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Soluble and insoluble polymeric 1,3-dithiane reagents for the synthesis of aldehydes from alkyl halides

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Abstract—Through the synthesis and study of model systems as proper dithiane derivatives, vinyl monomers and soluble copolymeric reagents containing 2-unsubstituted 1,3-dithiane rings, we attained the key synthon 1,3-dithiane-5-methanol. Through its reaction with commercial resins, new polymeric reagents useful for supported organic synthesis and combinatorial chemistry were developed. Exploiting the reactivity of position 2 in 1,3-dithiane rings, such polymeric reagents were employed in the production of aldehydes from alkyl halides through a process entirely free from unpleasant odors.

1. Introduction

In organic chemistry the great synthetic potentiality of sulfur(II) compounds such as thiols and dithiols, precursors of thioacetals or thioketals, is strongly handicapped by the very unpleasant odor of such materials. In previous papers[1–5] we have overcome this handicap through the fully odorless synthesis of polymeric reagents containing 1,3-propanedithiol or 2-substituted 1,3-dithiane functions, which were tested in the preparation of ketones from aldehydes and in the reduction of ketones, and proved effective for solid-phase synthesis exploitable in the field of combinatorial chemistry. The utility of thioacetal functions in the solid-phase synthesis is also reported as a way of protecting and anchoring the carbonyl function of methylarylketones to commercial aminomethyl polystyrene resins before carrying out transformations on the benzene ring.[6] Such a process requires, however, the unattractive handling of a 1,3-propanedithiol derivative to transform ketones into thioketals, and uses secondary amide bonds, not fully inert towards various reagents, for the immobilization of the thioketals on the commercial resin.

This work reports the functionalization of commercial chloromethylstyrene resins with the key synthon 1,3-dithiane-5-methanol (**6**) and their application to the production of aldehydes from alkyl halides, optimized through the synthesis of model molecules, proper vinyl monomers and soluble copolymeric reagents containing 2-unsubstituted 1,3-dithiane rings.

2. Results and discussion

The known 1,3-dithian-5-one[7] (**1**), obtainable from slightly odorous pure thioglycolic acid, having a reactive carbonyl group useful for the introduction of a linker in the position 5 of the 1,3-dithiane ring, the farthest from the thioacetalic carbon, appeared a reasonable precursor for the preparation of a synthon aimed to the functionalization of haloalkyl resins. Hence, **1** was prepared according to the literature,[7] reduced to the alcohol **2**,[8] and allowed to react with benzyl bromide obtaining in good yield from **1** the ether **3**, a model molecule of an umpoled thioacetal equivalent of methanal. The compound **3**, allowed to react first with *n*-butyllithium then with methanol-*d*, afforded the deuterated dithiane derivative **4** (Scheme 1), which showed the ^{1}H NMR spectrum corresponding to the substitution of the high-field proton at C(2) with deuterium, in full agreement with the known preferred equatorial deprotonation[9] and anomeric effect[10] in 1,3-dithianes. The obtained low yield (45.3%), probably due to a concomitant elimination reaction, made **2** an unacceptable synthon.

Wishing to find a reliable process for further spacing the ether linkage from sulfur atoms and preventing eliminations, we considered the 1,3-dithiane-5-methanol[11] (**6**) and accomplished its synthesis with an overall yield of 65% from **1**, through a Wittig reaction followed by hydrolysis and reduction with NaBH$_4$ of the enolether **5** (Scheme 2).

Keywords: Supported reagents; Umpolung reactions; 1,3-Dithianes; Aldehydes; Alkyl halides.

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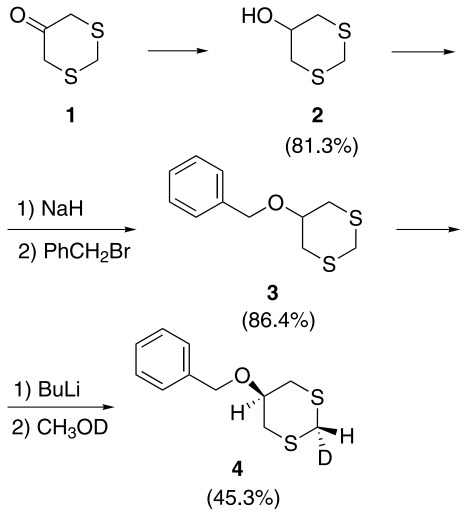
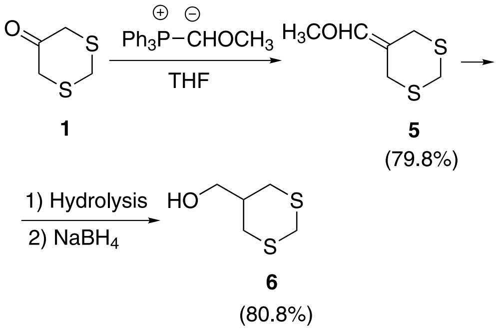
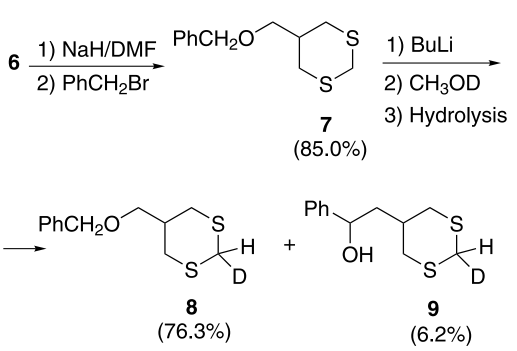


Scheme 1.



Scheme 2.

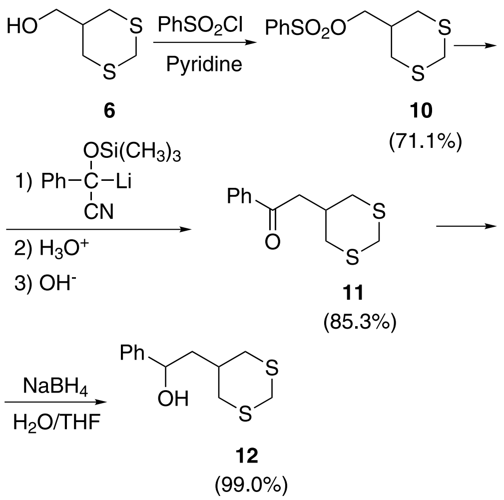
The alcohol **6** was submitted to several test reactions. It was transformed with benzyl bromide into the benzyl ether **7**, then lithiated and deuterated (Scheme 3). The process afforded after hydrolysis the expected **8** in 76.3% yield, together with **9** recovered in 6.2% yield.



