# Acidity of Benzoylcarbamates in Dimethyl Sulfoxide. Confirmation of Mixed *N*/*O* Alkylation in the Mitsunobu Reaction

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Seventeen benzoyl-, 4-methoxybenzoyl- and 4-nitrobenzoyl-carbamates have been synthesized *via* their corresponding isocyanates and their acidities determined in dimethyl sulfoxide solution. Their p$K_a$ values span an interval of nearly 5 p$K$ units (10.4–15.2). Selected derivatives have been investigated as amine synthons in the Mitsunobu reaction. In all cases mixtures of *N*- and *O*-alkylated products are obtained.

Phthalimide and its potassium salt are generally applied to *N*-alkylation with alcohols under Mitsunobu conditions and with halides under Gabriel conditions.[1] Recently, several other reagents have also been explored in this context,[2] particularly various diacylimides, acylcarbamates and imidodicarbonates. Wada and Mitsunobu[3] studied the reaction between simple alcohols, benzyl benzoylcarbamate, triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) and obtained *N*-alkylated products in 66–68% yields. However, in another trial with a protected uridine derivative,[4] a competing *O*-alkylation took place. Alkylation of the sodium salt of benzyl benzoylcarbamate with the corresponding bromide gave predominantly *N*-alkylation.[4]

In connection with a recent study dealing with $^{15}$N-labelled chiral Boc-amino acids using a series of imidodicarbonates under Mitsunobu conditions,[5a] we noticed that the yields correlated remarkably well with the p$K_a$ of the imidodicarbonate measured in dimethyl sulfoxide (DMSO).[5b] In the case of ethyl lactate, we concluded that a p$K_a$ in DMSO of around 13.5 or lower was required in order to achieve a satisfactory reaction under the usual experimental conditions.

This paper describes the synthesis of a set of benzoylcarbamates in which the carbamate part is directly related to *N*-protecting groups used in the synthesis of peptides and similar compounds. When attached to an amino acid, selective removal of the benzoyl group would consequently lead to the corresponding urethane-protected derivative.[6] With respect to the benzoyl part of the molecules, both unsubstituted and 4-$NO_2$- and 4-MeO-substituted derivatives have been made and their p$K_a$ values were measured in DMSO. To the best of our knowledge, no such measurements with this type of compounds have been carried out before. Finally, the behaviour of a few benzoylcarbamates in the Mitsunobu reaction was reinvestigated.

## Results and Discussion

The benzoylcarbamates studied in this paper were all made according to Scheme 1.

$$R^1C_6H_4\text{–}CO\text{–}NH_2 \longrightarrow R^1C_6H_4\text{–}CO\text{–}N{=}C{=}O \longrightarrow R^1C_6H_4\text{–}CO\text{–}NH\text{–}CO\text{–}OR^2$$

**Scheme 1** $R^1$ = H, 4-MeO or 4-$NO_2$; $R^2$ = Me, Bu$^t$, $CH_2CCl_3$, Bzl, $CH_2C_6H_4$-4-$NO_2$, 4-$CH_2C_5H_4N$ or 9-fluorenylmethyl

A solution of the isocyanate in dichloromethane was allowed to react with a small excess of the appropriate alcohol under anhydrous conditions and the resulting acylcarbamates were worked up as described in the Experimental section. The unsubstituted benzoylisocyanate was distilled, whereas the substituted ones were used without distillation or other purification. All compounds made are listed in Table 1. To the best of our knowledge, nine of the 17 substituted benzoylcarbamates synthesized in the present work have not been described before in the literature. Of the remaining eight compounds, four showed significantly higher melting points than those reported earlier.

Most of the benzoylcarbamates studied are practically insoluble (less than $10^{-3}$ mol dm$^{-3}$) in water. Therefore, and for comparison with the acidity of the earlier measured series of imidodicarbonates and tosylcarbamates,[5b] the acidity of the compounds studied in the present work was predominantly determined in DMSO solution (Table 1). Only the p$K_a$s for two benzoylcarbamates, $BzNHCO_2Me$ and BzNHPoc, could also be measured in aqueous solution using direct potentiometric titration of the neutral acid with the alkali.

