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Reactions

Polymer Reagents: Preparation of Polymer Esters of Thiocarboxylic Acids Based on Crosslinked Polystyrene

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Summary

The process of acylation of polymer thiols based on microporous poly(styrene-co-divinylbenzene) (crosslinking agent content 1-2%) with carboxylic acids was investigated depending of the degree of functionalization, on the crosslinking of the polymer carrier and on the structure of acids. In the presence of dicyclohexylcarbodiimide and 4-dimethylaminopyridine the acylation reactions can be conducted to high degrees of the transformation of SH groups already at room temperature. The extent of such refunctionalization reactions depends neither on the degree of functionalization of the starting polymer thiol nor on the structure of the acids. Reactions of polymer esters of thiocarboxylic acids with primary, secondary and tertiary alcohols activated with mercury (II) trifluoroacetate lead to low ester yields.

Introduction

Esters of thiocarboxylic acids are widely used in the protection and activation of the carboxylic group in organic syntheses (1). Their preparation by a reaction between acid chlorides and the respective thiols (2), thallium (3) and tin (4) thiolates has been reported. An easy and elegant method avoiding the use of expensive and poisonous Tl^{I} thiolates has been described by German authors (5). The method is based on the use of the respective carboxylic acids and thiols activated with dicyclohexylcarbodiimide; the reaction is catalyzed with 4-dimethylaminopyridine. An alternative method is that of the preparation of S-(2-pyridyl)thioesters (6). In this respect, polymer thiols have been investigated very little (7) and unsystematically, although in other reactions their suitability as polymer reagents has been documented (8,9). This study reports findings concerning the preparation of polymer esters of thiocarboxylic acids based on crosslinked poly{1-[4-(mercaptomethyl) phenyl] ethylene}, as well as their application in the acylation of primary, secondary and tertiary alcohols activated with $Hg(OCOCF_3)_2$.

Results and Discussion

Esters of S-thiocarboxylic acids bound on the polymer were

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prepared using polymer thiols with the degree of functionalization (D_f) 9-100% derived from microporous poly(styrene-co-divinylbenzene) with a 1% or 2% content of divinylbenzene units (DVB) and with the particle size 0.2-0.4 mm. The preparation of these polymer thiols (Ia-e) was based on the corresponding chloromethylated polymer; the conversion of CH_2Cl groups to mercapotomethyl groups was complete (10).

Polymer thiols were reacted with carboxylic acids in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) at reduced temperature in the initial stage of the reaction (for 15 min after DCC has been introduced at 0°C) and at 25°C within the whole subsequent reaction time:

$$\mathrm{PS - CH_2SH + RCOOH} \xrightarrow[\text{anhydrous THF/N}_2]{\text{DCC, DMAP}} \mathrm{PS - CH_2SCOR}$$

Ia - e II-VI (a - e)

Ia : 1% DVB, D_f = 100%
Ib : 2% DVB, D_f = 98%
Ic : 2% DVB, D_f = 63%
Id : 2% DVB, D_f = 36%
Ie : 2% DVB, D_f = 9%

II : $R = CH_3CH_2$
III : $R = CH_3(CH_2)_5CH_2$
IV : $R = (CH_3)_2CH$
V : $R = (CH_3)_3C$
VI : $R = C_6H_5$

The time dependence of reactions between propionic acid and polymer thiols Ia-d shows (Fig.1) that high conversions of thiol groups are reached already after 3-4 h of the reaction; further extension of the reaction time up to 48 h has no marked effect on the transformation of the remaining SH groups. Hence, in the case of microporous polymers based on poly(styrene-divinylbenzene) with a low degree of crosslinking the degree of their functionalization with mercapto groups is not an important factor which affects the course of this acylation reaction. In the IR spectra of all polymer thioesters the band of valency vibration of free SH groups at 2500 cm^{-1} is missing, while a strong band at 1680 cm^{-1} characteristic of the carbonyl of the thioester group appears. The conversions of mercaptogroups to thioester groups calculated from the results of sulfur determination reach high values in all the cases under investigation (Table I). After 48 h an almost quantitative transformation of SH groups was reached, without any obvious dependence on stereoelectronic factors of carboxylic acids (cf. reaction of the polymer thiol Ia). The conversion is also independent of the degree of functionalization of the polymer carrier with mercapto groups (cf. reactions of propionic and octanoic acid).

Low-molecular weight esters of thiocarboxylic acids are known to be suitable acylating agents. Their high reactivity towards the hydroxyl group of the alcohol is used to facilitate the preparation of those esters of the $RCOOR^1$ type in which the alcoholic component has a structure unsuited for the use of the classical esterification reaction (tert.alcohols; alcohols where structure of the alkyl group is such that it readily

Table I Conversion of SH groups (ξ) in the reaction between polymer thiols Ia-e with carboxylic acids (RCOOH) in the presence of dicyclohexylcarbodiimide in THF (25°C, 48 h) catalyzed with 4-dimethylaminopyridine; composition of polymer thioesters II-VI.

