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Resin-Immobilised Benzyl and Aryl Vinyl Sulfones: New Versatile Traceless Linkers for Solid-Phase Organic Synthesis.

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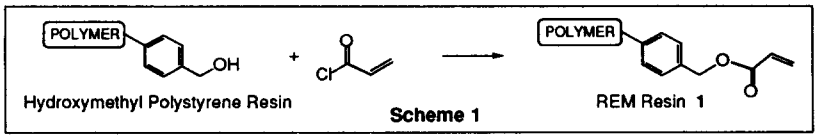
Abstract. New polystyrene-based resins containing benzyl and aryl vinyl sulfone groups are described. The vinyl sulfone group reacts efficiently with 2° amines, *via* conjugate addition, and the resin-bound 3° amine products can be quaternised through alkylation. Subsequent deamination to give 3° amines and the regenerated vinyl sulfone occurs in moderate to good yield. Both systems can be recycled and show moderate stability to acids and high stability to nucleophiles including Grignard reagents.

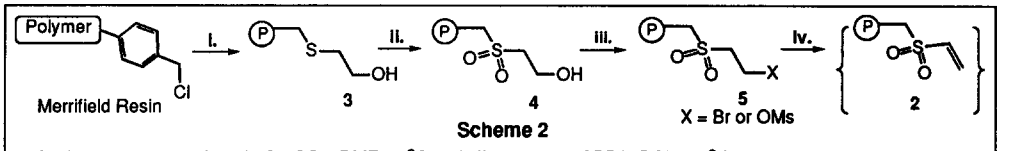
Solid-phase organic synthesis (SPOS) has been revolutionised in the quest to produce libraries of structurally diverse molecules both quickly and cheaply.[1,2] SPOS normally involves 'linking' molecules containing a reaction centre (to be modified) to an immobilised polymer backbone, which is otherwise inert, and then elaborating the reaction centre. Recent advances in the range of new reactions that can be achieved on solid supports are impressive and have been reviewed comprehensively.[3-5] Underpinning these advances are the equally impressive descriptions of new resin materials,[6] resin functional groups,[6] linkers,[7] reagents,[8] resin cleavage protocols,[9] and in combinatorial chemistry, new deconvolution methods.[10] Given that ideal resins should be extremely stable to a wide range of chemistries and accept high loadings of compound, there are major challenges that are associated with the support material . For example, polystyrene itself, the backbone polymer for several resins, forms anions upon treament with unstabilised carbanions, whereas the high molecular weight of the polyethylene glycol linkers used in Tentagel resins precludes the attainment of high loadings.[6] While the solution to these problems will require the advent of new support materials, we describe here the utility of benzyl and aryl vinyl sulfones in the 'traceless linker' synthesis of amines. These vinyl sulfone systems are stable to a wider range of chemistries than the REM benzyl ester system **1**.[11]



Scheme 1

In order to prepare the benzyl vinyl sulfone **2**, Merrifield resin was treated with mercaptoethanol to give the thioether alcohol **3**, Scheme 2, which after drying, routinely gave sulfur analyses consistent with 90-99% chlorine substitution (*ie.* 0.6 - 0.7 mmol of thioether g^{-1} resin) and displayed the expected OH stretch at 3500 cm^{-1} in IR spectra. Oxidation of the thioether gave the sulfone alcohol **4** which also displayed the expected OH

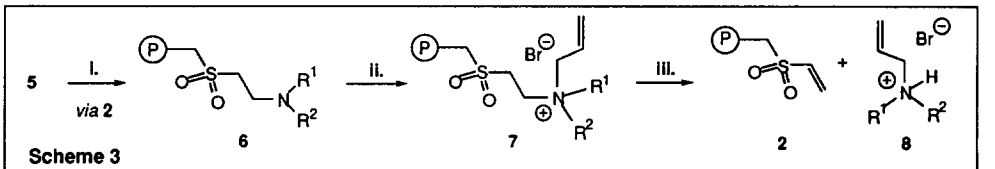
stretch at 3500 cm^{-1} in IR spectra as well as new bands at 1317 and 1119 cm^{-1}. This material was converted to either the bromide or mesylate **5** (X = Br or OMs), Scheme 2. The bromide gave the expected IR data.



