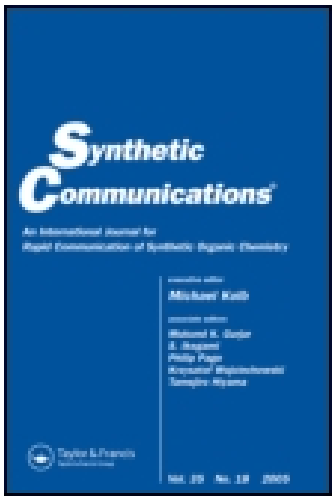

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# SYNTHESIS OF SOLID-PHASE BOUND SULFONATE ESTERS

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# SYNTHESIS OF SOLID-PHASE BOUND SULFONATE ESTERS

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## ABSTRACT

*p*-Pivaloyloxybenzenesulfonyl and methylsulfonyl residues were used as linkers to attach secondary alcohols to Wang resin and to Merrifield resin, respectively. *p*-Pivaloyloxybenzenesulfonates of alcohols were deprotected at the phenolic group and coupled with Wang resin by Mitsunobu reaction whereas mesylates were lithiated at the methyl group and subsequently connected with chloromethyl residues of Merrifield resin.

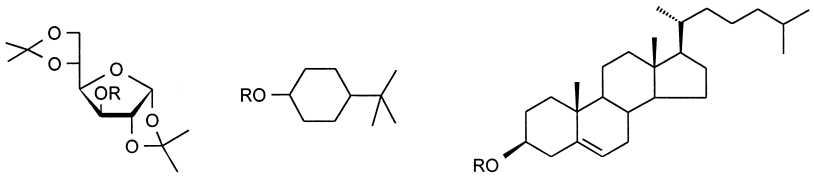
Synthesis of small molecules on polymers is a rapidly growing area of organic chemistry owing to the emergence of a combinatorial approach to drug discovery programmes.[1] The sulfonyl functional group plays a particularly important role in such syntheses[2] due to its ability to bind molecules to the polymer support, and at the same time making a cleavage of the target compound feasible by a variety of methods.[2–4] As a part of our program

*Corresponding author.

aimed at development of new polymer bound synthetic methodologies, we directed attention to the use of sulfonate linkers.

To the best of our knowledge, a polymer-bound sulfonylation of secondary alcohols has not been reported, so far. In this paper we present the methodologies based on *p*-pivaloyloxybenzenesulfonate esters and methanesulfonate esters. The first one employs sulfonates available from secondary alcohols and *p*-pivaloyloxybenzenesulfonyl chloride (**1**).[6] After deprotection, the phenolic group of the sulfonate ester is suitable to be attached to a polymer, possessing a terminal hydroxyl, by the Mitsunobu procedure. It should be noted that the preparation of **1**[6] from sodium *p*-hydroxybenzenesulfonate is easier than the preparation of its 4-acetoxy congener.[7] The second methodology uses readily available methanesulfonyl esters which after transformation into α-lithio sulfonate esters can easily be linked to the Merrifield chloromethyl resin.

In order to demonstrate the usefulness of the both approaches we selected three secondary alcohols **2–4** to bind them to the commercially available Wang resin *via* the *p*-oxybenzenesulfonyl linker and to the Merrifield chloromethyl resin *via* lithium anions of respective mesylates. The successful formation of solid-phase bound sulfonate ester was proved by liberation of the starting alcohol from the resin.




**2**: R = H
**5**: R = *p*-PivOC$_6$H$_4$SO$_2$
**8**: R = *p*-HOC$_6$H$_4$SO$_2$
**14**: R = CH$_3$SO$_2$

**3**: R = H
**6**: R = *p*-PivOC$_6$H$_4$SO$_2$
**9**: R = *p*-HOC$_6$H$_4$SO$_2$
**15**: R = CH$_3$SO$_2$

**4**: R = H
**7**: R = *p*-PivOC$_6$H$_4$SO$_2$
**10**: R = *p*-HOC$_6$H$_4$SO$_2$
**16**: R = CH$_3$SO$_2$

***Scheme 1.***

Alcohols **2–4** (compound **3** was used as a commercially available *trans–cis* mixture in a proportion *ca.* 4:1, respectively) were sulfonylated with **1** in the presence of pyridine to provide respective sulfonates **5–7** in good yields (93–94%). The pivaloyl residue was removed by treatment of compounds **5–7** with sodium methoxide in methanol to afford corresponding phenols **8–10**. Formation of **8–10** using *p*-hydroxybenzenesulfonyl chloride[8] according to the Takahashi et al. method[9] gave a low yield due to the selfsulfonylation reaction.





