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Direct Synthesis of Sulfonamides and Activated Sulfonate Esters from Sulfonic Acids

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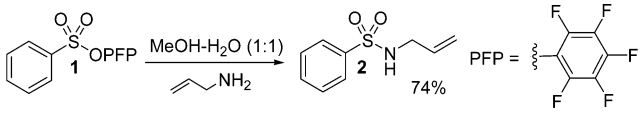
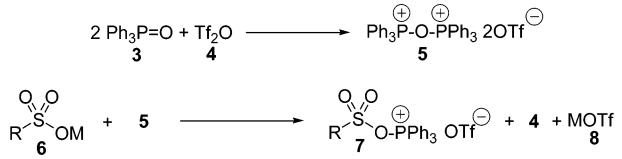
The importance of the sulfonamide unit in medicinal chemistry cannot be overstated.[1,2] This functional group constitutes the largest class of antimicrobial agents and has been shown to be a transition state mimetic of peptide hydrolysis and, in particular, as the critical motif for potent, irreversible inhibitors of cysteine proteases.[3−5] To date, the generation of sulfonamides has almost exclusively relied on the synthesis of sulfonyl chlorides that then undergo reactions with nucleophiles such as amines. As we and others have previously noted, sulfonyl chlorides do have disadvantages and they can be difficult to handle and not amenable to long-term storage.[6] In recent work, we have established the PFP-sulfonate as a shelf-stable alternative to sulfonyl chlorides. Such species undergo wide ranging reactions with amines, even under aqueous reaction conditions, to give sulfonamides in excellent yields (Scheme 1).[7]

Scheme 1. Reactivity of PFP-sulfonates in Aqueous Media



Despite the biological importance of sulfonamides, there currently exists no procedure for achieving the transformation of a sulfonic acid (or its salt) directly to a sulfonamide or sulfonate ester in one synthetic step. This is in sharp contrast to the numerous reagents and methodologies available to effect the conversion of a carboxylic acid to the corresponding amide or esters. However, our own experience matches that of others and we have been unsuccessful in applying these protocols to the coupling of sulfonic acids.[8] We herein report our results describing the first general method for the transformation of a sulfonic acid or its salt to the corresponding sulfonamide or pentafluorophenol (PFP)-activated ester.

Scheme 2. Activation of Sulfonic Acids by Triphenylphosphine Ditriflate



We reasoned that an intermediate such as **7** would be suitably activated toward nucleophiles and therefore undergo rapid reaction with amines and the PFP anion. Clearly, the driving force of this reaction would be the generation of the P═O π bond. This led us to identify the reagent triphenylphosphine ditriflate, which we anticipated would react with a sulfonate anion to generate intermediate **7** directly (Scheme 2).[9,10] We were delighted to observe that exposure of a commercially available sulfonic acid salt (pyridinium 4-toluenesulfonate) to the reagent **5** followed by either pentafluorophenol or allylamine gave the coupled products **10** or **11** in near quantitative yield (entry 1, Table 1).

Scheme 3. Sulfonate Esters and Sulfonamides from Sulfonic Acids

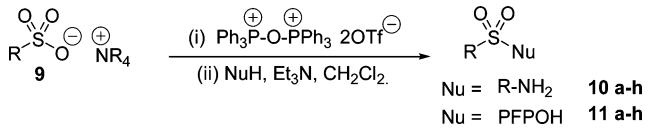
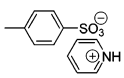
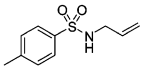
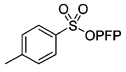
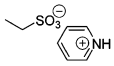
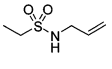
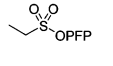
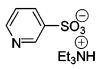
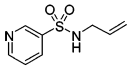
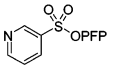
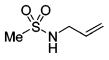
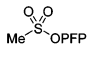
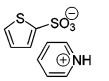
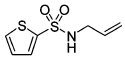
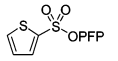
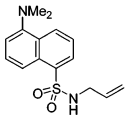
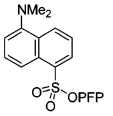
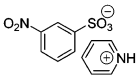
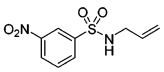
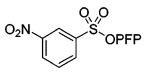
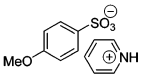
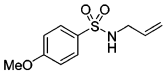
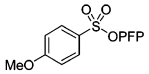


Table 1. Synthesis of PFP Sulfonate Esters and Sulfonamides

entry	sulfonic acid salt	product 10 a-h	product 11 a-h	isolated yield 10 (11) %
1				96 (98)
2				92 (82)
3				81 (74)
4				85 (77)
5				82 (76)
6				48 (52)
7				92 (94)
8				88 (74)

Keen to test the generality of our approach, we extended the range of sulfonic acid substrates in the coupling reaction.[11,12] As can be seen from Table 1, a wide range of PFP-sulfonates could be prepared using this methodology. We were also pleased to observe that amines appear to be equally applicable in the reaction. The results are outlined in Table 1.

