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Rate enhancement of PFP sulfonate ester aminolysis by chloride salts in organic and aqueous media

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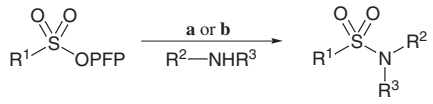
Abstract—We report here, a method of accelerating the rate of aminolysis of PFP sulfonates to yield sulfonamides using tetrabutylammonium salts. We have previously explored the utility of employing PFP sulfonates in the formation of sulfonamides; however we demonstrate here the advantages of combining the existing methodology with a revised protocol which allows the diversity within both the sulfonate ester and the amine to be extended.

Employing pentafluorophenyl (PFP) esters as replacements for sulfonyl chlorides in the synthesis of alkyl, aromatic and heteroaromatic sulfonamides[1] is becoming increasingly important in diversity orientated synthesis due to their increased shelf-life, aqueous stability and predictable reactivity towards nucleophiles.[2,3] Recently, we have also described a novel coupling procedure for the preparation of these compounds from sulfonic acids.[4] In most cases, a PFP sulfonate on conventional heating or under microwave irradiation reacts smoothly with amines to yield the corresponding sulfonamide (Scheme 1).[5]

During ongoing investigations in our laboratory however, we have noticed that certain examples, most notably aryl PFP sulfonates bearing electron donating groups and sterically hindered amines, react more slowly and often require increased temperatures. We wish to address this problem to improve the scope of the reaction and to make our procedure more amenable to parallel synthesis.



Scheme 1. Reagents and conditions: (a) 85 °C, THF or DMF, NEt_3, MW, 1 h; (b) 65 °C, THF, NEt_3, 1–3 h.

We envisaged that a nucleophilic catalyst such as 4-(dimethylamino)pyridine (DMAP), commonly employed in the activation of carboxylic acid chlorides and anhydrides may have the desired effect.[6] However, when we applied this familiar methodology to the reaction of PFP sulfonates, no acceleration in rate was observed and the reaction was often accompanied by decomposition products in addition to the desired sulfonamides. We reasoned that the sulfonate unit, being such a hard centre would react only slowly with a neutral nucleophile such as DMAP and that a hard nucleophile would be a more suitable choice as a nucleophilic catalyst.

We envisaged that a halide anion may be a more appropriate catalyst for the reaction by generating the corresponding sulfonyl halide in situ. We therefore embarked on initial studies to determine which halide might enhance the rate of a typical displacement reaction. We first chose to examine the reaction of hexylamine with pentafluorophenyl-*p*-toluenesulfonate (Scheme 2) using chloroform as the solvent, since this is a reaction that is known to proceed relatively slowly (8–10 h at reflux, 61 °C) and therefore an acceleration in rate would be easily measured. We chose as the source of halide anions the appropriate

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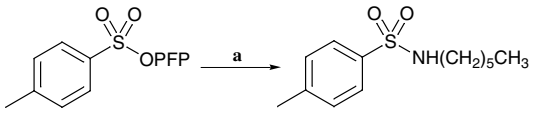


Scheme 2. Reagents and conditions: (a) hexylamine (2.5 equiv), $CHCl_3$, 61 °C, 10 h, 95%.

Table 1. Selection of nucleophilic halide catalyst for the acceleration of aminolysis of PFP sulfonate esters

