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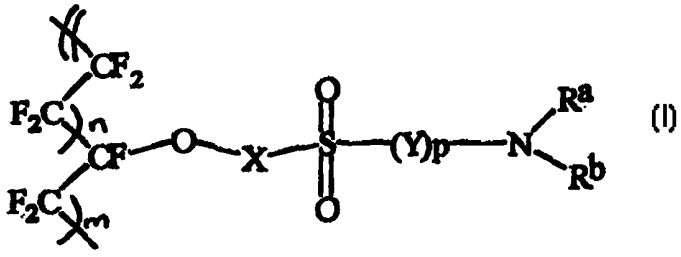
(54) Title: PERFLUORINATED RESINS AS A SUPPORT FOR SOLID PHASE REACTIONS

(57) Abstract

A polytetrafluoroethylene resin bearing a reactive functional group comprising a side chain having a sulphonamide or sulphonanilimide moiety like the one of formula (I): wherein n and m are each integers of from 1 to several hundred, m is a spacer group; Y is a spacer group; R^c is a linear or branched C_{1-6} aliphatic hydrocarbon group, optionally interrupted by heteroatoms; R^d is an aryl group, substituted by a reactive functional moiety such as a carboxy group, carboxyl group, sulphonyl group, amine, amide, thioester or the like. This resin is particularly useful in solid phase synthesis and in the manufacture of microreactors.



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"Perfluorinated Resins as a Support for Solid Phase Reactions"

The present invention concerns the preparation and use of chemically functionalised polymeric resins for use in solid-phase chemical synthesis.

Recent trends in the area of drug development, biotechnology and chemical research have moved towards producing large arrays of related molecules using combinatorial or permutational synthesis. These relatively new techniques are potentially capable of yielding libraries of millions of compounds which can be screened, if a suitable assay is available, to identify the required chemical, physical or biological property, eg biological activity. The new methods offer advantage because only a relatively small number of chemical reaction vessels need to be used, compared to the traditional methods in which a single compound is sequentially processed through various chemical transformations, usually one reaction step at a time. The new method, combinatorial synthesis, relies on the fact that under suitable conditions and in the presence of a single reagent or set of reagents, several to very many compounds can be converted simultaneously into

several to very many new products using a single reaction vessel.

The problems with combinatorial chemistry are manifold. First, the reaction chemistry needs to be irreversible, such that each of the starting materials in the mixture is converted to a new product in good yield. Second, at the present time it is most feasible to perform combinatorial chemistry in the "solid-phase", that is where the starting materials are covalently bonded to a polymeric support, usually cross-linked polystyrene. The advantages of solid-phase synthesis are that the products do not need to be purified by, for example, solvent extraction, distillation, recrystallisation or chromatography but rather are retained on the solid medium by washing away the excess reagents and impurities. Thus, in solid-phase synthesis it is necessary to confine the polymeric support so that it too is not washed away. The third problem concerns the deconvolution of the library which essentially requires identifying the chemical structure of the molecule, within the mixture, that shows the required biological activity or other desired property. Clearly, when one is dealing with mixtures of compounds, where the polymeric support for one compound looks identical to that for another, one requires the resynthesis of partial libraries of ever decreasing size, coupled with assay, in order to identify the active material. This method of deconvolution is time consuming and unnecessarily clumsy. Another way of effecting deconvolution is to tag the polymeric support with chemicals which can be used to decode the synthetic chemical history of the particular particle of polymeric support, independently to being able to carry out an activity assay on the material attached to the support. Such methods have been described in the

literature. Since typical particles of polymeric support are referred to as "resin beads" and are commercially available in the size 70-400 microns, deconvolution by such methods is a fiddly job requiring accurate and expensive instrumentation.

The fourth problem concerns checking the efficiency of the chemical synthesis and, in essence, this is a problem of scale. Individual beads possess, at most, only a few to several nanomoles of material attached to them and, therefore, it is extremely difficult to check either the efficiency of the synthesis or the purity of the synthetic product. In highly sensitive biological screening assays this can be a very serious problem as the impurity could be responsible for a positive result. The best way to overcome this last problem is to perform syntheses on a larger scale such that some material can be put aside for characterisation and analysis. While this solution offers very many advantages, the practice of a larger scale combinatorial syntheses requires the design and use of microreactors or other small individual reaction chambers into which larger quantities of resin material can be confined.

Small individual reaction chambers may be open or closable flasks, tubes, 'pins', wells and other types of standard laboratory apparatus. Microreactors may be designed to either A) contain resin beads within a porous enclosure which is pervious to reagent solutions and solvents, or B) microreactors may be themselves giant porous assemblies of resin material.

Several reports on the use of microreactors of type A for solid-phase syntheses on a polymeric support, in which the resin beads are enclosed within the

microreactor, have been described and include microreactors constructed from polypropylene, which is not inert and microreactors construed from almost totally inert frit glass and polytetrafluoroethylene. However, many reports supply little information on the design of the microreactors or on how they were used in synthesising libraries of compounds. The main purpose of some reports was to describe the incorporation of an addressable microchip into the microreactors which could be written to and read using radio waves. This elegant idea does require the microreactors to be of a size large enough to contain the addressable chip, which in itself is not a problem, but demands the use of sophisticated and moderately expensive equipment.

In WO-A-97/30784 we described the design and construction of visually addressable microreactors for use in combinatorial chemical synthesis. That publication describes vessel designs suitable for use with a whole range of different types of chemical environment (due to the inertness of the microreactors) and suitable for use with a whole range of different types sizes and numbers of addressable microreactors. The system was optimised for use with POSAM® (Permutational Organic Synthesis in Addressable Microreactors) where microreactor identification is performed visually, but is also suitable for use with radio-addressable microreactors or any other type of microreactor tagging system or solid support tagging system or hybrid tagging system including those which utilise laser or mass spectrometric or radioisotope or magnetic resonance or any other spectroscopic or fluorimetric or related methodology which uses electromagnetic radiation to detect the identity of, or communicate with, the microreactor.

The stability of our previously described POSAM® microreactors to the very wide range of reaction conditions employed in conventional organic synthesis is such that, in theory, almost every common synthetic protocol described to date in the chemical literature could be performed in the microreactor where all the reagents are solutions, liquids or gases and can reach the resin bound substrates (ie the entities which are being processed by the exposure to the reagents). Obviously heterogeneous reagents and other particulate matter above a certain size can not pass through the walls of the frit glass microreactors, and also reagents which dissolve glass (hydrofluoric acid) or react with PTFE (solvated electrons) are far from ideal. Nevertheless, there is an enormous practical potential for the use of POSAM® microreactors in chemical synthesis which is currently limited by:

a) the stability of the polymer-base support used in the commercially available resin materials that are currently employed for solid-phase chemical synthesis; and

b) the range of functional groups available in commercial resin materials.(For a comprehensive list examples of available resin materials, see the 1997 Nova solid-phase synthesis Catalogue).

These two issues are not unrelated because some functional groups would require such demanding conditions to work with that the resin polymer base would be destroyed under the required conditions.

The polymer base for almost all of the commercially available resin materials, whether modified with polyethylene glycol appendages to give Tentagel resins or otherwise, is 1-2% divinylbenzene cross-linked polystyrene in which approximately one in ten of the

phenyl rings derived from the styrene is modified to give a benzyl moiety to which different functional groups are attached. The chloromethyl (or benzyl chloride) derivative is called Merrifield resin and this material and its derivatives are mechanically fragile and swell several fold in most organic solvents (eg dimethylformamide, tetrahydrofuran, dichloromethane) but not all organic solvents (eg methanol). The reaction kinetics for chemical reactions performed on polystyrene-based resins is drastically effected by how swollen the resin becomes as it is solvated by the particular organic solvent. Polystyrene is also chemically sensitive to some hot organic solvents and is modified by solutions of the very strong nucleophiles/bases and the protic and Lewis acids commonly used in conventional synthesis.

Other polymer supports have found use in biochemical applications such as the preparation of affinity columns for isolating and/or binding to proteins, DNA, RNA etc. These systems are usually used in aqueous buffer solutions and the polymer support is usually derived from polysaccharide, polyamide, polyacrylate or polyacrylamide solid phases. These are, in general, unsuitable for organic synthesis.

The present invention seeks to overcome several disadvantages associated with present practices in solid-phase synthesis.

