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A facile synthesis of annulated azolo[*c*][1,2,4]thiadiazine *S*,*S*-dioxides

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ABSTRACT

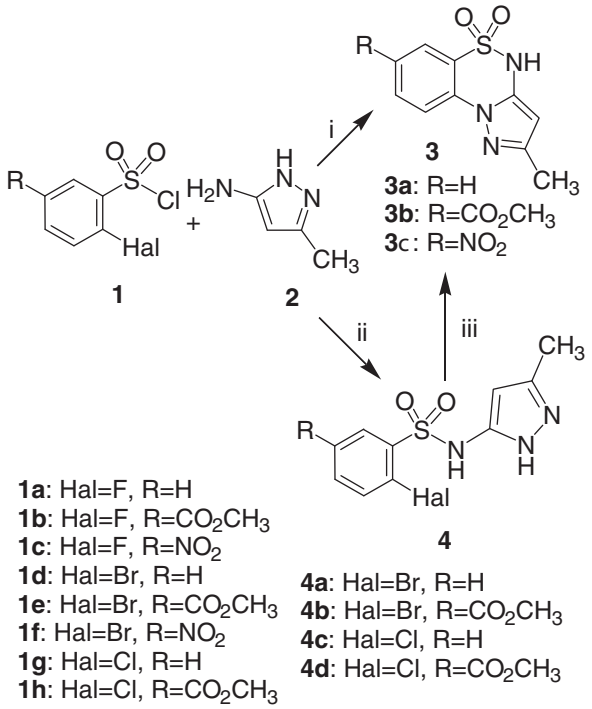
Condensations of *o*-halo-substituted benzenesulfonyl chlorides with 3-aminoazoles give the corresponding azolo[*c*][1,2,4]benzothiadiazine *S*,*S*-dioxides. *o*-Fluorobenzenesulfonyl chlorides and *o*-bromobenzene sulfonyl chlorides bearing a nitro group are reactive enough to give the desired azolo[*c*][1,2,4]benzothiadiazine *S*,*S*-dioxides in a one-pot, base-promoted reaction. In all other cases, open-chain sulfonylated 3-aminoazole intermediates are isolated. The latter are converted into the title compounds upon addition of a copper(I) catalyst.

Compounds containing the azolo[*c*][1,2,4]benzothiadiazine *S*,*S*-dioxide substructure have been shown to possess diuretic,[1] antihypertensive,[2] antibacterial,[3] and other[4] activities. A few synthetic pathways to the azolo[*c*][1,2,4]benzothiadiazine *S*,*S*-dioxide system have been developed. For example, a number of derivatives of pyrrolo[2,1-*c*][1,2,4]benzothiazine *S*,*S*-dioxide have been prepared through condensations of *o*-aminoarylsulfonyl amides with phthlaldehydic acid,[1,4] 2-functionalized benzonitriles,[5] γ-halocarboxylic acids,[6] and several dicarboxylic acids.[2,7] 4*H*-Tetrazolo[5,1-*c*][1,2,4]benzothiadiazine *S*,*S*-dioxides have been prepared through diazotation of 3-hydrazo-4*H*-1,2,4-benzothiadiazine *S*,*S*-dioxide derivatives.[3]

In this work we describe a convenient method for the preparation of azolo[*c*][1,2,4]benzothiadiazine *S*,*S*-dioxide derivatives from *o*-haloarylsulfonyl chlorides and 3-aminoazoles.

As shown in Scheme 1, the reaction of *o*-fluoroarylsulfonyl chlorides **1a**–**1c** with 3-methyl-1*H*-pyrazol-5-amine (**2**) results in the formation of novel pyrazolo[5,1-*c*][1,2,4]benzothiadiazine *S*,*S*-dioxides **3a**–**3c**. The same ring system is formed via the reaction of 2-bromo-5-nitrobenzenesulfonyl chloride (**1f**) with **2** (Scheme 1).

