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Solid-phase synthesis on functionalised fluoropolymer resins. Part 2: Preparation and properties of functional Merrifield-type resins possessing a perfluorinated polymer backbone

Shuyuan Liu, Mahmoud Akhtar and David Gani*

School of Chemistry, The University of Birmingham, Edgbaston, Birmingham B15 2T, UK

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Abstract

Monomers α,β,β-trifluorostyrene and 4-methyl-α,β,β-trifluorostyrene were prepared and were copolymerised under free-radical emulsion conditions to give highly stable, well defined lipophilic polymer resins. Benzylic halogenation of the polymer products gave 4-chloromethyl and 4-bromomethyl derivatives which could be elaborated through nucleophilic displacement of halide. The reaction of 4-fluorophenol with the 4-chloromethylated poly(trifluorostyrene) resin was followed by ^{1}H and ^{19}F NMR spectroscopy and proceeded more rapidly than for Merrifield resin. © 2000 Elsevier Science Ltd. All rights reserved.

Polystyrene (PS) has been the main base polymer of choice in synthetic applications of functionalised polymer supports since the advent of solid-phase (SP) peptide synthesis,[1] and the emergence of combinatorial chemistry.[2] Solid-phase organic chemistry now plays an increasingly important role in drug and catalyst synthesis and offers significant advantages over solution-phase alternatives in several instances.

Increasing the range of synthetic methods accessible to SP protocols and to be able to perform a larger repertoire of established solution phase chemistry requires the core polymer to be robust and chemically resilient. Polystyrene suffers intrinsic limitations associated with its chemical, mechanical and thermal stabilities, and hence, polystyrene based supports are not suitable for many applications where harsh conditions are required. Few of the fundamental problems associated with polystyrene and other polyethylene-based polymers have yet been overcome, but rather modifications to linker groups have been introduced to improve reaction performance.

Fluoropolymers and in particular polytetrafluoroethylene (PTFE) display outstanding chemical inertness and heat resistance, and are good candidates for the polymer backbone of resins for synthesis. In the previous article we showed that while functionalised derivatives of the fluoropolymer Nafion are robust and chemically resilient, they are not useful in solid-phase organic

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* Corresponding author.

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synthesis (SPOS),[3] apparently because the perfluoropolymer side chains cannot solvate in organic solvents. In order to overcome the lipophobicity problems of perfluoropolymers, 'functionalised hydrocarbon branched' fluoropolymer supports were developed. The first example of which we describe here is based upon poly(α,β,β-trifluorostyrene) (PTFS) (Fig. 1). As an analogue of PS, it was expected that it would be possible to transfer existing solid phase chemistries to such polymer supports and also significantly extend the range of possible reactions and applications, many of which currently are difficult on conventional supports.

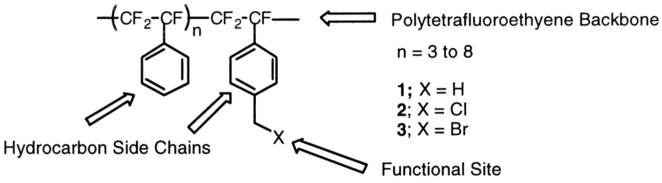


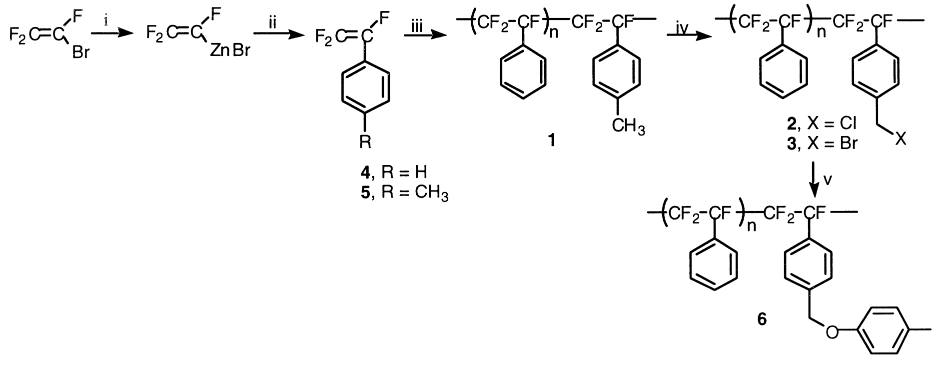
Figure 1. Structure of a hydrocarbon branched resin based on poly(trifluorostyrene)