First, the present invention concerns the development of alternative resin materials for use in synthesis that comprise a modified perfluorocarbon polymer backbone instead of polystyrene or other conventional polymers, in order to confer increased physical and/or chemical stability to new chemically functionalised

resins derived from these resin materials.

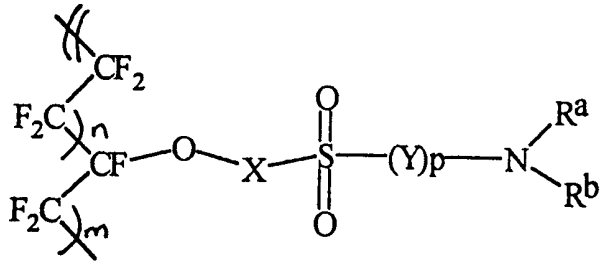
Second, the present invention concerns the development of resin materials containing perfluorocarbon polymer backbones which are modified with new functional groups, to allow a wider range of chemical manipulations and reactions to be performed in solid-phase synthesis. The synthetic steps could be performed in open vessels (for example in standard laboratory flasks), in closed vessels (for example in chromatography columns) or in type A microreactors where the resin material is contained within a porous container.

As a direct consequence of our ability to produce modified resins possessing perfluorocarbon polymer backbones that do not swell much in solvents and that can be customised to introduce new functional groups, the invention also encompasses microreactors of type B that are themselves giant porous assemblies of otherwise inert resin material.

Thus, the present invention also concerns the development of new resin materials that possess a modified perfluorocarbon polymer backbone (compared to commercially available resins used for solid-phase synthesis) to confer increased physical and chemical stability, and which can be formed into macroscopic shapes which are porous and which can be used in place of the microreactor in the POSAM® system or in standard laboratory flasks, for example, while still conferring all of the advantages of scale of synthesis and of labelling that are associated with microreactors.

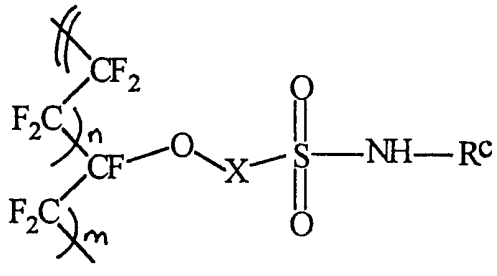
More particularly the invention relates to a polytetrafluoroethylene resin comprising a side chain

having a sulphonamide or sulphonanilinide moiety like the one of general formula I:



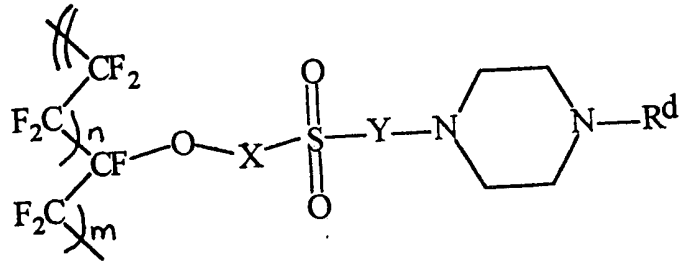
wherein n and m are each integers of from 1 to several hundred (for example up to 200);
p is 0 or 1;
X is a spacer group;
Y is a spacer group;
R^a may be H or a lower alkyl group (eg a C_{1-6} alkyl);
R^b may be any moiety bearing at least one reactive functional group;
or R^a and R^b may together form a C_4 - C_6 cyclic ring which may optionally contain further heteroatoms (eg N, S or O) and/or may optionally be substituted by a moiety containing at lest one reactive functional group.

In a preferred embodiment the resin has the general formula II:



wherein n and m are each integers of from 1 to several hundred (for example up to 200);
X is a spacer group; and
R^c is a C_{1-20} carboxy acid, carboxy ester, aliphatic alcohol, ether or amino acid derivative.

In a further preferred embodiment the resin has the general formula III:



wherein n and m are each integers from 1 to several hundreds (for example up to 200);
X is a spacer group;
Y is a linear or branched C_{1-6} aliphatic hydrocarbon group, optionally interrupted by heteroatoms; and R^d is an aryl group, substituted by a reactive functional moiety such as a carboxy group, carboxyl group, sulphonyl group, amine, amide, thioester or the like.

In general the spacer groups X and Y may be an suitable moiety, including branched or linear C_{1-20} hydrocarbon chains, optionally interrupted by heteroatoms, especially O, S or N. Preferably X is a group $-CF_2-Z-CF_2-$ where Z is a perfluoroalkylether group; or X is a group $-[CF_2-CF(CF_3)-O]_v-(CF_2)_w-$ where v is 0 or 1 and w is 1 to 4; or X is a group $-[CF_2]_y-$ where y is 1 to 8; or X is a group $-CHQ-(CH_2)q-$ where q is 1 to 10 and Q is H or an alkyl group, eg. a C_{1-6} alkyl group.

The invention further relates to the use of a polytetrafluoroethylene resin bearing a reactive functional group as a support matrix for solid-phase chemical reactions.

The invention further relates to a method of producing a solid-phase reactant for a solid-phase chemical reaction, the reactant comprising a polytetrafluoroethylene resin-substrate complex,

wherein said complex is produced by reacting a precursor substrate with a functional group on the polytetrafluoroethylene resin.

The invention further relates to a method of chemical synthesis involving a chemical reaction wherein one of the substrates of the reaction is in the form of a solid-phase polytetrafluoroethylene resin substrate complex.

The invention further relates to a microreactor comprising a resin material as a support matrix for a solid-phase chemical reaction, wherein the resin material is a polytetrafluoroethylene resin.

The invention further relates to such a microreactor wherein the resin a resin according to the invention as described above.

Type A microreactors work extremely well for the solid-phase synthesis of libraries of compounds containing hundreds of members and can deliver tens of milligrams of each library member. Technically there are no barriers to extending the methodology to thousands or even to tens of thousands of library members. In the POSAM® apparatus all components are constructed from glass and polytetrafluoroethylene (PTFE) but the resin beads have, up until now, been based upon the original Merrifield (functionalised polystyrene) type and, therefore, are not as chemically robust as would be desirable. While we have shown that aryl magnesium bromide Grignard reagents can be used with Merrifield based resins, great care is needed to limit the amount of reagent used and such Grignard reagents irreversibly damage the resin. Therefore, there is a requirement for resins which possess a more chemically inert

backbone in the use of unconfined resin and in its use in conjunction with inert microreactors of type A.

A further problem is the size of the existing Merrifield resin beads and their mechanical fragility. These are related issues. For example, one could imagine preparing the entire microreactor (type B) from the resin polymer (eg Merrifield resin or a derivative or precursor) itself. The further requirements for use in the POSAM® apparatus would be:

i) A mechanical stability approaching that of the existing frit glass or porous polypropylene container type A microreactors described previously.

ii) Size stability for use in precision glass vessel tubes where microreactors are stacked in the vessel tube, one on top of the other, in the usual way to facilitate the passage of solutions and solvents through the stacked array.

iii) A suitable tagging system.

If the mechanical and size stability of the construction material fulfils the requirements i) and ii), then requirement iii) presents no additional hurdles. Since several of the tagging systems described previously (and referred to above) for use with microreactors of type A and, in particular, the visual tagging systems (bar-coding, colour coding etc) are totally compatible with microreactors of type B.

Requirements i) and ii) are quite demanding. Merrifield resins are composed of polystyrene cross-linked with 1% or 2% divinylbenzene. The cross-linking is required to provide mechanical strength, but the

resin beads remain fragile even when sizes are kept to below 130 microns (0.13mm) diameter. Larger beads can be prepared but these break-up very easily and microreactors of type B would have a useful minimum size of 5mm and an optimum size of 13mm (or more) in diameter, ie 40-100 times larger (or more) in diameter to the beads currently available. The amount of cross-linking in the resin can be increased but this leads to both increased brittleness and decreased solvent accessibility. Since Merrifield resins and all other types of resin supports reported so far swell considerably (2-7 fold) in commonly used solvents (eg dichloromethane, tetrahydrofuran, dimethylformamide etc.) a brittle resin shatters on solvation and even less brittle beads change their size considerably. Thus, microreactors of type B composed of functionalised polystyrene cannot meet any of the requirements of chemical inertness, mechanical strength or size stability.

