HOBT immobilized on macroporous polystyrene beads: a useful reagent for the synthesis of amides

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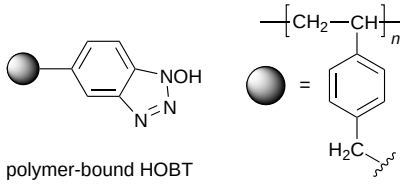
Polymer-supported 1-hydroxybenzotriazole (P-HOBT), prepared from macroporous polystyrene beads, was used to synthesize amides from primary and secondary amines.

Combinatorial chemistry has led to much research in the use of solid-phase organic synthesis techniques.[1] Polystyrene-supported 1-hydroxybenzotriazole (**P**-HOBT) was originally developed as a highly reactive *N*-acylating agent for the formation of peptide bonds.[2] Ongoing studies in our laboratory are directed at the development of **P**-HOBT as a generally useful acylating agent. We have utilized **P**-HOBT for the synthesis of medium-ring lactams from linear precursors,[3] the preparation of *N*-hydroxysuccinimide (NHS) esters[4] and the carbamate protection of amines.[5] A recent report describes the use of HOBT immobilized on an aminomethylated Merrifield resin for the synthesis of simple amides.[6] We are interested in utilizing **P**-HOBT for the derivatization of naturally occurring amines for improved chromatographic separation and identification properties. The use of HOBT immobilized on Merrifield type polystyrene resins, whose degree of swelling varies greatly depending on the solvent, would limit the variety of solvents utilized for amide formation. Herein, we report the use and advantages of HOBT immobilized on macroporous polystyrene beads for the amide derivatization of amines.



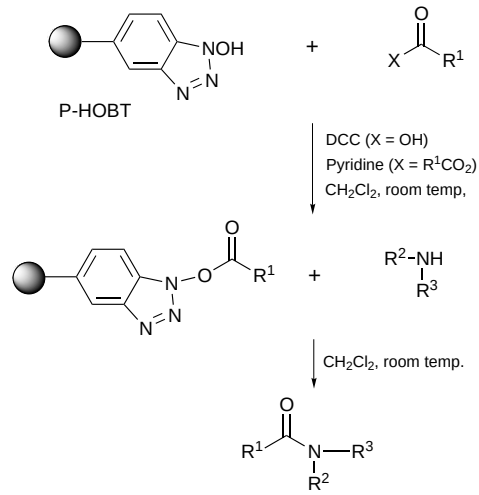
polymer-bound HOBT

We prepared **P**-HOBT using 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.[2]‡ We chose to use the macroporous SM-2 beads, designed as a chromatographic support for hydrophobic interaction chromatography, due to their ability to be used in aqueous, as well as organic solvents without swelling or contraction.[7] The number of active sites on the resin was determined by forming the polymer-bound acetate ester, followed by subsequent treatment with isopropylamine (large excess) to yield *N*-isopropylacetamide and recovered polymer. Based on the yield of recovered *N*-isopropylacetamide, three batches of polymer-bound reagent were prepared with activities of 0.27 (**1**) 0.25 (**2**) and 0.25 mmol g^{-1} (**3**), respectively.§ Polymers **1** and **2** were prepared and stored undessicated at room temperature for two years. At this time, both polymers retained *ca.* 90% of their original activity.

With the polymer in hand, the synthesis of a variety of amides was completed, as shown in Scheme 1. Acetamides, benzamides and amides of pyrene-1-carboxylic acid were chosen due to their potential for use as derivatization reagents for naturally occurring amines for improved chromatographic separation and detection properties. In general, the polymer-bound ester was formed by addition of the acid anhydride to the immobilized HOBT group in the presence of pyridine, or by coupling of the free carboxylic acid to the polymer using DCC as catalyst. The solvent in both cases was CH_2Cl_2. After washing the activated resin thoroughly, it was suspended in a solution of CH_2Cl_2 containing 0.8 equiv. of amine based on polymer activity. The reaction mixture was rocked for 4 h at room temperature, at which time filtration of the resin and subsequent concentration of the filtrate yielded the desired amide as the only observable product.¶‖ A summary of these results is given in Table 1. Of particular interest is entry **8**, in which water was used as a co-solvent to enhance the solubility of 6-aminohexanoic acid. The use of water did not have any deleterious effects on overall reactivity or diffusion through the polymer.

