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Use of Tetrabenzo[*a,c,g,i*]fluorene as an Anchor Group for the Solid/Solution Phase Synthesis of Ciprofloxacin.®

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Abstract: The affinity of tetrabenzo[*a,c,g,i*]fluorene for charcoal has been applied successfully to provide an alternative to existing solid phase synthesis methodology. In a synthesis of the quinolone antibacterial, Ciprofloxacin,® traditional solution phase synthesis has been coupled with efficient *pseudo*-solid phase purification.

Keywords: Affinity Purification; Solid/Solution Phase; Quinolone Antibiotics

With the advent of combinatorial synthesis [1], the focus of much academic and industrial research has been directed towards solid phase organic synthesis (SPOS) [2]. Conducting chemistry on molecules covalently bound to an insoluble polymeric resin has accessed large numbers of individual compounds for the potential use in drug lead discovery and optimisation. However, an inherent problem with the use of polymers in synthesis is their questionable compatibility with many reagents and reaction conditions. We sought to design a system which would combine the versatility of solution phase synthesis (homogeneous phase) with the ease of purification afforded by SPOS (heterogeneous phase).

The affinity of tetrabenzo[*a,c,g,i*]fluorene (Tbf), **1**, for charcoal has been utilised in the purification of peptides and proteins [3] and DNA [4] at Edinburgh. In general, the choice of solvent will influence the adsorption-desorption equilibrium [5] (Figure 1). It was proposed that a similar protocol be developed for general organic synthesis.

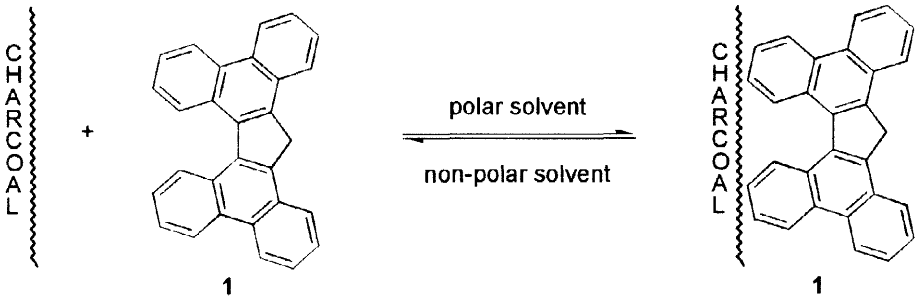

Figure 1.

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Organic compounds, covalently bound to Tbf *via* a suitable linker group could be reacted using traditional solution phase chemistry and the product purified by exploiting the affinity of the Tbf group for charcoal. Non-Tbf-bound compounds can be removed in the filtrate. As no covalent bonds are formed with the support, this may be described as a *pseudo*-solid phase purification step, and recovery of Tbf-bound product can be achieved by simple desorption from the carbon. The compound is then ready for the next synthetic step. Methodology was first developed (Figure 2) incorporating the Tbf-group for the solution synthesis of the antibacterial agent Ciprofloxacin,® **2**, which has been the subject of more conventional SPOS [6].

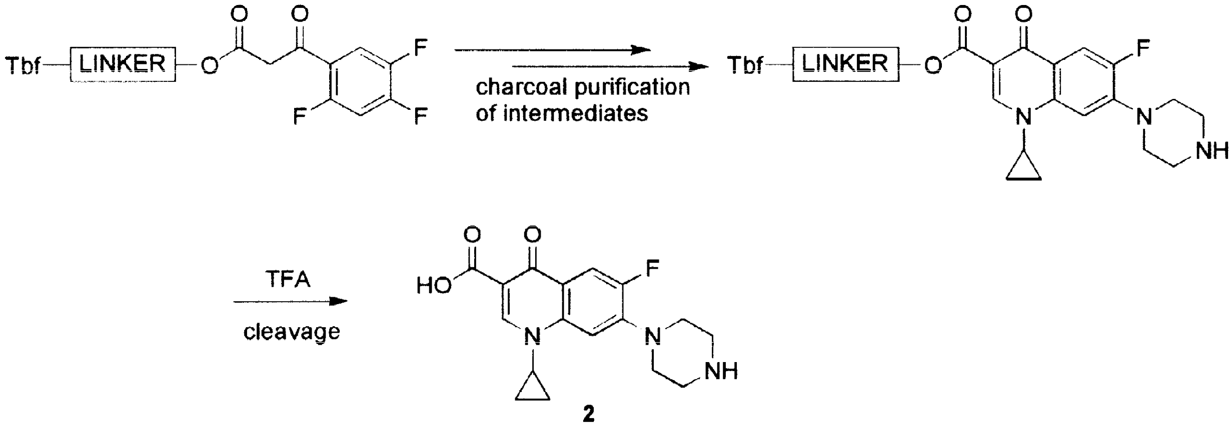

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Figure 2.

