Tetrahedron Letters 51 (2010) 6301–6304

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Organocatalyzed synthesis of ureas from amines and ethylene carbonate

Francesco Saliu *, Bruno Rindone

Department of Environmental Science, University of Milano-Bicocca, Piazza della Scienza 1, 20126 Milano, Italy

ARTICLE INFO

Article history:
Received 20 July 2010
Revised 20 September 2010
Accepted 22 September 2010
Available online 29 September 2010

Keywords:
2-Hydroxyethylcarbamates, 1,3-Disubstituted ureas
Organic catalysis
Solventless reaction

ABSTRACT

A new solventless method for the synthesis of symmetrical and unsymmetrical ureas, starting from ethylene carbonate and amines, is reported. 1,5,7-Triazabicyclo[4.4.0]dec-5-ene(TBD) and thioureas have been found to be efficient organocatalysts for this reaction.

1. Introduction

Avoiding phosgene in the synthesis of isocyanates and their derivatives, as ureas, is a hot topic in green chemistry.[1,2] The synthesis of ureas through phosgene substitutes is the subject of many reviews.[3] The most studied alternative routes are:

(a) the oxidative carbonylation of amines with carbon monoxide (CO) under various metal catalysts,[4–9]
(b) the direct reaction of carbon dioxide with amines,[10–15]
(c) the use of some phosgene substitutes such as carbonates, that are less toxic and more stable.[16–19]

Cyclic carbonates are green reagents and solvents that are nowadays industrially obtained from an insertion reaction of carbon dioxide into epoxides, using cheap catalysts such as homogeneous quaternary ammonium salts.[20] This is one of the most important methods for CO_2 fixation[21] and efforts are in progress all over the world to find more efficient heterogeneous catalysts.[22,23]

The reactivity of cyclic carbonates with nucleophiles can be explained on the HSAB principle basis.[24] Hard bases such as amines open the ring of cyclic carbonate reacting at the trigonal carbon of the carbonyl group to give 2-hydroxyethylcarbamates.

By using specific cyclic carbonates, which can form activated carbamates, isocyanates and ureas can be subsequently obtained.[25,26]

As a more general procedure, symmetrical and unsymmetrical ureas are formed from 2-hydroxyethylcarbamates via transamination, by adding an inorganic base catalyst such as NaOMe[27], CaO[28] or Cs_2CO_3.[29]

Moreover, K_2CO_3 and five-membered cyclic carbonates have been recently applied in the synthesis of 2-oxazolidinones starting from β-aminoalcohols and of 2-imidazolinones starting from diamines.[30]

We report in this Letter the first attempt to replace these catalysts with an organic greener catalyst.

Guanidine bases and thioureas are frequently used in the double hydrogen bonding activation of carbonyl.[31,32] A further advantage derives from the fact that these catalysts are commercially available in solid supported form. Interestingly, in a recent Letter,[33] the use of TBD on a solid support has been proposed in the synthesis of five-membered cyclic carbonates by carboxylation of epoxides. The subsequent addition of amines presented here could lead to an automated procedure to synthesize ureas.

2. Results and discussion

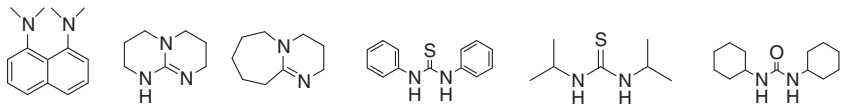
The first set of experiments was intended to optimize the reaction conditions for the synthesis of symmetrical 1,3-disubstituted ureas. Various organic catalysts and solvents (Table 1) were tested in the synthesis of 1,3-dicyclohexylurea (**2a**) from ethylene carbonate and cyclohexylamine (**1a**) (Scheme 1). TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) and 1,3-diisopropylthiourea were most effective in giving 1,3-dicyclohexylurea in good yield under solventless conditions (Table 1, entries 6 and 12). The lower conversion obtained in solution are presumably related with the lower reaction temperature.

We tested also if 1,3-dicyclohexylurea had an autocatalytic effect on the reaction (entry 16) by acting as hydrogen bond donor

* Corresponding author. Tel.: +39 02 64482813; fax: +39 02 64482839.
E-mail address: francesco.saliu@unimib.it (F. Saliu).

