprehensive Organic Functional Group Transformations*, Pergamon Press, Oxford, 1997, vol. 5, p. 981.
- 13 Y. Ono, *App. Catal. A*, 1997, **155**, 133.
- 14 These catalysts gave a PPC yield of 25–30% under the experimental conditions employed in this work.
- 15 T. Suzuki, H. Tomon and M. Okazaki, *Chem. Lett.*, 1994, 2151.
- 16 D. Barthomeuf, *J. Phys. Chem.*, 1984, **88**, 42; M. Selva, P. Undo and A. Perosa, *J. Org. Chem.*, 2001, **66**, 677.