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A Method for the Quantification of Resin Loading Using ^{19}F Gel Phase NMR Spectroscopy and a New Method For Benzyl Ether Linker Cleavage in Solid Phase Chemistry.

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Abstract. A simple and efficient method for monitoring and quantifying the extent of loading onto polymer resin supports for solid-phase synthesis using ^{19}F gel-phase NMR spectroscopy is described. This assay was utilised in the synthesis of an inositol monophosphatase inhibitor on Merrifield resin. A series of Merrifield resin derived benzylic ethers were prepared and were cleaved from the resin when treated with $SnCl_4$ at room temperature to give the expected alcohol, phenol or olefin. This new cleavage method was used to remove the inositol monophosphatase inhibitor from the resin.

The advancement of solid-phase organic synthesis (SPOS) has been driven by a desire to rapidly produce structurally diverse molecules,[1] and the range of reactions that can be performed in the solid phase has grown.[2,3] These advances in SPOS have required both the refinement of existing and the development of new analytical techniques to both monitor the progress of reactions and characterise the products of solid-phase syntheses.[4] Indeed, of the conventional methods, only FT-IR has been of generic use in providing direct, semiquantitative information on the extent of the conversion of the solid-phase material to a resin-bound product in a given reaction. Here we describe, in one part, a method capable of providing quantitative information on the extent of the conversion of a solid-phase material which utilises ^{19}F gel phase NMR spectroscopy and which is applicable to a wide range of reaction chemistries and resin-support materials. We also present a new method for cleaving Merrifield ethers.

Ever since Purdie and his associates first used methyl groups to protect and derivatise hydroxyl groups, the utility of selective protection has been widely applied in natural product synthesis. The O-benzyl group has found particular favour because not only is it easy to introduce, but is also easy to remove. The O-benzylic moieties of Merrifield ethers can be considered as simple protecting groups and should, in principle, be removable by any conventional benzyl group deprotection method. However, in practice, useful solution phase methods for benzyl group removal such as catalytic hydrogenolysis are ineffective, and typically Brønsted acidic conditions have been employed for their cleavage. In a second part, we describe the use of stannic chloride[5] as an alternative, facile and general method for effecting cleavage.

Given that ^{19}F-NMR signals are of proven utility in monitoring solid-phase reactions,[4,6] ^{19}F gel-phase NMR spectroscopy appeared to offer a good method for quantifying the extent of the derivatisation of a functionalised polymer material with a fluorinated substrate. To test the idea, the rates of the reaction of Merrifield resin with 2-fluorophenol in DMF at 60 °C in the presence of sodium hydride were examined. At

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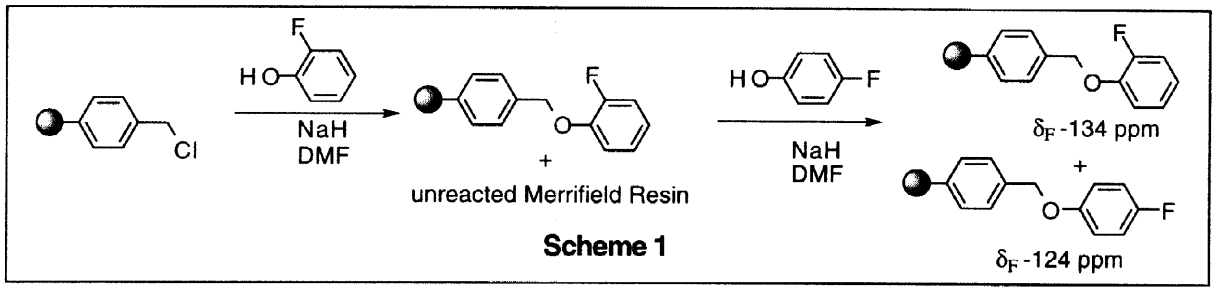
various time intervals portions of the reacting resin were removed and were reacted, exhaustively, with excess 4-fluorophenol in DMF at 60 °C in the presence of sodium hydride, Scheme 1.



