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A one-pot, non-catalytic approach to 1,2,4-benzothiadiazine-1,1-dioxides

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ABSTRACT

Condensations of *o*-halo-substituted benzenesulfonyl chlorides with 2-aminopyridines and amidines may give the corresponding 1,2,4-benzothiadiazine-1,1-dioxides under mild, non-catalytic conditions in nearly quantitative yields. The successful one-pot cyclization depends on three factors: (i) the nature of the *o*-halogen, (ii) the electronic character of the benzene ring substituent, and (iii) the steric load around the amidine unit. *O*-Fluorobenzenesulfonyl chlorides bearing methylcarboxyl- or nitro-group and *o*-chloro- and *o*-bromobenzenesulfonyl chlorides bearing nitro-group are reactive enough to give the desired 1,2,4-benzothiadiazine-1,1-dioxides in a one-pot base-promoted reaction. In all other cases, open-chain sulfonylated amidine intermediates are isolated. The latter are converted to the title compounds either in the presence of potassium carbonate or upon the addition of a copper(I) catalyst.

1. Introduction

Benzothidiazine-1,1-dioxides are a remarkably important class of heterocycles in the pharmacological area because of their broad range of biological activities, such as antihypertensive,[1,2] antimicrobial,[3] and antiviral[4] ones. In this connection several synthetic routes to the benzothiadiazine ring system have been developed. These synthetic routes can roughly be divided into two common approaches. In the first, non-catalytic, approach the ring is constructed through reactions of *o*-aminoaryl-sulfonamides with orthoesters[5,6] or acylating reagents[7–9] and *o*-haloaryl-sulfonamides with lactim ethers.[10] Main disadvantages of this approach are considerably harsh reaction conditions (e.g., pyrolytic conditions in the case of acylating reagents[7]) causing the formation of byproducts and a somewhat limited availability of *o*-aminosulfonamides narrowing the chemical space for drug design. An alternative approach to the 1,2,4-benzothiadiazine-1,1-dioxide ring is based on metal catalyzed reactions, such as: Friedel–Crafts ring closure of Michael adducts of chlorosulfonyl isocyanate and aniline derivatives,[11] a Cu(I)-catalyzed coupling of *o*-bromobenzylsulfonyl azide with functionalized terminal acetylene and ammonium chloride,[12] a cyclization of *o*-haloarylsulfonyl amidines in the presence of a copper bronze powder,[13] and a Fe(III)-mediated cyclization of *o*-bromobenzenesulfonamide with amidines.[14] However, transition metal-based protocols, although successful, have some inherent limitations, such as moisture sensitivity and environmental toxicity. In addition, their separation from polar reaction products, which is of particular importance for the synthesis of pharmaceutical fine chemicals because of their residual toxicity in the target compounds, is a central issue to consider. Given the limitations of the mentioned above synthetic approaches the development of efficient non-catalytic synthetic routes to the benzothiadiazine-1,1-dioxide ring system is necessary. In this contribution an efficient base-promoted synthesis of 4*H*-1,2,4-benzothiadiazine-1,1-dioxides from *o*-halobenzenesulfonyl chlorides and amidines or 2-aminopyridines is described.

2. Results and discussion

The 1,2,4-benzothiadiazine-1,1-dioxide is converted retrosynthetically into an *o*-halobenzenesulfonyl chloride and an amidine. These two components can be combined to give rise to the desired benzothiadiazine-1,1-dioxide ring by a two-step procedure involving the sulfonylation of the amidine and the aromatic nucleophilic substitution of the *ortho*-halogen atom. As noted above the latter step was carried out via Fe(III)[14] or copper bronze powder[13] mediated reaction. However, there are examples in which the intermolecular nucleophilic substitution of a halogen atom in activated *o*-halobenzenesulfonamides with nitrogen nucleophiles, such as aliphatic and aromatic amines, takes place under ambient non-catalytic conditions.[15] Consequently, a combination of enhanced reactivity of the *ortho*-halogen under the sufonylation conditions with sufficient nucleophilicity of the remaining amidine amine moiety should afford target benzothiadiazine dioxides via a one-pot procedure that would not require metal catalyst.