The acidity of the benzoylcarbamates measured in this work in DMSO solution is closely comparable with the acidity of the other wide family of Gabriel reagents,[2] most of which were imidodicarbonates.[5b] However, the following differences between the behaviours of these two classes should be mentioned.

1. The acidifying effect of replacement in the imidodicarbonates $Z_2NH$ (Z = $CO_2CH_2Ph$) and $Boc_2NH$ (Boc = $CO_2Bu^t$) of one Z- or Boc group with the benzoyl group ranges from 0.5 ± 0.1 p$K_a$ units (*e.g.* for the transfers between $Z_2NH$ and $BzNHCO_2CH_2Ph$, $ZNHCOOCH_2CCl_3$ and $BzNHCOOCH_2CCl_3$) to 1.9 p$K_a$ units (transfer from $Boc_2NH$ to BzNHBoc).

2. For the same group, $R^1$, in the series of the benzoyl carbamates the introduction of the (+R) electron-donating MeO substituent into the benzene ring *para* to the carbonyl group, decreases the acidity of these NH acids only slightly (0.1–0.5 p$K_a$ units). However, introduction of the strong electron acceptor $NO_2$ group into the same position in the benzoyl group increases the acidity by 1.4–1.9 p$K_a$ units.

3. For a fixed $R^1$, however, changes in $R^2$ can cause even more significant changes in the acidity of the NH acids studied in this work. Thus, for $R^1$ = Mbz or Bz the replacement of $R^2$ = Bu$^t$ with $CH_2CCl_3$ group increases the acidity of the corresponding benzoyl carbamates by 2.6–2.7 p$K_a$ units, whereas for $R^1$ = Nbz the analogous substituent effect is even larger (3.1 p$K_a$ units). However, for the same $R^1$, the acidity of the members of the present series of NH acids is only moderately sensitive to substitutions in the phenyl ring of the $CH_2Ph$ group ($R^2$ =

**Table 1** Data on synthetic acylcarbamates

| Compound | Yield (%) | M.p./ °C | Lit. m.p./ °C | p$K_a$ in DMSO |
|---|---|---|---|---|
| Mbz[a]–NH–CO–OMe | 69 | 114.5 | | 14.3 |
| Mbz–NH–CO–OBu$^t$ | 65 | 125.5 | 119–120[7] | 15.2 |
| Mbz–NH–CO–$OCH_2CCl_3$[b] | 62 | 172–173 | | 12.6 |
| Mbz–NH–CO–$OCH_2Ph$ | 72 | 118 | 103–105[8] | 13.9 |
| Mbz–NH–CO–$OCH_2C_6H_4$–4-$NO_2$[c] | 62 | 172.5 | | 13.6 |
| Bz–NH–CO–OMe | 56 | 118 | 117–118[9] | 14.0[d] |
| Bz–NH–CO–OBu$^t$ | 86 | 152–155 (decomp.) | 136–137[7] 146–147[10] | 15.0 |
| Bz–NH–CO–$OCH_2CCl_3$ | 99 | 126.5–127.5[11] | | 12.3 |
| Bz–NH–CO–$OCH_2Ph$ | 91 | 117–117.5[12] | 96–97[8] | 13.7 |
| Bz–NH–CO–$OCH_2C_6H_4$–4-$NO_2$ | 93 | 155–155.5[11] | | 13.1 |
| Bz–NH–Poc[a] | 93 | 140–141 | | 12.8[e] |
| Bz–NH–Fmoc[a] | 92 | 161–162 | | 14.5 |
| Nbz[a]–NH–CO–OMe | 41 | 197 | | 12.5 |
| Nbz–NH–CO–OBu$^t$ | 41 | 155.5–156 | 142–143.5[7] | 13.5 |
| Nbz–NH–CO–$OCH_2CCl_3$ | 48 | 171 | | 10.4 |
| Nbz–NH–CO–$OCH_2Ph$ | 51 | 151.5 | | 12.2 |
| Nbz–NH–CO–$OCH_2$–$C_6H_4$–4-$NO_2$ | 46 | 164 | | 11.7 |