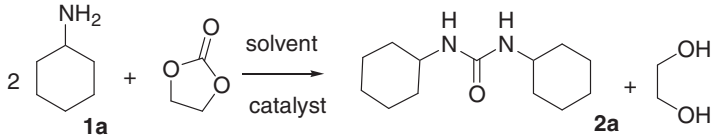
0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.09.107

Table 1
Effect of the catalyst and the solvent in the synthesis of 1,3-dicyclohexylurea from ethylene carbonate and cyclohexylamine

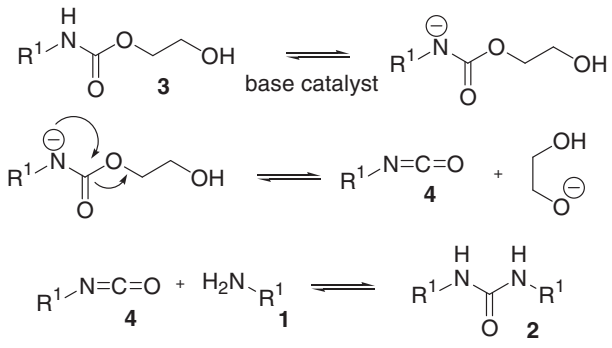
Catalysts: 

Entry	Catalyst	Solvent	Temperature (°C)	Yield[a] (%)
1	DBU	CH_2Cl_2	40	44
2	DBU	None	120	62
3	*p*-Toluenesulfonic acid	THF	65	15
4	*p*-Toluenesulfonic acid	CH_2Cl_2	40	21
5	1,3-Diisopropylthiourea	CH_2Cl_2	40	63
6	1,3-Diisopropylthiourea	None	120	76
7	1,3-Diphenylthiourea	CH_2Cl_2	40	56
8	1,3-Diphenylthiourea	None	120	72
9	1,3-Diphenylthiourea	Ethyl acetate	75	10
10	1,3-Diphenylthiourea	Toluene	110	5
11	DMAN	None	120	51
12	TBD	None	120	88
13	TBD[b]	CH_2Cl_2	100	65
13	TBD[c]	None	120	42
14	TBD	Acetonitrile	80	62
15	None	None	120	4
16	1,3-Dicyclohexylurea	None	120	6
17	1,3-Dicyclohexylurea	CH_2Cl_2	40	7

[a] Isolated yields in 1,3-dicyclohexylurea. Reaction conditions: 20 mmol of cyclohexylamine, 10 mmol of ethylene carbonate, 0.2 mmol of catalyst, reaction time 180 min.
[b] In autoclave.
[c] 0.02 mmol of catalyst.



Scheme 1. Preparation of 1,3-dicyclohexylurea from cyclohexylamine and ethylene carbonate.

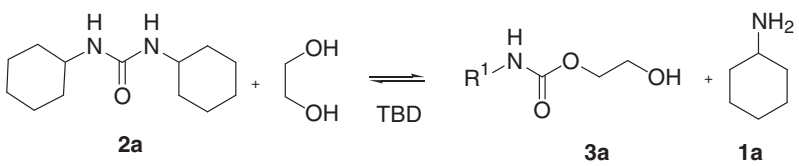


Scheme 2. Supposed hydrolysis mechanism of 2-hydroxyethylcarbamates.

like thioureas, but we observed no conversion, probably due to the poor solubility of this compound in organic solvents and in the solventless mixture too.

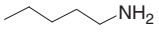
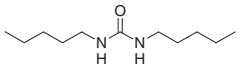
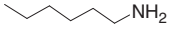
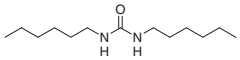
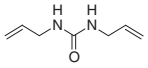
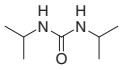
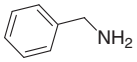
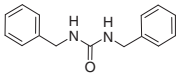
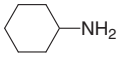
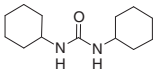
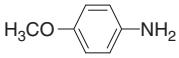
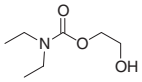
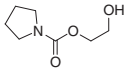
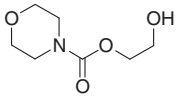
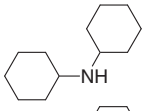
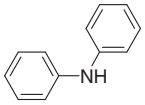
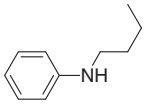
The generality of the reaction was examined by using various amines, as shown in Table 2. Aliphatic primary amines gave from good to excellent yields in the corresponding symmetrically disubstituted ureas, no conversion was observed with aromatic amines. Aliphatic secondary amines gave only the corresponding 2-hydroxyethylcarbamates.

