Short Note

Methyl (1aRS, 7aSR)-7-Formyl-1a-Phenyl-1,1a-Dihydroazirino[2,3-b]Benzo[e][1,4]Thiazine-7a(7H)-Carboxylate

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Short Note

Methyl (1aRS, 7aSR)-7-Formyl-1a-Phenyl-1,1a-Dihydroazirino[2,3-b]Benzo[e][1,4]Thiazine-7a(7H)-Carboxylate

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Abstract

The first representative of the aziridine-fused benzo[*e*][1,4]thiazine series was synthesized from methyl 2-bromo-2-phenyl-2*H*-azirine-2-carboxylate and benzo[*d*]thiazole in 74% yield. The reaction proceeds via the S_N2'-S_N2'-cascade to form the azirinylthiazolium salt followed by a water-induced thiazole ring expansion. The structure of the title compound was established based on ^{1}H, ^{13}C, 2D NMR spectroscopy, high-resolution mass spectrometry, and unambiguously confirmed by X-ray diffraction analysis.

Keywords: azirines; thiazoles; thiazines; *ortho*-fused heterocycles; X-ray diffraction

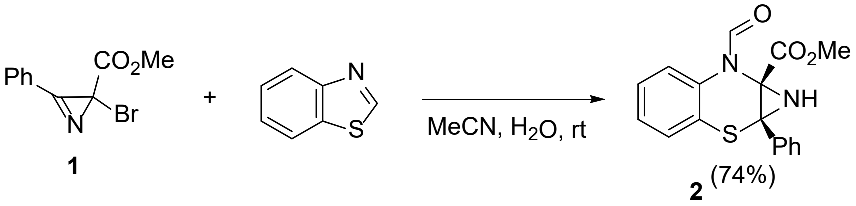
1. Introduction

Heterocyclic compounds containing a benzo[1,4]thiazine moiety have emerged as attractive building blocks in medicinal chemistry. The benzo[1,4]thiazine skeleton alongside its 2,3-hydrogenated and S-oxidized analogues are found in compounds exhibiting anticancer [1], antimicrobial [2], antifungal [3], antiviral [4], antihypertensive [5], anti-inflammatory [6], cardiovascular [7], anti-rheumatic [8], anti-allergic [9], and other biological activities [10,11]. Several synthetic strategies have been developed for the construction of the benzo[1,4]thiazine skeleton, the most common of which rely on cyclocondensation of o-aminothiophenols and related substrates with electrophiles [12]. There is much less information on the synthesis of these heterocycles via cyclization of substituted anilines [13,14], ring contraction of benzothiazocines [15] and ring expansion of benzo[*d*]thiazoles and benzo[*d*]thiazolines. In particular, using the latter approach, 3-alkylidene-substituted benzo[1,4]thiazines were prepared via intramolecular oxidative five-membered ring expansion in benzothiazolines [16]. Adib et al. reported intermolecular ring expansion of benzothiazoles using diaroylacetylenes and Meldrum's acid [17].

Herein, we describe the first synthesis of an aziridine-fused benzo[1,4]thiazine by intermolecular ring expansion of benzo[*d*]thiazole under the action of methyl 2-bromo-3-phenyl-2*H*-azirine-2-carboxylate (**1**) operating as a transannulation agent. Annulation reactions involving mono- and disubstituted azirines are well known and have been widely used in the synthesis of various pyrrolo-fused systems [18,19]. Trisubstituted azirines, in contrast, are inactive in annulation reactions and can react only in four ways: ring opening, ring expansion, addition to the C=N bond and substitution reaction [20]. The synthesis reported herein represents the first example of a transannulation reaction involving a trisubstituted azirine and provides access to a previously unknown class of azirino-fused benzo[1,4]thiazines.