Successful synthesis of a suitable anchor group, **3** (Figure 3), was achieved in good yield following an established procedure [7]. The linker group was designed to possess suitable benzyl alcohol functionality to permit binding to a precursor in the quinolone synthesis and also include *para*-alkoxy functionality to allow TFA-cleavage of the final product from the anchor system in a manner analogous to Wang resin [8].

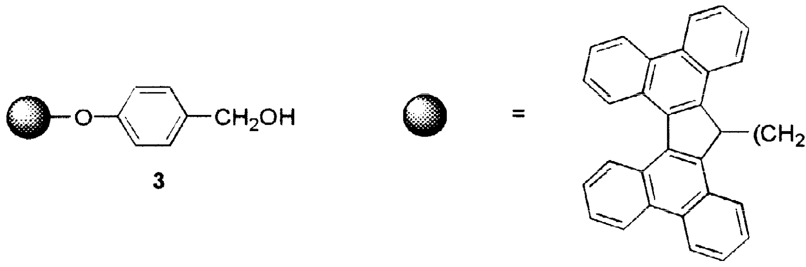

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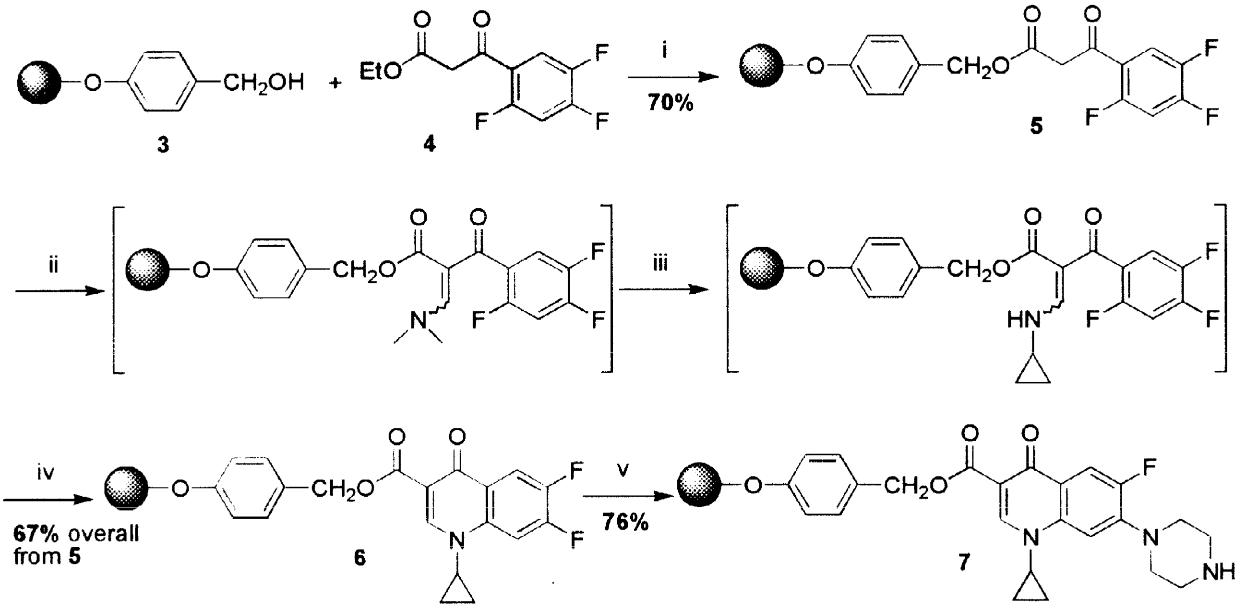
Figure 3.

Tbf-bound Ciprofloxacin,® 7, was synthesised in solution phase with traditional work-up and chromatographic purification in order to optimise reaction conditions (Figure 4). The quinolone precursor, β-ketoester, **4**, was synthesised [9] and bound to the anchor group, **3**, *via* a transesterification reaction. One-pot enamide formation [10], transamination and base cyclisation, yielded the Tbf-bound quinolone, **6**. Synthesis of 7 was completed by nucleophilic aromatic substitution with piperazine.



(i) cat. DMAP, toluene, reflux, 40h; (ii) $(CH_3)_2NCH(OCH_3)_2$, 6eq., THF, rt., 24h; (iii) cyclopropylamine, 12eq., THF, rt., 20h; (iv) tetramethylguanidine, THF, 20eq., reflux, 20h; (v) piperazine, pyridine, reflux, 6h.

