

# Synthesis of Functionalized Sulfonamides via 1,3-Dipolar Cycloaddition of Pentafluorophenyl Vinylsulfonate

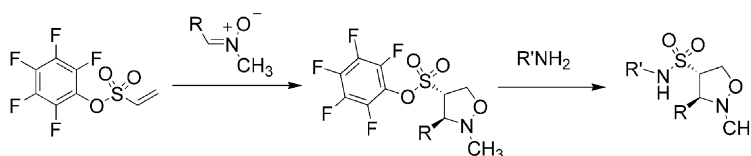
Stephen Caddick\* and Hannah D. Bush

Centre for Biomolecular Design and Drug Development, The Chemistry Laboratory,  
University of Sussex, Falmer, Brighton BN1 9QJ, U.K.

s.caddick@sussex.ac.uk

Received May 2, 2003

## ABSTRACT



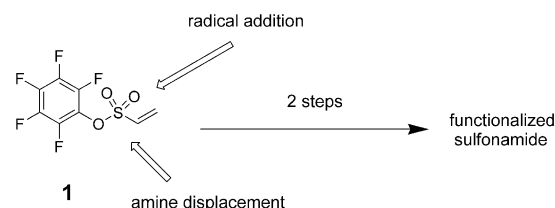
An efficient intermolecular 1,3-dipolar cycloaddition of a variety of nitrones to pentafluorophenyl (PFP) vinylsulfonate is described. The transformation produces stable “reversed” cycloadducts of unprecedented stereo- and regioselectivity. Subsequent amine displacement of the PFP moiety furnished functionalized sulfonamide products in good yields.

The sulfonamide structural motif is widely found in molecules of medicinal interest, particularly antibacterial agents.<sup>1a</sup> Their ability to act as carbonic anhydrase inhibitors has resulted in sulfonamides being used clinically for over 50 years in the treatment of diseases such as glaucoma, epilepsy, and heart failure.<sup>1b</sup> More recently, sulfonamides have been found to be potent cysteine protease inhibitors, which could possibly extend their therapeutic applications to include conditions such as Alzheimer’s Disease, arthritis, and cancer.<sup>2</sup>

The significant potential that still exists for sulfonamides as potent therapies for disease had led us to investigate novel routes to their synthesis. We have recently described a new strategy for sulfonamide formation, using the readily available and shelf-stable pentafluorophenyl vinylsulfonate **1**. In that work, we described intermolecular radical addition

reactions followed by substitution of the PFP group with a wide range of amine nucleophiles (Scheme 1).<sup>3</sup>

**Scheme 1.** Previously Described Strategy for Sulfonamide Formation



Encouraged by the impressive selective reactivity displayed by **1**, we decided to explore the scope of its reactivity and hence its general applicability for the preparation of structurally diverse sulfonamides. In this paper, we describe our preliminary findings concerning the 1,3-dipolar cycloadd-

(1) (a) Maren, T. H. *Annu. Rev. Pharmacol. Toxicol.* **1976**, *16*, 309. (b) Supuran, C. T.; Briganti, F.; Tilli, S.; Chegwiddden, W. R.; Scozzafava, A. *Bioorg. Med. Chem.* **2001**, *9*, 703. Scozzafava, A.; Menabuoni, L.; Mincione, F.; Briganti, F.; Mincione, G.; Supuran, C. T. *J. Med. Chem.* **2000**, *43*, 4542.

(2) Roush, W. R.; Gwaltney, S. L.; Cheng, J.; Scheidt, K. A.; McKerrow, J. H.; Hansell, E. *J. Am. Chem. Soc.* **1998**, *120*, 10994. Roush, W. R.; Cheng, J.; Knapp-Reed, B.; Alvarez-Hernandez, A.; McKerrow, J. H.; Hansell, E.; Engel, J. C. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2759.

