Tetrahedron Letters 54 (2013) 4023–4025

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A new procedure for the synthesis of 4-substituted-2*H*-1,2,3-benzothiadiazine 1,1-dioxides via directed *ortho*-lithiation of N^1-arylsulfonylhydrazonates

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ARTICLE INFO

Article history:
Received 3 March 2013
Revised 30 April 2013
Accepted 17 May 2013
Available online 23 May 2013

Keywords:
N^1-Arylsulfonylhydrazonates
Ortho esters
Directed *ortho*-lithiation
2*H*-1,2,3-Benzothiadiazine 1,1-dioxides

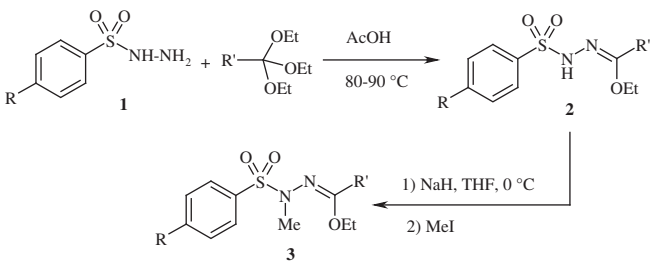
ABSTRACT

N^1-Arylsulfonylhydrazonates, which are readily available from commercial N^1-arylsulfonylhydrazides, undergo directed *ortho*-lithiation with an excess of lithium diisopropylamide and tetramethylethylenediamine to provide new 2*H*-1,2,3-benzothiadiazine 1,1-dioxide derivatives in yields ranging from 43% to 85%.

Sulfonamides have found many important applications in organic synthesis for examples, as protecting groups,[1] chiral auxiliaries[2–6] and directed metalation groups (DMGs).[7,8] In addition, the sulfonamide functionality is present in many biologically active compounds where it can function as a stable amide equivalent.[9,10] In particular, cyclic sulfonamides, of which there are many variations, are well documented in the literature. For example, aminothiadiazole 1,1-dioxides have shown antihypertensive and vasodilating properties,[11] whilst diuretic activity was found for several 1,2,4-benzothiadiazine 1,1-dioxide derivatives.[12] Sedative and mild tranquilizer activities have been reported for benzothiadiazine dioxides.[13] Particular mention should be made of 2*H*-1,2,3-benzothiadiazine 1,1-dioxides with a basic side chain at the 2-position, which are useful as central nervous system stimulants and as intermediates for the preparation of moth-proofing agents, pickling inhibitors and herbicides.[14]

A few reports have been published concerning the synthesis of 2*H*-1,2,3-benzothiadiazine 1,1-dioxide derivatives. The usual procedure for their preparation is a two-step approach involving chlorosulfonation of either *o*-formylbenzenesulfonate[15] or *o*-aminobenzophenones,[16] followed by ring-closure with hydrazine. We were unaware of any reports in the literature in which the 1,2,3-benzothiadiazine ring system has been synthesized directly from readily available N^1-arylsulfonylhydrazonates. As part of our continued efforts to develop synthetically useful anionic aromatic reactions for the synthesis of biologically active compounds,[17–21] we report in this communication the successful transformation of readily prepared N^1-arylsulfonylhydrazonates into 2*H*-1,2,3-benzothiadiazine 1,1-dioxide derivatives via an in situ sequence involving directed *ortho*-lithiation-cyclization reactions. These heterocycles were required for biological activity evaluations and as starting materials to prepare potential new drugs.

The starting N^1-arylsulfonylhydrazonates were prepared from the corresponding arylsulfonylhydrazides (Scheme 1). Treatment of arylsulfonylhydrazide **1** with a triethyl ortho ester in the presence of a catalytic amount of acetic acid gave the corresponding N^1-arylsulfonylhydrazonates **2** in high yields. Deprotonation of compounds **2** with NaH in THF followed by the addition of methyl iodide afforded the corresponding *N*-methyl-*N*-arylsulfonylhydrazonates **3** in good yields (Table 1).



Scheme 1.

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0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.05.082

Table 1
Synthesis of N^1-arylsulfonylhydrazonates **2a–e** and **3a–e**

Product	R	R′	Mp (°C)	Yield (%)
2a	H	Me	123–125	93
2b	H	Et	135–137	87
2c	H	Ph	152–154	92
2d	Me	Me	180–182	90
2e	Me	Ph	135–137	95
3a	H	Me	97–99	76
3b	H	Et	113–115	78
3c	H	Ph	100–102	84
3d	Me	Me	155–157	90
3e	Me	Ph	161–163	78

Table 2
Synthesis of 2*H*-1,2,3-benzothiadiazine 1,1-dioxides **4a–j**

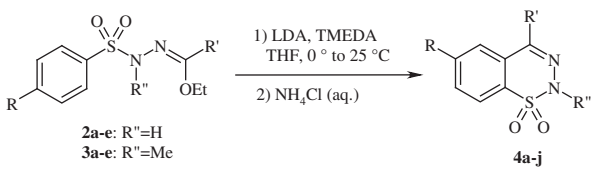
Product	R	R′	R″	Mp (°C)	Yield (%)
4a	H	Me	H	179–181	61
4b	H	Et	H	150–151	55
4c	H	Ph	H	166–168	48
4d	Me	Me	H	99–101	49
4e	Me	Ph	H	170–172	43
4f	H	Me	Me	132–134	85
4g	H	Et	Me	153–155	77
4h	H	Ph	Me	184–186	69
4i	Me	Me	Me	147–149	52
4j	Me	Ph	Me	188–189	47

