

Polymer-Bound *p*-Alkoxybenzyl Trichloroacetimidates: Reagents for the Protection of Alcohols as Benzyl Ethers on Solid-Phase

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Abstract: Wang and Tentagel resins were converted into their trichloroacetimidate derivatives and used as polymer-bound benzylating reagents for a variety of alcohols. Loading and cleavage proceed in good to excellent yields in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ and 1% TFA respectively. The resins have excellent shelf life. © 1998 Elsevier Science Ltd. All rights reserved.

The area of organic synthesis on polymeric supports has witnessed a great resurgence in recent years,¹ particularly in connection with methods of combinatorial drug discovery and chemical diversity.² A current trend is to extend the feasibility of organic reactions known to take place in homogenous phase to analogous reactions on solid supports. Although much progress has been documented in recent years,¹ the introduction of reactive functionalities on polymers that can serve as sites to anchor or temporarily protect organic molecules is a challenging endeavor. In this regard, only a few examples of the attachment of alcohols to a polymeric support system are known.³

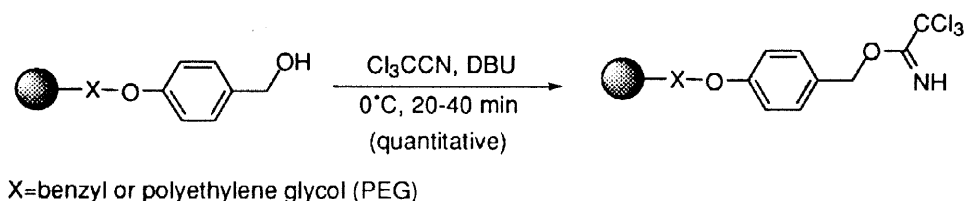
In 1974, we reported⁴ on the acid-catalyzed formation of O-benzylidene acetals from diols and a “benzaldehyde” Merrifield resin.⁵ A number of simple transformations of available hydroxy groups on the immobilized acetals were possible (esterification, etherification, $\text{S}_{\text{N}}2$ displacements, etc.). Acid hydrolysis then released the chemically modified original polyol from the resin in an overall process that is operationally identical to today’s efforts in achieving chemical diversity.

Continuing our interest in the development of methods for solid-phase organic synthesis,⁶ we describe a polymer-bound benzylating reagent for the etherification of alcohols. Benzyl ethers are among the most utilized functionalities for the temporary protection of alcohols in solution.⁷ They are usually compatible with a variety of synthetically useful transformations, particularly under basic conditions. Thus, the availability of a polymer-bound benzylating reagent capable of immobilizing alcohols under mild conditions, the possibility to utilize it as for analogous reactions in solution, and a mild method of cleavage to release the chemically modified alcohol would have wide appeal.

These conditions were in major part fulfilled by the trichloroacetimidate (TCA) derivative obtained from the Wang resin (polymer-bound *p*-benzyloxybenzyl alcohol)⁸, as well as a polyethyleneglycol hydroxymethyl-phenyl resin (PEG-HMP) also known as HMP-Tentagel.⁹

The preparation of the Wang trichloroacetimidate resin (maximum loading, 0.8 mmol/g) (Scheme 1), was achieved as follows: To a suspension of the resin (0.8 mmol) in dry CH_2Cl_2 (10 ml), was added trichloroacetonitrile (1.5 ml), and the mixture was cooled to 0°C . DBU (0.1 ml) was then added to the suspension dropwise over a period of 5 min, and the reaction was allowed to proceed at 0°C for 40 min. The resin was collected on a sintered glass filter and washed with CH_2Cl_2 , DMSO, THF and CH_2Cl_2 . By a similar procedure, but using polyethyleneglycol hydroxymethylphenyl (PEG-HMP) resin, the corresponding benzyl trichloroacetimidate resin was obtained (maximum loading, 0.25 mmol/g). The infrared spectra (KBr) showed the virtual disappearance of the hydroxy stretching band at $\sim 3500\text{ cm}^{-1}$ of the original polymer, with appearance of a strong $\text{C}=\text{N}$ stretching band at 1664 cm^{-1} . The resulting trichloroacetimidate resins were each treated with $\text{Ac}_2\text{O}/\text{Py}$ (or $\text{AcCl}/\text{Et}_3\text{N}$) and no AcO absorption bands were observed in the infrared spectra of the products, which indicated that the conversion of the polymer-bound benzyloxy group to benzyltrichloroacetimidate was complete. Both Wang and PEG-HMP trichloroacetimidate resins are very stable on storage in contrast with either *p*-methoxybenzyl or benzyl trichloroacetimidates in solution. For example, the Wang trichloroacetimidate resin can be left in an open container for two months with no change in its infrared spectrum or in its reactivity.