(3) Caddick, S.; Wilden, J. D.; Bush, H. D.; Wadman, S. N.; Judd, D. B. *Org. Lett.* **2002**, *4* (15), 2549.

dition reactions of **1** with a variety of functionalized nitrones.

Sulfonates are widely applicable dienophiles in both inter- and intramolecular cycloaddition reactions,<sup>4</sup> the latter being the subject of a review by Metz.<sup>5</sup> Their ability as dipolarophiles has yet to be investigated as thoroughly, although Chiacchio and co-workers have employed vinylsulfonamides in selective intramolecular cycloaddition reactions with a series of 1,3-dipoles.<sup>6</sup>

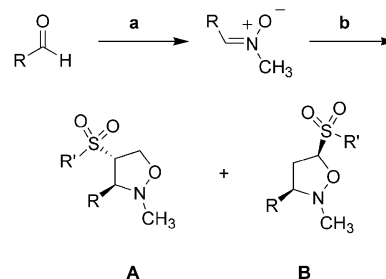
Intermolecular examples of sulfonates as dipolarophiles are infrequent; however, Chan and co-workers have recently shown that prop-1-ene-1,3-sulfone will undergo regio- and stereoselective 1,3-dipolar cycloaddition with both nitrile oxides and nitrones.<sup>7</sup>

Hence, we were intrigued to discover if **1**, whose vinyl portion is recognized as being especially electron deficient, would undergo cycloaddition to 1,3-dipoles. If successful, this would provide a direct route to heterocyclic PFP-sulfonates, which could subsequently be employed in the preparation of functionalized sulfonamides using our previously described amination methodology.<sup>3</sup>

Nitrones were initially of interest, as they are one of the most widely studied 1,3-dipoles and can be simply prepared from the corresponding aldehyde.<sup>8</sup> Following literature procedures,<sup>9</sup> we synthesized a variety of functionalized nitrones in excellent yield, which were then subjected to cycloaddition with **1** (Scheme 2). For the purpose of comparison, *C*-phenyl-*N*-methylnitrone was also used in reactions with phenyl vinyl sulfone and phenyl vinylsulfonate (Table 1, entries 1 and 2).

It is generally acknowledged that the cycloaddition of nitrones to olefins generates 5C-substituted isoxazolidines (Scheme 2, B). However, experimental observations have shown that the “reversed” 4C-substituted cycloadduct increasingly predominates when very electron-deficient dipolarophiles are involved (Scheme 2, A).<sup>10</sup> This “reversal” in regioselectivity is known to be a characteristic of only a small number of specific electron-deficient dipolarophiles; hence, the criterion for the formation of 4C-substituted isoxazolidines via cycloaddition is particularly selective.<sup>8</sup>

**Scheme 2.** Isoxazolidine Formation via 1,3-Dipolar Cycloaddition<sup>a</sup>



<sup>a</sup> Reaction conditions: (a) MeNH<sub>2</sub>·HCl (1.2 equiv), NaHCO<sub>3</sub> (3.0 equiv), DCM, 40 °C, 2 h. (b) R'SO<sub>2</sub>CHCH<sub>2</sub> (0.4–1.0 equiv), PhMe, 110 °C, 2–20 h.

Notably, Chan and co-workers observed reversed regioselectivity in the aforementioned nitrone cycloaddition reactions.<sup>7</sup>

This atypical behavior has been successfully explained by Houk and co-workers using frontier orbital theory,<sup>11</sup> who have wholly supported their hypothesis with numerous examples of 1,3-dipolar cycloadditions utilizing highly electron-deficient dipolarophiles such as phenyl vinyl sulfone.<sup>10a,b</sup>

With this information in hand, it was of great interest for us to observe the regiochemical outcome in the cycloaddition of nitrones with **1**. From literature precedent and theoretical considerations, it was reasonable to predict that we would achieve the trans 4C-substituted regioisomer as the major product.

