AN EFFICIENT APPROACH TO THE IMIDAZO[5,1-*c*][1,4]BENZOTHIAZINE SKELETON. A NOVEL TRICYCLIC RING SYSTEM

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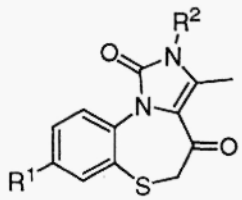
Abstract: Derivatives of a new type tricyclic system having a 1,4-benzothiazine skeleton are described. The reaction of 1-(2-mercaptophenyl)-2*H*-imidazol-2-ones **2** with excess formaldehyde in acid medium resulted in the formation of 2,4-dihydro-1*H*-imidazo[5,1-*c*][1,4]benzothiazin-1-one **3**. The starting compounds **2** were prepared by a modification of a previously described method of ring transformation of 3-(2-oxopropyl)-2(3*H*)-benzothiazolones in reactions with primary amines.

Introduction

The 1,4-benzothiazines are especially interesting because of their occurrence in nature as well as in medicinal chemistry. The well-recognized pharmacological properties of 1,4-benzothiazines include anti-inflammatory, antihistaminic, ataractic et al. activity (1). The interesting biological activities of 1,4-benzothiazines containing an additional heterocycle fused to the [c] edge of the benzothiazine nucleus (2-5) prompted us to synthesize compounds having an attachment of imidazole ring to 1,4-benzothizine system for biological evaluation.



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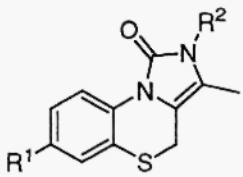

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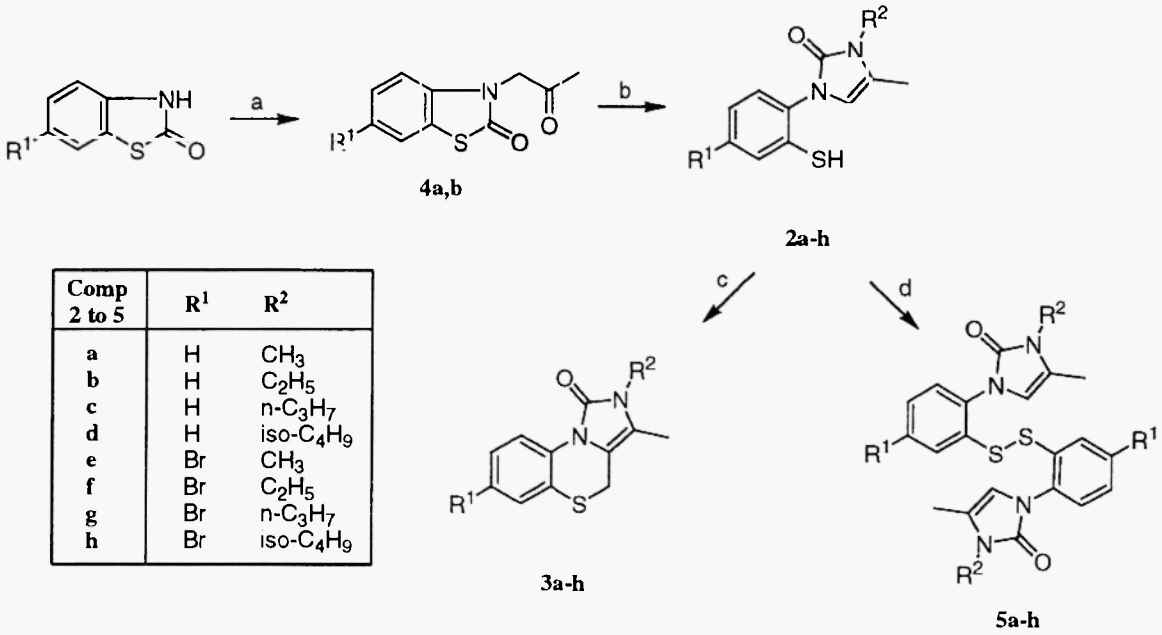
In a previous communication (6) we reported the synthesis of imidazo[5,1-*d*][1,5]benzothiazepines **1** by an intramolecular cyclization of derivatives of **2**. In the process of our investigation concerning the synthesis of unknown N, S-containing polycyclic systems, we prepared a new ring system - 2,4-dihydro-1*H*-imidazo[5,1-*c*][1,4]benzothiazin-1-one **3**. In this communication we report an effective method for the synthesis of imidazo[5,1-*c*][1,4]benzothiazines **3**, using 1-(2-mercaptophenyl)-2*H*-imidazol-2-ones **2** as starting materials under acid conditions. Compounds **2** have been prepared by modification of a previously described procedure for a ring transformation of the substituted 2(3*H*)-benzothiazolones **4** in reaction with primary amines (7).