Scheme 1



The formation of polymer-bound benzyl ethers from alcohols using the above described polymer reagents in the presence of Lewis acids was based on well-known methods for O-benylation utilizing benzyl trichloroacetimidate¹⁰ and *p*-methoxybenzyl trichloroacetimidate¹¹ in solution. In a typical experiment, the TCA resin (100 mg) was washed well with anhydrous THF (2 ml x 4) under nitrogen atmosphere to remove moisture. The resin was suspended in anhydrous cyclohexane (1.5 ml) and the alcohol (2 eq.), dissolved in 1.5 ml of CH_2Cl_2 , was added followed by stirring for 5 min at room temperature. After addition of $\text{BF}_3\cdot\text{OEt}_2$ (5 μl), the suspension was stirred for 5 to 10 min. The reaction was monitored by IR, following the disappearance of the absorption bands at 1664 cm^{-1} and 3340 cm^{-1} . In the cases of substrates containing carbonyl group(s) (entries 1, 2, 3, 5, 7, 11), strong carbonyl stretching bands in the region of $1700 - 1800\text{ cm}^{-1}$ appeared as evidence of attachment. In all cases except entry 8, where the product (geraniol) was found to be acid-labile, the alcohols were recovered after cleavage and weighed, and the loading yields were calculated as indicated in Table 1.

Scheme 2

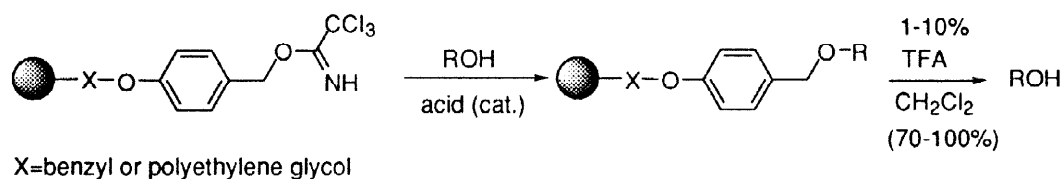

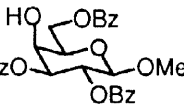
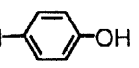
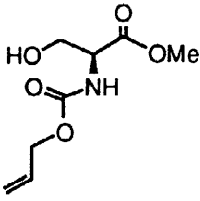
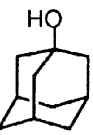
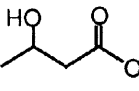
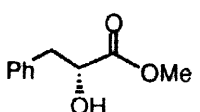
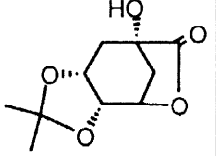

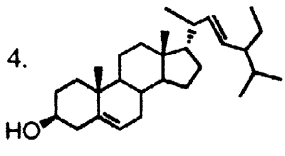
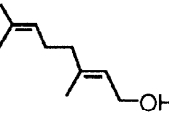
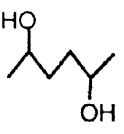
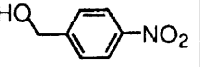
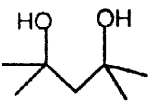