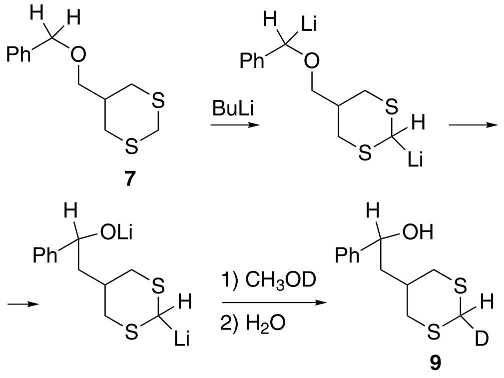
Scheme 3.

The structure of **9** was confirmed by preparing its non-deuterated analogue **12** from **6** through the ketone **11**, which was obtained from the benzenesulfonate ester **10** applying Hünig's umpolung procedure[12] of aromatic aldehydes (Scheme 4), then comparing the ^{1}H and ^{13}C NMR spectra of **9** and **12**.

The formation of **9** from **7** can be rationalized through a Wittig rearrangement of the benzylic ether[13] to the lithium alcoholate metallated at C(2), followed by deuteration with methanol-*d* and exchange H–D at the hydroxy group by addition of water (Scheme 5).

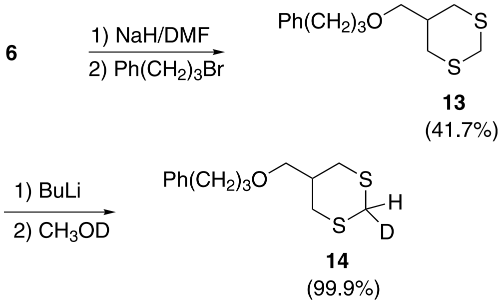


Scheme 4.



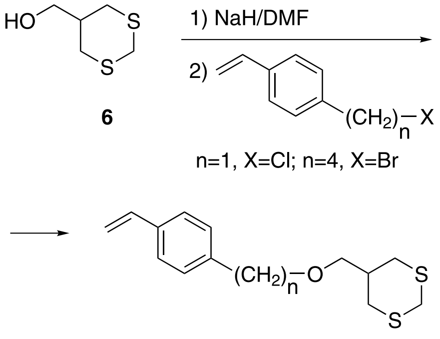
Scheme 5.

To avoid the presence of undesired products originating from the reactivity of the benzyl ether, **6** was transformed into the ether **13** with a chain of three methylene groups. After lithiation and deuteration **13** afforded **14** in quantitative yield (Scheme 6), proving that **6** is a good dithiane synthon for umpolung reactions, but the modest yield (41.7%) obtained in the synthesis of the model molecule **13** stimulated additional studies.



Scheme 6.

It appeared reasonable to synthesize new 1,3-dithiane vinyl monomers with or without a benzyl ether group by reacting **6** both with commercial (4-ethenylphenyl)chloromethane and with 1-bromo-4-(4-ethenylphenyl)butane[14] to reach monomeric then polymeric models and to test if the length of the spacer could affect the yield attained with 1-bromo-3-phenylpropane in the synthesis of **13**. The reactions reported in Scheme 7 gave the monomers **15** and **16**, respectively, confirming a good yield for **15** comparable with **7** and a modest yield for **16** comparable with **13**.



15 n=1 (88.9%); **16** n=4 (40.8%)

Scheme 7.

Under the conditions already used for the preparation of masked 1,3-propanedithiol linear copolymers,[1,2] **15** and **16** were copolymerized with styrene starting from feed molar ratios of dithiane monomer/styrene equal to 1:9 or 1:19, recording conversions higher than 95%. All the copolymers from **15** ($\mathbf{P1_{15(1:9)}}$, $\mathbf{P1_{15(1:19)}}$) and **16** ($\mathbf{P1_{16(1:9)}}$, $\mathbf{P1_{16(1:19)}}$) were recovered in the form of easily filtered powders after precipitation with methanol from their dioxane solutions. Such copolymers were tested in the transformation of 1-bromo-4-phenylbutane into the stable 5-phenylpentanal (**17a**), whose ^{1}H and ^{13}C NMR spectra are known[15] (Scheme 8).

The lithiation was found to cause a certain amount of cross-linking, as evidenced by the presence of variable percentages of gelatinous insoluble material together with the copolymeric products **P3**. The cross-linking was higher with copolymers more concentrated in dithiane units (1:9) and containing benzyl ether linkages. The use of the copolymeric reagent $\mathbf{P1_{16(1:19)}}$ with diluted dithiane units and without benzyl ether linkages gave a negligible cross-linking (Table 1). Since a low extent of side reactions is sufficient to produce a significant quantity of cross-linked material, the reported percentages of the insoluble fraction of **P3** was calculated on the assumption that the soluble and insoluble portions of **P3** had the same composition. The cleavage of the dithiane rings in **P3** with periodic acid or with mercury(II) perchlorate hydrate afforded the aldehyde **17a** (Table 1). Both soluble and insoluble portions of **P3** produced **17a**, but the yields of **17a** reported in the fifth column of the Table 1 refer only to the soluble one.

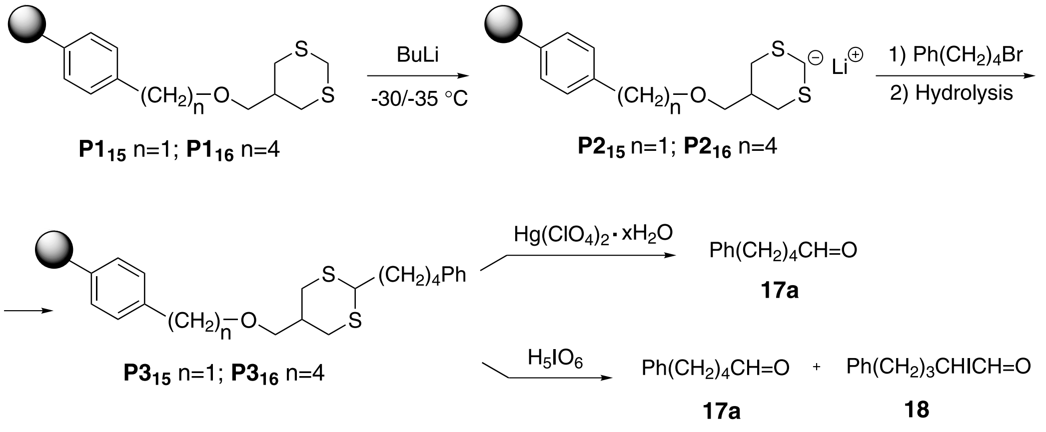
The reaction with mercury(II) perchlorate hydrate gave pure **17a** showing an aldehydic proton triplet at δ 9.74 in the ^{1}H NMR spectrum, while the reaction with periodic acid, besides **17a**, not unexpectedly[1] produced 5–10% of the iodine derivative **18**, showing an aldehydic proton doublet at δ 9.22, whose structure was deduced from the spectroscopic data compared with those of 2-iodohexadecanal[16] and other α-iodinated aldehydes.[17]

