Tetrahedron Letters 52 (2011) 224–227

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Expected and unexpected reactions of 1,3-benzothiazine derivatives, I. Ring transformation of β-lactam-condensed 1,3-benzothiazines into 4,5-dihydro-1,4-benzothiazepines and indolo-1,4-benzothiazepines

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ARTICLE INFO

Article history:
Received 28 July 2010
Revised 18 October 2010
Accepted 29 October 2010
Available online 4 November 2010

Keywords:
Ring enlargement
β-Lactam
1,3-Benzothiazine
Indolo-1,4-benzothiazepine

ABSTRACT

The ring-enlargement reactions of monochloro-β-lactam-fused 2-aryl-1,3-benzothiazines revealed that the reactions of *ortho*-nitro aryl-substituted derivatives with sodium methoxide in methanol provided two products, depending on the amount of the base. With 2 equiv of reagent, the expected 1,4-benzothiazepines were obtained. Somewhat surprisingly, treatment with a large excess of sodium methoxide led to the formation of indolo-1,4-benzothiazepines via a novel rearrangement. The structures of the new ring systems were determined by means of X-ray crystallography and NMR spectroscopy.

Condensed *S,N*-heterocycles constitute an important group of biologically active compounds targeted towards various therapeutic end-points. Besides β-lactam antibiotics (penicillins, cephalosporins)[1] and versatile pharmacophoric 1,5-benzothiazepines,[2] several members of this group are bioisosteres of various drugs, for example, 1,4-benzothiazepine derivatives are analogues of the well-known 1,4-benzodiazepine family, and a broad range of pharmacological effects has been observed for these heterocycles. 1,4-Benzothiazepines exert antidepressant activity,[3] antiarrhythmic activity,[4] reversal of P-glycoprotein-mediated multidrug resistance[5] and bile acid absorption inhibitory activity.[6]

The preparation of 1,4-benzothiazepines is usually achieved by ring closure of bifunctional compounds (e.g., aminothiol derivatives),[7] but for rare 4,5-dihydro-1,4-benzothiazepines whose preparation otherwise involves difficulties,[8–12] ring transformation reactions of β-lactam-condensed thiazines are also used.[9–12]

In the course of recent studies on *S*- and *N*-containing heterocycles, we prepared and isolated the 2,3-disubstituted 4,1-benzothiazepines: 3-ethoxycarbonyl-2-phenyl-3,5-dihydro-4,1-benzothiazepine and 3-ethoxycarbonyl-2-phenyl-1,5-dihydro-4,1-benzothiazepine, which are in a tautomeric relationship (imine–enamine) with each other.[11,13] Surprisingly, these 4,1-benzothiazepines could be separated by column chromatography and manifested the rare phenomenon of desmotropy. We recently devised a convenient synthesis for rare 2,3-disubstituted 4,5-dihydro-1,4-benzothiazepines from 2-aryl-4*H*-1,3-benzothiazines.[12] The Staudinger reactions of 1,3-benzothiazines with monochloroacetyl chloride furnished selectively *trans* monochloro-β-lactam-condensed thiazines. The ring expansion of azeto[2,1-*b*][1,3]benzothiazin-1-one derivatives with sodium methoxide afforded 1,4-benzothiazepines as single products in good yields.[12] On continuation of our work, we found that the ring-enlargement reaction of *ortho*-nitro-2-aryl-2a-chloro-4*H*-azeto[2,1-*b*][1,3]benzothiazin-1-one (**2a**) with an excess of sodium methoxide in methanol provided an unexpected product, **3**. Our present aim was to shift the reaction path of the previously examined ring-enlargement reactions towards such new compounds and to carry out structural investigations.

The reaction of **1a**[14] with chloroacetyl chloride in refluxing toluene furnished azeto[2,1-*b*][1,3]benzothiazin-1-one (**2a**) in good yield (Scheme 1). Compounds **2b,c** were obtained under similar conditions from **1b,c**.[14]

Surprisingly, treatment of monochloro-β-lactam **2a** with excess sodium methoxide led to the formation of the previously unknown indolo-1,4-benzothiazepine ring system **3a** via a novel rearrangement (Scheme 1). To investigate the possibility of the extension

