Pergamon

Tetrahedron Letters 41 (2000) 9825–9828

TETRAHEDRON LETTERS

Efficient synthesis of 4,4-disubstituted-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides

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Received 18 September 2000; accepted 10 October 2000

Abstract

A simple method for the preparation of 4,4-disubstituted-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides is described. Treatment of *N*-sulfonyl ketimines **2** and **3** with different carbon nucleophiles afforded the corresponding of 4,4-disubstituted-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides **1** in isolated yields of 35–84%.

Keywords: benzothiazines; carbanions.

Among the components of the bicyclic diazine group of heterocyclic compounds,[1] benzothiadiazine-*S*,*S*-dioxides are of special interest because of their biological properties. For instance, diazoxide has been shown to produce muscle relaxation[2] and bentazone is a potent herbicide.[3] Other members of this family show antihypertensive and vasodilating properties,[4] as well as sedative effects.[5] 4-Substituted-1*H*-2,1,3-benzothiadiazine-2,2,-oxides and their 3,4-dihydro analogues are also valuable intermediates in the preparation of disinfectants, bleaching agents and antiseptics.[6] Racemic[7] and optically active[8] 4,4-disubstituted compounds derived quinazolin-2(1*H*)-ones, C=O analogues of *S*,*S*-dioxides, have been recently reported as a novel group of non-nucleoside HIV-1 reverse transcriptase inhibitors.

To our knowledge, no 4,4-disubstituted analogue derived from 3,4-dihydro-1*H*-2,1,3-benzothiadiazine-2,2-dioxides is known, probably as a consequence of the procedures generally applied to the construction of the heterocyclic moiety. These are mainly based on the transformation of anilines bearing a carbonyl,[9] ester or a nitrile[10] group in the *ortho* position upon treatment with

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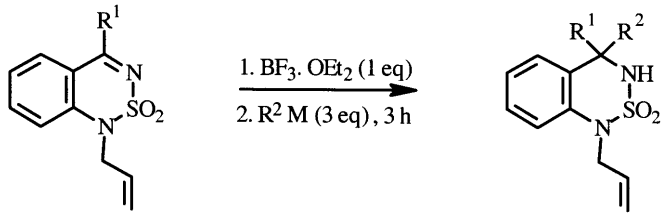
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01779-2

sulfamide giving rise to C-4 sp^2 derivatives. 3,4-Dihydro benzothiadiazines are available from 2-amino benzylamine and sulfuryl chloride[11] or sulfamide[12] or by reaction of *N*-alkyl-*N*′-arylsulfamides with trioxane.[13]

In connection with a program directed towards the synthesis of new drug candidates, we focused on unknown 4,4-disubstitued-3,4-dihydro-1*H*-2,1,3-benzothiadiazine-2,2-dioxides **1** (Table 1). In order to design a versatile and general approach, we chose to use easily available 4-substituted derivatives **2** and **3** as starting materials since an organometallic addition should provide a direct access to **1**. Although the electrophilic character of **2** and **3**, cyclic *N*-sulfonyl ketimines, was predicted to be low, the method would provide a short access to **1**. In this paper we report the efficient synthesis of 4,4-disubstituted derivatives **1** based on the addition of different carbon nucleophiles to **2** and **3** previously activated by association with $BF_3{\cdot}OEt_2$. The generality of this reaction is documented by a wide range of nucleophiles, which allow the obtention of polyfunctionalized derivatives.

Table 1
Organometallic addition to 4-substituted-1*H*-2,1,3-benzothiadiazine 2,2-dioxides



2: $R^1 = CH_3$
3: $R^1 = Ph$

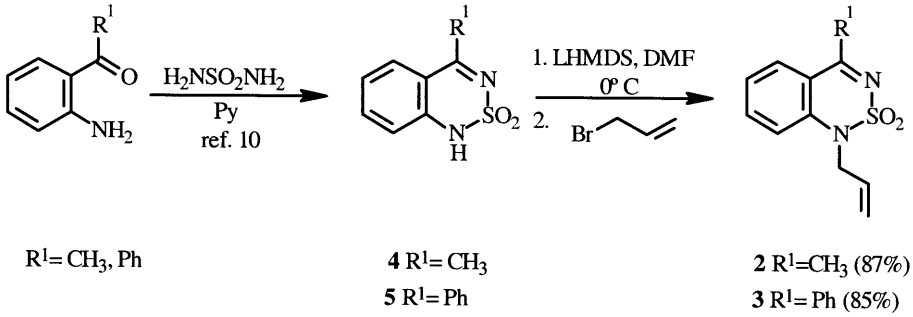
1

Entry	Starting material	R^2M	*T* (°C)	Product[14]	Yield (%)
1	**2**	EtMgBr	0–rt	**1a**	35
2	**2**	CH_2=CHMgBr	0–rt	**1b**	34
3	**2**	MeLi	−78	**1c**	65
4	**2**	PhLi	−78	**1d**	84
5	**2**	2-Li-1,3 dithiane	−78	**1e**	62
6	**2**	$LiCH_2CO_2Et$	−78	**1f**	75
7	**2**	$LiCH_2CONMe_2$	−78	**1g**	75
8	**2**	$LiCH_2SO_2Ph$	−78	**1h**	60
9	**2**	$LiCH_2SOTol$	−78–rt	**1i**[a]	45
10	**3**	PhLi	−78	**1j**	82
11	**3**	2-Li-1,3 dithiane	−78	**1k**	65
12	**3**	$LiCH_2CO_2Et$	−78	**1l**	55
13	**3**	$LiCH_2CONMe_2$	−78	**1m**	65
14	**3**	$LiCH_2SO_2Ph$	−78	**1n**	64
15	**3**	$LiCH_2SOTol$	−78–rt	**1o**	48

[a] It was isolated as a 60:40 mixture of diastereomers as a consequence of the inherent chirality of the sulfoxide, which results in the formation of a product with two stereogenic centers.