In order to devise solutions to overcome all of these problems we have examined the utility of chemically functionalised polytetrafluoroethylene (PTFE) resins. Dupont and other chemical companies have developed Nafion™ and similar perfluorinated functionalised resins for use as electrolyte membrane separators in electrochemical cells used by the chloralkali industry. The membranes are essentially a PTFE polymer backbone containing perfluorinated side-chains which possess an anionic group (carboxylate or sulfonate) which allows the passage of only cations but not anions through the membrane. The Nafion™ membrane itself has to withstand very harsh chemical conditions (25% NaOH) and considerable temperatures for long periods of time (several months). We have now recognised that this material and derivatives thereof is ideal for the

construction of new resins for use in solid-phase organic synthesis (and in particular for use in POSAM® microreactors).

The new resins described herein exhibit the following properties:

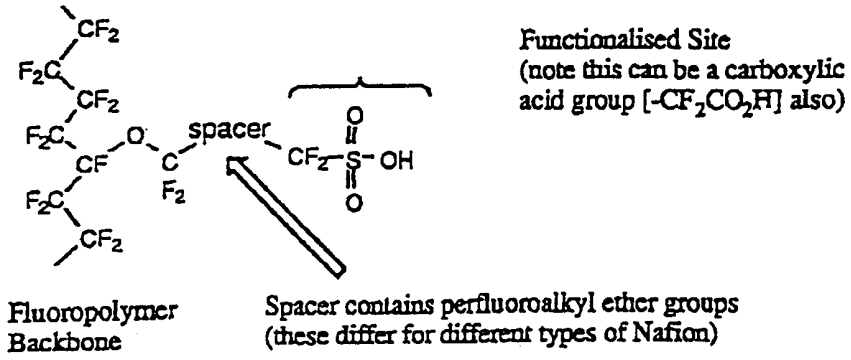
i) excellent chemical stability;

ii) mechanically robust up to the temperatures required for a range of useful solid-phase chemistries (180°C);

iii) does not solvate to the extent of polystyrene resins (the PTFE backbone is neither lipophilic or hydrophilic so that swelling is minimal); and

iv) the acid halide and ester forms of PTFE modified with appended sulfonic and carboxylic side-chains are heat-processible (unlike PTFE).

Whilst Nafion™ is extremely expensive and possesses a rather low level of chemical functionalisation (approx. 0.8 milliequivalents per gramme, before customisation), nonetheless, Nafion™ (see Formulae A below) was considered to be a good model to check the chemical stability and functionalisation properties of modified future polytetrafluoroethylene (PTFE)-based functionalised resins.

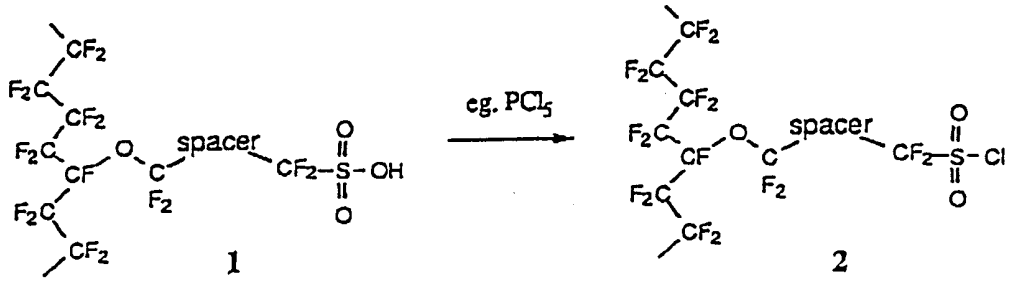


Formula A

General Structure of Nafion & Similar Resin Materials

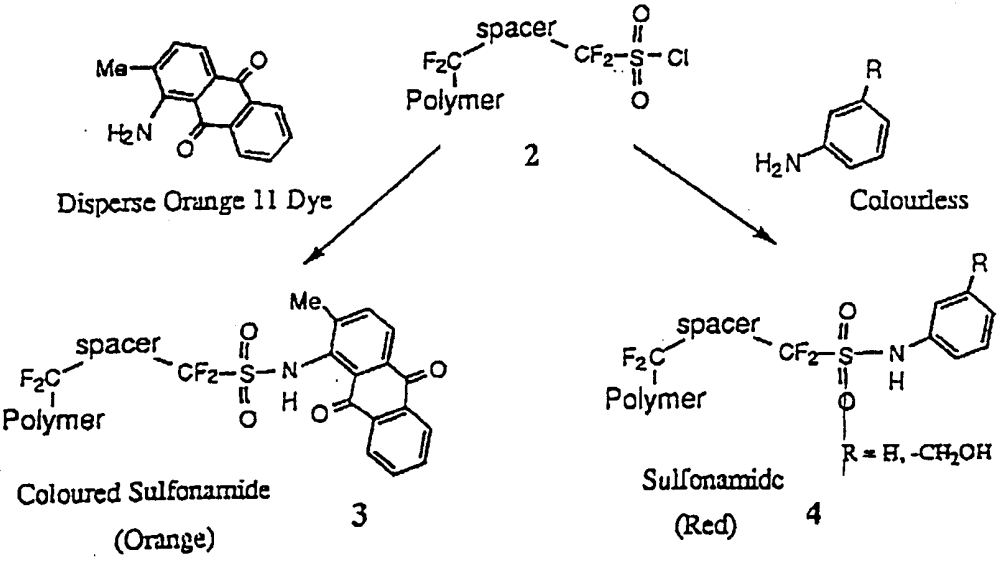
Accordingly, Nafion beads in the sulfonic acid form (1) were obtained from Aldrich Chemical Company and were

crushed at -150°C to give a course white powder. The sulfonic acid resin (1) was treated with phosphorous pentachloride for 24h at 80°C to give the sulfonyl chloride (2), see Scheme 1.



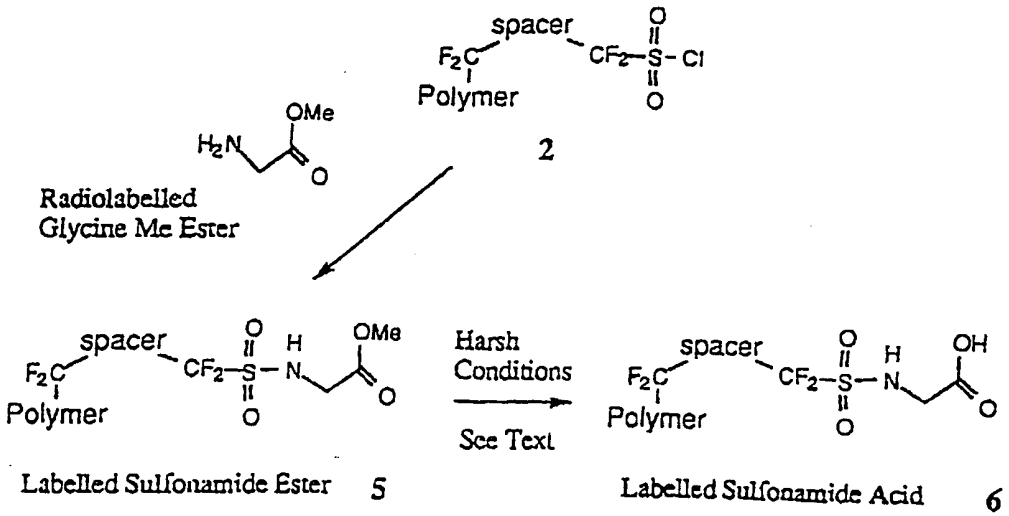
Scheme 1. Activation of Fluoropolymer Resin as the Sulfonyl Chloride

Reaction of samples of the sulfonyl chloride (2) with different amine "dyes" gave coloured insoluble Nafion sulfonamide derivatives confirming that the solid-phase reaction had occurred, see Scheme 2. While Disperse Orange dye is orange-coloured before the reaction with the sulfonyl chloride (2), the aniline precursors in the sulfanilamides (4) are not and the colour only develops when the sulfur-nitrogen bond in sulfanilamides (4) forms. This colour is due to the delocalisation of electrons on the nitrogen atom over the aromatic moiety and the difluorosulfonyl moiety and, therefore, acts as an indicator for the successful information of the required product.



