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Synthesis of Carbamates from Amines and Dialkyl Carbonates: Influence of Leaving and Entering Groups

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Abstract: A number of carbamates were synthesised through a halogen-free process by reacting amines with symmetrical and unsymmetrical carbonates. The results obtained showed a specific trend of preferred leaving groups (in the dialkyl carbonates) depending on whether a catalyst or a base was used. On the other hand, investigations conducted on the preferred entering groups (amines) for the synthesis of carbamates showed the same trend regardless of whether a catalyst or a base was used. Finally, in accordance with the results obtained, it was possible to synthesise sterically hindered carbamates in high yield by transesterification of methyl carbamate with a sterically hindered alcohol.

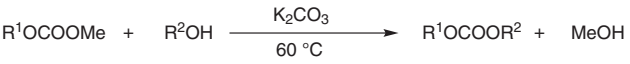
Key words: green chemistry, amine, dialkyl carbonate, carbamate, protecting groups

Carbamates are very useful compounds that are widely used in the synthesis of pesticides, fungicides, herbicides, pharmaceuticals, cosmetics and polyurethanes, in addition to being employed as protecting groups.[1] Industrially, carbamates are synthesised predominantly through the reaction of the relevant amine with phosgene[2] in a process that is highly toxic and produces large volumes of waste. In order to improve this phosgene-based synthetic procedure, many environmentally benign pathways have been investigated, for example, oxidative carbonylation, reductive carbonylation and methoxy carbonylation.[3] In particular, one of the most promising substitutes for phosgene as a carboxylating agent is dimethyl carbonate (DMC). This is a green reagent that is mainly produced in China by insertion of CO_2 into epoxides and cleavage of the resulting cyclic carbonate with methanol.[4] Direct synthesis of DMC from methanol and CO_2 has also been recently reported.[5]

Reactions between amines and DMC, as well as other symmetrical carbonates, have been investigated, and these studies have led to good yields of the respective carbamate. However, this process is not atom efficient due to the presence of the related alcohol as by-product.[6,7]

Another approach to the synthesis of carbamates is using the reaction of urea with symmetrical carbonates. This process is very efficient, although it can be used only when the two components (urea and carbonate) are either both aliphatic or both aromatic, which limits the possible number of accessible products.[8]

In this work we investigated the synthesis of carbamates by employing a new class of carbonates: unsymmetrical carbonates. Alkyl methyl carbonates are interesting because they can lead to the synthesis of different substituted carbamates depending on the preference of the leaving group. In fact, recent studies on the reaction of alcohols with methyl alkyl carbonates have shown that the methoxy anion's ability to act as a leaving group results in the preferential formation of the most hindered carbonate (Scheme 1).[9]

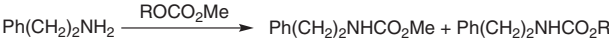


Scheme 1 Reaction of unsymmetrical carbonates with an alcohol

An immediate exploitation of the corresponding reaction with an amine would be the synthesis of *tert*-butoxycarbonyl (Boc) protected nitrogen through benign pathways. In fact, due to the prevalence of Boc-protected amines, which are usually formed by the reaction of an amine with di-Boc (currently still prepared from phosgene), this novel pathway would represent a significant advancement in chemistry beyond the use of halogens.

In this respect, the present work reports a study on the reactions of an amine with unsymmetrical carbonates, as well as on an investigation into the reactions of symmetrical dialkyl carbonates with a range of substituted amines. The data obtained will help to establish a scale of leaving and entering groups that will extend our knowledge on the reactivity of amines with unsymmetrical and symmetrical carbonates for the synthesis of carbamates.