[a] The following abbreviations have been used: Mbz is 4-methoxybenzoyl-; Nbz is 4-nitrobenzoyl-; Poc is 4-pyridylmethyloxycarbonyl-; Fmoc is 9-fluorenemethyloxycarbonyl-. [b] Carbon analysis 0.56% too low. [c] Carbon analysis 0.48% too low. [d] p$K_a$ = 10.30 in aqueous solution, see the text. [e] p$K_a$ = 10.30 in aqueous solution, see the text.

substituted benzyl group): the largest increase in the acidity ($R^1$ = Ph; $R^2$ changes from $CH_2Ph$ into $CH_2C_6H_4$–4-$NO_2$) is only 0.6 p$K_a$ units (compare also ref. 5*b*).

In water, the only measured compounds, $BzNHCO_2Me$ and BzNHPoc, have the same acidity, being 0.3 p$K_a$ units weaker than phenol [p$K_a(H_2O)$ = 10.00].[13] In DMSO solution, BzNHPoc exceeds $BzNHCO_2Me$ by 1.2 p$K_a$ units, whereas both are much stronger acids than phenol [p$K_a$(DMSO) = 18.0].[14] Evidently, determination of the p$K_a$s of this series of Gabriel reagents could be performed by titration of solutions of their water-soluble alkali metal salts with a strong acid.

An investigation of the Mitsunobu alkylation of some selected acylcarbamates using benzyl alcohol as the model alkylating agent (Scheme 2) has revealed that significant

$$R^1C_6H_4\text{–CO–NH–CO–}OR^2 + \text{Bzl–OH} \xrightarrow{\text{i}} R^1C_6H_4\text{–CO–N(Bzl)–CO–}OR^2 + R^1C_6H_4\text{–C(OBzl)=N–CO–}OR^2$$

**Scheme 2** *Reagents:* i, TPP and DEAD in THF. $R^1$ = H or 4-$NO_2$; $R_2$ = Bu$^t$, $CH_2CCl_3$, Bzl and $CH_2C_6H_4$–4-$NO_2$.

amounts of *O*-benzyl isomer, in addition to the *N*-benzyl derivative, are formed under our usual reaction conditions. Since these isomers are not readily removed from the crude mixtures by silica chromatography, these substrates appear less suitable than imidodicarbonates as amine synthons in this conversion. Typically the amount of *O*-benzyl derivatives present in the crude product mixture after chromatographic removal of the Mitsunobu side products is in the range of 20–25%. Particularly with the Nbz derivatives, the *O*-alkyl isomers sometimes seem to be sensitive to the chromatographic separation procedure and therefore the *O*-alkyl/*N*-alkyl ratios are significantly lowered in some cases. In a model experiment using ethyl (*S*)-lactate, thus mimicking our earlier alanine syntheses,[5a] more than half of the product formed (58%) was the *O*-alkyl isomer. The *N*- and *O*-alkyl isomers generally exhibited very similar chromatographic behaviour, thus making their separation rather impractical. In an attempt partly to circumvent this problem, the 42:58 mixture just mentioned was treated with 3 equiv. of Bu$^t$$NH_2$ in EtOH. After 24 h at room temperature, chromatographic work-up afforded Troc-(*R*)-alanine ethyl ester (Troc is trichloroethyloxycarbonyl) in 82% yield, as calculated from the content of *N*-alkyl isomer. The *O*-alkyl isomer appeared to be decomposed to products which were readily separated from the desired product in this case. Also, according to the same approach, the Nbz–N(Bzl)–CO–OBu$^t$ isomer (77:23 *N*/*O*-Bzl) mixture underwent nucleophilic cleavage in the presence of a small excess of 2-diethylaminoethylamine (DEAEA) in MeCN after a convenient extractive work-up.[6] Some (nonoptimized) results of Mitsunobu alkylations of selected substrates are compiled in Table 2.

To summarize, the acidity within the series of benzoylcarbamates prepared is slightly higher than for imidodicarbonates[5b] and it has been confirmed that acylcarbamates undergo Mitsunobu reactions,[3,4] but these are not as clean as with imidodicarbonates,[5a] and mixed *N*/*O*-alkylation does indeed take place as reported.[3,4] Nevertheless, selective monodeacylation of the crude mixture before work-up as reported in this paper might occasionally be synthetically useful.