Scheme 2. Reaction of Activated Fluoropolymer with Amine Dyes

The extent of amide formation was quantified by treating the sulfonyl chloride (2) with ^{14}C-labelled glycine methyl ester (labelled uniformly in glycine moiety) in the presence of tertiary amines for various time intervals. Scintillation counting showed that the radiolabelled sulfonamide ester (5) had been formed in each case. After 36 hours the reaction had proceeded to close to complete conversion and based on the ion exchange capacity of the crushed resin (0.8 meq. per gramme of resin), 50% of all the functionalised groups in the original resin had been converted to sulfonamide groups. It was expected that reactions involving the direct displacement of the chlorine atom from sulfur would be slow due to steric effects and the fluorophilic effect of the polymer backbone in the vicinity of the polymer backbone. These steric effects and the fluorophilic effect of the polymer backbone were less pronounced as the reaction chemistry was moved away to a position further from the polymer backbone, *vide infra*, as was expected.



Scheme 3. Assessment of the Stability of the Sulfonamide Group

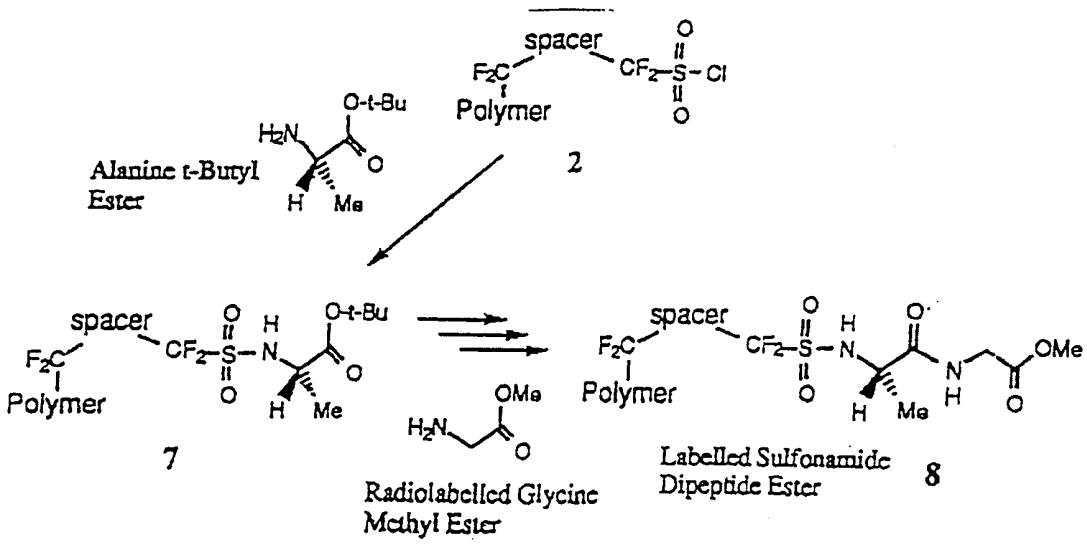
The stability of the sulfonamide linkage in radiolabelled sulfonamide (5) was tested in base (0.5 M sodium hydroxide in water and in methanolic tetrahydrofuran) and in acid and in the presence of 2M n-butyl lithium in hexanes or tetrahydrofuran by removing aliquots of each solution for scintillation counting and by scintillation counting the resin. The sulfonamide showed remarkable stability and only prolonged treatments in strong aqueous base or acid caused the hydrolysis or cleavage of the sulfonamide moiety. Although the ester group was cleaved first in aqueous sodium hydroxide (to give the sodium salt of acid (6) as determined by the IR spectrum) and in the presence of n-butyl lithium as expected, the sulfonamide linkage remained intact for considerable periods and for up to several days in the absence of a proton source.

The functionalised radio-labelled sulphonamide resin (5) was refluxed for two hours in toluene and the potential dissolution of the material was monitored by removing aliquots of the solvent for scintillation counting. The sulphonamide showed remarkable stability and none of the resin dissolved. The Merrifield resin shed some of its mass and polypropylene completely dissolved within several minutes under similar conditions.

The sulfonyl chloride (2) was also converted to its N-sulfonyl (2S)-alanine t-butyl ester derivative (7) as was confirmed by its infrared (IR) spectrum. The t-butyl ester was removed under acidic conditions to give the free acid (which showed the loss of carbonyl ester IR stretch) and this material was activated using standard peptide chemistry protocols and then treated with ^{14}C-labelled glycine methyl ester (labelled

uniformly in glycine moiety). The reaction proceeded quite rapidly and in good conversion to give the N-sulfonyl (2S)-alanyl glycine methyl ester derivative (8), as determined by scintillation counting, which showed amide and ester stretches in the IR spectrum as well as the correct increase in mass. The significant increase in reaction rate compared to that for the reaction to form the sulfonamide (5) is ascribed to the reduced steric effects and fluorophilic effects experienced by the incoming N-nucleophile at the further distance from the polymer backbone.

Thus, peptide bond formation can be performed on the fluoropolymer resin (see Scheme 4 below).



Scheme 4. Preparation of a Dipeptide Derivative

The stability of the amide linkage in radiolabelled N-sulfonyl (2S)-alanyl glycine methyl ester derivative (8) was tested in base and in acid and in the presence of n-butyl lithium, as before, by removing aliquots of each solution for scintillation counting. The amide was cleaved rapidly in the presence of base and in the

presence of n-butyl lithium under the same conditions for which the sulphonamide linkage in derivative (5) was completely stable.

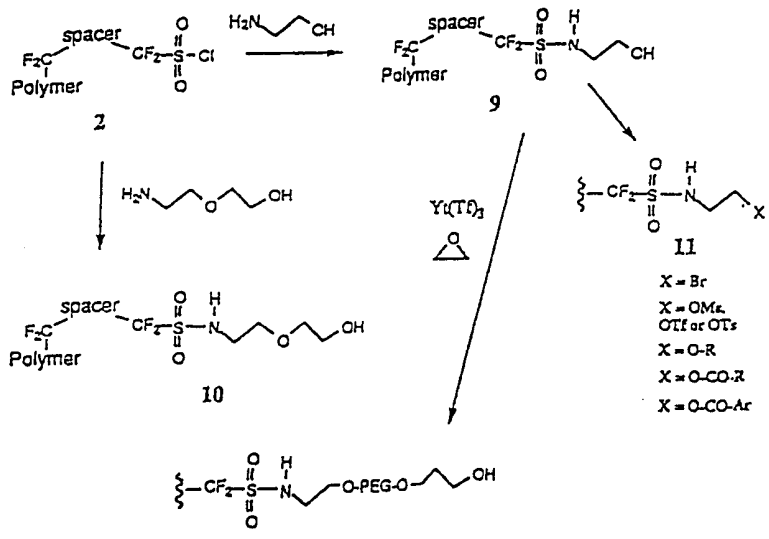
Reduction of the N-sulfonyl glycine methyl ester derivative (5) in tetrahydrofuran with lithium aluminium hydride or other reducing agents, gave the alcohol derivative (9) without loss of radioactivity from the resin. The same resin alcohol derivative (9) was formed by treatment of the resin sulfonyl chloride (2) with 2-aminoethanol. This resin (9) contains a terminal alcohol group (-OH) and this was converted to a wide range of potentially useful derivatives some of which were activated, for example, as in compounds such as (11, X=Br or other halogen, X=Ms, X=Ts and X=Tf, respectively) such that the terminal carbon atom could react with nucleophiles. Some examples are given in Scheme 5. Thus, reaction of alcohol (9) with PBr_3 gave the bromide (11, X=Br) (which could also be prepared directly from 2-bromoethylamine) whereas reaction with mesyl or tosyl chloride or trifluorosulfonic anhydride gave the sulfonate esters (11, X=Ms, X=Ts and X=Tf, respectively).