I	Acid	ξ	Analysis of polymer thioesters, calc./found			
	R	%		% C	% H	% S
Ia	C_2H_5	96	IIa	69.90/69.95	6.80/6.66	15.53/15.85
Ib	"	95	IIb	69.90/69.09	6.80/6.32	15.43/15.70
Ic	"	99	IIc	74.86/74.32	6.99/7.08	11.96/12.01
Id	"	97	IId	80.50/79.98	6.99/7.08	8.19/8.22
Ia	n-C_7H_{15}	91	IIIa	73.91/73.12	8.70/8.37	11.59/12.46
Ic	"	93	IIIb	77.13/76.83	8.52/8.41	9.51/9.91
Ie	"	87	IIIe	88.12/87.38	7.92/7.80	2.64/2.68
Ia	i-C_3H_7	99	IVa	70.91/69.92	7.27/6.75	14.55/14.61
Ia	t-C_4H_9	94	Va	71.79/71.18	7.69/6.95	13.68/14.03
Ia	C_6H_5	94	VIa	75.59/75.39	5.51/6.02	12.60/12.88

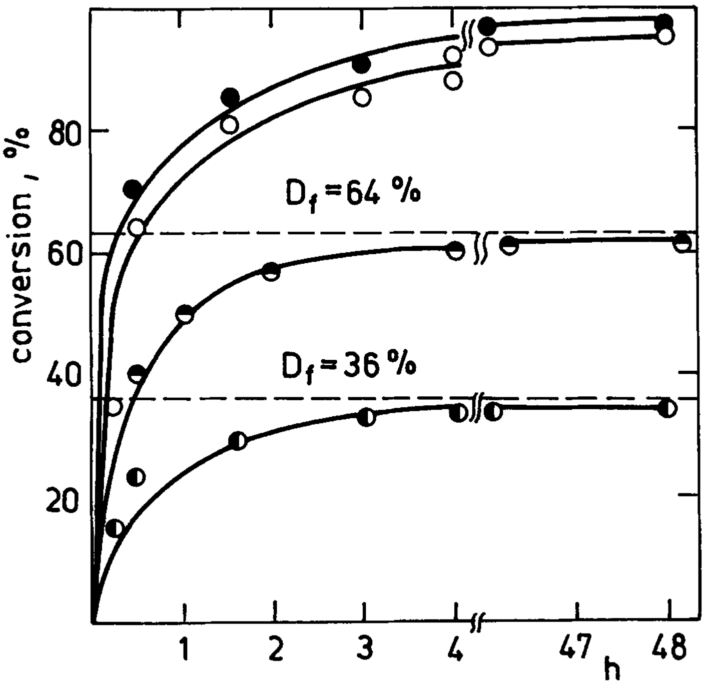

Figure 1 Process of formation of polymer esters of thiopropionic acid. Maximum achieved conversion (ξ) equals D_f Polymer: ● Ia, ○ Ib, ◓ Ic, ◐ Id.

undergoes acid catalyzed rearrangements) (11), or it is employed in the synthesis of macrocyclic lactones by the high dilution techniques (12). Soluble mercury (II) and silver (II) salts are used as reagents activating the S-C=O bond for the reaction of formation of an ester (11). This reaction is strongly affected by the type of the solvent and by the structure of the anion of the H_g^{II} salt, and allows relatively high ester yields to be achieved. The system mercury(II) trifluoroacetate in acetonitrile was found to be the most effective one for obtaining a high ester yield.

Possibilities of the application of polymer thioesters in reactions with alcohols in the preparation of noncyclic esters (RCOOR') have not been studied yet. We therefore investigated the reaction between polymer thioesters and some primary, secondary and tertiary alcohols in the presence of mercury (II) trifluoroacetate. The reactions were carried out at slightly elevated temperature. In all cases, however, the corresponding esters were obtained in low yields (Table II). The yield is not increased to any considerable degree by a change of the reaction temperature or by extending the reaction time. Judging by yields obtained with esters of S-thiopropionic (IIa) and S-thiopivalic (V) acids, the extent of acylation of 1-butanol is unfavourably affected by the bulkiness of the acyl group (-COR) of the polymer thioester. The structure of the R'-alcohol reaction component (R'OH) and the degree of functionalization of the polymer carrier of the thioester have no marked influence. Also, although the reaction of the more strongly swollen polymer IId (in the mixture CH_2Cl_2-CH_3CN) with cyclohexanol gives a somewhat higher yield of cyclohexylpropionate

Table II Acylation of alcohols (R'OH) with polymer thioesters in acetonitrile in the presence of $Hg(OCOCF_3)_2$ (yields of raw R'OCOR related to thioesters)