Results and Discussion

The preparation of imidazo[5,1-*c*][1,4]benzothiazines **3** from imidazolones **2** as a result of a two-stage synthesis is presented in Scheme 1.

Scheme 1



Comp 2 to 5	R^1	R^2
a	H	CH_3
b	H	C_2H_5
c	H	n-C_3H_7
d	H	iso-C_4H_9
e	Br	CH_3
f	Br	C_2H_5
g	Br	n-C_3H_7
h	Br	iso-C_4H_9

Reagents and conditions: (a) $ClCH_2COCH_3$, K_2CO_3, TEBA-Cl, DMF, r.t.; (b) R^2NH_2, water, reflux; (c) 37 % CH_2O, 85 % HCOOH, r.t.; (d) air oxygen

According to the previously described procedure the imidazolones **2** were synthesized through an interaction of 3-(2-oxopropyl)-2(3*H*)-benzothiazolone **4** with a great excess of the primary amine, in the presence of perchloric acid and by heating at 60-90 ^{0}C for 8-48 hours (7). In this case, along with the imidazolones **2** were obtained the corresponding disulfides **5** as by-products. This method has some disadvantages - with low yields and difficulties to purify the reaction product.

On the other hand the yield of the 1,4-benzotiazines depends to a great extent on the purity of the starting imidazolones **2**, due to their possible oxidation to disulfides. This prompted us to fend an alternative way by modifying the reaction conditions. The reaction was carried out in water with moderate excess of amine and were selected a shorter reaction time (3-8 h). After the starting benzothiazolones **4** were consumed (TLC), the excess of the amine was removed under vacuum and the products were isolated after acidification. These new reaction conditions lead to higher yields (68-94 %) and greater purity grade of the products, making them suitable for further synthetic applications.

Any attempt to purify imidazolones **2** results in a loss of the product, due to oxidation. As a result, imidazolones **2a-d**, which are thick oil substances, have not been isolated, but subjected to an immediate cyclization to **3a-d**. Compounds **2e-h** were obtained after acidification as solid substances, and were used in the next step of the cyclization without additional purification.

The cyclization of imidazolones **2** to tricyclic benzothiazines **3** was carried out through an interaction with formaldehyde under acid conditions. There have been attempts to perform this reaction in ethanol, in the absence of acid, but after 48 h boiling of the reaction mixture only a 6 % yield of cyclic product **3** was obtained. In the presence of catalytic amounts of hydrochloric acid, **3** was formed in moderate yield after 60 min boiling (TLC). On the other hand, we established that the reaction is more efficient when carried out in the presence of formic acid with formaldehyde, during 2 hours. The new 1,4-benzothizines **3a-h** are stable compounds, easily isolated in moderate to high yields (60-80 %) and purified by recrystallization.

The structures of new 1,4-benzothiazines **3a-h** are fully supported by elemental analysis and spectrographic (IR, ^{1}H-NMR and mass) data. The singlet for the methine proton of the imidazole ring at 6.05-6.10 ppm in **2a-h** disappears and reveals a singlet for the methylene thiazine protons at 3.69-3.74 ppm. The signals in ^{1}H-NMR were assigned using COSY experiments. The IR spectra of **3a-h** show an amidic CO-bands at 1690 cm^{-1}. No SH-band was noticed at 2450-2550 cm^{-1}.