We have previously shown the **P**-HOBT reagent to be completely recyclable for the synthesis of NHS esters.[4] Here we have re-used the same batches of **P**-HOBT **2** and **3** for the synthesis of all amides *via* two protocols. The first method involves reactivation of used **P**-HOBT to synthesize amides utilizing the same carboxylic acid partner. Once used, the resin was washed with CH_2Cl_2, Pr^iOH–CH_2Cl_2 and Et_2O to remove any remaining unbound reagents. The washed **P**-HOBT was then reactivated using the carboxylic acid or the acid anhydride as described above, followed by subsequent treatment with an amine to yield the amide product. Alternately, the spent **P**-HOBT was used to synthesize amides utilizing a different acid coupling partner, following a two step reactivation procedure. The used polymer was reacted with a large excess of isopropylamine (based on polymer activity), followed by a rigorous washing protocol, utilizing CH_2Cl_2, Pr^iOH–CH_2Cl_2, DMF, CH_2Cl_2 and Et_2O to yield the clean polymer. The regenerated polymer was subsequently used to prepare amides *via* the general protocol described above.

In summary, polymer-supported HOBT, synthesized from macroporous polystyrene beads, has been utilized for the synthesis of amides from carboxylic acids and primary and



Scheme 1

Table 1 Amide formation utilizing P-HOBT

Entry	Carboxylic acid	Amine	Yield (%)[a]
1	AcOH	Pr^iNH_2	88
2	AcOH	Cyclohexylamine	97
3	AcOH	Piperidine	87
4	AcOH	*n*-Hexylamine	91
5	AcOH	$BnNH_2$	96
6	AcOH	Pr^nNH_2	96
7	AcOH	3-Aminopropan-1-ol	99
8	AcOH	6-Aminohexanoic acid[b]	83
9	AcOH	Pyrrolidine	85
10	AcOH	1,5-Diaminopentane[a]	96
11	BzOH	Pr^iNH_2	83
12	BzOH	Cyclohexylamine	99
13	BzOH	Piperidine	96
14	BzOH	*n*-Hexylamine	94
15	BzOH	$BnNH_2$	86
16	BzOH	Pr^nNH_2	91
17	BzOH	3-Aminopropan-1-ol	63
18	BzOH	Pyrrolidine	77
19	BzOH	1,5-Diaminopentane[c]	72
20	Pyrenecarboxylic acid	Pr^iNH_2	92
21	Pyrenecarboxylic acid	Piperidine	99
22	Pyrenecarboxylic acid	3-Aminopropan-1-ol	79

[a] The amides were recovered as the only product (purity determined by ^1H NMR spectroscopy) and the yields were based on the amount of amine used. [b] DMF–H_2O (70 : 30) used as solvent in place of CH_2Cl_2. [c] Formed *N*,*N*′-diacetyl-1,5-diaminopentane.

secondary amines. The polymeric reagent displays high reactivity, is recyclable and can be used with a variety of solvents, including water. We feel that this reagent provides an efficient and facile pathway to prepare amides in high yields and purity. We are currently utilizing this method for the derivatization of amines from biological sources, and for the preparation of small molecule amide libraries.

The authors thank the University of Maryland, Baltimore County for financial support.