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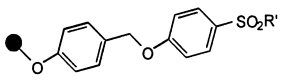
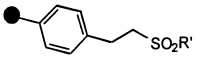
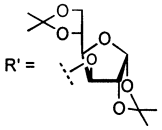
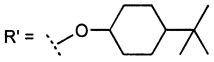
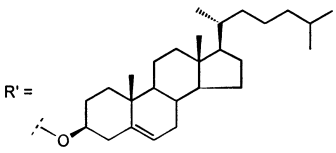
Phenols **8–10** were attached to the Wang resin by the Mitsunobu reaction[9–11] to give the corresponding polymer-supported alcohols **11–13** in yields 75, 79 and 94%, respectively, deduced by elemental analysis of sulfur. Alcohols **2–4** can be easily cleaved from the polymer by reduction of **11–13** with $LiAlH_4$ to provide an additional proof of bounding the R′ substituent to the polymer.

Mesyl esters **14–16** were prepared from the alcohols **2–4** by standard procedures. Formation of respective α-lithio sulfonates was performed according to the Musicki and Widlanski procedure.[5] An alkylation of lithiated sulfonates with the commercially available Merrifield resin proceeded smoothly to afford respective resin-linked compounds **17–19**. The yield of alkylation: 73, 75 and 79%, respectively, was deduced, by the sulfur analysis as above. The resin-bound sulfonate esters **17–19** can be cleaved, with $LiAlH_4$ as above, to provide **2–4** in 90, 69, 80% yield, respectively.

In summary, we demonstrated that the sulfonyl linkers can be easily attached to secondary alcohols by sulfonylation and to terminals of the Wang resin by the Mitsunobu reaction, or else to the Merrifield resin by alkylation with the lithiated mesyl esters. It should be pointed out that the commercially available chlorosulfonylated polystyrene PS-TsCl (Argonaut Technologies, 1.59 mmol/g) reacts easily with primary alcohols,[12] whereas with the secondary alcohols **2–4** it affords corresponding sulfonates in 13, 15 and 5% yield only (estimated after cleavage from the resin by

***Table 1.***

| |  |  |
|---|---|---|
| R' =  | **11** | **17** |
| R' =  | **12** | **18** |
| R' =  | **13** | **19** |





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$LiAlH_4$ reduction). It should be noticed that both methodologies proposed by us do not leave any free sulfonyl-acid group on the resin, contrary to the sulfonylation of alcohols performed with the use of chlorosulfonylated resins. It can be critical if the reaction carried out on a resin employed acid sensitive reactants.

## EXPERIMENTAL

Melting points were determined on a *Kofler* hot-stage apparatus with microscope and are uncorrected. $^1$H NMR spectra were obtained on *Brucker Avance 500* and *Varian Gemini AC-200* spectrometers for solution in $CDCl_3$. Chemical shifts are expressed in ppm downfield from the signal for $Me_4Si$. IR spectra were recorded on a *Perkin Elmer FT-IR Spectrum 2000* spectrophotometer. Mass spectra were determined with an *AMD 604 Inectra GmbH* spectrometer. Optical rotations were measured using a *JASCO P 3010* polarimeter at ambient temperature. All reactions were performed under atmospheres of dry $N_2$ in anhydrous solvents distilled from the following desiccants: $CH_2Cl_2$ and pyridine from $CaH_2$, and THF from Na-benzophenone. Wang and Merrifield resins were reagent grade and used as purchased without further purification. Column chromatography was performed on Merck Silica gel (230–400 mesh).