R' in	PS — CH_2SCOR			Time	Yield, %
R'OH	Type	COR	mmol s/g	h	R'OCOR
t-Butyl	IIa	Propionyl	4.95	5	19
t-Butyl	IIa	"		24	25[a]
Cyclohexyl	IIa	"		24	31
Butyl	IIa	"		14	30
Butyl	IIa	"		72	33[b]
Cyclohexyl	IIb	"	4.91	24	28
Cyclohexyl	IIc	"	3.75	24	28
Cyclohexyl	IId	"	2.57	24	22
Cyclohexyl	IId	"		48	29[c]
Cyclohexyl	IId	"		5	27[b,c]
Butyl	IIIa	Octanoyl	3.89	24	18
Butyl	Va	Pivaloyl	4.38	48	12

[a] 26% at 30°C, 20% at 70°C. [b] Yield according to GLC. [c] In the mixture CH_3CN-CH_2Cl_2 at 30°C.

compared with the same reaction in CH_3CN, this yield is still very low. The unsatisfactory extent of the esterification reactions under study may be due to the fact that the reaction of thioester groupings accessible on the polymer surface in its initial stage gives rise to a rigid and dense crosslinked structure of S-Hg-S crosslinks, impermeable to further molecules of both alcohol and $Hg(OCOCF_3)_2$. Another factor unfavourable to the acylation with polymer thioesters may also consist in the mercurization of the crosslinked polystyrene matrix with mercury(II) trifluoroacetate which proceeds very readily with the formation of reactive phenylmercurytrifluoroacetate structures (13) able to react with the accessible thioesters by a consecutive reaction, but also with the formation of additional crosslinks.

Hence, it is obvious that, from the practical viewpoint, polymer thioesters based on crosslinked polystyrene are not suitable for acylation reactions of alcohols activated with $Hg(OCOCF_3)_2$. During the preparation of this manuscript, Mohanraj and Ford (14) published a study concerning preparation of the polymer ester of 12-hydroxy-S-thiododecanic acid based on poly(styrene-co-divinylbenzene) and its application in the preparation of the respective lactone under conditions similar to those reported in our study. This acylation-esterification reaction also gave rather unsatisfactory results; however, the simple preparation of polymer thioesters from the readily available polymer thiol and the simple and yet perfect separation of the insoluble, nonvolatile and nontoxic sulfur compound (polymer) from the reaction system motivate the investigation of other reactions in which this new type of polymer reagents could be successfully used.

Experimental Part

Acetonitrile and dichloromethane were redistilled from P_2O_5 prior to use; anhydrous tetrahydrofuran was obtained by distillation from potassiumbenzophenoneketyl under nitrogen. Mercury(II) trifluoroacetate was prepared by a procedure described earlier (9). Crosslinked polymer thiols based on poly(styrene-co-divinylbenzene) were obtained by a method described earlier (10). All the other chemicals (Fluka, Aldrich) were used without preliminary repurification.

The IR spectra were recorded with a Perkin Elmer 500 B apparatus. Gas-chromatographic analyses were performed with a CHROM 5 apparatus provided with a flame-ionization detector and a steel column 0.3 120 cm (packed with INERTON AW-DMCS + 5% SP - 2100, carrier gas N_2).

General procedure for preparation of polymer thioesters II-VI

To polymer thiol Ia-e (6.0 mmol of SH groups), 6 ml of anhydrous THF, 6.0 mmol of carboxylic acid and 74 mg of 4-dimethylaminopyridine (0.61 mmol) were added, and the mixture was stirred under N_2 at room temperature for 15 min. To the mixture cooled to 0°C, 1.240 g of dicyclohexylcarbodiimide (6.0 mmol) was added at once, the mixture was left to stand at 0°C for 15 min., and after that, it was maintained under N_2 at 25°C. After a chosen time the polymer was separated by filtration, washed on the glass filter with hot ethanol and THF and extracted with the same solvent in a Soxhlet apparatus for 6 h. On drying (130 Pa, 40°C, 24 h) the polymers were characterized by elemental analysis and IR spectra.

General procedure for the reaction between polymer thioesters II-VI and alcohols

To 0.500 g of polymer thioester in 1.50 ml CH_3CN or CH_2Cl_2, 2 equivalents of alcohol were added. The mixture was left to stand at room temperature for 12 h. After that, 1.5 of the equivalent amount of $Hg(OCOCF_3)_2$ (related to the amount of polymer thioester) dissolved in CH_3CN (4 M solution) was added. The mixture was magnetically stirred with a teflon stirrer and maintained at the chosen temperature; the solution over the polymer was continuously analyzed by GLC. After the chosen time the solution over the polymer was separated, the polymer was washed three times with 5 ml CH_2Cl_2, the solvent was distilled off from the joined organic fractions, and the residue was chromatographically analyzed on $SiO_2/CHCl_3$. In all cases it was found that the isolated ester (without further purification) contains also the esters of trifluoroacetic acid and the respective alcohol in an amount 6-11 mol.% (related to alcohol) as an impurity; all esters were identified by GLC by comparing them with the authentic samples.

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