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A New Route to Sulfonamides via Intermolecular Radical Addition to Pentafluorophenyl Vinylsulfonate and Subsequent Aminolysis

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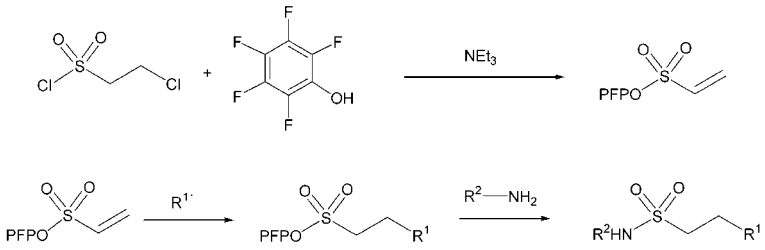
ABSTRACT

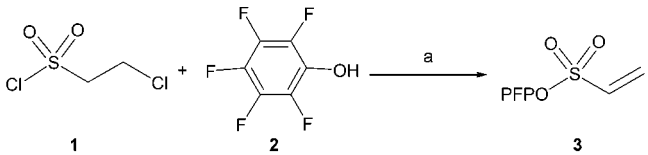


Various radical species generated from either the corresponding iodo- or bromo- compounds and tri-*n*-butyltin hydride were added in an intermolecular fashion to the activated acceptor pentafluorophenyl vinylsulfonate. The products of each reaction were then subjected to aminolysis with a variety of different amines.

Sulfonamides have long been the focus of pharmaceutical interest as a result of their potent antimicrobial and biological activity.[1] Recently, this functional group has also been identified as a transition state mimetic of peptide hydrolysis and, in particular, as the critical motif for potent, irreversible inhibitors of cysteine proteases, suggesting wider applicability to protease inhibition.[2,3] Because of the vast potential that is displayed within this class of compounds and their relative difficulty in preparation, new strategies to functionalized sulfonamides are continually being sought. We here report a new strategy for the construction of sulfonamides with structural features of potential biological interest, including amino acid and C-linked glycoside derivatives using intermolecular radical coupling methodology.[4,5]

Our approach begins with the surprisingly stable, novel, pentafluorophenyl vinylsulfonate **3**, easily prepared from commercially available pentafluorophenol **2** and 2-chloroethane-1-sulfonyl chloride **1** (Scheme 1).

Scheme 1. Synthesis of Pentafluorophenyl Vinylsulfonate



1 2 3

a. NEt_3, CH_2Cl_2, 0 °C, 59%

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(1) For a review, see: Hansch, C.; Sammes, P. G.; Taylor, J. B. *Comprehensive Medicinal Chemistry*; Pergamon Press: Oxford, 1990; Vol. 2, Chapter 7.1. For recent biological applications, see: Hanson, P. R.; Probst, D. A.; Robinson, R. E.; Yau, M. *Tetrahedron Lett.* **1999**, *40*, 476.

(2) McKerrow, J. H.; James, M. N. G.; Cysteine Proteases: Evolution, Function and Inhibitor Design. In *Perspectives in Drug Discovery and Design*; Anderson, P. S., Kenyon, G. L., Marshall, G. R., Eds.; ESCOM Science Publishers: Leiden, 1996; Vol. 6.

(3) Roush, W. R.; Gwaltney, S. L., II; Cheng, J.; Scheidt,; McKerrow, J. H.; Hansell, E. *J. Am. Chem. Soc.* **1998**, *120*, 10994.

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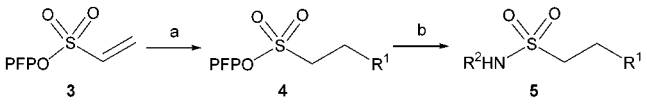
The *bifunctional* acceptor **3** is highly susceptible to attack by both radical and nucleophilic species (particularly amines) with simultaneous displacement of pentafluorophenol.[6] Therefore, by using a combination of radical and ionic chemistry, we are able to generate a diverse range of sulfonamide products (Scheme 2).