On the basis of the recorded yields, the best procedure for the obtainment of **17a** uses the model copolymeric reagent $\mathbf{P1_{16(1:19)}}$, characterized by a low concentration of dithiane units and absence of benzyl ether linkages, and carries out the cleavage of the dithiane rings with mercury(II) perchlorate hydrate.

Under analogous conditions, the model copolymeric reagent $\mathbf{P1_{15(1:19)}}$ containing benzyl ether linkages gave yields only slightly lower than $\mathbf{P1_{16(1:19)}}$, in spite of the Wittig rearrangements, which consumes *n*-butyllithium forming alcoholate and produces a significant cross-linking under lithiation.

Considering that the (4-ethenylphenyl)chloromethane, precursor of $\mathbf{P1_{15}}$, is commercially available, and that the preparation of 1-bromo-4-(4-ethenylphenyl)butane, precursor of $\mathbf{P1_{16}}$, is rather laborious and expensive, for most applications the recommended copolymeric reagent model is $\mathbf{P1_{15}}$ with a low concentration of dithiane units.

On this basis reagents for solid phase syntheses can be



Scheme 8.

Table 1. Synthesis of the aldehyde **17a** from **P1**$_{15}$ and **P1**$_{16}$ with excess of 1-bromo-4-phenylbutane

Polymer **P1**	% Yield of insoluble **P3**	% Yield of soluble **P3**	Cleavage reagent	% Yield of **17a** from **P1**
P1$_{\mathbf{15(1:9)}}$	32.2	63.4	H_5IO_6	35.2
P1$_{\mathbf{15(1:19)}}$	11.5	86.2	H_5IO_6	40.1
P1$_{\mathbf{15(1:19)}}$	11.5	86.2	$Hg(ClO_4)_2\cdot xH_2O$	56.6
P1$_{\mathbf{16(1:9)}}$	15.5	79.8	H_5IO_6	43.4
P1$_{\mathbf{16(1:19)}}$	0.7	98.9	$Hg(ClO_4)_2\cdot xH_2O$	62.7

properly prepared by anchoring **6** to commercial resins of Merrifield type.

2.1. Solid phase synthesis of aldehydes using transformed Merrifield resins

We prepared cross-linked supports with a low concentration of well accessible 1,3-dithiane units and tested them in the synthesis of aldehydes from alkyl halides, anchoring **6** to the commercial Merrifield resin having a CH_2Cl loading of 0.8 mmol g^{-1} of resin, cross-linked with 1% divinylbenzene (DVB), which showed a good swelling in DMF and THF and a good reactivity towards the alkoxide ions. The nominal CH_2Cl group loading was checked by addition of excess of sodium methoxide and titration of the chloride ions with standard silver nitrate. The commercial resin **R0** was transformed into the active dithiane resin **R1** through the reaction with the sodium salt of **6** in the empirically optimized molar ratio 1:1.5, monitoring the process by the disappearing of the IR band at 1263 cm^{-1} (C–Cl) and the appearing of that at 1092 cm^{-1} (C–O) (Scheme 9).

The resin **R1**, allowed to react with excess *n*-butyllithium in analogy with a previous work,[3] quite likely underwent the Wittig rearrangement to a small extent, nevertheless, it turned red owing to the deprotonation of the dithiane ring (**R2**). The red colour persisted after washing the beads with anhydrous THF to remove the excess of base that could interfere with the successive alkylation step, and disappeared when an excess of alkyl halide was added to the mixture. From the alkylated resin **R3** the aldehyde was recovered by cleavage with mercury(II) perchlorate hydrate. Optimized conditions for preparative syntheses are as follows: 1,3-dithiane units in **R1**:*n*-butyllithium:alkyl halide molar ratios = 1:1.25:1.50; no washing of **R2** with anhydrous THF; lithiation time and temperature: 2 h between −30 and −35 °C. Shorter lithiation times as well as the use of **R0** with high chlorine loading decreased the yields of the aldehyde referred to the CH_2Cl units. No traces of double alkylation of the dithiane ring with formation of ketones were found in any experiment. Table 2 collects some characteristic data of the reaction performed. The yields of aldehyde in the last column refer to the CH_2Cl units in **R0**.

Table 2. Chemical modifications of the commercial resin **R0** and synthesis of aldehydes

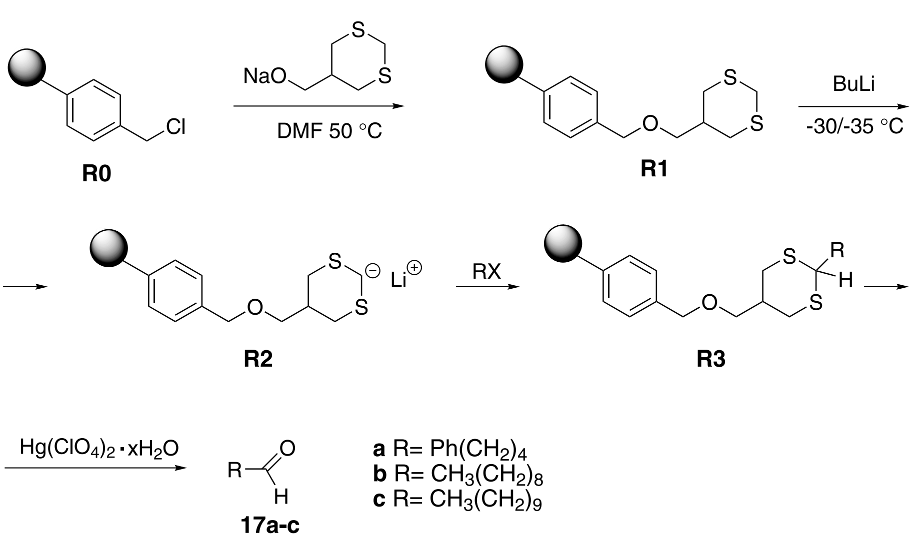
R0 (mmol Cl/g)[a]	**R1** (% yield from **R0**)	**R3** (% yield from **R1**)	RX	RCHO (% yield from **R0**)
0.822	96.7	98.3	$C_6H_5(CH_2)_4Br$	**17a** (61.3)
0.806	97.3	95.8	$CH_3(CH_2)_8Br$	**17b** (48.0)
0.806	98.1	97.2	$CH_3(CH_2)_9Br$	**17c** (57.3)

[a] Determined by titration.