## Experimental

*General Procedures.*—M.p.s were recorded on a Gallenkamp apparatus and are uncorrected. All solvents used as reaction media were of the best commercial grade and were dried over molecular sieves (4A). All reagents used in the Mitsunobu reaction were purified as described earlier[5a] and were dried thoroughly before use. TLC analyses were performed on 0.25 mm thick precoated silica plates (Merck DC-Fertigplatten Kieselgel 60 $F_{254}$) with MePh–MeCN (2:1) or light petroleum–$Et_2O$ mixtures as developer. Spots were visualized by inspection under UV light at 254 nm or preferentially, after brief heating, by exposure to $Cl_2$ followed by dicarboxidine spray. $^1$H NMR spectra were routinely recorded on a JEOL JNM-EX 270 at 270 MHz in $CDCl_3$. In all cases the NMR data were in full agreement with the proposed structures. Elemental analyses were carried out on all solid, novel compounds by Mikro Kemi AB, Uppsala, Sweden and gave satisfactory results for CHN (±0.3%, unless otherwise indicated). Yields, m.p.s and other information about the compounds are compiled in Tables 1 and 2.

*Preparation of Alkyl N-Benzoylcarbamates.—General procedure.* Freshly distilled benzoyl isocyanate[15] (7.35 g, 50 mmol) in dry $CH_2Cl_2$ (50 $cm^3$) was added dropwise with stirring under

**Table 2** Mitsunobu alkylation of selected acylcarbamates

| Substrate | Alkylating agent | Total yield[a] (%) | *O*-Alkylation[b] (%) |
|---|---|---|---|
| Bz–NH–CO–$OCH_2Ph$[11] | BzlOH | 98 | 25 |
| Bz–NH–CO–$OCH_2CCl_3$[11] | BzlOH | 94 | 19 |
| Bz–NH–CO–$OCH_2C_6H_4$-4-$NO_2$[11] | BzlOH | 71 | 20 |
| Nbz–NH–CO–$OCH_2CCl_3$ | BzlOH | 82 | 9[c] |
| | Et (*S*)-lactate | 69 | 58 |
| Nbz–NH–CO–OBu$^t$ | BzlOH | 65 | 23[d] |

[a] After flash chromatography of the crude product on silica. [b] Relative to the total yield, determined by $^1$H NMR spectroscopy, of the product mixture after flash chromatography. The isomers were not separated. [c] *N*-Alkyl/*O*-alkyl ratio *ca.* 3.35 (corresponding to *ca.* 23% *O*-alkyl derivative) before chromatography. $\delta_H(CDCl_3)$ *N*-Bzl isomer: 8.26 and 7.67 (ABq, 4 H, Nbz), 5.14 (s, 2 H, Bzl), 4.67 (s, 2 H, Troc); *O*-Bzl isomer: 8.26 and 7.86 (ABq, 4 H, Nbz), 5.40 (s, 2 H, Bzl), 4.77 (s, 2 H, Troc). [d] *N*-Alkyl/*O*-alkyl ratio *ca.* 3.0 (corresponding to *ca.* 25% of *O*-alkyl isomer) before chromatography. $\delta_H(CDCl_3)$ *N*-Bzl isomer: 8.26 and 7.64 (ABq, 4 H, Nbz), 5.01 (s, 2 H, Bzl), 1.18 (s, 9 H, Bu$^t$); *O*-Bzl isomer: 8.26 and 7.85 (ABq, 4 H, Nbz), 5.32 (s, 2 H, Bzl), 1.44 (s, 9 H, Bu$^t$).

argon to an ice-cold solution of the alcohol (5% excess except for 4-pyridylmethanol and 4-nitrobenzyl alcohol when equivalent amounts were used), also in $CH_2Cl_2$ (25–100 cm$^3$), over 1–2 h. After standing overnight at room temp., the solvent was removed, leaving a solid residue which was thoroughly rinsed with ether (light petroleum for the 9-fluorenemethyl derivative) and dried *in vacuo*. The yield of crude, essentially pure product was nearly quantitative. In the reactions with the two alcohols mentioned, the products precipitated from the reaction mixtures and were collected. They were further purified by recrystallization and in one case ($BzNHCO_2Bu^t$) by column chromatography on silica ($CH_2Cl_2$–acetone, 4:1) followed by recrystallization. For additional details, see Table 1.

