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LETTERS

1,3-Dithiane Polymers for the Supported Synthesis of Ketones

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Abstract: The synthesis of polymeric reagents containing an odourless propane-1,3-dithiol functionality is reported. Their usefulness for the solid phase synthesis of ketones via the umpoled alkylation of 1,3-dithianes is demonstrated. © 1998 Elsevier Science Ltd. All rights reserved.

Thioacetals and thioketals have a great potential in organic chemistry, but they are often neglected due to their unpleasant smell. In this letter we present a method to overcome such problems through the synthesis of polymeric reagents containing propane-1,3-dithiol, useful for the protection of carbonyl groups in the form of 1,3-dithianes, as exemplified by their use in the transformation of aldehydes into thioacetals, then thioketals[1] and finally ketones. Our polymeric reagents offer the advantages of the polymer supported synthesis (simple separation and purification) and the avoidance of traces of volatile sulfhydryl compounds in each step of the entire process, requiring benzenesulphonyl chloride and potassium thioacetate as low molecular weight sulphur reagents.

The necessary polymeric reagents were prepared in linear form by transforming commercial 4-chloromethylstyrene (**1**) into various monomers and by copolymerizing them with styrene. Preformed copolymers and resins containing 4-chloromethylstyrene units were not used because of the accumulation, in the polymeric structure, of spurious chemical functions produced during subsequent unquantitative reactions. Soluble copolymers were preferred because they allowed ordinary spectroscopic analyses or the use of solution phase methodologies for inspection of all the supported reactions; nevertheless adequately crosslinked resins are considered worthy of attention as reagents for general synthetic applications and as useful tools for new methodologies in combinatorial chemistry.

Linear copolymers containing 1,3-propanedithiol (**P6**) and their precursors were synthesized according to Scheme 1. The reported reactions are those which gave the most favourable results. Owing to the high tendency of the vinyl compounds towards radical polymerization during handling, the best results were obtained when the excess diethyl malonate was removed from **2**[2] by distillation, **3**[3] was flash chromatographed from silica gel to remove the product of double alkylation at the methylene group of the malonic ester, **4**[4], after crystallization from ethanol, was directly copolymerized with styrene, and propane-1,3-dithiol functions in the polymeric material were reached by transforming the copolymers **P4** into **P5** then into **P6**. This gave recrystallized **4** in 58% yield from **1**, **P4** was prepared by total conversion of the monomers, and the propane-1,3-dithiol functions contained in **P6** resulted higher than 95% of the monomer units **4** present in **P4**.

Monomer **4**, submitted to the reaction with potassium thioacetate, afforded the expected monomer **5**[5] as an oil in almost quantitative yield, this was uncrystallizable and produced copolymers with styrene having intrinsic viscosity values, in dioxane, averagely lower than those of copolymers **P5** obtained from **P4**, a sign of lower molecular weights.

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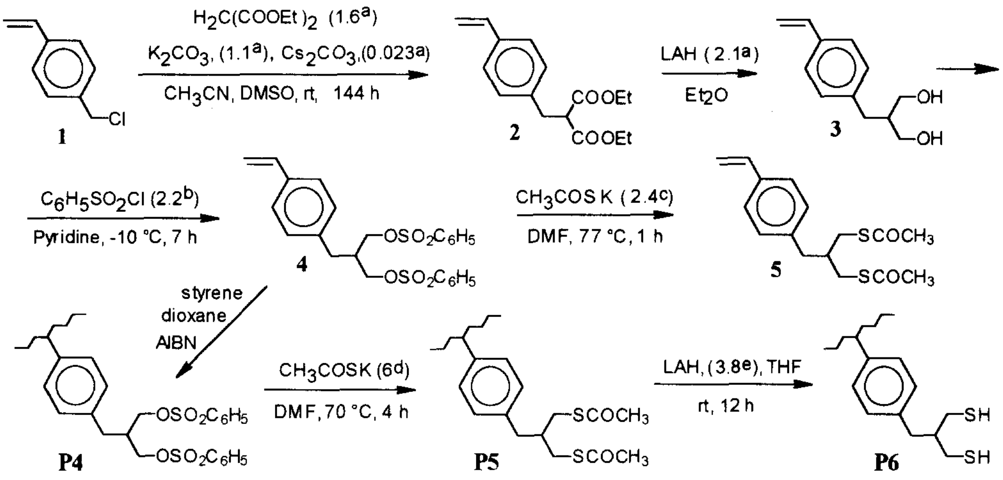


[a] mol per mol of **1**; [b] mol per mol of **3**; [c] mol per mol of **4**; [d] mol per theoretical[6] mol of **4** unit in **P4**; [e] mol per theoretical[6] mol of **5** unit in **P5**