*p*-Pivaloyloxybenzenesulfonyl chloride was obtained from commercially available sodium salt of *p*-hydroxybenzenesulfonic acid according to the procedure described in Ref. 6. Compound **3** was used as a commercially available *trans–cis* mixture in a ratio of *ca.* 4:1, respectively. Therefore compounds **6**, **9** and **15** are the mixtures of *trans* and *cis* isomers.

**Synthesis of compounds 5–7**. Compounds **5–7** were obtained from the respective alcohols **2–4** (10 mmol) by treatment with *p*-pivaloyloxybenzenesulfonyl chloride (14 mmol) in pyridine solution (20 mL) at 0°C, overnight. The standard work up followed by chromatographical purification afforded compounds **5–7** in about 93% yield.

**1,2:5,6-Di-*O*-isopropylidene-3-*O*-(*p*-pivaloyloxybenzenesulfonyl)-α-D-glucofuranose (5)**. Compound **5** was obtained from **2** according to the procedure described above (92%). Colorless solid; mp. 81–83°C; $[\alpha]_D^{22}$-70.1 (*c* 0.6, $CH_2Cl_2$); IR ($CHCl_3$): 844, 1105, 1375, 1757 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 1.17, 1.22 (2s, 6H, 5,6-*O*-isoprop), 1.37 (s, 9H, Piv), 1.32, 1.49 (2s, 6H, 1,2-*O*-isoprop), 3.88–4.08 (m, 4H, H-4,5,6a,6b), 4.80 (m, 1H, H-3), 4.86 (d, 1H, *J* 3.7 Hz, H-2), 5.94 (d, 1H, *J* 3.7 Hz, H-1), 7.22–7.30, 7.84–8.02 (2m, 4H, phenyl); MS (EI, HR) *m/z*: $(M+H)^+$ calcd for $C_{23}H_{33}O_{10}S$: 501.17944. Found: 501.17804; Anal. Calcd for $C_{23}H_{32}O_{10}S$ (500.58): C, 55.19; H, 6.44; S, 6.41. Found: C, 55.19; H, 6.57; S, 6.40.





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**4-*tert*-Butylcyclohexyl *p*-pivaloyloxybenzenesulfonate (6)**. Compound 6 was obtained from **3** according to the procedure described above (90%). Colorless solid; IR ($CHCl_3$): 827, 1109, 1366, 1756, 2960 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) selected signals: δ 0.81 (s, 9H, *tert*-butyl), 0.84 (s, 9H, *tert*-butyl), 1.37 (s, Piv), 4.30–4.46, 4.76–4.80 (2m, 1H of *cis* and *trans*, H-1), 7.21–7.30, 7.90–7.98 (2m, 4H, phenyl); Anal. Calcd for $C_{21}H_{32}O_5S$ (396.559): C, 63.61; H, 8.13; S, 8.09. Found: C, 63.66; H, 8.30; S, 7.88.

**5-Cholesten-3β-yl (*p*-pivaloyloxybenzenesulfonate) (7)**. Compound **7** was obtained from **4** according to the procedure described above (91%). Colorless solid; mp. 117–119°C; $[\alpha]_D^{22}$-32.3 (*c* 0.4, $CH_2Cl_2$); IR ($CHCl_3$): 934, 1109, 1163, 1365, 1757, 2952 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) selected signals: δ 1.35 (s, 9H, Piv), 4.27–4.44 (m, 1H, H-3), 5.32 (m, 1H, H-6), 7.22–7.29, 7.90–7.97 (2m, 4H, phenyl); MS (LSIMS, HR) *m*/*z*: $(M + Na)^+$ calcd for $C_{38}H_{58}O_5SNa$: 649.39026. Found: 649.39011.

**Synthesis of compounds 8–10**. Compounds **8–10** were obtained from the respective *p*-pivaloyloxybenzenesulfonate esters **5–7** (6 mmol) by treatment with NaOMe (10 mmol) in MeOH solution (10 mL) at *r.t*. After 6 h the reactions were neutralised with solid carbon dioxide, and extracted with $CH_2Cl_2$. The extracts were washed with water, dried ($MgSO_4$) and evaporated to give the crude products **8–10**. Chromatographic purification afforded compounds **8–10** in about 90% yield.

