3,5-Isoxazoles from α-bromo-pentafluorophenyl vinylsulfonates: Synthesis of sulfonates and sulfonamides†

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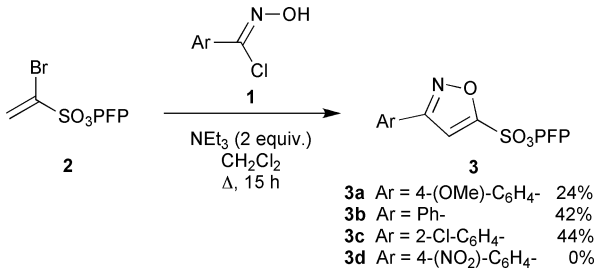
The regioselective 1,3-dipolar cycloaddition of α-bromo-pentafluorophenyl vinylsulfonate with nitrile oxides has been used to rapidly access a range of 3,5-isoxazoles which could be converted directly to their corresponding sulfonamides.

The high incidence of the isoxazole motif in drug and drug-like molecules has resulted in the development of a plethora of methods for the synthesis of this valuable fragment.[1–6] One route available for the synthesis of isoxazoles is *via* 1,3-dipolar cycloadditions of nitrile oxides with alkynes or alkyne equivalents.[7–9] However, the synthesis of the alkynyl substrates required can be problematic and the cycloadditions can suffer from modest selectivities.[10,11] An alternative, using alkenes bearing an appropriate leaving group, can offer complimentary regioselectivities in dipolar cycloaddition reactions to their corresponding alkynes.[12–14]

We have had a long-standing interest in the use of arylsulfonate esters as surrogates for sulfonyl chlorides in sulfonamide synthesis.[15–17] In addition, we have shown the compatibility of these useful functional groups with a range of other methods including radical and 1,3-dipolar cycloaddition reactions.[16,18–21] We wished to expand this repertoire of chemistry to the preparation of collections of functionalised isoxazoles. The use of alkynylsulfonates in cycloaddition reactions, although known, has not been well taken up in the literature, presumably due to the lack of readily available substrates.[22–24] We envisaged that vinylsulfonates, as the pentafluorophenyl (PFP) esters substituted with an appropriate leaving group, would provide an ideal alkyne equivalent.

We initiated our investigations with a study of the reaction of two equivalents of chlorooxime **1**, and α-bromo PFP vinylsulfonate **2** in CH_2Cl_2 in the presence of two equivalents of NEt_3, and in each case observed isoxazoles **3a–c** as single regioisomers, albeit in low yield (Scheme 1).[25] Presumably, the reaction proceeds *via* elimination of HCl from chlorooxime **1** to generate the corresponding nitrile oxide, cycloaddition with **2** to derive an isoxazoline, and then elimination of HBr to form the isoxazole **3**. However, reaction of vinylsulfonate **2** with the nitrile oxide derived from **1** (Ar = 4-(O_2N)-C_6H_4-) to form isoxazole **3d** did not reach completion and only the corresponding isoxazoline was isolated under these conditions. We were pleased to note that in these cases only isoxazoles bearing the vinylsulfonate motif were isolated, with no evidence for the formation of brominated isoxazoles derived from the elimination of sulfur dioxide and pentafluorophenol.[26]



Scheme 1 Synthesis of isoxazoles from α-bromo PFP vinylsulfonates.

We then sought to optimise the conditions for the reaction of vinylsulfonate **2** with the nitrile oxide derived from **1** (Ar = 4-(MeO)-C_6H_4-), varying both reagent stoichiometry and solvent (Table 1). As expected, reduction of the equivalents of chlorooxime and base (Table 1, Entries 1–3) proved detrimental to the yield of the reaction, and reactions did not reach complete conversion in an acceptable time frame. The reaction was significantly improved, in both rate and yield, at room temperature (21 °C) by increasing the quantity of base. Indeed, the reaction could be readily performed at room temperature in a few hours albeit in a relatively low yield (Table 1, Entry 5). Both yield and rate could be significantly improved by switching to a less polar solvent, toluene (Table 1, Entry 10), and hindered by use of a more polar medium, DMF (Table 1, Entry 11). Although the reaction could be carried out at elevated temperature in toluene (Table 1, Entry 4), reduced yields were observed without a noticeable practical rate advantage (Table 1, Entry 11). From this preliminary study it would appear that the transformation of vinylsulfonate **2** to its corresponding isoxazole **3** was best carried out at room temperature utilising a non-polar solvent.

