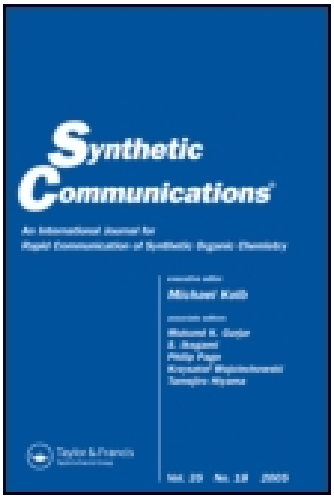

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REACTIONS OF DIMETHYL CARBONATE WITH ALIPHATIC AMINES UNDER HIGH PRESSURE

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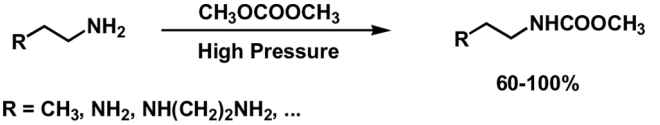
GRAPHICAL ABSTRACT



Abstract *A facile synthesis of methyl carbamates from primary amines and dimethyl carbonate has been achieved at room temperature using high pressure. High-pressure synthesis of methyl carbamates described herein provides access to the target molecules in an efficient and environmentally friendly way without solvent or catalyst. Better conversion and selectivity than previously published procedures were obtained.*

Keywords Carbomethylation; dimethyl carbonate; green chemistry; high-pressure reaction

INTRODUCTION

Environmental concerns have put great pressure on the chemical industry to develop green reagents for organic synthesis.[1] Dimethylcarbonate (DMC) was found to be a suitable substitute for toxic reagents such as phosgene, alkyl halides, and dimethyl sulfate.[2–4] Depending on the reaction conditions and hardness of nucleophile, DMC can act either as carbomethylating or methylating agent.[5] For instance, DMC reacts with alkyl amines at low temperatures to form carbamates. The uncatalyzed reaction is generally slow and usually accompanied with methylation as the most important side reaction.[6] On the other hand, reaction of amines with DMC conducted at elevated temperatures (over 130 °C) results in N-methylation as the dominant (or even exclusive) reaction.[7,8] Besides that, in some reactions formation of ureas was also observed.[9]

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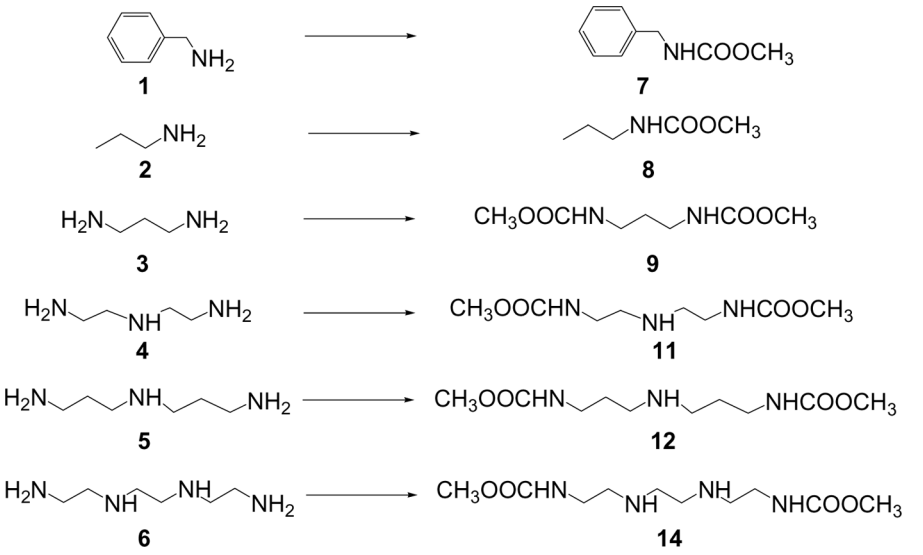
To increase reaction rate and selectivity, various basic and acidic catalysts were successfully employed: 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU),[10] ytterbium triflate,[11,12] Lewis acids (Cu,[13] Mn,[14] Sc,[6] Y and Yb compounds,[15] thiocyanic acid,[16]) alkoxides,[7,17,18] and ion exchange resins.[19] However, design of environmentally friendly chemical processes implies omission of all unnecessary chemicals or catalysts, and the specific uncatalysed process is the ultimate goal in green chemistry.

