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Microwave-assisted synthesis of 1,3-dihydro-[1,2,5]thiadiazolo[3,4-*b*]pyrazine-2,2-dioxides

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Abstract—1,3-Dihydro[1,2,5]thiadiazolo[3,4-*b*]pyrazine-2,2-dioxides are obtained in a good yield from the reaction of 2,3-diamino pyrazines with sulfamide under microwave conditions.

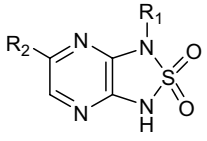
To attenuate toxicity and/or improve the pharmacokinetic profile of biologically active molecules, the medicinal chemist frequently utilizes a variety of bioisosteric replacements.[1] One such bioisostere, the sulfonylurea group, has been used as a surrogate for amides, ureas, thioureas, nitrosoureas, carbamates, and sulfonamides.[2] However, the limitations of the chemical methods available for the preparation of this unit have probably contributed to its limited use in medicinal chemistry.

Sulfonylureas are commonly prepared from the reaction of an amine with sulfamide[2b,3] or, alternatively, they can be obtained using sulfuryl chloride.[4] Other milder methodologies described in the literature involve the use a catecholsulfate,[5] the displacement by an amine of the *N*-oxazolidinone group from a sulfamoyl *N*-oxazolidinone,[6] or by sequential activation of the imidazole group in *N*,*N*′-sulfuryldiimidazoles using methyl triflate followed by nucleophilic displacement with a variety of amines and anilines.[7] Unsymmetrical sulfonylureas can also be prepared from the reaction of an amine with a sulfamoyl chloride. In turn, sulfamoyl chlorides can be obtained from the corresponding sulfamic acid by a reaction with phosphorus pentachloride[8] or by treatment of an amine with sulfuryl chloride.[2c,9]

Our interest in the use of this functional group in our own research programs prompted us to search for a convenient method for the preparation of cyclic sulfonylureas. In particular we were interested in pyrazine derivatives of type **1** (see Scheme 1). To the best of our knowledge such structures have not been described previously in the literature. Similar bicyclic ring systems in which the pyrazine ring of **1** is replaced by a pyridine[10] or a benzene[2b,11] ring have been documented.

It was envisaged that derivatives of type **1** could be prepared from the corresponding diamines **5** using methodologies such as described above. The synthesis of the requisite diamine precursors is outlined in Scheme 2.

The key steps in the synthesis of the required intermediates **5** involve a regioselective nucleophilic aromatic substitution of the 3-bromo moiety of 2-amino-3,5-dibromopyrazine **3** (obtained by bromination of commercially available 2-aminopyrazine **2** with bromine in chloroform in the presence of pyridine[12]) with an



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Scheme 1. Target pyrazine derivatives.

Keywords: Microwave; Sulfonylureas; Suzuki reaction; Nucleophilic aromatic substitution.
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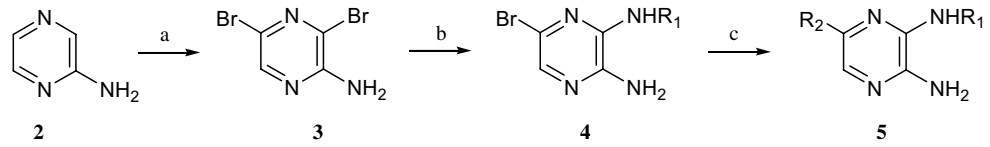


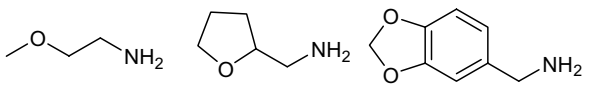
Scheme 2. Synthesis of intermediates **5**. (a) Br_2, Pyr, $CHCl_3$; (b) R_1NH_2, DIPEA, EtOH, MW, 140 °C, 35 min; (c) $R_2B(OH)_2$, Na_2CO_3 (2 M), $Pd(dppf)_2Cl_2$·DCM, toluene/EtOH (2:1), 90 °C, 24 h.

appropriate amine, followed by a Suzuki reaction with the corresponding boronic acid.[13]

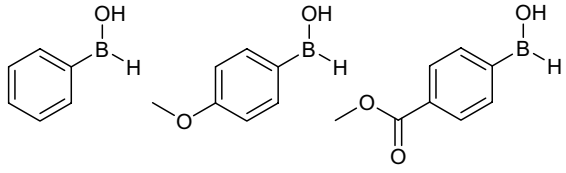
The nucleophilic aromatic substitution of the 3-bromo substituent of **3** by an amine was carried out in the microwave in the presence of DIPEA in EtOH.[13,14] Three different primary amines were used (Scheme 3) and the yields ranged from 80% to 94% after the purification by silica gel chromatography. The purities determined by HPLC were good and the structures were assigned by NMR. Comparing ^{1}H NMR spectra, an upfield shift is seen for H-6 of the pyrazine, from 8.16 ppm in compound **3** to approximately 7.45 ppm in the substitution products **4**.