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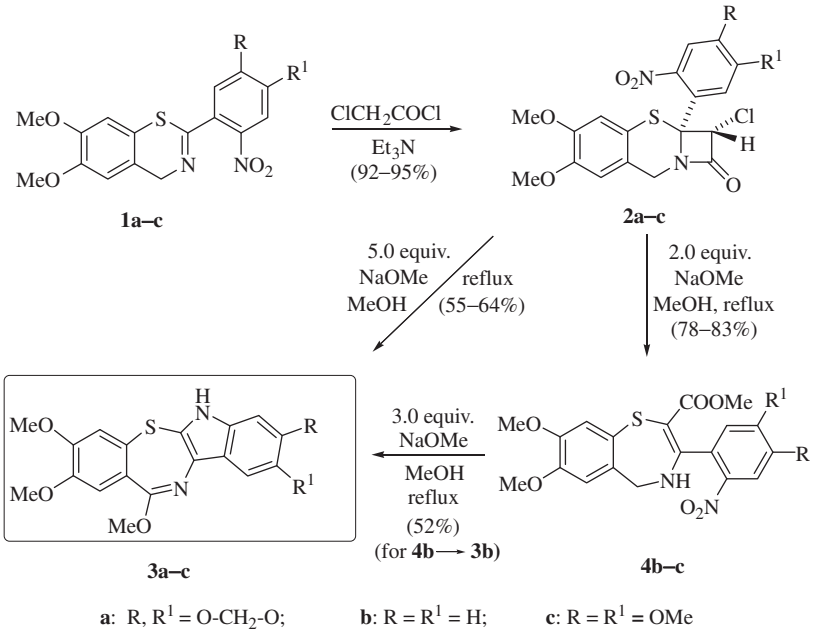
doi:10.1016/j.tetlet.2010.10.160



Scheme 1.

of this novel ring expansion, compounds **2b,c** were also reacted under the same conditions and indolo[2,3-*b*][1,4]benzothiazepines **3b,c** were obtained in good yields. The reactions of monochloro-β-lactam derivatives **2b,c** with 2 equiv of sodium methoxide in dry methanol at reflux temperature afforded the expected products **4b,c** (Scheme 1). NMR investigations demonstrated the presence of the enamine tautomers of 4,5-dihydro-1,4-benzothiazepines only. In contrast to the 4,1-benzothiazepine derivatives, desmotropy was not observed for the 1,4-benzothiazepines.[11,12] In this latter reaction, the first step is most probably alcoholysis of the β-lactam ring in **2b,c**, resulting in α-chloro esters,[11] which leads to the products **4b**,**c** through episulfonium salts after elimination of HCl.

Investigations have been performed on the reaction mechanism of the formation of **3a–c** from **2a–c**. Treatment of **4b** with 3 equiv of sodium methoxide provided **3b** (Scheme 1), which indicated 1,4-benzothiazepines **4** as one of the possible intermediates in the formation of indolo-1,4-benzothiazepines **3** (Scheme 2).

Cyclizations of *o*-nitroaryl-alkene type compounds to the 1-hydroxyindole skeleton under basic conditions are known in the literaure.[15] The second step of the present ring transformation of **2** via **4** most probably involves the formation of *N*-hydroxyindole derivatives **8** under treatment with sodium methoxide (Scheme 2). Addition of methanol to **8** provides intermediate **9**. The formation of **3** can be further explained through intermediate **10**, followed by 1,5-proton shift. Further studies relating to the possible reaction mechanism are in progress.

The unexpected structures of the novel ring expansion products could be inferred from the NMR spectra only after the crystal structure of **3a** had been determined (Fig. 1).[16]

The structures of the compounds were also supported by IR and ^{1}H and ^{13}C NMR, and for **3a–c**, also by ^{15}N NMR spectroscopy (Supplementary data). Additionally, techniques such as HMQC, HMBC and DEPT were employed. The spectral data are given in Tables 1 and 2 (Supplementary data).

