Application of Polymer-Bound Thiazolium Salts to the Synthesis of Acyloins and Benzoins: Effects of Solvent and Substituents of the Thiazolium Nucleus

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Covalent immobilization of the thiazole nucleus on a chloromethylated polystyrene copolymer results in the formation of a catalytically active thiazolium salt, capable of repeated acyloin and benzoin condensations. The nature of the solvent and the substituents on the thiazolium nucleus has been found to have marked effects of the rate of catalysis.

During the course of our studies on the mechanism of exchange of C—2 proton of thiazolium salts [1,2], we had an occasion to examine the available methods for the synthesis of acyloins and benzoins, which served as starting material for the preparation of the desired thiazoles. A review of the literature indicated that a limited number of benzoins may be prepared in poor to good yields from the cyanide catalysed condensation of their corresponding aromatic aldehydes (benzoin condensation) [3,4]. Apart from its limited applicability, the major shortcoming of this method is due to its inability to catalyse the condensation of aliphatic aldehydes (acyloin condensation) [5]. Acyloins are prepared from the reaction of their corresponding aliphatic esters with sodium or potassium [6]. The latter method suffers from difficult experimental procedures.

On the other hand, thiazolium salts have long been known to catalyse acyloin and benzoin condensations of aliphatic and aromatic aldehydes respectively [7]. However, difficulties associated with the recovery of the catalyst from the reaction mixture have prevented the application of thiazolium salts to the synthesis of acyloins and benzoins on a preparative scale. In fact, no reference to the recovery of the catalyst has been made even in more recent reports on this subject [8,9].

Although the application of functionalized polymers in organic synthesis has been a subject of extensive investigations [10-12], no attention has been paid to thiazolium salts in the form of polymeric catalysts. This and the amazing number of diverse chemical transformations catalysed

by thiazolium salts [13-15] led us to evaluate the prospects of immobilization of the thiazolium nucleus on an insoluble polymer. A highly chloromethylated polystyrene copolymer provides the desired matrix, and a subsequent S_N2 displacement of chlorine by N—3 of the thiazole nucleus results in the formation of covalently bound thiazolium salt on the polymer (Scheme I).

4-Methyl-5-(2'-hydroxyethyl)thiazole is easily obtained from the sulfite cleavage of thiamin [16], and accordingly its 3-methyl and 3-benzyl derivatives have recently been used as catalysts for acyloin and benzoin condensations [8,9]. We have found however that the presence of the 5-(2'-hydroxyethyl) group decreases the activity of the catalyst, possibly by providing an alternate and competing route (Scheme 1, b), which leads to the formation of a fused perhydrofurothiazoline ring system (IV). This has been shown for 2-(1'-hydroxyalkyl) and 2-(1'-hydroxyaryl) derivatives of thiamin in protic [17] and aprotic [18,19] media under the influence of a variety of bases. Also, a very high yield (90%) for this conversion has been observed in the case of 2-(1'-hydroxyalkyl)-3,4-dimethyl-5-(2'-hydroxyethyl)-thiazolium iodides, which are analogous to intermediate I, Scheme 1 [20].

It should be noted that the presence of the 4-5 double bond of the thiazolium nucleus is of paramount importance in restoring the aromatic character of the thiazolium ring in the transition state of the reaction. This, in fact, is equivalent to the conversion of enamine II to imine III, whose formation is essential for the production of acyloin
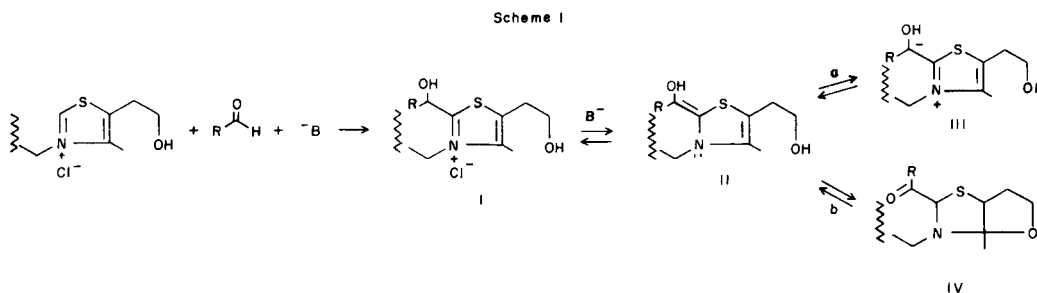
Scheme I

or benzoin (Scheme 1, a).

