



Isocyanates - Part 3.⁷

Synthesis of Carbamates by DMAP-Catalyzed Reaction of Amines with Di-*tert*-butyldicarbonate and Alcohols

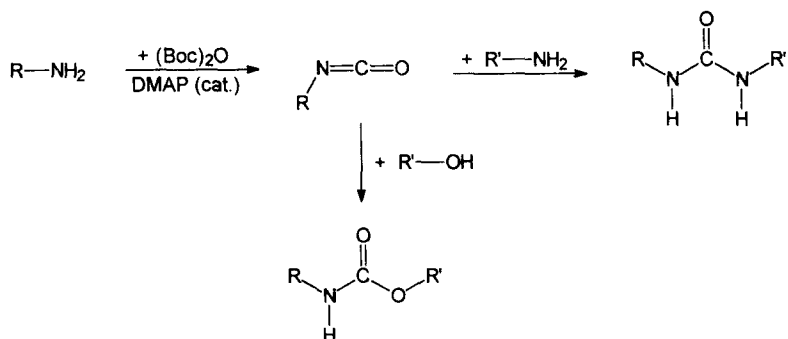
Hans-Joachim Knölker* and Tobias Braxmeier

Institut für Organische Chemie, Universität Karlsruhe, Richard-Willstätter-Allee, 76131 Karlsruhe, Germany

Abstract: Carbamates are prepared by DMAP-catalyzed reaction of amines with di-*tert*-butyldicarbonate and subsequent trapping of the intermediate isocyanates with alcohols.

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Carbamates (urethanes) are of importance as biologically active compounds (*e.g.* carbamate insecticides), and they are frequently used in organic synthesis for the protection of amines.¹ Among the most widely utilized protecting groups for this purpose are the Moc (methoxycarbonyl), the Boc (*tert*-butoxycarbonyl), the Cbz (benzyloxycarbonyl), the Alloc (allyloxycarbonyl), the Teoc (2-trimethylsilylethoxycarbonyl), and the Troc (2,2,2-trichloroethoxycarbonyl) group.² The most common method for preparation of these carbamates is the reaction of amines with the corresponding dialkyldicarbonate or alkyl chloroformate. An alternative method for the synthesis of carbamates is the reaction of an isocyanate³ with the corresponding alcohol.⁴ We recently described a novel procedure for the synthesis of isocyanates under mild conditions (10 min at room temperature) by the DMAP-catalyzed reaction of alkyl- and arylamines with (Boc)₂O (di-*tert*-butyldicarbonate).^{5,6} The isocyanates can be isolated quantitatively provided that sterically hindered amines are employed. *In situ* trapping of the isocyanates by an additional equivalent of an amine provides ready access in high yields to symmetrical and unsymmetrical ureas.⁷ We now report a useful synthesis of a broad range of carbamates by the DMAP-catalyzed reaction of amines with di-*tert*-butyldicarbonate and subsequent addition of alcohols. This procedure provides a simple and convenient alternative for the introduction of the above-mentioned protecting groups onto primary amines.



The transformation of arylamines **1** into arylisocyanates by the DMAP-catalyzed reaction with di-*tert*-butyldicarbonate was previously shown to proceed quantitatively with 2,6-disubstituted derivatives because the resulting sterically hindered arylisocyanates were fairly stable under the reaction conditions and further reaction with the *tert*-butyl alcohol to *tert*-butyl *N*-mesitylcarbamate was not observed.^{5,6} Conversion of mesitylamine into mesityl isocyanate by reaction with di-*tert*-butyldicarbonate in presence of DMAP followed by addition of 1.4 eq of alcohol (see general procedure) afforded the corresponding *N*-mesitylcarbamates **2a-2i** in high yields (Table 1).⁸

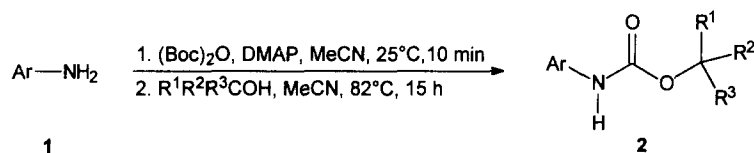


Table 1. Synthesis of *N*-arylcabamates **2**.