Table 1 Optimisation of cycloaddition between nitrile oxide (derived from **1**) and **2** *via* Scheme 1

Entry	**1** (equiv.)	NEt_3 (equiv.)	Solvent	Temp[a]/°C	Time	Yield (%)
1	1	1.2	CH_2Cl_2	rt	72 h	0
2	1	1.2	CH_2Cl_2	40	12 h	0
3	1	1.2	PhMe	110	12 h	0
4	1.5	2.5	PhMe	110	30 min	60
5	1.5	2.5	CH_2Cl_2	rt	2 h	52
6	1.5	2.5	PhMe	rt	1.5 h	87
7	1.5	5	CH_2Cl_2	40	20 min	50
8	1.5	5	PhMe	110	10 min	81
9	1.5	5	CH_2Cl_2	rt	1.5 h	48
10	1.5	5	PhMe	rt	1 h	92
11	1.5	5	DMF	rt	20 min	43

[a] Reactions at elevated temperature carried out at reflux.

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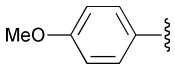
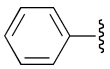
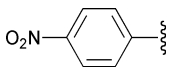
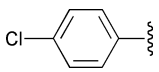
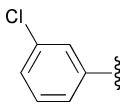
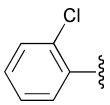
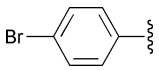
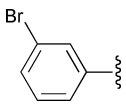
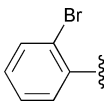
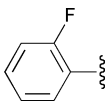
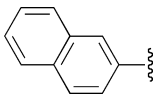
† Electronic supplementary information (ESI) available: Experimental procedures and data for sulfonates **3** and sulfonamides **4**. See DOI: 10.1039/b911098d

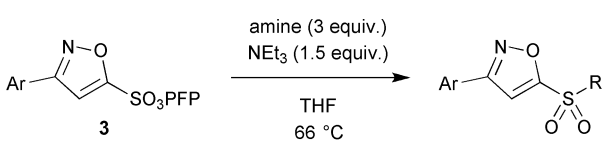
Table 2 Evaluation of microwave heating and substrate scope in reaction of nitrile oxide with **2**

Entry	Ar	Yield (%) Thermal[a]	Microwave[b]
1		92	85
2		86	54
3		50	30
4		88	52
5		75	24
6		87	84
7		87	75
8		69	63
9		86	61
10		68	70
11		80	46

[a] Reaction conditions: **1** (1.5 equiv.), **2**, NEt_3 (2.5 equiv.), MePh, 21 °C, 1 h. [b] Reaction conditions: **1** (1.5 equiv.), **2**, NEt_3 (2.5 equiv.), MePh, 100 °C, 3 or 2 × 3 min.

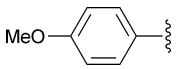
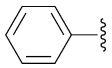
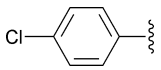
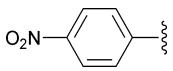
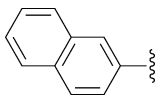
We have previously had considerable success improving both the rate and yield of cycloaddition reactions of vinylsulfonates by use of microwave heating.[27] Hence, we sought to apply this approach to the synthesis of isoxazoles bearing sulfonate esters, and to evaluate the effect of the nature of the nitrile oxide on the selectivity of the cycloaddition reaction (Table 2). However, we found that cycloaddition could be promoted at room temperature using a range of nitrile oxides derived from chlorooximes **1** and sulfonates **2** to generate isoxazoles **3**. Using this protocol we have prepared a series of isoxazoles bearing halogenated benzene substituents at C-3 (Table 2, Entries 4–10). We were pleased to observe the exclusive formation of the 5-substituted product **3** in all cases, with no evidence for brominated isoxazoles. It should be noted that under these improved reaction conditions even previously unsuccessful examples using chlorooximes such as **1** (Ar = 4-(O_2N)-C_6H_4-) gave rise to isoxazole product **3d** (Table 2, Entry 3) in moderate yield. It appears that the 1,3-dipolar cycloaddition of nitrile oxide **1** with **2** fits the expected pattern with respect to the electronics of the nitrile oxide. Thus, reactions generally proceed in higher yield with electron-rich dipolar components, which react well with the vinylsulfonate substrate **2**. This is evident when a comparison is made between chlorooximes bearing halogenated benzene substituents at C-3; thus the 2- or 4-substituted chlorooxime **3** (Table 2, Entries 4, 6, 7 and 9) both give consistently higher yields than the corresponding 3-substituted analogues (Table 2, Entries 5 and 8) where mesomeric donation from the halogen lone pairs into the nitrile oxide cannot occur. As with reactions carried out under conventional heating (Table 2), reactions under microwave conditions gave generally lower yields, and in some cases significant reduction was observed (Table 2, Entry 5). However, it should still be noted that there is an appreciable reduction in reaction times.

