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Polymeric Reagents with Propane-1,3-dithiol Functions and Their Precursors for Supported Organic Syntheses

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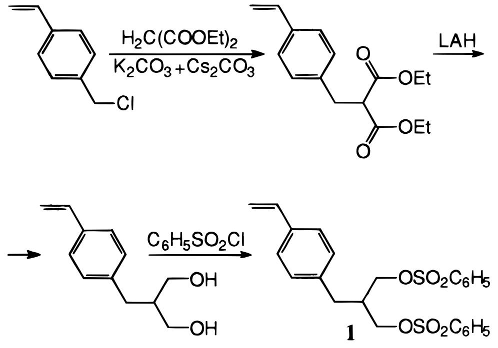
Reliable completely odorless syntheses of soluble copolymeric reagents of styrene type containing propane-1,3-dithiol functions able to convert carbonyl compounds into 1,3-dithiane derivatives and to support other useful transformations are reported together with their progenitor copolymers containing benzenesulfonate or thioacetate groups perfectly stable in open air and suitable for unlimited storage. The effectiveness of the prepared reagents as tools for polymer-supported syntheses to produce ketones by aldehyde umpolung and alkylation is tested in the conversion of benzaldehyde to phenyl *n*-hexyl ketone starting from copolymers with different contents of active units and molecular weights. To facilitate the adaptation of the prepared soluble copolymeric reagents to other possible applications, a table of solvents and nonsolvents is presented.

Introduction

Recently we have reported in a preliminary communication[1] how to harness the great synthetic potentialities of thioacetals and thioketals by preparing, with a completely odorless synthesis, polymeric reagents[2,3] of styrene type containing propane-1,3-dithiol functions effective in producing ketones by aldehyde umpolung and alkylation after the formation of 1,3-dithiane derivatives. Such polymeric reagents were obtained through a procedure based on the use of the difunctional monomer **1** prepared from commercial 4-vinylbenzyl chloride (Scheme 1), its copolymerization with styrene, and chemical modification of its copolymers. The transformation of preformed poly(4-vinylbenzyl chloride) was discarded to avoid excessive accumulations in the polymeric structure of spurious undesirable chemical functions due to unquantitative reactions.

The present work reports reliable syntheses from **1** of soluble polymeric reagents containing propane-1,3-dithiol functions suitable for various applications such as protection or reduction to CH_2 of carbonyl groups and transformation of aldehydes into ketones or difunctional systems, exploitable also in the field of combinatorial chemistry, then compares, in connection with different copolymer compositions and molecular weights, their effectiveness as tools for polymer-supported reactions in test conversions of benzaldehyde into 1-phenylheptan-1-one. Such soluble polymeric reagents, when their solvents and nonsolvents fit the requirements of the reactions and isolation procedures where they are involved, offer the important advantage with respect to the insoluble ones of profiting from homogeneous reaction conditions and sparing large excess of other reagents. However, in view of wider general synthetic applications, combinatorial chemistry included, cross-linked polymeric systems are now under study.

Scheme 1



Results and Discussion

Monomer **1** and styrene were copolymerized in dioxane solution by a radical initiator in three different molar ratios, nominally 1:9 or 1:5 or 1:1, and two different monomer concentrations, nominally 4.4 and 8.5 M, to give a variety of six copolymers **P1** and just as many descendants **P2**−**P6** (Schemes 2 and 3, Table 1), characterized by different active function contents and molecular weights (see later). Preliminary copolymerization experiments with any of the mentioned feed compositions and concentrations, monitored by HPLC analysis, showed with conversion only modest variations of the molar ratio of the unreacted monomers still present. In the preparative copolymerizations, brought to 98−100% conversions, the HPLC analysis of the residual solution confirmed that in no case did the real mole content of **1** or styrene units in the copolymer diverge from that calculated from the experimental molar ratio of the monomers submitted to

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(1) Bertini, V.; Lucchesini, F.; Pocci, M.; De Munno, A. *Tetrahedron Lett.* **1998**, *39*, 9263.