In conclusion, the presented method for synthesis of annelated imidazo[5,1-*c*][1,4]benzothiazines is very convenient because of its simplicity, high yields and short reaction time. The new compounds could have potential pharmacological activity there are currently screened, which would reveal new aspects of the structure-activity relationships for this particular type of chemical substances.

Experimental

Melting points were determined on a Boetius hot-stage microscope and are uncorrected. The IR spectra were determined on a Specord 71 IR spectrometer (Carl Zeiss, Germany) in nujol. ^{1}H-NMR spectra were recorded on a Bruker AM 400 spectrometer with TMS as internal standard. Mass spectra were obtained with Hewlett Packard 5972 GC-MSD (EI-70 eV). The reactions were followed by TLC on silica gel plates (Merck, 60 F_{254}) using toluene/chloroform/ethylacetate (3:1:1) solvent system (I) for compounds **2** and hexane/ethylacetate/acetic acid (20:20:0.1) solvent system (II) for the rest.

3-(2-Oxopropyl)-2(3*H*)-benzothiazolone (4a)

To a mixture of 2(3*H*)-benzothiazolone (7.56 g, 50 mmol), fine powdered potassium carbonate (4.14 g, 30 mmol) and TEBA (200 mg) in DMF (20 ml) was added chloroacetone (4 ml, 50 mmol). The reaction mixture was stirred for 30 min at 20-25 ^{0}C and then poured under stirring into 150 ml of water. The resulting precipitate was filtered, washed with water and recrystallized from isopropanol. Yield 87%. Colorless needles with m.p. 104-106 °C. (Lit. (8) m.p. 104-106 ^{0}C).

6-Bromo-3-(2-oxopropyl)-2(3*H*)-benzothiazolone (4b)

Following the above procedure, starting from 11.5 g (50 mmol) 6-bromo-2(3*H*)-benzothiazolone, leads to the ketone **4b** in 82%. M.p. 158-159 °C (from acetonitrile).

2,3-Dimethyl-2,4-dihydro-1*H*-imidazo[5,1-*c*][1,4]benzothiazin-1-one (3a)

3-(2-Oxopropyl)-2(3*H*)-benzothiazolone (**4a**) (1.04 g, 5 mmol) and 35 % aqueous methylamin (2.9 ml, 30 mmol) were heated at 60-70 °C in a pressure tube. The mixture was stirred at the same temperature until no starting material could be detected by TLC (4 hours, solvent system I). The tube was cooled down to r.t. and NaOH (5 ml, 5 %) was added. The excess of methylamine was removed under vacuum and the reaction mixture was filtered (if necessary to get rid of the disulfide). After being acidified with 5 % HCl, the product **2a** separates as thick, heavy oil. After decanting, the oil was dissolved in 85 % formic acid (5 ml) and 37 % formaldehyde (0.75 ml, 10 mmol) was added to it. The reaction mixture was stirred at r.t. (2 hours, TLC) and then poured in water. The precipitation formed was filtered, washed with water and dried. Yield 0.70 g, (60 %). M.p. 197-199 °C (from ethanol). ^{1}H-NMR spectrum ($CDCl_3$): 2.08 (s, 3H, CH_3), 3.25 (s, 3H, NCH_3), 3.69 (s, 2H, SCH_2), 7.04-8.47 (m, 4H, ArH). IR spectrum: 1700, 1670. Anal. Calcd for $C_{12}H_{12}N_2OS$ (232.24): C, 62.05; H, 5.21; N, 12.06; Found: C, 62.42; H, 5.42; N, 12.14. MS *m/z* (intensity): 233 (16), M^+ 232 (93), 231 (45), 217 (18), 174 (13), 130 (7), 116 (7), 56 (100)

2-Ethyl-3-methyl-2,4-dihydro-1*H*-imidazo[5,1-*c*][1,4]benzothiazin-1-one (3b)