It was very pleasing to observe that **1** readily underwent cycloaddition with a variety of nitrones to give the isoxazolidine cycloadducts (Table 1). The addition was successful with a variety of *C*-aryl-*N*-methyl and *C*-alkyl-*N*-methyl nitrones, including species with electron-withdrawing nitro and halogen functionalities, and electron-donating methoxy, allyloxy, and alkyl substituents. The cycloaddition could also be achieved with poly and heteroaromatic systems such as naphthyl and furyl rings. Consequently, this methodology represents a general and versatile route to highly functionalized heterocycles.

A NOE analysis of entry 12 (Table 1) confirmed that cycloadducts of this type were indeed trans 4C-substituted as predicted and represents further evidence to support the prior rationalization of related cycloadditions.<sup>12</sup>

An interesting theme that emerged from our study was the excellent regioselectivity we observed in the cycloadducts. Even for the previously reported cycloaddition of phenyl vinyl sulfone to *C*-phenyl-*N*-methyl nitrone<sup>10a</sup> (Table 1, entry 1), we attained a significantly improved product ratio of 94:6 A:B simply by performing the cycloaddition at elevated temperatures. We presume that this result is

(4) Metz, P.; Fleischer, M.; Fröhlich, R. *Tetrahedron* **1995**, *51*, 711. Bovenschulte, E.; Metz, P.; Henkel, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 202. Klein, L. L.; Deeb, T. M. *Tetrahedron Lett.* **1985**, *26*, 3935. Distler, H. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 300. Jiang, L. S.; Chan, W. H.; Lee, A. W. M. *Tetrahedron* **1999**, *55*, 2245.

(5) Metz, P. *J. Prakt. Chem.* **1998**, *340*, 1.

(6) Chiacchio, U.; Corsaro, A.; Rescifina, A.; Bkaithan, M.; Grassi, G.; Piperno, A.; Privitera, T.; Romeo, G. *Tetrahedron* **2001**, *57*, 3425.

(7) Zhang, H.; Chan, W. H.; Lee, A. W. M.; Wong, W. Y. *Tetrahedron Lett.* **2003**, *44*, 395.

(8) Grünanger, P.; Vita-Finzi, P. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; J. Wiley & Sons: New York, 1991; Vol. 49, Part 1, Chapter 3.3. Torrsell, K. B. G. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis—Novel Strategies in Synthesis*; VCH: New York, 1987; Chapter 1.5. Confalone, P. N.; Huie, E. M. In *Organic Reactions*; J. Wiley & Sons: New York, 1988; Vol. 36, Chapter 1. Padwa, A.; Fisera, L.; Koehler, K. F.; Rodriguez, A.; Wong, G. S. K. *J. Org. Chem.* **1984**, *49*, 276. Black, D. St. C.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, 205.

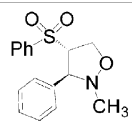
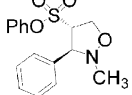
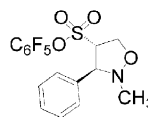
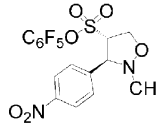
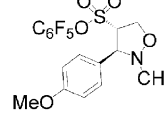
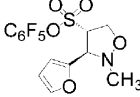
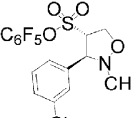
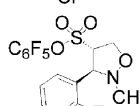
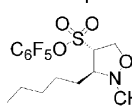
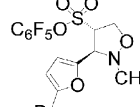
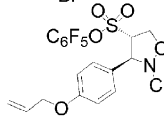
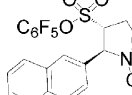
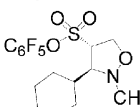
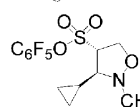
(9) For example, see: Chan, K. S.; Yeung, M. L.; Chan, W.; Wang, R. J.; Mak, T. J. *Org. Chem.* **1995**, *60*, 1741. Heaney, F.; Rooney, O.; Cunningham, D.; McArdle, P. *J. Chem. Soc., Perkin Trans. 2* **2001**, 373. Baruah, A. K.; Prajapati, D.; Sandhu, J. S. *Tetrahedron* **1988**, *44*, 6137.

