Trichlorophenol (TCP) sulfonate esters: A selective alternative to pentafluorophenol (PFP) esters and sulfonyl chlorides for the preparation of sulfonamides†

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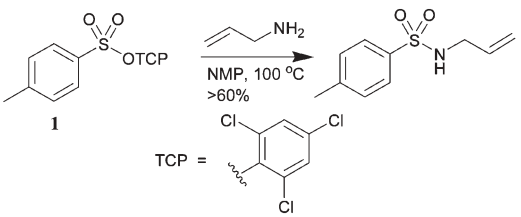
2,4,6-Trichlorophenol (TCP) sulfonate esters undergo effective aminolysis under conventional heating and microwave irradiation; the reactivity of these species is such that chemoselective transformations of PFP sulfonate esters can be achieved.

We have described in detail the applicability of pentafluorophenol (PFP) sulfonates as replacements for sulfonyl chlorides[1] in the formation of sulfonamides, which are extremely important antibacterial agents[2] and a valuable structural motif in medicinal chemistry.[3–6] In particular, the ease of handling of PFP sulfonates and their tolerance to a wide range of reaction conditions has proved particularly attractive.[7] There is, however, a degree of resistance to the use of PFP-activated esters on a large and general scale. Some are reluctant to utilise polyfluorinated aromatics, since they perceive them to be toxic. Other potential barriers include the high cost of pentafluorophenol, which renders it uneconomic as a potential replacement for the much cheaper sulfonyl chlorides. Here we report our progress in developing alternatives to PFP sulfonates and sulfonyl chlorides, in order to address the limitations of these species, while retaining the benefits of sulfonate esters that we have previously noted.[7]

We wished to explore the applicability of other phenols, which might act as acceptable leaving groups for the aminolysis reaction while giving stable intermediate compounds. 2,4,6-Trichlorophenol (TCP) presented itself to us as an ideal candidate due to its known lower toxicity (currently marketed as a household antiseptic agent in the UK) and its low cost. Keen to establish the reactivity of a TCP sulfonate ester and to compare its reactivity with our established methodology, we prepared TCP ester **1** (Scheme 1). Initial experiments indicated that amine displacement was a possibility and thus further work was warranted.



Scheme 1 Sulfonamide formation from TCP sulfonate esters.

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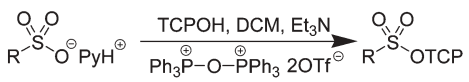
Initially, we required a route to TCP esters that did not employ the sulfonyl chloride or similar activated species as an intermediate.[8] We were keen to test our previously established methodology, utilising the coupling reagent triphenylphosphine ditriflate for this purpose.[9] Indeed, we successfully employed the reagent in the formation of a variety of TCP sulfonate esters in good yields. The results of a preliminary study are presented in Table 1.

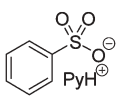
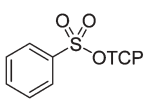
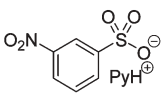
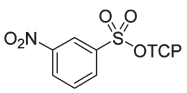
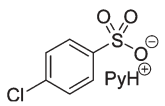
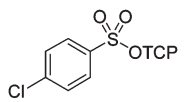
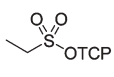
With a range of TCP sulfonate esters in hand, we were now in a position to investigate their reactions with amines and to assess the relative merits of this method in comparison to the analogous reactions of PFP sulfonates. As outlined earlier, aminolysis of TCP esters had been effected under conventional heating conditions. We were keen to develop a microwave (MW) protocol for this reaction, building on our previous work in this area.[10] Our first task was therefore to compare the thermal and MW reactions.

We observed that the MW-assisted aminolysis of two electron-rich aryl TCP sulfonates proceeded at a faster rate than the comparable reaction under conventional heating. This is notable because we have found that such sulfonates are particularly resistant to such aminolysis reactions. Our findings are presented in Table 2.

Having established that MW irradiation was at least as effective and potentially superior to conventional heating, we set about searching for the optimal MW conditions that would give the best

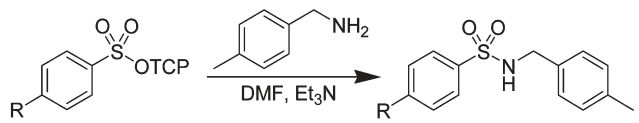
Table 1 TCP ester synthesis employing triphenylphosphine ditriflate

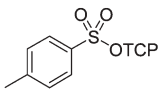
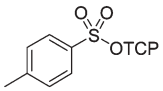
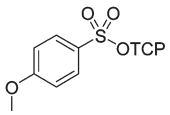
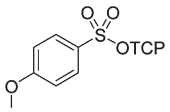


Entry	Sulfonic acid	Product	Yield (%)[a]
1			78
2			74
3			80
4			65

[a] Isolated yields.