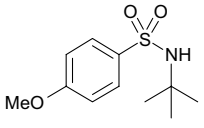
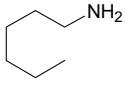
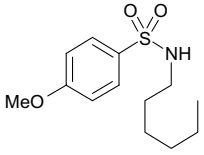
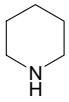
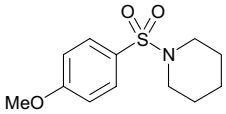
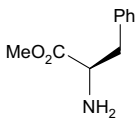
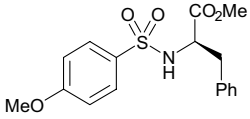
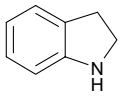
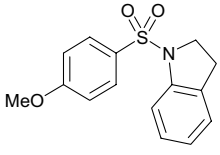
Entry	Additive	Equiv's	Time for 100% conversion	Yield (%)
1	None	—	10 h	85
2	Bu_4NF	1.0	—	—
3	Bu_4NCl	1.0	75 min	94
4	Bu_4NCl	0.1	6.5 h	89
5	Bu_4NBr	1.0	5.5 h	91
6	Bu_4NBr	0.1	9.5 h	88
7	Bu_4NI	1.0	12 h	84
8	Et_3NBnCl	1.0	80 min	90

tetra-*n*-butylammonium salts due to their high solubility in organic solvents.[7] The results of our investigations are outlined in Table 1.

Clearly, the addition of halide salts has a marked impact on the rate of the reaction. It is evident that the greatest enhancement in rate is achieved by the addition of one equivalent of a suitably soluble chloride source (in the case of fluoride, only decomposition products are observed). In contrast to the familiar Finkelstein reaction, commonplace in organic chemistry, the addition of iodide appears to have no beneficial effect on the reaction and may even inhibit the formation of the sulfonamide.[8] Addition of an alternative chloride source (entry 8) leads essentially to the same result as obtained in entry 3 and gives further evidence for our hypothesis that the cation plays no significant role in the rate acceleration.

We rationalise this observation by consideration of the relative hardness of the sulfonate centre and the attacking nucleophilic catalyst. The SO_3PFP motif is a hard electrophile and will therefore be attacked most rapidly by a hard nucleophile. The hardest of the halide nucleophiles (excluding fluoride) is chloride and therefore the rate of attack of this nucleophile will be the greatest of all of the halides. Once formed, the sulfonyl chloride is then free to react with a molecule of amine, a known facile process. Thus, despite sulfonyl bromides and iodides

Table 2. Reaction of amines with PFP-*p*-methoxybenzenesulfonate in the absence and presence of chloride anion

Entry	Amine	Reaction time (a) no additive (b) 1.5 equiv Bu_4NCl		Product and yield
		(a)	(b)	
1		>7 days	7.5 h	 a. 67%[a] b. 89%
2		45 min	5 min	 a. 91% b. 96%
3		55 min	10 min	 a. 88% b. 85%
4		1.5 h	25 min	 a. 77% b. 75%
5		>7 days	13 h	 a. 38%[a] b. 84%

[a] Reaction incomplete after 7 days.

being (presumably) more reactive than their chloride counterparts, the rate of their formation from the PFP sulfonate and iodide or bromide renders the addition of these salts ineffective as nucleophilic catalysts for this reaction.

Following our identification of a potential nucleophilic catalyst, we were keen to demonstrate its effectiveness in a number of reactions with reference to the reactions without additives. We were particularly keen to demonstrate its effectiveness in the reaction of electron rich aryl PFP sulfonates (known to be significantly less reactive than their electron poor counterparts and even less reactive than alkyl PFP sulfonates) and amines which have reduced nucleophilicity, either due to steric hindrance or due to delocalisation (e.g., anilines). We chose therefore to examine the reaction of pentafluorophenyl-*p*-methoxybenzenesulfonate with a number of amines. DMF was chosen as the solvent due to the enhancement in rate above many other solvents as we have previously noted.[5,9] The results are outlined in Table 2.

