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A general synthetic strategy for 1,3-dihydro-2,1,3-benzothiadiazole 2,2-dioxides (benzosulfamides)

Dawn E. Colyer, Andrew Nortcliffe, Simon Wheeler *

Sandwich Chemistry, Pfizer Global R and D, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK

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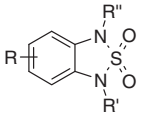
ABSTRACT

A general route to benzosulfamides is presented, allowing for flexible installation of substituents.

1,3-Dihydro-2,1,3-benzothiadiazole 2,2-dioxides (referred to herein as benzosulfamides) can be generalised by structure **1**.



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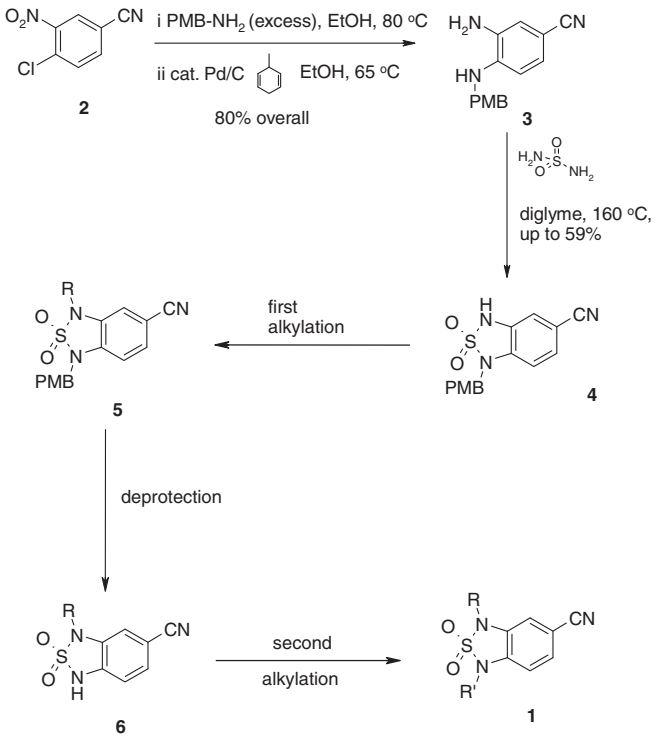
Despite their potential for diversity-oriented synthesis, and consequent attractiveness to the pharmaceutical industry, such compounds, have, with few exceptions,[1] seen only sporadic use in drug discovery programs. Their use in supramolecular chemistry has been more extensive but has also been limited to a handful of publications.[2] Such a paucity of work can most likely be explained by the absence of synthetic routes that allow for independent variation of all R groups indicated in structure **1**. The best solution to this problem disclosed to date relies on the chemoselective mono-deprotection of bis-carbamate protected benzosulfamides[2a] and is thus, in general, limited to materials where the ring is symmetrically substituted. The current Letter advances a new method which allows for late stage variation of either or both nitrogen substituents. Previously published chemistry[1] has installed one of these groups, constructed the ring and only then installed the other substituent, thus considerably reducing the flexibility of the synthesis.

Our general plan for achieving our aim was to prepare a 1,2-dianiline with one nitrogen bearing a protecting group. Building the sulfamide ring could be followed by alkylation of the unprotected nitrogen, then deprotection and alkylation of the nitrogen thereby revealed. We decided to employ *p*-methoxybenzyl (PMB) as our protecting group due to its long history in sulfamide chemistry.[3] Benzonitrile **2** was selected as the starting material for studies to test our strategy as a very similar compound had previously been converted into an analogue of dianiline **3**.[4] Additional motivation was supplied by the recognition that the nitrile of **2** could be converted into a variety of other functional groups once fully substituted benzosulfamides **1** had been prepared. With these strategic and tactical decisions made we set about reducing our ideas to practice. Our results are outlined in Scheme 1.



Scheme 1. Synthetic route to benzosulfamides **1** (PMB = *p*-methoxybenzyl).

* Corresponding author. Tel.: +44 1304 649173; fax: +44 1304 651987.
E-mail address: simon.wheeler@pfizer.com (S. Wheeler).