The syntheses utilized the precursors 1-allyl-4-methyl-1*H*-2,1,3-benzothiadiazine-2,2-dioxide **2** and the analogue 4-phenyl substituted derivative **3**, which were prepared as indicated in Scheme 1 from 2-amino acetophenone and 2-amino benzophenone, respectively, following the method

described by Wright[9] to generate the thiadiazine ring and further *N*-allylation of **4** and **5** (LHDMS, DMF, allyl bromide 87% for **2** and 85% for **3**). We choose the *N*-allyl substituent with the aim of further functionalizing this chain en route to more complex structures.



Scheme 1.

Reaction of EtMgBr with **2** did not give the desired addition product, the starting material being recovered unchanged after several days. We then tried to increase the electrophilic character of ketimine **2** by precomplexation with different Lewis acids. Previous treatment of **2** with zinc bromide or ytterbium triflate, followed by addition of the Grignard reagent allowed the formation of the 4-ethyl-4-methyl substituted derivative **1a** in low yield. The best results were obtained by using $BF_3{\cdot}OEt_2$ as Lewis acid (Table 1, entry 1). When a THF solution of **2** was sequentially treated with $BF_3{\cdot}OEt_2$ (1 equiv., rt, 30 min) and EtMgBr (3 equiv., 0°C to rt) a 35% yield of **1a** could be isolated pure after flash column chromatography.[‡] This reaction was extended to a series of organometallic derivatives and the results are included in Table 1. Thus, vinyl magnesium bromide behaved similarly giving rise to **1b** in 34% isolated yield (Table 1, entry 2). The moderate yield which resulted from Grignard reagents could be improved by using the more nucleophilic MeLi, which gave 4,4-dimethyl substituted compound **1c** in a 65% yield (Table 1, entry 3). Treatment of **2** with PhLi in the conditions indicated in Table 1 (entry 4) provided an 84% yield of **1d**.

To further extend the scope of this 1,2-addition process, we focused on the synthesis of 4,4-disubstitued-3,4-dihydro-1*H*-2,1,3-benzothiadiazine-2,2-dioxides **1** bearing a more functionalized substituent at C-α or C-β. With this aim, the use of stabilized lithium carbanions was checked. Reaction of **2** with an excess of the lithium salt derived from 1,3-dithiane (*n*-BuLi, −78°C) smoothly yielded compound **1e** (Table 1, entry 5, 62%), a α-formyl tertiary carbinamine precursor. Lithium enolates derived from ethyl acetate and *N*,*N*-dimethyl acetamide were also able to give the addition products **1f** and **1g** upon reaction with **2** in good yields (Table 1, entries 6 and 7). Other stabilized anions such as those resulting from the in situ treatment of methyl phenyl sulfone with *n*-BuLi or methyl *p*-tolyl sulfoxide with LDA reacted with **2** in the presence of $BF_3{\cdot}OEt_2$ to give the corresponding addition products **1h** and **1i** (Table 1, entries 8 and 9).

[‡] Typical experimental procedure for the preparation of **1a**: To a solution of the imine (1 equiv.) in dry tetrahydrofuran (10 mL) in a dry flask under N_2 was added $BF_3{\cdot}OEt_2$ (1 equiv.), the reaction mixture was stirred at room temperature for 1 h. EtMgBr (3 equiv.) was added at 0°C and then allowed to warm to ambient temperature and the mixture was stirred for 4 h. It was hydrolyzed with saturated aqueous NH_4Cl, extracted with ethyl acetate, dried over sodium sulfate and evaporated to give the crude product. The crude material was purified by flash chromatography (AcOEt/Hexane 1:3) to give **1a** (34% yield).

Reagents such as Me_2CuLi, $AlEt_2CN$, TMSCN or KCN did not react with the mixture **2**/$BF_3{\cdot}OEt_2$, even at room temperature and long reaction times, and, in the latter case, in the presence of 18-crown-6. These results indicate that ketimine addition does not occur when the nucleophilicity of the organometallic species is low.

The behavior of 1-allyl-4-phenyl-1*H*-2,1,3-benzothiadiazine-2,2-dioxide **3** in these addition reactions was also evaluated. When a solution of **3** previously complexed with 3 equiv. of $BF_3{\cdot}OEt$ was treated with lithium anions, indicated in Table 1 (entries 10–15), the corresponding 1,2-addition products **1j–o** were obtained in moderate to good yields. In spite of the presumably lower reactivity of benzophenone ketimine analogue **3**, reaction occurred under similar conditions to **2** being completed at a similar rate in 3 hours. (Table 1). Reactive anions such as PhLi (entry 10) behaved similarly to the stabilized ones (2-Li-1,3-dithiane, $LiCH_2CO_2Et$, $LiCH_2CONMe_2$, $LiCH_2SOTol$ and $LiCH_2SO_2Ph$, entries 11–15).

The scope of the reaction regarding the *N*-protecting group variation remains to be evaluated, but according to the results presented it is likely that little influence will be observed by changing this group provided the new protecting groups are compatible with the organometallic reagent to be used.

In summary, we have found conditions for the synthesis of 4,4-disubstituted-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides based on organometallic addition to 4-substituted-1*H*-2,1,3-benzothiadiazine 2,2-dioxides.

Acknowledgements

The Spanish PROFARMA program (Ministerio de Industria y Ministerio de Sanidad) supported this research. Two of us (M.P. and M.T.A.) thank Lilly S. A. for financial support.

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