

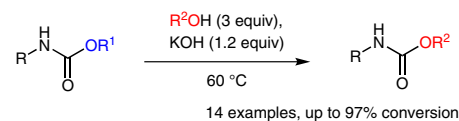
Base-Catalyzed Transcarbamoylation

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Abstract Inorganic bases such as NaH, KOt-Bu, NaOH, or KOH are efficient catalysts to promote the transcarbamoylation reaction between urethanes and a variety of primary and secondary alcohols under mild conditions. They constitute an alternative to organometallic catalysis and can be applied to aliphatic or aromatic urethanes.

Key words urethane, carbamate, transcarbamoylation, transurethanization, base

Urethanes as well as ureas are classically prepared starting from isocyanate reactants or intermediates.^{1–3} Isocyanates such as 4,4'-diphenylmethane diisocyanate (MDI) and toluenemethyl diisocyanate (TDI) are widely used in polymer chemistry to prepare polyurethanes. To avoid the use of toxic isocyanates,⁴ various synthetic sustainable routes have been investigated,⁵ including the ring-opening polymerization of cyclic carbonates with diamines⁶ or ring-opening polymerization of aliphatic cyclic urethanes.⁷ However, most of these isocyanate-free routes do not allow segmented polyurethanes, commonly used commercially, to be obtained. To synthesize these commercial polyurethanes, new routes have been developed by using a transcarbamoylation between a diol and a diurethane in the presence of a titanium or a tin catalyst.^{8,9} A bicyclic organic base, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) can also be used catalyze this reaction.¹⁰ This transcarbamoylation, also called transurethanization, involves the reaction of an alcohol with a carbamate group **1** to obtain a new carbamate **2** (Scheme 1). This reaction has also been studied on small molecules for its application in organic synthesis.¹¹ Several metal catalysts are known to be able to activate the carbonyl group and catalyze transcarbamoylation,¹² such as titanium(IV)

isopropoxide,¹³ tin,¹⁴ bismuth triflate,¹⁵ zinc acetate,¹⁶ or lanthanum(III)^{17,18} salts. However, these reaction conditions require rather high temperatures, around 100 °C, and the metal catalysts can be hard to remove from the product.



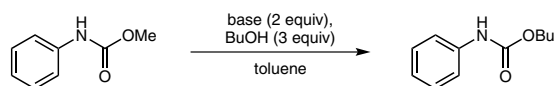
Scheme 1 Transcarbamoylation reaction of a urethane (R^1 = aliphatic or aromatic group and R^2 = aliphatic group)

Bases such as sodium hydroxide or metal alkoxides are often used for transesterification reactions¹⁹ and they are known to be more efficient than acid catalysts.²⁰ The transcarbamoylation reaction is similar but it requires a higher energy input, as the urethane carbon is far less electrophilic than an ester carbon. Even though these two reactions are very similar mechanistically, little work has been carried out on transcarbamoylation.

Most examples of transcarbamoylation have been reported for ring-closing reactions and involve the use of strong bases such as LiHMDS,²¹ sodium hydride,^{22,23} or sodium methoxide.²⁴ Thus, the reaction mixture has to be heated for reaction to occur, sometimes at temperatures up to 200 °C in the latter case. In some circumstances, with highly reactive carbamates, such as sulfonyl carbamates, transcarbamoylation occurs simply by heating with an alcohol.¹¹ To the best of our knowledge, the only example of this reaction catalyzed by soft bases was published by Tundo et al. who showed that potassium *tert*-butoxide at 60 °C could catalyze this reaction to give new carbamates or Boc-protected amines.²⁵ They performed the reaction in pure alcohol (10 equiv) without additional solvent and observed the formation of undesired amine as a side product.

In this Letter, we describe the reaction conditions of transcarbamoylation using inorganic bases to avoid formation of side products. Different inorganic bases were compared for this reaction and we studied the impact of parameters such as temperature, substrate and concentration of base, and alcohol on transcarbamoylation. We show herein that bases milder than the ones classically used allow transcarbamoylation with good conversions under mild conditions. Using inorganic bases as catalysts, the reaction can be performed under gentle heating (60 °C).