α,β,β-Trifluorostyrene (TFS) **4** was first synthesised by Cohen in 1949[4] and was successfully polymerised by Prober in 1953.[5] Extensive studies on the synthesis of TFS based polymers and copolymers have been reported,[6] and the stability of PTFS based polymers has been utilised in ion exchange applications where sulfonated PTFS systems have been developed. Here, the functionality was either introduced before[7] or after[6c,8] polymerisation, and, in principle, either of these two strategies could be employed to synthesise **1** or **2**. The first approach mirrors conventional routes to functionalised pre-formed polystyrene,[1] and involves a Friedel–Crafts type 'halogenomethylation'. This reaction was expected to be difficult for PTFS and to give *meta* substitution, due to the electron-withdrawing nature of the backbone, as was observed by Hodgdon in the sulfonation of PTFS.[8a]

This approach gives random functionalisation and might present problems with site distribution, regio-isomerisation and additional crosslinking-bridge side reactions and was therefore not pursued further. The alternative site-directed approach, to introduce functional precursors by means of co-polymerisation, Scheme 1, was considered, and was expected to lead to well defined site distribution and uniform *para* substitution. Furthermore, it was expected that *para*-methyl groups (as reactive precursors) could be introduced from *para*-methyl-α,β,β-trifluorostyrene (MTFS) comonomer **5** and then be converted to chloromethyl and bromomethyl groups through benzylic halogenation reactions of copolymer **1** after copolymerisation.

Of the methods described for the synthesis of α,β,β-trifluorostyrene derivatives,[6c,9] Burton's method[10] is accepted as the most useful.[6d,7,11] Accordingly, trifluorovinyl bromide was reacted with activated zinc dust and the resulting trifluorovinyl zinc bromide was cross coupled with either iodobenzene or 4-iodotoluene in the presence of palladium(0) to give TFS **4** and MTFS **5**, Scheme 1.[10]

Both radical and ionic polymerisation of TFS are known to be difficult.[6,12] Due to the large size of fluorine atoms, relative to hydrogen, TFS is more than four times less reactive towards free radical (trichloromethyl radical) attack than styrene.[13] A 2+2 cycloaddition which occurs at higher temperatures also competes with polymerisation,[5,6c,11,14] resulting in low molecular weight PTFS under normal suspension polymerisation conditions.[6] Thus emulsion polymerization at low temperature, using high concentrations of emulsifier, appeared be the only useful method to synthesise relatively high-molecular PTFS.[5–7,15] When polymerisations under such conditions[5]



Scheme 1. Reagents and conditions. (i) Zinc dust, DMF, 50°C, 3 h; (ii) iodobenzene (for **4**) or 4-iodotoluene (for **5**), Pd(0)(PPh$_3$)$_4$, DMF, 50°C, 48 h; (iii) $K_2S_4O_8$, dodecylamine hydrochloride, H_2O, 50°C, 72 h; (iv) BTMA ICl$_4$, AIBN, Ph-CF$_3$, 85°C, 72 h to give **2**. NBS, C_6H_6, sunlamp light, 0.5–8 h to give **3**; (v) 4-fluorophenol, NaH, DMF, 0°C, 1 h then **2**, rt, 3 h

were carried out poly(α,β,β-trifluorostyrene) PTFS and TFS-MTFS copolymer **1** (Scheme 1) were obtained. In the co-polymerisation of TFS **4** and MTFS **5**, the incorporation of MTFS in the *para*-methyl PTFS copolymer **1** according to microanalytical and ^{1}H NMR spectral data, Fig. 2, was in excellent accordance with the starting compositions of the two monomers. This result suggests that TFS and MTFS possess similar reactivity and should give rise to a uniform distribution.

