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Direct synthesis of *N*-methylurethanes from primary amines with dimethyl carbonate*

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Abstract: The mechanism of the reaction between amines with dimethyl carbonate (DMC) has been investigated. Whereas in the absence of bases, they give methylation and carboxymethylation reactions without selectivity ($B_{Al}2$ and $B_{Ac}2$ mechanisms, respectively), in the presence of bases, the $B_{Ac}2$ mechanism prevails. The carbamate already formed reacts further with DMC via the $B_{Al}2$ mechanism to give the corresponding *N*-methyl derivative. Such pronounced double selectivity has been explained in terms of Pearson's Hard–Soft Acid-Base (HSAB) theory.

Accordingly, *N*-methylcarbamates have been prepared from primary aliphatic and aromatic amines, either at reflux temperature of DMC (90 °C) or at 230 °C in autoclave. The reaction can be carried out in one step or through the isolation of the carbamate and the subsequent methylation reaction with DMC. This method is the direct synthesis, in high yield and selectivity, of secondary *N*-methylamines from the corresponding primary amines.

Keywords: Dimethyl carbonate; amines; carbamates; *N*-methylamines; green chemistry.

INTRODUCTION

Dimethyl carbonate (DMC) is a green reagent [1] whose ambident electrophilic properties have been reported [2]: its reaction with nucleophiles gives both methylation and carboxymethylation derivatives [3] (eqs. 1 and 2, respectively).

We recently evidenced that the selectivity among the two reaction pathways depends on the nature of the nucleophile [4]. In fact, harder nucleophiles react with the carbonyl of DMC (the harder electrophilic site) via $B_{Ac}2$ mechanism, while softer nucleophiles react with the methyl of DMC (the softer electrophilic site) via $B_{Al}2$ mechanism.

$$Y^- + CH_3OCOOCH_3 \rightleftharpoons Y\text{-}COOCH_3 + CH_3O^- \quad B_{Ac}2 \tag{1}$$

$$Y^- + CH_3OCOOCH_3 \longrightarrow Y\text{-}CH_3 + CH_3OCOO^- \quad B_{Al}2 \tag{2}$$

In some cases, such discrimination was shown to be complete: more than 99 % selectivity was obtained for the *O*-methylation of phenols and the mono-methylation of CH_2 acidic compounds like

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arylacetonitriles, arylacetates, aryloxyacetic esters, sulfones, sulfoxides, and lactones [5]. Actually, in the latter cases, the mono-methyl derivative is the final outcome of a series of reactions that proceed selectively. This particular selectivity has been explained in terms of Pearson's Hard–Soft Acid-Base (HSAB) theory [6]: operating in the presence of a base, the carbanion of a CH_2 acidic compound is hard in character and attacks the carbonyl of DMC via $B_{ac}2$ mechanism (eq. 3); the resulting softer nucleophile (because of the presence of the EWG group $COOCH_3$), now reacts with the methyl group of DMC via $B_{al}2$ mechanism (eq. 4). The anion CH_3O^- so formed is hard enough to react with the carbonyl and restores the DMC molecule.

The combination of the dual electrophilic character of DMC with its reaction products, allows two consecutive steps to occur selectively, to influence both reaction outcome and yields: at first, the hard–hard reaction occurs and produces a soft anion only; then, a soft–soft nucleophilic displacement leads to the final product. Since hard–soft and soft–hard interactions are inhibited by the HSAB theory, either double methylation and double carboxymethylation do not occur; as a result, the mono-methylated specie is obtained in very high yield (eq. 5).

$$ArCH^-X + CH_3OCOOCH_3 \rightleftharpoons ArCH(COOCH_3)X + CH_3O^- \quad (3)$$

$$ArC^-(COOCH_3)X + CH_3OCOOCH_3 \longrightarrow ArC(CH_3)(COOCH_3)X + CO_2 + CH_3O^- \quad (4)$$

$$ArC(CH_3)(COOCH_3)X + CH_3O^- \rightleftharpoons ArC^-(CH_3)X + CH_3OCOOCH_3 \quad (5)$$

As for nitrogen nucleophiles, we have already reported that primary aromatic amines with DMC undergo mono-*N*-methylation under continuous-flow conditions: mono-*N*-methyl anilines and their urethanes were continuously collected at the end of a plug-flow reactor, operating under gas–liquid phase-transfer catalysis (GLPTC) conditions: *N*,*N*-dimethylated products were present in trace amounts only (Table 1) [7].

