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Synthesis of novel benzoxathiazepine-1,1-dioxides by means of a one-pot multicomponent reaction

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ABSTRACT

A simple one-pot synthesis of benzoxathiazepine-1,1-dioxides is described. Increased yields are afforded when suitable substituents are present in one of the starting materials. These additional substituents also provide a handle for further functionalization.

Multicomponent reactions (MCRs) are convergent reactions in which three or more starting materials react to form a product. A MCR has distinct advantages over a stepwise process, including the removal of the need to purify after each chemical transformation and the ability to produce a large number of derivatives around a common scaffold by varying each of the components involved in the reaction.[1] However, it has the requirement that the reagents must react in a defined and predictable way to yield a major desired product, whilst minimizing side reactions which would result in the formation of by-products. The outcome of a MCR is dependent on a variety of reaction parameters, such as solvent, temperature, catalyst, concentration, as well as the interaction of the functional groups in the starting materials and the products. Such considerations are of particular importance in connection with the design and discovery of novel MCRs.

Benzo-fused rings are prevalent in pharmacologically active drugs. In particular, benzoxathiazepines such as **1** (Fig. 1) have generated considerable interest as potential treatments for hypertensive disorders[2] as well as diabetes.[3]

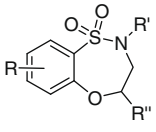
Although there are several syntheses of scaffolds analogous to **1** reported in the literature, they generally rely on the use of potentially hazardous key steps and/or multistep synthetic sequences.[4] As a result of their potential interest to the pharmaceutical industry and due to the lack of satisfactory synthetic methods to prepare them, an expedient synthesis of benzoxathiazepines **1** would be desirable.

During recent studies within our research group, we have shown that sulfonamides such as **2** efficiently ring-open epoxides when heated in 1,4-dioxane in the presence of catalytic amounts of tetra-*n*-butylammonium halides. Subsequent activation and cyclization allowed us to prepare a range of N-alkylated-4-substituted isothiazolidine-1,1-dioxides, **4** (Scheme 1).[5]

We envisaged that the application of this methodology to substrates bearing an adequately positioned leaving group in the intermediate **7** could lead to a rapid synthesis of benzoxathiazepines **1** via a MCR, (Scheme 2). Herein we report the development of a novel MCR in which an *ortho*-halo sulfonyl chloride **5**, an amine and an epoxide react in a sequential fashion to furnish exclusively, a benzoxathiazepine derivative **1**. This one-pot process would be expected to give entry to privileged structures in high yields, with the added benefits of not requiring purification of any of the reaction intermediates, additionally it would also benefit from using readily available starting materials. Furthermore, suitably functionalized examples of **1**, would allow the option for further structural elaboration.

The proposed synthetic route to benzoxathiazepines **1** involves the addition of a primary amine to an *ortho*-halo sulfonyl chloride **5** and the subsequent reaction of the resulting sulfonamide **6** with an epoxide to give alcohol **7**. Finally, the aromatic nucleophilic substitution reaction (S_NAr) of the aryl halide would result in the formation of the desired cyclized compound **1**.

On the basis of the previous work developed within our group, the sulfonamide formation would be expected to occur at ambient temperature whilst the epoxide ring-opening would require heating.[5] The first step was expected to be very fast and quantitative; in addition, the S_NAr reaction could not proceed until the epoxide had reacted with the sulfonamide **6** to form an alcohol **7**. Bearing these points in mind, we thought that there was an attractive opportunity for the potential development of a MCR synthesis of compounds with the general structure **1**.



1

Figure 1. 3,4-Dihydro-2*H*-benzo[*b*][1,4,5]oxathiazepine-1,1-dioxides **1**.

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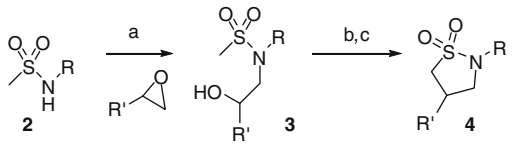


Scheme 1. Synthesis of N-alkylated-4-substituted isothiazolidine-1,1-dioxides **4**. Reagents and conditions: (a) 1,4-dioxane, K_2CO_3, *n*-Bu_4NCl, 100 °C; (b) $PhSO_2Cl$ (1.2 equiv), pyridine, DMAP (cat.), 50 °C; (c) *n*-BuLi (2.2 equiv), THF, −78 °C → rt, 2 h.