3. Conclusions

We performed the synthesis of polymeric reagents endowed with thioacetal reactivity for supported organic reactions and combinatorial chemistry using commercial Merrifield resins and a proper 1,3-dithiane synthon, obtained through an odorless synthesis, unsubstituted at the position 2 and carrying at the position 5 a suitable alcoholic function for the formation of stable ether bonds.

After having examined and then discarded the 5-hydroxy-1,3-dithiane (**2**) as a possible synthon, we prepared the fully



Scheme 9.

satisfactory 1,3-dithiane-5-methanol (**6**). Through synthesis and study of the model molecules and soluble copolymers **7**, **9**, **12**, **13**, **14**, **15**, **16**, $\mathbf{P1_{15}}$ and $\mathbf{P1_{16}}$, we demonstrated that **6** can be easily anchored to a polymeric material by forming benzyl ether or alkyl ether bridges with chloromethylphenyl or various ω-bromoalkylphenyl residues, respectively.

The presence of benzyl ether groups has the handicap of producing by treatment with *n*-butyllithium small amounts of alcoholate through the Wittig rearrangement, increasing the consumption of the lithium reagent. Nevertheless, materials that show such handicap, like those derived from the Merrifield resins, have the advantage of being prepared from commercial products, while those not containing benzyl ether groups and not undergoing the Wittig rearrangement, require rather laborious and expensive preparations and show only a slightly higher efficiency (compare $\mathbf{P1_{15}}$ and $\mathbf{P1_{16}}$ in the Table 1). For these reasons the use of reagents derived from commercial products has to be preferred for most applications.

The effectiveness of **6** for the preparation from commercial Merrifield resins of valuable polymeric reagents for solid-phase synthesis was demonstrated with the transformation of alkyl halides into aldehydes containing an additional carbon atom.

4. Experimental

4.1. General

Melting points were determined on a Leica Galen III hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance DPX 300 Spectrometer at 300 and 75.5 MHz, respectively, using TMS as internal standard and were assigned with the help of standard NOE-difference, COSY and HETCOR experiments. Mass spectra were obtained with a GC-MS Ion Trap Varian Saturn 2000 instrument (EI mode, filament current 10 μA). Infrared spectra were measured on a Perkin-Elmer 2000 FTIR spectrophotometer, using KBr discs. Commercial solvents and reagents were purchased from Aldrich unless otherwise stated. Petroleum ether refers to the fraction with boiling point 40–60 °C. Flash-chromatographic separations were performed on Merck Silica gel (0.040–0.063 mm). Commercial 90% (4-ethenylphenyl) chloromethane was crystallized twice from pentane at −70 °C and distilled at reduced pressure (99% pure by ^{1}H NMR). 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. Merrifield resins (particle size 200–400 mesh, 1% DVB, CH_2Cl loading of 0.8 mmol g^{-1}) were purchased from Fluka. The solvents for polymer syntheses and transformations were carefully dried, deoxygenated and distilled under nitrogen. 1,3-Dithiane-5-one (**1**)[7], 1,3-dithiane-5-ol (**2**),[8] 1-bromo-4-(4-ethenylphenyl)butane[14] and 1-bromo-4-phenylbutane[18] were prepared according to the literature.

4.1.1. 5-Methoxymethylene-1,3-dithiane (5). To a vigorously stirred suspension of commercial methoxymethyltriphenylphosphonium chloride (11.01 g, 32.1 mmol) in anhydrous THF (50 mL) potassium *t*-butoxide (3.49 g, 31.1 mmol) was rapidly added under nitrogen at room temperature. The ensuing dark red mixture was further stirred for 1 h, cooled to −25 °C and treated in 5 min under stirring with 1,3-dithian-5-one **1**[7] (1.71 g, 12.7 mmol) in THF (25 mL), further stirred at −20 to −25 °C for 8 h, then added with water (50 mL) and Et_2O (100 mL). The organic layer was separated, washed with water and dried (Na_2SO_4). Evaporation at reduced pressure left a dark oil, which was purified by flash-chromatography (petroleum ether/Et_2O 100:5) to afford **5** (1.65 g, 79.8%). Mp 85–86 °C (Et_2O/pentane, white needles). IR (KBr) ν_{max} cm^{-1}: 1666 (C=C), 1215, 1130 (C–O). ^{1}H NMR ($CDCl_3$) δ_H 3.29 (d, 2H, $J=0.6$ Hz, 6-H, trans to OCH_3), 3.47 (d, 2H, $J=0.6$ Hz, 4-H, cis to OCH_3), 3.64 (s, 3H, OCH_3), 3.95 (s, 2H, 2-H), 6.08 (quintet, 1H, $J=0.6$ Hz, 1′-H). ^{13}C NMR ($CDCl_3$) δ_C 27.7 (4-C), 33.3 (6-C), 33.7 (2-C), 59.8 (OCH_3), 108.1 (5-C), 142.4 (1′-C). *m/z* (EI) 162 (M^+, 100%). Found: C, 44.20; H, 6.19. $C_6H_{10}OS_2$ requires: C, 44.41; H, 6.21.