Our objective in this work was to investigate reaction of DMC with aliphatic mono- and polyamines under high pressure, with the aim of increasing the rate and the selectivity of carbomethylation reactions. The major premise for use of high pressure is the known fact that high pressure is beneficial for number of condensation reactions.[20,21] For example, it has been shown that the uncatalyzed synthesis of alkyl carbamates from primary aliphatic amines and DMC in supercritical carbon dioxide at 130 °C readily takes place.[22] Success of the reaction was attributed to the compressed CO_2, which favors formation of substituted ammonium carbamate, thus inhibiting the undesirable N-methylation reaction.

RESULTS AND DISCUSSION

In this study, uncatalyzed carbomethylations of benzylamine **1**, propylamine **2**, 1,3-diaminopropane **3**, diethylenetriamine **4**, bis-(3-aminopropyl)amine **5**, and triethylenetetramine **6** (Scheme 1) have been conducted, and results are collected in Table 1.

The inspection of Table 1 reveals that use of high pressure (8 kbar) has a beneficial effect on carbomethylation reaction. In spite of the absence of any catalyst,



Scheme 1. Reaction of DMC with the selected amines (**1**–**6**) tested under HP conditions.

Table 1. Reactions of DMC with aliphatic amines under high pressure[a]

Entry	Substrate	Product	Pressure (kbar)	Time (h)	Yield (%)
1	**1**	**7**	8	16	100
2	**1**	**7**	—	24	5
3	**1**	**7**	—	24[d]	10
4	**2**	**8**	8	16	96
5	**2**	**8**	—	24	5
6	**2**	**8**	—	24[d]	50
7	**3**	**9**	8	16	60
8	**3**	**9**	—	24	5
		10			70[c]
9	**3**	**9**	—	24[d]	5
		10			83[c]
10	**4**	**11**	8	16	100
11	**4**	**11**	—	24	42
12	**4**	**11**	—	24[d]	81
13	**5**	**12**	8	16	100[b]
14	**5**	**12**	8	3	100
15	**5**	**12**	8	0.5	90
16	**5**	**12**	1	16	100
17	**5**	**12**	0.05	16	80
18	**5**	**12**	—	24	51
		13			46[e]
19	**5**	**12**	—	24[d]	46
		13			30[e]
20	**6**	**14**	8	16	95
21	**6**	**14**	—	24	17
22	**6**	**14**	—	24[d]	60

[a]Room temperature, DMC/bis-amine ratio 10:1 (5:1 for each amino group).
[b]Yields estimated by ^{1}H NMR spectroscopy.
[c]Monocarbonylated product **10**.
[d]Reaction was conducted at 50 °C.
[e]Monocarbonylated product **13**.

in most reactions total conversion of amine to carbomethylated product occurred. For instance, reaction of benzyl amine **1** and DMC at 8 kbar for 16 h resulted in the total conversion of **1** to carbamate **7** (entry 1), as estimated by NMR analysis. Under identical reaction conditions (rt, 8 kbar, 24 h), propyl amine **2**, 1,3-diaminopropane **3**, diethylenetriamine **4**, bis-(3-aminopropyl)amine **5**, and triethylenetetramine **6** produced carbamates **8**, **9**, **11**, **12**, and **14** in good yields (60–100%) (entries 4, 7, 10, 13, and 20). Less reactive aromatic amines such as *m*-anisidine and aniline gave no reaction.