Table 1. Representative Polymer-Bound Alcohols on Wang and PEG-HMP Resins

Alcohols	Yield (%)	Alcohols	Yield (%)	Alcohols	Yield (%)
1. 	95 ^b	5. 	80	10. 	98
2. 	98	6. 	70	11. 	95 ^d
3. 	95 ^{b,d}	7. 	82	12. 	90 ^e
4. 	72	8. 	95 ^c	13. 	90 ^e
		9. 	82	14. 	80

a. Method of determining the yields: Alcohols were cleaved in TFA (10% in CH_2Cl_2) from 100 mg of loaded resins, and weighed. Yield = $(\text{Wa}/\text{MWa})/[(\text{Wr}-\text{Wa})/\text{Cr}]$. Wa: weight of alcohol cleaved from the resin (mg); MWa: molecular weight of the alcohol (mg/mmol); Wr: weight of the loaded resin (0.050 g); Cr: capacity of resin (0.8 mmol/g). b. Also done on PEG-HMP resin. c. Product is unstable in acidic medium. d. Loading was activated with $\text{BF}_3\cdot\text{OEt}_2$ or $\text{Tr}^+\text{ClO}_4^-$. Other alcohols were loaded using $\text{BF}_3\cdot\text{OEt}_2$ as the catalyst. e. Over 95% of the diol was monobenzylation.

Although the etherification could be completed in CH_2Cl_2 alone, the addition of cyclohexane was found to be beneficial without compromising the swelling properties of the Wang resin. Table 1 lists a variety of alcohols representing major classes of organic compounds that were immobilized on the Wang and PEG-HMP trichloroacetimidate resins. Thus, primary, secondary, and tertiary alcohol groups belonging to different classes or organic molecules could be immobilized in good to excellent yields with loading capacities approaching 0.8 mmol/g. The yield in the case of hindered alcohols could be improved by utilizing a five-fold excess or by recycling. It is noteworthy that no racemization was observed in the cases of the α -amino acid derivatives or the α -hydroxy esters (entries 2, 3). Also no β -elimination took place, as evidenced by the excellent yield of etherification of ethyl β -hydroxy butyrate (entry 11).

In spite of the high reactivity of TCA resins under acidic catalysis, monobenzylation of symmetrical diols was achieved by treatment of TCA Wang resin and excess amounts of diols (5–10 eq) with $\text{BF}_3\cdot\text{OEt}_2$. To our knowledge, only primary alcohols have been monoprotected through trityl ether linkage using trityl chloride resins. However, using TCA Wang resin, as shown in Table 1, primary (entry 12), secondary (entry 13) and tertiary alcohols (entry 14) can be monobenzylation on solid phase. In each case, the reaction took only 5 min in comparison to 24 h for solid phase tritylation reactions.^{3b}

Monobenzylation of 1,6-hexanediol and 2,5-hexanediol (entry 12 and 13) on resin were confirmed by acylation and the presence of a strong C=O ester stretching absorption band in IR spectrum. The acetylation products were cleaved from resin and the structures were determined by NMR and compared with those of the authentic monoacetates synthesized in solution. In both cases, over 95% monoacetylated products were obtained. The remaining hydroxy group in resin-bound 2,4-dihydroxy-2,4-dimethylpentane was extremely sterically hindered, and attempts to functionalize the hydroxy group such as acylation and trichloroacetimidation failed.

Cleavage of the polymer-bound benzyl ethers¹² and recovery of the corresponding alcohols (70%-quantitative) could be effected by stirring of the resin in a solution of 1% TFA in CH₂Cl₂. At this concentration, p-iodophenol (entry 10) was released into the solution within 30 min. Benzylic and allylic alcohols (entries 8, 9) were released within 1 h, and the other alcohols were cleaved within 2-4 h. In the presence of 10% TFA in CH₂Cl₂, most alcohols were released within 30 min. Sodium bicarbonate was normally added after TFA cleavage to neutralize the solution, and the resulting salt was filtered with resin.

It should be noted that under the mild conditions of acidic cleavage, all the alcohols except that in entry 8 were recovered without undergoing any chemical or stereochemical change, as evidenced by comparisons of physical constants such as optical rotation (entries 2,3), HPLC analysis (>95% purity, entries 1, 6, 8, 11, 14), and other criteria, mp, t.l.c. MS (entries 4, 5, 7) with authentic samples.

The following paper outlines the scope of reactions that can be effected with such polymer-bound benzyl ethers in the context of chemical and functional diversity.

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