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Immobilization of glyoxylic acid on Wang resin

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Abstract

We report herein the simple preparation of immobilized glyoxylic acid, where the acid function is either linked through an amide or an ester bond to Wang resin. These compounds represent interesting aldehyde inputs for the generation of new libraries of small molecules. © 2000 Elsevier Science Ltd. All rights reserved.

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Resin-bound aldehydes have been used in combinatorial chemistry on solid support in a very large range of different types of reactions. In most cases, the preparation of the resin-bound aldehyde is performed by linking a preformed aldehyde to the polymer or by generating the aldehyde functionality from a resin-bound primary alcohol by various oxidation methods (e.g. Swern oxidations or ozonolysis). In contrast, despite their versatility in solution phase chemistry, resin-bound glyoxylic acid ester or amide derivatives have received only little attention. They have been mostly used in combination with peptide synthesis, where glyoxylyl peptides provide an important way for the assembly of large constructs from smaller fragments through efficient chemical reactions, such as hydrazone, oxime and thiazolidine chemical ligations.[1] To date, literature methods for immobilizing glyoxylic acid have exclusively employed polymers compatible with aqueous solvents, and the aldehyde function is usually generated via periodic oxidation of a terminal serine.[2]

As part of our ongoing research in combinatorial chemistry we wished to employ a glyoxylic entity bound on polystyrene resin, due to its high loading, its mechanical properties, its ability to swell in a wide range of organic solvents, and its compatibility with lipophilic reagents. We decided to prepare two types of glyoxylic linkers, one being anchored through an amide bond to the polymeric support, the other via an ester functionality. To prepare the amide-based linker, we tried to transfer directly the literature procedures based on serine mentioned above to a polystyrene-bound amine, but no significant amount of the expected compounds was obtained, probably due

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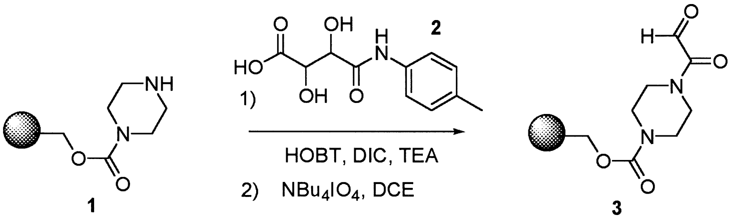
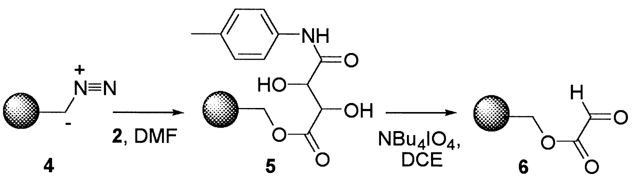
to the low solubility of sodium periodate in resin-compatible solvents. Concerning the ester-linked immobilized glyoxylic acid, we anticipated severe problems during the coupling procedure. The primary hydroxyl group of serine is likely to undergo an unwanted acylation reaction and would hence require elaborate protection schemes. In order to avoid the solubility problems as well as the undesired acylation reactions, we developed a procedure using a immobilized tartranilic acid derivative combined with tetrabutylammonium periodate to perform the oxidation of the diol. This method has led to the desired glyoxylyl resins, with both amide and ester anchors.

For the preparation of amide linked glyoxylic acid derivative **3** (Scheme 1), we first coupled (–)-4-methyltartranilic acid **2**, to the previously prepared piperazine Wang resin **1**[3] by the intermediate preparation of an active ester. Compound **2** has good solubility in DMF, is commercially available or easily accessible adapting literature procedures.[4] No acylations of the hydroxyl functions were observed and the coupling efficiency has been determined[5] to be 81% based on the theoretical loading of the resin. The oxidative cleavage of the diol was smoothly carried out using tetrabutylammonium periodate readily soluble in 1,2-dichloroethane. Reactions with sodium periodate or lead tetraacetate did not lead to the desired product.



Scheme 1.

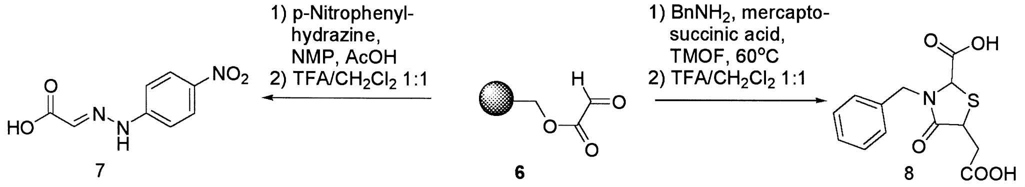
Following the same strategy, we tried to obtain derivative **6** (Scheme 2) where glyoxylic acid is bound directly to Wang resin through an ester bond. However, several attempts to perform the coupling reaction using various coupling agents [e.g. diisopropylcarbodiimide (DIC), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP)] did not lead to significant amounts of resin-bound tartranilic acid, as judged by ^{1}H NMR analysis of the crude product after cleavage from the resin.