The synthesis depicted in Scheme 2 was initially attempted in a stepwise fashion. Treatment of 2-fluorobenzenesulfonyl chloride **5a** with benzylamine and potassium carbonate in 1,4-dioxane at room temperature yielded the corresponding sulfonamide **6a** in a 92% yield. A solution of **6a** in 1,4-dioxane was then heated at 100 °C in the presence of tetra-*n*-butylammonium bromide (*n*-Bu_4NBr), K_2CO_3 and *O*-benzyl glycidyl ether **9a**.[6] We were pleased to observe that, after 16 h, not only had the ring-opening of the epoxide occurred to give 38% of alcohol **7a**, but the S_NAr reaction had also occurred to some extent, generating the benzoxathiazepine **1a** in a 34% yield (Scheme 3).

This observation encouraged us to attempt the one-pot MCR using the same experimental conditions. Thus, 2-fluorosulfonyl chloride **5a** (R = H) was treated with benzylamine and the commercially available epoxides, benzyl glycidyl ether **9a** or (*R*)-1,2-epoxy-hex-5-ene **9b**, in refluxing 1,4-dioxane, using K_2CO_3 as the base (Scheme 4, Table 1, entries 1 and 7). After 72 h, the desired benzoxathiazepines **1a** and **1g** were isolated in 76% and 58% yield, which equate to a step average of 91% and 83%, respectively.[7]

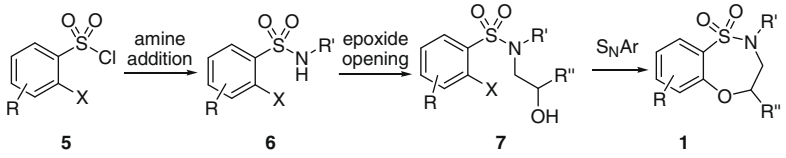
The same experimental protocol was then successfully applied to a variety of starting 2-fluorosulfonyl chlorides substituted with additional halogen atoms on the benzene ring. The yields of isolated products were similar or higher to those observed for the unsubstituted systems (Table 1), which is the expected trend when electron-withdrawing substituents are present on the aromatic ring during S_NAr reactions. The relative position of the electron-withdrawing group with respect to the leaving group also played a role in the observed yields. Thus, a chlorine atom causes a larger increase in the yield when it is at the 3-position in the starting material, than when it is at the 4-position (Table 1, entries 3, 9 and 4, 10), and in both cases an increase in yield was observed when compared to the unsubstituted cases (Table 1, entries 1 and 7). The lower yield observed when the chlorine was at the 5-position could be rationalized on the basis of steric hindrance (Table 1, entry 5). Compound **1c** (Table 1, entry 3) was isolated in a 91% yield, which is considerably higher than the 62% overall yield of the stepwise process. This result illustrates the convenience and efficiency of the MCR for the synthesis of compounds of the general structure **1**. When enantiopure epoxides were used no loss of chirality was observed during the sequence (Scheme 4).[8]

In order to study the generality of this method, 2-chlorosulfonyl chlorides were also utilized as starting materials. A wide range of substituted 2-chlorosulfonyl chlorides are readily available. When 2-chlorosulfonyl chloride **5b** (R = H) was subjected to the general cyclization conditions with benzylamine and epoxide **9b**, only the corresponding alcohol was isolated from the reaction mixture. The solvent was changed to *N*,*N*-dimethylformamide and the temperature of the reaction mixture was increased to 120 °C, and using these new conditions, a modest 25% yield of the benzoxathiazepine **1g** was obtained (Scheme 5, Table 2, entry 1).