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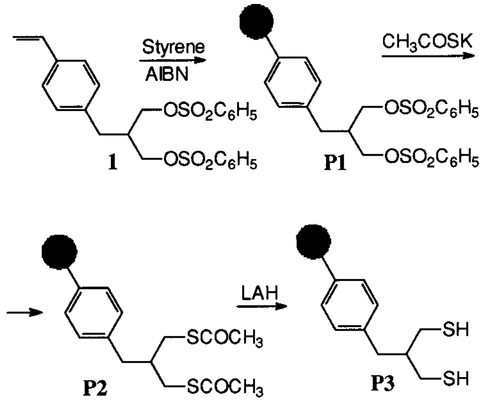
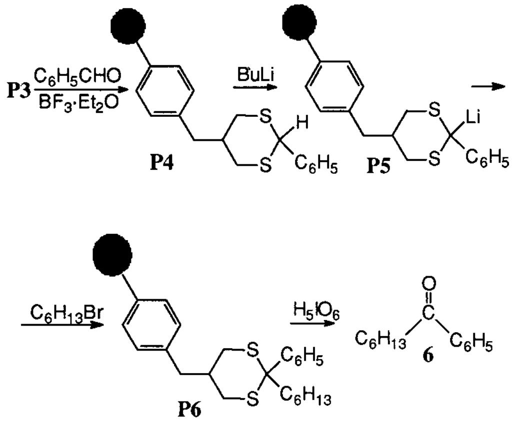
Table 1. Copolymerization Data of the Monomer 1 with Styrene in Dioxane at 60 °C and Intrinsic Viscosities of Copolymers P1 Measured in Dioxane at 30 °C

copolymer	**1**, g (mmol)	styrene, g (mmol)	monomer molar ratio **1**: styrene	dioxane mL/ (monomer **1** molarity)	AIBN, g	yield, g (%)	[η] (mL/g)
P1$_{1:9(4.4M)}$	3.327 (7.0400)	6.612 (63.4841)	1:9.02	16.0/(4.41)	0.196	9.807 (97)	16
P1$_{1:9(8.5M)}$	3.462 (7.3257)	6.893 (66.1821)	1:9.03	8.6/(8.55)	0.210	10.203 (97)	21
P1$_{1:5(4.4M)}$	3.480 (7.3642)	3.835 (36.8212)	1:5.00	10.0/(4.42)	0.148	7.132 (96)	16
P1$_{1:5(8.5M)}$	3.035 (6.4222)	3.348 (32.1453)	1:5.01	4.5/(8.57)	0.131	6.193 (95)	19
P1$_{1:1(4.4M)}$	4.705 (9.9559)	1.036 (9.9470)	1:1.00	4.5/(4.42)	0.114	5.731 (98)	15
P1$_{1:1(8.5M)}$	4.822 (10.2035)	1.069 (10.2638)	1:1.01	2.4/(8.53)	0.118	5.867 (98)	20

Scheme 2



Scheme 3



the copolymerization by more than 0.5%. On this basis the prepared copolymers **P1** were used in the successive chemical transformations with reaction stoichiometry calculated attributing to **P1** the composition of the feed which produced **P1** itself. It must be noted that the copolymers with composition 1:9 or 1:5 were easily obtained in the form of powders, while those at 1:1 yielded crumbly foams. In all the copolymers **P1** the presence of benzenesulfonate functions was proved by the IR bands at 1364 and 1189 cm^{-1}, already found in monomer **1**. The copolymers **P1** generated from a given feed monomer molar ratio (1:9, 1:5, or 1:1), but with different monomer concentrations (4.4 or 8.5 M), showed significantly higher intrinsic viscosity values in connection with the higher monomer concentration (Table 1), in agreement with the formation of copolymers having higher molecular weights.