Reactions of *o*-haloarylsulfonyl chlorides **1d,e** and **1g,h** gave rise to *N*-(3-amino-1*H*-pyrazol-5-yl)-2-halobenzenesulfonamides **4a**–**d** (Scheme 1). Sulfonamides **4a,b** were readily transformed into the corresponding 4*H*-pyrazolo[5,1-*c*][1,2,4]benzothiadiazine *S*,*S*-dioxide derivatives **3** through a copper(I)-catalyzed intramolecular nucleophilic displacement. Unlike compounds **4a,b**



Scheme 1. The preparation of pyrazolo[5,1-*c*][1,2,4]benzothiadiazine *S*,*S*-dioxides (i) DMF, K_2CO_3, 20–90 °C; (ii) Py, reflux; (iii) DMF, K_2CO_3, CuI, DMEDA, Ar, 20–90 °C.

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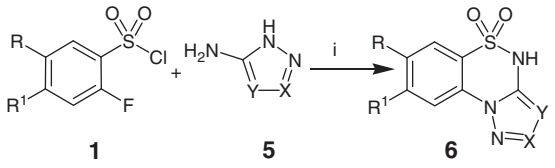


1a: R=R^1=H
1b: R=CO_2CH_3 R^1=H
1c: R=NO_2 R^1=H
1i: R=H R^1=NO_2

5a: X=CH, Y=C-CN
5b: X=CH, Y=N
5c: X=Y=N
5d: X=C-CO_2CH_3 Y=N

6a: R=R^1=H, X=C-CO_2CH_3 Y=N
6b: R=CO_2CH_3, R^1=H, X=CH, Y=C-CN
6c: R=CO_2CH_3, R^1=H, X=CH, Y=N
6d: R=CO_2CH_3, R^1=H, X=Y=N
6e: R=NO_2, R^1=H, X=CH, Y=N
6f: R=H, R^1=NO_2, X=CH, Y=N

Scheme 2. Preparation of annulated 2*H*-1,2,4-benzothiadiazine *S*,*S*-dioxides **6**. Reagents and conditions: (i) DMF, K_2CO_3, 20–90 °C.

sulfonamides **4c,d** did not undergo the intramolecular nucleophilic displacement under either catalytic or non-catalytic conditions.

Variation of the azole part was studied by reacting methyl 3-(chlorosulfonyl)-4-fluorobenzoate (**1b**) with 3-aminoazoles **5a–c** (Scheme 2). The reactions proceeded in one pot under non-catalytic conditions resulting in the corresponding annulated 2*H*-1,2,4-benzothiadiazine *S*,*S*-dioxides **6** (Scheme 2).

The ^{1}H NMR spectra of compounds **3** and **6** recorded in DMSO-d_6 revealed broad singlets due to NH protons in the range of 12–13 ppm. The 3-CH protons (Fig. 1) of compounds **3** manifested themselves as characteristic singlets at 5.9–6.0 ppm. The ^{13}C NMR spectra of compounds **3** and **6** showed characteristic signals due to C-3a in the range of 135–140 ppm. Characteristic symmetric and asymmetric vibrations of the sulfo-group were observed in the

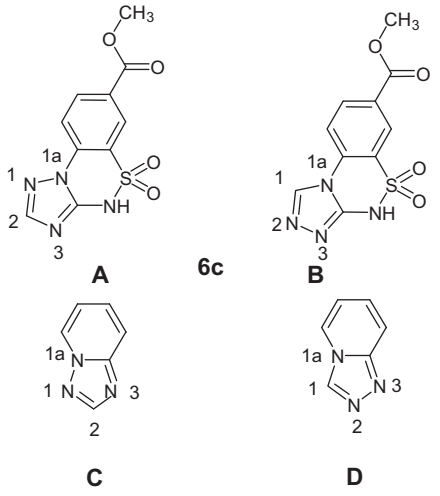


Figure 2. Structural considerations for compound **6c**.