Scheme 2.

We then explored the activated diazo linker **4** for the preparation of compound **6** (Scheme 2). The synthesis of the highly reactive diazo linker **4** on Wang resin was performed according to literature procedures[6] starting from Wang aldehyde resin. The addition of 2 equivalents of the tartranilic acid **2** to the diazo linker **4** in DMF gave the expected ester **5** cleanly and in high yields (78%).[5] Upon addition of the acid the colour of the diazo resin changed from dark red to yellow, which offers a practical visualization of the coupling step. The subsequent oxidation of the tartaric acid derivative with tetrabutylammonium periodate led to the desired ester-bound glyoxylic acid **6**.

The formation of the aldehyde function had to be proven unambiguously by its conversion into a well-defined chemical moiety, to allow isolation, identification and quantification of the resulting product. In this respect, we found that the conversion of the bound aldehyde into the corresponding *p*-nitrophenylhydrazone derivative **7** (Scheme 3) was a practical and high-yielding method, which allowed the characterization of the product after cleavage from the resin by LCMS and ^{1}H NMR.



Scheme 3.

The preparation of aldehydes **3** and **6** opens the way for their use as starting materials in very different types of reactions. For example, modifying literature procedures,[7,8] we treated **6** with benzylamine in trimethylorthoformate (TMOF) followed by the addition of mercaptosuccinic acid. The mixture was kept at 60°C for two days, leading to the thiazolidinone derivative **8** in 33% yield (unoptimized), after cleavage from the resin.

In conclusion, we report herein the first synthesis of resin-bound glyoxylic acid, linked through either an ester or an amide bond to polystyrene Wang resin. These immobilized aldehyde compounds should provide valuable starting materials for a range of reaction types, e.g. reductive aminations or Ugi reactions,[9] allowing the preparation of new diverse libraries of small molecules.

Preparation of glyoxylic amide 3. To a solution of (–)-4-methyltartranilic acid **2** (3.39 g, 14.1 mmol) and 1-hydroxybenzotriazole (1.91 g, 14.1 mmol) in DMF (70 mL), *N*,*N*′-diisopropylcarbodiimide (2.21 mL, 14.1 mmol) was added dropwise at 0°C during 10 min. Stirring is maintained for another 0.5 h at 0°C, then for 0.5 h at rt. Resin **1**[3] (1.77 g, ca. 1.8 mmol), swelled in DMF, was added in several portions to the active ester solution and the reaction stirred for another 1 h. The resin was filtered, washed with DMF, dichloromethane, methanol and 10% acetic acid in dichloromethane, and then added to a solution of tetrabutylammonium periodate (6.1 g, 14.1 mmol) in 1,2-dichloroethane (50 mL). The mixture was shaken overnight at rt, filtered, the resin washed as described above and dried in vacuo. For yield determination, a sample of **3** (100 mg) was converted into a hydrazone by treatment with a solution of *p*-nitrophenylhydrazine (154 mg, 1.0 mmol) in *N*-methyl-2-pyrrolidinone (1.9 mL) and acetic acid (0.1 mL). After stirring overnight at rt, the resin was filtered and washed as previously. The product was cleaved off the resin by treatment with TFA/dichloromethane (2 mL, 1:1 v:v) for 30 min and obtained after evaporation of the solvents in 81% yield.

Preparation of glyoxalate 6. The activated diazo linker **4** was synthesized according to literature procedures.[6] A solution of **2** (1.15 g, 4.8 mmol) in DMF (20 mL) was added to a suspension of the activated resin **4** (1.0 g, ca. 2.4 mmol) in DMF (15 mL). The mixture was shaken for 45 min during which time the resin turned yellow and effervescence was observed. The resin was filtered, washed with DMF, dichloromethane, methanol and 10% acetic acid in dichloromethane. The resin was subsequently added to a solution of tetrabutylammonium periodate (3.5 g, 8.08 mmol) in 1,2-dichloroethane (15 mL). The mixture was shaken overnight at rt, filtered and the resin washed as described above. A small sample of **6** was converted into the corresponding *p*-nitrophenylhydrazone as described above. The overall yield was determined to be 78% based on the theoretical loading of the resin.

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