(10) (a) Sims, J.; Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 5798. (b) Bimanand, A. Z.; Houk, K. N. *Tetrahedron Lett.* **1983**, *24*, 435. (c) Seidl, H.; Huisgen, R.; Knorr, R. *Chem. Ber.* **1969**, *102*, 904.

(11) Houk, K. N.; Sims, J.; Duke, R. E., Jr.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287. Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301.

(12) For details, see Supporting Information.

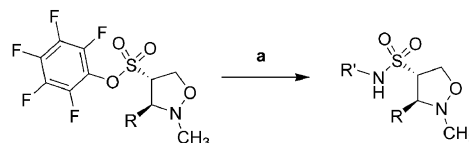
**Table 1.** Cycloaddition of Functionalized Nitrones to **1**

entry	R	R'	product	yield A % <sup>a</sup>
1	Ph	Ph		65 <sup>b</sup>
2	Ph	PhO		77 <sup>c</sup>
3	Ph	C <sub>6</sub> F <sub>5</sub> O		67 <sup>d</sup>
4	<i>p</i> -NO <sub>2</sub> Ph	C <sub>6</sub> F <sub>5</sub> O		65
5	<i>p</i> -MeOPh	C <sub>6</sub> F <sub>5</sub> O		70
6	Furyl	C <sub>6</sub> F <sub>5</sub> O		75
7	<i>m</i> -ClPh	C <sub>6</sub> F <sub>5</sub> O		63
8	<i>o</i> -FPh	C <sub>6</sub> F <sub>5</sub> O		46
9	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	C <sub>6</sub> F <sub>5</sub> O		66
10	2-Br-Furyl	C <sub>6</sub> F <sub>5</sub> O		44
11	<i>p</i> -Allyloxy-Ph	C <sub>6</sub> F <sub>5</sub> O		69
12	2-Naphthyl	C <sub>6</sub> F <sub>5</sub> O		65
13	Cyclohexyl	C <sub>6</sub> F <sub>5</sub> O		54
14	Cyclopropyl	C <sub>6</sub> F <sub>5</sub> O		51

<sup>a</sup> Isolated yields. Regioselectivity of A:B = 100:0 except where indicated.<sup>b</sup> A:B = 94:6. <sup>c</sup> A:B = 99:1. <sup>d</sup> A:B = 98:2.

consistent with a thermodynamically controlled process, especially considering that isoxazolidines are prone to undergo cycloreversion at high temperatures.<sup>8</sup>

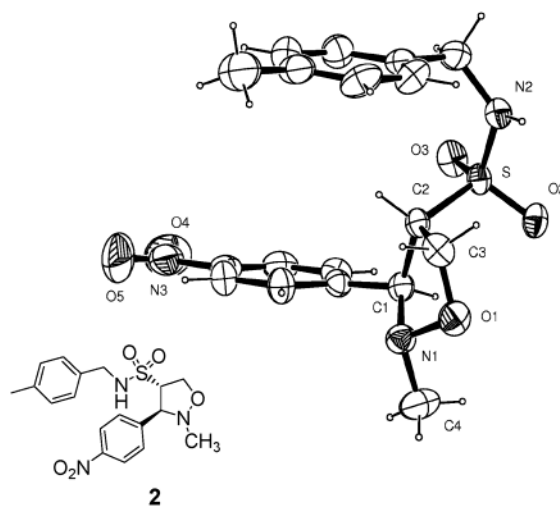
Once the PFP-substituted isoxazolidines had been successfully produced, our attention was turned to the conversion into sulfonamides via amine displacement of the PFP moiety (Scheme 3). On the basis of our prior work,<sup>3</sup> we

**Scheme 3.** Sulfonamide Formation from PFP-Substituted Isoxazolidines<sup>a</sup>

<sup>a</sup> Reaction conditions: (a) R'NH<sub>2</sub> (3.0 equiv), DBU (1.0–1.4 equiv), THF, 65 °C, 1–5 h.