4.1.2. 1,3-Dithiane-5-methanol (6). Compound **5** (2.03 g, 12.5 mmol) was dissolved in Et_2O (50 mL) and carefully added under nitrogen and magnetic stirring with 48% aqueous tetrafluoroboric acid at 0 °C (12 mL). After removal of the cooling bath, the homogeneous mixture was left 3 h at room temperature, washed with saturated aqueous solution of $NaHCO_3$, then with water and dried (Na_2SO_4). The elimination of the solvent at reduced pressure left a residue of crude aldehyde that was taken up into Et_2O (20 mL) and treated with $NaBH_4$ (0.30 g, 7.9 mmol) in water (4 mL). The two-phase mixture was stirred vigorously for 2 h, the organic layer was separated and the aqueous one extracted with Et_2O (5×5 mL). The combined organic phases were washed with water, dried (Na_2SO_4) and evaporated at reduced pressure to afford **6** as an oil that soon crystallized. Recrystallization from Et_2O/pentane at −30 °C gave pure **6** as a white solid (1.52 g, 80.8%). Mp 60–61 °C. IR (KBr) ν_{max} cm^{-1}: 3391 (OH), 1062 (C–O). ^{1}H NMR (CD_3OD) δ_H 2.00 (m, 1H, 5′-H), 2.64 (dd, 2H, $J_1=13.9$ Hz, $J_2=9.5$ Hz, 4′-H_{axial}), 2.85–2.90 (m, 2H, 4′-$H_{equatorial}$), 3.56 (d, 2H, $J=6.7$ Hz, 1-H), 3.60 (dt, 1H, $J_1=13.9$ Hz, $J_2=1.3$ Hz, 2′-$H_{equatorial}$), 3.92 (d, 1H, $J=13.9$ Hz, 2′-H_{axial}). ^{13}C NMR (CD_3OD) δ_C 32.4 (2′-C), 32.6 (4′-C and 6′-C), 39.4 (5′-C), 66.1 (1-C). *m/z* (EI) 150 (M^+, 100%). Found: C, 39.91; H, 6.80. $C_5H_{10}OS_2$ requires: C, 39.97; H, 6.71.

4.2. Synthesis of dithianic ethers 3, 7, 13, 15 and 16

The appropriate solid alcohol **2** or **6** (4 mmol) was added at 0 °C under nitrogen to the suspension of pure NaH (from the commercial 60% dispersion in oil washed with 3×5 mL of dry Et_2O) in dry DMF (9.5 mL) and left to react for 2 h at room temperature. The mixture cooled to 0 °C was treated with the pure alkyl halide (molar ratio, alcohol:NaH:alkyl halide = 1:1.2:0.9 unless otherwise stated) and stirred for 20 min at 0 °C and 6 h at room temperature. Water (30 mL) was then added, the organic products were extracted with pentane (3×30 mL), the combined organic layers were washed with water and dried (Na_2SO_4). Removal of the solvent at reduced pressure left a residue, which was purified by flash-chromatography (petroleum ether/Et_2O 100:5).

4.2.1. 5-Phenylmethoxy-1,3-dithiane (3). Oil, 86.4%. IR (film) ν_{max} cm^{-1}: 1088, 1069 (C–O), 738, 727, 698 (benzene ring). ^{1}H NMR ($CDCl_3$) δ_H 2.72 (dd, 2H, $J_1=13.9$ Hz, $J_2=10.1$ Hz, 4-H$_{axial}$), 2.90–2.96 (m, 2H, 4-H$_{equatorial}$), 3.30 (dt, 1H, $J_1=13.9$ Hz, $J_2=1.6$ Hz, 2-H$_{equatorial}$), 3.72–3.79 (m, 1H, 5-H), 3.82 (d, 1H, $J=13.9$ Hz, 2-H$_{axial}$), 4.60 (s, 2H, 1′-H), 7.25–7.38 (m, 5H, aromatic protons). ^{13}C NMR ($CDCl_3$) δ_C 30.9 (2-C), 33.8 (4-C and 6-C), 70.6 (1′-C), 74.1 (5-C), 127.7, 127.9, 128.5 (protonated aromatic carbons), 137.9 (1″-C). *m*/*z* (EI) 226 (M$^+$, 31%). Found: C, 58.28; H, 6.19. $C_{11}H_{14}OS_2$ requires: C, 58.37; H, 6.23.

4.2.2. 5-Phenylmethoxymethyl-1,3-dithiane (7). Oil, 85.0%. IR (film) ν_{max} cm^{-1}: 1102 (C–O), 738, 719, 698 (benzene ring). ^{1}H NMR ($CDCl_3$) δ_H 2.25 (m, 1H, 5-H), 2.66 (dd, 2H, $J_1=13.9$ Hz, $J_2=9.4$ Hz, 4-H$_{axial}$), 2.84–2.91 (m, 2H, 4-H$_{equatorial}$), 3.49 (d, 2H, $J=6.4$ Hz, 1′-H), 3.55 (dt, 1H, $J_1=13.9$ Hz, $J_2=1.5$ Hz, 2-H$_{equatorial}$), 3.85 (d, 1H, $J=13.9$ Hz, 2-H$_{axial}$), 4.51 (s, 2H, 1″-H), 7.26–7.38 (m, 5H, aromatic protons). ^{13}C NMR ($CDCl_3$) δ_C 31.9 (2-C), 32.3 (4-C and 6-C), 35.7 (5-C), 73.1 (1′-C and 1″-C), 127.6, 127.7, 128.4 (protonated aromatic carbons), 138.1 (1‴-C). *m*/*z* (EI) 240 (M$^+$, 84%). Found: C, 60.07; H, 6.67. $C_{12}H_{16}OS_2$ requires: C, 59.96; H, 6.71.

4.2.3. 5-(3-Phenylpropoxy)methyl-1,3-dithiane (13). Oil, 41.7%. IR (film) ν_{max} cm^{-1}: 1115 (C–O), 747, 719, 700 (benzene ring). ^{1}H NMR ($CDCl_3$) δ_H 1.91 (m, 2H, 2″-H), 2.23 (m, 1H, 5-H), 2.65 (m, 4H, 4-H$_{axial}$+3″-H), 2.86 (m, 2H, 4-H$_{equatorial}$), 3.42 (d, 2H, $J=6.5$ Hz, 1′-H), 3.42 (t, 2H, $J=6.3$ Hz, 1″-H), 3.58 (dt, 1H, $J_1=13.9$ Hz, $J_2=1.4$ Hz, 2-H$_{equatorial}$), 3.85 (d, 1H, $J=13.9$ Hz, 2-H$_{axial}$), 7.16–7.30 (m, 5H aromatic protons). ^{13}C NMR ($CDCl_3$) δ_C 31.2 (2″-C), 31.9 (2-C), 32.26 (4-C and 6-C), 32.34 (3″-C), 35.6 (5-C), 70.3 (1″-C), 73.7 (1′-C), 125.8, 128.3, 128.5 (protonated aromatic carbons), 141.9 (1‴-C). *m*/*z* (EI) 268 (M$^+$, 100%). Found: C, 62.55; H, 7.47. $C_{14}H_{20}OS_2$ requires: C, 62.64; H, 7.51.

