Observations on the reactivity of pentafluorophenyl sulfonate esters†

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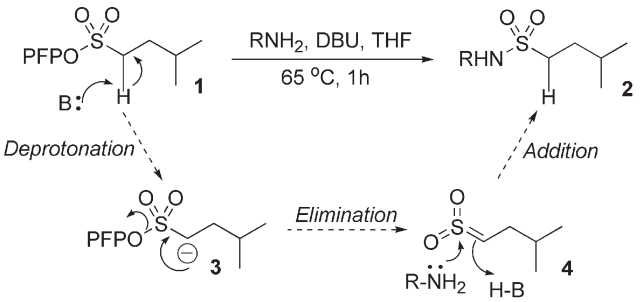
Studies on displacement reactions of alkyl pentafluorophenyl (PFP) sulfonates with amines are consistent with a mechanism involving an elimination-addition pathway; comparisons between the reactivity of PFP-sulfonates with sulfonyl chlorides and PFP-sulfonates with PFP-esters are also presented.

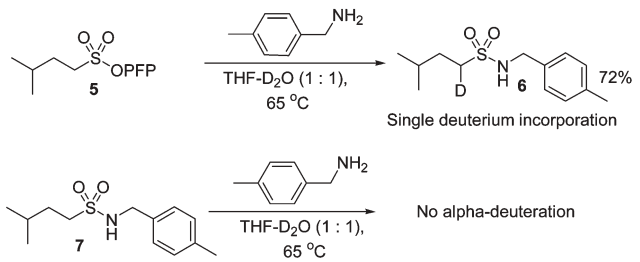
The sulfonamide structural motif is widely found in molecules of medicinal interest, particularly anti-bacterial agents.[1] More recently the observation that the sulfonamides can act as transition state mimetics of peptide hydrolysis and irreversible inhibitors of cysteine proteases has had a dramatic impact on the potential applications of this functional group in medicinal chemistry.[2] In recent years we have introduced the pentafluorophenyl (PFP) sulfonate ester as a new functional group for the synthesis of sulfonamides.[3] In particular, the advantages of 'shelf stability' and easy purification have led us to suggest PFP sulfonates as potential replacements for the corresponding sulfonyl chlorides.[4] We herein report significant new observations and applications which further support the proposition that sulfonyl chlorides may eventually be replaced by PFP-sulfonates. These new results enhance our understanding of the reactivity of this novel functional group and enable us to gauge its comparative reactivity with reference to sulfonyl chlorides.

In our early work on the synthesis of functionalised PFP sulfonates *via* free-radical chemistry, we were somewhat surprised by the stability of alkyl PFP sulfonates to acidic and basic work-up conditions and their resistance to undergoing aminolysis at low temperatures. It was observed that although alkylsulfonyl chlorides react with nucleophilic amines at 0 °C, the analogous alkyl PFP sulfonates were inert to such conditions. However, when heated to temperatures above 65 °C in a suitable solvent with a strong base such as DBU, reaction of PFP-sulfonates with a variety of amines (including primary, secondary, heterocyclic and amino acid derivatives) proceeded smoothly to give the sulfonamide in excellent yields.[3] The apparent requirement for DBU in the reactions of PFP-sulfonates suggested that the reaction might be proceeding *via* a sulfene intermediate, as is known to operate for alkyl sulfonyl chlorides (Scheme 1).[5]

In support of this mechanism we observed that exposure of the PFP sulfonate **5** to 4-methylbenzylamine in THF–D_2O led to the isolation of **6**, a product containing one deuterium atom at the α-position as compared to the anhydrous reaction (Scheme 2). In order to demonstrate that deuteration was occurring prior to sulfonamide formation, a sample of the unlabelled sulfonamide **7** was exposed to identical conditions as for the displacement reaction. In this case, no deuterium incorporation was observed, strongly suggesting the operation of the elimination–addition mechanism outlined above (Scheme 1).



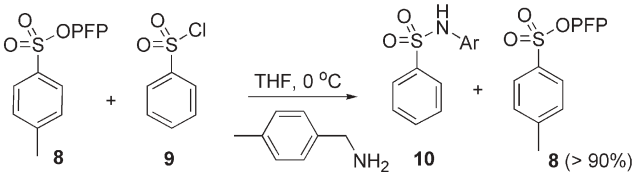
Scheme 1



Scheme 2

Having established a likely mechanistic pathway, we then compared the reactivity of the PFP sulfonate esters and their sulfonyl chloride counterparts. Our first approach to this was to establish if an amine would react preferentially with either a PFP sulfonate ester or a sulfonyl chloride. We therefore examined the reaction of one equivalent of a simple primary amine (4-methylbenzylamine) with a mixture of benzenesulfonyl chloride and *p*-toluenepentafluorophenyl sulfonate (Scheme 3). We observed that this reaction gave solely the product **10**, derived only from reaction with the sulfonyl chloride **9**. The PFP sulfonate ester **8** was recovered in near quantitative yield.