Table 2 Thermal *vs.* MW aminolysis reactions of TCP sulfonate esters



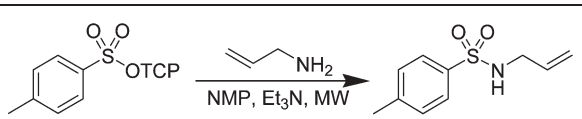
Entry	Sulfonate ester	Method	Temp./°C	Time/h	Yield (%)[a]
1		Thermal	85	4.5	51
2		MW	85	1.0	68
3		Thermal	85	6.0	66
4		MW	85	1.0	65

[a] Isolated yields.

yields in the shortest reaction time. Our first findings indicated that, although DMF was an excellent solvent for the aminolysis reaction, yields could often be compromised by the liberation and further reaction of dimethylamine at elevated temperatures. In view of this, we elected to employ *N*-methylpyrrolidone (NMP) as the solvent for the aminolysis reaction due to its similar properties to DMF, but without the propensity to liberate dimethylamine at elevated temperatures.[11] Following this change, we embarked upon a series of experiments to establish the optimum conditions for aminolysis. The reaction between TCP tosylate and allylamine was chosen, and the results are presented in Table 3.

Having established an optimal set of reaction conditions for the reaction between TCP tosylate and allylamine, we were keen to expand the scope of these conditions and see if they would prove equally successful with a range of other amines. We therefore examined the reaction of a number of amines with a variety of TCP sulfonate esters under the optimised conditions. Our results are shown in Table 4.

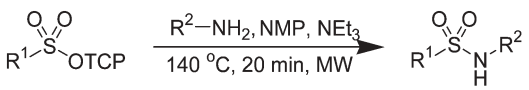
Table 3 Optimisation of the MW-mediated aminolysis reaction of TCP tosylate

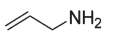
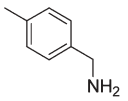
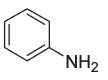
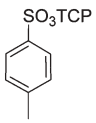
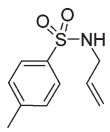
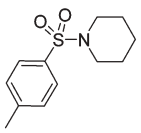
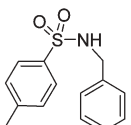
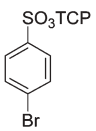
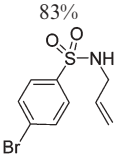
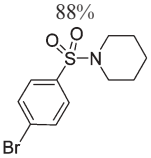
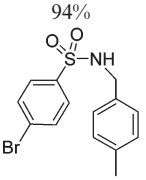
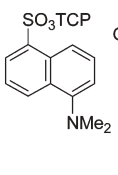
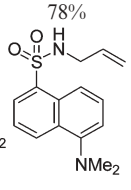
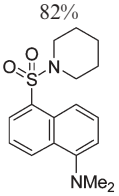
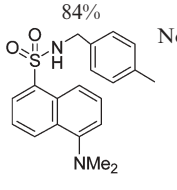


Entry	Temp./°C	Solvent	Time/min	Yield (%)[a]
1	85	DMF	60	56
2	85	NMP	60	50
3	140	NMP	60	83
4	140	NMP	20	91
5	140	NMP	10	83

[a] Isolated yields.

Table 4 Reaction of TCP sulfonate esters with various amines[a]

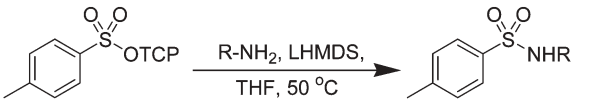


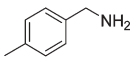
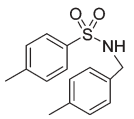
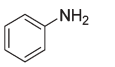
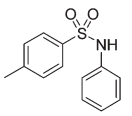
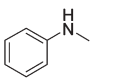
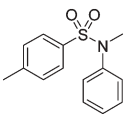
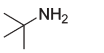
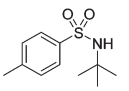
TCP ester	Amine			
				
				No reaction
	83%	88%	94%	
				No reaction
	78%	82%	84%	
				No reaction
	77%	89%	91%	

[a] Isolated yields.