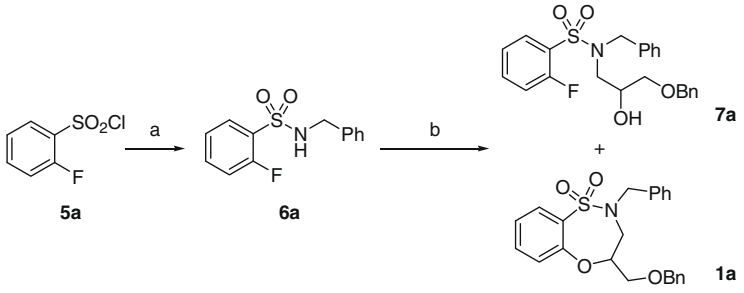
Once again the introduction of electron-withdrawing groups to the aromatic ring resulted in increased reaction yields, as had already been observed for the corresponding fluorides. With these more active substrates the MCR could be performed at lower temperatures with 1,4-dioxane as the preferred solvent. When 2-chloro-6-methylsulfonyl chloride was used as the starting material, the intermediate alcohol **7b** was the only product isolated (Table 2, entry 4). This result could be explained by the steric hindrance imposed by the methyl group that forces the sulfonyl group to twist and prevents the interaction between the alkoxide moiety and the leaving group.

The halogen substituents present on the aromatic ring of the benzoxathiazepines **1** confer a drug-like profile and also provide a synthetic handle for the introduction of further functionalization by means of a palladium-catalyzed cross-coupling reaction. An example of this type of modification is highlighted below (Scheme 6).

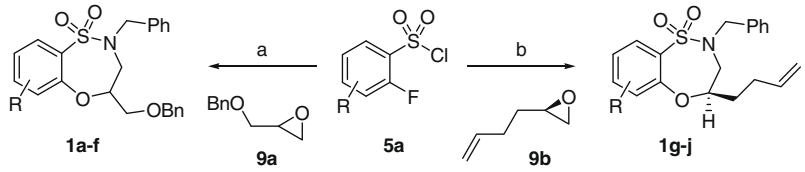
A selection of the prepared benzoxathiazepines, **1** were subjected to palladium-catalyzed Suzuki cross-couplings (Table 3), using a variety of boronic acids **10**.[9] In general, the yields of these cross-coupling products **11a–c** were good, however, a lower yield



Scheme 2. Synthetic strategy for the MCR synthesis of benzoxathiazepines **1**.



Scheme 3. Stepwise benzoxathiazepine **1** formation. Reagents and conditions: (a) benzylamine, K_2CO_3, 1,4-dioxane, 92%. (b) *O*-benzyl glycidyl ether **9a**, K_2CO_3, *n*-Bu_4NBr, 1,4-dioxane, 100 °C, 16 h, **7a** (38%) and **1a** (34%).

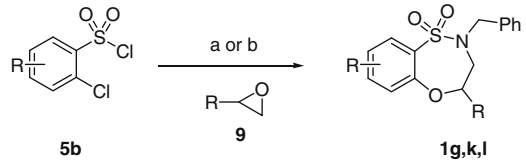


Scheme 4. One-pot MCR of benzoxathiazepines **1**. Reagents and conditions: (a) benzylamine **8**, K_2CO_3, *n*-Bu_4NBr, 1,4-dioxane, 100 °C, 72 h, 76% (when R = H); (b) benzylamine **8**, K_2CO_3, *n*-Bu_4NBr, 1,4-dioxane, 100 °C, 72 h, 58% (when R = H).

Table 1
Synthesis of benzoxathiazepines **1** from 2-fluorosulfonyl chlorides **5a**

Entry	Product	Time (h)	Yield (%)
1	**1a**	72	76
2	**1b**	72	79
3	**1c**	72	91
4	**1d**	72	86
5	**1e**	72	77
6	**1f**	168	72
7	**1g**	72	58
8	**1h**	72	76
9	**1i**	72	84
10	**1j**	72	76