Scheme 1

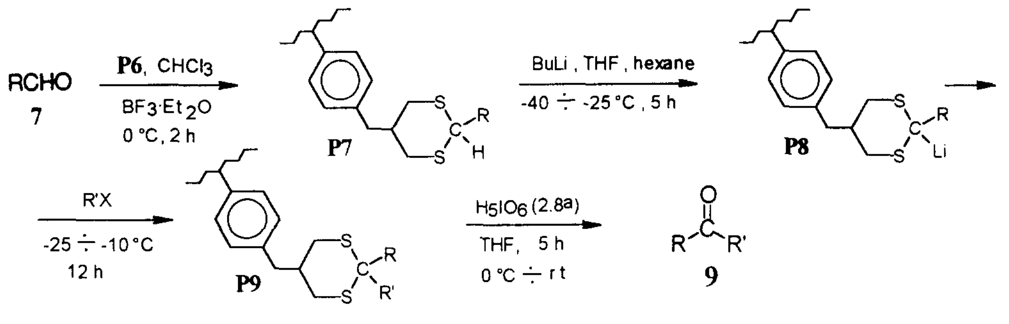
In dioxane solution, at temperatures between 50 and 60 °C with AIBN as initiator (from 2 to 0.2% by weight of monomers), monomer **4** was easily homopolymerized and copolymerized with styrene in the molar ratios 1:1, 1:2, 1:4 up to total conversion. However only copolymers **P4** 1:1, obtained with AIBN 2%, temperature 60 °C and a 4.4 M dioxane solution of monomers, were used for the subsequent productions of polymeric reagents devoted to the treatment of aldehydes.

Homopolymers of **4** and copolymers **P4**, **P5** and **P6**, whose structures were fully confirmed by IR, ^{1}H and ^{13}C-NMR analyses, showed a marked tendency to form foams from various solvents (**P6** could be precipitated as a powder by dropping its benzene solution into petroleum ether). The solid polymeric reagents **P6** containing sulfhydryl groups were stable under a nitrogen atmosphere undergoing some ageing in the air as shown by the fact that after one day it was unable to give clear solutions in different solvents. In any case the copolymers **P5**, precursors of **P6**, appeared perfectly stable in the air and suitable for unlimited storage. Freshly prepared **P6** from weighed samples of vacuum dried **P5**, submitted to iodometric titration, showed a content of SH groups always higher than 95% of the theoretical value[6].

The stable styrenic backbone, obtainable from ordinary commercial products, assured high compatibility with many reagents and gave a useful hydrophobic contribution to the solubility of the macromolecules in non-aqueous solvents.

The ability of **P6** to form 1,3-dithianes with aldehydes, then to produce carbanionic intermediates active towards nucleophilic substitutions on alkyl halides, and finally to release ketones was proved through the reactions shown in Scheme 2.

Aldehydes **7** were allowed to react with about 10% molar excess of the theoretical[6] propane-1,3-dithiol units contained in **P6**, then the excess was capped with acetone. The reaction with 2-thiophenecarboxaldehyde profited from chlorotrimethylsilane (4.5 mol per mol of **7**) in place of boron trifluoride etherate. In the sequence **P7**→**P8**→**P9** the reagents were used in increasing molar excess (theoretical[6] 1,3-dithiane unit in **P7** : BuLi : R'X= 1 : 1.2 : 1.4). When R'X was methyl iodide or hexyl iodide R-CO-Bu was formed as byproduct together with the expected ketone **9**. The unreacted excess of BuLi exchanged with the alkyl iodide affording butyl iodide which reacted with **P8** introducing a butyl group on the carbon 2 of **P9** dithiane units. When **P9** gave rise to a methyl ketone, as for R= 2-naphthyl, R'= methyl, the dithiane ring cleavage with periodic acid caused the iodination of the methyl group yielding the iodomethyl 2-naphthyl ketone as byproduct. This was avoided by carrying out the cleavage with mercury^{II} perchlorate trihydrate (3.0 mol per theoretical[6] mol of 1,3-dithiane unit in **P9**).



^{a} mol per theoretical[6] mol of 1,3-dithiane unit in **P9**

Scheme 2

All the products obtained from the decomposition of **P9** (Table 1) were known and showed IR, ^{1}H and ^{13}C-NMR spectra fully consistent with the molecular structure and coincident with those available in the literature.