	Aryl	R ¹	R ²	R ³	2 , Yield [%]
a	2,4,6-Trimethylphenyl	H	H	H	99
b		CH ₃	H	H	98
c		CH ₃	CH ₃	H	83 [a]
d		Ph	H	H	96
e		CH=CH ₂	H	H	99
f		CCl ₃	H	H	93
g		CH ₂ SiMe ₃	H	H	84 [a]
h	2-Methoxy-4-methylphenyl	CH ₃	CH ₃	CH ₃	88 [b]
i		CD ₃	CD ₃	CD ₃	88 [b, c]
j		CH ₃	H	H	91
k		Ph	H	H	98
l		CH=CH ₂	H	H	97

[a] Isolation of *tert*-butyl *N*-mesitylcarbamate **2h** (**c**: 8%, **g**: 2%) as by-product.

[b] In this case the reaction mixture was heated for 60 h at 82°C.

[c] 28 eq of (CD₃)₃COD were added; products: 80% **2i** and 8% **2h**.

Traces of *N,N'*-dimesitylurea were formed under these conditions. Due to steric hindrance, the 2.8 eq of *tert*-butyl alcohol, resulting from 1.4 eq di-*tert*-butyldicarbonate, can obviously not compete with the less hindered alcohols subsequently added. Only for the reaction of mesityl isocyanate with *iso*-propyl alcohol (**c**) and trimethylsilylethyl alcohol (**g**) minor amounts of *tert*-butyl *N*-mesitylcarbamate **2h** were obtained. However, addition of *tert*-butyl alcohol (1.4 eq) to the initially formed mesityl isocyanate and subsequent heating of the reaction mixture at reflux for 60 h afforded the *tert*-butyl *N*-mesitylcarbamate **2h** in 88% yield. This result suggests, that the formation of *N*-Boc derivatives of sterically hindered primary amines with the (Boc)₂O/DMAP reagent system⁹ is caused by reaction of an intermediate isocyanate with the *tert*-butyl alcohol

generated in the process. Our assumption was unequivocally confirmed by treating the intermediate mesityl isocyanate with 28 eq of $[D_{10}]$ *tert*-butyl alcohol at 82°C for 60 h. The 10:1 ratio of deuterated to non-deuterated *tert*-butyl alcohol in the reaction mixture was exactly reflected by the 91% incorporation of the $(CD_3)_3CO$ group providing the $[D_9]$ *tert*-butyl *N*-mesitylcarbamate **2i**. In a further reaction with $[D_{10}]$ *tert*-butyl alcohol it was shown, that the *tert*-butoxy group of *tert*-butyl *N*-mesitylcarbamate **2h** is not exchanged under the reaction conditions. Thus, it can be concluded that using the $(Boc)_2O$ /DMAP reagent⁹ *N*-Boc derivatives of primary amines result from reaction of the intermediate isocyanates⁶ with *tert*-butyl alcohol. In contrast, reaction of a primary amine, *e.g.* mesitylamine or *p*-anisidine, with $(Boc)_2O$ without any base present, provides the *N*-Boc derivative by a classical addition-elimination mechanism.

Also the DMAP-catalyzed reaction of mono-*ortho*-substituted arylamines, *e.g.* 2-methoxy-4-methylaniline, with di-*tert*-butyldicarbonate provided isocyanates.^{5,6} Trapping of the isocyanate by subsequent addition of 1.4 eq of alcohol afforded the corresponding carbamates **2j–2l** in excellent yields (Table 1).⁸

The alkyl *N*-arylcabamates **2** exhibit a hindered rotation of the N–CO bond in the NMR spectra at room temperature. Using dynamic 1H NMR spectroscopy the coalescence temperature of carbamate **2d** was determined: $T_C = 323$ K. At temperatures below 298 K the rotation is sufficiently slow on the NMR time scale to allow the observation of two separated signals for the N–H proton and the CH_2 group. The conformer of **2d** with a *Z* arrangement of the mesityl ring and the carbonyl O-atom predominates in solution by 3.3 : 1. For this case the free enthalpies of activation can be determined: $\Delta G^\ddagger_{Z \rightarrow E} = 16.6$ kcal/mol, $\Delta G^\ddagger_{E \rightarrow Z} = 15.9$ kcal/mol.¹⁰

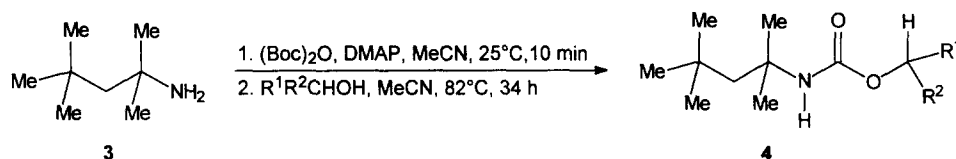


Table 2. Synthesis of *N*-*tert*-octylcarbamates **4**.