Table 1 Continuous-flow reactions of aromatic primary amines with DMC under GL–PTC conditions, from ref. [7].

Entry	Amine	$ArNH_2$	MNM	DNM	Carbamate	NMCarbamate
1	Aniline[a]	54.3	40.8	1.6	trace	3.3
2	*o*-Toluidine[b]	27.7	47.0	0.3		25.0
3	*o*-Chloroaniline[b]	14.6	62.7			22.7
4	*p*-Chloroaniline[a]	10.1	70.0			19.9

K_2CO_3 coated with 5 wt% of PEG 6000; T = 180 °C.
[a]DMC/anilines molar ratio = 4.0.
[b]DMC/anilines molar ratio = 10.0. MNM = Mono *N*-Methylation; DNM = *N*,*N*-Dimethylation; NMCarbamate = *N*-Methylcarbamate.

The aim of this work is to explain the connection of the reactivity of primary aliphatic and aromatic amines with HSAB theory and the preparation of urethanes and their *N*-methyl derivatives, operating under basic conditions. We do not refer here to the reactions carried out in the presence of zeolites under acidic catalysis, since in the latter case selectivity and behavior follow yet-unexplored reaction pathways [8].

Different bases, temperatures, and conditions (atmospheric pressure and autoclave) have been investigated in order to obtain the desired products.

Actually, this method is the homologation of primary amines to the corresponding secondary *N*-methylamines, in high yield and selectivity, according to a one-step procedure.

RESULTS AND DISCUSSION

Unlike the mechanism that accounts for the reactions of CH_2 acidic compounds, eq. 6 is shifted to the right (compare eq. 3), and eq. 7 to the left (compare eq. 5): the decarboxymethylation of *N*-methyl urethanes does not occur spontaneously (eq. 8), and a successive hydrolysis is needed to produce the *N*-methylated amine.

$$RNH_2 + CH_3OCOOCH_3 \rightleftharpoons RNH(COOCH_3) + CH_3OH \quad B_{Ac}2 \tag{6}$$

$$RNH(COOCH_3) + CH_3OCOOCH_3 \longrightarrow RN(CH_3)(COOCH_3) + CO_2 + CH_3OH \quad B_{Al}2 \tag{7}$$

$$RN(CH_3)(COOCH_3) + CH_3OH \rightleftharpoons RNH(CH_3) + CH_3OCOOCH_3 \tag{8}$$

It is well known that bases significantly accelerate aminolysis and transamination reactions [9]. The base removes H^+ from protonated nitrogen during or after the attack, thereby increasing the negative charge on the nitrogen atom [10]. As we reported elsewhere [4], this behavior can be accounted in accordance with HSAB theory, since the presence of a base enhances the hardness of the nucleophile. Consequently, reactivity with harder electrophiles (the carbonyl carbon, in this case) is enhanced and aminolysis reactions proceed much faster.

We report here the reactions of aliphatic and aromatic amines in the absence and presence of strong bases, and the reaction of the urethanes with DMC in the presence of bases. The corresponding *N*-methyl derivatives can be obtained in one step either under atmospheric pressure at DMC reflux temperature (90 °C), or operating in autoclave at high temperatures. Reaction mechanisms are discussed in relation to the reaction outcomes.

Reaction of amines with DMC in the absence of bases

Without a base and at reflux temperature, aliphatic amines gave both alkylation and carboxymethylation reaction without appreciable selectivity (Table 2).

Table 2 Reaction of amines and DMC in the absence of a base.

Entry	Amine	T (°C)	Time (h)	MNM (%)	DNM (%)	Carbamate (%)
1	Benzylamine	90	6	12	6	4
2	Aniline	200	24	15	37	9

Conditions: Amine/DMC molar ratio: 1/40. MNM = Mono *N*-Methylation; DNM = *N,N*-Dimethylation.

As expected, aliphatic amines react faster, while aromatic ones need high temperature (and autoclave) to react in a reasonable time. They react via both $B_{Al}2$ and $B_{Ac}2$ pathways, and demonstrate the intermediate character of amine nitrogen toward DMC, in terms of hardness and softness.

