Convenient protection of amines as carbamates using polymer-bound HOBT as catalyst

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COMMUNICATION

A method for the facile protection of primary and secondary amines as carbamate (Cbz, Fmoc and *t*-Boc) derivatives using polymer bound 1-hydroxybenzotriazole (HOBT) is reported.

The widespread use of combinatorial libraries in the search for biologically active lead compounds has led to recent advances in the use of solid-phase organic synthesis techniques.[1] As a result, more recently, a variety of organic reactions have been successfully carried out in the solid phase.[2] Our current research is directed at the development of polymer bound reagents for amino group modification, including the use of polymer-bound 1-hydroxybenzotriazole (**P**-HOBT). **P**-HOBT was originally developed as a highly reactive N-acylating agent for the formation of peptide bonds,[3] and has recently been used for the synthesis of simple amides.[4] Other successful polymer-bound acylating agents include *N*-hydroxysuccinimide,[5] carbodiimide[6] and triphenylphosphine.[7] We have utilized **P**-HOBT for the synthesis of medium-ring lactams from linear precursors,[8] and the preparation of *N*-hydroxysuccinimide (NHS) esters.[9] Moreover, we have shown **P**-HOBT to be recyclable and stable for extended periods under ambient conditions.[9] Herein, we report the convenient protection of primary and secondary amines as fluorenylmethoxycarbonyl (Fmoc), benzyloxycarbonyl (Cbz) and *tert*-butoxycarbonyl (*t*-Boc) carbamates utilizing **P**-HOBT.

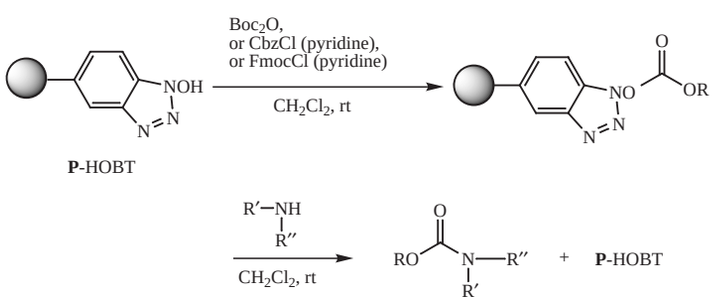
P-HOBT was prepared from Bio-Rad SM-2 dried macroporous beads (polystyrene–divinylbenzene copolymer resin, 100–200 mesh, MW cutoff 2000) according to the method of Fridkin and Patchornik.[3] The activity of **P**-HOBT was determined to be 0.25 mmol g^{-1} based on the synthesis of *N*-isopropylacetamide.[9] For the protection reaction, **P**-HOBT was suspended in CH_2Cl_2 and reacted with Boc_2O, or with Fmoc-Cl or Cbz-Cl in the presence of pyridine (1.5 equiv. based on **P**-HOBT used) to yield the immobilized carbonates (Scheme 1). The resulting polymer was collected by filtration and re-suspended in CH_2Cl_2 (or 3 : 1 DMF–H_2O, depending on amine solubility). The amine, as limiting reagent, was added and the suspension was rocked for 3–20 hours. The suspension was subsequently filtered, and the filtrate concentrated under reduced pressure to yield the carbamate product, which was analyzed to be pure by TLC and/or ^1H NMR.

Although yields of some reactions were near quantitative, others gave lower yields of product. In these cases, if the reaction of the amine were incomplete, then the carbamate product should be contaminated with the amine. In reactions involving volatile amines, any unreacted amine is potentially removed during the concentration step. In contrast, the presence of much higher boiling amines (*e.g.* 1,5-diaminopentane, 3-aminopropan-1-ol, valine) should be observed in the filtrate if unreacted. In the cases studied, unreacted amine was not observed in the concentrated filtrate. A possible explanation for this is the inefficient removal of the amine or carbamate product from the immobilized reagent during filtration and subsequent washing. The fact that we can reactivate the polymer and reproduce the reaction with no loss of polymer activity, or unexpected products, suggests there is no formation of resin bound carbamates.

A variety of primary and secondary amines were chosen, including those with other reactive functional groups (*e.g.* 3-aminopropan-1-ol, 6-aminohexanoic acid, valine). In all cases, reactions were selective for the amino group. Utilizing the general reaction protocol, Fmoc and Cbz derivatives were obtained in fair to excellent yields, although the yields were poor to fair for the *t*-Boc derivatives. This may be due to steric hindrance at the polymer active site from the *tert*-butyl group in either the polymer activation step with Boc_2O (resulting in inefficient polymer loading), or during the coupling step. Steric arguments may also be invoked to explain the rather poor yield of the Fmoc derivative of diisopropylamine (35%, Table 1). The only aromatic amine used in this study was *p*-phenetidine, which provided a fair yield of the Cbz derivative (65%), but a rather poor yield of the Fmoc derivative (30%). Based on the rather low product recovery, other aromatic amines were not studied.

