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Consecutive alkylation–reduction reactions of 2*H*-1,2,3-benzothiadiazine 1,1-dioxide derivatives. Synthesis of 2-alkyl-, 3-alkyl-, and 2,3-dialkyl-3,4-dihydro-2*H*-1,2,3-benzothiadiazine 1,1-dioxides

Márta Porcs-Makkay, Angéla Pandur, Gyula Simig, Balázs Volk *

Egis Pharmaceuticals Plc., Chemical Research Division, PO Box 100, Budapest H-1475, Hungary

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Dedicated to Professor Károly Lempert on the occasion of his 90th birthday

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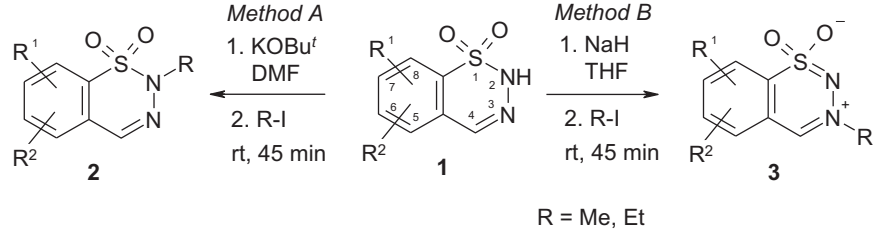
ABSTRACT

Various protocols have been elaborated for the efficient synthesis of 3,4-dihydro-2*H*-1,2,3-benzothiadiazine 1,1-dioxides and their corresponding 2-alkyl-, 3-alkyl-, and 2,3-dialkyl derivatives. The importance of both the position of the primarily introduced alkyl substituent and the sequence of the alkylation and reduction steps has been investigated in detail.

1. Introduction

The chemistry of 2*H*-1,2,3-benzothiadiazine 1,1-dioxide derivatives (**1**, Scheme 1) is scarcely investigated. Apart from the unsubstituted congener, 2*H*-1,2,3-benzothiadiazine 1,1-dioxide (**1a**) itself,[1–3] only a small number of representatives of this family was described, bearing a substituted amino,[4] a hydrazino,[5] or a substituted phenyl[6] moiety at position 4.



1	R^1	R^2
a	H	H
b	7-Cl	8-Cl
c	7-Cl	H
d	6-MeO	H

Scheme 1.

In a recent publication[3] we have described the synthesis of compounds **1** bearing various substitution patterns on the aromatic ring. Then, our detailed study[7] on the monoalkylation of 2*H*-1,2,3-

* Corresponding author. Tel.: +36 1 8035874; fax: +36 1 8035613; e-mail address: volk.balazs@egis.hu (B. Volk).

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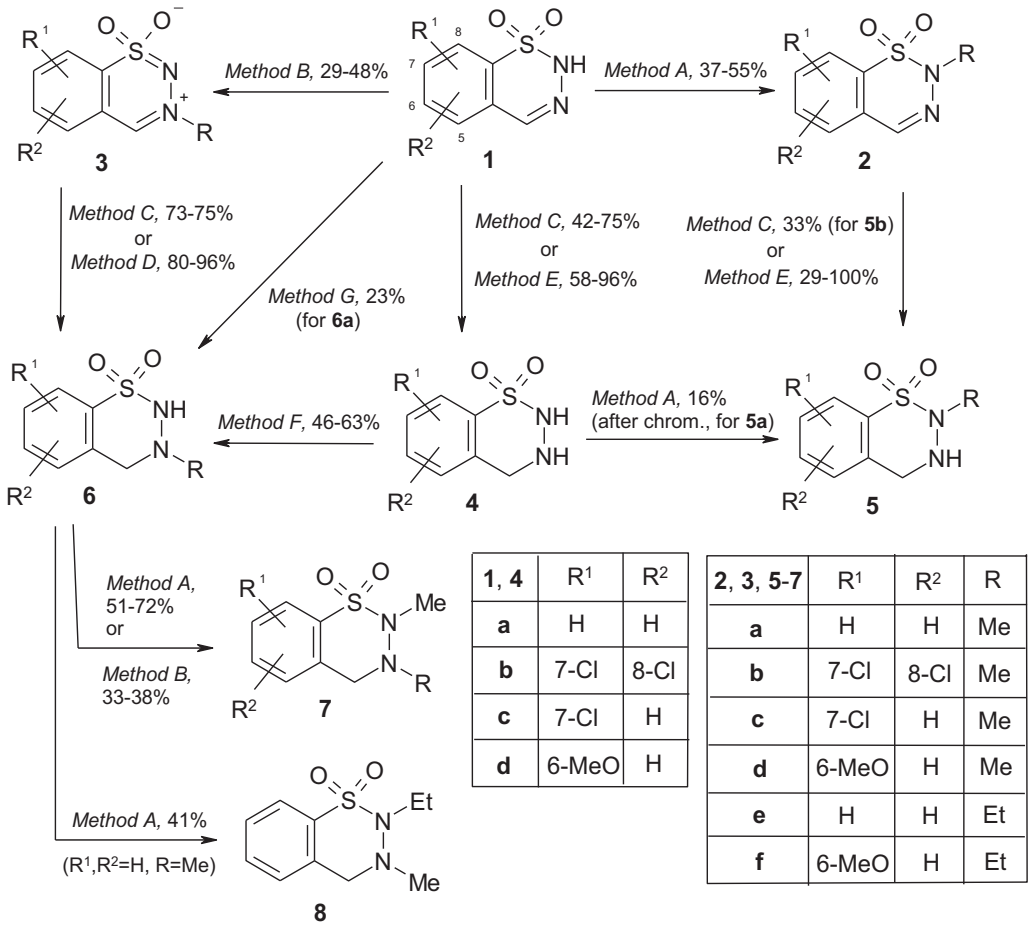
benzothiadiazine 1,1-dioxides variously substituted at the aromatic ring (**1a**–**d**) revealed that reactions with methyl and ethyl iodide (MeI, EtI) led to the formation of both *N*(2)- and *N*(3)-alkylated products (Scheme 1). When KO^{t}Bu was used as the base in DMF (Method A), the *N*(2)-alkyl derivative (**2**) was the major product, while use of NaH in THF (Method B) favored the formation of the *N*(3)-alkylated mesoionic product (**3**). Due to the substantially different solubility of the two products formed in the reactions, the desired compound could easily be prepared in each case.[7]