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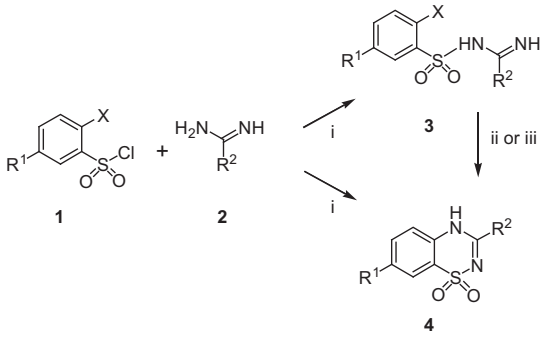
A systematic study of reactions of *o*-halobenzenesulfonyl chlorides **1** with amidines **2** and aminopyridines **5** (Schemes 1 and 2) revealed clear structural requirements to reagents to allow their clean and high-yielding one-pot conversion to the title compounds under non-catalytic conditions. Thus, reactions of sulfonyl chlorides **1a**–**f**, **1h**, and **1i** with amidines **2** (Scheme 1) resulted in open-chain sulfonylated products **3** in high yields. Isolated adducts **3a**, **3b**, **3e**, **3g**–**j**, **3n**, and **3l** are then nearly quantitatively converted to corresponding benzothiadiazine-1,1-dioxides **4** via nucleophilic substitution of the halogen in the presence of potassium carbonate in DMF. Bromine-substituted adducts **3c**, **3f**, **3k**, and **3m** require the addition of copper(I) iodide and *N*,*N*-dimethylethylenediamine (DMEDA) to complete the thiadiazine ring closure. It is interesting to note that the use of DMEDA instead of 1,10-phenanthroline as reported by Chang et al.[12] allowed us to achieve generally better conversions and a clean workup.



