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A New Scavenger Resin for Amines

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Abstract: Isatoic anhydride (1) can be attached to Merrifield resin by alkylation on its nitrogen. A maximum loading of 3.2 mmol of anhydride/g of 5 was achieved. This resin, due to the highly reactive anhydride moiety, completely removes primary and secondary aliphatic amines from reactions where they are used in excess. © 1998 Elsevier Science Ltd. All rights reserved.

Combinatorial chemistry in conjunction with high throughput biological screening has dramatically increased the number of potential drug candidates which must be synthesized. To satisfy this need, a wide variety of synthetic manipulations have been developed on polymer support which allows the preparation of a multitude of complex molecules.^{1,2} The primary advantage of this technique is that it allows the use of excess reagents which can then simply be removed by washing the resin with appropriate solvents.

Alternatively, this rationale can be used in solution-phase syntheses where reactive scavenger resins are added to the completed reaction to remove any excess reagents. The advantage of this technique is that the reaction can be monitored, the product remains in solution and its purity can be determined by standard methods.

Several polymer-supported quenching reagents have been designed to remove isocyanates, isothiocyanates, acid chlorides, sulfonyl chlorides, and amines.³⁻⁶ Resins used to capture amines contain an isocyanate or acid chloride as the reactive functionality. Polymer-supported isocyanate is prepared from aminomethyl resin and triphosgene,⁵ both of which are rather expensive. Additionally, loading is limited to approximately 1 mmol of NCO/g of resin. This report describes the design, preparation and use of a new high-loading scavenger resin based on an anhydride moiety.

Isatoic anhydride (IA) (1, R = H) is an internally protected and activated form of 2-aminobenzoic acid. The C-4 carbonyl of the heterocyclic ring is highly susceptible to attack by a variety of nucleophiles to give 3 along with carbon dioxide as the only by-product.⁷ The nitrogen of 1 (R = H) can be readily alkylated by deprotonation with sodium hydride followed by reaction with an alkyl halide to give an N-substituted isatoic anhydride.⁸



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This makes the nitrogen an ideal attachment site for functionalization of a polystyrene support. Merrifield resin (4), the least expensive of functionalized polystyrene resins, contains a benzylic chlorine which can serve as a suitable alkylating agent. Treatment of 4 (3.5 mmol of Cl/g) with 1 in the in the presence of sodium hydride gives the IA resin 5. Two strong IR absorptions at 1784 and 1727 cm⁻¹ are observed, indicative of the resinbound anhydride. The loading, as deduced by Cl analysis, was determined to be approximately 2.8 mmol anhydride/g. Additional exposure of the resin 5 to the same reaction conditions raised the maximum loading to 3.2 mmol anhydride/g of 5. The use of a lower loading Merrifield resin (1.7 mmol of Cl/g) resulted in a resin 5 with a maximum loading of approximately 1.5 mmol anhydride/g.



To demonstrate the utility of 5 as a scavenger for amines, phenyl isothiocyanate (6) and N-methylisatoic anhydride (8) were reacted with various amines to produce thioureas 7 and anthranilamides 9. Upon completion of the reaction the IA resin was added and within 30-90 min no detectable amount of amine was observed by ¹Hnmr. For example, Figure 1 illustrates the results of the reaction of 6 with nonylamine to produce 7e. The alkyl region of the nmr of the crude reaction mixture clearly shows the NCH₂ protons of the product at $\delta 3.62$ and excess nonylamine at $\delta 2.67$ ppm. After treatment of the reaction mixture with 5, the upper spectrum shows complete disappearance of the amine. Doisuthine (9e), a naturally occurring anthranilamide isolated from Thai *Glycosmis* species, is readily prepared in nearly quantitative yield and high purity employing this method.

Preparation of IA resin: Merrifield resin 4 (2.0 g, 3.5 mmol of Cl/g) was swelled with 15 mL of DMA. In a separate flask was dissolved 5.7 g (35 mmol) of isatoic anhydride in 40 mL of DMA. To this solution was added 840 mg of sodium hydride in portions. After the evolution of hydrogen ceased, the mixture was stirred at room temperature for 1 h then this solution was added to the preswelled resin 4 and the mixture was shaken for 48 h. The solvent was drained and the resin was sequentially washed with DMF (3x), CH₂Cl₂ (4x), THF (1x) and then was dried under vacuum to give 2.55 g of 5. The resin was recycled using 17 mmol of 1 and sodium hydride to furnish 5 with a loading of 3.2 mmol anhydride/g.

Preparation of the lower-loading resin using 2.0 g of 4 (1.7 mmol of Cl/g) was identical to the above procedure except 17 mmol of 1 and sodium hydride were used and furnished 2.41 g of 5 with a loading of 1.5 mmol anhydride/g (after recycle).

Typical procedure for the reaction of 6 or 8 with amines: To a solution of 1 mmol of either 6 or 8 in 7 mL of CH_2Cl_2 was added 1.2 mmol of amine. After stirring the mixture at room temperature for 14 h⁹, 100 mg of the IA resin 5 (3.2 mmol anhydride/g)¹⁰ was added. The mixture was stirred at room temperature for 90 min then the resin was filtered and the solvent evaporated to give the product (see Table 1).





Table 1. Reaction of 6 and 8 with amines

No.	R ₁	R ₂	Yield (%)	Purity (%) HPLCa	Reference
7a		н	91	99	11
7 b		н	99	97	12
7 c	CH ₂ CH ₂ CH ₂	н	98	99	13
7 d		н	97	98	14
7 e	rrC9H₁9	н	96	96	15
7 f		CH₃	94	99	16
7 g	-CH2CH2OCH2CH2-		95	99	11
9a		н	96	99	17
9b		н	99	99	18
9 c		CH ₃	97	98	19

^aColumn: Waters Radial-Pak 8NVC186; mobile phase: CH₃CN/H₂O (60:40) 1 ml/min; UV detection at 220 nm



Figure 1.¹H-NMR of reaction mixture of 7 e before (lower spectrum) and after treatment with 5.

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- 9. Reactions were typically run overnight however this length of time is not needed for these reactive starting materials.
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