In the course of our medicinal chemistry studies to develop new pharmaceutically active ingredients suitable for the prevention or treatment of the symptoms of the diseases of the central nervous system (CNS) accompanied by the various forms of anxiety disorders (among others general anxiety disorder, panic disorder, agoraphobia, social phobia, other types of phobias, posttraumatic stress disorder), possibilities were now sought for the further derivatization of **1** and related compounds. Thus, saturation of the C=N double bond and alkylation of the unsubstituted nitrogen atoms in position 2 or 3 (in this order or vice versa) were envisaged in order to extend the scope of synthetic variations. While the introduction of more complex R groups with potential CNS effects [e.g., (ω-dialkylamino)alkyl, etc.] into positions 2 and 3 was also among our further plans, we decided to study the reduction and selective alkylation issues of this compound family first with simple alkylating agents such as MeI and EtI.

2. Results and discussion

Now we report on the saturation of the hetero ring of compounds **1**–**3**, bearing various substitution patterns on the aromatic ring and *N*-alkylations (methylation or ethylation) in positions 2 and 3 (Scheme 2).



1, 4	R^1	R^2
a	H	H
b	7-Cl	8-Cl
c	7-Cl	H
d	6-MeO	H

2, 3, 5-7	R^1	R^2	R
a	H	H	Me
b	7-Cl	8-Cl	Me
c	7-Cl	H	Me
d	6-MeO	H	Me
e	H	H	Et
f	6-MeO	H	Et

Scheme 2. *Method A*: KO^{t}Bu, MeI or EtI, DMF, rt, 0.5–9 h.[7] *Method B*: NaH, MeI or EtI, THF, rt, 0.5–5 h.[7] *Method C*: H_2/PtO_2, AcOH (for **5b**) or THF+AcOH, 10 bar, rt. *Method D*: $NaBH_4$, MeOH, rt, 1–5 h. *Method E*: $NaBH_4$/TFA, CH_2Cl_2, 0–5 °C, 1 h. *Method F*: CH_2O, H_2/Pd/C, AcOH, 10 bar, rt. *Method G*: CH_2O, H_2/PtO_2, AcOH, 10 bar, rt.

Attempted catalytic hydrogenation of **1a** on Pd/C at 10 bar was unsuccessful. On the other hand, hydrogenation of compounds **1** and *N*(3)-alkyl derivatives **3** on PtO_2 catalyst (Method C) gave in most cases acceptable results. Surprisingly, 2-methyl derivatives could not at all (**2a**) or not efficiently (**2b**) be reduced under similar conditions or even with a larger amount of catalyst.

Hydride reduction proved to be a general and efficient method for the saturation of the C=N double bond of compounds **1**, **2**, and **3**. The reduction of mesoionic compounds **3** to saturated derivatives **6** with sodium borohydride in methanol (Method D) gave high yields. However, transformation of compounds **1** and **2** to 3,4-dihydro derivatives **4** and **5**, respectively, required harsher reaction conditions. The reduction with sodium borohydride in the mixture of trifluoroacetic acid (TFA) and CH_2Cl_2 (Method E, for the optimization of the reaction conditions, see below) furnished the whole series of 2-unsubstituted (**4a**–**e**) and 2-alkylated (**5a**–**e**) 3,4-dihydro derivatives successfully, in moderate to excellent yields. Yields of all reduction steps are summarized in Table 1.

As the next step, alkylation reactions of 3,4-saturated compounds **4** to 2-alkyl- (**5**) and 3-alkyl (**6**) derivatives, and the