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A practical procedure for the preparation of carbamates from azides

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Abstract

A practical procedure for the direct conversion of azides to carbamates has been found. High yields are obtained when primary and secondary aliphatic azides, as well as α-azido esters, are treated in THF with Me_3P and several chloroformates (ClCOOBn, ClCOOMe, ClCOOEt, $ClCOOCH_2CCl_3$, $ClCOOCH_2CH{=}CH_2$). © 1999 Elsevier Science Ltd. All rights reserved.

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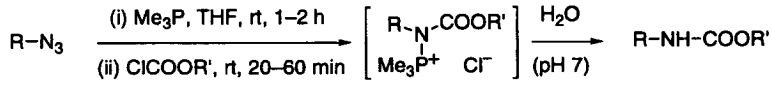
Protection of amines as carbamates (R-NH-COOR′) is of paramount importance in organic chemistry,[1] activated alkoxycarbonyl species (XCOOR′) being the reagents most frequently used for this transformation. Since aliphatic amine groups are generally introduced via azide groups, the finding of methods for the direct conversion of azides to protected amines has a real, practical interest. Most procedures reported so far for the direct conversion of azides to their *N*-Boc derivatives are based on the azide catalytic reduction followed by in situ protection with Boc_2O,[2] but they have not been extended to other carbamates. In fact, the catalytic hydrogenation is not convenient for the preparation of some other carbamates, because of the obvious reagent and/or product instability under such conditions (in cases like *N*-Cbz, i.e. for *N*-benzyloxycarbonyl derivatives, or *N*-Alloc, i.e. for *N*-allyloxycarbonyl derivatives).

An alternative method for catalytic reduction is the treatment of $R\text{-}N_3$ with phosphines to give phosphazenes,[3] followed by hydrolysis and addition of the appropriate reagent (protecting group). However, if the organic azide contains functional groups prone to being hydrolysed or reacting with the amine group which is being generated, this protocol is clearly unsuitable, so that a straigthforward conversion of azides to carbamates is required. We report here on optimum conditions for the direct transformation of azides to several carbamates, using Me_3P and commercially available chloroformates,[4] which may be summarised as follows (Scheme 1).



Scheme 1.

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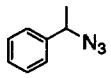
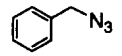
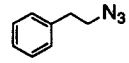
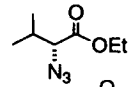
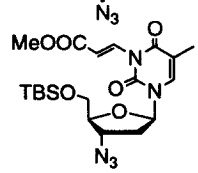
Table 1
Conversion of azides, via trimethylphosphazenes, to carbamates

Azide	ClCOOR'	Carbamate yield	Azide	ClCOOR'	Carbamate yield
	R' = Me	89%		R' = Bn	97%
id.	R' = Et	91%		R' = Bn	93%
id.	R' = CH_2CCl_3	92%		R' = Bn	84%
id.	R' = allyl	90%		R' = Bn	89%
id.	R' = Bn	90%			

Addition of 1.1 equiv. of alkyl, allyl or arylalkyl chloroformates to the phosphazene solutions arising from Me_3P and azides, at room temperature (rt), afforded white suspensions. A final aqueous workup hydrolysed phosphonium intermediates to water-soluble $Me_3P{=}O$ and the desired carbamates, in excellent yields (Table 1). The reaction worked for a variety of chloroformates: methyl, ethyl, 2,2,2-trichloroethyl (Troc), allyl (Alloc), and benzyl (Cbz, or *Z*). An α-azido ester derived from valine also gave the Cbz derivative without diketopiperazine formation or epimerisation (optical purity was checked by HPLC on an OD-H chiral column; in this case, to reach a high yield, addition of reagents had to be performed at −78°C and buffered water was added at 0°C). Finally, in connection with studies on nucleosides,[5] a more functionalised molecule was tested (last entry of Table 1); when the catalytic hydrogenation of the azide group was attempted, concomitant reduction of the double bond linked to N-3 took place, which made more difficult the subsequent removal of this chain (protecting group); the method here reported solved the problem.

In a typical experiment, a 1.0 M solution of Me_3P in THF (1.05 mL) is added at rt to 1.0 mmol of the azide in THF (3 mL). When the phosphazene formation is complete (1–2 h, as monitored by TLC), 1.1–1.2 mmol of benzyl chloroformate or other chloroformates is added. A precipitate appears slowly. Stirring at rt for 20–60 min, quenching with phosphate buffer (pH 7), extraction with CH_2Cl_2, drying of the organic layers, and evaporation of the solvent affords the pure carbamates (in most cases, column chromatography is not required).

In summary, the simplicity and efficiency of the phosphazene route makes it the best choice for the R-N_3 to R-NH-COOR′ transformation. We have found at present only one limitation: the phosphazene basicity prevents the preparation of carbamates unstable under basic conditions, such as *N*-Fmoc (*N*-fluorenyloxycarbonyl) derivatives.

Acknowledgements

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