The fact that secondary amines do not give ureas and the observation of traces of isocyanates in the crude reaction mixture from primary amines both suggest that isocyanates could be intermediates in these reactions. In an attempt to isolate cyclohexylisocyanate the best result was achieved by carrying out the reaction in dichloromethane with paratoluenesulphonic acid, obtaining this



Scheme 3. Reverse reaction to confirm the reversibility. K_E = [**2a**][$HO(CH_2)_2OH$]/[**3a**][**1a**].

Table 2
TBD catalyzed synthesis of 1,3-symmetrically disubstituted ureas

Entry	Amine	Product	Yield[a] (%)
1[b]			84
2[b]			86
3[b]			74
4[b]			68
5			76
6			88
7		No reaction	–
8[b]			80
9			96
10			94
11		No reaction	–
12		No reaction	–
13		No reaction	–

[a] Yields refer to isolated pure products characterized by IR, GC–MS, and ^{1}H NMR. Reaction conditions: 20 mmol of amine, 10 mmol of ethylene carbonate, 0.2 mmol of TBD, 120 °C, 120 min.
[b] 90 °C.

product in 13% yield. Reaction monitoring by IR spectroscopy shows the OH band after few seconds from the start and subsequently the formation of the characteristic band of isocyanate and of the bands of 1,3-dicyclohexylurea.

It has been reported[34] that, in the presence of basic amines, carbamates dissociate into isocyanates and alcohols, and afterward isocyanates react with amines to form ureas. All these were shown to be equilibrium reactions. Similarly, in the reaction reported herein, the in situ generated 2-hydroxyethylcarbamate (**3**) could undergo a base catalyzed hydrolysis, that involves an elimination step (Scheme 2). This hypothesis is slightly different from the transamination reported with inorganic catalysts.[28] To confirm the reversibility and to determine the equilibrium constant we put 1,3-dicyclohexylurea and an excess of ethylene glycol (100:1) in dichloromethane at 50 °C for 48 h and we checked the formation of the corresponding 2-hydroxyethylcarbamate (**3a**) (Scheme 3). We found a very high value of the K of the equilibria (ca 3.8×10^4) that is probably related with the poor solubility of 1,3-dicyclohexylurea. Thus, the precipitation of products is the key that can enable our solventless reaction to go to completion. Investigations are underway to have further details of the mechanism.

On the basis of these observations we developed a two-step procedure for the synthesis of unsymmetrical ureas (Scheme 4). In the first step a primary amine (**1**) reacts with ethylene carbonate to give the corresponding 2-hydroxyethylcarbamate (**3**). In the second step the 2-hydroxyethylcarbamate reacts under organic base catalysis with another primary amine or with a secondary amine to give disubstituted (**5**) or trisubstituted ureas (**6**), respectively (Table 3). Starting from secondary amines, in any case, no ureas are formed. Although this method is fast and high yielding, the formation of symmetrical ureas as side products is its major drawback and column chromatography and recrystallization are needed to obtain the desired products in high purity.

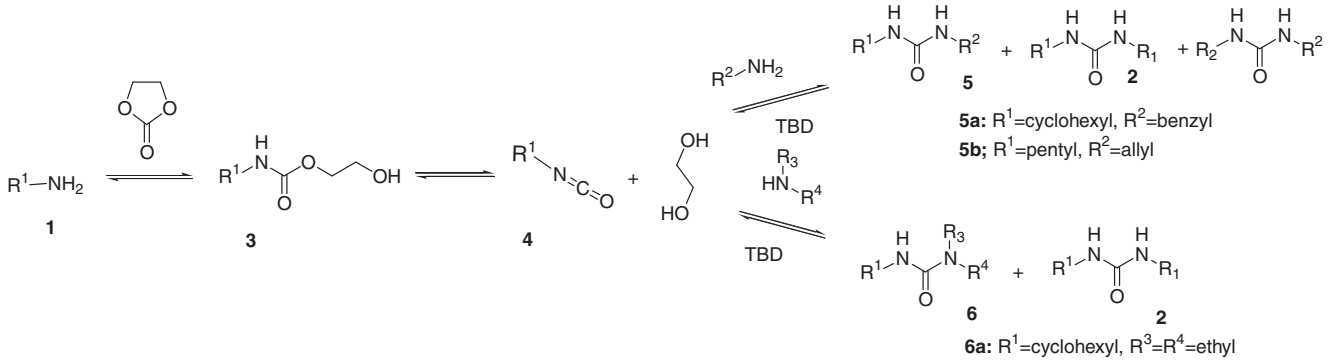
In conclusion, the synthesis of 1,3-disubstituted symmetrical and unsymmetrical ureas from ethylene carbonate and the corresponding amines was performed in good to excellent yields using TBD as catalyst under solventless conditions.