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As expected the initial S_NAr reaction proceeded smoothly to give the PMB-protected nitroaniline. Such compounds are well known in the chemical literature and it is recognised that similar intermediates bearing a variety of substituents on the benzene ring can be prepared by different methods.[5] Once such intermediates are in hand reduction of the nitro group, which can be achieved with chemoselectivity over most other functional groups, will give access to the analogues of dianiline **3**. At this stage the cyclisation conditions first disclosed by Teufel[6] (which have proven to be general, having been applied to a wide variety of substrates[7]) can be employed. Thus we reduced the nitro group in **2** using catalytic hydrogenation to obtain **3** in good yield. We then applied Teufel's conditions and added a suspension of dianiline **3** and commercially available sulfamide to diglyme (diethylene glycol dimethyl ether) preheated to 160 °C. After 30 min at this temperature benzosulfamide **4** was isolated by pouring the cooled reaction mixture into diethyl ether and filtering off the precipitated product (Scheme 1). As well as temperature and solvent (pyridine was ineffective even at 160 °C in a microwave reactor), this reaction was found to be critically dependent on the purity of the starting dianiline. Much reduced yields were encountered on running this reaction with **3** containing even minor levels of impurities. Extensive efforts to find alternative reaction conditions were made. Sulfuryl chloride in CH_2Cl_2 gave no reaction, nor did sulfonyl diimidazole. Forming the diquaternary salt of sulfonyl diimidazole[8] (using methyl iodide) and attempting the cyclisation led only to methylation of **3**. No reaction was observed with catechol sulfate[9] and only a trace reaction with the carbamate reagent disclosed by workers at Lilly.[10] Evidence from the literature suggests that the ease of these cyclisation reactions varies with substituents on the benzene ring so it is likely that the nitrile group of **3** retards the reaction. It should be noted that, despite these difficulties, **4** has been routinely prepared on gram scale.

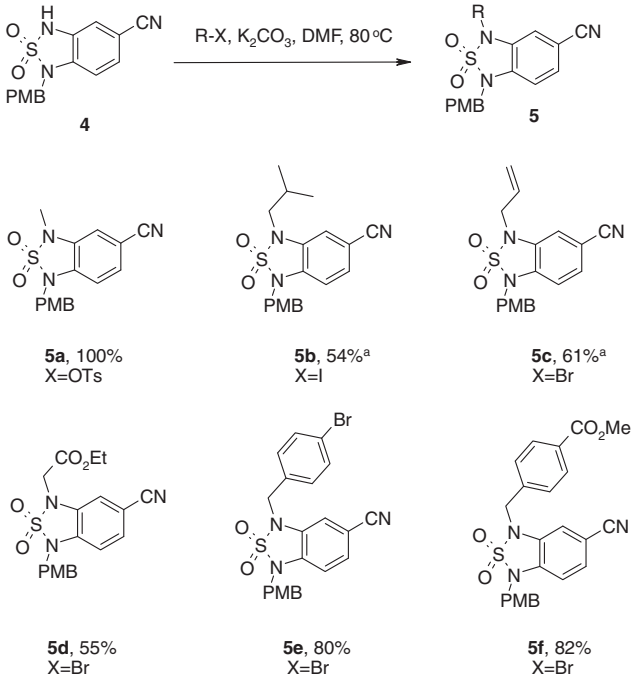
With appreciable quantities of benzosulfamide **4** in hand, we examined its alkylation. The results of this study are shown in Scheme 2. As will be readily observed benzosulfamide **4** can be alkylated with a variety of electrophiles in moderate to good yields. Thus unfunctionalised alkyl groups could be appended (**5a** and **5b**) as could groups bearing residues suitable for further manipulation (**5c** and **5d**). Benzyl groups could also be attached where sites for continued synthesis were also incorporated (**5e** and **5f**). All these products were obtained after a few hours in DMF at 80 °C, with the exception of **5d** where reaction at room temperature was used, otherwise extensive decomposition was observed. For simple alkyl groups the iodide leaving group was necessary whilst bromide sufficed for more activated electrophiles. The exception to this general trend was methylation where methyl tosylate was found to be an effective alkylating agent.

We next attempted the deprotection of **5a** to give **6a**. This was found to be successful in neat TFA at reflux (Scheme 3).

