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The Use of Trichloroacetimidate-activated Resin for Ester Formation

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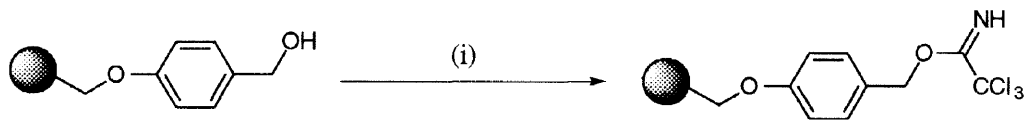
Abstract: The preparation of trichloroacetimidate-activated Wang resin is described. The resin is used to prepare carboxylic, phosphonic, and sulfonic esters and carboxylic thioesters, thiol ethers, and thiol resin. The role of Lewis acid catalysis in ester formation is explored.

Introduction

Many of the methods of attaching molecules to the solid phase have parallels in solution phase protecting group chemistry.[1] A recent example is the use of the trichloroacetimidate group to activate Wang resin for ether formation.[2] We have found this resin to be of general utility in the formation of a range of esters. In particular we describe its use in the formation of resin-bound carboxylic, phosphonic, and sulfonic esters and carboxylic thioesters.

Preparation of Trichloroacetimidate Resin



Scheme 1. (i) CCl_3CN, 50% aq. KOH, *n*-Bu_4NHSO_4, CH_2Cl_2, 0 °C, 1 h, then 25 °C, 24 h (96%).

Trichloroacetimidate resin can be formed readily from Wang resin by adding trichloroacetonitrile in the presence of aqueous potassium hydroxide and a phase transfer catalyst (Scheme 1).[3] Gentle stirring of the suspension during the addition of trichloroacetonitrile gave a resin loading of only 59% (by Cl analysis). This improved to 96% when the reaction mixture was agitated by bubbling nitrogen through it. This procedure[4] contrasts with the anhydrous conditions reported previously.[2] The resulting trichloroacetimidate resin has excellent shelf-life as it can be stored in a desiccator for at least six months with no degradation as observed by FTIR spectroscopy.

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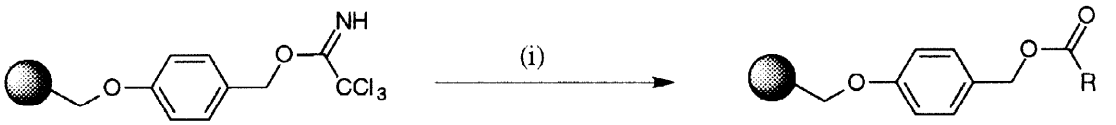
Carboxylic Ester Formation

Several methods have been reported for making ester linkages to an alcohol on resin, including: DCC or DIC-DMAP coupling, transesterification, and addition of acid chloride or acid anhydride.[1] However on occasions these approaches give poor yield, for example the use of DCC-DMAP system was inefficient for attaching bromoacetic acid.[5] It is known that benzyl trichloroacetimidate reacts with a variety of carboxylic acids in the presence of $BF_3.Et_2O$ to give the corresponding esters in high yields.[6] We therefore explored this reaction on Wang resin, and specifically investigated the need for Lewis acid catalysis.



Scheme 2. (i) RCO_2H (5 eq. ± $BF_3.Et_2O$), CH_2Cl_2 or 1,2-dimethoxyethane or a mixture,[7] 23 °C.

A series of substituted acetic acids were used, to study the effect of acid pK_a on reactivity. Ester formation was complete in 2 hours at 23 °C when bromoacetic acid (pK_a = 2.7) was added to the resin in the absence of $BF_3.Et_2O$.[8] The progress of reaction was monitored by FTIR spectroscopy which showed the total disappearance of bands associated with trichloroacetimidate and appearance of a strong band at 1738 cm^{-1}. Similar results were obtained with chloroacetic acid (pK_a = 2.9) and cyanoacetic acid (pK_a = 2.5). With acetic acid (pK_a = 4.8), the reaction was much slower and was nearly complete after 32 hours, as evidenced by the minor residual bands of trichloroacetimidate and appearance of a strong band at 1729 cm^{-1}.