Thus, a first set of experiments (Table 1) was carried out in order to investigate the reactivity of a primary amine, (2-phenylethyl)amine, with several unsymmetrical carbonates (1:2 molar ratio) in the presence of a catalyst at 60 °C.[10] The reaction was monitored by ^{1}H NMR spectroscopy (see Supporting Information). A catalytic amount of zinc acetate (5% mol) was employed, as at



Scheme 2 Reaction of unsymmetrical carbonates with (2-phenylethyl)amine

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Table 1 Reactions of Unsymmetrical Carbonates with (2-Phenylethyl)amine in the Presence of $Zn(OAc)_2$[a]

$ROCO_2Me$ R	Conv. (%)	Product distribution (mol%)	
		$Ph(CH_2)_2NHCO_2Me$	$Ph(CH_2)_2NHCO_2R$
n-Oct	69.5	26.5	43.0
i-Pr	69.4	25.5	43.9
Bn	63.1	40.7	22.5
t-Bu	4.8	1.5	3.3

[a] Reaction conditions: $ROCO_2Me$ (2 equiv), $Ph(CH_2)_2NH_2$ (1 equiv), $Zn(OAc)_2$ (0.05 equiv), 60 °C, 48 h.

higher loading, no significant increase in the rate of reaction was observed.

The most significant result is that the reaction between (2-phenylethyl)amine and *tert*-butyl methyl carbonate occurs at a slower rate than with any other carbonate. This observation was expected and is most likely due to the steric effect of the bulky carbonate. Secondly, the methoxy anion was found to be a better leaving group in comparison to others derived from aliphatic alcohols, with a 2:1 ratio of selectivity in favour of *N*-phenylethyl alkyl carbamate. However, when benzyl methyl carbonate was reacted with the amine, the methyl carbamate was preferentially obtained. It is also unusual that, while the anion derived from a benzyl alcohol was shown to be a better leaving group than that derived from methanol, the benzyl methyl carbonate was less reactive than the octyl or prop-2-yl methyl carbonate, which resulted in a lower conversion of the amine into the carbamate.

Table 2 Reactions of Unsymmetrical Carbonates with (2-Phenylethyl)amine in the Presence of *t*-BuOK[a]

$ROCO_2Me$ R	Time (min)	Conv. (%)	Product distribution (mol%)	
			$Ph(CH_2)_2NHCO_2Me$	$Ph(CH_2)_2NHCO_2R$
n-Oct	60	100	55.7	44.3
i-Pr	60	100	68.2	31.8
Bn	10	100	58.0	42.0
t-Bu	2 h	25.8	18.0	7.8

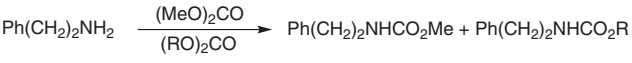
[a] Reaction conditions: $ROCO_2Me$ (2 equiv), $Ph(CH_2)_2NH_2$ (1 equiv), *t*-BuOK (0.25 equiv), 60 °C.

As expected, a trend of increasing leaving group ability from the *tert*-butoxide through to the methoxy moiety was found: $BnO^- > MeO^- > OctO^-$ *i*-$PrO^- > t$-BuO^-.

A similar set of experiments was then carried out using potassium *tert*-butoxide to observe if the amine reacts differently in the presence of a strong base.[10] A 25 mol% loading of base was used to achieve a rate of reaction slow enough to allow the carbamate formation to be followed by ^1H NMR analysis; Table 2 summarises the results obtained.

The data shows that the use of a strong base leads to the formation of different products to those observed when a zinc catalyst is used. The trend of best leaving groups is opposite to that inherent in the previous set of experiments. Thus, phenylethyl methyl carbamate was observed as the main product in all the reactions. In addition, the overall rate of reaction is faster. The sterically hindered *tert*-butyl methyl carbonate was the least reactive carbonate, while benzyl methyl carbonate was the most reactive. Reactions involving *tert*-butyl methyl carbonate and prop-2-yl methyl carbonate showed an approximate 2:1 selectivity in favour of the methyl carbamate; exhibiting an opposite trend to the results seen in Table 1. However, in the reactions between the amine and either octyl methyl carbonate or benzyl methyl carbonate, no significant selectivity was observed.