Table 1 Impact of the Base on Reaction Conversion^a



Entry	Base (2 equiv)	Conversion (% ^b , <i>t</i> = 4 h)	Conversion (% ^c , <i>t</i> = 20 h)
1	LiOH	0	3
2	NaOH	38	87
3	KOH	70	95
4	KOt-Bu	47	88
5	NaH	41	45
6	TBD	23	90
7	N(CH ₂ CH ₃) ₃	0	0
8	DABCO	0	0
9	–	0	0

^a Reaction conditions: PhNHCO₂Me (1 equiv, 0.3 M in toluene), BuOH (3 equiv), 60 °C.

^b Determined by HPLC analysis.

^c Determined by HPLC and NMR analysis.

First, the impact of the base was studied. Conversions of methyl *N*-phenylcarbamate to butyl *N*-phenylcarbamate via transcarbamoylation, determined by HPLC (Figure S1) or NMR analysis (Figure S2) are summarized in Table 1. Various hydroxides (2 equiv) were used with only three equivalents of alcohol and compared to stronger bases such as sodium hydride and potassium *tert*-butoxide. Lithium hydroxide was ineffective (Table 1, entry 1), possibly due to its poor dissociation in toluene. Sodium hydroxide catalyzed the reaction, but with potassium hydroxide as a base the reaction was faster (Table 1, entry 2). Sodium hydride did not result in full conversion into the desired product (Table 1, entry 5), probably because it can also deprotonate the more acidic urethane. Potassium hydroxide was therefore chosen for the rest of the studies (Table 1, entry 3). No trace of amine was found when this set of conditions was used (Table 1, entries 1–5); whereas when alcohol (isopropanol) was used as the solvent, degradation occurred, leading to the formation of the amine.²⁵ Finally, the organocatalyst 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) was also tested and showed very good conversion after 20 hours. Other organic bases such as triethylamine and 1,4-diazabicy-

clo[2.2.2]octane (DABCO, Table 1, entries 7 and 8) did not afford the desired product. Attempts to use acidic catalysis with trifluoroacetic acid or sulfuric acid failed to promote transcarbamoylation (data not shown). As expected, no reaction occurred in the absence of a base (Table 1, entry 9), proving the catalytic effect of other bases.

The effect of quantity of base (KOH) to catalyze the reaction was then studied, and the results are reported in Table 2. Decreasing the number of equivalents of base led to a slower reaction, but it was noticed that even a catalytic amount of base gave a 50% conversion after four hours (Table 2, entries 6–8). As expected, increasing the temperature allowed a significant reduction of reaction time due to better reaction kinetics and probably better elimination of the methanol formed during the reaction (Table 2, entries 5, 9, and 10). At 40 °C a conversion of 23% was obtained after four hours, offering very mild reaction conditions (Table 2, entry 2) with KOH as a base.

Table 2 Impact of the Amount of Base and Temperature on Reaction Conversion^a

Entry	Temp (°C)	KOH (equiv)	Conversion (% ^b , <i>t</i> = 4 h)
1	20	1.2	0
2	40	1.2	23
3	50	1.2	54
4	60	2	80
5	60	1.2	60
6	60	0.3	57
7	60	0.2	54
8	60	0.1	50
9	80	1.2	90
10	100	1.2	95

^a Reaction conditions: PhNHCO₂Me (1 equiv), BuOH (3 equiv), 0.3 M in toluene.

^b Determined by HPLC and NMR analysis.

The reactivity of a variety of alcohols with methyl *N*-phenylcarbamate was investigated using 1.2 equivalents of KOH at 60 °C (Table 3).²⁶

All primary alcohols tested in this study (propanol, isopropanol, butanol, octanol, and methoxyethanol) showed excellent reactivity. The number of equivalents of primary alcohol could be lowered to two equivalents without impacting the conversion significantly (Table 3, entry 5).