The Suzuki reaction was carried out using three electronically different boronic acids to see if any differences in the reactivity could be seen (Scheme 4).[15] Yields of coupled products **5** ranged from 66% to 100% with *p*-methoxycarbonylphenylboronic acid giving the poorest results. The crude reaction mixture was purified using Dowex ion-exchange resin (H^+ form). ^{1}H NMR spectra showed the characteristic aromatic protons of the phenyl group and an upfield shift of the pyrazine H-5 ranging from 0.3 to 0.45 ppm depending upon the compound.

With diamines **5** in hand we now turned our attention to the preparation of the desired cyclic sulfonylureas. Among the different synthetic methods available, we tested those involving the use of sulfamide,[3] sulfuryl chloride,[4] and catecholsulfate,[5] as sources of the synthon XSO_2X (X being a leaving group). The use of sulfuryl chloride[4] or catecholsulfate[5] under various conditions did not give rise to the desired products. Finally we tried to effect formation of the cyclic derivatives using sulfamide under the reflux in pyridine as such



Scheme 3. Amines used in the S_NAr reaction.



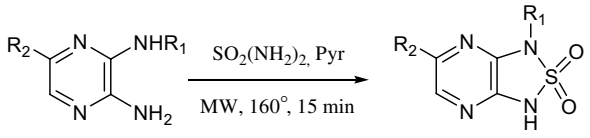
Scheme 4. Boronic acids used in the Suzuki reaction.

conditions have been successfully used for reactions of sulfamide with alkyl amines[2a,3] and anilines.[2b,d] In our hands, with 2,3-diaminopyrazines **5**, none of the desired sulfonylureas **1** were observed neither after 24 h nor after three days reaction time. The poor nucleophilicity of the heterocyclic amine is likely to be the main cause of reaction failure. It is well known that the use of microwave irradiation can facilitate reactions where prolonged heating is essential and can dramatically affect both yields and the rate of the chemical reactions.[16] In the case of the cyclization with sulfamide as reagent it was quickly ascertained that clean product formation could be achieved under such conditions. After trying different temperatures and times, we found that the best conditions to effect cyclization were to heat reactions at 160 °C for 15 min at 200 W of power.[17]

Table 1 shows the yields and purities obtained with different R_1 and R_2 groups after purification of the crude reaction mixtures with Bond Elut SAX cartridges (anion exchange interaction). All the desired sulfonylureas **1** were obtained in good to excellent yields and purities, the presence of electron-withdrawing or donating groups in the para position of the R_2 substituent did not affect the sulfonylurea formation. All the compounds were characterized by ^{1}H NMR[18] and ES-MS to confirm their structural integrity.

Table 2 shows the main differences found in the ^{1}H NMR spectra between diamines **5** and sulfonylureas **1**. It can be seen that there is a considerable upfield shift

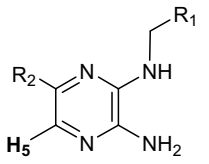
Table 1. Yields and purities of sulfonylureas **1** after SAX purification (all the products have been analyzed for structural integrity by ^{1}H NMR[18])



Compound	R_1	R_2	Yield (%)	Purity[a]
1a	$CH_{3a}O(CH_2)_2$	Ph	90	93
1b	$CH_3O(CH_2)_2$	*p*MeOPh	74	73
1c	$CH_3O(CH_2)_2$	*p*(MeOCO)Ph	87	88
1d	2-$THFCH_2$	Ph	90	99
1e	2-$THFCH_2$	*p*MeOPh	84	99
1f	2-$THFCH_2$	*p*(MeOCO)Ph	79	89
1g	3,4-$(OCH_2O)PhCH_2$	Ph	86	99
1h	3,4-$(OCH_2O)PhCH_2$	*p*MeOPh	89	99
1i	3,4-$(OCH_2O)PhCH_2$	*p*(MeOCO)Ph	77	95

[a] By HPLC at 210 nm.