*Preparation of 4-methoxybenzoyl- and 4-nitrobenzoyl-carbamates.* For the synthesis of the 4-methoxybenzoyl- and 4-nitrobenzoyl-carbamates, the crude isocyanates were used.[16] The isocyanate (≤ 10 mmol), dissolved in dry $CH_2Cl_2$ (10 cm$^3$), was added dropwise with stirring under argon to an ice-cold solution of the alcohol (1.0 equiv., 1.1 equiv. for Bu$^t$OH) in $CH_2Cl_2$ (5–15 cm$^3$) over 20 min. After another 30 min at 0 °C and 2 h at room temp., the solvent was evaporated (Nbz–NH–CO–OMe and Nbz–NH–CO–$OCH_2Ph$ crystallized directly from the reaction mixture) giving solids or oils which were triturated with diethyl ether or chromatographed (Nbz–NH–CO–OBu$^t$ and Nbz–NH–CO–$OCH_2CCl_3$ in $CH_2Cl_2$–acetone, 9:1) on silica and then purified by recrystallization. For additional details, see Table 1.

*Mitsunobu Alkylation of Acylcarbamates. Typical Procedure: Benzylation of* $NbzNHCO_2Bu^t$.—A solution of $NbzNHCO_2Bu^t$ (393 mg, 1.48 mmol) and benzyl alcohol (177 mg, 1.63 mmol) in dry THF (3.0 cm$^3$) was chilled in ice under dry argon and treated with triphenylphosphine (467 mg, 1.78 mmol) in small portions with rapid stirring. Neat diethyl azodicarboxylate (336 mg, 1.93 mmol) was introduced dropwise with vigorous agitation over a period of 20 min and stirring in ice for 1 h and at ambient temperature for 5 h. The solvent was stripped off at reduced pressure and the remaining sticky mass was dissolved in $Et_2O$ and chromatographed on silica using light petroleum–$Et_2O$ (3:1) as eluent. A central fraction weighing 342 mg was collected and $^1$H NMR spectroscopy indicated that it consisted of a mixture of *N*-Bzl and *O*-Bzl derivative (ratio 77:23; the crude product before chromatography showed the ratio 75:25). The combined yield of *N*- and *O*-Bzl derivatives was 65%. For $^1$H NMR data, see Table 2.

*Nucleophilic Cleavage of* N-*Alkyl*/O-*Alkyl Isomer Mixture. Model Experiment:* $N^2$-*Diethylaminoethylamine-mediated Cleavage of* N-/O-*Bzl Mixture Derived from 4-Nitrobenzoyl* tert-*Butyl Carbamate.*—The above product mixture (308 mg, 0.86 mmol) was suspended in dry MeCN (1.9 cm$^3$) and treated with DEAEA (184 mm$^3$, 1.5 equiv.) in small portions with rapid stirring. The resulting brick-red slurry was stirred overnight at room temperature, whereafter most of the solvent was stripped off at reduced pressure. The oily residue was partitioned between $Et_2O$ (40 cm$^3$) and 1 mol dm$^{-3}$ $KHSO_4$ (20 cm$^3$), and the extract was washed and dried as usual to give crude BzlNHBoc (*ca.* 120 mg, *ca.* 90% pure, *ca.* 80% yield as calculated from this component in the crude mixture).

*p*$K_a$ *Determination in DMSO Solutions.*—The p$K_a$ determinations were performed at 25 °C using potentiometric titration of the NH acids with a solution of $Bu_4NOH$ in a mixture of benzene and Pr$^i$OH (4:1). The detailed description of the technique used was given previously.[5b]

*p*$K_a$ *Determinations in Water.*—A standard potentiometric technique was used for measuring the acidity of a few title compounds.[13] The measured p$K_a$s for DMSO as well as for aqueous solution are listed in Table 1.

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