Urethanes from amines in the presence of strong bases

Strong bases (potassium *tert*-butylate or sodium methoxide) catalyze the reaction of aliphatic and aromatic amines to give the corresponding carbamates quantitatively at 90 °C (eq. 9).

$$RNH_2 + CH_3OCOOCH_3 \xrightarrow{\text{base}} RNHCOOCH_3 + CH_3OH \tag{9}$$

In these conditions, high yields of carbamates are obtained in few minutes (Table 3). Since aliphatic amines are harder nucleophiles than aromatic ones, they react faster with the carbonyl of DMC (entries 3–7). No *N*,*N*-dimethyl derivates were observed.

Table 3 Reaction of amines and DMC in the presence of a base.

Entry	Amine	Time (min)	Base	Carbamate (%)
1	*p*-Anisidine[a]	25	C_4H_9OK	77
2	*p*-Chloroaniline[b]	20	C_4H_9OK	86.5
3	Benzylamine[c]	1	C_4H_9OK	100
4	*n*-Decylamine[d]	3	CH_3ONa	100
5	Hexane-1,6-diamine	10	CH_3ONa	100
6	*n*-Octylamine	5	CH_3ONa	100
7	Phenethylamine	5	CH_3ONa	100

Conditions: Reflux temperature. 90 °C; amine/base/DMC molar ratio: 1/1.2/40.
[a]After 18 h, 73 % of *N*-methylcarbamate.
[b]After 18 h, 87 % of *N*-methylcarbamate.
[c]After 0.5 h, 70 % of *N*-methylcarbamate.
[d]After 6 h, 78 % of *N*-methylcarbamate.

N-methylurethanes from amines in the presence of strong bases

If the reaction is protracted, the initially formed carbamates undergo further reaction with DM and give the corresponding *N*-methylurethanes (eq. 10 and Table 3). The base is necessary: no reaction occurs in its absence, as verified in an independent experiment.

$$RNHCOOCH_3 + CH_3OCOOCH_3 \xrightarrow{\text{base}} RN(CH_3)COOCH_3 + CO_2 + CH_3OH \quad (10)$$

However, the reaction needs to be carried out in the absence of atmospheric carbon dioxide, as it reacts with the base and methylation reactions come to a stop. Under the conditions of entry 4, Table 3, *n*-decylamine was reacted with DMC under nitrogen atmosphere: after 3 min, 100 % of the carbamate was produced.

Ninety-nine percent of $n\text{-}C_{10}H_{21}N(CH_3)COOCH_3$ was obtained only after 21 h at reflux temperature (20 % after 2 h, and 46 % after 5 h).

The behavior of amines in the presence and in the absence of a base reported on Tables 2 and 3 confirms that, since the hardness of the nucleophile is increased while operating in the presence of a base, the $B_{Ac}2$ rate is dramatically accelerated, and carboxymethyl derivatives are quantitatively obtained. Once formed, the urethanes need the presence of a base to further react with DMC. In these conditions, their RN^-COOCH_3 anions, softer nucleophiles than RNH_2, undergo solely $B_{Al}2$ reactions. No $RN(COOCH_3)_2$ products—deriving from a double $B_{Ac}2$ reaction—were observed under such conditions.

N-methylurethanes from amines in the presence of K_2CO_3

Weaker bases like potassium carbonate can be used instead of alkoxides. Higher temperatures must be used, and the reaction is performed in an autoclave; at that temperature, the direct formation of monomethyl and dimethyl derivatives cannot be totally avoided (eqs. 11 and 12); they come from two consecutive $B_{Ac}2$ mechanisms.

$$RNH_2 + CH_3OCOOCH_3 \longrightarrow RNHCH_3 + CO_2 + CH_3OH \quad (11)$$

$$RNHCH_3 + CH_3OCOOCH_3 \longrightarrow RN(CH_3)_2 + CO_2 + CH_3OH \quad (12)$$

In these conditions, harder amines react in 22 h and give the corresponding carbamates and *N*-methylcarbamates, while mono- and dimethyl derivatives, if any, are present in lower amount (entries 3 and 4, Table 4); anilines react slower, and their softness is responsible for the formation of mono- and dimethylated products in higher amount.

Table 4 Reactions of aliphatic and aromatic amines in the presence of K_2CO_3 after 22 h.

Entry	Amine	Substrate	MNM	DNM	Carbamate	NMCarbamate
1	Aniline	41.8	6.2	2.6	8.3	41.0
2	*p*-Chloroaniline	38.4	6.3	2.1	5.7	47.5
3	*p*-Anisidine	0.5	1.3	13.4	1.8	83.0
4	*n*-Octylamine	—	—	1.2	53.7	45.0
5	Phenethylamine	—	—	—	77.0	23.0

Conditions: T = 180 °C; amine/DMC/K_2CO_3 molar ratio: 1/3/40.
MNM = Mono-*N*-Methylation; DNM = *N*,*N*-Dimethylation; NMCarbamate = *N*-Methylcarbamate.