A comparison of different reaction conditons on the efficiency of biscarbomethylation reaction is illustrated for substrate **2** (Fig. 1, Table 1, entries 4–6). When the reaction time was shortened in the case of bis-(3-aminopropyl)amine **5** from 16 to 3 h, a similar result was obtained (entry 14). Further shortening of reaction time to 30 min gave somewhat smaller conversion to bis-carbamate (90%, entry 15). The reduction of pressure to 1 kbar did not affect full conversion to product **12** (entry 16), while further decrease in reaction pressure to 50 bar diminishes reaction yield

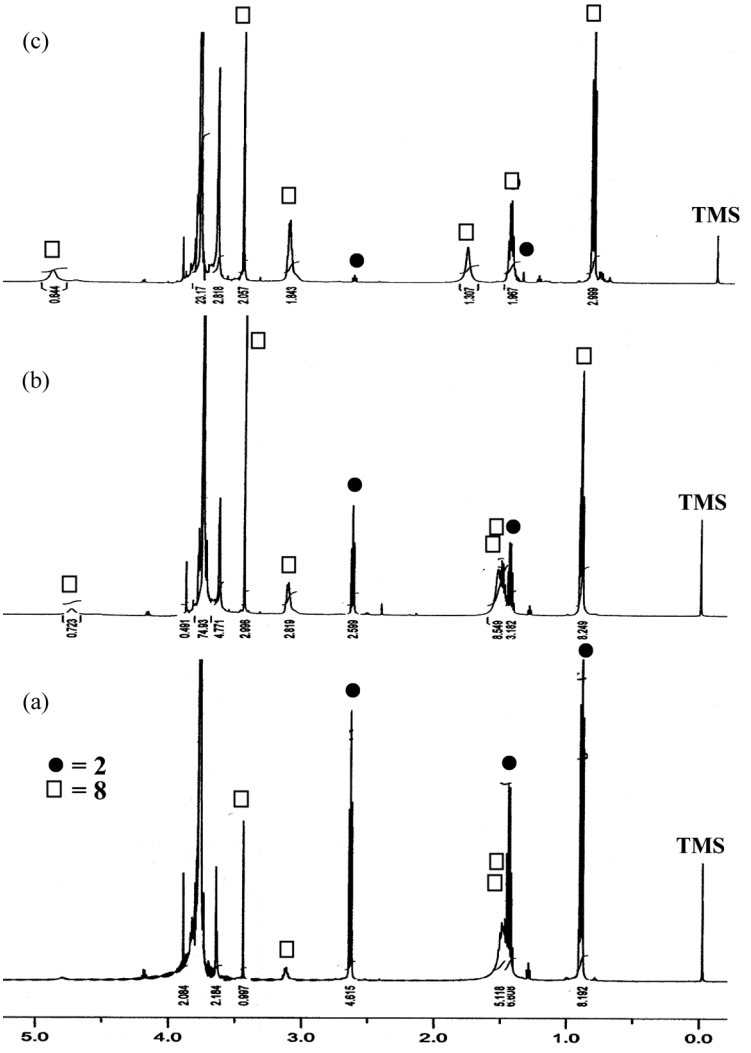
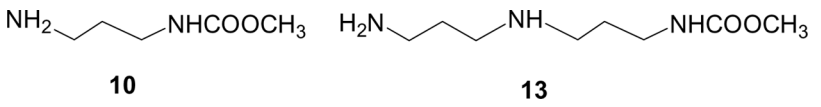


Figure 1. High field regions of ^{1}H NMR spectra for the reaction of **2** with DMC: (a) rt, 24 h (entry 6), (b) 50 °C, 24 h (entry 6), and (c) rt, 8 kbar, 16 h (entry 4).

to 80% (entry 17). It should be noted that in all experiments conducted under elevated pressure, no presence of monocarbamate was detected. Comparison of these results with experiments conducted under ambient pressure revealed that high pressure significantly enhances reaction rate even without catalysts employed. Reaction of **5** conducted at room temperature for 24 h afforded 51% of bis-carbamate **12** and 46% of monocarbamate **13** (entry 18, Scheme 2). Increase in temperature to 50 °C diminishes the reaction yield of both monocarbamate **13** and dicarbamate **12** (entry 19). Instead, formation of a side product, presumably cyclic urea, was evident.