Table 1. Products from aldehyde umpoled alkylation

7, R	R'X	Oxidation of **P9**	Products	Yield, %	References
Phenyl	C_4H_9Br	H_5IO_6	Phenyl butyl ketone	92	7a, 8a
2-Thienyl	$C_6H_{13}Br$	H_5IO_6	2-Thienyl hexyl ketone	97	9
2-Thienyl	$C_6H_{13}I$	H_5IO_6	2-Thienyl hexyl ketone	85	
			2-Thienyl butyl ketone	3	10
2-Naphthyl	CH_3I	H_5IO_6	2-Naphthyl methyl ketone	38	7b, 8b
			2-Naphthyl iodomethyl ketone	28	11
	CH_3I	$Hg(ClO_4)_2 \cdot 3H_2O$	2-Naphthyl methyl ketone	76	
			2-Naphthyl butyl ketone	4	12
Benzyl	C_2H_5Br	H_5IO_6	Benzyl ethyl ketone	58	7c, 8c

The ^{1}H and ^{13}C-NMR investigation of **P7**, accomplished by synthesizing and studying the model molecules **10**[13] and **11**[14] *cis* and *trans* (Figure 1) as well as by exploiting known NMR data of properly substituted 1,3-dithianes[15,16] and Bruker WIN-DAISY simulations, allowed us to confirm the presence in **P7** of 2,5-disubstituted 1,3-dithiane rings. Their conformational equilibrium was strongly shifted towards the conformer **a** for all the *trans* isomers and for the *cis* isomers with bulky R groups in the equatorial position like phenyl or 2-naphthyl, for which the ^{1}H-NMR spectra showed only one signal for the proton in the position 2 between 4.13

and 5.41 ppm. The conformer **b** was significantly present only in the *cis* isomers with R=2-thienyl or benzyl, for which in the same ^{1}H-NMR region two distinct signals appeared.

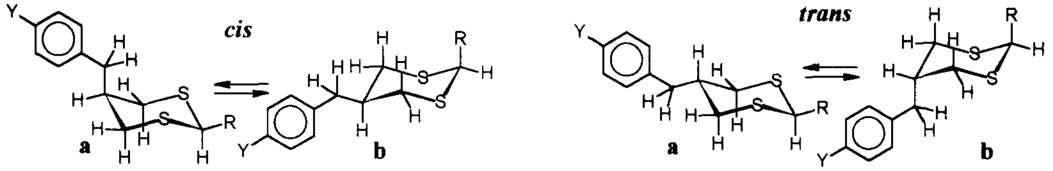


Figure 1. **P7** : Y= polymer chain, R= phenyl, 2-thienyl, 2-naphthyl, benzyl; **10** : Y= H, R= phenyl; **11** : Y= H, R= 2-thienyl

Experimental. Bruker DPX 300 NMR spectrometer and Perkin Elmer System 2000 FT-IR spectrometer were used. Chemical shifts are reported on the δ scale and are referred to TMS. Microanalyses of the new compounds **2**, **3**, **4**, **5**, **10** and **11** *cis* and *trans* were in satisfactory agreement with the calculated values (C± 0.36; H±0.13).

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References and Notes

1. Seebach, D., Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231-237.
2. **2**: bp 161-166 °C/0.02 torr; IR (film) cm^{-1} 1734, 1228, 1151, 1034, 992, 910; ^{13}C-NMR (CDCl$_3$) ppm 168.8, 137.5, 136.5, 136.1, 129.0, 126.3, 113.5, 61.5, 53.8, 34.4, 14.0.
3. **3**: mp 52-53.5 °C (ether-pentane); IR (KBr) cm^{-1} 3290, 1031, 980, 910; ^{13}C-NMR (CDCl$_3$) ppm 139.6, 136.5, 135.6, 129.2, 126.3, 113.3, 65.3, 43.8, 34.0.
4. **4**: mp 89-90 °C (ethanol); IR (KBr) cm^{-1} 1356, 1187, 973, 913; ^{13}C-NMR (CDCl$_3$) ppm 136.8, 136,3, 136.2, 135.4, 134.0, 129.4, 129.1, 127.9, 126.5, 113.8, 68.4, 40.0, 32.9.
5. **5**: oil; IR (film) cm^{-1} 1694, 991, 908; ^{13}C-NMR (CDCl$_3$) ppm 195.2, 138.5, 136.5, 135.8, 129.3, 126.3, 113.4, 40.3, 38.8, 31.9, 30.6.
6. Calculated from the molar ratio of the comonomers submitted to polymerization.
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13. **10*cis***: mp 115-116 °C (ether-hexane); ^{13}C-NMR (CDCl$_3$) ppm 140.2, 139.2, 129.3, 128.7, 128.5, 128.4, 127.9, 51.4, 36.0, 35.8, 30.8. **10*trans***: mp 135-137 °C (ethanol); ^{13}C-NMR (CDCl$_3$) ppm 138.5, 138.3, 129.2, 128.7, 128.6, 128.5, 127.8, 126.5, 51.4, 43.0, 37.6, 37.3.
14. **11*cis***: mp 96-97.5 °C (hexane); ^{13}C-NMR (CDCl$_3$) ppm 144.0, 139.3, 129.3, 128.5, 127.0, 126.9, 126.3, 126.1, 43.4, 39.3, 34.0, 33.7. **11*trans***: mp 103-104 °C (ethanol); ^{13}C-NMR (CDCl$_3$) ppm 141.2, 138.6, 129.2, 128.6, 126.7, 126.5, 126.1, 125.6, 45.1, 42.2, 36.8, 36.7.
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