These activated derivatives of compound (11) could be reacted with a wide range of oxygen-, sulphur-, nitrogen- or phosphorus- centred nucleophiles, as was expected. For example, the bromide (11, X=Br) reacted with 3-fluorophenol and thiophenol to give the ether and thioether respectively. The thioether could be oxidised to the sulfone using the same range of oxidants that are used for solution phase chemistry. The 3-fluorophenyl ether derivative displaced a new signal in the ^{19}F-NMR spectrum well separated from the aliphatic fluorine signals due to the polymer backbone. Thus, 3-fluorophenol could be used as a convenient

reporter for the kinetics and extent of the reaction of other phenols with activated resins (such as 11, X=Br or other halogen, X=Ms, X=Ts and X=Tf, respectively) simply by quenching the reaction in excess 3-fluorophenol and examining the ^{19}F-NMR spectrum of the product. The list of leaving groups (11, X=Br or other halogen, X=Ms, X=Ts and X=Tf) is by no means comprehensive and several other leaving groups would work well, as those skilled in the art would know. For example, Mitsunobu type activations of resin material (9) also worked.

A polyethylene glycol chain was added to the alcohol (9) through the Lewis acid catalysed reaction with ethylene oxide. This gave a resin material (10A) which possesses a similar terminal functional group type to the commercially available Tentagel resins, except for the base polymer which is not polystyrene but the more stable perfluoropolymer shown in Formula 1.

The reaction of the sulfonyl chloride (2) with 2-(2'-aminoethoxy) ethanol gave the derivative (10) which could also be functionalised by activation as for the resin alcohol (9), *vide supra*.



Scheme 5.

10A

The reaction of the sulfonyl chloride (2) with 3-aminopropanol gave an alcohol derivative which could also be functionalised by activation as for the resin alcohol (9), *vide supra*. Treatment of the sulfonamidopropyl bromide derivative (11, X=CH_2Br) with excess butyl phenylvinyl phosphonite at 110°C gave the required Arbusov vinyl phosphine oxide reaction product (11, X=$CH_2P(O)(Ph)$-$CH=CH_2$), as for similar solution-phase reactions that have been described in the literature. The resin-bound vinyl phosphine oxide reacted with secondary amines via conjugate addition, as had been described for solution phase reactions, and the resulting immobilised tertiary amines (11, X=$CH_2P(O)(Ph)$-CH_2CH_2NRR') could be quaternised on nitrogen with common alkylating agents and could be eliminated from the resin to give a new tertiary amine and to regenerate the resin-bound vinyl phosphine oxide (11, X=$CH_2P(O)(Ph)$-$CH=CH_2$) which could be used in further reaction cycles. This type of system is referred to as a traceless linker connection because the product tertiary amine contains no trace of its synthetic origin. While this is a novel system, the chemistry is similar to that which has been described in the literature for an acrylate ester of Merrifield resin.

Note that the phosphine oxide system is chiral at the P-atom and, therefore, the system could be elaborated to provide a chiral resin for the asymmetric synthesis of amines. The principle has been demonstrated in

solution phase chemistry and has been described in the literature and is within the capabilities of one skilled in the art.

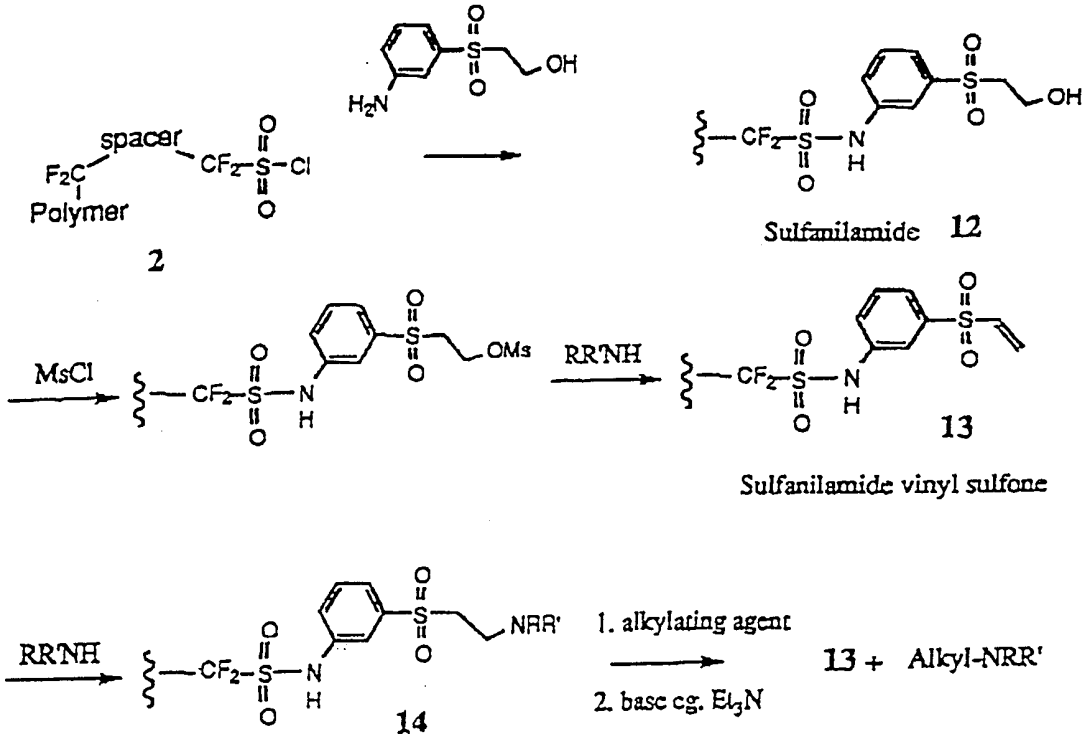
The reaction of the sulfonyl chloride (2) with 2-aminoacetaldehyde diethylacetal followed by acid hydrolysis of the acetal gave the aldehyde derivative which was able to react rapidly with amines including hydrazines. This aldehyde derivative is expected to be functionally equivalent to commercially available resins based on polystyrene supports, except more stable. Other aldehyde functionalised resins including those containing aromatic aldehydes could be prepared using similar protocols.

The reaction of the sulfonyl chloride (2) with 1,2-diaminoethane and 1,3-diaminopropane, respectively, gave the required resin-bound sulfonamide amines. These amines were assessable to aldehydes including 3-fluorobenzaldehyde through standard type dehydration reactions, to give imines. The formation of the imide was verified through treatment with sodium borohydride and the products were analysed by ^{19}F-NMR spectroscopy which showed a new aromatic-F signal in each case.

The reaction of the sulfonyl chloride (2) with 2-(3-aminophenylsulfonyl)ethanol gave the required resin-bound sulfanilamide derivative (12). Treatment of the terminal alcohol group with mesyl chloride and elimination of the mesyl group gave the aryl vinyl sulfone (13) which could be trapped through a conjugate addition reaction with a secondary amine to give a resin bound tertiary amine (14), as for the vinylphosphine oxide (11, X=$CH_2P(O)(Ph)$-CH_2CH_2NRR) described above, see Scheme 6. The resulting resin-bound tertiary amine could be quarternised on nitrogen

with common alkylating agents and could be eliminated from the resin to give a new tertiary amine and to regenerate the resin-bound vinyl sulfone (13) which could be used in further reaction cycles. This type of system is referred to as a traceless linker connection because the product tertiary amine contains no trace of its synthetic origin.

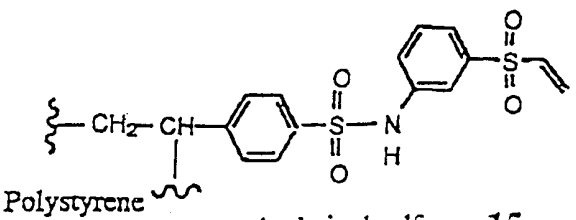
By analogy to the well established chemistry of vinyl phosphine oxides and vinyl sulphones, these moieties were expected to serve as receptors for other nucleophiles, for example, sulphur and carbon based nucleophiles, and take part in electrocyclic reactions with dienes and 1,3-dipoles. This was verified for the resin bound vinyl sulphone system and this further extends their potential utility and synthesis.



Scheme 6

While aryl vinyl sulfone (13) is a novel system, the chemistry is similar to that which has been described in the literature for an acrylate ester of Merrifield resin. This system, in the form of the secondary amine addition products to aryl vinyl sulfone (13), was found to be extremely stable to unstabilised carbanion chemistry, including alkyl and aryl magnesium halides. Where the secondary amine possessed aldehyde, ketone or ester groups (for example when methyl piperidine-4-carboxylate was used as the secondary amine), it was possible to perform clean Grignard addition reaction to give the required alcohols.