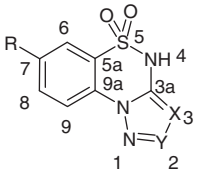


Figure 1. Atom numbering scheme for compounds **3** and **6**.

IR spectra of compounds **3** and **6** at 1110–1135 cm^{-1} and 1289–1318 cm^{-1}, respectively.

As shown in Figure 2, the reaction of methyl 3-(chlorosulfonyl)-4-fluorobenzoate (**1b**) with 4*H*-1,2,3-triazol-3-amine (**5b**) could give two cyclization products **6c** (structures **A** and **B**).

In structure **A**, C-2 is connected to two sp^2 nitrogen atoms, N-1 and N-3, whereas in structure **B**, C-1 is bound to an sp^3 nitrogen N-1a and sp^2 nitrogen N-2. Analysis of the literature shows that C-2 of [1,2,4]triazolo[1,5-*a*]pyridine (structure **C** in Fig. 2), which is analogous with structure **A**, appears at 154 ppm in the ^{13}C NMR spectrum.[8] The ^{13}C NMR spectrum of compound **6c** reveals the signal for C-2 at 153.7 ppm. Notably, C-1 of structure **D** (Fig. 2), which is analogous to structure **B**, appears at 136 ppm in the ^{13}C NMR spectrum.[8] Therefore, on the basis of its ^{13}C NMR spectrum, compound **6c** is ascribed to structure **A**.

Additional synthetic evidence for structure **A** for **6c** is derived from its N-methylation reaction. Scheme 3 shows that three isomeric products **7a**–**7c** might be expected as a result of the methylation.

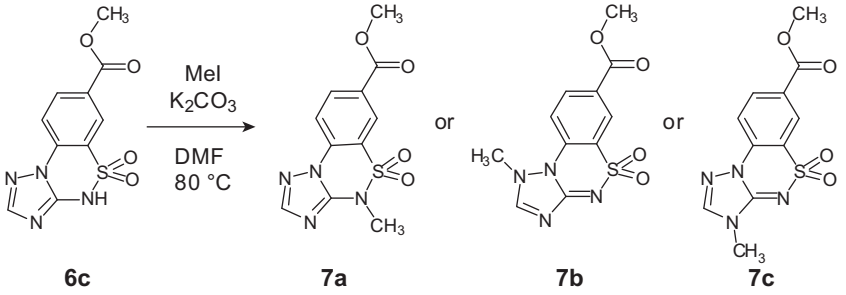
The ^{1}H NMR spectrum of compound **7** showed two closely lying singlets at 3.85 and 3.93 ppm corresponding to two methyl groups. Nuclear Overhauser effect (NOE) analysis (Fig. 3) revealed that the methyl group appearing as a singlet at 3.93 ppm had NOEs with protons H-6 and H-8, while the remaining methyl group singlet at 3.85 ppm demonstrated NOEs with protons H-9 and H-2. This means that the former methyl signal corresponds to a carboxymethyl group, while the latter corresponds to the N-Me group. Therefore, compound **7** exists in form **7b**. This provides additional confirmation of structure **A** ascribed above to compound **6c**.

As shown in Scheme 4, the azolo[*c*][1,2,4]benzothiadiazine unit is considerably stable under basic and acidic conditions allowing for flexible functional group transformations. For example, hydrolysis of the ester groups in **6a** and **6c** gives rise to carboxylic acids **8** and **9**, respectively. Reduction of the nitro-group in **6e** and **6f** readily yields amines **10** and **11**.

In summary, we have described a new and efficient approach to a variety of azolo[*c*][1,2,4]benzothiadiazine *S*,*S*-dioxides. The title compounds were prepared through one- or two-step reactions of *o*-haloarylsulfonyl chlorides and aminoazoles. The reported approach broadens considerably the scope of the available methods for the preparation of azolo[*c*][1,2,4]benzothiadiazine *S*,*S*-dioxides. This method allows variation of the number of substituents on both the benzene and azole rings, as well as the azole fragment itself.