This compound was synthesized following the procedure for compound **3a**, using 70 % aqueous ethylamine and compound **4a** as starting materials. Yield 0.86 g, (72 %). M.p. 171-173 °C (from ethanol). ^{1}H-NMR spectrum ($CDCl_3$): 1.32 (t, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.74 (s, 2H, SCH_2), 3.79 (q, 2H, NCH_2), 7.07-8.53 (m, 4H, ArH). IR spectrum: 1690, 1665. Anal. Calcd for $C_{13}H_{14}N_2OS$ (246.26): C, 63.35; H, 5.71; N, 11.38; Found: C, 63.46; H, 6.11; N, 10.97. MS *m/z* (intensity): M^+ 246 (100), 231 (13), 217 (26), 203 (6), 175 (10), 174 (11), 149 (13), 148 (14), 70 (24)

3-Methyl-2-propyl-2,4-dihydro-1*H*-imidazo[5,1-*c*][1,4]benzothiazin-1-one (3c)

3-(2-Oxopropyl)-2(3*H*)-benzothiazolone (**4a**) (1.04 g, 5 mmol) and propylamine (2.5 ml, 30 mmol) dissolved in water (5 ml) were heated for 4 h with boiling until no starting materials could be detected (TLC). After cooling down to room temperature, NaOH (5 ml, 5 %) was added and the reaction mixture was further processed in the same manner as described for compound **3a.** Yield 0.92 g, (71 %). M.p. 140-142 °C (from ethanol). ^{1}H-NMR spectrum ($CDCl_3$): 0.97 (t, 3H, CH_3), 1.69 (m, 2H, CH_2) 2.09 (s, 3H, CH_3), 3.61 (t, 2H, NCH_2), 3.69 (s, 2H, SCH_2), 7.05-8.49 (m, 4H, ArH). IR spectrum: 1680, 1660. Anal. Calcd for $C_{14}H_{16}N_2OS$ (260.29): C, 64.59; H, 6.19; N, 10.76; Found: C, 64.78; H, 6.40; N, 10.38. MS *m/z* (intensity): M^+ 260 (100), 259 (13), 245 (8), 231 (9), 218 (17), 217 (38), 175 (11), 148 (29), 147 (17), 130 (7), 107 (6)

2-Isobutyl-3-methyl-2,4-dihydro-1*H*-imidazo[5,1-*c*][1,4] benzothiazin-1-one (3d)

This compound was synthesized following the procedure for compound **3c**, using isobutylamine and compound **4a** as starting materials. Yield 1.02 g, (74 %). M.p. 162-164 °C (from ethanol). ^{1}H-NMR spectrum ($CDCl_3$): 0.96 (d, 6H, CH_3), 2.08 (s, 3H, CH_3), 2.10 (m, 1H, $CH(CH_3)_2$), 3.45 (d, 2H, NCH_2), 3.70 (s, 2H, SCH_2), 7.03-8.50 (m,

4H, ArH). IR spectrum: 1700, 1675. Anal. Calcd for $C_{15}H_{18}N_2OS$ (274.22): C, 65.67; H, 6.61; N, 10.21; Found: C, 65.45; H, 7.15; N, 10.13. MS *m/z* (intensity): M^+ 274 (100), 231 (21), 218 (61), 217 (56), 203 (14), 175 (11), 149 (57), 148 (22), 130 (6), 109 (6), 108 (6), 57 (8)

7-Bromo-2,3-dimethyl-2,4-dihydro-1*H*-imidazo[5,1-*c*][1,4]benzothiazin-1-one (3e)

1-(4-Bromo-2-mercaptophenyl)-3,4-dimethyl-1,3-dihydro-2*H*-imidazol-2-one (**2e**) (0.60 g, 2 mmol) was dissolved in formic acid (5 ml 85 %) and of 37 % formaldehyde (4 mmol) were added. The reaction mixture was stirred for 1-2 hour at r.t. until the starting material is fully consumed (TLC). The reaction mixture poured in water, the precipitation formed was filtered, washed with water and dried. Yield 0.50 g, (80 %). M.p. 202-204 °C (from ethanol). ^{1}H-NMR spectrum ($CDCl_3$): 2.08 (s, 3H, CH_3), 3.25 (s, 3H, NCH_3), 3.69 (s, 2H, SCH_2), 7.35-8.38 (m, 3H, ArH). IR spectrum: 1710, 1685. Anal. Calcd for $C_{12}H_{11}BrN_2OS$ (311.15): C, 46.32; H, 3.56; N, 9.01; Found: C, 46.01; H, 3.49; N, 9.04. MS *m/z* (intensity): 313 (12), 312 (64), M^+ 311 (31), 310 (63), 309 (22), 253 (5), 173 (6), 147 (5), 56 (100)