1a: X = F R^1 = H

1b: X = Cl R^1 = H

1c: X = Br R^1 = H

1d: X = F R^1 = CO_2Me

1e: X = Cl R^1 = CO_2Me

1f: X = Br R^1 = CO_2Me

1g: X = F R^1 = NO_2

1h: X = Cl R^1 = NO_2

1i: X = Br R^1 = NO_2

2a: R^2 = Me

2b: R^2 = Ph

3a: X = F R^1 = H, R^2 = Me

3b: X = Cl R^1 = H, R^2 = Me

3c: X = Br R^1 = H, R^2 = Me

3d: X = F R^1 = CO_2H, R_2 = Me

3e: X = Cl R^1 = CO_2Me, R^2 = Me

3f: X = Br R^1 = CO_2Me, R^2 = Me

3g: X = Cl R^1 = NO_2, R^2 = Me

3h: X = Br R^1 = NO_2, R^2 = Me

3i: X = F R^1 = H, R^2 = Ph

3j: X = Cl R^1 = H, R^2 = Ph

3k: X = Br R^1 = H, R^2 = Ph

3l: X = Cl R^1 = CO_2H, R^2 = Ph

3m: X = Br R^1 = CO_2Me, R^2 = Ph

3n: X = Cl R^1 = NO_2, R^2 = Ph

3o: X = Br R^1 = NO_2, R^2 = Ph

4a: R^1 = H, R^2 = Me

4b: R^1 = CO_2Me, R^2 = Me

4c: R^1 = NO_2, R^2 = Me

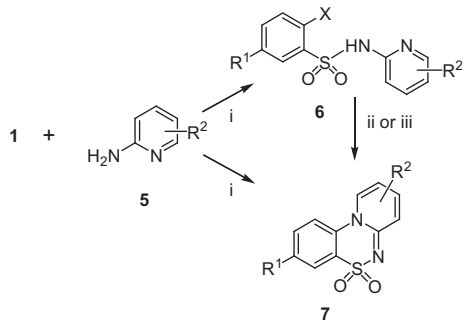
4d: R^1 = H, R^2 = Ph

4e: R^1 = CO_2Me, R^2 = Ph

4f: R^1 = NO_2, R^2 = Ph

4g: R^1 = CO_2H, R^2 = Ph

Scheme 1. Preparation of 1,2,4-benzothiadiazine-1,1-dioxides through the reaction of different *o*-halobenzenesulfonyl chlorides with amidines. Reagents and conditions: (i) CH_2Cl_2, aq NaOH, 0–10 °C; (ii) K_2CO_3, DMF, 100 °C; (iii) K_2CO_3, CuI, DMEDA, DMF, 100 °C.



5a: R^2 = H

5b: R^2 = 3-Me

5c: R^2 = 4-Me

5d: R^2 = 5-Me

5e: R^2 = 6-Me

6a: X = F R^1 = R^2 = H

6b: X = Cl R^1 = R^2 = H

6c: X = Br R^1 = R^2 = H

6d: X = Cl R^1 = CO_2Me, R^2 = H

6e: X = Br R^1 = CO_2Me, R^2 = H

6f: X = Cl R^1 = CO_2Me, R^2 = 4-Me

6g: X = Br CO_2Me, R^2 = 4-Me

6h: X = Cl R^1 = CO_2Me, R^2 = 5-Me

6i: X = Br R^1 = CO_2Me, R^2 = 5-Me

6j: X = Cl R^1 = CO_2Me, R^2 = 6-Me

6k: X = Br R^1 = CO_2Me, R^2 = 6-Me

7a: R^1 = R^2 = H

7b: R^1 = CO_2Me, R^2 = H

7c: R^1 = NO_2, R^2 = H

7d: R^1 = CO_2Me, R^2 = 4-Me

7e: R^1 = CO_2Me, R^2 = 5-Me

Scheme 2. Preparation of 1,2,4-benzothiadiazine-1,1-dioxides through the reaction of different *o*-halobenzenesulfonyl chlorides with 2-methylpyridine. Reagents and conditions: (i) pyridine, reflux, (ii) K_2CO_3, DMF, 80 °C, (iii) K_2CO_3, CuI, DMEDA, DMF, 80 °C.

Interestingly, the reaction of 4-fluoro-3-chlorosulfonyl-methylbenzoate **1d** with methylamidine **2a** readily gives open-chain sulfamoyl-4-fluoro-benzoic acid **3d**. A similar result was obtained in the case of the reaction of 4-chloro-3-chlorosulfonyl-methylbenzoate **1e** with phenylamidine **2b** giving rise to sulfamoyl-4-chlorobenzoic acid **3l**. Presumably this occurs on account of the good solubility of the intermediate sulfonylated amidines in aqueous NaOH in which the hydrolysis of the ester group takes place. All attempts to carry out cyclization reactions of acids **3d** and **3l** to yield the corresponding thiadiazine-1,1-dioxide rings were unsuccessful.

On the contrary, the reaction of **1d** with phenylamidine **2b** readily gives benzothiadiazine-1,1-dioxide carboxylic acid **4g**. This indicates that in the latter case the rate of aromatic nucleophilic substitution is faster than that of the hydrolysis. Finally, both the sulfonylation and cyclization steps proceed in one-pot in case of the reaction of fluoronitrobenzenesulfonyl chloride **1g** with **2a** and **2b** giving rise to benzothiadiazine-1,1-dioxides **4c** and **4f**, respectively. To our knowledge this constitutes the first example of a one-pot non-catalytic construction of the thiadiazine-1,1-dioxide ring. Additionally, this is a straightforward method for preparation of nitrobenzothiadiazine dioxides. The latter were formerly prepared by nitration of the parent benzothiadiazine dioxides.[16]

The versatility of the one-pot approach to the benzothiadiazine-1,1-dioxides could be possibly expanded by the use of stronger intramolecular nucleophiles, such as sulfonylated 2-aminopyridine derivatives. Indeed, the reactions of parent 2-aminopyridine