**3-*O*-(*p*-Hydroxybenzenesulfonyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (8).** Compound **8** was obtained from **5** according to the procedure described above (92%). Yellow solid; mp. 139–143°C; $[\alpha]_D^{22}$-66.6 (*c* 1.0, $CH_2Cl_2$); IR ($CHCl_3$): 844, 1076, 1167, 1374, 3247 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 1.17, 1.22 (2s, 6H, 5,6-*O*-isoprop), 1.32, 1.49 (2s, 6H, 1,2-*O*-isoprop), 1.75 (br s, 1H, -OH), 3.88−4.11 (m, 4H, H-4,5,6a,6b), 4.77 (m, 1H, H-3), 4.83 (d, 1H, *J* 3.6 Hz, H-2), 5.93 (d, 1H, *J* 3.6 Hz, H-1), 6.90–6.98, 7.79–7.88 (2m, 4H, phenyl); MS (LSIMS, HR) *m*/*z*: $(M + Na)^+$ calcd for $C_{18}H_{24}O_9SNa$: 439.10387. Found: 439.10611; Anal. Calcd for $C_{18}H_{24}O_9S$ (416.46): C, 51.92; H, 5.81; S, 7.7. Found: C, 51.93; H, 6.01; S, 7.53.

**4-*tert*-Butylcyclohexyl *p*-hydroxybenzenesulfonate (9).** Compound was obtained from **6** according to the procedure described above (90%). White solid; IR ($CHCl_3$): 942, 1165, 1349, 1590, 2957 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) selected signals: δ 0.81 (s, 9H, *tert*-butyl), 0.83 (s, 9H, *tert*-butyl), 4.24–4.41, 4.72–4.75 (2m, 2H, H-1), 6.91–6.99, 7.75–7.83 (2m, 4H, phenyl); MS (EI, HR) *m*/*z*: $M^+$ calcd for $C_{16}H_{24}O_4S$: 312.13953. Found: 312.98758; Anal. Calcd for $C_{16}H_{24}O_4S$ (312.44): C, 61.51; H, 7.74. Found: C, 60.86; H, 7.90.

**5-Cholesten-3β-yl (*p*-hydroxybenzenesulfonate) (10).** Compound **10** was obtained from **7** according to the procedure described above (91%).





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Colorless solid; mp. 110–114°C with decomposition; $[\alpha]_D^{22}$-35.2 (*c* 1.0, $CH_2Cl_2$); IR ($CHCl_3$): 867, 937, 1166, 1351, 1590, 3247 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) selected signals: δ 4.20–4.38 (m, 1H, H-3), 5.29 (m, 1H, H-6), 6.91–6.99, 7.75–7.83 (2m, 4H, phenyl); Anal. Calcd for $C_{33}H_{50}O_4S$ (542.84): C, 73.02; H, 9.28; S 5.91. Found: C, 72.95; H, 9.57; S 5.83.

**General procedure for the preparation of polymer bound sulfonate esters 11–13 *via* Mitsunobu procedure:** To a suspension of Wang resin (0.5 g, 0.54 mmol) in $CH_2Cl_2$ (8 mL) were added phenol **8** (0.91 g, 2.2 mmol) and $PPh_3$ (0.58 g, 2.2 mmol). The mixture, stirred and then cooled to 0°C, was treated with DEAD (diethyl azodicarboxylate) (0.38 g, 2.2 mmol) over 10 min and then the reaction was allowed to warm to *r.t*. The mixture was stirred for 24 h, then filtered and washed (2 × 10 mL each) $CH_2Cl_2$, MeOH, THF, 2:1 THF-water, THF, MeOH, $CH_2Cl_2$ and $Et_2O$ then dried for 6 h under vacuum to give the resin **11**. IR (KBr): 834, 1073, 1373 $cm^{-1}$. Elemental analysis indicating 2.0% S, gives 75% yield. Cleavage by $LiAlH_4$ (10 equiv.) in THF at 60°C provided alcohol **2** (80% yield).