Scheme 2

i. 10 eq. mercaptoethanol / Cs_2CO_3, DMF, 20°C, 3 d.; ii. excess *m*-CPBA, DCM, 20°C, 12 h (or excess Oxone, aq. DMF, 20°C, 12 h); iii. PBr_3 DCM, 20°C, 16 - 24 h (or 10 eq. Mesyl Cl, Pyridine, DCM, 20°C, 2 hr.); iv. base

The 2'-bromoethyl- and 2'-mesylethyl- benzyl sulfones **5** (X = Br or OMs) were used as masked forms of vinyl sulfone **2** in several conjugate addition reactions with 2° amines (including tetrahydroisoquinoline [THIQ], piperidines, morpholine, pyrrolidine and dioctylamine) to give resin-bound 3° amine products. These were washed, treated with allyl bromide, to give the quaternised ammonium salts, and the products were treated with DIPEA to effect elimination and release the 3° allylamines (as HBr salts) from the resin, Scheme 3. Overall yields from the starting 2° amines (assuming 100% conversion of **3** to **6**) ranged from 5 to 60%. In certain cases the purities of the eliminated amines **8** were ≥ 95% as judged from ^1H and ^{13}C-NMR spectra.



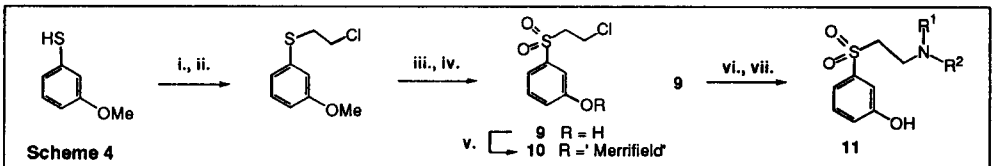
Scheme 3

i. 5 - 10 eq. amine, DMF, 20°C, 16 h; ii. 5 - 10 eq. allyl bromide, DMF, 20°C, 24 h; iii. 5 eq. DIPEA, DCM, 20°C, 16 h.

The regenerated resin **2** could be recycled by re-reaction with more secondary amine. The best overall yields were obtained using the material derived from the mesylate (**5**, X = OMs) and it is possible that, to account for the observation, either the brominating agent (PBr_3) was reacting with the nascent bromide (**5**, X = Br), or, the elimination reaction to give the desired vinyl sulfone was much slower than for the mesylate.

Given our interest in stable functionalised resins, which would not themselves be altered by the reaction chemistry, we wished also to assess the utility of aryl vinyl sulfones. Note that the benzylic protons in the sulfone **6** are likely to possess *solution-phase* pK_a values of *ca.* 22 such that they would be much more acidic than the other α-protons (pK_a ~ 29).[12] Thus, under basic conditions the benzylic C-atom could be nucleophilic and might give rise to unwanted side reactions under certain conditions.

In order to prepare a masked aryl vinyl sulfone, the *m*-hydroxyphenyl 2'-chloroethyl sulfone **9** was prepared from *m*-thioanisole as outlined in Scheme 4.



Scheme 4

i. 1.1 eq. N-chlorosuccinimide, DCM, 45 min, 20°C; ii. excess ethene; iii. 2.2 eq. mCBPA, DCM, 20°C, 18 h; iv. 3 eq, BBr_3, DCM, 0 °C → 20°C, 12 h; v. HMPolystr., Mitsunobu reactn. vi. DBU , DCM, 20°C, 1.5 h; vii. 1.05 eq. amine, DCM, 20°C, 2 h.

The compound **9** was efficiently attached to *p*-hydroxymethyl-functionalised polystyrene resin (1.2 mmol g^{-1})[6] through its phenolic O-atom using the Mitsunobu reaction[13] and the mass of the dried resin product

10 showed an appropriate increase. Elemental analysis of the aryl ether-linked Merrifield resin **10** gave the expected data and further characterisation by IR spectroscopy showed the expected new bands for the sulfone group and for the aryl ether stretch at 1226 cm^{-1}. Treatment of resin **10** with a range of 2° amines or with DBU failed to yield useful quantities of the expected 3° amine product. Therefore, sulfone **9** was treated directly with DBU and then THIQ to afford the required addition product **11.** The compound gave the expected ^1H-, ^{13}C-NMR and IR spectral data and the required mass and microanalytical data and was, therefore, attached to the hydroxymethylated polystyrene resin[6] under Mitsunobu conditions.[13] The resin product **12a** ($R^1 = R^2$ = THIQ) showed the expected mass increase, indicating high conversion efficiency, and displayed bands at 1312 and 1144 cm^{-1} in IR spectra for the sulfone and at 1247 cm^{-1} for the aryl ether. The resin **12a** ($R^1 = R^2$ = THIQ) was N-allylated or benzylated to give 4° amines (**13a, 13b**) which could then be eliminated in high overall yield, Table 1, to give the required 3° amines and immobilised aryl vinyl sulfone **14.**