Our investigations suggested that the conditions established in Table 3 as being those most favourable for sulfonamide formation only hold true when the amine is a simple aliphatic species and relatively nucleophilic. Those amines with lowered nucleophilicity, such as anilines (as demonstrated in Table 4), appear to require alternative reaction conditions to undergo efficient reaction with the sulfonate esters, and this is consistent with our previous experience with PFP sulfonate esters. We therefore embarked on studies to establish conditions that would be suitable for efficient aminolysis of TCP sulfonates with lower nucleophilicity amines, such as anilines. Extensive studies in our laboratory, employing various MW power input levels, reaction times, solvents and catalysts (primarily chloride ion),[12] failed to yield satisfactory results; the product in each case being obtained in either low yield or contaminated with significant quantities of decomposition material resulting from the prohibitively high temperatures required to drive the reaction to completion. It occurred to us that substituting triethylamine for a stronger base may assist the reaction by deprotonation of the aniline prior to displacement. We chose to employ lithium hexamethyldisilazide (LHMDS) as the base with a variety of both anilines and aliphatic amines. We observed that good yields of the corresponding sulfonamides could be obtained in most cases without excessive reaction times and under conventional heating at 50 °C. Table 5 presents our findings. The success obtained with anilines (Table 5, entries 4 and 5) is particularly notable, as we have previously found that these tend

Table 5 LHMDS as a base for sulfonamide formation



Entry	Amine	Product	Time/h	Yield (%)[a]
1			4.0	72
2			4.0	78
3			6.0	92
4			18	75

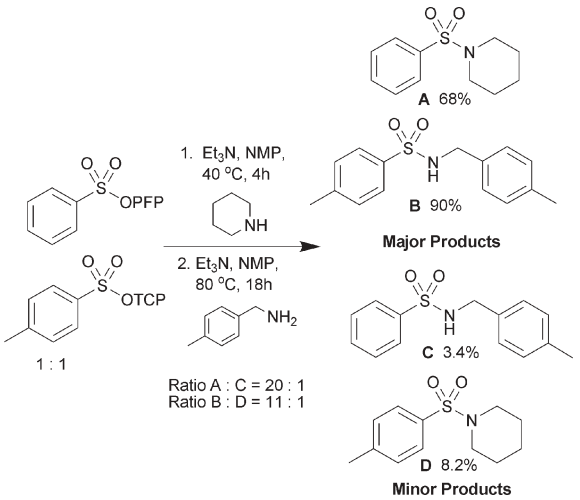
[a] Isolated yields.

to be challenging substrates for sulfonamide formation. Most significantly, however, was our finding that employing LHMDS gave superior results in the formation of sulfonamides from hindered amines such as *tert*-butylamine, an example that we have previously noted to be inefficient due to the extreme levels of steric encumbrance. We envisaged that this alternative protocol would therefore be suitable for less nucleophilic amines such as anilines, nucleophilic species, and more sensitive substrates where higher temperatures are undesirable. The results of this study are outlined in Table 5.

Having identified reaction conditions for the formation of sulfonamides from TCP sulfonates with a variety of amines, including the less nucleophilic and more challenging hindered examples, we wished to continue and compare their reactivity with PFP sulfonates, with a view to exploiting their differing reactivity in selective sulfonamide formation.

In order to measure the level of selectivity that could be obtained between a PFP sulfonate and a TCP sulfonate in a simple aminolysis reaction, we took an equimolar solution of PFP benzene sulfonate and TCP tosylate and sequentially exposed them to amines under different reaction conditions. Gratifyingly, we observed that the products obtained from the reaction at low temperatures were almost exclusively those derived from the PFP sulfonate. The TCP sulfonate could be isolated at this point, or, upon exposure to another amine at higher temperatures, could then, in turn, be converted smoothly to the sulfonamide in good yields. A representative example is given in Scheme 2.

In conclusion, we have described the synthesis and utility of a new class of activated sulfonate ester that can be employed successfully in the synthesis of sulfonamides. In addition to this, we have identified suitable reaction conditions that are successful for both simple nucleophilic amines and more challenging examples, such as anilines or hindered amines.



Scheme 2 Selective sulfonamide formation from TCP sulfonate esters and PFP sulfonate esters.

We have also demonstrated how the differing reactivity of these two classes of compound can be exploited in selective sulfonamide formation.

Finally, we have addressed the issues of cost associated with pentafluorophenol, in that trichlorophenol is at least ten times as cheap.[13] The perceived problems with polyfluorinated aromatics can also be circumvented by the use of TCP sulfonate esters in sulfonamide formation.

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Notes and references

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