4.2.4. 5-(4-Ethenylphenyl)methoxymethyl-1,3-dithiane (15). (From **6**:NaH:(4-ethenylphenyl)chloromethane = 1:1.20:1). Mp 62–63 °C (Et_2O/pentane, white solid), 88.9%. IR (KBr) ν_{max} cm^{-1}: 1125, 1109 (C–O), 994, 922 ($CH_2{=}CH$), 826 (benzene ring). ^{1}H NMR ($CDCl_3$) δ_H 2.24 (m, 1H, 5-H), 2.66 (dd, 2H, $J_1=13.9$ Hz, $J_2=9.3$ Hz, 4-H$_{axial}$), 2.84–2.90 (m, 2H, 4-H$_{equatorial}$), 3.48 (d, 2H, $J=6.4$ Hz, 1′-H), 3.57 (dt, 1H, $J_1=13.9$ Hz, $J_2=1.2$ Hz, 2-H$_{equatorial}$), 3.85 (d, 1H, $J=13.9$ Hz, 2-H$_{axial}$), 4.50 (s, 2H, 1″-H), 5.24 (dd, 1H, $J_1=10.9$ Hz, $J_2=0.9$ Hz, 2⁗-H$_{cis}$), 5.75 (dd, 1H, $J_1=17.6$ Hz, $J_2=0.9$ Hz, 2⁗-H$_{trans}$), 6.71 (dd, 2H, $J_1=17.6$ Hz, $J_2=10.9$ Hz, 1⁗-H), 7.26–7.29 (m, 2H, 2‴-H), 7.38–7.41 (m, 2H, 3‴-H). ^{13}C NMR ($CDCl_3$) δ_C 31.9 (2-C), 32.2 (4-C and 6-C), 35.7 (5-C), 72.9 (1″-C), 73.1 (1′-C), 113.9 (2⁗-C), 126.3 (3‴-C and 5‴-C), 127.8 (2‴-C and 6‴-C), 136.5 (1⁗-C), 137.1, 137.7 (quaternary aromatic carbons). Found: C, 63.21; H, 6.90. $C_{14}H_{18}OS_2$ requires: C, 63.11; H, 6.81.

4.2.5. 5-(4-(4-Ethenylphenyl)butoxy)methyl-1,3-dithiane (16). (From **6**:NaH:1-bromo-4-(4-ethenylphenyl)butane = 1:1.4:1.4). Oil, 40.8%. IR (film) ν_{max} cm^{-1} 1118 (C–O), 991, 906 ($CH_2{=}CH$), 843 (benzene ring). ^{1}H NMR ($CDCl_3$) δ_H 1.57–1.71 (m, 4H, 2″-H and 3″-H), 2.18 (m, 1H, 5-H), 2.61 (t, 2H, $J=7.4$ Hz, 4″-H), 2.62 (dd, 2H, $J_1=13.9$ Hz, $J_2=9.2$ Hz, 4-H$_{axial}$), 2.84 (m, 2H, 4-H$_{equatorial}$), 3.40 (d, 2H, $J=6.5$ Hz, 1′-H), 3.42 (t, 2H, $J=6.2$ Hz, 1″-H), 3.56 (dt, 1H, $J_1=13.9$ Hz, $J_2=1.4$ Hz, 2-H$_{equatorial}$), 3.84 (d, 1H, $J=13.9$ Hz, 2-H$_{axial}$), 5.18 (dd, 1H, $J_1=10.9$ Hz, $J_2=1.0$ Hz, 2⁗-H$_{cis}$), 5.69 (dd, 1H, $J_1=17.6$ Hz, $J_2=1.0$ Hz, 2⁗-H$_{trans}$), 6.69 (dd, 1H, $J_1=17.6$ Hz, $J_2=10.9$ Hz, 1⁗-H), 7.11–7.14 (m, 2H, 2‴-H), 7.31–7.34 (m, 2H, 3‴-H). ^{13}C NMR ($CDCl_3$) δ_C 27.9 (3″-C), 29.2 (2″-C), 31.9 (2-C), 32.2 (4-C and 6-C), 35.4 (4″-C), 35.6 (5-C), 71.0 (1″-C), 73.7 (1′-C), 112.9 (2⁗-C), 126.2 (3‴-C and 5‴-C), 128.6 (2‴-C and 6‴-C), 135.2 (quaternary aromatic carbon), 136.7 (1⁗-C), 142.1 (quaternary aromatic carbon). Found: C, 66.26; H, 7.89. $C_{17}H_{24}OS_2$ requires: C, 66.18; H, 7.84.

4.3. Deuteration of dithianic ethers 3, 7 and 13

A 0.1 M solution of the proper ether **3**, **7** or **13** in dry THF (1.3 mmol) was treated under stirring with a 1.6 M hexane solution of *n*-butyllithium in the molar ratio 1:1.3 at −30 °C under nitrogen. The homogenous solution was stirred 40 min at −30 to −35 °C, then quenched with methanol-*d* (0.5 mL) and treated with saturated ammonium chloride (0.5 mL). The organic layer was separated and the aqueous phase extracted with Et_2O (2×20 mL). The combined organic layers were dried (Na_2SO_4), evaporated and submitted to flash-chromatography (petroleum ether/Et_2O 100:5) to obtain the products **4**, **8** or **14**. After the recovery of the product **8**, the column, further eluted with Et_2O/methanol 100:5, afforded **9**, which was purified through a second flash-chromatography (petroleum ether/Et_2O 3:1) giving an oily product whose ^{1}H and ^{13}C NMR data in $CDCl_3$ were coincident with those of the non-deuterated derivative **12**, with the exception of the absence of the signal of 2′-H$_{equatorial}$ and the following variations concerning axial proton and carbon in the position 2′ δ_H 3.76 (br s); δ_C 31.4 (t, $J_{13C-D}=22$ Hz).