The transformation of each one of the copolymers **P1** into **P2** then into **P3** (Scheme 2) occurred with practically quantitative yields. The transformation **P1** → **P2** caused the disappearance of the IR bands at 1364 and 1189 cm^{-1} due to the benzenesulfonate functions, the appearance of a band at 1694 cm^{-1} due to the thioacetate group, and a typical signal in the ^{13}C NMR spectrum at $\delta = 195.2$ ppm referred to TMS due to the thiocarboxylic carbon. As for **P1**, the copolymers **P2** corresponding to the nominal monomer composition 1:9 or 1:5 were in the form of powders, and those at 1:1 were in the form of crumbly foams. The transformation **P2** → **P3** caused the disappearance of the IR thioacetate band at 1694 cm^{-1} and the appearance of a band at 2568 cm^{-1} due to the SH groups. All six copolymers **P3** were prepared initially in the form of crumbly foams, ready for most uses, but each one of them was obtained in the form of powder by precipitation from solvent/nonsolvent (see Experimental Section). The contents of SH groups either in the pulverulent **P3** or in the foamy ones obtained from weighed samples of **P2** were determined by iodometric titration and always were higher than 96% of the theoretical[4] value. The freshly prepared **P3** were soluble in various solvents and remained as such also after storage under nitrogen atmosphere for several months, but they did not give perfectly clear solutions if exposed in open air for 1 day probably due to the oxidative transformation of SH groups into disulfide bridges producing insolubilization through a cross-linking process between different polymer chains. As expected, the progenitor copolymers **P1** and **P2** were perfectly stable in open air and suitable for unlimited storage.

The six copolymers **P3** were compared, as polymeric reagents, in the benzaldehyde umpolung reaction followed by alkylation with 1-bromohexane, and production of 1-phenylheptan-1-one (**6**), through the intermediate formation of the polymer-supported 1,3-dithiane structures **P4**−**P6** (Scheme 3, Table 2). Using a molar ratio propane-1,3-dithiol units:benzaldehyde = 1:0.85, the reacting benzaldehyde was always fully consumed, and after capping the unreacted thiol functions with an excess of acetone, the six copolymers **P4** were obtained in the form of soluble powders perfectly stable in the air. The formation of 2-monosubstituted 1,3-dithiane structures (**P4**, Scheme 3) was confirmed for each prepared **P4** by ^{1}H and ^{13}C NMR spectra, profiting from a previous study[1] with purposely made model molecules and Bruker WIN-DAISY simulations. The presence in the ^{1}H NMR spectra

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[4] Calculated from the molar ratio of the comonomers submitted to polymerization.

Table 2. Formation of 6 from Umpoled Benzaldehyde Alkylation

copolymer	benzaldehyde, g (mmol)	**6** (yield %)
P6$_{1:9(4.4M)}$	0.212 (1.998)	79
P6$_{1:9(8.5M)}$	0.221 (2.082)	79
P6$_{1:5(4.4M)}$	0.258 (2.431)	79
P6$_{1:5(8.5M)}$	0.244 (2.299)	79
P6$_{1:1(4.4M)}$	0.280 (2.638)	75
P6$_{1:1(8.5M)}$	0.238 (2.243)	74

of **P4** of only one signal at $\delta = 5.11$ ppm due to the proton in the 2 position of the 1,3-dithiane ring accounted also for a conformational equilibrium of the same ring strongly shifted for both the trans and cis isomers toward the conformer with the phenyl group in equatorial position.

The transformations **P4** → **P5** → **P6** (Scheme 3), carried out with increasing excess of the reagents (see Experimental Section), gave all six copolymers **P6** in the form of stable soluble powders. The ^{1}H NMR spectra of **P6** revealed the disappearance of the signal characteristic of **P4** at $\delta = 5.11$ ppm, in agreement with the substitution of the proton in the 2 position of the 1,3-dithiane ring with the hexyl group.

The formation of **6** from each one of the six copolymers **P6** was carried out through the decomposition of the 1,3-dithiane units with periodic acid (Scheme 3) and was quantitatively determined by HPLC analysis to ascertain the effectiveness of all the different samples as polymeric reagents. The copolymers **P6** with lower contents of 1,3-dithiane units descending from initial copolymerizations with nominal monomer molar ratios 1:9 and 1:5 afforded practically identical yields, while those richer in active units (monomer molar ratio 1:1) gave yields slightly lower (Table 2). The variation of the molecular weights, originating from the nominal monomer concentrations 4.4 or 8.5 M, had no significant effects on the yields of **6** from copolymers with the same active unit contents.

