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Preparation and ring transformation of isomeric β-lactam derivatives of bicyclic 1,3-thiazines

Lajos Fodor [a,b,c,*,†], Péter Csomós [a,b,c], Ferenc Fülöp [c], Antal Csámpai [d], Pál Sohár [d,*,‡]

[a] Institute of Health Care and Environmental Sanitation Studies, Szent István University, H-5700 Gyula, Szent István u. 17–19, Hungary
[b] Central Laboratory, County Hospital, H-5701 Gyula, PO Box 46, Hungary
[c] Institute of Pharmaceutical Chemistry, University of Szeged, and Research Group of Stereochemistry of the Hungarian Academy of Sciences, H-6720 Szeged, Eötvös u. 6., Hungary
[d] Institute of Chemistry, Eötvös Loránd University, H-1518 Budapest, PO Box 32, Hungary

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ABSTRACT

Ketene–imine cycloaddition reactions between *cis*- and *trans*-2-aryl-4a,5,6,7,8,8a-hexahydro-4*H*-3,1-benzothazines and chloroacetyl chloride in the presence of base were investigated. Because of the diastereotopic C=N faces of cyclohexane-condensed thiazines, both of the possible Staudinger addition product monochloro-β-lactam stereoisomers were obtained for both the cis and the trans compounds. The novel azetidin-2-ones were transformed into the corresponding 3-ethoxycarbonyl-2-aryl-1,5,5a,6,7,8,9,9a-octahydro-4,1-benzothiazepines with sodium ethoxide in a one-step procedure. Structural and stereochemical analyses of the synthesized compounds were carried out by means of IR and NMR spectroscopy.

1. Introduction

As well as their significant pharmacological effects,[1] β-lactams serve as useful intermediates in organic syntheses.[2–12] In particular, their use as valuable scaffolds has been exploited in the preparation of a wide variety of functionalized structures, including natural products (alkaloids and medicines),[2] aminosugars,[3] different peptidomimetics[4] and chiral catalysts.[5] Derivatives of 2-azetidinones have also been utilized as powerful synthetic intermediates for a broad range of heterocycles.[6–12] These latter compounds can be obtained either indirectly from β-lactams via bifunctional compounds,[6] such as β-amino acid derivatives and amino alcohols, or directly through various ring transformations.[7–11] The interconversions of heterocyclic rings into other heterocycles are generally fascinating and frequently elegant tools in synthetic organic chemistry. Via ring-enlargement reactions of halo-β-lactams, numerous ring expansions have been achieved: products such as pyrrolidin-2-ones,[7] bicyclic γ-lactams[8] or macrocyclic β-amino amides (valuable intermediates in the syntheses of homalium alkaloids)[9] have been obtained, and the reaction mechanisms of these transformations have been studied. Regarding ring-contraction reactions of halo-azetidin-2-ones, there are interesting recent examples, which lead to the formation of aziridines.[10]

In the course of our recent studies on S- and N-containing condensed-skeleton heterocycles, we investigated the reactions of 1,3- and 3,1-benzothiazines differently condensed with a β-lactam ring.[11] The ring expansion of 2-chloro-2a-arylazeto[2,1-*b*][1,3]benzothiazin-1-one derivatives (Fig. 1, compounds of type **A**) with sodium methoxide afforded 1,4-benzothiazepines as single products in good yields.[11a,b] Further, the ring transformations of (2*R**,2a*S**)-2-chloro-2a-aryl-2,2a-dihydro-2*H*,4*H*-azeto[1,2-*a*][3,1]benzothiazin-1-ones (Fig. 1, compounds of type **B**) with sodium ethoxide in ethanol provided differently substituted (*R**)-3-ethoxycarbonyl-2-aryl-3,5-dihydro-4,1-benzothiazepines and 3-ethoxycarbonyl-2-aryl-1,5-dihydro-4,1-benzothiazepines.[11b] Surprisingly, the tautomers obtained could be separated by column chromatography and proved to be unexpectedly stable in solution, and these pairs of compounds exhibit the rare phenomenon of desmotropy. Because of the importance of this phenomenon, as a continuation of our studies we were interested in the reactivities of their saturated analogues, β-lactam-condensed *cis*- and *trans*-2-aryl-4a,5,6,7,8,8a-

* Corresponding authors. E-mail addresses: fodor@pandy.hu (L. Fodor), sohar@chem.elte.hu (P. Sohár).
† Synthesis.
‡ Spectroscopy.

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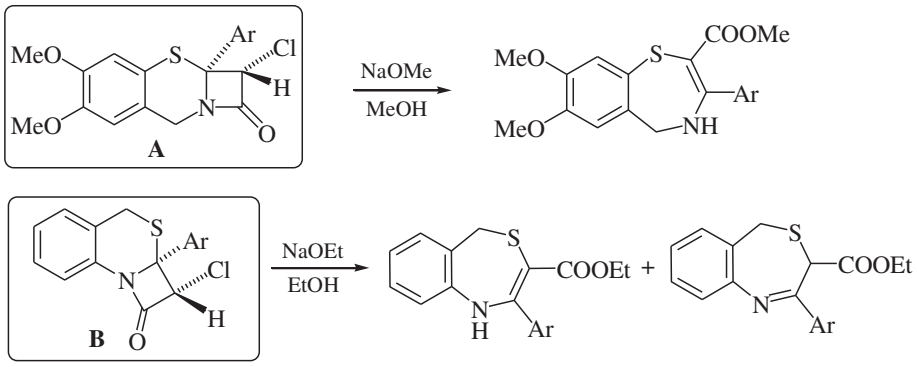


Fig. 1. Ring transformation reactions of monochloro azeto[2,1-*b*][1,3]benzothiazin-1-one (**A**) and azeto[1,2-*a*][3,1]benzothiazin-1-one (**B**) derivatives.