2. Results and Discussion

Bromoazirine **1** required for the present study was prepared according to the published procedure [21]. We found that azirine **1** reacts with benzothiazole in acetonitrile already at room temperature and is completely consumed within 10 h, yielding a mixture of several difficult to separate products. However, the addition of water dramatically improves the selectivity. When a 3:2 acetonitrile–water mixture was used as the solvent, only one product, aziridinobenzothiazine **2**, was observed. The compound was isolated by column chromatography, and subsequent recrystallization from a diethyl ether–hexane mixture provided analytically pure compound **2** (Scheme 1).



Scheme 1. Synthesis of azirinobenzothiazine **2**.

The structure and stereochemistry of product **2** were confirmed by the single-crystal X-ray diffraction analysis (Figure 1). According to the crystallographic data, the formyl group of the molecule is *cis*-oriented to the aziridine ring.

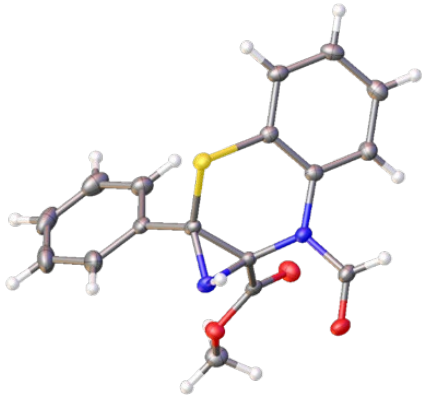
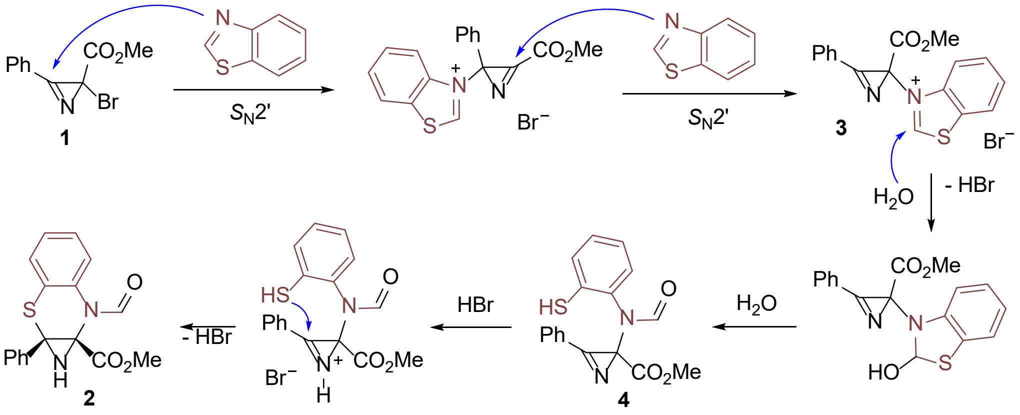


Figure 1. Molecular structure of azirinobenzothiazine **2**; thermal ellipsoids are drawn at a 50% probability level.

A plausible mechanism for the formation of azirinobenzothiazine **2** is depicted in Scheme 2. The reaction begins with nucleophilic substitution of bromine by benzothiazolium substituent to form salt **3**. This exchange proceeds in two stages via an *S*N2'-*S*N2' cascade mechanism and is similar to the known reaction of azirine **1** with pyridines leading to pyridinium salts [22]. Subsequent nucleophilic addition of water to intermediate **3** occurs with elimination of HBr. Opening of the thiazolium ring, most likely promoted by another water molecule, yields thiophenol **4**, which undergoes intramolecular HBr-catalyzed cyclization to give the final product **2**.



Scheme 2. Proposed mechanism for the formation of azirinobenzothiazine **2**.