The deactivating effect of the 5-(2'-hydroxyethyl) group is especially pronounced in the case of acyloins. This may be due to the longer reaction time required for their production (*vide infra*). Under identical experimental conditions, lower yields of acyloins and benzoins were obtained with a polymer containing 4-methyl-5-(2'-hydroxyethyl)-thiazole [(1), 45%; (2), 16%; (3), 94%; (4), 91%; (5), 90%] as compared to a polymer containing 4,5-dimethylthiazole (Table). Subsequently, the latter, which retains its 4-5 double bond throughout the course of the reaction, was employed for the preparation of the insoluble catalyst (Scheme 2).

Scheme 2

I, R = CH$_3$(CH$_2$)$_2$; 2, R = CH$_3$(CH$_2$)$_{14}$; 3, R = ⬡; 4, R = furyl; 5, R = ⬡-NO$_2$
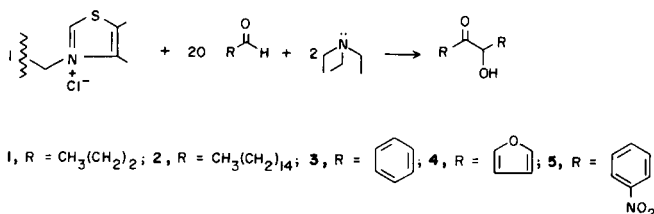
We now report that large quantities of acyloins and benzoins may be prepared from the reaction of their respective aldehydes in the presence of small amounts of thiazolated polymer. The major advantage of this method is due to the simple recovery of the catalyst, providing a convenient and economical synthesis of these classes of compounds. Furthermore, the present approach is superior, not only with respect to product yields but also in its range of applicability, as compared to cyanide catalysed benzoin condensation. For example, whereas our method results in 96% yield of furoin 4, the benzoin condensation of 2-furaldehyde affords furoin in yields low enough to increase the commercial value of the product by a factor of 45 [5]. Also, the latter method is totally inapplicable to the

synthesis of 4,4'-dinitrobenzoin (5), which is obtained in 94% yield by the use of thiazolated polymer (Table). In the case of acyloins, although the yields are lower as compared to benzoins, economy and convenience of the experimental procedure justify the preference of this approach over acyloin condensation.

In the case of benzoins (3-5, Table), additional stability of the imine α-carbanion (III, Scheme 1), is provided by the resonance contribution of the aromatic ring [21]. This, in turn, results in excellent yields in short reaction times. For acyloins, longer reaction times are required due to the absence of such resonance stabilization (1-2, Table). Furthermore, a lower yield may be expected for palmitoin (2) because of the hindrance of approach of its large prerequisite aldehyde molecule to the thiazolium nucleus which is located in the close proximity of the polymeric backbone.

A variety of bases may be used to generate the catalytically active thiazolium ion [2,9,13,18]. The use of hydroxides was avoided since they are known to also cause opening of the thiazolium ring, rending it inactive [13]. Alkoxides were also not considered since they are known to be excellent catalysts for aldol condensation of aliphatic aldehydes. Triethylamine, on the other hand, is a poor catalyst for aldol condensation and is incapable of opening the thiazolium ring. The use of six equivalent moles of triethylamine with respect to the number of moles of thiazolium salt has been noted in more recent reports [9]. We have found however that the use of two equivalent moles of the base is advantageous. Considering the long reaction times required for the production of acyloins, a large excess of the base promotes aldol condensation of the aliphatic aldehydes [22].