Table 2. Relevant NMR data (ppm)[a] of diamines **5** and sulfonylureas **1**



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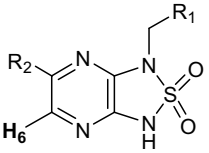

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Compound	H-5	C-5	NCH_2	NCH_2	Compound	H-6	C-6	NCH_2	NCH_2	Δ_{H5-H6}	Δ_{C5-C6}	$\Delta_{CH_2(4)-CH_2(5)}$	$\Delta_{CH_2(4)-CH_2(5)}$
5a	7.88	126.5	3.67	41.2	**1a**	7.33	113.4	4.12	40.8	0.55	13.1	−0.45	0.4
5b	7.81	125.7	3.67	41.2	**1b**	7.20	110	4.1	40.9	0.61	15.7	−0.43	0.3
5c	7.82	125.9	3.71	40.8	**1c**	7.38	112.3	4.15	40.9	0.44	13.6	−0.44	−0.1
5d	7.87	126.2	3.43	45.3	**1d**	7.28	111.2	3.89	45.5	0.59	15.0	−0.46	−0.2
			3.86					4.05				−0.19	
5e	7.71	124.3	3.40	46.2	**1e**	7.18	110	3.88	45.5	0.53	14.3	−0.48	−0.5
			3.88					4.04				−0.16	
5f	7.92	126.4	3.41	46.2	**1f**	7.44	114.5	3.92	45.1	0.48	11.9	−0.51	1.1
			3.88					4.06				−0.18	
5g	7.79	125.3	4.63	45.1	**1g**	7.34	113.0	4.9	44.2	0.45	12.3	−0.36	0.9
5h	7.71	124.2	4.62	45.0	**1h**	7.19	111.6	4.9	44.1	0.52	12.6	−0.36	0.9
5i	7.82	126.5	4.55	43.9	**1i**	7.38	114.8	5.00	44.2	0.44	11.7	−0.38	−0.3

[a] ^{1}H NMR spectroscopy was performed in $CDCl_3$ with a few drops of added CD_3OD (except **5a**,**b**,**d**–**f** where only $CDCl_3$ was used).

(0.4–0.5 ppm) of H6 in the ^{1}H spectra of **1** as compared to compound **5**. The same effect can be seen in the ^{13}C NMR spectra for C6 of compounds **1** and C5 of compounds **5**; in this case the upfield shifts range from 11 to 16 ppm.

It can be concluded that a simple microwave-assisted methodology to obtain heterocyclic sulfonylureas has been developed. The method is rapid, high-yielding and involves the use of the inexpensive reagent sulfamide. Of particular note is that poor nucleophilic amines react well. Studies involving the application of the methodology to other heterocyclic diamines are currently underway in our laboratories.

Acknowledgements

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14. *General procedure for S_NAr reactions*. A mixture of 2-amino-3,5-dibromopyrazine **3** (1 equiv) a primary amine (1.2 equiv) and DIPEA (1.2 equiv) in EtOH was placed in the microwave (CEM Discover) and heated at 140 °C (150 W) for 35 min. The solvent was removed under reduced pressure and the residue was taken up with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the resulting crude product was purified by column chromatography.
15. *General procedure for Suzuki reactions*. Bromo-pyrazine **4** (100 mg) was suspended in degassed toluene/EtOH (2:1, 1.2 mL). $Pd(dppf)_2Cl_2$·DCM (5 mol %), the appropriate boronic acid (1.5 equiv) and Na_2CO_3 2 M (3 equiv) were added and the mixture was degassed with nitrogen and then shaken for 24 h at 90 °C. The solvent was removed under reduced pressure in an EZ-2 apparatus and the residue was purified using Dowex Resin. Samples were dissolved in MeOH and approximately 1.5 g of Dowex resin/mmol of the product was added and shaken for 18 h. The solution was filtered and the resin washed with MeOH, DCM and MeOH. Finally the compounds were extracted from the resin with 2 mL of NH_3 (7 N in MeOH). After 2 h of shaking, the resins were filtered and the filtrate collected and solvent removed in an EZ-2 apparatus.
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17. *General procedure for cyclization reactions*: A mixture of pyrazine **5** (1 equiv) and sulfamide (3.5 equiv) in pyridine was placed in the microwave (CEM Discover) and heated at 160 °C (200 W) for 15 min. The residues were purified using Bond Elut SAX (Strong Anion Exchange) cartridges (Varian) that were first soaked with ACN. The crude samples were introduced in the cartridges, 7 mL of ACN was then passed through in order to eliminate the pyridine and excess of sulfamide. Finally compounds were eluted with 5% HOAc in ACN and the solvent was removed in an EZ-2 apparatus.
18. ^1H NMR spectra of all compounds can be found in the supporting information.