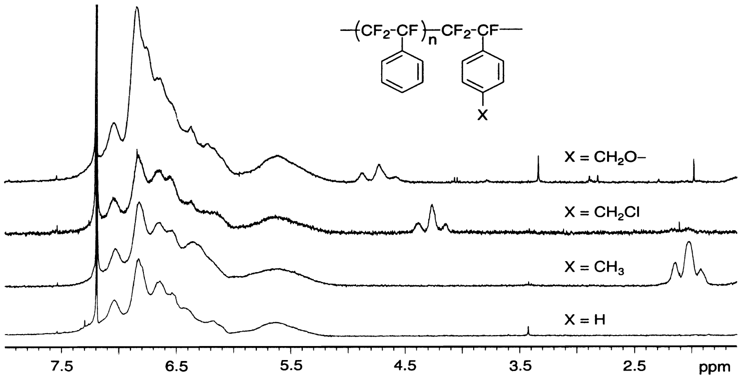


Figure 2.

Halogenation of the TFS-MTFS copolymer to give functionalisation sites were performed under a range of conditions.[16,17] Benzyltrimethylammonium tetrachloroiodate (BTMA ICl$_4$)[17] proved to be most useful in the chlorination of PMTFS to give compound **2** (CMPTFS) (Fig. 2) and *N*-bromosuccinimide (NBS)[16b,c] was useful in bromination of the PMTFS copolymer to give compound **3** (BMPTFS), Scheme 1.

The PTFS polymers were brittle white solids, of molecular weights in the range of 1×10^5 to 5×10^5,[5] and gave satisfactory elemental analyses. The molecular weights as determined by GPC are in the range 4×10^4 to 3×10^6 with up to 2×10^4 repeat units and suggest that the polymers possess high polydispersities. FTIR spectra showed characteristic strong C–F stretching bands

(1077–1272 cm^{-1}). The NMR spectra of the PTFS polymers suggested the construction of the polymer to be a random event, similar to PS polymers. Multi-signals for the same type of nucleus suggest the polymer structure is a mixture of isotactic, syndiotactic and heterotactic triads and the whole skeleton is very stiff.

PTFS polymers are thermally stable and their behaviour is distinctive. Although it was reported that the glass transition temperature ($T_{g)}$ of PTFS was 202°C by differential scanning calorimetric (DSC) measurements[18] and similar values by calculation,[19] our DSC analysis showed that there were neither observable T_g nor melting points (T_m). The polymer did not start decomposing until about 350°C. This is not surprising because the backbone and aryl groups of PTFS are very stiff due to the large size of fluorine atoms and the steric hindrance prevents the rotation of the phenyl group (at glass transition) and along the backbone (at melt). Thus, the resin does not respond to heating and cooling, hence, it can be used over a wide range of temperatures. The resin was either soluble or swellable in a range of solvents, including chloroform, DMF, acetone and benzene and therefore of potential use in liquid phase organic synthesis where reactions occur in homogeneous solution.[20] The insolubility of PTFS resin in solvents, such as methanol, allows precipitation and therefore makes work-up very simple and easy.

The solubility of PTFS resins in $CDCl_3$ and other solvents, together with the relatively transparent ^1H NMR spectrum of PTFS polymer supports (the proton signals occur between 5.2 and 7.5 ppm), offers advantages in monitoring multi-step supported syntheses (Fig. 2).

The ability of the functional site in the chloromethyl derivative of PTFS **2** to react with nucleophiles was tested with 4-fluorophenol (Scheme 1). The -CH_2Cl and -CH_2O- ^1H NMR signals in resin-bound form were used directly to estimate the absolute extent of reaction and the rate of the reaction (Fig. 2). The reaction was complete within 3 h at room temperature as judged by ^1H and ^{19}F NMR spectra. The kinetics of the reaction were examined using real-time in-situ NMR techniques and were found to be competitive with the rates for Merrifield resin.

Thus PTFS based resins appear to be ideal for the construction of supported systems and of potential in organic synthesis.

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