3. Experimental

All chemicals were purchased from Sigma–Aldrich and used without further purification. Reaction products were characterized by comparison with the IR, GC–MS, and ^{1}H NMR of known compounds. Yields were determined after isolation.

3.1. Representative experimental procedure for the synthesis of 1,3-disubstituted symmetrical ureas (2)

Experiments were carried out by mixing ethylene carbonate (10 mmol) with a primary amine (**1**, 20 mmol) and the catalyst (0.2 mmol) and by heating at the desired temperature for 120 min. The reaction mixture was cooled and the crude product was purified on silica gel (R = 100) by eluting with the mixture dichloromethane–ethyl acetate (85:15). The procedure for the iso-



Scheme 4. TBD-catalyzed synthesis of unsymmetrical ureas.

Table 3
Yield in the TBD-catalyzed synthesis of unsymmetrical ureas

Entry	First amine added	Second amine added	Unsymmetrical urea product	Yield[a] (%)
1	Cyclohexylamine	Benzylamine	(**5a**)	60
2	Pentylamine	Allylamine	(**5b**)	58
3	Cyclohexylamine	Diethylamine	(**6a**)	88
4	Cyclohexylamine	Piperidine	(**6b**)	92
5	Piperidine	Cyclohexylamine	None	—
6	Allylamine	Morpholine	(**6c**)	90
7[b]	Morpholine	Pentylamine	None	—
8[b]	Hexylamine	Morpholine	(**6d**)	65

[a] Yields refer to isolated pure products characterized by IR, GC–MS, and ^{1}H NMR. Reaction conditions: 20 mmol of ethylene carbonate, 20 mmol of the first amine, 20 mmol of the second amine, 0.2 mmol of TBD catalyst, 90 °C, 180 min.
[b] 0.2 mmol of 1,3-diisopropylthiourea catalyst.

lation of 1,3-dicyclohexylurea required only dilution of the reaction mixture with 20 mL of water and filtration. The solid residue was then washed with dichloromethane. The collected organic fraction was concentrated in 5 mL of dichloromethane and filtered again. 1-3-Dicyclohexylurea was recovered as a white crystalline solid. The validation of this isolation method was assessed by testing a standard solution of 1,3-dicyclohexylurea, cyclohexylisocyanate and cyclohexylamine. The absolute recovery of 1,3-dicyclohexylurea ranged from 94% to 103%.

3.2. Representative experimental procedure for the synthesis of disubstituted unsymmetrical ureas (5) and for the synthesis of trisubstituted unsymmetrical ureas (6)

Ethylene carbonate (10 mmol) and a primary amine (**1**, 10 mmol) were heated at 70 °C for 1 h to afford the corresponding 2-hydroxyethylcarbamate (**3**). This transformation can be sped up by reacting the solventless mixture under microwave irradiation. TBD (0.2 mmol) and a second amine (another primary amine to afford a disubstituted urea (**5**) or a secondary amine to afford a trisubstituted urea (**6**), 10 mmol) were added to the reaction mixture and were heated at the desired temperature for 120 min.

N-Allyl-4-morpholinecarboxamide **6c** IR (KBr): 3268, 2911, 2804, 1742, 1530 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.22–3.71 (m, 10H), 5.05 (d, J = 9.2 Hz, 1H), 5.13 (d, J = 16.1 Hz, 1H), 5.62 (br, 1H) 5.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.5, 57.2, 76.7, 116.1, 134.9, 157.1; MS (EI 70 eV) m/z: 170 (M^+), 141, 127, 114, 86, 70, 57.

Acknowledgments

We warmly thank Giovanni Di Gennaro, Matteo Berra, Emanuele Fossati, Marcello Dusini, Alessandra Saliu, and Moira Pringle for their collaboration.