	R ¹	R ²	4 , Yield [%]
a	CH ₃	H	85 [a]
b	CH ₃	CH ₃	62 [a]
c	Ph	H	96 [a, b]
d	CH=CH ₂	H	97 [a]
e	CCl ₃	H	99

[a] Isolation of *N,N'*-di-*tert*-octylurea as by-product.

[b] Reaction for 17 h at reflux in MeCN.

Sterically hindered alkylamines, especially *tert*-alkylamines, can be conveniently transformed into alkyl isocyanates by the DMAP-catalyzed reaction with $(Boc)_2O$.^{5,6} Thus, conversion of *tert*-octylamine (1,1,3,3-tetramethylbutylamine) **3** into *tert*-octyl isocyanate by DMAP-catalyzed reaction with $(Boc)_2O$ followed by addition of 1.4 eq of alcohol afforded the corresponding *N*-*tert*-octylcarbamates **4** in high yields (Table 2).⁸

In conclusion, we have demonstrated that the DMAP-catalyzed reaction of alkyl- and arylamines with di-*tert*-butyldicarbonate and subsequent trapping of the intermediate isocyanates by addition of alcohols provides access to a broad range of *N*-alkyl and *N*-arylcabamates which represent useful protecting groups.

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References and Notes

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8. General procedure for the synthesis of *N*-aryl- and *N*-alkylcarbamates:
All reactions were performed in anhydrous acetonitrile. To a solution of di-*tert*-butyldicarbonate (1.4 eq) in acetonitrile were added successively a solution of 4-dimethylaminopyridine (1.0 eq) in acetonitrile and a solution of the amine (1.0 eq) in acetonitrile. After stirring for 10 min at room temperature, the alcohol (1.4 eq) was added. The reaction mixture was heated for 15–34 h at 82°C. Evaporation of the solvent and flash chromatography (ethyl acetate/hexane) of the residue on silica gel provided the carbamate.
All products were characterized by IR-, ¹H NMR-, ¹³C NMR-, mass spectra, and elemental analysis.
Benzyl *N*-mesitylcarbamate (**2d**): colorless crystals, mp 122°C; IR (KBr): ν = 3272, 1692, 1610, 1522 cm⁻¹; ¹H NMR (500 MHz, CDCl₃, 296 K): δ = 2.16 (br s) and 2.22 (br s, Σ 6 H), 2.26 (s, 3 H), 5.14 (br s) and 5.19 (br s, Σ 2 H), 5.78 (br s) and 6.03 (br s, Σ 1 H), 6.89 (s, 2 H), 7.32 (m, 5 H); ¹³C NMR and DEPT (126 MHz, CDCl₃): δ = 18.22 (2 CH₃), 20.91 (CH₃), 67.02 (CH₂), 128.18 (2 CH), 128.41 (CH), 128.56 (2 CH), 128.95 (2 CH), 130.89 (C), 135.59 (C), 136.52 (2 C), 136.94 (C), 154.47 (CO); MS (75°C) m/z (%) = 269 (M⁺, 46), 134, (43), 91 (100). Analysis calcd. for C₁₇H₁₉NO₂: C, 75.80; H, 7.11; N, 5.20; found: C, 75.67; H, 7.16; N, 5.38.
Allyl *N*-1,1,3,3-tetramethylbutylcarbamate (**4d**): colorless oil; IR (neat): ν = 3354, 1708, 1649 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 1.00 (s, 9 H), 1.37 (s, 6 H), 1.69 (s, 2 H), 4.50 (d, J = 3.7, 2 H), 4.72 (br s, 1 H), 5.18 (d, J = 10.4, 1 H), 5.28 (d, J = 17.1, 1 H), 5.90 (m, 1 H); ¹³C NMR and DEPT (126 MHz, CDCl₃): δ = 29.44 (2 CH₃), 31.43 (3 CH₃), 31.56 (C), 51.54 (CH₂), 54.09 (C), 64.69 (CH₂), 117.29 (CH₂), 133.31 (CH), 154.22 (CO); MS (25°C) m/z (%) = 198 (M⁺–15, 4), 142 (100), 98 (38), 57 (18), 41 (46); HRMS: calc. for C₁₁H₂₀NO₂ (M⁺–CH₃): 198.1494, found: 198.1483.
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