

# Catalytic production of urethanes from amines and alkyl halides in supercritical carbon dioxide

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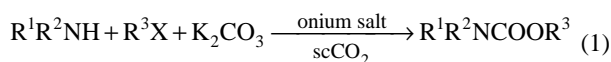
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Some common onium salts catalysed selective urethane production from amines and alkyl halides in supercritical carbon dioxide, which acted not only as an alternative to organic solvents but also as a phosgene replacement; the reaction efficiency was 50–100 times higher than that attained in heptane.

The most widely utilized method for the synthesis of urethanes uses highly toxic phosgene as a reagent in organic solvents, which are also toxic and flammable. Therefore the conventional method involves environmental and safety problems.

Owing to the above mentions, much effort has been directed toward alternative routes for preparation of urethanes using carbon dioxide as a phosgene replacement.<sup>1–8</sup> Carbon dioxide is well known to react rapidly with amines to form carbamic acid ammonium salts.<sup>9</sup> However, as the nucleophilicity of the carbamate anion is lower than that of the amine formed in the equilibrium of the salt formation reaction, the reaction of the carbamate salts with alkyl halides does not selectively afford urethanes.<sup>2</sup> So, the activation of the carbamate anion was attempted by addition of crown ethers<sup>5</sup> and strong bases.<sup>4</sup> Monsanto's chemists have achieved a highly selective urethane synthesis process using very strong bases (*e.g.* CyTMG: *N*-cyclohexyl-*N',N',N'',N''*-tetramethylguanidine).<sup>7</sup> However, because a stoichiometric amount of CyTMG was necessary in the reaction, the Monsanto process could not replace the conventional method.

We have successfully synthesized urethanes in high yields from amines, alkyl halides, potassium carbonate and a catalytic amount of an onium salt in supercritical carbon dioxide (scCO<sub>2</sub>) [eqn. (1)]. Supercritical carbon dioxide is an attractive



alternative to organic solvents as it is environmentally benign, essentially nontoxic, inexpensive, nonflammable and has relatively low critical conditions ( $P_c = 73$  atm,  $T_c = 31$  °C).<sup>†</sup>

The results of the one-pot urethane production are summarized in Table 1. Not only aliphatic primary and secondary amines but also aromatic amines reacted well. As these are catalytic reactions, the low yields should be improved by increasing the amount of catalyst or extending the reaction time.

The effect of catalyst on the conversion of a pyrrolidine, butyl chloride and potassium carbonate system in scCO<sub>2</sub> is given in Table 2. The reaction could be catalysed by ammonium salts and a phosphonium salt. Among these, the catalysts that afforded the best results were tetrabutylammonium bromide and trioctylammonium chloride, which are commonly used in industry.

Sanchez and co-workers also reported a phosgene-replaced urethane synthesis in heptane using amines, alkyl halides, potassium carbonate and tetrabutylammonium hydrogensulfate, as a solid/liquid phase-transfer reagent, without any additional carbon dioxide.<sup>3</sup> In their system, the carbonyl source was potassium carbonate. In order to determine the carbonyl source in our system, we tried a reaction in scCO<sub>2</sub> with pyrrolidine, butyl chloride and potassium phosphate in place of potassium

**Table 1** Bu<sub>4</sub>NBr catalysed urethane production from R<sup>1</sup>R<sup>2</sup>NH, R<sup>3</sup>X and K<sub>2</sub>CO<sub>3</sub> in scCO<sub>2</sub><sup>a</sup>

R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup> X	Bu <sub>4</sub> NBr/ mol%	t/h	Yield (%) <sup>b</sup>
	–(CH <sub>2</sub> ) <sub>4</sub> –	BuCl	5	2	quant. (85)
	–(CH <sub>2</sub> ) <sub>4</sub> –	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> Cl	5	2	76
	–(CH <sub>2</sub> ) <sub>4</sub> –	Bu <sup>s</sup> Br	5	2	73
	–(CH <sub>2</sub> ) <sub>5</sub> –	BuCl	5	2	quant. (85)
	–(CH <sub>2</sub> ) <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> –	BuCl	15	2	72 (62)
Me	Me	BuCl	5	2	86 (81)
Et	Et	BuCl	5	2	90 (82)
Bu	Bu	BuCl	5	2	74
C <sub>6</sub> H <sub>11</sub>	C <sub>6</sub> H <sub>11</sub>	BuCl	5	2	72
Ph	Me	BuCl	5	2	quant. (94)
Bu	H	BuBr	5	1	quant. (90)
CH <sub>2</sub> =CHCH <sub>2</sub>	H	BuBr	5	1	quant. (90)
Bn	H	BuBr	5	1	91 (85)
Ph	H	BuCl	20	4	75

<sup>a</sup> Reaction was conducted at 100 °C, 80 atm in a 50 ml stainless steel autoclave containing amine (5 mmol), alkyl halide (8 mmol) and K<sub>2</sub>CO<sub>3</sub> (10 mmol). <sup>b</sup> Estimated by <sup>1</sup>H NMR, isolated yield in parentheses.