References and notes

1. Kirk-Othmer. In *Encyclopaedia of Chemical Technology*, 4th ed.; Wiley, New York, 1995; Vol. 14, p 902.
2. Weissermel, K.; Arpe, H. J. In *Industrial Organic Chemistry*, 2nd ed.; WCH: Weinheim, 1993; p 373.
3. Bigi, F.; Maggi, R.; Sartori, G. *Green Chem.* **2000**, *2*, 140–148.
4. Shi, F.; Deng, Y. Q. *J. Catal.* **2002**, *211*, 548–551.
5. Bartolo, G.; Salerno, G.; Mancuso, R.; Costa, M. *J. Org. Chem.* **2004**, *69*, 4741–4750.
6. Bolzacchini, E.; Meinardi, S.; Orlandi, M.; Rindone, B. *J. Mol. Catal.* **1996**, *111*, 281.
7. McCusker, J. E.; Msain, A. D.; Johnson, K. S.; Grasso, C. A.; McElwee-White, N. *J. Org. Chem.* **2000**, *65*, 5216–5222.
8. Gabriele, B.; Salerno, G.; Costa, M. *Top. Organomet. Chem.* **2006**, *18*, 239.
9. Diaz, D. J.; Darko, A. K.; McElwee-White, L. *Eur. J. Org. Chem.* **2007**, *27*, 4453–4465.
10. Ion, A.; Parvulescu, V.; Jacobs DeVos, P. D. *Green Chem.* **2007**, *9*, 158–161.
11. Jiang, T.; Ma, X.; Zhou, Y.; Liang, S.; Zhang, J.; Han, B. *Green Chem.* **2008**, *10*, 465.
12. Ogura, H.; Tekeda, K.; Tokue, R.; Kobayashi, T. A. *Synthesis* **1978**, 394–396.
13. Fournier, J.; Bruneau, C.; Dixneuf, P. H.; Lecolier, S. *J. Org. Chem.* **1991**, *56*, 4456–4458.
14. Cooper, C. F.; Falcone, S. *J. Synth. Commun.* **1995**, *25*, 2467–2474.
15. Yamazaki, N.; Higashi, F.; Iguchi, T. *Tetrahedron Lett.* **1974**, *13*, 1191–1194.
16. Fu, Z. H.; Ono, Y. *J. Mol. Catal.* **1994**, *91*, 399.
17. Angeles, E.; Santillan, A.; Martinez, I.; Ramirez, A.; Moreno, E.; Salmon, M.; Martinez, R. *Synth. Commun.* **1994**, *24*, 2441–2447.
18. Aresta, M.; Barloco, C.; Quaranta, E. *Tetrahedron* **1995**, *51*, 8073.
19. Rivetti, F.; Romano, U.; Delledonne, D. *Green Chem.* **1996**, *34*, 332. and references cited therein.
20. Fukuoka, S.; Kawamura, M.; Komiya, K.; Tojo, M.; Hachiya, H.; Hasegawa, K.; Aminaka, M.; Okamoto, H.; Fukawa, I.; Konno, S. *Green Chem.* **2003**, *5*, 497–507.
21. Aresta, M.; Quaranta, E.; Tommasi, I.; Giannoccaro, P.; Ciccarese, A. *Gazz. Chim. Ital.* **1995**, *125*, 509–538.
22. Darensbourg, D. J.; Holtcamp, M. W. *Coord. Chem. Rev.* **1996**, *153*, 155–174.
23. Shaikh, A. G.; Sivaram, S. *Chem. Rev.* **1996**, *96*, 951–976.
24. Tomita, H.; Sanda, F.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 3678–3685.
25. Schmidt, H.; Hollitzer, O.; Seewald, A.; Steglich, W. *Chem. Ber.* **1979**, *112*, 727–733.
26. Laufer, D. A.; Doyle, K.; Zhang, X. *Org. Prep. Proc. Int.* **1989**, *21*, 771–776.
27. Hayashi, T.; Yasuoka, J. Eur Pat, EP 846679, 1998; *Chem. Abstr.* **1998**, *129*, 40921.
28. Fujita, S.; Bhanage, B. M.; Kanamaru, H.; Arai, M. *J. Mol. Catal. A: Chem.* **2005**, *23*, 43–48.
29. Jagtap, S. R.; Patil, Y. P.; Panda, A. G.; Bhanage, B. M. *Synth. Commun.* **2009**, *39*, 2093–2100.
30. Xiao, L.; Xu, L.; Xia, C. *Green Chem.* **2007**, *9*, 369–372.
31. Pikho, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062–2064.
32. Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418–5427.
33. Barbarini, A.; Maggi, R.; Mazzacani, A.; Mori, G.; Sartori, G.; Sartorio, R. *Tetrahedron Lett.* **2003**, *442*, 2931–2934.
34. de Aguirre, I.; Collot, J. *Bull. Soc. Chim. Belg.* **1989**, *98*, 19.