Figure 4.

Extensive studies of the factors influencing the adsorption-desorption equilibrium of pure Tbf-bound compounds with charcoal developed those conditions which yielded the greatest recovery of material. Analysis by ultraviolet (UV) spectrometry (364nm) indicated that adsorption of the substrate onto charcoal was quantitative using DCM/methanol (3:2) as the polar solvent. Isolating the carbon residue by centrifugation and stirring in toluene at 40°C afforded desorption of Tbf-bound compounds with a recovery in excess of 80% by UV (Figure 5).

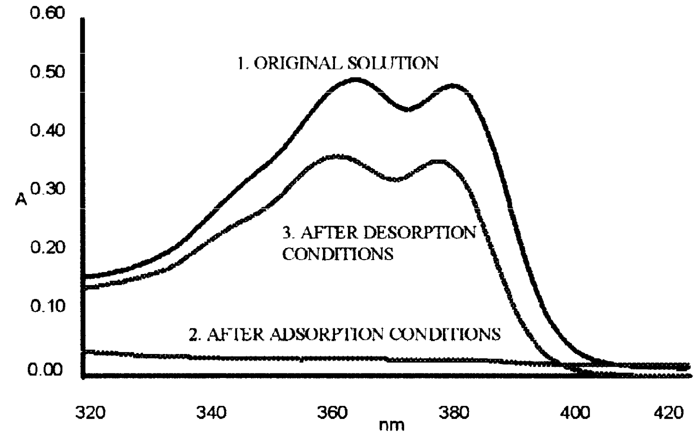
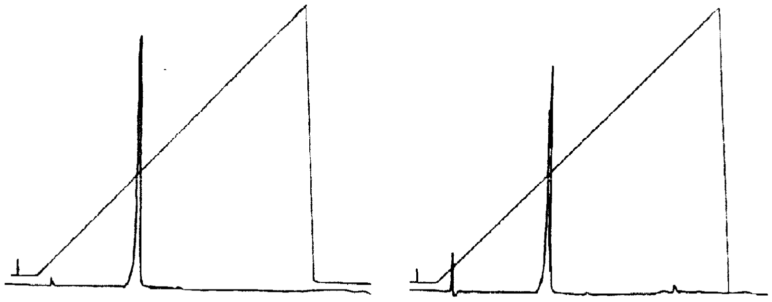


Figure 5

Of crucial importance to the success of this procedure was the quantity of charcoal used for adsorption. It was observed that addition of charcoal in excess of 1g/0.1mmol Tbf-compound reduced the recovery of material after the desorption step. It was reasoned that this may be due to undesired adsorption processes occurring as larger quantities of charcoal were added. Recovery of Tbf-bound material was enhanced by pre-washing the charcoal with toluene, possibly preventing excessive adsorption occurring.

The reproducible protocol for recovering pure Tbf-compound adsorbed onto charcoal was tested as a purification method by trials on crude samples of compounds **5** and **6**. Solution phase synthesis of these compounds was performed as normal, but instead of traditional work-up and purification, the crude residue was subjected to the described charcoal protocol. The excellent selectivity of the procedure was confirmed by TLC which indicated that only Tbf-compounds were recovered and no other reagents were present in the toluene washings. In order to compare directly the efficiency of the process with traditional methods, chromatography was performed to isolate the desired compound (*e.g.* from unreacted starting material). The new purification protocol compared highly favourably with traditional methods and furnished **5** and **6** in 60% and 59% respectively (70% and 67% by normal work-up and chromatography).

The synthesis and isolation of Ciprofloxacin® **2**, was completed using a similar procedure. After adsorption of **7** onto charcoal from the crude mixture, cleavage of the quinolone from the Tbf-anchor group with 90% aqueous TFA in DCM yielded the desired product in 57% yield from **6**. This was observed to be >95 % pure by reverse phase HPLC (Figure 6).



Manufacturer's sample *Tbf-cleaved sample*

Figure 6.

The successful synthesis of Ciprofloxacin® **2**, has shown that traditional solution phase synthesis can be performed efficiently on molecules covalently bound to a Tbf anchor group. More importantly, however, the high affinity of Tbf for charcoal has enabled a *pseudo*-solid phase purification protocol of organic molecules to be developed. This has allowed us to take maximum advantage of solution phase chemistry whilst also capturing the undoubted benefits which heterogeneous purification methods afford. Furthermore, it is envisaged that this technique will make a valuable contribution to the multiple parallel synthesis of arrays of compounds.

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