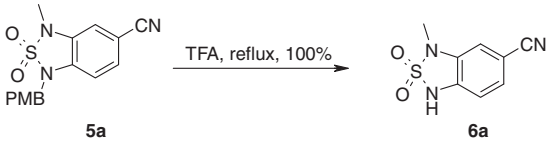
Use of milder conditions (room temperature with or without dilution with CH_2Cl_2) led to no reaction; alternative deprotection conditions (DDQ or ceric ammonium nitrate) gave only decomposition of **5a**. We also discovered that it was necessary to work up the reaction using buffer; use of water or aqueous base led to decomposition.

With access to **6a** secure, attention was switched to introducing a substituent on the second nitrogen. This proved to be possible using the same conditions as the first alkylation, albeit with generally lower yields, and is shown in Scheme 4. Alkylations with representative alkyl, allyl and benzyl electrophiles were all successful suggesting that benzosulfamide **6a** is likely to undergo alkylation with a similar range of electrophiles as previous substrate **4**. Disappointingly, reaction with ethyl acrylate failed to furnish any product despite longer reaction times and multiple equivalents of electrophile.

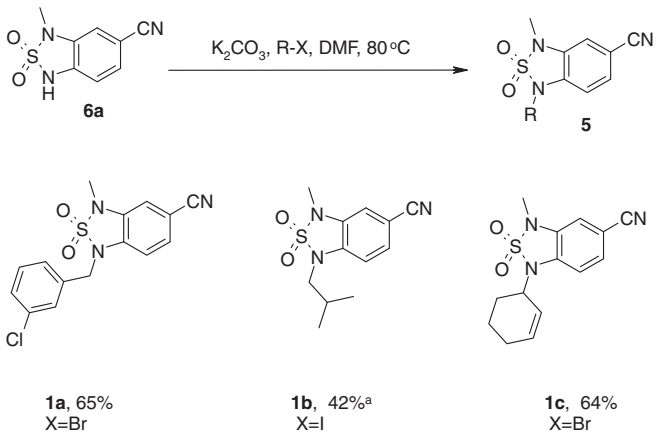
Having shown that we could construct benzosulfamides bearing a variety of substituents we were also interested in their reagent toleration and set out to explore this by transforming the nitrile of **5** into a variety of other useful functional groups. The successful implementation of this plan is shown in Scheme 5. Thus full[11] or partial reduction of the nitrile was possible to give the correspond-



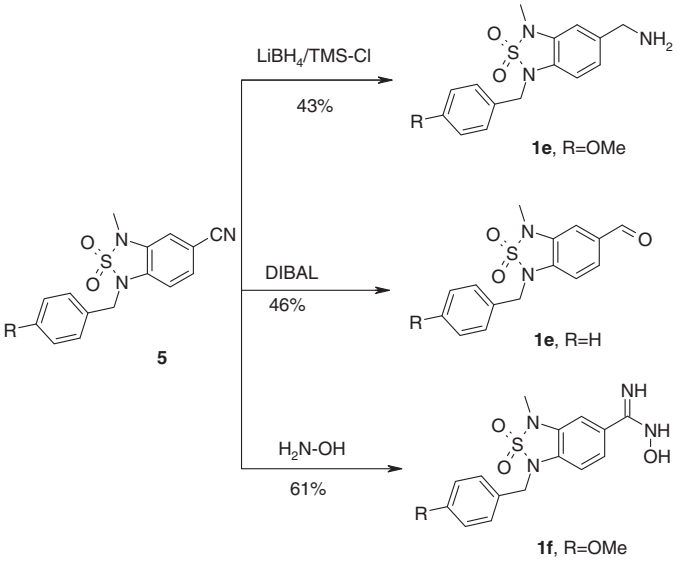
Scheme 2. Alkylations of **4**, products generated and isolated yields. Standard conditions: 1 equiv of **4**, 1.2 equiv of electrophile, 1.3 equiv of K_2CO_3: (a) required 2.4 equiv of electrophile.



Scheme 3. Deprotection of benzosulfamide **5a**.



Scheme 4. Introduction of a substituent onto the second nitrogen atom. Standard conditions were the same as given in Scheme 2: (a) required 4 equiv of electrophile.