A series of benzoic acids were also studied. In general they were found to react more slowly. Ester formation was complete for the most acidic acid, *o*-nitrobenzoic acid (pK_a = 2.2) after 32 hours. In the same time, only partial conversion was observed for *o*-chlorobenzoic acid (pK_a = 2.9) and *p*-nitrobenzoic acid (pK_a = 3.4). No loss of the trichloroacetimidate was apparent by FTIR spectroscopy after 32 hours with benzoic acid (pK_a = 4.2). Complete conversion was achieved in 2 hours for all these benzoic acids in the presence of 0.7 equivalents (with respect to the trichloroacetimidate sites) of $BF_3.Et_2O$.

Formation of Phosphonic and Sulfonic Esters

The success in forming carboxylic esters on resin, prompted us to explore the formation of phosphonic and sulfonic esters. Because of the low pK_as of these acids it was reasoned that no Lewis acid catalysis would be required. This was found to be the case. For example, reaction of trichloroacetimidate-activated Wang resin with phenylphosphonic acid (1.2 equivalents, 23 °C, 1 hour), led to formation of the phosphonic ester in 70% yield based on phosphorus analysis.

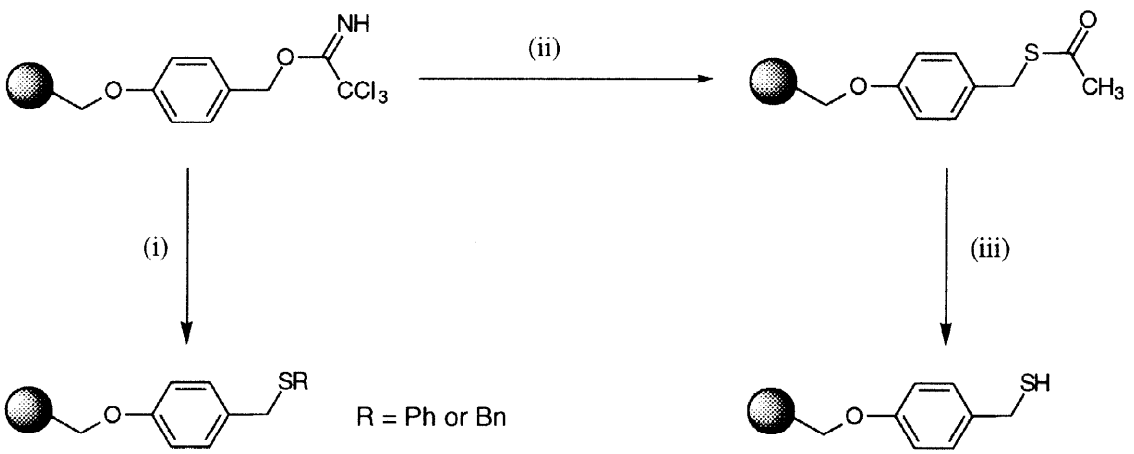
Reaction of trichloroacetimidate-activated Wang resin with (±)-10-camphorsulfonic acid (1.5 equivalents, 23 °C, 30 minutes), led to formation of the sulfonic ester in moderate yield (54% based on S analysis). When this reaction was carried out with 2,4,6-trinitrobenzenesulfonic acid (DANGER: explosive) (1.3 equivalents, 23 °C, 2 hours), the reaction appeared complete after 2 hours. The nitro stretching frequencies were observed at 1545 and 1357 cm^{-1}. The sulfonic ester appears to be stabilised on the resin and is not hydrolysed by water present in the reaction mixture. A similar stability has been observed for resin-bound triflic ester. This was formed accidently when attempting to use triflic acid to catalyse the reaction between trichloroacetimidate-activated Wang resin and a benzyl alcohol. The role of the triflic acid was assumed to be simply that of a Bronsted acid.[9] However when the resin was treated with triflic acid (2.5 equivalents in dimethoxyethane, 23 °C, 5 hours, 5 eq. benzyl alcohol) the

triflate formed on the resin. It was detected by gel-phase fluorine NMR spectroscopy ($\delta(CF_3) = -77$ ppm).

Thiol Ethers, Thioesters and Thiol Resin Formation

There is a growing interest in sulfur chemistry on resin.[10] In order to get a high sulfur loading on resin, we investigated the use of trichloroacetimidate activated resin for making thiol ethers and thioesters. Reaction of the resin with either thiophenol or benzyl mercaptan in the presence of $BF_3.Et_2O$ (0.7 equivalents) led to formation of the corresponding thiol ethers in over 97% yield based on sulfur analysis (Scheme 3).