4.4. 2-(1,3-Dithian-5-yl)-1-phenylethanone (11)

Alcohol **6** (0.366 g, 2.44 mmol) was dissolved in dry pyridine (2 mL) and treated at −10 °C with benzenesulfonyl chloride (0.38 mL, 2.98 mmol). The mixture was stirred at −10 °C for 4 h, then treated with cold 2 M H_2SO_4 (50 mL) and ethyl acetate (20 mL). The organic layer was separated, washed with 2 M H_2SO_4, then three times with water and dried (Na_2SO_4). The solvent was removed at reduced pressure and the residue crystallized from absolute ethanol to afford the benzenesulfonate ester **10** as white needles (0.503 g, 71.1%. Mp 71–72 °C. IR (KBr) ν_{max} cm^{-1}: 1353, 1339, 1184, 1176 (S–O), 754, 744, 684 (benzene ring). Found C, 44.70; H, 4.80. $C_{11}H_{14}O_3S_3$ requires: C, 44.49; H, 4.86). A solution of diisopropylamine (0.27 mL, 1.93 mmol) in anhydrous THF (2 mL) was treated with a 1.66 M hexane solution of *n*-butyllithium (1.2 mL, 1.99 mmol) at −75 °C under nitrogen, stirred at the same temperature for 10 min and added with benzaldehyde *O*-trimethylsilyl cyanohydrin (0.398 g, 1.94 mmol) in dry THF (0.5 mL). The thick yellow suspension immediately formed after 10 min was treated with the solution of **10** (0.401 g, 1.38 mmol) in dry THF (0.5 mL). Stirring was continued 2 h at −60 °C, then the temperature was left to rise in 2 h from −60 to 0 °C. The orange solution was treated with 1 M HCl (20 mL) and methanol (10 mL), stirred overnight at room temperature and extracted with Et_2O (3×20 mL). The combined organic layers were washed twice with 1 M aqueous NaOH, three times with water and dried (Na_2SO_4). After elimination of the solvent at reduced pressure the residue, purified by flash-chromatography (petroleum ether/ethyl acetate 4:1), afforded the ketone **11** (0.281 g, 85.3%). Mp 137–138 °C (ethanol, white leaflets). IR (KBr) ν_{max} cm^{-1}: 1682 (C═O), 750, 734, 689 (benzene ring). ^{1}H NMR (DMSO-d_6) δ_H 2.45 (m, 1H, 5′-H), 2.70 (dd, 1H, J_1=13.7 Hz, J_2=8.6 Hz, 4′-H_{axial}), 2.89 (ddd, 2H, J_1=13.7 Hz, J_2=2.7 Hz, J_3=1.0 Hz, 4′-$H_{equatorial}$), 3.25 (d, 2H, J=6.5 Hz, 2′-H), 3.74 (dt, 1H, J_1=13.6 Hz, J_2=1.0 Hz, 2′-$H_{equatorial}$), 3.87 (d, 1H, J=13.6 Hz, 2′-H_{axial}), 7.51–8.00 (m, 5H, aromatic protons). ^{13}C NMR (DMSO-d_6) δ_C 30.3 (2′-C), 30.4 (5′-C), 33.5 (4′-C and 6′-C), 42.4 (2-C), 127.8 (3″-C and 5″-C), 128.7 (2″-C and 6″-C), 133.2 (4″-C), 136.7 (1″-C), 198.5 (CO). *m/z* (EI) 238 (M^+, 68%). Found C, 60.38; H, 6.01. $C_{12}H_{14}OS_2$ requires: C, 60.46; H, 5.92.

4.5. 2-(1,3-Dithian-5-yl)-1-phenylethanol (12)

Ketone **11** (0.063 g, 0.26 mmol) in THF (3 mL) was added to $NaBH_4$ (0.058 g, 1.5 mmol) in water (0.4 mL), then the mixture was vigorously stirred for 3 h and extracted with Et_2O (3×5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated at reduced pressure to afford **12** (quantitative yield). Mp 72–74 °C (Et_2O/pentane at −30 °C, white solid). IR (KBr) ν_{max} cm^{-1}: 3548 (OH), 1059 (C–O), 754, 738, 699 (benzene ring). ^{1}H NMR ($CDCl_3$) δ_H 1.80–1.95 (m, 2H, 2-H), 2.10 (br s, 1H, OH), 2.15 (m, 1H, 5′-H), 2.54–2.65 (m, 2H, 6′-H and 4′-H), 2.84–2.93 (m, 2H, 6′-H and 4′-H), 3.58 (dt, 1H, J_1=13.8 Hz, J_2=1.5 Hz, 2′-$H_{equatorial}$), 3.76 (d, 1H, J=13.8 Hz, 2′-H_{axial}), 4.78 (br m, 1H, 1-H), 7.26–7.36 (m, 5H, aromatic protons). ^{13}C NMR ($CDCl_3$) δ_C 31.6 (2′-C), 31.7 (5′-C), 34.7 (4′-C or 6′-C), 35.7 (4′-C or 6′-C), 44.0 (2-C), 71.9 (1-C), 125.7, 127.8, 128.7 (protonated aromatic carbons), 144.5 (1″-C). Found C, 59.89; H, 6.66. $C_{12}H_{16}OS_2$ requires: C, 59.96; H, 6.71.

4.6. Copolymers P1$_{15}$ and P1$_{16}$

Monomer **15** or **16** and styrene (molar ratio 1:9 and 1:19) together with the calculated volume of deoxygenated dioxane to give 8.5 M solutions and AIBN (2% weight of the monomers) were introduced in a vial with a side arm and subjected to three freeze-pump-thaw cycles at −78 °C. After sealing and stirring the vial containing the homogenous solution was heated at 60 °C in a thermostatic bath for 72 h. The cooled viscous clear content of the vial was diluted with dioxane (5 mL per g of monomer charge) and slowly poured with vigorous stirring into methanol (15 times the volume of the dioxane solution). The powdery precipitate was filtered, washed with methanol and dried under vacuum at room temperature up to constant weight. Yields were always greater then 95% of the mass of the used monomers.

