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Phthalimide Resin Reagent for Efficient Mitsunobu Amino-Dehydroxylation

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Abstract: A phthalimide-containing resin has been designed and prepared from trimellitic anhydride. It provides an efficient route to primary amines from corresponding alcohols via Mitsunobu coupling with subsequent hydrazine-induced cleavage. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: nucleosides; amination; polymer support.

The trend in transferring traditional solution phase chemistry onto solid phase has grown enormously since R. B. Merrifield introduced solid phase chemistry for peptide synthesis in 1963.[1] Easy workup and increased yields have made it a method of choice in the synthesis of macromolecules.[2] Developments in combinatorial chemistry expanded the field further.[3] Polymers have been used not only as a support for substrates but increasingly for reagents as well.[4-7]

Mitsunobu coupling of phthalimide to alcohols has been widely used *en route* to primary amines over the years.[8,9] It is a facile reaction that affords near quantitative yield of the functionalized imide; however, the workup typically requires laborious chromatographic purification, with triphenylphosphine oxide and DEAD adduct being the major byproducts. Polymer-bound triphenylphosphine was introduced in 1992 as a way to simplify purification.[6] We decided to prepare a solid phase phthalimide reagent that would make the process significantly more efficient, with the possibility of using excess DEAD and Ph_3P. Subsequent hydrazinolysis releases the primary amine into the solution along with very little or no contaminants.

The solid phase reagent could be used for a variety of purposes including (i) facile selective conversion of less sterically hindered alcohols to corresponding primary amines and (ii) resin-based combinatorial library generation starting with an alcohol.

The initial stages of the work included the synthesis of the phthalimide analogue for resin coupling. Trimellitic anhydride (**1**) was fused with 2 eq ammonium carbonate to yield the corresponding imide, which was tritylated in 95% yield. Protected imide (**2**) was coupled to aminomethyl polystyrene resin in dimethylacetamide (DMA) with PyBOP and diisopropylethylamine

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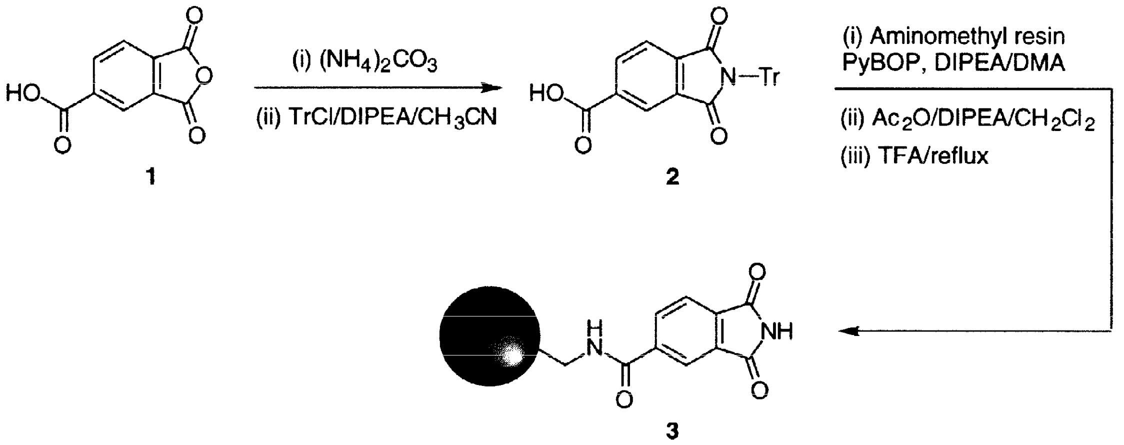
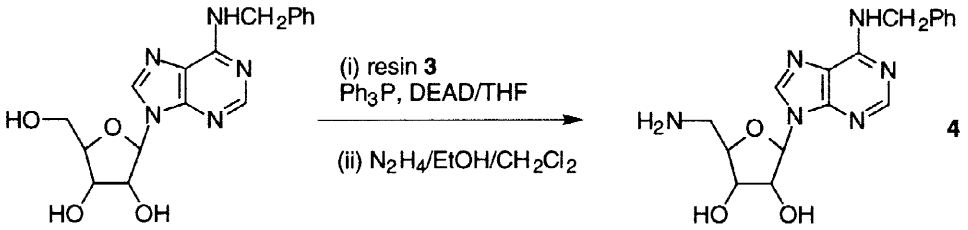
(DIPEA), and unreacted amines on the resin were capped with acetic anhydride. Coupling efficiency was estimated in the subsequent TFA-promoted detritylation step (see Scheme 1). Trityl absorption was monitored at 400 nm and was found to change linearly with concentrations up to 300 μM (standard curve generated by treating a known amount of **2** with TFA). The resin with the highest phthalimide loading was obtained when using 10 eq of both **2** and PyBOP over 48 h (80% loading); reducing excess reagents to 5 eq resulted in 69% loading, while shorter coupling time (24 h) decreased the loading to 55%.

Scheme 1



Activated resin was tested in a Mitsunobu reaction with 1.3-fold excess of N^6-benzyladenosine. The nucleoside was coupled to the resin under standard Mitsunobu conditions[9], and subsequent hydrazinolysis in CH_2Cl_2/EtOH resulted in > 96% yield of the 5'-amino-5'-deoxy-N^6-benzyladenosine product (using resin as the limiting reagent). Excess hydrazine was removed *in vacuo*, and the product was shown to be pure by reverse phase HPLC.