With the reaction conditions described (3 equiv), secondary and tertiary alcohols such as isopropanol and *tert*-butanol did not react with the carbamate (Table 3, entries 2 and 9), although no degradation byproducts were observed. The amount of alcohol had to be increased to six equivalents to observe reaction with isopropanol (Table 3, entry

Table 3 Reaction of Various Alcohols with Methyl *N*-Phenylcarbamate^a

Entry	Alcohol	Conversion (%, ^b t = 4 h)	Conversion (%, ^c t = 20 h)
1	PrOH (3 equiv)	54	83
2	<i>i</i> -PrOH (3 equiv)	0	0
3	<i>i</i> -PrOH (6 equiv)	65	90
4	BuOH (3 equiv)	60	95
5	BuOH (2 equiv)	52	90
6	BuOH I (1 equiv)	7	18
7	octanol (3 equiv)	76	85
8	methoxyethanol (3 equiv)	62	97
9	<i>t</i> -BuOH (3 equiv)	0	0
10	<i>t</i> -BuOH (6 equiv)	0	0
11	<i>t</i> -BuOH (as solvent)	0	0

^a Reaction conditions: PhNHCO₂Me (1 equiv, 0.3 M in toluene), alcohol, KOH (1.2 equiv), 60 °C.

^b Determined by HPLC analysis.

^c Determined by HPLC and NMR analysis.

3), but no product was obtained when *tert*-butanol was used, either in six equivalents or as solvent, probably due to steric hindrance (Table 3, entries 10 and 11).²⁵

Several solvents were evaluated under the optimized reaction conditions, and the conversions of the transcarbamoylation reaction of methyl *N*-phenylcarbamate with butanol are reported in Table 4.

Table 4 Impact of the Solvent on Reaction Conversion^a

Entry	Solvent	Conversion (%, ^b t = 4 h)	Conversion (%, ^c t = 20 h)
1	toluene	60	95
2	MeCN	44	76
3	cyclohexane	71	80

^a Reaction conditions: PhNHCO₂Me (1 equiv, 0.3 M in toluene), BuOH (3 equiv), KOH (1.2 equiv), 60 °C.

^b Determined by HPLC analysis.

^c Determined by HPLC and NMR analysis.

In the three solvents tested (toluene, acetonitrile, cyclohexane), good conversions were obtained, with a significant difference between acetonitrile and toluene (Table 4, entries 1 and 2). However, it was noticed that, when a small amount of water (2 vol%) was added to the reaction mixture, the reaction was much slower and only went to 50% conversion. Solvation of the inorganic base by the water may decrease its reactivity. It is therefore important to use anhydrous solvents to improve conversions.

As aromatic and aliphatic urethanes can have different reactivities due to the possible delocalization of the nitrogen lone pair into the aromatic ring, the reactivity of aliphatic urethanes was compared using the same reaction

conditions (Table 5). We found that aliphatic urethanes could also be transcarbamoylated to new urethanes, but the aromatic urethane was slightly more reactive than an aliphatic urethane with similar *N*-substituent (Table 5, entries 1, 6). This difference can be explained because the aromatic urethane carbon is more electrophilic than in the aliphatic analogue. However, a small aliphatic substituent (ethyl) instead of the bulky cyclohexyl group allowed high conversion (Table 5, entries 3 and 4). Again, a secondary alcohol (isopropanol) did not react under this set of conditions (Table 5, entries 2 and 5).

Table 5 Transcarbamoylation Reaction of Aliphatic and Aromatic Urethanes with Different Alcohols^a

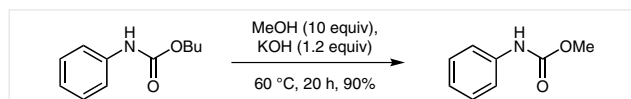
Entry	Urethane (reactant)	Alcohol (3 equiv)	Conversion (% ^b , t = 4 h)
1	PhNHCO ₂ Me	BuOH	60 ^b
2	EtNHCO ₂ Me	<i>i</i> -PrOH	0 ^c
3	EtNHCO ₂ Me	BuOH	86 ^c
4	EtNHCO ₂ Me	CH ₃ OCH ₂ CH ₂ OH	72 ^c
5	C ₆ H ₁₁ NHCO ₂ Me	<i>i</i> -PrOH	0 ^c
6	C ₆ H ₁₁ NHCO ₂ Me	BuOH	40 ^c
7	C ₆ H ₁₁ NHCO ₂ Me	CH ₃ OCH ₂ CH ₂ OH	28 ^c

^a Reaction conditions: urethane (1 equiv, 0.3 M in toluene), alcohol (3 equiv), KOH (1.2 equiv), 60 °C.