Notes and References

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‡ *Immobilization of HOBT on polystyrene beads* (ref. 2): A suspension of 3-nitro-4-chlorobenzyl alcohol (5.01 g, 26.7 mmol), dried BioRad SM-2 macroporous beads (5.00 g, polystyrene–divinylbenzene copolymer resin, 100–200 mesh, MW cutoff 2000, Bio-Rad Laboratories) and anhydrous $AlCl_3$ (5.01 g, 37.6 mmol) in 30 ml of nitrobenzene was heated at 65–70 °C for 3 days. The suspension was cooled to room temperature and filtered. The polymer was then washed with a solution of 1 M HCl in dioxane (3 × 25 ml), DMF (3 × 25 ml), MeOH (3 × 25 ml) and CH_2Cl_2 (3 × 25 ml), and finally dried *in vacuo*. The 3-nitro-4-chloro benzylated polystyrene was heated to reflux in a mixture of hydrazine monohydrate and ethylene glycol monoethyl ether (4 : 6, v/v; 30 ml) for 20 h. The reaction mixture was cooled to room temperature and the polymer was filtered and washed with H_2O (3 × 25 ml) and CH_2Cl_2 (3 × 25 ml). The polymer was resuspended in a mixture of concentrated aq. HCl and dioxane (1 : 1, v/v; 50 ml) and the suspension was heated at reflux for 20 h. At this time, the polymer was filtered and washed with H_2O (5 × 50 ml), MeOH (3 × 50 ml) and Et_2O (3 × 25 ml), and finally dried *in vacuo* at room temperature to yield 4.90 g of **P**-HOBT.

§ *Assay of hydroxy group content in P-HOBT* **2**: To a suspension of **P**-HOBT **2** (0.450 g) in CH_2Cl_2 (5 ml) was added Ac_2O (0.32 g, 0.30 ml, 3.1 mmol) and pyridine (0.20 g, 0.20 ml, 2.5 mmol). The suspension was subsequently rocked for 1 h at 25 °C. At this time, the polymer was filtered, washed with CH_2Cl_2 (25 ml), DMF (2 × 40 ml), CH_2Cl_2 (3 × 25 ml) and anhydrous Et_2O (3 × 25 ml). The polymer was re-suspended in CH_2Cl_2 (5 ml) followed by the addition of isopropylamine (0.208 g, 0.300 ml, 3.52 mmol). The suspension was rocked at 25 °C for 3.5 h. The polymer was then filtered and washed with CH_2Cl_2 (3 × 25 ml). The filtrate and washings were combined and concentrated to yield 0.0113 g of *N*-isopropyl acetamide as a clear oil. This gave an activity of 0.248 mmol g^{-1} for **P**-HOBT **2**. All other polymers were tested in this fashion.

¶ *Typical experimental procedure for the synthesis of amides:* A suspension of **P**-HOBT **2** (0.33 g, 0.25 mmol g^{-1}, 0.083 mmol), Ac_2O (0.026 g, 0.024 ml, 0.25 mmol, 3.0 equiv.) and pyridine (0.021 g, 0.021 ml, 0.26 mmol, 3.2 equiv.) in CH_2Cl_2 (10 ml) was rocked for 1 h at 25 °C. At this time, the polymer was filtered, washed with DMF (2 × 10 ml), CH_2Cl_2 (3 × 10 ml) and anhydrous Et_2O (3 × 10 ml). The polymer was resuspended in CH_2Cl_2 (10 ml) followed by the addition of 3-aminopropan-1-ol (0.0051 g, 0.0052 ml, 0.068 mmol, 0.82 equiv. based on **P**-HOBT **2**). The suspension was rocked at 25 °C for 3.5 h. The polymer was then filtered and washed with CH_2Cl_2 (3 x 15 ml). The filtrate and washings were combined and concentrated to yield 0.0079 g (99%) of *N*-acetyl-3-aminopropan-1-ol as a white solid.

‖ All other amides were formed in an analogous fashion as *N*-acetyl-3-aminopropan-1-ol. The ^1H NMR and mass spectral data of all of the prepared compounds were consistent with the expected structures.

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Received in Corvallis, OR, USA, 17th November 1997; 7/08273H