Scheme 5. Transformation of the nitrile residue into other functional groups.

ing primary amine or the aldehyde, respectively. Preparation of the amidoxime was also successful. This group is a precursor to numerous heterocycles either directly or after catalytic hydrogenolysis of the N–O bond.[12]

In summary we have developed a flexible route to a diverse range of benzosulfamides employing a mono-protected 1,2-dianiline as the starting material. The key advantage of this method is that it is possible to add substituents to *both* nitrogen atoms at a late stage in the synthesis. Furthermore we have demonstrated that the sulfamide moiety is resilient to a range of reaction conditions and therefore that further derivatisations are possible. An obvious weak point of this work is the need to use refluxing TFA to remove our chosen protecting group. In future it may be possible to conduct the deprotection under milder conditions by use of the 2,4-dimethoxybenzyl protecting group[13] or to use allyl protection and deprotect using a metal catalyst.[14] We anticipate that these advances will lead to the greater popularity of the benzosulfamide motif in the pharmaceutical industry.[15]

Acknowledgements

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15. Selected experimental procedures. *Cyclisation to benzosulfamide*: Diglyme was deoxygenated by bubbling N_2 through it for 10 min. After this time 3 mL of diglyme was heated to 160 °C (internal temperature). Dianiline **3** (1.533 g, 6.05 mmol) and sulfamide (698 mg, 7.26 mmol) were then added as a suspension in diglyme (6 mL) rinsing in with more diglyme (1 mL). After 30 min at 160 °C the reaction was cooled to room temperature and poured into Et_2O (75 mL) causing **4** to precipitate as an off-white solid (1.135 g, 6.05 mmol, 59%). ^{1}H NMR (400 MHz, methanol-d_4): 3.77 (3H, s), 4.78 (2H, s), 6.31 (1H, d, J = 6.3 Hz), 6.75 (1H, d, J = 2.0 Hz), 6.77 (1H, dd, J = 6.3, 2.0 Hz), 6.87 (2H, d, J = 9.0 Hz), 7.38 (2H, d, J = 9.0 Hz). ^{13}C NMR (100 MHz, methanol-d_4): 45.1, 54.5, 101.1, 105.2, 111.1, 113.8, 120.8, 121.1, 128.3, 128.8, 137.8, 139.5, 159.5. MS (ESI): m/z 314 $[M-1]^-$.
Alkylation of benzosulfamide: To a stirred solution of sulfamide **4** (207 mg, 0.66 mmol) in DMF (3 mL) was added K_2CO_3 (181 mg, 1.32 mmol) followed by MeOTs (257 mg, 1.38 mmol) and the whole stirred at 80 °C for 2 h. The reaction was cooled and diluted with H_2O (10 mL). EtOAc (5 mL) was added and the layers separated. The organic layer was washed with H_2O (2 × 20 mL), then with brine (10 mL), dried over $MgSO_4$ and evaporated to give **5a** as a brown solid (216 mg, 0.66 mmol, 100%). ^{1}H NMR (400 MHz, $CDCl_3$): 3.36 (3H, s), 3.81 (3H, s), 4.88 (2H, s), 6.58 (1H, d, J = 8.2 Hz), 6.90 (2H, d, J = 8.8 Hz), 6.93 (1H, d, J = 1.6 Hz), 7.18 (1H, dd, J = 8.2, 1.6 Hz), 7.35 (2H, d, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 28.4, 46.2, 55.5, 104.7, 108.6, 110.2, 114.8, 119.0, 125.2, 127.2, 129.1, 130.1, 132.4, 160.0.
Deprotection of the PMB group: Protected sulfamide **5a** (500 mg, 1.52 mmol) was suspended in TFA (5 mL) and heated under reflux for 2 h. The reaction was then cooled to room temperature and diluted with EtOAc (30 mL). The resulting solution was washed with pH 7.0 buffer solution (2 × 30 mL) then with brine (30 mL). The organic was dried over $MgSO_4$ and evaporated to give a brown solid. This was triturated with MeOH (5 mL) and the insoluble material filtered off. Evaporation of the liquors gave **6a** as an off-white solid (318 mg, 1.52 mmol, 100%). ^{1}H NMR (400 MHz, methanol-d_4): 3.25 (3H, s), 6.93 (1H, d, J = 8.2 Hz), 7.20 (1H, d, J = 1.6 Hz), 7.31 (1H, dd, J = 8.2, 1.6 Hz). ^{13}C NMR (100 MHz, methanol-d_4): 26.4, 104.5, 110.0, 118.9, 126.0, 126.6, 132.0. MS (ESI): m/z 208 $[M-1]^-$.