Of note, several reactions were carried out utilizing water as a co-solvent due to amine solubility. The water did not appear to affect reactivity or recovery of products. This suggests the reaction may be optimized to the convenient protection of water soluble amines (*e.g.* amino acids) with a suitable choice of aqueous buffer or aqueous buffer/organic solvent systems. We are currently studying this possibility.

In summary, a new method has been developed for the facile protection of amino groups as carbamate moieties utilizing



Scheme 1 General method for carbamate protection of amines

Table 1 Carbamates obtained *via* **P**-HOBT

Amine Used	Carbamate products (% yield)		
	N-Cbz	*N*-Fmoc	*N*-*t*-Boc
isopropylamine	60	78	35
piperidine	84	85	43
n-hexylamine	86	79	21
L-valine benzyl ester	74	82	
1,5-diaminopentane[a]	68	67	
6-aminohexanoic acid[b]	61	99	
3-aminopropan-1-ol		92	
L-valine[b]	60	43	
p-phenetidine	65	30	
benzylamine		99	
pyrrolidine		88	
diisopropylamine		35	

[a] bis-carbamate derivative, [b] DMF–H_2O (3:1) used as solvent in place of CH_2Cl_2.

polymer bound HOBT. The major advantages of this method include the ability to prepare protected amines in pure form with no work-up, and the potential for automation. As a result, this methodology is not only amenable to combinatorial chemistry, but will also be useful for the protection of amino moieties in complex, biologically active compounds, including the use of aqueous reaction conditions for water soluble amines.

Experimental section

General

All carbamate forming reactions utilizing **P**-HOBT were carried out in 8 ml Extract-Clean™ solid phase extraction tubes (from Alltech Associates, Inc.), equipped with a disposable inlet cap and a one-way stopcock on the outlet. Reactions were mixed by gentle rocking and filtration was carried out using a 12-port solid phase extraction manifold connected to a water aspirator. All yields reported are isolated yields of products obtained directly by concentration of the filtrate from the **P**-HOBT mediated carbamate forming reaction, with purity based on thin-layer chromatography (TLC) and NMR spectroscopy. Mass spectra were obtained by the Mass Spectrometry Laboratory at the University of Maryland, College Park, Maryland.

N,*N*′-Bis(benzyloxycarbonyl)-1,5-diaminopentane

Benzyl chloroformate (0.060 g, 0.050 ml, 0.35 mmol, 2.6 equiv.) was added to a suspension of **P**-HOBT (0.135 mmol, 0.541 g, 0.25 mmol g^{-1}, 1.0 equiv.) in 5 ml of CH_2Cl_2, followed by the addition of pyridine (0.039 g, 0.040 ml, 0.49 mmol, 3.6 equiv.). The suspension was rocked at 25 °C for 1 h. At this time, the polymer was filtered, washed with CH_2Cl_2 (3 × 5 ml), DMF (3 × 5 ml), CH_2Cl_2 (3 × 5 ml) and dry Et_2O (3 × 5 ml). The dried polymer was suspended in CH_2Cl_2 (5 ml) followed by the addition of 1,5-diaminopentane (0.0061 g, 0.0070 ml, 0.060 mmol, 0.88 equiv. of NH_2 groups based on activated polymer). The suspension was rocked at 25 °C for 5 h. The polymer was then filtered and washed with CH_2Cl_2 (4 × 5 ml). The filtrate and washings were combined and concentrated to yield 0.015 g (68%) of *N*,*N*′-bis(benzyloxycarbonyl)-1,5-diaminopentane. ^{1}H NMR (300 MHz, $CDCl_3$, TMS internal reference) 1.35 (m, 2H, Cbz-NHCH$_2$CH$_2$C*H*$_2$CH$_2$CH$_2$NH-Cbz), 1.50 (m, 4H, Cbz-NHCH$_2$C*H*$_2$CH$_2$C*H*$_2$CH$_2$NH-Cbz), 3.17 (m, 4H, Cbz-NHC*H*$_2$CH$_2$CH$_2$CH$_2$C*H*$_2$NH-Cbz), 4.80 (br s, 2H, 2 N*H*), 5.08 (s, 4H, 2 ArC*H*$_2$O), 7.34 (br s, 10H, Ar*H*) (FAB LRMS Calcd. for $C_{21}H_{27}N_2O_4$ $[M + 1]^+$ 371; Found: $[M + 1]^+$ 371).

All other carbamate products were formed in an analogous fashion to *N*,*N*′-bis-Cbz-1,5-diaminopentane. All carbamate products provided satisfactory ^{1}H NMR and MS analysis.

Acknowledgements

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