It is clear from these experiments that PFP sulfonates, both alkyl and aryl, are significantly less reactive than the comparable



Scheme 3

† Electronic supplementary information (ESI) available: experimental details for the mechanistic studies. See http://www.rsc.org/suppdata/cc/b5/b501212k/

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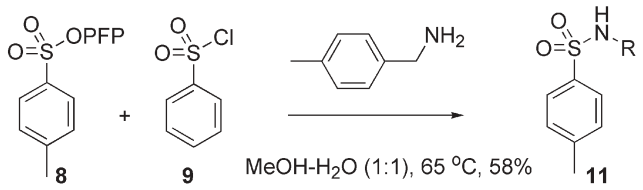
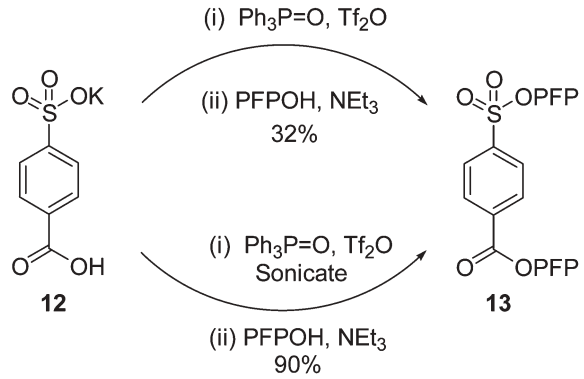


Scheme 4



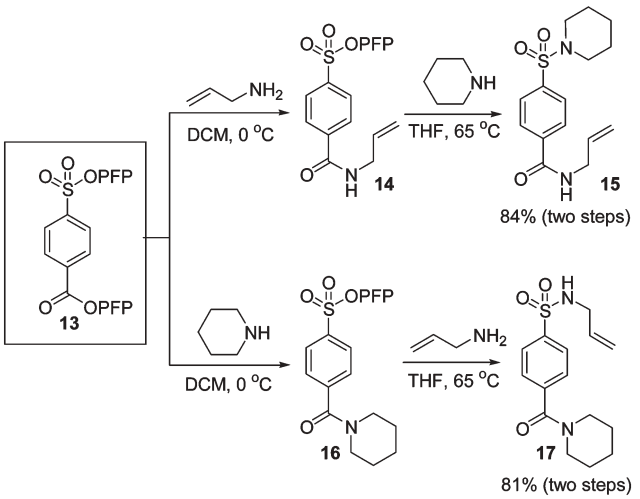
Scheme 5

sulfonyl chlorides. This feature along with our previous observations regarding stability led us to explore the possibility that PFP sulfonates might be employed under reaction conditions that were not compatible with sulfonyl chlorides. Our first approach to this focused on the possibility of carrying out reactions in aqueous media. Thus, a representative sulfonyl chloride (benzenesulfonyl chloride) was mixed with a comparable PFP sulfonate ester (*para*-toluenepentafluorophenyl sulfonate, PFP tosylate) in an aqueous medium. Addition of one equivalent of a primary amine (4-methylbenzylamine) led to the isolation of the sulfonamide **11** derived from the reaction of PFP tosylate **8** with the amine. None of the product corresponding to reaction with benzenesulfonyl chloride was observed (Scheme 4). Presumably, the sulfonyl chloride **9** is hydrolysed rapidly under the reaction conditions.

The utility of PFP esters in the coupling of carboxylic acids and amines or alcohols is well documented and known to be a facile process even at low temperatures.[6] We therefore wished to compare the reactivity of a PFP sulfonate and a PFP carboxylate in a substrate that would demonstrate the synthetic utility of their differing reactivities.

In order to carry out such a comparison we prepared the bis-PFP derivative **13** from **12** and our recently described coupling protocol[4] (triphenylphosphine ditriflate/pentafluorophenol) (Scheme 5). It was noted that in this case, and in other cases where poor solubility in DCM is a problem, sonication can be used to enhance the solubility and reduce reaction times.[7,8]

Addition of 1 equiv. of allylamine to the bis-PFP ester **13** at 0 °C led to amide **14** formation exclusively. Subsequent addition of piperidine and heating of the mixture to 65 °C led to the sulfonamide **15** in excellent yield (Scheme 6). Inverse addition of the two amines in this protocol leads to the products **16** and then **17**. Any of the four products is readily isolated and purified by recrystallisation or column chromatography. It is notable that even



Scheme 6

employing an excess of amine (5 equiv.) at 0 °C in the first step, the reaction is chemoselective and leads only to the product derived from the reaction of the PFP-ester.

The exquisite chemoselectivity observed here offers excellent opportunities for diversity-oriented organic synthesis.

In summary we have shown that PFP-sulfonates are versatile intermediates for the synthesis of sulfonamides under mild conditions. The comparative studies presented in this paper highlight the potential benefit of using PFP-sulfonates as opposed to sulfonyl chlorides.

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