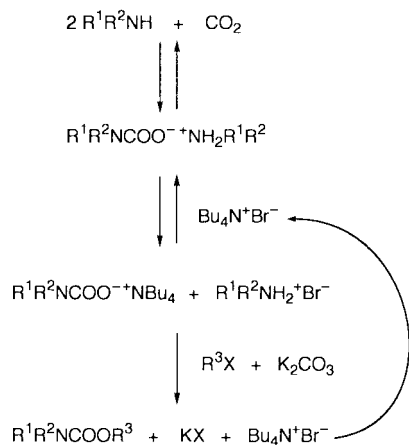
carbonate. From the resulting 98% yield of urethane, it was confirmed that scCO<sub>2</sub> acts not only as a solvent but also as a direct starting material for the urethane in our reaction system.<sup>10</sup>

Consequently, the mechanism of the reaction could be explained as follows (Scheme 1). First, the amine readily forms the carbamic acid ammonium salt upon the introduction of liquid carbon dioxide. The salt starts to dissolve in scCO<sub>2</sub> as the temperature increases. At the reaction temperature (100 °C), the ion exchange reaction takes place between the carbamate salt and tetrabutylammonium bromide. As a result, the carbamate anion is activated by the tetrabutylammonium ion and readily reacts with alkyl halide to form urethane and potassium halide in the presence of potassium carbonate. At the same time, tetrabutylammonium bromide is regenerated to complete the catalytic reaction cycle. If tetrabutylammonium bromide is absent, the amine formed by the reverse reaction of the equilibrium of the carbamate salt formation attacks alkyl halide

**Table 2** Effect of catalyst on conversion of pyrrolidine, butyl chloride and K<sub>2</sub>CO<sub>3</sub> in scCO<sub>2</sub><sup>a</sup>

Catalyst	Yield (%) <sup>b</sup>
Bu <sub>4</sub> NHSO <sub>4</sub>	69
Bu <sub>4</sub> NBr	74
Bu <sub>4</sub> NI	51
Bu <sub>4</sub> PBr	48
[CH <sub>3</sub> (CH <sub>2</sub> ) <sub>15</sub> NMe <sub>2</sub> Et]Br	66
[CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> ] <sub>3</sub> MeNCl	73

<sup>a</sup> Reaction was conducted at 100 °C, 80 atm in a 50 ml stainless steel autoclave containing pyrrolidine (5 mmol), butyl chloride (6 mmol), K<sub>2</sub>CO<sub>3</sub> (10 mmol) and catalyst (0.5 mmol) without stirring for 2 h. <sup>b</sup> Estimated by <sup>1</sup>H NMR.



Scheme 1

to form highly alkylated amines, and as a result the selectivity of the urethane formation decreases.

Our reaction system is the first example of catalytic urethane production. Also we found that the efficiency of the reaction in  $scCO_2$  is 50–100 times higher than that attained in heptane. Indeed, the urethane yield was less than 2% with pyrrolidine and butyl chloride, and less than 1% with butylamine and butyl bromide, in heptane.

In conclusion, we have achieved catalytic one-pot urethane synthesis from amines and alkyl halides in supercritical carbon dioxide and also achieved a phosgene replacement and organic solvent replacement by using common onium salts as catalysts. Our process is environmentally benign and also has benefits economically.

## Notes and references

† *Typical experimental procedure:* For carrying out the reactions in  $scCO_2$ , a 50 ml stainless steel autoclave (Taiatsu Techno portable reactor TVS-N2) was used. Potassium carbonate (10 mmol), tetrabutylammonium bromide (0.25 mmol), pyrrolidine (5 mmol) and butyl chloride (8 mmol) were successively placed in the reaction vessel. The vessel was sealed and then liquid carbon dioxide (*ca.* 12.3 g) was introduced from a cylinder at room temperature. The reaction system was heated with a boiling water bath (*ca.* 100 °C). The pressure of the mixture reached *ca.* 80 atm and the mixture was stirred magnetically for 2 h. In completion, the reaction vessel was cooled with an ice bath and the pressure was released slowly to atmospheric pressure. The residual mixture was extracted with chloroform and the yields of urethane were estimated by  $^1H$  NMR.

- 1 T. Tsuda, H. Washita, K. Watanabe, M. Miwa and T. Saegusa, *J. Chem. Soc., Chem. Commun.*, 1978, 815; T. Tsuda, K. Watanabe, K. Miyata, H. Yamamoto and T. Saegusa, *Inorg. Chem.*, 1981, **20**, 2728.
- 2 Y. Yoshida, S. Ishii and T. Yamashita, *Chem. Lett.*, 1984, 1571; Y. Yoshida, S. Ishii, M. Watanabe and T. Yamashita, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 1534.
- 3 V. G. Parra, F. Sanchez and T. Torres, *Synthesis*, 1985, 282.
- 4 Y. Hori, Y. Nagano, J. Nakao, T. Fukuhara and H. Taguchi, *Chem. Express*, 1986, **1**, 224.
- 5 M. Aresta and E. Quaranta, *J. Org. Chem.*, 1988, **53**, 4153; M. Aresta and E. Quaranta, *J. Chem. Soc., Dalton Trans.*, 1992, 1893; M. Aresta and E. Quaranta, *Tetrahedron*, 1992, **48**, 1515.
- 6 K. J. Butcher, *Synthesis*, 1994, 825.
- 7 W. D. McGhee, B. L. Parnas, D. P. Riley and J. J. Talley, U.S. Patent No. 5,223,638, June 29, 1993; W. McGhee, Y. Pan and D. P. Riley, *J. Chem. Soc., Chem. Commun.*, 1994, 699; W. McGhee, D. P. Riley, K. Christ, Y. Pan and B. Parnas, *J. Org. Chem.*, 1995, **60**, 2820.
- 8 A. Inesi, V. Mucciante and L. Rossi, *J. Org. Chem.*, 1998, **63**, 1337.
- 9 J. T. Edsall, *Biophysical Chemistry*, Academic Press, New York, 1958, vol. 1, 571.
- 10 We also tried the reaction without potassium carbonate in  $scCO_2$ , and the urethane was obtained in a yield of 8%.

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