Typical procedure for the preparation of annulated azolo[*c*][1,2,4]benzothiadiazine *S*,*S*-dioxides **3** from sulfonyl chlorides **1a–1c** and **2.**

To a stirred solution of a 3-aminoazole **2** (0.005 mol) and K_2CO_3 (1.38 g, 0.01 mol) in DMF (50 mL) was added dropwise a solution of sulfonyl chloride **1** (0.005 mol) in DMF (50 mL). The mixture was stirred for 2 h at room temperature and then for 8 h at 80 °C. The solvent was removed under reduced pressure and the residue was dissolved in deionized H_2O (200 mL). The pH of the solution was adjusted to 1 with concentrated HCl causing precipitation of a colorless solid. The precipitate was filtered and washed with H_2O (3 × 75 mL) and with *i*-PrOH (2 × 10 mL).



Scheme 3. Methylation of compound **6c**.

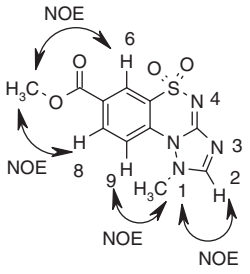
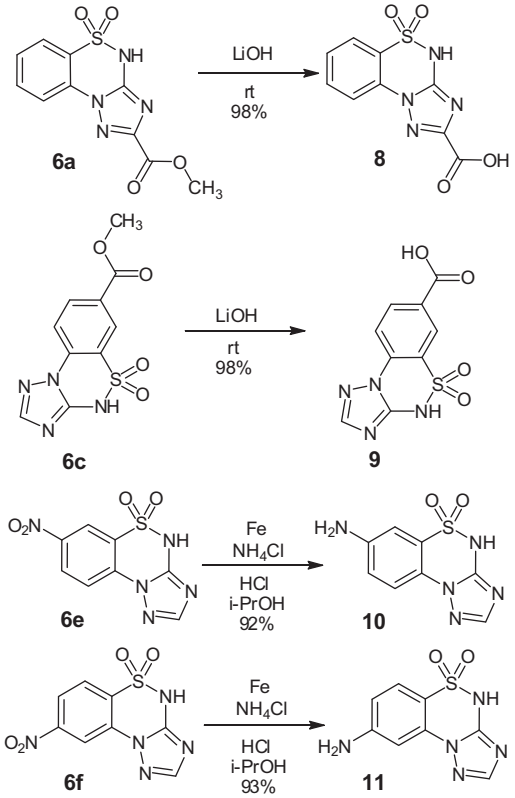


Figure 3. The NOE evidence for structure **7b**.



Scheme 4. Reactions of various azolo[*c*][1,2,4]benzothiadiazine *S*,*S*-dioxides.

2-Methyl-4*H*-pyrazolo[5,1-*c*][1,2,4]benzothiadiazine *S*,*S*-dioxide (3a)

Yield 0.8 g (68%) from **1a**, 1.07 g (91%) from **4a.** mp 243 °C (dec).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.26 (s, 3H, CH_3), 5.77 (s, 1H, ArH), 7.25 (t, $^3J_{HH}$ = 8 Hz, 1H, ArH), 7.29 (d, $^3J_{HH}$ = 8 Hz, 1H, ArH), 7.70 (t, $^3J_{HH}$ = 8 Hz, 1H, ArH), 7.96 (d, $^3J_{HH}$ = 8 Hz, 1H, ArH), 11.50 (br s, 1H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.45, 88.96, 117.19, 118.73, 122.00, 123.85, 135.17, 137.36, 145.03, 155.75.

MS (CI): m/z (%) = 234 (100) $[M-H]^+$.

Anal. Calcd for $C_{10}H_9N_3O_2S$: C, 51.05; H, 3.86; N, 17.86. Found: C, 51.09; H, 3.85; N, 17.83.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.040.

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