It is interesting to note that the presence of a secondary amino group makes a significant difference in terms of reactivity toward DMC, leading to the unidentified



10 13

Scheme 2. Structure of monocarbamates **10** and **13** formed during the reaction of **3** (and **5**) with DMC under atmospheric pressure.

side reactions. These side reactions are evident only in the cases of triamines **4, 5**, and tetramine **6**, when reactions are conducted at atmosperic pressure at room temperature or at 50 °C (entries 11, 12, 21, and 22). No side reaction was detected in any experiment with diamine **3** (entries 7–9). Evidently, high-pressure conditions effectively suppressed all undesired side reactions.

CONCLUSIONS

In summary, the high-pressure synthesis of alkyl carbamate described herein provides access to the target molecules in an efficient and environmentally friendly way, even without catalyst added. It provides better conversion and selectivity than previously published procedures. Easy workup procedure and the absence of toxic or hardly removable side products are also highly advantageous. The reaction could be applied to different polyamines, providing they have at least one nonaromatic primary amino group. Furthermore, the presence of secondary amino groups does not affect reaction yield and composition of products.

EXPERIMENTAL

General Procedure

High-pressure reactions were performed using the high-pressure piston–cylinder apparatus, and pentane as piezotransmitter liquid in a high pressure Teflon vessels. Mixtures of DMC (900 mg, 10 mmol) and amine (2 mmol) were subjected to high pressure at room temperature for the time period indicated in Table 1. Excess of DMC was removed in vacuo to obtain products, which were analyzed by either gas chromatography (GC) or ^{1}H NMR spectroscopy. Products obtained in high-pressure reactions (with the exception of **9**) were of sufficient purity to be used without purification for further chemical transformations. All new compounds gave satisfactory spectroscopical data.

Selected Spectroscopic Data for Carbamates

Compound 7. ^{1}H NMR ($CDCl_3$): $\delta = 3.66$ (3H, s), 4.33 (2H, s), 5.41 (1H, br s), 7.27–7.28 (5H, m); ^{13}C NMR ($CDCl_3$): $\delta = 40.3$, 47.4, 122.6, 122.7, 123.9, 133.9, 152.5. CHN: calc. for $C_9H_{11}N_1O_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.34; H, 6.73; N, 8.39.

Compound 8. ^{1}H NMR ($CDCl_3$): $\delta = 0.66$ (3H, t, $J = 7.2$ Hz), 1.23–1.30 (2H, m), 2.86–2.87 (2H, m), 3.38 (3H, s), 5.51 (1H, br s).

Compound 9. ^{1}H NMR ($CDCl_3$): $\delta = 1.18$–1.27 (2H, m), 2.78–2.79 (4H, m), 3.22 (6H, s), 6.25 (2H, br s).

Compound 11. ^{1}H NMR ($CDCl_3$): $\delta = 1.50$ (1H, br s), 2.71–2.73 (4H, m), 3.18–3.18 (4H, m), 3.58 (6H, s), 5.29 (2H, s); ^{13}C NMR ($CDCl_3$): $\delta = 40.5$, 48.5, 51.9, 157.2. CHN: calc. for $C_{10}H_{21}N_3O_4$: C, 43.83; H, 7.82; N, 19.17. Found: C, 43.77; H, 7.76; N, 19.09.

Compound 12. ^{1}H NMR ($CDCl_3$): $\delta = 1.43$ (1H, br s), 1.64–1.65 (4H, m), 2.64 (4H, t, $J = 6.5$ Hz), 3.21–3.27 (4H, m), 3.63 (6H, s), 5.57 (2H, br s); ^{13}C NMR ($CDCl_3$): $\delta = 29.3$, 38.9, 46.9, 51.5, 157.1. CHN: calc. for $C_{10}H_{21}N_3O_4$: C, 48.57; H, 8.56; N, 16.99. Found: C, 48.58; H, 8.36; N, 17.02.

Compound 14. ^{1}H NMR ($CDCl_3$): $\delta = 1.77$ (2H, br s), 2.33–2.37 (4H, m), 2.60–2.62 (4H, m), 3.11–3.13 (4H, m), 3.60 (6H, s), 5.27 (2H, br s).

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