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Direct conversion of Fmoc-protected amines into *O*-alkyl carbamates by the Mitsunobu reaction: a practical strategy for the solid-phase synthesis of carbamates

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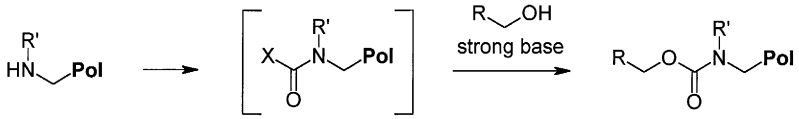
Abstract

Support-bound, Fmoc-protected amines react with aliphatic alcohols in the presence of ADDP, PBu_3, and DIPEA to yield *O*-alkyl carbamates. The reaction presumably proceeds via *O*-alkylation of an intermediate carbamate anion.

Keywords: amino acids and derivatives; carbamates; Mitsunobu reactions; solid-phase synthesis.

Synthetic protocols which enable the use of aliphatic alcohols are well suited for the preparation of compound libraries, because a large number of alcohols are commercially available and can generally be stored for long periods. One possibility to covalently bind alcohols to intermediates on solid phase is the conversion of support-bound primary or secondary amines into carbamates (Scheme 1). For this purpose the amine is generally first converted into a carbamoyl chloride by treatment with phosgene or a synthetic equivalent thereof, and then with an alcohol in the presence of a strong base.[1] Alternatively, support-bound 4-nitrophenyl carbamates can be converted into other carbamates by treatment with alcohols, again under strongly basic reaction conditions.[2] We found none of these strategies to be suitable for the automated production of compound libraries on solid phase, because variable results are frequently obtained, and the strong bases often lead to precipitates and clogging of tubes.



Scheme 1. X: Cl, 4-$(O_2N)C_6H_4O$

We present herein a new strategy for the conversion of support-bound amines into carbamates, which requires soluble reagents only, and which is therefore well suited for robotic synthesizers.

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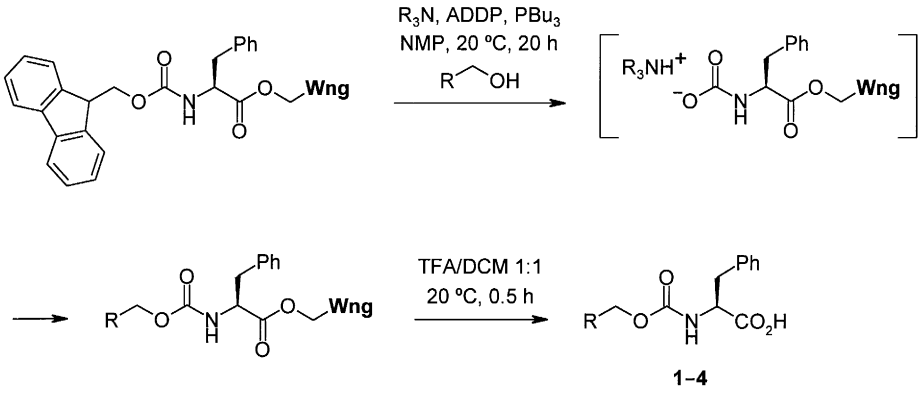
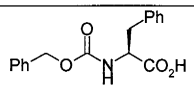
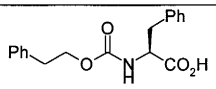
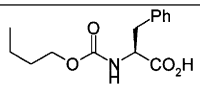
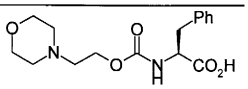
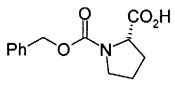
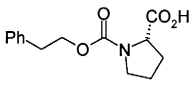
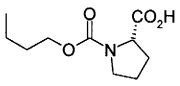
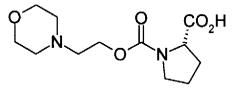
This new synthesis is based on the *O*-alkylation of ammonium carbamates under the conditions of the Mitsunobu reaction.[3] The required ammonium carbamates were generated in situ by treatment of Fmoc-amines with DIPEA or triethylamine (Scheme 2). For instance, treatment of support-bound Fmoc-phenylalanine with primary aliphatic alcohols in the presence of azodicarboxylic acid dipiperidide (ADDP), tributylphosphine, and a tertiary amine led to clean formation of the corresponding carbamates, which were released from the support by treatment with trifluoroacetic acid (TFA) in dichloromethane (DCM).[4] The yields and purities of representative crude products are given in Table 1.[5]