To support the findings of these preliminary investigations, a series of competitive reactions was carried out between equal quantities of two symmetrical carbonates and (2-phenylethyl)amine, in the presence of zinc acetate (Table 3) or potassium *tert*-butoxide (Table 4).[11]



Scheme 3 Competitive reaction of two symmetric carbonates and (2-phenylethyl)amine

The results achieved in the presence of a catalyst (Table 3) are consistent with those obtained with unsymmetrical carbonates (Table 1). The relative distributions of phenylethyl methyl and phenylethyl alkyl carbamates are consistent with those observed in Table 1, but the selectivity towards phenylethyl methyl carbamate is higher. However di-*tert*-butyl carbonate did not react under these conditions.

Table 3 Competition of Symmetrical Carbonates with (2-Phenylethyl)amine in the Presence of $Zn(OAc)_2$[a]

Carb. **1**	Carb. **2**	Amine Conv. (%)	Product distribution (mol%)	
			$Ph(CH_2)_2NHCO_2Me$	$Ph(CH_2)_2NHCO_2R$
$(MeO)_2CO$	$(BnO)_2CO$	71.1	17.8	53.3
$(MeO)_2CO$	$(i\text{-}PrO)_2CO$	59.9	56.0	3.9
$(MeO)_2CO$	$(n\text{-}OctO)_2CO$	51.4	45.5	5.9
$(MeO)_2CO$	$(t\text{-}BuO)_2CO$	51.5	51.5	0

[a] Reaction conditions: $MeOCO_2Me$ (2 equiv), $ROCO_2R$ (2 equiv), $Ph(CH_2)_2NH_2$ (1 equiv), $Zn(OAc)_2$ (0.05 equiv), 60 °C, 48 h.

Table 4 Competition of Symmetrical Carbonates with (2-Phenylethyl)amine in the Presence of *t*-BuOK[a]

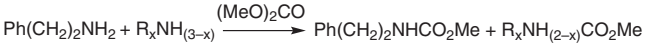
Carb. **1**	Carb. **2**	Conv. (%)	Product distribution (% mol) after 60 min	
			$Ph(CH_2)_2NHCO_2Me$	$Ph(CH_2)_2NHCO_2R$
$(MeO)_2CO$	$(BnO)_2CO$	100[b]	53.1	46.9
$(MeO)_2CO$	$(i\text{-PrO})_2CO$	100[c]	77.3	22.7
$(MeO)_2CO$	$(n\text{-OctO})_2CO$	100[d]	57.2	42.8
$(MeO)_2CO$	$(t\text{-BuO})_2CO$	100	100	0

[a] Reaction conditions: $MeOCO_2Me$ (2 equiv), $ROCO_2R$ (2 equiv), $Ph(CH_2)_2NH_2$ (1 equiv), *t*-BuOK (0.25 equiv), 60 °C.
[b] After 5 min.
[c] After 30 min.
[d] After 10 min.

The results obtained by reacting (2-phenylethyl)amine with symmetrical carbonates in the presence of potassium *tert*-butoxide (Table 4) correlate with those detailed in Table 2, although following a more distinct trend. The methyl carbamate was the main product in all cases, although in the reactions involving dioctyl and dibenzyl carbonate, the selectivity was not high. However, it is evident from the results obtained that the reactivity of the carbonate, which appears to be in direct correlation with its steric bulk, plays a more significant role than the possible transesterification reactions between the carbonates.

The most likely explanation for the data presented here is that the formation of the carbamate in the presence of a catalyst occurs through direct nucleophilic attack upon the carbonate. In the presence of a base, the amine also forms the carbamate by nucleophilic attack, but in this case the carbamate is able to undergo transesterification with the alcohol, which is the main reaction by-product. The results shown in Table 2 suggest that primary alcohols partake in transesterification of carbamates more readily than secondary or tertiary alcohols, hence, the selectivity observed in the reactions of octyl or benzyl methyl carbonate is not significant. On the other hand, there is a pronounced selectivity in *tert*-butyl or prop-2-yl methyl carbonate. The effect is less evident in the data given in Table 4 as the symmetrical carbonate first needs to undergo nucleophilic attack in order to produce the alcohol to then partake in transesterification of the carbamate.