4.7. Copolymers P3$_{15}$ and P3$_{16}$

A solution of **P1**$_{15}$ or **P1**$_{16}$ in anhydrous THF (1.2 mmol of 1,3-dithiane units at 0.1 M concentration) mechanically stirred at −40 °C under nitrogen was treated with a 1.6 M solution of *n*-butyllithium in hexane and further stirred at −30 to −35 °C for 1 h, during which a marked increase of the viscosity was observed owing to the formation of **P2**. The mixture was treated with 1-bromo-4-phenylbutane (1,3-dithiane units:*n*-buthyllitium:1-bromo-4-phenylbutane = 1:1.25:1.50), stirred for 2 h while the temperature was left slowly to rise from −30 to −15 °C, then it was kept at −10 °C overnight. Water (50 mL) and dichloromethane (100 mL) were added and the layers allowed slowly to separate. The organic layer was cautiously removed, while the insoluble portion of cross-linked **P3** remained floating between the two phases, then additional extractions with dichloromethane (2×100 mL) were performed using the same precautions. The combined organic layers were washed with water, dried (Na_2SO_4) and the solvent was removed at reduced pressure. The crumbly residue of **P3** was taken up in the appropriate solvent [(toluene for **P3**$_{15(1:9)}$ (0.10 g mL^{-1}) and **P3**$_{15(1:19)}$ (0.14 g mL^{-1}); dioxane for **P3**$_{16(1:9)}$ (0.08 g mL^{-1}) and **P3**$_{16(1:19)}$ (0.16 g mL^{-1})] and slowly poured into methanol (20 times the volume of the solution). The powdery precipitate of **P3** was filtered, washed with methanol and pump-dried at room temperature to constant weight. From the remaining mixture of aqueous phase and cross-linked **P3** any residual dichloromethane was eliminated in vacuo, the insoluble material was filtered, washed thoroughly with water and methanol then pump-dried at room temperature to constant weight.

4.8. Reaction of P3 with mercury(II) perchlorate hydrate

A THF solution of polymer **P3** (0.55 mmol of 2-alkylated 1,3-dithiane units at 0.2 M concentration) was treated under nitrogen and magnetic stirring with a solution of mercury(II) perchlorate hydrate (1,3-dithiane units:mercury ions = 1:2.5, considering a minimum content of 42% metal in the used reagent) in THF (15 mL). The mixture was stirred 1 h at room temperature then $NaHCO_3$ (0.75 g, 8.9 mmol) was added in the minimum amount of water. Stirring was continued for 5 min, flash-chromatography silica gel (5 g) was added and most of the solvent removed at in vacuo. The obtained coarse powder was charged on a flash-chromatography column packed with pentane/Et_2O 100:5 (20 g of silica gel in a 20 mm diameter column) and **17a** was eluted with this eluent.

4.9. Reaction of P3 with periodic acid

A weighted amount of polymer **P3** (corresponding to 0.45 mmol of 2-alkylated 1,3-dithiane units) was dissolved in THF (4.5 mL) under nitrogen and magnetic stirring at 0 °C, and treated with a 0.40 M solution of periodic acid in THF (3.4 mL, 1.36 mmol). The cooling bath was removed and stirring continued at room temperature for 2 h. Et_2O (50 mL) was carefully added, the organic solution separated, washed with 1.6 M sodium sulfite solution, then with water and dried (Na_2SO_4). After removal of the solvent the flash-chromatography of the residue (pentane/acetone

100:5) afforded a mixture of **17a**[15] and **18** whose NMR spectra in $CDCl_3$ allowed to assign the following signals: ^{1}H NMR δ_H 4.38 (m, 1H, 2-H); 9.22 (d, 1H, $J=2.9$ Hz, 1-H). ^{13}C NMR δ_C 191.5 (1-C).

4.10. Resins R1

NaH (6.0 mmol, from a corresponding amount of a commercial 60% dispersion in mineral oil washed with 3×10 mL of dry Et_2O) was suspended under nitrogen in dry DMF (15 mL) and treated under magnetic stirring with **6** (0.820 g, 5.45 mmol). The mixture was further stirred for 3 h at room temperature, then added with the proper amount (corresponding to 3.60 mmol of chloromethyl groups) of resin **R0** and diluted with 15 mL of anhydrous DMF. After stirring for additional 6 h in an oil bath at 50 °C, the resin was filtered, washed with peroxide-free THF and extracted under magnetical stirring for 1 h with the same solvent (50 mL). After filtration, the washing with THF was repeated, then the resin was filtered and washed in turn with peroxide-free THF, methanol, water and again methanol. The collected resin was pump-dried at room temperature to constant weight: more than 97% of the expected amount of **R1** was always recovered.

4.11. Resins R3

Resin **R1** (an amount corresponding to 1.4 mmol of 1,3-dithiane units) was suspended under nitrogen in the minimum amount of anhydrous THF necessary to give an easy to stir slurry (0.13 g resin mL^{-1}), cooled to -60 °C and added with a 1.6 M solution of *n*-butyllithium in hexane. The temperature was raised rapidly to -35 °C and the suspension of the beads, which turned deep red owing to their transformation into **R2**, was magnetically stirred at -35 to -30 °C for 2 h. The pure alkyl halide (1-bromo-4-phenylbutane, or 1-bromononane, or 1-bromodecane) was then added (1,3-dithiane units:*n*-butyllithium:alkyl halide = 1:1.25:1.50), the temperature was left to rise to -15 °C in 1 h and the reaction mixture kept at -10 °C overnight. The pale yellow resin **R3** was filtered, washed with peroxide-free THF and magnetically stirred for 1 h with the same solvent. After filtration, this treatment was repeated once again and finally **R3** was filtered, washed in turn with peroxide-free THF, methanol, water, methanol and pump-dried at room temperature to constant weight.

4.12. Aldehydes 17a–c from resins R3

Resin **R3** (an amount corresponding to 0.4 mmol of 2-alkylated 1,3-dithiane units) was suspended in peroxide-free THF (0.27 g mL^{-1}) under nitrogen and added with a 0.5 M THF solution of mercury(II) perchlorate hydrate (1,3-dithiane units:mercury ions = 1:3, calculated on the basis of a 42% metal content in the salt). The mixture was stirred for 1 h at room temperature, then it was treated with a saturated aqueous solution of $NaHCO_3$ (1 mL). The heterogeneous mixture was extracted with Et_2O (5×5 mL), the organic layers were combined, the solvent was eliminated at reduced pressure and aldehydes **17a–c** were recovered from the residue by flash-chromatography (petroleum ether/Et_2O 100:5).

4.13. Determination of the chlorine loading in Merrifield resins R0

A weighted sample of **R0** (1 g) was suspended under nitrogen in dry DMF (12 mL) and added with solid sodium methoxide (CH_2Cl units:methoxide ion = 1:2.5). The mixture was stirred 6 h at 50 °C, then the resin was filtered and accurately washed with water (150 mL in small portions). The aqueous filtrate was made strongly acidic with 65% nitric acid (1 mL) and briefly boiled. After cooling, the chloride ions were determined according to Volhard procedure, correcting for a blank titration without resin sample.

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