The observed dependence of yields on the copolymer compositions in the synthesis of **6**, as well as the production of intermediates **P1**$_{1:1}$ and **P2**$_{1:1}$ not in the form of well-filtrable powders (see above), indicates the monomer molar ratio 1:1, which is quite high for polymeric reagents, as an upper limit of the content of active units in the prepared copolymers.

Considering that other possible applications of the prepared soluble copolymeric reagents must meet the requirements of solvents and nonsolvents for given chemical processes, several solubility tests have been achieved and are presented in Table 3. Some common solvents that are potential reagents for the propane-1,3-dithiol functions were not examined with **P3**.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded at 75.5 and 300 MHz, respectively. Chemical shifts are reported on the δ scale and are referred to TMS. FTIR spectra of the polymers were performed on thin films obtained from CH_2Cl_2 solutions on KBr plates. Viscosities were measured in dioxane at 30 °C with an Ubbelohde microviscometer. HPLC analyses were performed at room temperature, at constant flow rate (1 mL/min), and with UV detection (254 nm) using a 25 × 0.46 cm Hypersil ODS 5 μm column. GC-FID analyses were performed using a DB-5, 30 m, i.d. 0.32 mm, film 1 μm capillary column. Commercial chemicals were from Aldrich. 2-[(4-Ethenylphenyl)methyl]propane-1,3-diol bisbenzenesulfonate (**1**) was prepared as previously reported[1] and carefully crystallized from ethanol. Commercial styrene was washed with a 5% NaOH aqueous solution, dried over KOH pellets, and distilled under nitrogen at reduced pressure. Azobisisobutyronitrile (AIBN) was crystallized from methanol. The solvents for copolymer syntheses and transformations were carefully dried, deoxygenated, and distilled under nitrogen.

Table 3. Solvents and Nonsolvents of the Copolymers P1, P2, P3, P4, and P6

solvent[a]	**P1**	**P2**	**P3**	**P4**	**P6**
tetrahydrofuran	++	++	++	++	++
dioxane	++	++	++	++	++
dichloromethane	++	++	++	++	++
chloroform	++	++	++	++	++
pyridine	++	++	++	++	++
benzene	+	++	++	++	++
toluene	+	++	++	++	++
cyclohexanone	++	++		++	+
methylethyl ketone	++	++		+	+
acetone	++	+		−	−
dimethyl sulfoxide	++	−		− −	− −
dimethylformamide	++	++	++	++	−
ethyl acetate	+	+	+	+	+
acetonitrile	− −	− −	− −	−	− −
acetic acid	− −	− −	− −	− −	− −
ethanol	− −	− −	− −	− −	− −
methanol	− −	− −	− −	− −	− −
diethyl ether	− −	− −	− −	− −	− −
petroleum ether 40−60 °C	− −	− −	− −	− −	− −

[a] ++ good solvent; + moderate solvent; − moderate nonsolvent; − − good nonsolvent.

Copolymers P1. Monomer **1** and styrene (nominal molar ratio 1:9, 1:5, or 1:1) together with the calculated volume of deoxygenated dioxane necessary to give nominal 4.4 or 8.5 M solution of the monomers and AIBN (2 wt % of the monomers) were introduced in a vial with a sidearm and submitted to three freeze−pump−thaw cycles at −78 °C under nitrogen. After sealing and stirring, the vial containing the homogeneous solution was heated in a thermostatic bath at 60 °C for 70 h. The cooled viscous clear content of the vial was diluted with dioxane to about 3.5 mL per g of monomer charge, poured into stirred methanol (about 10 times the volume of the dioxane solution) to precipitate the copolymer **P1**, and submitted to HPLC determination (eluent CH_3OH/H_2O, 7:3 v/v, internal standard xanthene) to determine both the unreacted monomers and calculate the copolymerization conversion and the mole content of the monomeric units inserted in the copolymer. The precipitated **P1** was in turn filtered, pump-dried, dissolved in dioxane, reprecipitated in methanol, and again filtered and pump-dried at room temperature to constant weight. IR (ν cm^{-1}): 1364, 1189 (benzenesulfonate). The copolymerization data for the prepared samples **P1**$_{1:9(4.4M)}$, **P1**$_{1:9(8.5M)}$, **P1**$_{1:5(4.4M)}$, and **P1**$_{1:5(8.5M)}$ in the form of powders and **P1**$_{1:1(4.4M)}$ and **P1**$_{1:1(8.5M)}$ in the form of crumbly foams are reported in Table 1.

