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# Solid-phase synthesis on functionalised fluoropolymer resins. Part 1: Nafion resin sulfonamide-immobilised carboxylic acid derivatives and aryl vinyl sulfones

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**Abstract**

The preparation and properties of Nafion resin sulfonamide systems derived from methyl glycinate and from 3-hydroxyethylaniline are described. Nafion derivatisation reactions were slow and maximum achievable functionalisations were 50% of the ion exchange capacity. In aqueous solution the resin derivatives were acid and base labile but in organic solvents the systems were stable to powerful nucleophiles and to heat. An aryl vinyl sulfone derivative used in the synthesis of tertiary amines afforded very pure products.


Solid-phase organic synthesis (SPOS) is a useful and often complementary alternative to conventional solution-phase synthesis. SPOS normally involves 'linking' molecules containing a reaction centre to a polymer support that is otherwise inert, and then elaborating the reaction centre. The reaction centre may be a substrate or a reagent. Advances in the range of chemistries that have been utilised on polymer supports are impressive[1–3] as are the underpinning advances in new resin materials,[4] resin functional groups,[4] linkers,[5] reagents,[6] resin cleavage protocols,[7,8] and analytical chemistry.[8,9] To date almost all efforts have been concerned with developing 1–2% cross-linked polystyrene-based systems for SPOS. Multiparallel SPOS is particularly useful in preparing libraries of related compounds and avoids many of the problems associated with assessing reaction efficiency, purity and 'deconvolution' in 'split and mix' protocols. Recently we described POSAM™, an efficient and versatile SPOS protocol for preparing compound libraries on the 0.01 to 1.0 mmol scale.[10] Here, the apparatus is constructed only from glass and PTFE and thus is suitable for reactions requiring particularly demanding conditions. Existing resin materials based upon polystyrene limit the utility of SPOS because polystyrene is mechanically fragile, unstable to oxidants, strong acids and bases and to temperatures above 120°C. Mindful of such limitations, we set-out to evaluate the potential of more stable polymers including those containing

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perfluorocarbon backbones. Here we describe the preparation, properties and evaluation in SPOS of Nafion-based systems.

The profound thermal, mechanical and chemical stabilities of PTFE are well established and are ideally suited for applications in SPOS. However, suitably functionalised PTFE derivatives are extremely difficult to prepare by copolymerisation with tetrafluoroethene (TFE) because substituents larger than an F-atom retard the rate of the radical polymerisation process substantially and lead to a low incorporation of the substituted comonomer.[11] Moreover, TFE is a highly toxic and explosive gas and requires pressurising and heating for controlled polymerisation. Nafion resins (DuPont) are the products of copolymerisation reactions of TFE and trifluorovinyl ethers possessing perfluoroalkylsulfonyl fluoride side-chains. After hydrolysis the sulfonic acid products, Fig. 1, are used as ion selective membranes in electrochemical cells by the chloralkali industry, or, as resin-bound super acids.[11] Recently, the cation exchange properties of Nafion resin have been used to support Pd(II) catalysts.[12]