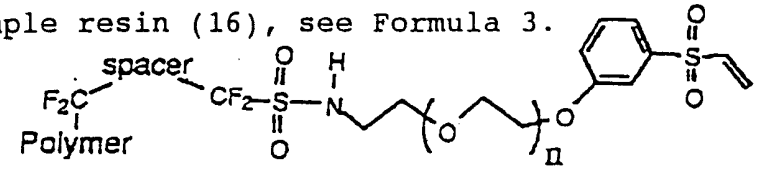
For comparison, a similar aryl sulphone system (15) was prepared using polystyrene based resins containing an aryl sulphonyl chloride (eg based on Dowex 50 and Amberlite resins), see Formula 2. While the addition of secondary amines to the aryl vinyl sulfone system (15) and the alkylation and elimination steps occurred with some facility, as for the fluoropolymer aryl vinyl sulfone (13), the resin was not stable to excess Grignard reagents. This example serves to underline the significant advantages over the previous art of solid phase organic synthesis offered by the functionalised fluoropolymer based resins.



Aryl vinyl sulfone 15

Fig. 2

Other aryl vinyl sulfone systems were prepared by reacting N,N-dialkyl-2-aminoethylsulfonyl phenols with activated resins derived from materials (9, or 10 or 13). In these systems the aryl group was linked to the fluoropolymer through an ether linkage to give for example resin (16), see Formula 3.



n = 0,1 or several

Fig. 3 Aryl vinyl sulfone **16**

Meta-aryl group substitution is preferred, as for material (16) but ortho- and para- substitution would also function. The vinyl group in material (16) was generated through an alkylation step, followed by base catalysed elimination in chemistry analogous to that used for the conversion of material (14) to (13) in Scheme 6, above.

As is apparent to one skilled in the art, any stable and unhindered connection between the N-atom of the sulfonamide and the C-atom which bears the vinyl sulfonyl group, whether it be aryl, benzylic or aliphatic, or even an N-atom in certain cases, would allow the system to function in the required manner. Indeed, any stable and unhindered connection between any stable fluoropolymer, whether its side-chains are perfluorinated or not, and the C-atom which bears the vinyl sulfonyl group, whether it be aryl, benzylic or aliphatic, or even an N-atom in certain cases, would allow the system to function in the required manner. Furthermore, any stable and unhindered connection between any stable fluoropolymer, whether its side-chains are perfluorinated or not, and the C-atoms which bear the functional group heteroatoms mentioned above

(for example the alcohol, ether or ester bearing C-atom in resins possessing a terminal OH or OR or OAr or O-acyl, ureathane or other carbon acid or heteroatom acid ester group; the carbonyl C-atom in aldehyde, ketone, carboxylic acid, carboxylic ester and carboxamide derivatives, however substituted; the amino bearing C-atom in resins possessing terminal amino or amide groups, however substituted and including hydrazines and hydroxylamines; the C-atom bearing the thiol or thioether functionality in thiol and thioether containing resins, the C-atom bearing the phosphorus atom in phosphine and phosphine oxide and phosphonate containing resins, however substituted, and the C-atom which bears the sulfonyl group in vinyl and other olefinic and non-olefinic sulfones and sulfonamides, sulfoxides and sulfonic acids, however substituted) whether such aryl groups are benzylic or aliphatic, or even an N-atom in certain cases, would allow the system function in the required manner to some extent and, therefore, would be covered under this invention if used for the purposes of synthesising organic molecules in the solid phase.

Within the spirit of this invention bis- and tris-functionalised materials could be produced from a single fluoropolymer side chain to increase the loading capacity of the resins. For example, reaction of the resin sulfonyl chloride with tris-(hydroxymethyl)aminomethane or similar amines would give a derivatives of the type; fluoropolymer-SO_2-NH-$C(CH_2OH)_3$ which potentially could be further functionalised through each of the OH groups.

The unfunctionalised crushed resin starting material (eg Nafion™) or the methyl ester derivative could be formed into shapes including shapes analogous to those

corresponding to POSAM® microreactors (type B microreactors) by compression at 140-240°C in a mould. The moulded shapes were chemically treated in several instances with the reagents and under the conditions outlined above to give functionalised type B microreactors resin shapes. These showed similar chemical loading properties to the non-compressed crushed resin and could be used for organic synthesis in open vessels. Thus, the principle of using macroscopic functionalised frit resin blocks in solid-phase synthesis is established.

It is known that Nafion™ resins are cross-linked and this would explain why it is difficult to heat process the crushed resin even as its methyl ester derivative. mIt would therefore be desirable for forming mechanically reliable type B microreactors to use fluoropolymer materials that are cross-linked to a lesser extent than Nafion™ NR50 material.

Experimental concerning the preparation of chemically functionalised polymer resins and fluorpolymer resins for use in solid-phase chemical synthesis.

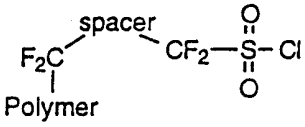
^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini 300 (^{1}H, 300 MHz; ^{13}C, 75.4 MHz) or Varian Gemini 200 (^{1}H, 200 MHz; ^{13}C, 50.3 MHz) spectrometers. Chemical shifts are described in ppm downfield from tetramethylsilane and are reported as follows: position, (δ_H or δ_C) [relative integral, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet and br = broad), coupling constant (*J* /Hz, if of practical importance) and assignment (numbered according to the IUPAC nomenclature for the compound)]. ^{1}H spectra were referenced internally on ^{2}HOH (δ 4.68 ppm) and $CHCl_3$ (δ 7.27 ppm). Infra-red spectra were recorded on a Perkin-Elmer 1710 FT-IR spectrometer or a Nicolet InspectIR FT-IR using silicon ATR crystal. The samples were prepared as KBr discs or single beads. The frequencies (υ) as absorption maxima are given in wavenumbers (cm^{-1}) relative to a polystyrene standard. Microanalyses were determined in the microanalytical laboratory at the University of St Andrews. Mass spectra and accurate mass (HRMS) measurements were recorded in St Andrews on a VG 70-250 SE. Melting points were determined on either a Reichert hot stage (< 230 °C) or an Electrothermal (>230 °C) apparatus and are uncorrected.

Reagents were used without purification unless otherwise stated. Quantities of reagents were calculated from the manufacturers' stated purities. Experiments were conducted at room temperature (20-25 °C) unless otherwise stated. All reactions that employed organometallic regents or other moisture sensitive reagents were performed in dry solvent under an atmosphere of dry nitrogen or argon in oven-dried and/or flame-dried glassware. Solutions in organic

solvents were dried over anhydrous magnesium sulfate and concentrated or evaporated under reduced pressure on a Büchi rotary evaporator unless otherwise stated.

The solvents used were either distilled or of analar quality and were dried according to literature procedures: ethanol and methanol were dried over magnesium turnings; dichloromethane, DMF, pyridine and triethylamine were distilled over calcium hydride; THF and diethylether (referred to as ether) were dried over sodium and benzophenone. Thionyl chloride was distilled over sulphur, and the initials fractions were always discarded. All other chemicals were of analytical grade or were recrystallised or distilled before use.

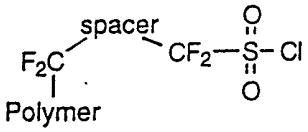
Nafion-Cl



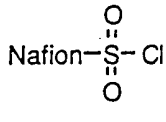
Nafion beads [Nafion® NR50; 10-35 Mesh, hydrogen ion form, Eqiv. wt .1250 (max.), ion-exchange capacity 0.8meq/g] (1 g, 0.8 mmol) were crushed at -150 °C to give a course white powder. Dry toluene (20 cm^3) and phosphorous pentachloride (4.16 g, 20 mmol) were added and the mixture refluxed for 24 h. The resulting mixture was cooled and then filtered, before the filterate was washed with cuprous amount of dry dichloromethane. The slightly brown solid was then dried under reduced pressure at 60 °C to give the Nafion chloride in quantitative recovery (base on weight).

DATA: υ_{max}(single bead)/cm^{-1} 1270 and 1185 (SO_2) and 1050 (SO_2Cl).