Copolymers P2. A 0.71 M solution of potassium thioacetate in DMF stirred under nitrogen at 65 °C was treated with just enough solution of **P1** in DMF (0.23 g/mL) to reach one theoretical[4] mol of **1** unit in **P1** per six moles of potassium thioacetate and further stirred at the same temperature for another 4.5 h. The reaction was monitored by following the appearance in the polymer IR spectrum of the band at 1694 cm^{-1} due to the thioacetate group and the disappearance of the bands at 1364 and 1189 cm^{-1} due to the benzenesulfonate function. The reaction mixture was vacuum-evaporated at 60 °C to remove about the 90% of the DMF; then the residue was in turn worked up with water, filtered, thoroughly washed with water, squashed, dissolved in CH_2Cl_2, and dried over anhydrous Na_2SO_4. The crude **P2** obtained by evaporation of the solvent at reduced pressure was in turn dissolved in toluene (about 6 mL/g of **P2**), poured into methanol (about 10 times the volume of the toluene solution), filtered, thoroughly washed with methanol, and pump-dried at room temperature to constant weight. The samples **P2**$_{1:9(4.4M)}$, **P2**$_{1:9(8.5M)}$, **P2**$_{1:5(4.4M)}$, and **P2**$_{1:5(8.5M)}$ were obtained in the form of powders, while **P2**$_{1:1(4.4M)}$ and **P2**$_{1:1(8.5M)}$ in the form of crumbly foams. IR

(ν cm^{-1}): 1694 (thioacetate). ^{13}C NMR (CDCl$_3$, δ ppm): 195.2 (thiocarboxylic carbon).

Copolymers P3. A solution of **P2** in THF (0.05 mmol of theoretical[4] propane-1,3-dithiol diacetate units per mL) maintained under stirring in a nitrogen atmosphere at 0 °C was treated with a 1 M homogeneous solution of LAH in THF (theoretical[4] propane-1,3-dithiol diacetate units: LAH = 1:1.2 for all the copolymers **P2**$_{\mathbf{1:9}}$ and **P2**$_{\mathbf{1:5}}$ and 1:4 for all the copolymers **P2**$_{\mathbf{1:1}}$), then the cooling bath was removed and the stirring continued overnight at room temperature. The reaction mixture was in turn cooled to 0 °C, treated under nitrogen with deoxygenated 5 M aqueous HCl (LAH:HCl = 1:8), and vigorously stirred with CH$_2$Cl$_2$ (about 1.5 times the volume of the mixture). Abandoning the nitrogen protection, the organic phase was rapidly separated, washed once with deoxygenated water, dried over anhydrous Na$_2$SO$_4$ for a few minutes, and pump-evaporated. All the samples **P3** appeared in the form of crumbly foams, ready for most uses. Using carefully deoxygenated solvents, the foamy **P3** were dissolved in toluene (15 mL/g of **P3**), poured into petroleum ether 40−60 °C (about 15 times the volume of toluene), filtered, washed with petroleum ether, and pump-dried to constant weight to give **P3**$_{\mathbf{1:9(4.4M)}}$, **P3**$_{\mathbf{1:9(8.5M)}}$, **P3**$_{\mathbf{1:5(4.4M)}}$, **P3**$_{\mathbf{1:5(8.5M)}}$, **P3**$_{\mathbf{1:1(4.4M)}}$, and **P3**$_{\mathbf{1:1(8.5M)}}$ all in the form of powders. IR (ν cm^{-1}): 2568 (SH).