Scheme 2. Wng: 1% cross-linked polystyrene with Wang linker. R_3N: DIPEA or NEt_3

Table 1
Yields and purities of the crude carbamates prepared according to Scheme 2

Product				
Entry	**1**	**2**	**3**	**4**
Yield (^{1}H NMR)	82%	60%	40%	64%
Purity (HPLC; 214 nm/254 nm/ELS)	60%/47%/97%	49%/62%/94%	29%/23%/92%	28%/29%/91%
Product				
Entry	**5**	**6**	**7**	**8**
Yield (^{1}H NMR)	81%	76%	96%	78%
Purity (HPLC; 214 nm/254 nm/ELS)	82%/58%/94%	83%/65%/92%	-/-/88%[a]	-/-/100%[a]

[a] The product showed no significant absorption at 214nm/254 nm.

This new carbamate synthesis proceeds smoothly with primary aliphatic alcohols, whereas secondary alcohols generally give poor results. When α-amino acids were used as the support-bound amine no significant racemization could be detected[5] making this procedure suitable for the solid-phase preparation of chemically modified peptides.

In conclusion, a mechanistically new synthesis of carbamates has been developed, which is based on readily available, stable reagents, and which is compatible with standard peptide synthesizers and pipetting robots for parallel solid-phase synthesis.

Acknowledgements

We thank Vibeke Rode for recording LC-MS spectra and Hanne Bultoft and Annemarie R. Varming for analyzing products **1** and **5** by HPLC on chiral stationary phase.

References

1. For illustrative examples performed in solution, see: Derwing, C.; Hoppe, D. *Synthesis* **1996**, 149–154; Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097–6108.
2. Zaragoza, F. unpublished results. Alcohols can also be preactivated in homogeneous phase by conversion into 4-nitrophenyl carbonates or chloroformates, and then coupled with a support-bound amine.
3. For a related synthesis of symmetric carbonates in solution, see: Hoffman, W. A. *J. Org. Chem.* **1982**, *47*, 5209–5210. Oxazolidin-2-ones have been prepared from 2-aminoethanol and CO_2 under Mitsunobu conditions: Kodaka, M.; Tomohiro, T.; Okuno, H. *J. Chem. Soc., Chem. Commun.* **1993**, 81–82. Carbamates have been prepared in solution by *O*-alkylation of carbamate anions with alkyl halides: McGhee, W.; Riley, D.; Christ, K.; Pan, Y.; Parnas, B. *J. Org. Chem.* **1995**, *60*, 2820–2830; Gómez-Parra, V.; Sánchez, F.; Torres, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 695–697; Gómez-Parra, V.; Sánchez, F.; Torres, T. *Synthesis* **1985**, 282–285; Yoshida, Y.; Ishii, S.; Yamashita, T. *Chemistry Lett.* **1984**, 1571–1572.
4. Typical procedure: *N*-(Benzyloxycarbonyl)proline (**5**). To *N*-Fmoc proline esterified with Wang resin (0.104 g, 0.078 mmol; Novabiochem) were added, in the order given, *N*-methylpyrrolidinone (NMP; 1.5 mL), benzyl alcohol (0.205 mL, 1.98 mmol, 25 equiv.), a suspension of ADDP (0.330 g, 1.31 mmol, 17 equiv.) in NMP (1.5 mL), PBu_3 (0.25 mL, 1.00 mmol, 13 equiv.), and DIPEA (0.6 mL). The mixture was shaken at 20°C for 20 h, filtered, and the support was extensively washed with NMP, DCM, and methanol. DCM (1.5 mL) and TFA (1.5 mL) were added, and after shaking at 20°C for 0.5 h, the mixture was filtered and the filtrate was concentrated under reduced pressure. 24 mg of the title compound was obtained, identical by ^{1}H NMR to an authentic sample (for purity and yield, see Table 1).
5. All crude products were analyzed by LC-MS, HPLC (214 nm, 254 nm, evaporative light-scattering (ELS)), and ^{1}H NMR. Yields were determined by ^{1}H NMR using DMSO-d_5 as internal standard. Compounds **1** and **5** were identical by ^{1}H NMR to authentic (purchased) samples. No significant racemization of products **1** and **5** occurred under the conditions of carbamate anion generation/Mitsunobu reaction, as determined by HPLC on chiral stationary phase.