As part of this investigation, a series of competitive reactions between a range of amines and DMC was also carried out to determine the reactivity of the entering groups (Table 5).[12]



Scheme 4 Competitive reaction of dimethyl carbonate with different amines (x = 1 or 2)

The results presented here demonstrate that primary aliphatic amines reacted significantly faster than (2-phenylethyl)amine, since the reactions of the former reached equilibrium in 24 hours. The secondary amine, dibutylamine, was too sterically hindered to be able to attack the dimethyl carbonate. Aniline did not react at all, presumably because aromatic amines are weaker nucleophiles than aliphatic amines.[6]

Table 5 Competition of Amines with Dimethyl Carbonate in the Presence of $Zn(OAc)_2$[a]

Amine **1**	Amine **2**	Product distribution (mol%) after 48 h	
	$[R_xNH_{(3-x)}]$	$Ph(CH_2)_2NHCO_2Me$	$R_xNH_{(2-x)}CO_2Me$
$Ph(CH_2)_2NH_2$	$n\text{-BuNH}_2$[b]	83.8	100.0
$Ph(CH_2)_2NH_2$	$n\text{-OctNH}_2$[b]	86.0	100.0
$Ph(CH_2)_2NH_2$	$(n\text{-Bu})_2NH$	85.3	0.0
$Ph(CH_2)_2NH_2$	$BnNH_2$	74.1	78.8
$Ph(CH_2)_2NH_2$	$PhNH_2$	67.5	0.0

[a] Reaction conditions: $Ph(CH_2)_2NH_2$ (1 equiv), $R_xNH_{(3-x)}$ (1 equiv), DMC (4 equiv), $Zn(OAc)_2$ (0.1 equiv), 60 °C (x = 1 or 2).
[b] Reaction complete after 24 h.

Table 6 Competition of Amines with Dimethyl Carbonate in the Presence of *t*-BuOK

Amine **1**	Amine **2**	Product distribution (mol%) after 5 min	
		$Ph(CH_2)_2NHCO_2Me$	$R_xNH_{(2-x)}CO_2Me$
$Ph(CH_2)_2NH_2$	$n\text{-BuNH}_2$	94.4	98.2
$Ph(CH_2)_2NH_2$	$n\text{-OctNH}_2$	93.9	98.5
$Ph(CH_2)_2NH_2$	$(n\text{-Bu})_2NH$	96 (100)[b]	5.9 (49)[c]
$Ph(CH_2)_2NH_2$	$BnNH_2$	97.6	89.0
$Ph(CH_2)_2NH_2$	$PhNH_2$	91.1	0.0

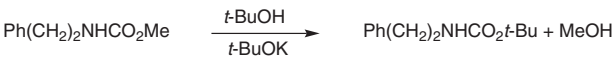
[a] Reaction conditions: $Ph(CH_2)_2NH_2$ (1 equiv), $R_xNH_{(3-x)}$ (1 equiv), DMC (4 equiv), *t*-BuOK (0.25 equiv), 60 °C (x = 1 or 2).
[b] Product formed after 10 min.
[c] Product formed after 2 h.

The results of competitive reactions carried out in the presence of a base (Table 6) were similar to those obtained in the presence of zinc acetate, with aliphatic amines reacting faster than (2-phenylethyl)amine.[12]

The competitive reaction between (2-phenylethyl)amine, and dibutylamine shows that 49% of the secondary amine was converted into the corresponding carbamate after two hours at 60 °C. These data clearly indicate that steric hindrance is less of an obstacle to the formation of a carbamate when the reaction is carried out in the presence of a strong base. Under these mild conditions aniline did not react.