Scheme 1

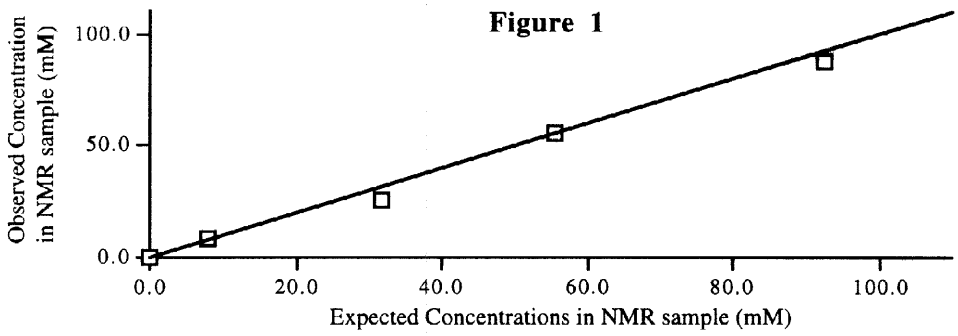
Examination of the resin samples by ^{19}F gel-phase NMR spectroscopy showed a major broad signal corresponding to the 2-fluorophenol derivative at -134 ppm (from external $CFCl_3$ at 0 ppm), for extended initial reaction times, and a major broad signal corresponding to the 4-fluorophenol derviative at -124 ppm, for short initial reaction times. Thus, it was evident that ^{19}F gel-phase NMR spectroscopy was useful in providing information directly on the extent of the reaction.

In these experiments it was only possible to obtain qualitative, rather than quantitative, information on the extent of reactions. In order to quantify the amount of fluorine (and hence compound) on the resin we needed to measure the relative intensities of resin bound fluorine and a known concentration of an internal fluorine standard in solution (*eg.* fluorobenzene) in the ^{19}F NMR spectrum. To obtain meaningful measurements, there needed to be sufficient delay between RF pulses, such that the solid phase and solution phase nuclei would be similarly relaxed. Experiments were therefore set up to determine the spin-lattice relaxation time constant (T_1) for the 2-fluorophenyl Merrifield ether.

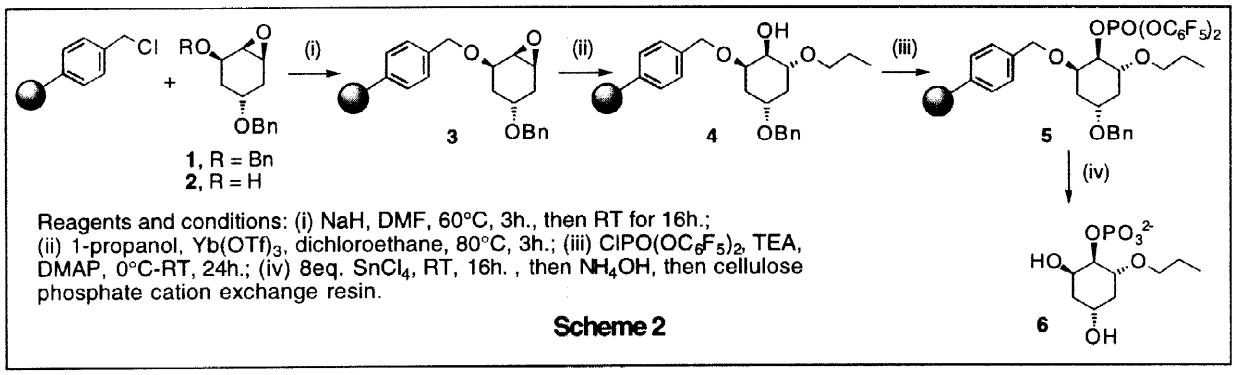
The optimal solvent system for simultaneously swelling and dispersing the resin in a homogeneous form within the RF coils was deuterated chloroform:benzene:fluorobenzene (50:49:8:0.2). The resin would either sink or rise up and float in other mixtures of these solvents. For a 100%-loaded 2-fluorophenyl Merrifield ether sample,[7] (30 mg, 1.84 mmol F g^{-1} resin), a T_1 value of 4.2±0.6 s was measured for the fluorophenyl ether signal using the inversion recovery technique. In order to accurately quantify the fluorine concentrations from the NMR data, the interpulse relaxation delay was set to 25 s which is at least five times the longest spin-lattice relaxation time constant (T_1). Integration of the two ^{19}F NMR signals at -113 ppm and -134 ppm due to the solution-phase fluorobenzene reference standard and gel-phase fluorophenyl ether, respectively, gave an excellent correlation with the expected fluorine content for the Merrifield derivative.[7] In order to determine whether it would be possible to quantify the extent of a solid-phase reaction in 'blind' samples, portions of the 100% loaded 2-fluorophenyl Merrifield ether,[7] were blended with unfunctionalised Merrifield resin to give samples which contained varying amounts of resin-bound fluorine. NMR spectra were recorded and Figure 1 shows a plot of the theoretical (solid line) *versus* the experimentally determined (data points) resin-bound F-atom content in samples containing 30 mg of the blended resin.

The excellent correlation for the determined F-atom content provides a high level of confidence in monitoring loading reactions and in quantifying the number of sites available in resin samples.