Absolute ethanol was used as the reaction solvent. However, utilization of a 50:50 mixture of chloroform-ethanol was found to be beneficial for aldehydes wich are not sufficiently soluble in ethanol (2, 5). It is of interest to note

Table

Synthesis of Acyloins and Benzoins

	Acyloin, Benzoin	Yield (%)	Reaction time (hours)	Mp (°C), Bp (torr) Found	Reported	Molecular Formula (a)
1,	Butyroin	83	96	111-113 (12-13 torr)	110-113 [23]	C$_8$H$_{16}$O$_2$ 144.08
2,	Palmitoin	53	96	77-78	77-78 [24]	C$_{32}$H$_{64}$O$_2$ 480.32
3,	Benzoin	100	12	137-138	137 [3]	C$_{14}$H$_{12}$O$_2$ 212.12
4,	Furoin	96	12	139-140	138-139 [25]	C$_{10}$H$_8$O$_4$ 192.12
5,	4,4'-Dinitrobenzoin	94	12	163-164	164 [26]	C$_{14}$H$_{10}$N$_2$O$_6$ 302.08

(a) Comparison of spectral data (ir, nmr, uv) and thin layer chromatography with authentic samples also confirmed structure and purity of the reported acyloins and benzoins.

that the use of aprotic solvents such as dioxane, tetrahydrofuran or chloroform results in much lower yields of acyloins and benzoins. Under our experimental conditions, no product formation (acyloin or benzoin) could be detected in dry dioxane or tetrahydrofuran. In the case of chloroform, the low yields obtained [(1), 21%; (2); 7%; (3); 32%; (4), 26%; (5), 17%] may in fact be due to the presence of small amounts of ethanol (1%) used as stabilizer for this solvent. Participation of various protic solvents in the generation of the negative charge at the C—2 position of thiazolium salts has been discussed previously [1,2].

Slight darkening of the catalytically active polymer, was not found to upon repeated use for different reactions, have a pronounced effect on its catalytic efficiency. Nevertheless, it is advisable to devote a batch of the active polymer to one type of reaction. In this manner, after twenty cycles the same batch of the active polymer was found to catalyse the benzoin condensation of benzaldehyde in 91% yield.

EXPERIMENTAL

General.

The ^{1}H nmr were recorded on a Varian FT-80 nmr spectrometer using tetramethylsilane as the internal standard. Melting points were determined in open capillary tubes on an Electrothermal apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 267 spectrophotometer and ultraviolet spectra were obtained in ethanol solution on a Varian Carry 14 spectrophotometer. Thin layer chromatography was performed on silica gel (Macerey-Nagel Co., Plygram Sil G/uv 254).

Preparation of Catalyst.

Chloromethylated polystyrene copolymer (98% styrene + 2% divinylbenzene) was obtained according to the procedure of Merrifield [27], except that the reaction time was increased to two hours (5.74 mmoles of chlorine per g of chloromethylated polymer). To 5.0 chloromethylated polymer, suspended in 10 ml of acetonitrile, was added 13.5 g of 4,5-dimethylthiazole [2] and the reaction mixture was left on a steam bath for four days. The thiazolated polymer was then filtered and washed with fifteen 20 ml portions of ethanol. After drying to constant weight, a weigh gain of 2.95 g was observed which corresponds to 3.28 mmoles of thiazolium salt per g of thiazolated polymer.

Preparation of Acyloins and Benzoins.

A three-neck flask equipped with an addition funnel and nitrogen inlet and outlet tubes was charged with 2.0 g of catalyst (6.56 mmoles of thiazolium salt), 10 ml of absolute ethanol (or 10 ml of a 50:50 mixture of chloroform-ethanol in the cases of 2 and 5), and 1.84 ml (13.12 mmoles) of triethylamine. To the stirring mixture under a nitrogen atmosphere was then added 0.13 mole of freshly distilled aldehyde during the course of one hour. At the end of the period given in the Table, the reaction mixture was acidified by the addition of 13.5 mmoles of ethanolic hydrochloric acid. The catalyst was separated from the product by suction filtration, followed by washing of the active polymer with the reaction solvent. Palmitoin (2), benzoin (3), furoin (4), and 4,4'-dinitrobenzoin (5) separated from triethylamine hydrochloride by crystallization from ethanol. For butyroin (1), the hydrochloride was separated by aqueous ex-ethanol. For butyroin (1), the hydrochloride was separated by aqueous extraction, followed by distillation of the product.

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