Scheme 2



When D,L-α-*O*-benzyl glycerol was reacted with the resin, the primary carbon was aminated in 85% yield selectively, as in N^6-benzyladenosine. An allylic carbon was aminated in cinnamyl alcohol in 93% yield. The products were 85-95% pure by TLC. A somewhat hindered secondary alcohol in menthol did not get converted to the amine.

In summary, we prepared a phthalimide-containing resin that can be used for conversion of hydroxyl functionalities of primary alcohols to primary amines with workup being limited to simple filtration. The resin can also be useful for attaching complex molecules such as nucleosides to a solid support for combinatorial library construction. The materials for the preparation of the resin are inexpensive and readily available, and the overall yield for the preparation of the linker is > 90%.

Fusion conditions. To a melt of 2 g trimellitic anhydride (10.4 mmol) at 200 ^{0}C was added 1 g (1 eq, 10.4 mmol) ammonium carbonate and the material was heated to 280 ^{0}C over 20 min in a 25 mL Erlenmeyer flask in a molten salt bath (53% KNO_3, 40% $NaNO_2$, 7% $NaNO_3$) heated with a hot plate. One g of ammonium carbonate (1 eq, 10.4 mmol) was then added in small portions with stirring so that the mixture remained molten at all times, and the temperature was held constant at 280 ^{0}C for 20-30 min. The melt was cooled to room temperature, and the crude product was recrystallized from water to yield 1.9 g (95% yield) of the corresponding imide as an off-white solid. The scale-up of this procedure to 35 g trimellitic anhydride was carried out in 80% yield, with decarboxylation as the major side reaction; this can be minimized by keeping the bath temperature under 290 ^{0}C.

Tritylation conditions. To a suspension of 1 g trimellitic imide (5.2 mmol) in 40 mL CH_3CN, 1.45 g trityl chloride (5.2 mmol) and 1.35 mL DIPEA (1.5 eq, 7.8 mmol) were added, and the mixture was stirred under reflux overnight. The solvent was evaporated and the residue partitioned between EtOAc and water. The solvent was removed, the residue was dried *in vacuo*, and product **2** was isolated as a yellow foam (2.14 g, 95% yield). In a scale-up of this reaction the yield decreases with increasing amounts of reagents due to marginal solubility of trimellitic imide in CH_3CN. When reacting 15 g trimellitic imide in 400 mL solvent, the yield can be as low as 30%, with excess trityl chloride removed by extensively washing the recovered solid with hexane, and the product selectively solubilized in chloroform.

Resin preparation. To aminomethyl polystyrene resin (100 mg; 0.13 mmol; 100-200 mesh; 1% divinylbenzene-crosslinked polystyrene from Advanced ChemTech) presoaked in 5 mL DMA for 1 h, 563 mg (1.3 mmol) **2** and 676 mg (1.3 mmol) PyBOP predissolved in 3 mL DMA were added, and the mixture was basified with 0.45 mL (2.6 mmol) DIPEA. Resin suspension was gently shaken on a platform shaker for 24 or 48 h. Following filtration, the polymer was washed with 100 mL CH_2Cl_2 and resuspended in 10 mL CH_2Cl_2. DIPEA (0.5 mL) and acetic anhydride (0.5 mL) were added and the mixture was stirred for 2 h, then filtered and air dried. The resin was suspended in 6 mL TFA and shaken overnight. Deprotected resin **3** was filtered, washed with 5% $Et_3N/CHCl_3$, then rinsed with CH_2Cl_2 and air dried. Overall resin recovery was >97% after 3 steps.

Coupling procedure. To a stirred solution of 110 mg Ph_3P (0.42 mmol), 66 μL DEAD (0.42 mmol) and 113 mg resin **3** (84 μmol phthalimide) in 10 mL dry THF (distilled from $LiAlH_4$ under Ar) was added 39 mg N^6-benzyladenosine (109 μmol). After stirring for 2 h at room temperature the beads were filtered and washed thoroughly with EtOAc and hot CH_2Cl_2. The resin was then air dried to yield 142 mg of the nucleoside resin adduct.

Cleavage conditions. To a stirred suspension of 142 mg of resin-bound nucleoside in 7 mL CH_2Cl_2 was added 200 μL hydrazine hydrate in 3 mL EtOH. The suspension was stirred at reflux for 3 h. The resin was washed with 20 mL CH_2Cl_2, and the combined filtrate was evaporated to dryness *in vacuo* to yield 29 mg **4** (81 mmol, 96%). The purity was confirmed by silica TLC and C_{18} reverse phase HPLC.

^{1}H NMR data for 5'-amino-5'-deoxy-N^6-benzyladenosine **4** (500 MHz, MeOH): δ 3.23 (d, 1, H5"), 3.32 (d, 1, H5'), 4.24 (m, 1, H4'), 4.39 (dd, 1, H3'), 4.78 (dd, 1, H2'), 4.83 (s, 1, CH_2), 5.99 (d, 1, H1'), 7.2-7.7 (m, 5, phenyl), 8.15 (s, 1, H2), 8.26 (s, 1, H8).

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