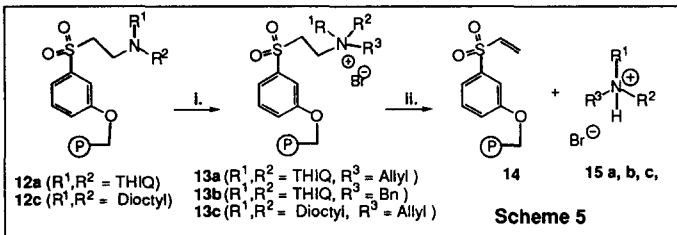


Table 1

15	R^1, R^2	R^3	Yield[1]	Purity
a	THIQ	Allyl	74	>95
b	THIQ	Benzyl	83	>95
c	Dioctyl	Allyl	65	>95

[1] Overall; Calculated from resin loading

Scheme 5

i. 5 - 10 eq. allyl or benzyl bromide, DMF, 20°C, 16 h. ii. 5 eq. DIPEA, DCM, 20°C, 16 h.

Reaction of resin **14** with different 2° amines, or, re-reaction with the same amine, occurred in good yield and **14** could be recycled several times to give the required products. These properties compare with those of the REM system.[11] Preliminary studies indicate that for the 3° amines **12**, complete N-alkylation is difficult and requires the use of activated acid-free alkylating agents to achieve high conversions at 20°C.

In the construction of the first aryl vinyl sulfone system **14** we chose to place the phenolic resin tether in the *meta*-position in order to confer maximum stability towards acids. When tested for acid stability, the THIQ adduct **12a** ($R^1 = R^2$ = THIQ) was completely stable to 12.5 equivalents of 1.5% TFA in DCM solution for 24 hours at 20°C. The acid-treated material was alkylated and processed in the usual way to give the expected 3° amine product **15a** in 81% yield. However, the material **12a** ($R^1 = R^2$ = THIQ) was completely hydrolysed within 2 hours by treatment with aqueous 95% TFA to give the resin-bound benzyl alcohol and the starting phenol, as judged by IR spectral analysis of the resin and NMR spectral analysis of the cleaved product.

It was envisaged that the replacement of the acrylic ester in the reported REM system **1**[11] by a vinyl sulfonylphenyl ether would confer considerable stability to the adducts towards bases and nucleophiles. To test the stability of adduct **12a** ($R^1 = R^2$ = THIQ) to basic nucleophiles, **12a** was treated with 20 eqvs. of sodium methoxide in THF for 3 hours at 21°C and it remained completely intact. Under the same conditions the THIQ adduct of REM resin was transesterified to give the resin-bound benzyl alcohol, as was expected.

To assess the robustness of the aryl sulfone system to strongly basic nucleophiles, sulfone **14** was reacted ethyl piperidine 4-carboxylate and the product was treated with 6 equivalents of PhMgBr in THF. After N-alkylation of the 3° amine and then treatment with DIPEA, the expected diphenyl 3° alcohol was obtained in 35% recovery together with 10% of unreacted ethyl ester, under non-optimised conditions. A similar reaction performed using the analogous REM adduct gave essentially only the cleaved resin-bound benzyl alcohol. Treatment of the vinyl sulfone **14** with 4-benzoylpiperidine gave the required resin-bound 3°

amine which displayed a carbonyl stretching band at 1678 cm^{-1} in IR spectra. Treament of this with 10 eqvs. of PhMgBr in THF followed by N-alkylation with benzyl bromide and treatment of the product with DIPEA gave the required alcohol in pure form in 85% yield. A similar reaction sequence performed using the benzyl vinyl sulfone **2** gave the identical pure tertiary alcohol in 86% yield. The use of larger excesses of Grignard reactions in all cases lead to products contaminated with polymer derived impurities. This underlines the need for more stable resin supports but, nevertheless, demonstrates the utility of polystyrene-immobilised aryl sulfones in SPOS under some of the most basic conditions used in organic synthesis.

It is interesting to note that at least three ammonia-lyase enzymes appear to utilise very similar chemistry in catalysing their deamination reactions, except N-protonation rather than N-alkylation is used to activate the N-atom for the elimination.[14] Each of the enzymes operate *via* the intermediacy of a dehydroalanine residue.

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Abbreviations

DCM, dichloromethane; DIPEA, diisopropylethylamine; HMPolystr., hydroxymethylated polystyrene resin; TFA, trifluoroacetic acid; THF, tetrahydrofuran; THIQ, tetrahydroisoquinoline.

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