Previously, we have described the application of arylsulfonate esters in the synthesis of sulfonamides, and so we sought to convert a small collection of the aforementioned isoxazole sulfonates into sulfonamides (Table 3).[15,16] The application of our standard conditions to the aminolysis of isoxazole sulfonate esters using primary, secondary and aromatic amines generated a range of functionalised isoxazole sulfonamides reproducibly and in good to moderate yields (Scheme 2 and Table 3). The reactions of primary amines proceeded smoothly and in good yields for both benzylamine and allylamine. Both the more hindered α-branched amines, *iso*-propylamine (R = NH*i*Pr) and *tert*-butylamine (R = NH*t*Bu), required the addition of tetrabutylammonium (TBA) chloride (2 equiv.) in order to facilitate aminolysis in a reasonable timescale (1–3 h).[17] Reaction of secondary amine *N*-methyl-*N*-benzylamine (R = NMeBn) and aniline (R = Ph) proved problematic, as we had previously observed, generally providing low conversions and yields under standard heating at reflux in THF with or without the addition of TBACl for 3 h. However, prolonged reaction times, 16–24 h, brought about complete conversion of the vinylsulfonate ester and allowed isolation of the desired sulfonamide **4** (R = NMeBn and R = NHPh) in moderate to good yields (Table 3). The nature of the isoxazole 5-substutuent, Ar, does not seem to affect the yield of the aminolysis reaction significantly, with the nature of the nucleophile generally determining the degree of success of the transformation. However, it is notable that electron-poor isoxazole **3** (Ar = 4-(NO_2)-C_6H_4-) generally gave especially disappointing yields with less reactive amines (Entry 4) whereas electron-rich isoxazole **3** (Ar 4-(MeO)-C_6H_4-) gave uniformly high yields.



Scheme 2 Synthesis of sulfonamides **4** by aminolysis of **3**.

Table 3 Sulfonamides **4** prepared from sulfonate ester **3** *via* aminolysis

		Yield (%)					
Entry	Ar	R = NHC_6H_4Me	R = $NHCH_2CH{=}CH_2$	R = NH^iPr[a]	R = NH^tBu[a]	R = NMeBn[b]	R = NHPh[b]
1		71	66	89	63	84	93
2		95	64	79	49	69	46
3		83	60	74	47	62	68
4		72	69	81	37	23	44
5		83	69	82	42	73	46

[a] TBACl (2 equiv.) added. [b] TBACl (3 equiv.) added; reactions required 16–24 h to reach complete conversion.

Conclusions

In conclusion, we have described a concise route for the regioselective synthesis of a range of sulfonate esters and sulfonamides in good yields, based upon regioselective 1,3-dipolar cycloaddition of an alkynylsulfonate surrogate, α-bromo-pentafluorophenyl vinylsulfonate, with an *in situ*-generated nitrile oxide. These functionalised building blocks can be readily elaborated in one step to the corresponding sulfonamides, and these offer the opportunity for the generation of diverse collections of isoxazoles which can be readily manipulated and of value for the synthesis of diverse compound collections.

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Notes and references

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