As can be seen from Table 1, a number of functional groups are tolerant to the reaction conditions. The procedure is effective with sulfonate salts of aromatic, aliphatic, and heterocyclic substrates. It is important to note at this stage that the choice of counterion in the sulfonic acid salt is not trivial. Although metal salts of sulfonic acids appear, at least in theory, good substrates for this reaction, they are often less than ideal due to poor solubility or due to their tendency to be hygroscopic. We have found that the pyridine or

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Scheme 4. Coupling of 3-Nitrobenzene Sulfonic Acid with Amines

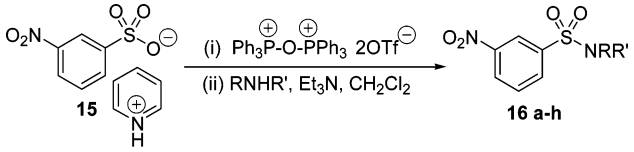
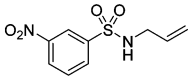
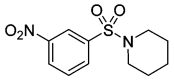
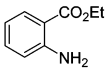
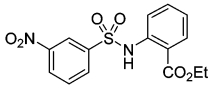
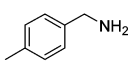
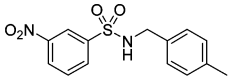
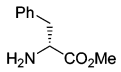
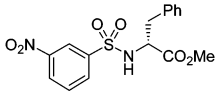
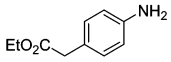
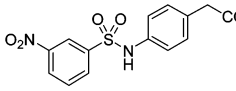


Table 2. Amine Diversity in Sulfonamide Synthesis

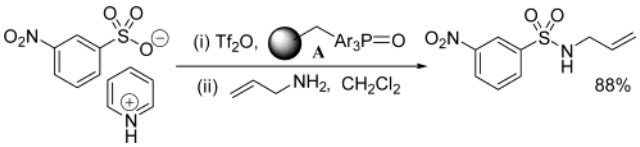
entry	*amine*	*product 16 a-h*	*isolated yield %*
1			92
2			84
3			94
4			93
5			61
7			88

triethylamine salts of sulfonic acids are often suitable substrates for this reaction since they are easily prepared from the parent acid and are not particularly hygroscopic and usually soluble in organic solvents. They are also easily purified by recrystallization (though this is often not required). In cases where solubility of these salts is particularly poor, the tetrabutylammonium salt may be employed without significant decrease in yield or reaction efficiency.

Greatly encouraged by our initial studies, we wished to demonstrate the generality of the approach to the synthesis of a diverse range of sulfonamides. We chose, in this case to examine the reaction of 3-nitrobenzene sulfonic acid pyridine salt with a number of common amines (Scheme 4). The results are outlined in Table 2. Gratifyingly, it was observed that the reaction is not limited to simple amines but enjoys success with primary, secondary, and amino acid derivatives. Even electron-deficient anilines (entry 3, Table 2) are applicable in the reaction.

It became clear to us that a phosphine oxide that could be more easily removed from the reaction medium after the coupling had taken place would greatly simplify our novel coupling protocol and may enable us to eliminate chromatography entirely from the procedure. We therefore obtained the commercially available polystyrene-supported phosphine oxide **A**. To our delight, when we substituted triphenylphosphine oxide for this analogous supported phosphine oxide, comparable yields of coupled product were obtained (Scheme 5).[13] In addition to this, purification could be achieved without the use of column chromatography, simply by filtering off the resin and then washing the filtrate with water to remove any remaining salts. We were also pleased to observe that the resin is recyclable and can be employed in another coupling reaction. No loss in efficiency was observed after 5 cycles, and

Scheme 5. Solid-Supported Phosphine Oxide: A Cleaner Alternative



providing that the resin is washed thoroughly after each cycle, no activation of the phosphine oxide is required. This observation represents a major advance in reaction efficiency since a single batch of phosphine oxide resin can be used to generate a diverse range of sulfonamides.

We have also established that, if required, the resin may be pretreated with triflic anhydride and then isolated by filtration and stored under vacuum prior to use. This modification allows excess triflic anhydride to be removed prior to the coupling reaction and is particularly noteworthy if the resin is to be utilized in a parallel fashion.

In conclusion, we have described a new synthesis of sulfonamides and activated sulfonate esters from the sulfonic acid salt using the activating agent triphenylphosphine ditriflate. The reaction has been shown to display good functional group tolerance and is high yielding. We have also demonstrated that triphenylphosphine oxide, which can be troublesome to remove at the end of the reaction, may be replaced by a solid-supported variant from which the reaction products may be removed by washing. In summary, we believe that this functional group transformation may obviate the requirement to generate and use sulfonyl chlorides for the synthesis of sulfonamides and activated sulfonate esters.

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Supporting Information Available: Characterization data for the sulfonate esters and the functionalized sulfonamides. This material is available free of charge via the Internet at http://pubs.acs.org.

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