The directed aromatic *ortho*-metalation reaction[22] has been developed into a broadly useful protocol for the regioselective construction of polysubstituted aromatic compounds, and has been used for the efficient synthesis of several heterocyclic ring systems and bioactive molecules.[23,24] Sulfonamides constitute powerful but under developed directing groups.[25] Hauser first achieved the metalation of secondary and tertiary arylsulfonamides and then described the synthesis of heteroannelation products.[26–29] Also, inter- and intramolecular anionic Friedel–Crafts equivalent condensations of arylsulfonamides have been described by Snieckus.[30–34] The protocol reported herein constitutes a mild method for the LDA-TMEDA mediated conversion of N^1-arylsulfonylhydrazonates **2a–e** and **3a–e** into 4-substituted-2*H*-1,2,3-benzothiadiazine 1,1-dioxides **4a–j** (Scheme 2).

Initially, an optimization of the reaction conditions for the synthesis of compounds **4a–j** was undertaken. Treatment of **2a** with different equivalents of LDA at either ambient or low temperatures failed, in all cases, to provide any of the desired products, and only recovered starting sulfonylhydrazonate **2a** was obtained. As the regioselectivity in *ortho*-metalation reactions is influenced by additives,[35,36] and by variation of the metalating agent,[37] compound **2a** was treated with 3 equiv of LDA-TMEDA, at 0 °C followed by quenching with NH_4Cl to afford the corresponding benzothiadiazine 1,1-dioxide **4a** with a conversion of 61%. The combination of *n*-BuLi-TMEDA yielded only 18% of the cyclized product. Attempts to enhance the yield through the use of an alternative base (LHMDS) and additive (HMPA), and higher reaction temperatures provided no significant benefit. Increasing the number of equivalents of LDA-TMEDA afforded the desired product **4a** along with a complex mixture of by-products.

Application of the LDA-TMEDA conditions[38] (3 equiv for **2a–e** and two equivalents for **3a–e**) yielded the corresponding 1,2,3-benzothiadiazine 1,1-dioxides in good yields (Table 2).

The results shown in Table 2 indicate the scope and potential limitations of this process. *N*-Methyl-*N*-arylsulfonylhydrazonates **3a–e** provided respectable yields of the products, whereas the corresponding *N*-arylsulfonylhydrazonates **2a–e** reacted less efficiently. Although *p*-methyl deprotonation occurs[7,39] in the presence of excess LDA conditions, products **4d**, **4e**, **4i** and **4j** illustrate the successful cyclization of secondary and tertiary arylsulfonylhydrazonates, albeit in variable yields.



Scheme 2.

We speculate that the reaction, possibly driven by the complex-induced proximity effect[40,41] (CIPE), proceeds via *ortho*-lithiation of the aryl sulfonamide. The resulting carbanion then attacks the iminic carbon group which leads to the cyclized product.

In summary, the efficient process described in this Letter has enabled us to prepare 4-substituted 2*H*-1,2,3-benzothiadiazine 1,1-dioxides from inexpensive and readily available N^1-arylsulfonylhydrazides. The potential anti-inflammatory activity of these new products is under investigation in our laboratory.

Acknowledgments

The authors thank the DGRST (Direction Générale de la Recherche Scientifique et de la Rénovation Technologique) of the Tunisian Ministry of Higher Education and Scientific Research for financial support of this research.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.082.

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38. Typical cyclization procedure: A flame-dried, argon-flushed, round-bottomed flask containing a solution of ethyl N^1-phenylsulfonyl acetohydrazonate (**2a**) (172 mg, 0.71 mmol) and TMEDA (0.32 mL, 2.31 mmol) in THF (10 mL) was cooled to 0 °C and treated dropwise with a freshly prepared solution of LDA (2.31 mmol, in 5 mL of THF) precooled to 0 °C. The resulting yellow solution was stirred at 0 °C for 1.5 h, and then warmed to room temperature and quenched with saturated aqueous NH_4Cl (10 mL). The mixture was concentrated in vacuo and the aqueous phase extracted with ethyl acetate (3×20 mL). The organic phase was washed with brine (3×5 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (30% EtOAc:70% hexane) to afford 85 mg of 4-methyl-2*H*-1,2,3-benzothiadiazine 1,1-dioxide (**4a**). Mp = 179–181 °C; IR (cm^{-1}): 3220 (NH), 1650 (C=N), 1334 and 1168 (SO_2). ^1H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H, N=C–CH_3), 7.84–7.99 (m, 4H, ArH), 11.36 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.25, 122.37, 127.88, 128.24, 132.04, 132.44, 133.66, 150.21. HRMS (ES) found MH^+ m/z = 197.0519, $C_8H_9N_2O_2S$ requires 197.0511.
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