Scheme 2. Sulfonamide Synthesis from Pentafluorophenyl Vinylsulfonate[a]

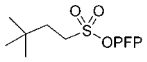
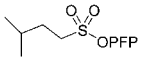
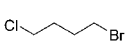
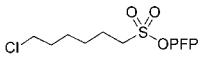
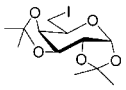
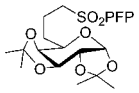
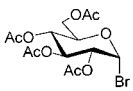
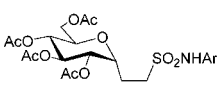
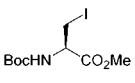
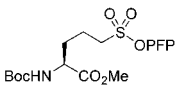
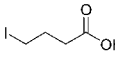
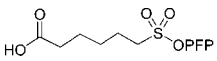


a. R_1-X, Bu_3SnH, AIBN, PhMe, 110 °C. **b.** R_2-NH_2, THF, DBU, 65 °C.

Our approach offers several advantages over traditional methods for the synthesis of sulfonamides. First, sulfonyl chlorides (traditionally used to synthesize sulfonamides) are highly reactive and often unstable species. In contrast, the pentafluorophenyl esters are stable to a variety of conditions including column chromatography and even basic workup procedures. Second, the radical reaction may be optimized prior to the introduction of functionality from the amine, therefore minimizing potential side reactions.

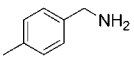
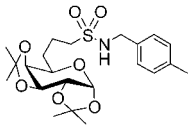
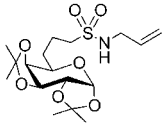
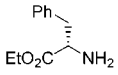
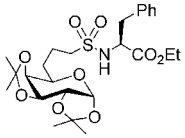
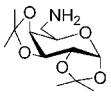
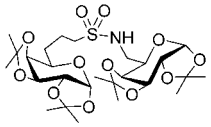
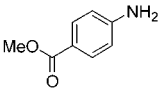
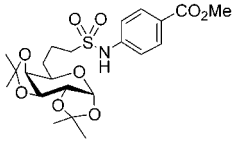
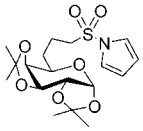
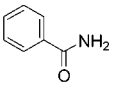
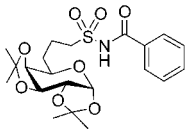
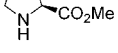
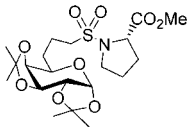
We have found the intermolecular tin-mediated radical addition of a number of organo-halide precursors is a facile process leading to the corresponding alkyl sulfonate esters in moderate to good yields (Table 1). We were particularly encouraged by the observation that this reaction is not limited to simple alkyl radicals or stabilized radical species but that the method is applicable to the synthesis of derivatized sugar and amino acid species. In some cases, for example, entry 5, amine displacement may be carried out prior to purification to enable separation from radical reduction products. Following purification by column chromatography, aminolysis proceeds smoothly to furnish the sulfonamide in near quantitative yields. Table 2 outlines the results of various aminolysis reactions after radical addition of the 6-iodo-D-galactose species (Scheme 3). Particularly noteworthy are entries 3, 6, and 8, which demonstrate, first, the applicability of this approach toward the synthesis of derivatized heterocyclic compounds and, second, potential for the synthesis of glycopeptide conjugates.

Table 1. Examples of Intermolecular Addition to Pentafluorophenyl Vinylsulfonate

entry	RX	equivalents	product	yield %*
1		3.0		85
2		3.0		93
3		3.0		77
4		2.5		71
5		2.5		41†
6		3.0		46
7		3.0		30

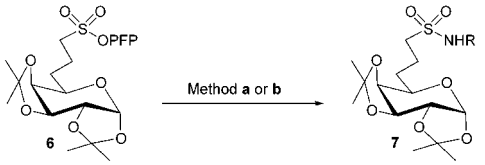
[a] Product derived from direct amine displacement of radical addition product. Ar = 4-methylbenzylamine [b] Isolated yields

Table 2. Examples of Amine Displacement

entry	nucleophile	method	product	yield %*
1		a		93
2		a		71
3		a		92
4		a		55
5		a		96
6		b		99
7		b		58
8		a		90

[a] Isolated yields.