Two steps preparation of *N*-methylurethanes

Another route to the *N*-methylcarbamate is the standard two-step procedure: first, the synthesis of the carbamate at reflux temperature, according to the condition of Table 2, is completed; then, the subsequent methylation is carried out in autoclave at 230 °C with K_2CO_3 as a base (Table 5). Because of the high temperature, reaction time is reduced, while *N*,*N*-dimethylation products were not observed.

Table 5 Reactions of carbamates with DMC in the presence of K_2CO_3, after 4 h.

Entry	Carbamate	*N*-Methylcarbamate (%)
1	*p*-$CH_3OPhNHCOOCH_3$	95
2	$PhNHCOOCH_3$	100
3	*n*-$C_8H_{17}NHCOOCH_3$	97
4	$PhCH_2CH_2NHCOOCH_3$	100

Conditions: Temperature: 230 °C, Carbamate/K_2CO_3/DMC molar ratio: 1/3/40.

CONCLUSIONS

The reactivity of amines with DMC can be explained according to the HSAB theory, since DMC molecule presents an ambident electrophilic character: it reacts with hard nucleophiles (amines in the presence of strong bases) according to a $B_{Ac}2$ mechanism, and the carbonyl group is involved. The anions of the so-produced urethanes, being softer in character, react now according to a $B_{Al}2$ mechanism with the softer part of the molecule, the methyl group, and give the *N*-methyl derivatives.

The combination of the dual electrophilic character of DMC with its reaction products allows two consecutive steps to occur in a selective way. Since hard–soft and soft–hard interactions are inhibited, either double methylation and double carboxymethylation do not occur. Accordingly, primary amines give the corresponding *N*-methyl secondary derivatives in high yield and selectivity, without appreciable production of *N*,*N*-dimethyl compounds.

The results of Tables 4 and 5 compared with those already described on Table 1 [7] show that operating under batch conditions it is not possible to complete in one step the transformation of primary

amines into secondary amines. In fact, reaction 8 is prevented and a further hydrolysis procedure is needed for obtaining pure *N*-methyl amines. However, selectivity is high and work-up easy; moreover, once the reason of the mechanism according to the HSAB theory is understood, one can perform carboxylation reaction and alkylation reaction with different alkyl carbonates and alkylating agents, respectively, in order to get the desired product in the easier way.

EXPERIMENTAL SECTION

All used compounds were ACS grade and were employed without further purification.

GC analyses were performed using a 30-m, CP-sil 24 CB capillary column. GC–MS analyses were performed on a mass detector at 70 eV coupled to a gas chromatograph fitted with a 30-m capillary column. All reaction compounds were compared with authentic samples.

Preparation of carbamates with strong bases at reflux temperature (Table 3): The reactions were carried out in a three-necked, 100-mL round-bottomed flask with a reflux condenser and a magnetic bar. Amines (9.3 10^{-3} mol: *p*-anisidine, *p*-chloroaniline, benzylamine, *n*-decylamine, hexane-1,6-diamine, *n*-octylamine, and phenethylamine), the base and DMC were charged in a 1.0/1.2/40 molar ratio respectively, under a flux of N_2 to remove the possible CO_2 formed as by-product (DMC is the solvent of the reaction). The bases employed were sodium methylate or potassium *tert*-butoxide. Temperature was 90 °C (reflux of DMC).

Preparation of *N*-methylcarbamates in the presence of K_2CO_3 (Table 4): The amine (9.3 10^{-3} mol), K_2CO_3, and DMC were charged in a 1.0/3.0/40 molar ratio respectively and were charged in a 250-mL autoclave equipped with a sample tube and a magnetic bar. The autoclave was heated with an electric mantle at 180 °C.

Two steps preparation of *N*-methylcarbamates (Table 5): The carbamates (9.3 10^{-3} mol) prepared and isolated according to the above-described procedure, were introduced in stainless steel autoclave (250 mL) equipped with a sample tube and a magnetic bar; K_2CO_3 and DMC were charged in a 1.2 and 40 molar ratio with respect to the carbamate.

The reaction temperature was 230 °C (DMC is the solvent of the reaction).

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