Please note



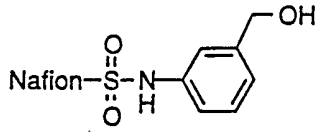
is abbreviated to



General Procedure for the coupling of Nafion-SO_2Cl with Amines/Amino acids

To a gently stirred suspension of Nafion-chloride (80 mg, 72.5 μmol) in dry dichloromethane (15 cm^3) was added a suspension of amine/amino acid (0.64 mmol) and pyridine (200 mm^3, 2.36 mmol) [if the amine/amino acid exits as a hydrochloride salt, then 10 equivalents of pyridine are used) in dry dichloromethane (10 cm^3). The mixture was then stirred at room temperature for 96 h, filtered, washed with water/methanol/DCM/water/methanol/DCM and the resin dried under reduced pressure to a constant weight. Typically the weight of the resin obtained is near quantitative.

Formation of sulfonanilimide of 3-aminobenzylalcohol 4



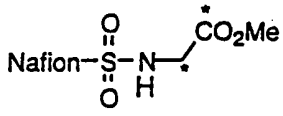
Following the general procedure above, 3-aminobenzylalcohol was converted in the sulfanilamide **4**, (which had a reddish colour) in quantitative yield.

DATA: υ_{max}(single bead)/cm^{-1} 1470 (CH_2Ar), 1320 (sulfonamide), 1220 and 1150 (SO_2) and 820 (meta disub. aromatic). (See Scheme 2)

[U-^{14}C]-Glycine methylester hydrochloride

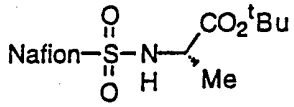
To a stirred suspension of glycine (200 mg, 2.67 mmol; containing 5 μCi of [U-^{14}C]-glycine; 11.1 x 10^6 dpm) in dry methanol (15 cm^3) was added dropwise thionyl chloride (350 mm^3, 4 mmol) at 0 °C. The ice-bath was removed and the solution refluxed for 90 min. The solvents were removed under reduced pressure and the crude material suspended in water (10 cm^3) and then concentrated under reduced pressure to give a white solid in quantitative recovery. Radioactivity yield (76%, 42,375 dpm/mg). mp 172 °C (decomp.) [lit., 175 °C (decomp)]; δ_H(200 MHz; ^2H_2O) 3.81 (3 H, s, OCH_3) and 3.95 (2 H, s, CH_2).

[U-^{14}C]-Glycine methylester sulfonamide 5



Following the general procedure above, the sulfonamide **5** was obtained in 48% yield (according to radioactivity). (see also Scheme 3)

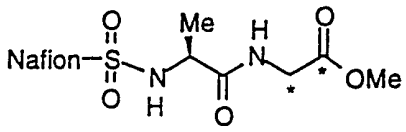
(2S)-Alanine sulfonamide 7



Following the general procedure above, the (2S)-alanine t-butylester sulfonamide **6** was obtained in quantitative recovery. The t-butyl ester was then removed by addition of TFA (5 molar equivalents) in dry dichloromethane. The mixture was stirred at room temperature for 3 h, before being filtered, washed with water/methanol/DCM/water/methanol/DCM and the alanine sulfonamide **7** was dried under reduced pressure to a constant weight.

DATA: υ_{max}(single bead)/cm^{-1} 1740 (C=O), 1320 (sulfonamide) and 1210 and 1150 (SO_2)
(See also Scheme 4)

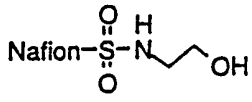
Methyl (2S)-alaninyl-[U-^{14}C]-glycinate sulfonamide 8



To a gently stirred suspension of the alanine sulfonamide **7** (100 mg, 83.3 mm^3) in dry DMF (10 cm^3) was added *N*-methylmorpholine (91 mm^3, 0.833 mmol). A solution of [U-^{14}C]-glycine methylester hydrochloride (20.8 mg, 0.166 mmol), *N*-methylmorpholine (91 mm^3, 0.833 mmol) and PyBOP in in dry DMF (5 cm^3) was then added in one portion to the above suspension. The reaction mixture was then stirred at room temperature for 96 h. The resin was filtered, washed with water/methanol/DCM/water/methanol/DCM and the resin dried under

reduced pressure to a constant weight and specific radioactivity. Yield 11.5% (based on radioactivity). (see also Scheme 4)

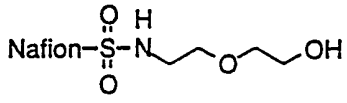
Formation of of 3-aminopropanol sulfonamide 9



Following the general procedure above, 3-aminopropanol was converted in the sulfonamide 9 in quantitative yield. (see also Scheme 5)

DATA: υ_{max}(single bead)/cm^{-1} 1510 and 1480 (CH_2), 1320 (sulfonamide), 1220 and 1150 (SO_2).

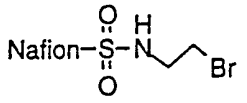
Formation of 2-(2-aminoethoxy)ethanol sulfonamide 10



Following the general procedure above, 2-(2-aminoethoxy)ethanol was converted in the sulfonamide **10** in quantitative yield. (see also Scheme 5)

DATA: υ_{max}(single bead)/cm^{-1} 1510 and 1480 (CH_2), 1320 (sulfonamide), 1220 and 1150 (SO_2).

Reaction of sulfonamide 9 with phosphorous tribromide

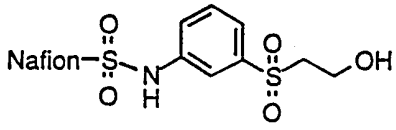


To a stirred suspension of the 3-aminopropanol sulfonamide 9 (200 mg) in dry DCM was added phosphorous tribromide (100 mg). The mixture was stirred at room temperature for

72 h, filtered, washed with water/ methanol/ DCM/ water/ methanol/ DCM and the resin dried under reduced pressure to a give the bromide **11** in quantitative recovery.

DATA: υ_{max}(single bead)/cm^{-1} 1510 and 1480 (CH_2), 1320 (sulfonamide), 1220 and 1150 (SO_2).

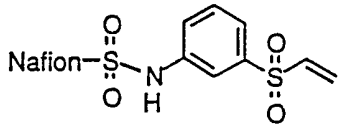
Formation of 2-(3-aminophenylsulfonyl)ethanol sulfanilamide 12



Following the general procedure above, 2-(3-aminophenylsulfonyl)ethanol was converted in the sulfanilamide **12** (which had a reddish colour) in quantitative yield. (see also Scheme 6)

DATA: υ_{max}(single bead)/cm^{-1} 1510 and 1480 (CH_2), 1320 (sulfonamide), 1220 and 1150 (SO_2), 750 and 680 (meta disubst. aromatic).

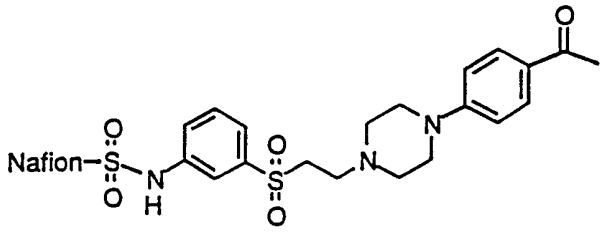
Formation of sulfanilamide vinyl sulfone 13



To a suspension of the alcohol **12** (700 mg) in dry dichloromethane (10 cm^3) was added triethylamine (1.95 cm^3) and mesyl chloride (0.54 cm^3) at room temperature. After 36 h, the resin was filtered off and washed with DCM (50 cm^3), 20% triethylamine in DCM (50 cm^3) and DCM (50 cm^3). The resin was dried under vacuum at 45 °C (yield 0.673 mg).

DATA: υ_{max}(single bead)/cm^{-1} 1320 (sulfonamide), 1212 and 1150 (SO_2), 760 and 680 (meta disubst. aromatic). (see also Scheme 6)

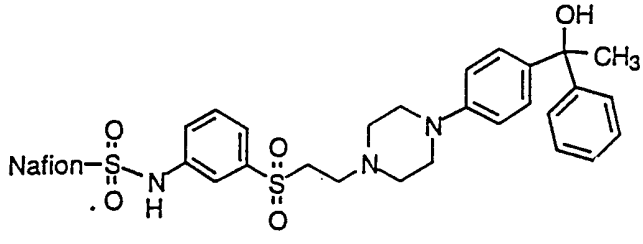
Nafion sulfanilamide piperazino-4-acetophenone adduct 14A



To a suspension of the vinyl sulfone **13** (673 mg) in DMF (HPLC grade, 10 cm^3) was added piperazino-4-acetophenone (500 mg) at room temperature. The whole suspension was agitated for 72 h and then the resin was filtered off and washed with DMF (30 cm^3), DCM (50 cm^3) and methanol (50 cm^3). The resin was dried under vacuum at 45 °C (yield 0.653 mg).