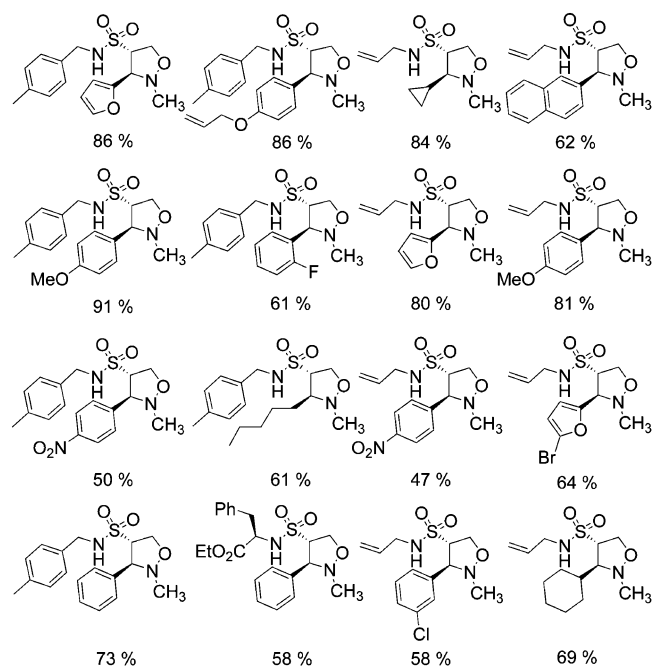
envisaged that treatment of the PFP derivatives with amines under basic conditions would furnish the desired sulfonamides.

As anticipated, aminolysis proceeded smoothly to give the sulfonamide products in good yield. Structural evidence provided by X-ray crystallographic analysis of compound **2** (2-methyl-3-(4-nitro-phenyl)-isoxazolidine-4-sulfonic acid 4-methyl-benzamide), indicated that the transformation was achieved with clean retention of stereochemistry (Figure 1).<sup>3</sup>

**Figure 1.** 2-Methyl-3-(4-nitro-phenyl)-isoxazolidine-4-sulfonic acid 4-methyl-benzamide.

Comprehensive results from the displacement reactions are presented in Figure 2, which illustrates that a variety of sulfonamides can be prepared from the novel cycloadducts derived from **1**.

In conclusion, we have shown that pentafluorophenyl vinylsulfonate **1** is an active participant in regio- and



**Figure 2.** Isoxazolidine sulfonamides formed from PFP-substituted cycloadducts via aminolysis.

stereoselective cycloaddition reactions with a wide range of functionalized nitrones. The regio- and stereochemical

outcome of these cycloadditions is consistent with prior theoretical predictions for electron-deficient alkenes. However, our findings demonstrate that modification of reaction conditions can lead to significantly improved levels of regioselectivity. The PFP-isoxazolidines are shelf-stable and can be transformed into a variety of sulfonamides using a simple substitution protocol. The application of 1,3-dipolar cycloaddition methodology to sulfonates such as **1** offers an excellent opportunity for the preparation of diverse compound collections of potentially valuable sulfonamide structures.

**Acknowledgment.** We thank the EPSRC and Glaxo-SmithKline for generous financial support of this work. We also thank the Association for International Cancer Research, BBSRC, Novartis, Pfizer, and AstraZeneca for the support of our program. We also thank the University of Sussex for providing funds to establish the Centre for Biomolecular Design and Drug Development. We also gratefully acknowledge the contributions of Dr. A. G. Avent, Dr. A. Abdul-Sada, Dr. P. B. Hitchcock, and the EPSRC Mass Spectroscopy Service at Swansea.

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

OL0347388