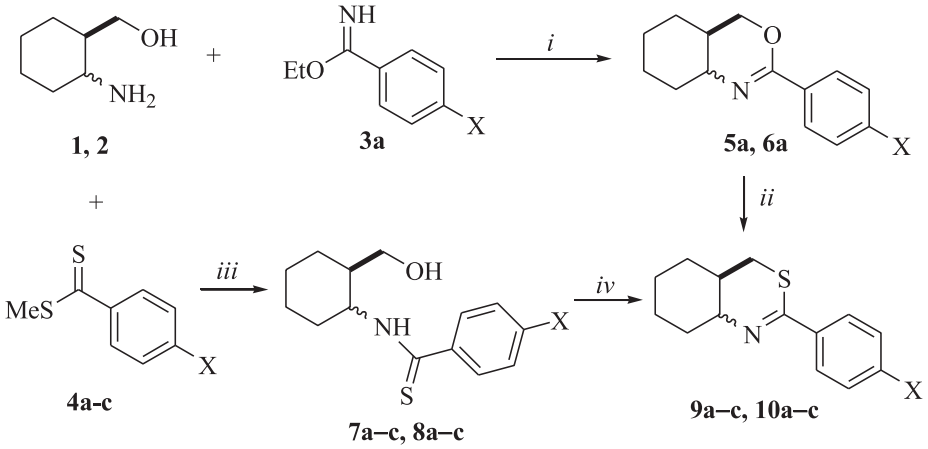
hexahydro-4*H*-3,1-benzothazines, and set out to investigate their reactions with sodium ethoxide in ethanol.

2. Results and discussion

The intermediate *cis*- and *trans*-1,3-thiazines **9a** and **10a** were prepared in two ways (Scheme 1). Compounds **9a** and **10a** were first obtained in moderate yields through the sulfur-exchange reactions of the corresponding oxazines **5a** and **6a** (prepared from amino alcohol **1** or **2** and ethyl benzimidate) by treatment with phosphorus pentasulfide (Scheme 1).[12] For the target thiazines, we additionally devised another convenient method, which provided the intermediate thiazines in relatively good overall yields. We succeeded in obtaining thiobenzamides **7a**–**c**, **8a**–**c** in excellent yields in a one-step process, through the reactions of amino alcohols **1** and **2** with substituted methyl dithiobenzoates under acid catalysis. The direct one-pot ring closure of thiobenzamides in 10% hydrochloric acid in ethanol provided thiazines **9a**–**c** and **10a**–**c** in moderate yields. It is noteworthy that the preparation of this type of compounds (which possess 1,3-thiazine or 1,3-thiazole substructures) from bifunctional amino alcohols generally needs an additional step for protection (usually with acetyl, mesyl or tosyl) of the hydroxy group during the synthesis of the thioamide or in the ring-closure step.[13]

For the preparation of monochloro-β-lactams **11**–**14** (Scheme 2), we used the Staudinger reaction of cyclic C=N moiety of **9** and **10** with chloroacetyl chloride in refluxing toluene. Control of the diastereoselectivity in the Staudinger reaction and its investigation are challenging issues.[14] Generally the reaction of a ketene with an imine produces two new stereogenic centres, thus the product might be a mixture of *cis*- and *trans*-2-azetidinone derivatives, depending on the ability of the zwitterionic intermediate to undergo isomerization.[14] In our earlier studies, when 2-substituted 1,3-thiazine derivatives were involved in Staudinger reactions, the addition took place in such a way that the relative configuration of the vicinal substituents in the β-lactams formed was cis (Fig. 1, compounds of types **A** and **B**).[11a,b] To our surprise, the Staudinger reactions of our *cis* and *trans* thiazines, **9a**–**c** and **10a**–**c**, each furnished two diastereomers, **11** and **12**, and **13** and **14**, respectively, which were separated by column chromatography.[15] Structural investigations revealed a cis relationship between the chloro and aryl substituents in all four products **11**–**14**. Thus, four of the eight possible diastereomers were isolated: **11a**–**c** and **13a**–**c** were obtained as cis and trans major β-lactam products, while isomers **12a**–**c** and **14a**–**c** were obtained as minor products. Similar examples usually occur when a chiral imine is utilized in the asymmetric Staudinger reaction for the preparation of β-lactams.[16]

As we were interested in how the reaction conditions influence the diastereoselectivity of the cycloaddition reaction, the effects of different solvents, different reaction temperatures and different sequences of addition of the reagents were examined in the cases of compounds **11a** and **12a**. The results are presented in Table 1. The



a: X = H; **b**: X = Cl; **c**: X = Me; *cis*: **1**, **5**, **7**, **9**; *trans*: **2**, **6**, **8**, **10**

i) cat. CH_3COOH, EtOH, reflux, 36 h, yields: 75–82%; *ii*) P_2S_5, neat, 120 °C, 3 h, yields: 38–42%; *iii*) cat. F_3CSO_3H, EtOH, reflux, 5 d, yields: 72–88%; *iv*) 10% HCl/EtOH, reflux, 2 h, yields: 52–62%

Scheme 1. Preparation of *cis*- and *trans*-2-aryl-1,2,4a,5,6,7,8,8a-octahydro-4*H*-3,1-benzothiazines.