**Resin 12**. IR (KBr): 950, 1165, 1365 $cm^{-1}$. Elemental analysis indicating 2.2% S, gives 79% yield. The yield determinated by $LiAlH_4$ cleavage was 70%.

**Resin 13**. IR (KBr): 862, 936, 1164, 1364 $cm^{-1}$. Elemental analysis indicating 2.1% S, gives 94% yield. The yield determinated by $LiAlH_4$ cleavage was 87%.

**Synthesis of compounds 14–16.** Compounds **14–16** were obtained from the respective alcohols **2–4** (10 mmol) by treatment with methylsulfonyl chloride (14 mmol) in pyridine solution (20 mL) at 0°C, overnight. The standard work up followed by chromatographic purification afforded compounds **14–16** in about 85% yield.

**1,2:5,6-Di-*O*-isopropylidene-3-*O*-methylsulfonyl-α-D-glucofuranose (14)**. Compound **14** was obtained from **2** according to the procedure described above (81%). Colorless crystals; mp. 82–83.5°C (from $Et_2O$-hexane); $[\alpha]_D^{22}$-46.2 (*c* 0.7, $CH_2Cl_2$); IR ($CHCl_3$): 844, 1077, 1179, 1372, 2992 $cm^{-1}$; [lit.,[13] mp. 80–82°C; $[\alpha]_D^{22}$-49.0 (*c* 1.0, $CHCl_3$)].

**4-*tert*-Butylcyclohexyl methylsulfonate (15).** Compound **15** was obtained from **3** according to the procedure described above (85%). Colorless crystals; IR ($CHCl_3$): 926, 1171, 1332, 1352, 2959 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) selected signals: δ 0.85 (s, 9H, *tert*-butyl), 0.87 (s, 9H, *tert*-butyl), 3.0 (s, 3H, Ms), 3.01 (s, 3H, Ms), 4.48–4.65 (m, 1H, H-1), 4.95–5.02 (m, 1H, H-1); (lit.[14] provides data of pure *trans* and *cis* isomers).

**5-Cholesten-3β-yl methylsulfonate (16)**. Compound **16** was obtained from **4** according to the procedure described above (85%). Colorless crystals; mp 120–122°C (from hexane); $[\alpha]_D^{22}$-31.5 (*c* 0.78, $CH_2Cl_2$); IR ($CHCl_3$): 931, 1179, 1333, 1359, 2952 $cm^{-1}$; (lit.,[15] mp. 115–116°C).





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**General procedure for the alkylation of Merrifield resin with α-lithio sulfonate esters:** To a solution of **14** (0.81 g, 2.4 mmol) in THF (12 mL) and DMPU (4 mL) was added dropwise at −70°C the solution of butyllithium in hexane (2.5 M, 1 mL, 2.5 mmol). After 15 min, the Merrifield resin (0.5 g, 0.6 mmol), was added in one portion. The stirring was continued at the same temperature for 20 min and then at −25°C for 5 h. The reaction was quenched at −25°C by an addition of 5 mL of MeOH, then filtered and washed (2 × 20 mL each) with MeOH, 2:1 THF-water, water, 2:1 THF-water, THF, MeOH, $CH_2Cl_2$ and $Et_2O$ then dried for 6 h under vacuum to give the resin **17**. IR (KBr): 1075, 1169, 1216, 1373 $cm^{-1}$. Elemental analysis indicating 2.06% S, gives 73% yield. The yield determinated by $LiAlH_4$ cleavage was 90%.

**Resin 18.** IR (KBr): 904, 942, 1166, 1365 $cm^{-1}$. Elemental analysis indicating 2.3% S, gives 75% yield. The yield determinated by $LiAlH_4$ cleavage was 69%.

**Resin 19.** IR (KBr): 937, 1166, 1364 $cm^{-1}$. Elemental analysis indicating 2.0% S, gives 79% yield. The yield determinated by $LiAlH_4$ cleavage was 80%.

## ACKNOWLEDGMENT

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