DATA: υ_{max}(single bead)/cm^{-1} 2950, 2843, 1650 (C=O), 1320 (sulfonamide), 1212 and 1150 (SO_2), 760 and 680 (meta disubst. aromatic). (See also Scheme 6)

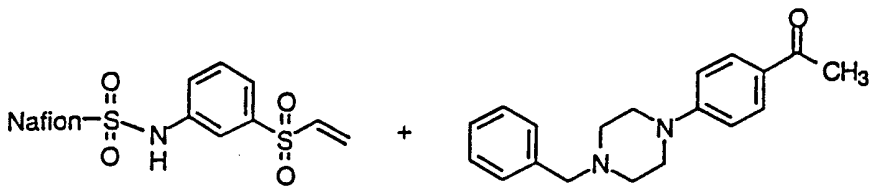
Reaction of adduct 14 with phenylmagnesium bromide



To a cooled suspension of the ketone **14A** (630 mg) in dry THF (5 cm^3) at 0 °C was added dropwise phenylmagnesium bromide (1 M solution in toluene; 950 mm^3; 0.95 mmol) and the suspension allowed to reach room temperature overnight. After 15 h, 50% aqueous ammonium chloride (25 cm^3) was added. The resin was filtered off and washed with water (50 cm^3), THF (50 cm^3), DCM (50 cm^3) and methanol (50 cm^3). The resin was dried under vacuum at 60 °C (Yield 0.602 mg).

Single bead FT-IR analysis of the resin showed largely unreacted resin-bound ketone. Repeat experiments confirmed that the Grignard addition was ineffective. Alkylation and elimination, as described below, gave largely unreacted ketone 17 (and very little alcohol), showing that there is a size exclusion limit on Nafion

Sulfanilamide vinyl sulfone 13 and *N*-benzyl-piperazino-4-acetophenone 17



To a suspension of the ketone **14** (601 mg) in DMF (HPLC grade, 10 cm^3) was added benzyl bromide (1.13 cm^3). The whole suspension was agitated for 24 h and the resin was filtered off and washed with DMF (30 cm^3) and DCM (50 cm^3).

The resin was re suspended in DCM (7 cm^3) and then IDEA (0.6 cm^3, 3.4 mmol) was added. After 24 h agitation the resin was filtered and then washed with DCM (50 cm^3) and methanol (50 cm^3). The resin was dried under vacuum at 50 °C (yield 0.597 mg).

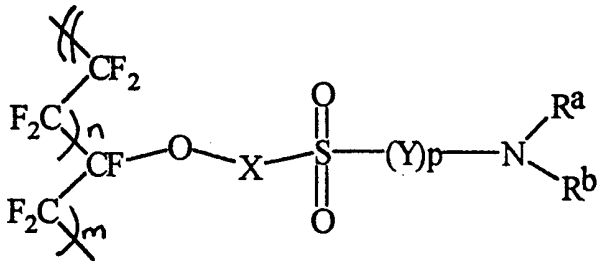
The solvent was then removed from the filtrate under reduced pressure to give a orange liquid was purified through a small column of silica (1 g) topped with potassium carbonate to give an. off-white solid (4 mg, 13.6 μmol).

Data for **17**: (HRMS: found: $[M + H]^+$, 295.1805. Calc. for $C_{28}H_{26}NO_5P$: 295.1810); υ_{max}(film)/cm^{-1} 2950, 2843, 1670 (C=O) and 1599 (aromatic); δ_H(300 MHz; C^2HCl_3) 2.51 (3 H, s, CH_3), 2.57-2.61 (2 H, m, piperazine), 3.34-3.38 (2 H, m, piperazine), 3.57 (2 H, s, benzyl), 6.84-6.87 (2 H, m, Ar-H), 7.26-7.40 (5 H, m, Ar-H benzyl) and 7.85-7.88 (2 H, m, Ar-H), *m/z* (CI) 295 $[M + H]^+$ and 279 $[M + H - O]^+$.

CLAIMS

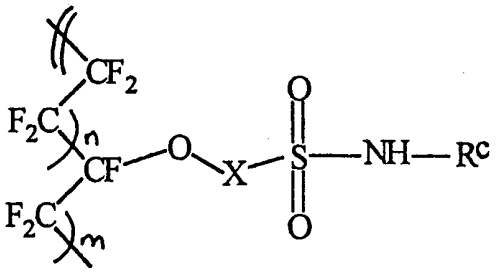
1. A polytetrafluoroethylene resin comprising a side chain having a sulphonamide or sulphonanilimide moiety.

2. A resin as claimed in Claim 1 of general formula I:



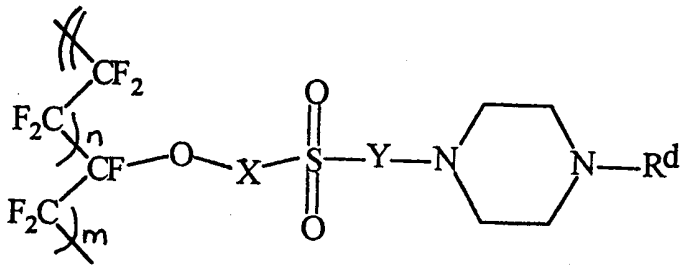
wherein n and m are each integers of from 1 to several hundred;
p is 0 or 1;
X is a spacer group;
Y is a spacer group;
R^a is H or a lower alkyl group;
R^b is any moiety bearing at least one reactive functional group; or R^a and R^b may together form a C_4 - C_6 cyclic ring which may optionally contain further heteroatoms (eg N, S or O) and/or may optionally be substituted by a moiety containing at lest one reactive functional group.

3. A resin as claimed in Claim 2 of general formula II:



wherein n and m are each integers of from 1 to several hundred,
X is a spacer group;
R^c is a C_{1-20} carboxy acid, carboxy ester, aliphatic alcohol, ether or amino acid derivative.

4. A resin as claimed in Claim 2 of general formula III:



wherein n and m are each integers of from 1 to several hundred,
X is a spacer group;
Y is a linear or branched C_{1-6} aliphatic hydrocarbon group, optionally interrupted by heteroatoms;
R^d is an aryl group, substituted by a reactive functional moiety such as a carboxy group, carboxyl group, sulphonyl group, amine, amide, thioester or the like.

5. Use of a polytetrafluoroethylene resin bearing a reactive functional group as a support matrix for solid-phase chemical reactions.

6. A method of producing a solid-phase reactant for a solid-phase chemical reaction, said reactant comprising a polytetrafluoroethylene resin-substrate complex, wherein said complex is produced by reacting a precursor substrate with a functional group on the polytetrafluoroethylene

resin.

7. A method of chemical synthesis involving a chemical reaction wherein one of the substrates of said reaction is in the form of a solid-phase polytetrafluoroethylene resin substrate complex.

8. A microreactor comprising a resin material as a support matrix for a solid-phase chemical reaction, wherein said resin material is a polytetrafluoroethylene resin.

9. A microreactor as claimed in Claim 8 wherein the resin is as claimed in any one of Claims 1 to 3.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 98/02263

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C08F8/34 C12N11/08 G01N33/545

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C08F C12N G01N

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 304 377 A (CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE) 22 February 1989 see claims 1-31	1-9
Y	EP 0 562 877 A (ORTHO DIAGNOSTIC SYSTEMS INC.) 29 September 1993 see claims 1-47	1-9
Y	US 5 270 193 A (J. W. D. EVELEIGH) 14 December 1993 see claims 1-18	1-9
Y	EP 0 156 588 A (APPLIED BIOSYSTEMS, INC.) 2 October 1985 see claims 1-27; figures 1-6	1-9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the international search report
13 November 1998	25/11/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Permentier, W

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INTERNATIONAL SEARCH REPORT

Interi ;al Application No
PCT/GB 98/02263

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 0 168 363 A (J. PORATH) 15 January 1986 see claims 1-6	1
A	EP 0 008 100 A (BASF AG) 20 February 1980 see claims 1-12	1
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