This fluorophenol based assay was used to optimise the attachment of an epoxide to Merrifield resin. Recently we reported on the preparation of the *bis*-O-benzylated dihydroxycyclohexene oxide, **1**, starting from quinic acid, and its conversion to an inositol monophosphatase inhibitor.[8] In order to pursue the analogous solid-phase synthesis of the inhibitor, the monobenzyl protected dihydroxycyclohexene oxide **2** was reacted



with Merrifield resin to give the Merrifield ether, **3** in 91% yield, Scheme 2, under conditions optimised by removing a small portion of the reacted resin and assessing the extent of reaction through treatment with excess *p*-fluorophenolate and ^{19}F gel phase NMR spectroscopic analysis of the product. The epoxide **3** was treated with propan-1-ol in the presence of ytterbium triflate, under conditions previously optimised for the analogous solution-phase chemistry,[9] to give the required resin bound alcohol **4**, (FTIR; ν_{max} OH = 3400 cm^{-1}) in quantitative conversion as judged by the mass increase of the resin. Reaction of the resin-bound alcohol with excess *bis*-pentafluorophenyl chlorophosphate,[10] gave the required resin bound phosphate triester **5**, in quantitative conversion, which displayed the expected IR spectral chacteristics and a ^{31}P-NMR signal at -10 ppm in a gel phase sample. The sensitive phosphate moiety in triester **5** would not survive treatment with HF or triflic acid resin cleavage protocols. However, we knew that the Lewis acid $SnCl_4$ had been used to selectively remove benzyl ether groups from carbohydrates,[5] and had shown that the reagent was effective in cleaving simple primary and secondary alkyl Merrifield ethers (see below) to give the required alcohol in excellent yield, Figure 2. To assess whether the reagent was applicable to our synthesis, the triester **5** was treated with stannic chloride and then the excess tin residues were removed by passage of an aqueous solution of the cleavage product through a cellulose phosphate ion exchange column. Greater than 95% pure **6** was obtained in 56% yield as the *bis*-cyclohexylammonium salt from **3** and this (*1R,2R,4R,6R*)-phosphatase inhibitor **6** displayed identical physico-chemical and biological properties to the authentic material.[8]



Scheme 2

In the work on the Lewis acid catalysed benzyl ether cleavage system, primary, secondary and tertiary alcohols and phenols were attached to Merrifield resin, Figure 2, and gave the expected mass increase, were fully loaded as judged by the fluorophenol based assay, and displayed the expected ether stretch at ~1100 cm^{-1}. Treatment of each one with 10 equivalents of stannic chloride followed by aqueous work-up and extraction into DCM gave the expected alcohol in yields ranging from 70-95%. The one exception to this was the tertiary

alcohol derived resin **9** which gave a 50% yield of the olefin **14** upon cleavage, in accord with a mechanism whereby the O-atom chelates to the tin atom to displace chloride ion and generate a benzylic carbocation, or, for resin **9**, the more stable tertiary carbocation which loses a proton to give **14**. Note that $TiCl_4$ was also useful in cleaving Merrifield ethers.

The rate of the cleavage reaction was investigated for the two fluorinated Merrifield ethers **12** and **13** using gel-phase ^{19}F-NMR spectroscopy. Accordingly, a 1.5-fold excess of stannic chloride was added to each of the resin samples, **12** and **13**, suspended in d-chloroform, and the increase in the intensities of the ^{19}F signals at -142 ppm and -124 ppm, due to the resin cleaved products, respectively were monitored with respect to time. In each case the reaction was rapid and was complete within 1.5 and 4 h, respectively, at 30°C.

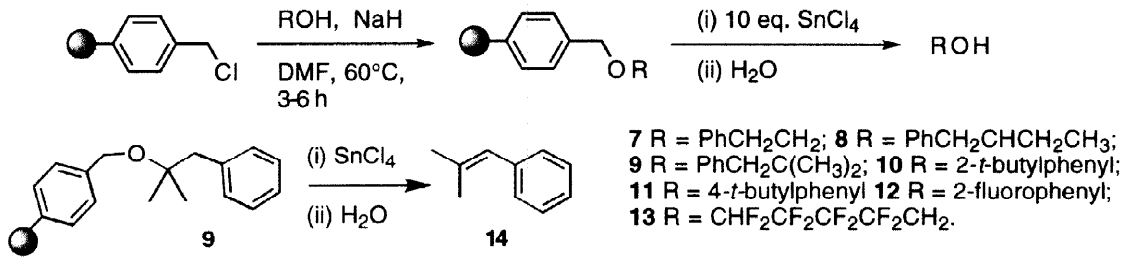


Figure 2

We believe that the ^{19}F-NMR spectroscopic assay and the $SnCl_4$ mediated Merrifield resin cleavage reaction will be widely applicable in SPOS.

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