Resin-bound thiolacetic ester was formed by reacting activated resin with thiolacetic acid in the presence of $BF_3.Et_2O$.[11] The yield was 93% based on sulfur analysis. Cleavage of the thioester with either lithium benzyloxide, at 23 °C, or *n*-BuLi at 0 °C, gave the thiomethyl Wang resin.[12] Using lithium benzyloxide, the cleavage proceeded in 91% yield to give a sulfur loading on the resin of 0.77 mmol/g as determined by sulfur analysis. The cleavage of the acetate group was monitored by the disappearance of the carbonyl absorption band at 1688 cm^{-1}.



Scheme 3. (i) thiophenol or benzyl mercaptan (5 eq.), $BF_3.Et_2O$ (0.7 eq.), anhydrous CH_2Cl_2, 23 °C, 16 h, (97%); (ii) thiolacetic acid (5 eq.), $BF_3.Et_2O$ (0.8 eq.), anhydrous DME, 23 °C, 16 h (93%); (iii) LiOBn, anhydrous THF, 23 °C, 2 h; wash with H_2O, (91%).

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4. *Preparation of Trichloroacetimidate Resin.* To a suspension of Wang resin (loading 1.08 mmol/g; 2 g) in CH_2Cl_2 (30 mL) was added 50% aqueous potassium hydroxide (5 mL) and tetra-*n*-butylammonium hydrogen sulfate (0.29 g). The suspension was cooled to 0 °C with gentle agitation by a stream of nitrogen.

Trichloroacetonitrile (1.73 mL, 17.3 mmol) was then introduced dropwise. Nitrogen bubbling was continued at 0 °C for 1 hour. The suspension was then shaken at 25 °C for 24 hours, and filtered. The pale yellow resin was washed successively with THF-H_2O 3:2 (3 x 25 mL), CH_2Cl_2 (3 x 25 mL), THF-H_2O 3:2 (3 x 25 mL), H_2O (3 x 25 mL), THF (3 x 25 mL), CH_2Cl_2 (3 x 25 mL), and dried *in vacuo* for 48 hours. FTIR (CH_2Cl_2): 3340 cm^{-1} (m, N-H), 1664 cm^{-1} (s, C=N), 798 cm^{-1} (m, C-Cl), 650 cm^{-1} (m, C-Cl).

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6. Kokotos, G.; Chiou, A. *Synthesis* **1997**, 168-170.
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8. *Preparation of Bromoacetylated Wang Resin.* A solution of bromoacetic acid (56 mg, 0.405 mmol) in anhydrous CH_2Cl_2 (4 mL) was added to trichloroacetimidate resin (loading 0.81 mmol/g; 100 mg). The suspension was stirred gently at 23 °C for 2 hours, then filtered. The resin was washed with CH_2Cl_2 (3 x 5 mL), THF-H_2O 3:2 (3 x 5 mL), THF (3 x 5 mL), CH_2Cl_2 (3 x 5 mL), and dried *in vacuo* for 48 hours.
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11. *Formation of Thiolacetic Ester Resin.* To a suspension of trichloroacetimidate resin (loading 0.81 mmol/g; 500 mg) in anhydrous 1,2-dimethoxyethane (6 mL) was added thiolacetic acid (150 mL, 2.03 mmol). After 30 minutes of gentle stirring at 23 °C, $BF_3.Et_2O$ (40 µL, 0.32 mmol) was added dropwise. The suspension was gently stirred at 23 °C for 16 hours, then filtered. The resin was washed with CH_2Cl_2 (3 x 10 mL), THF-H_2O 3:2 (3 x 10 mL), H_2O (3 x 10 mL), THF (3 x 10 mL), CH_2Cl_2 (3 x 10 mL), and dried *in vacuo* for 48 hours.
12. *Cleavage of Thioester Resin.* A solution of lithium benzyloxide (0.52 mmol) in anhydrous THF (2 mL) was added to the thioester resin (loading 0.82 mmol/g; 20 mg). The suspension was gently stirred at 23 °C for 2 hours, then filtered. The resin was washed with CH_2Cl_2 (3 x 5 mL), THF-H_2O 3:2 (3 x 5 mL), H_2O (3 x 5 mL), THF (3 x 5 mL), CH_2Cl_2 (3 x 5 mL), and dried *in vacuo* for 48 hours.