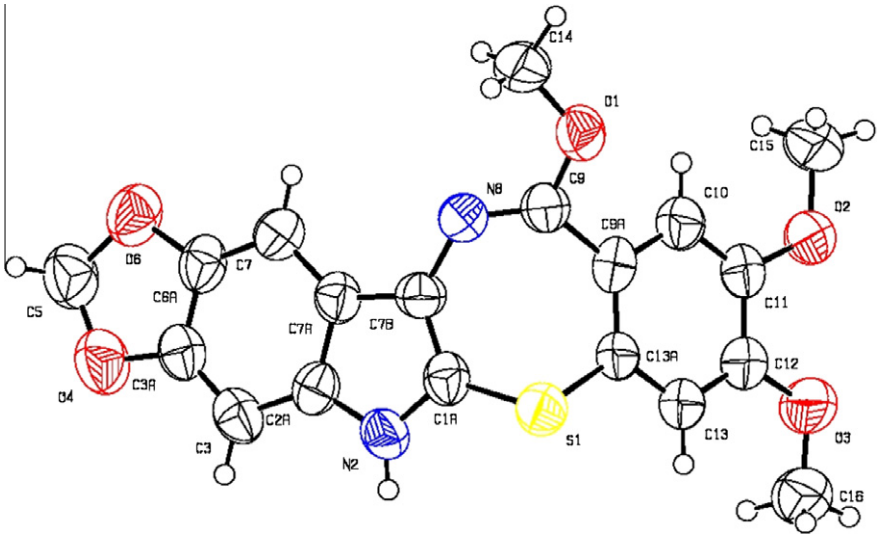
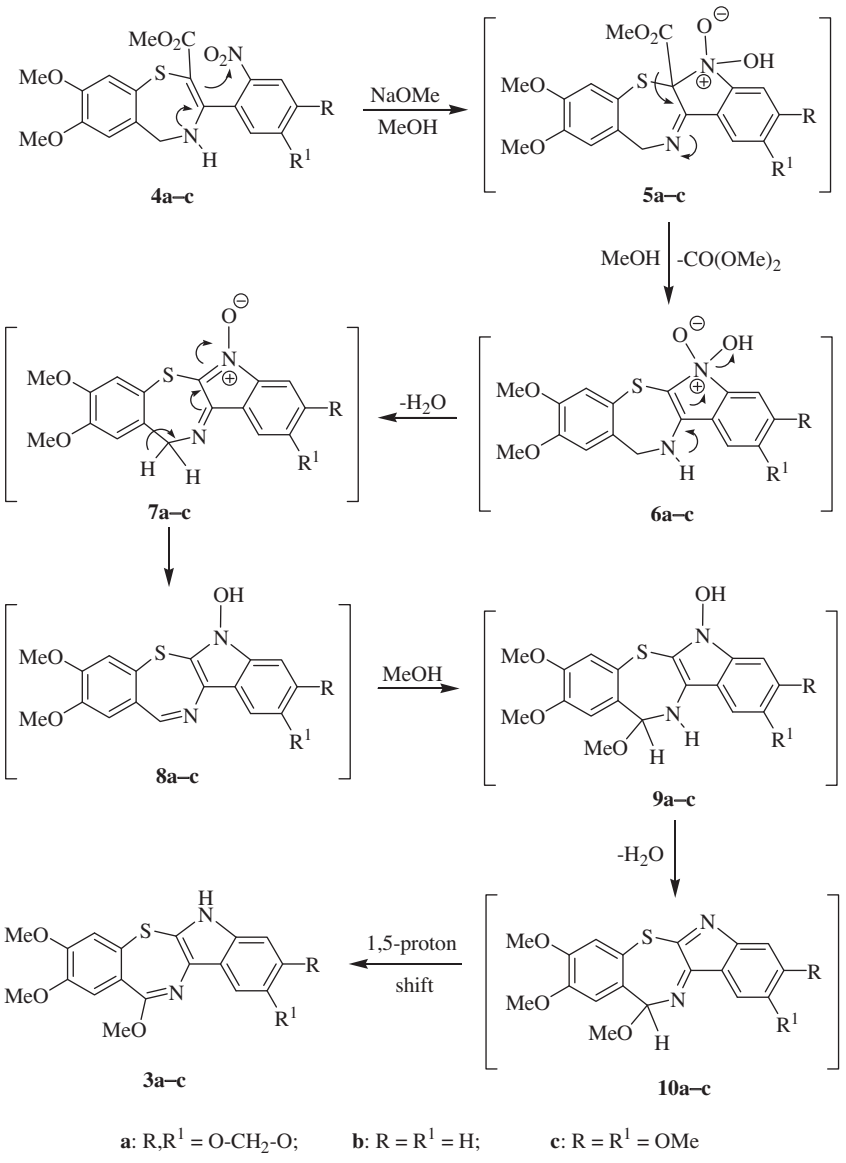


Figure 1. An ORTEP diagram of **3a**, showing the atomic numbering of the non-hydrogen atoms. Hydrogen positions are shown, but not labelled.



Scheme 2.

In summary, we have developed a convenient and general synthesis of the new ring system, indolo[2,3-*b*][1,4]benzothiazepines (**3a–c**), from *ortho*-nitro-2-aryl-2a-chloro-4*H*-azeto[2,1-*b*][1,3]-benzothiazin-1-ones **2a**–**c** using 5 equiv of sodium methoxide in methanol under reflux. The structures of the novel ring expansion products were proved by means of NMR spectroscopy and X-ray crystallography. In order to study the structure–reactivity relationships, the preparation of further derivatives is in progress.

Acknowledgements

The authors express their thanks to the Hungarian Scientific Research Foundation (OTKA) for financial support. The European Union and the European Social Fund have provided financial support to the project under the grant agreement no. TÁMOP 4.2.1./B-09/KMR-2010-0003.

Supplementary data

Supplementary data (general information, synthesis, procedures and spectral data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.160.

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16. *Crystal data:* **3a** Rigaku R-axis Rapid diffractometer, Mo-Kα radiation, λ = 0.71073 Å $C_{19}H_{16}N_2O_5S$, M = 384.40, platelet, colourless, monoclinic space group $C2/c$, a = 36.654(2), b = 6.9390(4) (6), c = 15.2300(8) Å, β = 113.124(1)°, V = 3562.4(3) Å^3, Z = 4, D_c = 1.433 mg m^{-3}, μ = 0.216 mm^{-1}, T = 294 K, R = 0.0625, R_w = 0.1897, R_{tot} = 0.0825, N = 2038, CCDC reference number: 783262.