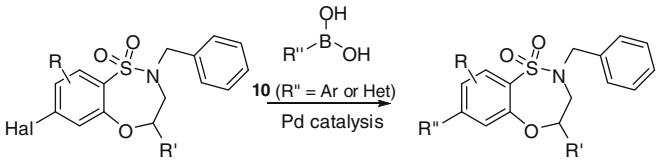
and incomplete conversion was afforded when the substrate **1h** containing an alkene functionality was employed, affording **11d** in a 36% isolated yield (Table 3, entry 4).[10,11]



Scheme 5. Synthesis of benzoxathiazepines **1** from 2-chlorosulfonyl chlorides. Reagents and conditions: (a) benzylamine **8**, **9a** or **9b**, K_2CO_3, *n*-Bu_4NBr, DMF, 120 °C, 72 h; (b) benzylamine **8**, K_2CO_3, 1,4-dioxane, 100 °C, 72 h.

Table 2
Synthesis of benzoxathiazepines **1** from 2-chlorosulfonyl chlorides **5b**

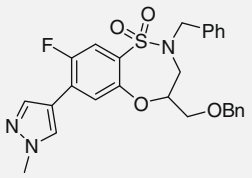
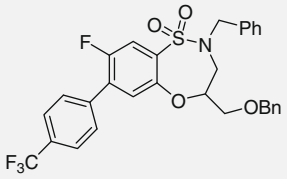
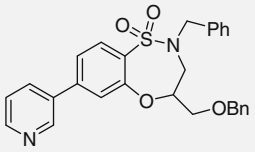
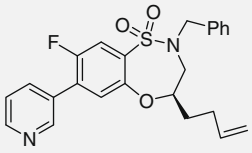
Entry	Product	Temp (°C)	Yield (%)
1	**1g**	120	25
2	**1k**	100	48
3	**1l**	100	67
4	**7b**	100	59



Scheme 6. Palladium-catalyzed diversification of halogenated benzoxathiazepines **1**.

In summary, we have identified a cheap, general, high yielding and rapid route to benzoxathiazepines, which can be completed in one pot from the commercially available starting materials. Suitably functionalized products have been shown to be useful substrates for further elaboration via palladium-catalyzed cross-couplings. This transformation broadens the applicability of this methodology, and allows the rapid synthesis of complex novel molecules of potential pharmacological interest. Further studies directed towards the chemical elaboration of benzoxathiazepines

Table 3
Palladium-catalyzed cross-couplings

Entry	Product	Starting material	Yield (%)
1	**11a** 	**1b**	88
2	**11b** 	**1b**	71
3	**11c** 	**1d**	72
4	**11d** 	**1h**	36

1 and the extension of this methodology towards the synthesis of benzothiadiazepines are currently underway.

Acknowledgements

We thank Simon Hamilton and Sophie Strickfuss from the MSD analytical research group at Hoddesdon for mass spectrometry work and chiral HPLC analysis.