^b Determined by HPLC and NMR analysis.

^c Determined by NMR analysis.

Higher molecular mass carbamates were obtained by this reaction, but this reaction is reversible and can allow the conversion of high molecular-mass carbamates into smaller molecular-mass ones. However, a large excess of the alcohol has to be used to reach good conversion (Scheme 2), because the butanol formed during the reaction remains in solution.

**Scheme 2** Reaction with short chain alcohol

In conclusion, we have shown that the transcarbamoylation reaction catalyzed by inorganic bases such as NaOH and KOH allows high-yielding conversion of carbamates to other carbamates using mild conditions. It can be carried in various solvents with only two equivalents of alcohol, which could make it a suitable reaction for the synthesis of complex molecules. It is an alternative to metal-catalyzed transcarbamoylation. Transcarbamoylation catalyzed by inorganic bases is of particular interest in the field of polymer chemistry to provide efficient sustainable routes for the synthesis of polyurethanes without the use of metal catalysts or toxic isocyanates.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1588866>.

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- (26) **General Procedure for Transcarbamoylation**
In a 25 mL round-bottom flask, the urethane (0.66 mmol) was dissolved in dry toluene (2 mL). The alcohol (3 equiv, 1.98 mmol) and the base (1.2 equiv, 0.79 mmol) were added, and the reaction mixture was heated at 60 °C with continuous agitation. Samples were taken at regular time intervals and analyzed by HPLC and ¹H NMR spectroscopy to estimate conversion. To isolate the pure product, water (10 mL) and EtOAc (10 mL) were added to the reaction mixture. The organic layer was separated, dried over MgSO₄, filtered, and the solvent was evaporated. The residue was purified by silica column chromatography eluting with a 10–50% EtOAc–cyclohexane gradient. The fractions were concentrated under reduced pressure to give the desired product.
Butyl N-Phenylcarbamate
White solid (115 mg, 90% yield). HPLC: *t*_R = 16.1 min (linear gradient, 0–60% B, 20 min). ¹H NMR (300 MHz, DMSO-*d*₆): δ = 9.57 (s, 1 H), 7.43 (d, *J* = 7.5 Hz, 2 H), 7.24 (t, *J* = 7.5 Hz, 2 H), 6.95 (t, *J* = 6 Hz, 1 H), 4.05 (t, *J* = 6.8 Hz, 2 H), 1.46–1.72 (m, 2 H), 1.23–1.46 (m, 2 H), 0.89 (t, *J* = 7.3 Hz, 3 H) ppm.
Octyl N-Phenylcarbamate
White solid (135 mg, 82% yield). HPLC: *t*_R = 18.9 min (linear gradient, 0–60% B, 20 min). ¹H NMR (300 MHz, CDCl₃): δ = 7.38 (d, *J* = 7.5 Hz, 2 H), 7.31 (t, *J* = 7.5 Hz, 2 H), 7.06 (t, *J* = 7.5 Hz, 1 H), 7.06 (br s, 1 H), 4.16 (t, *J* = 6.8 Hz, 2 H), 1.59–1.76 (m, 2 H), 1.12–1.45 (m, 10 H), 0.79–0.89 (m, 3 H) ppm.
2-Methoxyethyl N-Phenylcarbamate
White solid (120 mg, 93% yield). HPLC: *t*_R = 14.5 min (linear gradient, 0–60% B, 20 min). ¹H NMR (300 MHz, CDCl₃): δ = 7.22–7.49 (m, 4 H), 6.99–7.12 (m, 1 H), 6.64–6.83 (m, 1 H), 4.33 (t, *J* = 4.5 Hz, 2 H), 3.65 (t, *J* = 4.5 Hz, 2 H), 3.42 (s, 3 H).