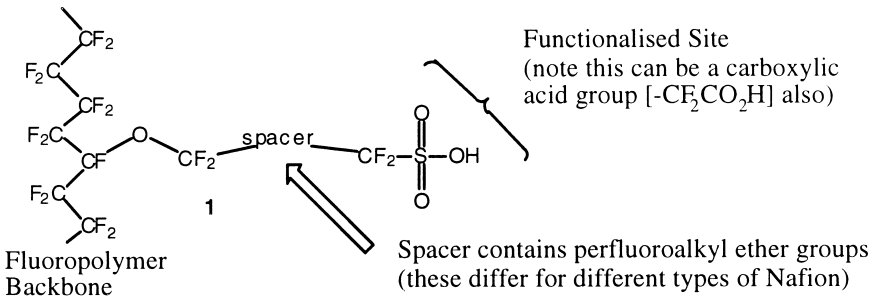


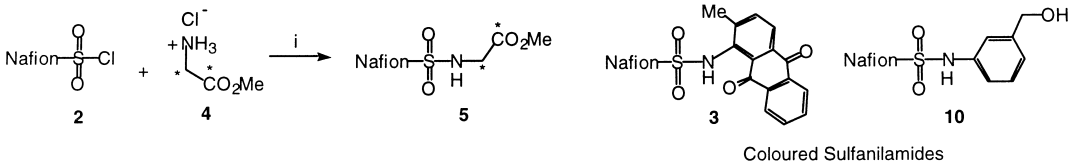

Figure 1. General structure of Nafion and similar resin materials

Nafion® NR50 is a perfluoroalkyl sulfonic acid resin (ion exchange capacity ca. 0.8 millimoles $g^{-1}$) available as 10–35 mesh cylindrical pellets. This material was used to prepare functionalised fluoropolymer model systems to evaluate the stability and utility of fluoropolymers in SPOS. To increase the surface area of the Nafion resin and ensure that the sulfonic acid groups were accessible to reagents, the pellets were ground at ca. –180°C, under liquid nitrogen, in a mortar to give a coarse (ca. 50–100 μM) white powder. At higher temperatures the resin was too plastic and became squashed rather than ground. In order to activate the fluoropolymer resin as its sulfonyl chloride **2**, the powdered polymer **1** was refluxed with excess thionyl chloride or excess phosphorus pentachloride in toluene for up to several days. Phosphorus pentachloride treatment for 36 h was found to give the best results as judged by analysing the DCM† washed, and then dried, products from several repeat reactions of differing duration. The resin mass increased in accord with expectations and resin **2** displayed a new IR absorbing band at 1180 $cm^{-1}$. Reaction of a small amount of resin **2** with disperse orange 11 dye gave a coloured sulfonamide derivative **3** confirming that the sulfonyl moiety was activated either as just the chloride or as a mixture of the chloride and the anhydride.

† Abbreviations: DCM, dichloromethane; TFA, trifluoroacetic acid; DMF, dimethylformamide; PyBOP, benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate; NMM, *N*-methyl morpholine; DIPEA, diisopropylethylamine.

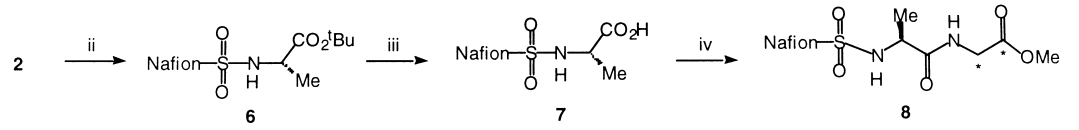
In order to quantify the site availability of the activated resin it was decided to react the material with a radiolabelled amine of known specific activity. Accordingly, $^{14}$C-[U]-glycine was converted to its methyl ester **4**, using thionyl chloride and methanol, and the solvents and acidic gases were removed under reduced pressure. The final specific activity of the $^{14}$C-[U]-glycine methylester hydrochloride salt **4** was $3.8\times10^6$ dpm mmol$^{-1}$. The reaction of the activated resin **2** with the labelled amine **4** was assessed using a range of solvents and bases under a wide variety of conditions. Refluxing the resin **2** in dry DCM in the presence excess pyridine and amine **4** for 5 days, optimised conditions, resulted in the formation of sulfonamide **5** in a 50% radiochemical yield, Scheme 1. This was calculated by comparing the specific radioactivity of the product ($1.52\times10^6$ dpm g$^{-1}$) with the starting amine after determining the ion exchange capacity of the crushed resin **1** (0.8 mmol g$^{-1}$). It was already becoming evident that reactions involving the displacement of groups from the sulfonyl S-atom of the resin were slow in organic solvents, presumably due to combined steric and fluorophilic effects of the polymer backbone and side-chains.

The stability of the sulfonamide linkage in the radiolabelled sulfonamide **5** was tested under aqueous basic and acidic conditions by stirring samples of the resin and removing aliquots of the supernatant solution for scintillation counting. Even under mild conditions (0.25 M HCl or 0.25 M NaOH) the sulfonamide linkage was hydrolysed within several hours. However, the sulfonamide group in **5** showed remarkable stability in organic solvents and was stable to 2.8 M *n*-butyl lithium and lithium aluminium hydride for prolonged periods. The ester moiety of **5** was accessible to *n*-butyl lithium and gave the tertiary alcohol as was determined by cleavage of the product from the resin (in acid) and subsequent analysis by $^1$H NMR spectroscopy.



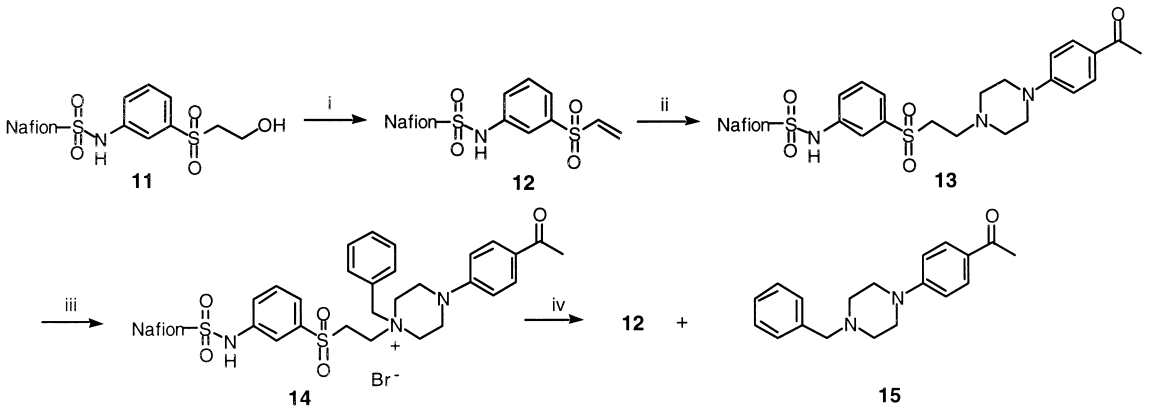

Scheme 1.