References and notes

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4. As an example, in Ref. 3a, the ring closure of an alcohol onto an aryl fluoride using NaH in DMF has been used. See also: (a) White, E. H.; Lim, H. M. *J. Org. Chem.* **1987**, *52*, 2162–2166; (b) Bliss, A. D.; Cline, W. K.; Hamilton, C. E.; Sweeting, O. *J. Org. Chem.* **1963**, *28*, 3537–3541; (c) Penso, M.; Albanese, D.; Landini, D.; Lupi, V.; Tagliabue, A. *J. Org. Chem.* **2008**, *73*, 6686–6690.
5. Cleator, E.; Sheen, F. J.; Bio, M. M.; Brands, K. M. J.; Davies, A. J.; Dolling, U.-H. *Tetrahedron Lett.* **2006**, *47*, 4245–4248.
6. The ring-opening of epoxides with sulfonamides has been outlined in the literature, see: Baker, B. R.; Kadish, A. F.; Querry, M. V. *J. Org. Chem.* **1950**, *2*, 400–401; The conditions outlined here were discovered in our previous work, see Ref. 5, which were adapted from Albanese et al., see: Albanese, D.; Landini, D.; Penso, M.; Petricci, S. *Tetrahedron* **1999**, *20*, 6387–6394.
7. *General procedure for the multicomponent cyclization reaction*: sulfonyl chloride (1.0 mmol) was added to a solution of K_2CO_3 (2.5 mmol) and tetra-*n*-butylammonium bromide (0.1 mmol) in 1,4-dioxane (10 mL/g). Benzylamine (1.0 mmol) and epoxide (1.0 mmol) were added and the reaction mixture was heated to reflux and stirred for 72 h. The reaction mixture was allowed to cool to room temperature and was diluted with water (10 mL/g). The mixture was extracted with EtOAc (3 × 15 mL/g) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude products were purified by silica gel flash chromatography. Characterization of benzoxathiazepine **1d**. Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.75 (1H, d, J = 8.4, Ar–H), 7.30–7.13 (12H, m, Ar–H), 4.49 (2H, s, OCH_2Ph), 4.45 (1H, d, J = 14.4, NCH_ACH_BPh), 4.26–4.20 (1H, m, OCH), 3.84 (1H, d, J = 14.4, NCH_ACH_BPh), 3.76 (1H, dd, J = 15.2 and 10.8, CH_ACH_BOBn), 3.66–3.62 (1H, m, NCH_ACH_BCH), 3.48–3.44 (1H, m, NCH_ACH_BCH), 3.20 (1H, dd, J = 15.2 and 1.6, CH_ACH_BOBn); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 155.8, 139.8, 137.6, 135.2, 133.0, 130.1, 129.0, 128.7, 128.4, 128.1, 127.4, 124.9, 124.0, 77.8, 73.8, 70.1, 51.9, 49.5; HRMS (ESI+) calcd for $C_{23}H_{22}ClNNaO_4S$ 466.0856 $[M+Na]^+$, found 466.0859 $[M+Na]^+$.
8. Determined by chiral HPLC. Conditions, Chiral AD; eluent 20% *iso*-propyl alcohol in hexanes containing 0.1% TFA.
9. Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366.
10. *General procedure 1 for the Suzuki coupling*: the aryl halide (1.0 equiv), boronic acid (1.05 equiv), $PdCl_2$dppf–CH_2Cl_2 adduct (10 mol %) and potassium phosphate, dibasic (2.0 equiv) were added to a sealable tube containing a magnetic stir bar. Dioxane (10 mL/g) was added and the mixture was degassed by evacuating the system and back-filling with nitrogen for three times. The tube was sealed, heated to 100 °C and stirred for 19 h. The reaction was quenched by the addition of water (10 mL/g), the product was extracted with EtOAc (3 × 10 mL/g) and the combined organics were concentrated in vacuo to yield the crude product. The product was purified using silica gel flash chromatography.
11. *General procedure 2 for the Suzuki coupling*: the benzoxathiazepine (1 equiv) was dissolved in dioxane (10 mL/g) and the boronic acid (1.05 equiv) and palladium (diphenylphosphino)dichloride were added (3 mol %). Sodium carbonate (2 M, 1.2 equiv) was then added and the reaction mixture was heated to reflux for 90 min. The reaction was quenched by the addition of water (10 mL/g) and then extracted with EtOAc (3 × 10 mL/g). The combined organic layers were dried ($MgSO_4$), filtered and then concentrated in vacuo to give a yellow oil which was purified by column chromatography. Characterization of **11a**. Clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.84 (2H, m) 7.70–7.62 (4H, m) 7.58–7.46 (4H, m) 7.42–7.23 (4H, m), 4.63 (3H, m) 4.27–4.25 (1H, m) 4.0 (3H, s), 3.92–3.87 (2H, m), 3.78–3.74 (1H, m), 3.58–3.55 (1H, m) 3.28 (1H, d, J = 14 Hz); ^{13}C NMR (60 MHz) δ_C 138.0, 137.6, 135.1, 132.2, 132.1, 131.9, 130.1, 130.0, 128.8, 128.5 (m), 128.4, 128.2, 127.9, 127.6, 121.4 (d), 116.6, 116.3, 77.2, 73.6, 70.1, 51.6, 49.5, 39.3; HRMS (ESI+) calcd for $C_{27}H_{27}FN_3O_4S$ 508.1706 $[M+H]^+$, found: 508.1726 $[M+H]^+$.