The results reported in Tables 5 and 6 follow the expected trend of increasing rate of reaction of the amine with increasing pK_a values.[13] Butylamine has the highest pK_a, while aniline has the lowest; in the case of dibutylamine, the steric effect is more important in determining the rate of reactivity. Thus, the reactivity of the entering groups follows the trend: $BuNH_2$, $OctNH_2$ > $Ph(CH_2)_2NH_2$, $BnNH_2$ >> $(Bu)_2NH$ >> $PhNH_2$.

Finally, while good selectivity towards a more hindered carbamate is possible when reacting an amine with an unsymmetrical carbonate in the presence of a catalyst, the rate of reaction is far too slow to be viable. However, a methyl carbamate can be formed very quickly and this is surely a great advantage. In fact, according to the data collected here, if the methyl carbamate is reacted with an excess of alcohol in the presence of a strong base (Scheme 5), it is possible to recover sterically hindered carbamates in high yield (~70%) via transesterification.



Scheme 5 Transesterification of methyl carbamate with an alcohol

Table 7 reports the formation of a more hindered carbamate via transesterification of a methyl carbamate after a relatively short time when reacting carbamates derived from primary amines.[14] Carbamates derived from secondary amines are too sterically hindered to allow the reaction to progress at an appreciable rate with primary alcohols, and not at all with more bulky reagents. There appears to be little difference between the reactivity of carbamates derived from primary aliphatic and aromatic amines, with both giving good yields when reacted with octan-1-ol and *tert*-butanol. It is also clear that primary alcohols undergo transesterification more readily than bulky alcohols, which supports the findings reported in Tables 2 and 4.

It is also noteworthy that, as a result of the transesterification with *tert*-butanol, the nitrogen within a *tert*-butyl carbamate is Boc-protected. Thus, this process can open up the way to a new methodology for N-protection in organic chemistry.

In this respect, a number of transesterification reactions were carried out at differing temperatures in order to achieve the Boc-protected amine in higher yield;[15] Figure 1 shows the results obtained. It is clear that reaction time has a greater overall effect upon the yield of *tert*-butyl carbamate than increasing the temperature. Comparing the results obtained after two hours at 60 °C and 19 hours at 90 °C, the ratio of butyl to methyl carbamate changes from roughly 60:30 to 80:20, with less free amine present. On the other hand, comparing the results obtained after 19 hours at 60 °C and 90 °C, shows the same ratio of carbamates but with a lower degree of N-methylation. In fact, it is known that, at higher temperature, the nitrogen of the carbamate acts as a soft nucleophile leading to the methyl derivative.[6,16]

Table 7 Formation of Hindered Carbamate via Transesterification[a]

Carbamate	Alcohol	Product distribution (mol%)		
		Me carbamate	R carbamate	Free amine
n-OctNHCO$_2$Me	*n*-OctOH	30.7	67.9	1.4
n-OctNHCO$_2$Me	*t*-BuOH	36.1	57.5	6.4
Ph(CH$_2$)$_2$NHCO$_2$Me	*n*-OctOH	27.7	69.7	2.7
Ph(CH$_2$)$_2$NHCO$_2$Me	*t*-BuOH	33.2	57.5	9.3
(*n*-Bu)$_2$NCO$_2$Me	*n*-OctOH	94.4	3.3	2.3
(*n*-Bu)$_2$NCO$_2$Me	*t*-BuOH	100.0	0.0	0.0

[a] Reaction conditions: $R_xN_{(2-x)}CO_2Me$ (1 equiv), ROH (10 equiv), *t*-BuOK (1.25 equiv), 60 °C, 2 h.