Copolymers P4. Foamy **P3** freshly prepared from a weighed sample of **P2** was dissolved under nitrogen in CHCl$_3$ (0.070 mmol of theoretical[4] propane-1,3-dithiol units per mL) and treated at 0 °C under stirring with benzaldehyde in molar deficit and boron trifluoride diethyl etherate (propane-1,3-dithiol units:benzaldehyde:BF$_3$ = 1:0.85:1) for 1 h. The reaction mixture, which by GC-FID analysis contained no benzaldehyde, was treated with an excess of acetone (propane-1,3-dithiol units:acetone = 1:1) and left overnight at 0 °C. The mixture, after dilution (1:2) with CH$_2$Cl$_2$, was washed with a 5% aqueous solution of K$_2$CO$_3$, dried over anhydrous K$_2$CO$_3$, and pump-evaporated to give crude **P4**, which was dissolved in THF (15 mL/g of **P4**) and poured into petroleum ether 40−60 °C (about 18 times the volume of THF). The precipitate was filtered, washed with petroleum ether, and pump-dried at room temperature to constant weight. The weight thus determined was considered, for the successive reactions, the reference weight of **P4** containing as many equivalents of 2-phenyl-1,3-dithiane units as moles of the used benzaldehyde. All the samples **P4**$_{\mathbf{1:9(4.4M)}}$, **P4**$_{\mathbf{1:9(8.5M)}}$, **P4**$_{\mathbf{1:5(4.4M)}}$, **P4**$_{\mathbf{1:5(8.5M)}}$, **P4**$_{\mathbf{1:1(4.4M)}}$, and **P4**$_{\mathbf{1:1(8.5M)}}$ were obtained in the form of stable powders. ^{1}H NMR (CDCl$_3$, δ ppm): 5.11 (H2 of the 1,3-dithiane ring).

Copolymers P6. A solution of **P4** in THF (0.1 mmol of 2-phenyl-1,3-dithiane units per mL) mechanically stirred under nitrogen at −40 °C was treated with a 1.6 M solution of *n*-butyllithium in hexane and further stirred for 4 h at −30 °C, although the viscosity increased due to the formation of **P5**. Then 1-bromohexane (2-phenyl-1,3-dithiane units:*n*-butyllithium:1-bromohexane = 1:1.2:1.4) was added and the solution stirred for 1 h at −20 °C and 15 h at −10 °C, then treated with water (2.5 times the volume of the solution) and extracted with CH$_2$Cl$_2$. The extracts were dried over anhydrous Na$_2$SO$_4$, pump-evaporated to dryness, dissolved in toluene (about 4 mL/mmol of 2-phenyl-1,3-dithiane units for each **P6** except for **P6**$_{\mathbf{1:1(8.5M)}}$, which required 6 mL/mmol), poured into petroleum ether 40−60 °C (20 times the volume of toluene), filtered, and pump-dried at room temperature to constant weight. All the samples **P6**$_{\mathbf{1:9(4.4M)}}$, **P6**$_{\mathbf{1:9(8.5M)}}$, **P6**$_{\mathbf{1:5(4.4M)}}$, **P6**$_{\mathbf{1:5(8.5M)}}$, **P6**$_{\mathbf{1:1(4.4M)}}$, and **P6**$_{\mathbf{1:1(8.5M)}}$ were obtained in the form of stable powders.

1-Phenylheptan-1-one (6). A solution of **P6** in THF (0.1 mmol of 2-hexyl-2-phenyl-1,3-dithiane units per mL) was treated under stirring at 0 °C with a 0.35 M solution of H$_5$IO$_6$ in THF (molar ratio 1:3) and stirred for another 3 h at room temperature. The reaction mixture was in turn treated under stirring with a 1.6 M aqueous solution of Na$_2$SO$_3$ to remove any color, dried over anhydrous Na$_2$SO$_4$, and filtered. The solid was extracted with additional THF. The content of ketone **6** in the solution obtained from each one of the six copolymers **P6** was carefully determined by HPLC analysis (eluent CH$_3$CN/H$_2$O, 7:3 v/v, internal standard 1-phenyldecan-1-one) (Table 2). Pure **6** was obtained from the THF solution by evaporation of the solvent and column chromatography on Merck silica gel 60 (230−400 mesh) (eluent pentane/acetone, 100:5), showing an ^{1}H NMR spectrum in perfect agreement with the known one.[5]

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[5] *The Aldrich Library of FT-NMR Spectra*; Pouchert, C. J., Behnke, J., Eds.; Aldrich Chemical Co., 1993; Vol. 2, p 804B.