3. Materials and Methods

3.1. General Instrumentation

The melting point was determined on a Stuart SMP30 melting-point apparatus. NMR spectra were recorded on a Bruker Avance 400 spectrometer in DMSO-*d*$_6$. ^{1}H and ^{13}C{1H} NMR spectra were calibrated according to the residual signal of DMSO-*d*$_6$ (δ = 2.50 ppm) and the carbon atom signal of DMSO-*d*$_6$ (δ = 39.5 ppm), respectively. High-resolution mass spectra were recorded with a Bruker maXis HRMS-QTOF, via electrospray ionization. Thin-layer chromatography (TLC) was conducted on aluminum sheets precoated with SiO_2 ALUGRAM SIL G/UV254. Column chromatography was performed on silica gel 60 M (0.04–0.063 mm). Commercially available benzo[*d*]thiazole was used without further purification. All solvents were distilled and dried prior to use. Single crystals of compound **2** were grown by slow evaporation of its solution in diethyl ether–hexane–dichloromethane mixture. Crystallographic data were collected on a SuperNova, single source at offset/far, HyPix3000 diffractometer using graphite monochromatic Cu–K*α* radiation (λ = 1.54184 A). The crystal was kept at 99.9(2) K during data collection. Using the Olex2 [23], the structure was solved with the ShelXT [24] structure solution program using the Intrinsic Phasing method and refined with the ShelXL [25] refinement package using Least Squares minimization. CCDC 2503941 contains crystallographic data for compound **2**. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

3.2. Methyl (1aRS,7aSR)-7-formyl-1a-phenyl-1,1a-dihydroazirino[2,3-b]benzo[e][1,4]thiazine-7a(7H)-carboxylate (2)

To a solution of bromoazirine **1** (127 mg, 0.5 mmol) in MeCN–H_2O (3:2, 2.5 mL) mixture benzo[*d*]thiazole (135 mg, 1 mmol, 2 equiv) was added, and the resulting mixture was stirred at room temperature for 4.5 h. The product was extracted with ethyl acetate (2×5 mL), and the organic layer was dried over Na_2SO_4. Evaporation of the solvent followed by column chromatography (eluent hexane–ethyl acetate, from 5:1 to 1:1) and recrystallization from the diethyl ether–hexane mixture gave compound **2** (120 mg, 74%) as a colorless solid.

Mp = 157–158 °C. ^{1}H NMR (400 MHz, DMSO-*d*$_6$), δ, ppm: 8.86 (s, 1H), 7.64–7.62 (m, 1H), 7.54–7.52 (m, 1H), 7.43–7.40 (m, 1H), 7.34–7.29 (m, 6H), 4.74 (s, 1H), 3.31 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-*d*$_6$), δ, ppm: 165.7, 162.6, 137.2, 135.2, 128.4, 128.2, 127.9, 127.7, 127.0, 126.4, 126.3, 122.1, 57.1, 55.5, 52.9.

HRMS (ESI/Q-TOF) *m*/*z*: [M+H]$^+$ Calcd for $C_{17}H_{15}N_2O_3S^+$ 327.0798; Found 327.0807.

4. Conclusions

The first representative of aziridine-fused benzo[*e*][1,4]thiazine series was synthesized from methyl 2-phenyl-2-bromo-2*H*-azirine-2-carboxylate and benzothiazole in 74% yield. The reaction proceeds via the *S*$_N$2′-*S*$_N$2′-cascade sequence to form the intermediate azirinylbenzothiazolium salt followed by the water-induced thiazole ring expansion. The structure of the product was established using ^{1}H, ^{13}C, [^{1}H, ^{13}C]-HSQC, [^{1}H, ^{13}C]-HMBC NMR spectroscopy, HRMS, and confirmed by X-ray diffraction analysis.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. ^{1}H, ^{13}C{1H}, 2D NMR spectra of compound **2; ** crystallographic data for compound **2**.

Author Contributions: Conceptualization, M.S.N. and N.V.R.; methodology I.P.F., A.V.A. and N.V.R.; investigation, I.P.F.; writing-original draft preparation, I.P.F. and A.V.A.; writing-review and editing, A.V.A. and N.V.R.; supervision, M.S.N.; project administration, M.S.N. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: Data are contained within the article or Supplementary Materials.

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Conflicts of Interest: The authors declare no conflicts of interest.

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