Scheme 3[a]

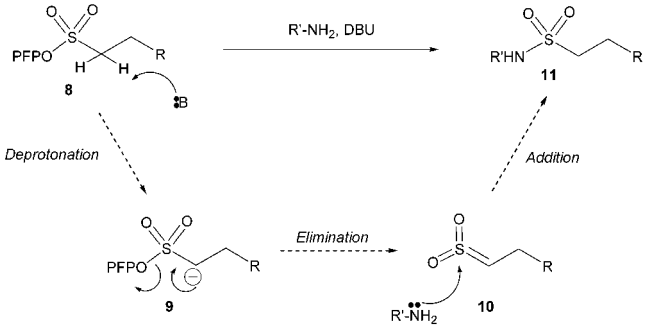


[a] Method a: RNH_2, THF, DBU, 65 °C. Method b: NaH, THF, 0 °C.

It is interesting to note that the displacement reaction will only proceed when a strong base such as DBU or sodium hydride is present in the reaction medium, even with a nucleophilic amine. In light of this fact we postulate that the reaction mechanism, rather than proceeding via the well documented direct displacement of a leaving group by amine,[7] actually involves deprotonation of the sulfonate moiety, followed by rapid extrusion of pentafluorophenol to give intermediate **10**. This *sulfene* mechanism has been shown by King et al. to be the predominant mechanistic pathway for the hydrolysis of sulfonyl halides at high pH.[8] Lyashchuk et al. have also demonstrated that the sulfene mechanism operates in the pyridine-catalyzed reaction of alkanesulfonyl chlorides with phenols,[9] adding further support for our proposed mechanism.

In conclusion, we have demonstrated that the bifunctional intermediate **3** is an excellent acceptor for intermolecular radical reactions and have shown its applicability as a building block for sulfonamide synthesis via nucleophilic attack by a range of nitrogen nucleophiles. We suggest that the pentafluorophenylsulfonate motif is a potential replacement for the more reactive sulfonyl chloride unit, which is difficult to prepare and handle and liberates hydrogen chloride on exposure to nucleophiles. We are currently exploring other related displacement reactions and investigating the applicability of this approach to the generation of libraries of biologically significant sulfonamides.

Scheme 4. Proposed Mechanism of Amine Displacement



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

OL026181M

(4) For other examples of *C*-glycoside formation using intermolecular radical methodology, see: SanMartin, R.; Tavassoli, B.; Walsh, K. E.; Walter, D. S.; Gallagher, T. *Org. Lett.* **2000**, *2*, 4051 and references therein.

(5) For a complete overview of intermolecular radical-mediated carbon−carbon bond formation, see: Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon Press: New York, 1986. Curran, D. P.; *Synthesis* **1988**, 417 and 419.

(6) For related work, see: Caddick, S.; Hamza, D.; Wadman, S. N.; Wilden, J. D. *Org. Lett.* **2002**, *4*, 1775. Salvino, J. M.; Kumar, N. V.; Orton, E.; Airey, J.; Kiesow, T.; Crawford, K.; Mathew, R.; Krolikowski, P.; Drew, M.; Engers, D.; Krolikowski, D.; Herpin, T.; Gardyan, M.; McGeehan, G.; Labaudiniere, R. *J. Comb. Chem.* **2000**, 691−697.

(7) For a complete overview of this mechanism, see: Gordon, I. M.; Maskill, H.; Ruasse, M. F.; *Chem. Soc. Rev.*, **1989**, *18*, 123 and references therein.

(8) King, J. F.; Lam, J. Y. L.; Skonieczny, S. *J. Am. Chem. Soc.*, **1992**, *114*, 1743.

(9) Lyashchuck, S. N.; Skrypnik, Y. G.; Besrodnyi, V. P.; *J. Chem. Soc., Perkin Trans. 2* **1993**, *6*, 1153.