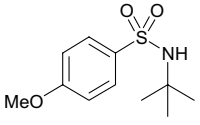
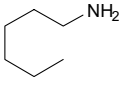
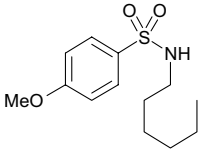
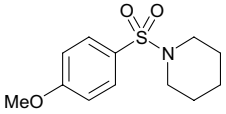
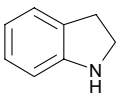
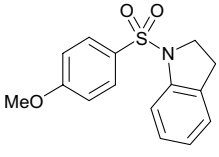
We were pleased to observe that in all cases, addition of 1.5 equiv of tetrabutylammonium chloride resulted in a significant increase in the rate of the displacement reaction. We were particularly gratified to observe that even amines of a lower nucleophilicity such as anilines (entry 5) and hindered examples (entry 1) could be successfully employed whereas previously, the low reactivity of both the amine and the electron rich PFP sulfonate would have led to prohibitively long reaction times and most probably decomposition of the starting materials.

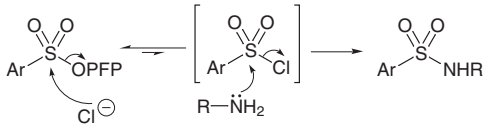
Presumably, the reaction mechanism proceeds via nucleophilic attack of chloride at the sulfonate centre leading to the more reactive sulfonyl chloride in situ. We were concerned that this method of accelerating the reaction would prohibit the application of these PFP sulfonates and amines in aqueous media, one of the many advantages of employing PFP sulfonates as replacements for sulfonyl chlorides that we have previously reported.[10] We therefore embarked on experiments that would demonstrate the scope of the chloride accelerated procedure with aqueous solvent mixtures. Reaction of PFP-*p*-methoxybenzenesulfonate with amines in a 25% water–THF or DMF mixture (to ensure solubility of the PFP sulfonate) in the presence of one equivalent of tetrabutylammonium chloride at 65 °C, gave the results outlined in Table 3.

Although sulfonyl chlorides have previously been utilised in aqueous systems,[11] it is often the case that for a homogeneous system, under basic conditions, hydrolysis of the sulfonyl chloride and major reduction in yields is often observed as we have previously noted.[10] We were therefore surprised to observe that the addition of water to the reaction medium had no detrimental effect on either the reaction rate or yield, in particular for those examples that require several hours (Table 3, entries 1 and 4). In fact, addition of water may accelerate the reaction in some cases. This is probably due to an increase in solvent polarity under aqueous conditions.

It is interesting to note that although the sulfonyl chloride is likely to be generated in situ, this species is not observed by TLC analysis of the reaction mixture at

Table 3. Bu_4NCl promoted reaction of amines with PFP-*p*-methoxybenzenesulfonate in 25% aqueous THF

Entry	Amine	Reaction time	Product and yield
1		7 h	 85%
2		5 min	 90%
3		5 min	 92%
4		14.5 h	 92%



Scheme 3. Mode of action of chloride ion in the acceleration of sulfonamide formation in PFP sulfonates.

any point. This suggests strongly (as may be expected) that the putative sulfonyl chloride is formed only in very low concentrations at equilibrium. Rapid irreversible reaction of this species with amine then removes it from the equilibrium and ensures the reaction proceeds to completion (Scheme 3). This protocol therefore combines the reactivity of sulfonyl chlorides with the stability and ease of handling of PFP sulfonates that we have previously noted,[2] as a useful method of sulfonamide formation under these conditions.

In conclusion, we have described a protocol that extends the scope of both amines and PFP sulfonates in the formation of sulfonamides. We have demonstrated that less reactive PFP sulfonates can exhibit enhanced reactivity towards amines by the addition of a chloride ion source. We have shown that a normally unreactive PFP sulfonate (PFP-*p*-methoxybenzenesulfonate) can be reacted with a variety of amines, including less nucleophilic examples (i.e., anilines and sterically hindered examples) in excellent yields and with dramatic rate enhancements. We have also demonstrated that the revised protocol is tolerant to aqueous reaction conditions without any significant loss in efficiency.

Acknowledgements

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11. For a recent example see: Sdira, S. B.; Felix, C. P.; Giudicelli, M.-B. A.; Seigle-Ferrand, P. F.; Perrin, M.; Lamartine, R. J. *J. Org. Chem.* **2003**, *68*, 6632–6638.