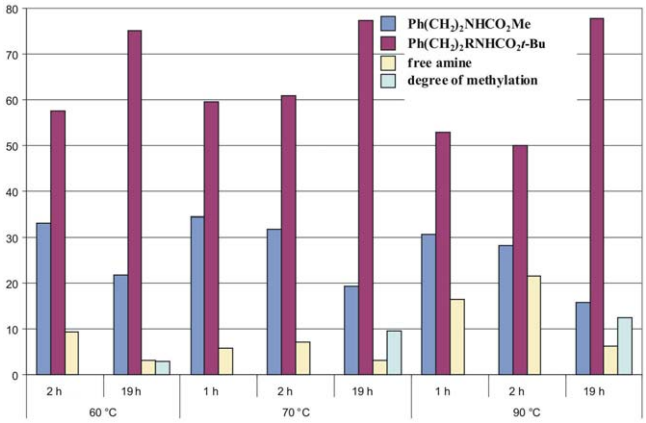


Figure 1 Formation of *N*-phenylethyl *tert*-butyl carbamate via transesterification[15]

In conclusion, the reaction of amines with carbonates in the presence of a catalyst follows the same trend of leaving groups observed for the alcohols in the presence of a weak base. Unsymmetrical carbonates always lead to the more hindered product, with the sole exception of benzyl methyl carbonate. Reactions with symmetrical carbonates confirmed the order of leaving groups, albeit with a more distinct trend. The scale of entering groups followed the expected trend, with reactivity being dictated by the pK_a of the amines, with the exception of dibutylamine, where steric hindrance dominates.

The reaction of amines with carbonates in the presence of a strong base gave quite different results to those of alcohols. This is due to the transesterification of the carbamate taking place after nucleophilic attack by the amine. In these cases, the readiness of an alcohol to undergo trans-

esterification had the greatest influence on the results obtained. Finally, the results achieved have enabled a rapid route to the synthesis of various carbamates (including *tert*-butyl carbamate) by tuning of the transesterification equilibrium.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) General procedure for the reaction of unsymmetrical carbonates with (2-phenylethyl)amine (Table 1 and Table 2): In a 25 mL round-bottom flask, the amine (9.30 mmol) and the carbonate (18.50 mmol) were added, followed by either zinc acetate (0.46 mmol) or potassium *tert*-butoxide (2.30 mmol). The reaction mixture was heated to 60 °C with continuous agitation. Samples were taken at regular time intervals and analysed by ^{1}H NMR spectroscopy (see Supporting Information).

(11) General procedure for the reaction of symmetrical carbonates with (2-phenylethyl)amine (Table 3 and Table 4). In a 25 mL round-bottom flask, the amine (9.30 mmol), DMC (18.50 mmol) and the carbonate (18.50 mmol) were added, followed by either zinc acetate (0.46 mmol) or potassium *tert*-butoxide (2.30 mmol). The reaction mixture was heated to 60 °C with continuous agitation. Samples were taken at regular time intervals and analysed by ^{1}H NMR spectroscopy (see Supporting Information).

(12) General procedure for the reaction of amines with dimethyl carbonate (Table 5 and Table 6). In a 25 mL round-bottom flask, phenyl ethyl amine (4.65 mmol) the selected amine (4.65 mmol) and DMC (18.50 mmol) were added, followed by either zinc acetate (0.460 mmol) or potassium *tert*-butoxide (1.60 mmol). The solution was heated to 60 °C with continuous agitation. Samples were taken at regular time intervals and analysed by ^{1}H NMR spectroscopy (see Supporting Information).

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(14) General procedure for the transesterification of a urethane with an alcohol Table 7: In a 25 mL round-bottom flask, the urethane (9.30 mmol) and the alcohol (93.00 mmol) were added, followed by potassium *tert*-butoxide (11.60 mmol). The contents were heated to 60 °C with continuous agitation. Samples were taken at regular time intervals and analysed by ^{1}H NMR spectroscopy.

(15) General procedure for the transesterification of methyl carbamates with alcohols (Table 7). In a 25 mL round-bottom flask, the selected methyl carbamate (9.30 mmol) and the selected alcohols (93.00 mmol) were added, followed by potassium *tert*-butoxide (11.60 mmol). The solution was heated to the relevant temperature with continuous agitation. Samples were taken at regular time intervals and analysed by ^{1}H NMR spectroscopy (see Supporting Information).

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