Polymer-supported Thiazolium Salt Catalysts: A Model System for the Thiamine Dependent Enzymes

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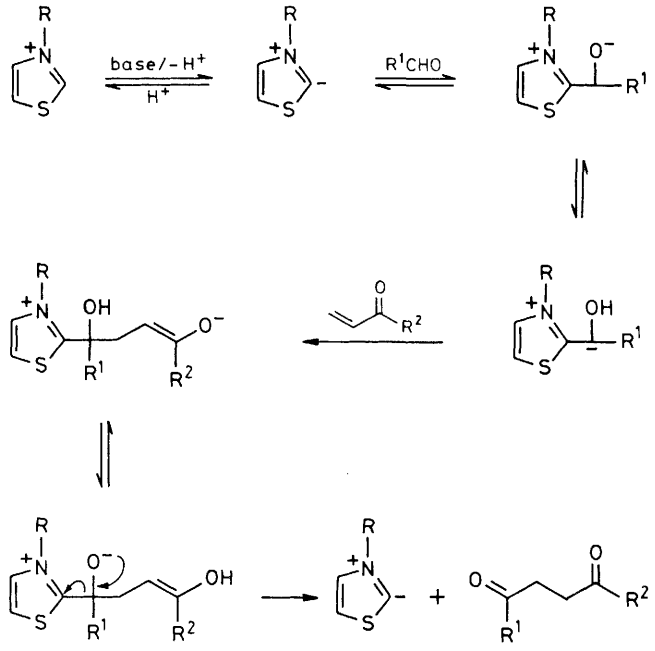
A polymer-supported thiazolium salt has been prepared which catalyses the addition of aldehydes to activated olefins in the absence of added base.

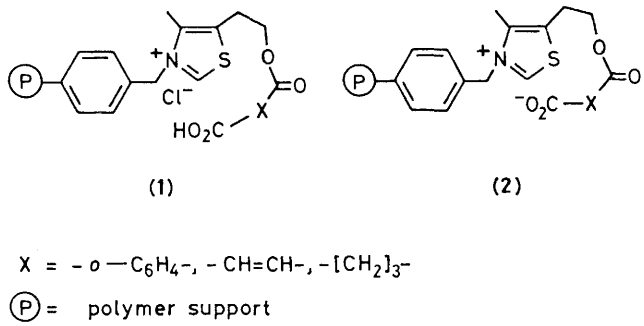
Nucelophilic addition of aldehydes to activated olefins using thiazolium salts as 'umpolung' catalysts, has been reported by Stetter and co-workers.[1–7] The mechanism (Scheme 1) has been described by Stetter and Kuhlmann[1] and closely parallels a



Scheme 1

reaction sequence which, according to Breslow,[8] is responsible for the biochemical properties of thiamine. Since thiamine behaves *in vivo* as an enzyme co-factor, we considered that it might be possible to construct a model system related to thiamine dependent enzymes which would be suitable for catalysis of the above addition reaction.

The work of Breslow[8] and Stetter[5] suggests that any thiazolium salt which is unsubstituted in the 2-position should have potential catalytic activity. An intermediate in thiamine production, 5-(2-hydroxyethyl)-4-methylthiazole, is readily available, and its quaternisation with benzyl chloride gives a product showing excellent catalytic activity in the presence of a base.[5] We have succeeded in preparing a corresponding polymeric catalyst by refluxing an acetonitrile solution of the same thiazole in the presence of Merrifield resin.† The product obtained is an active catalyst but only, as expected from the mechanism in Scheme 1, in the presence of added base (*e.g.* triethylamine). This polymeric catalyst did not adequately meet our requirements in as much as it did not possess all of the functionality required to effect the desired reaction. Moreover added base catalyses unwanted side reactions which are a greater problem with the polymer-bound salt than with its monomeric counterpart, the attainable catalyst concentration being much lower as a consequence of the bulky backbone of the resin. Reduction of the base concentration reduces the rate of the desired, as well as undesired, reactions and therefore does not increase selectivity. Our solution to the problem uses the apparently redundant hydroxyethyl group on the thiazole to incorporate a base onto the resin in the proximity of the active site. Thus, treatment of the polymer-supported thiazolium salt with a suitable anhydride produced the half ester (**1**). Washing the resin with base (triethylamine) then produced the zwitterionic species (**2**). The active sites of this polymer contain all the functionalities required to catalyse the addition of aldehydes to activated olefins. The reaction proved highly specific, if rather slow, a consequence of the restricted



(1) (2)

X = -o—C_6H_4-, -CH=CH-, -$[CH_2]_3$-

Ⓟ = polymer support

catalyst levels which can be applied. We have found that the resins produced using phthalic, maleic, and glutaric anhydrides are all effective catalysts‡ and the reaction is easily carried out by refluxing an ethanolic solution of the reagents over the resin. The catalyst can then be removed by filtration and reused. By contrast, pre-treatment of the unesterified catalyst with base (triethylamine), in an attempt to leave an active thiazolium ylide on the resin, fails to produce an active catalyst.

At present, the synthetic utility of the polymeric catalysts is less than that of the homogenous system.[9] In a typical reaction, only about 10% conversion was observed after 24 h although selectivity (*ca.* 80%) was comparable with that of the conventional method.[9] Currently the resin survives only 4—6 cycles. Microanalytical data suggest that *ca.* 10% of the aromatic residues in the initial polymer were chloromethylated and that only about 25% of these were quaternised by the thiazole. Accumulated side reactions resulted in the analysis of the final catalyst failing to give any clear indication of the extent of esterification. Thus, the coverage of the polymer by the required active sites is likely to be very low. In view of this, the disappointing yields and rates are not surprising. It is possible that a more open polymer matrix would give superior results by increasing the available space around the functional groups.

So far, we have only examined the system using heptanal and but-1-en-3-one as substrates. However, there is no reason to believe that the immobilised catalyst will not be efficacious for other additions catalysed by 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride.

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† A commercially available chloromethylated polystyrene.

‡ Surprisingly, initial results using the resin derived from succinic anhydride proved disappointing.