The activated resin **2** was also converted to its *N*-sulfonyl (2*S*)-alanine *t*-butyl ester derivative **6** {FTIR; 1735 (C=O, ester), 1320 (sulfonamide) and 1210 and 1150 cm$^{-1}$ ($SO_2$)} in 80% recovery and the *t*-butyl group was removed using TFA/DCM quantitatively,[13] Scheme 2. The carboxylic acid was activated using NMM/PyBOP and was then treated with $^{14}$C-[U]-labelled glycine methyl ester **4**. The *N*-sulfonyl (2*S*)-alanyl glycine methyl ester derivative **8** was obtained after only 24 h, with a radiochemical yield of only 30% {FTIR; 1740 (C=O, ester), 1680 (C=O, amide), 1320 (sulfonamide) and 1210 and 1150 cm$^{-1}$ ($SO_2$)}. As longer reaction times did not improve the yield, it seems probable that the shorter periods required for the coupling derive from the reduced steric and fluorophilic effects experienced by the incoming *N*-nucleophile at greater distances from the polymer backbone. (The low overall yield may reflect anhydride formation during the activation step).




Scheme 2. Reagents and conditions: (i) Pyridine, DCM, 5 days; (ii) Ala-O$^t$Bu·AcOH, pyridine, DCM, 96 h; (iii) TFA, DCM, 12 h; (iv) **4**, PyBOP, DMF, NMM

The sulfonyl chloride **2** was reacted with 3-aminobenzyl alcohol **9** to give a stable red coloured sulfonanilamide **10** in quantitative recovery.[13] Likewise, reaction of the activated resin **2** with 2-(3-aminophenylsulfonyl)ethanol gave the resin-bound sulfonanilamide **11** {FTIR; 1510 and 1480 ($CH_2$), 1320 (sulfonamide) and 1210 and 1150 ($SO_2$) and 750 and 680 $cm^{-1}$ (*m*-disubstituted aromatic)}, Scheme 3.




Scheme 3. Reagents and conditions: (i) Ms-Cl, $Et_3N$, 20 h; (ii) piperazino-4-acetophenone, DMF, 72 h; (iii) $PhCH_2Br$, DMF, 24 h; (iv) DIPEA, DMF, 24 h

Treatment of the terminal alcohol **11** with mesyl chloride and elimination of methanesulfonic acid from the product (using triethylamine) gave the aryl vinyl sulfone **12**. The conjugate addition of piperazino-4-acetophenone to the vinyl sulfone slowly gave the expected resin bound tertiary amine **13** which displayed new absorbances in its FTIR spectrum at 2950, 2850 and 1650 (C=O) $cm^{-1}$. The resin bound diamine **13** was quaternised at its non-deactivated *N*-atom, using benzyl bromide, as has been described for the analogous polystyrene-based vinyl sulfones.[14] Treatment of the quaternised salt **14** with DIPEA regenerated the sulfonanilimide vinyl sulfone **12** and afforded the tertiary amine, *N*-benzylpiperazino-4-acetophenone **15** in greater than 98% purity, as judged by $^1H$ and $^{13}C$ NMR spectroscopy,[15] albeit in low overall yield (ca. 5%), Scheme 3. *N*-Benzyl tetrahydroisoquinoline was also prepared in a similarly high purity and in low yield. Again it was evident that all reactions were very slow and interestingly, the carbonyl group of the resin-bound tertiary amine **13** reacted very slowly (if at all) with Grignard and aryl lithium reagents, as judged by FT-IR spectroscopy and preparative work-up. Recovered material showed no mass loss and contained no polymer decomposition products such as is common for polystyrene based systems.

From the results reported here it is evident that fluoropolymers offer considerable potential as inert support materials for SPOS, although Nafion derivatives are not ideal. Two properties of Nafion NR50 probably limit its suitability for SPOS most. The first is 'clustering' of functional sites which appears to allow site interference and the formation of symmetric sulfonic and carboxylic acid anhydrides during activation steps. This property, of course, restricts initial loadings at least. The second is the combined highly polar nature of the functional groups and non-lipophilic perfluorinated nature of the polymer side-chains. These are sterically demanding and do not solvate in organic solvents to allow the resin to swell, ultimately causing poor reaction kinetics, unlike in

aqueous solutions. A polymer possessing a perfluorinated backbone and lipophilic side-chains that are capable of solvating in organic solvents is described in the following article.

## Acknowledgements

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15. Data for **15**: {(HRMS: found: $[M+H]^+$, 295.1805. Calcd for $C_{19}H_{22}N_2O$: 295.1810); $\nu_{max}$(thin film)/$cm^{-1}$ 2950, 2842, 1670 (C=O) and 1599 (aromatic); $\delta_H$(300 MHz; $C^2HCl_3$) 2.51 (3H, s, $CH_3$), 2.57–2.61 (4H, m, piperazine), 3.34–3.38 (4H, m, piperazine), 3.57 (2H, s, benzyl), 6.84–6.87 (2H, m, Ar–H), 7.26–7.40 (5H, m, Ar-H) and 7.85–7.88 (2H, m, Ar-H); *m*/*z* (CI) 295 $[M+H]^+$}.