7-Bromo-2-ethyl-3-methyl-2,4-dihydro-1*H*-imidazo[5,1-*c*][1,4]benzothiazin-1-one (3f)

The compound was synthesized following the procedure for compound **3e** using **2f** (0.63 g, 2 mmol) as starting materials. Yield 0.52 g, (80 %). M.p. 178-179 °C (from ethanol). ^{1}H-NMR spectrum ($CDCl_3$): 1.32 (t, 3H, CH_3), 2.14 (s, 3H, CH_3), 3.74 (s, 2H, SCH_2), 3.78 (q, 2H, NCH_2), 7.39-8.43 (m, 3H, ArH). IR spectrum: 1690, 1660. Anal. Calcd for $C_{13}H_{13}BrN_2OS$ (325.17): C, 48.02; H, 4.03; N, 8.62; Found: C, 48.26; H, 4.09; N, 8.46. MS *m/z* (intensity): 327 (16), 326 (100), M^+ 325 (34), 324 (98), 323 (19), 311 (9), 309 (9), 296 (21), 294 (21), 254 (8), 228 (10), 227 (10), 173 (14), 147 (8), 70 (39)

7-Bromo-3-methyl-2-propyl-2,4-dihydro-1*H*-imidazo[5,1-*c*][1,4] benzothiazin-1-one (3g)

The compound was synthesized following the procedure for compound **3e** using **2g** (0.50 g, 1.5 mmol) as starting materials. Yield 0.42 g, (83 %). M.p. 193-195 °C (from ethanol). ^{1}H-NMR spectrum ($CDCl_3$): 0.97 (t, 3H, CH_3), 1.67 (m, 2H, CH_2) 2.09 (s, 3H, CH_3), 3.61 (t, 2H, NCH_2), 3.69 (s, 2H, SCH_2), 7.35-8.4 (m, 3H, ArH). IR spectrum: 1680, 1660. Anal. Calcd for $C_{14}H_{15}BrN_2OS$ (339.26): C, 49.57; H, 4.16; N, 8.26; Found: C, 49.25; H, 4.19; N, 7.96. MS *m/z* (intensity): 341 (16), 340 (100), M^+ 339 (25), 338 (98), 296 (33), 394 (30), 354 (10), 252 (13), 228 (28), 227 (15), 226 (28), 225 (12), 173 (16), 148 (10), 147 (12), 84 (13), 63 (11)

7-Bromo-2-isobutyl-3-methyl-2,4-dihydro-1*H*-imidazo[5,1-*c*][1,4]benzothiazin-1-one (3h)

The compound was synthesized following the procedure for compound **3e** using **2h** (0.68 g, 2 mmol) as starting materials. Yield 0.57 g, (81 %). M.p. 170-172 °C (from ethanol). IR spectrum: 1700, 1670; ^{1}H-NMR spectrum ($CDCl_3$): 0.96 (d, 6H, CH_3), 2.05 (m, 1H, $CH(CH_3)_2$), 2.07 (s, 3H, CH_3), 3.44 (d, 2H, NCH_2), 3.69 (s, 2H, SCH_2), 7.34-8.44 (m, 3H, ArH). Anal. Calcd for $C_{15}H_{17}BrN_2OS$ (353.22): C, 51.00; H, 4.85; N, 7.93; Found: C, 51.25; H, 4.45; N,

7.67. MS *m/z* (intensity): 355 (18), 354 (99), M^+ 353 (21), 352 (96), 311 (16), 309 (15), 297 (61), 296 (63), 282 (12), 280 (11), 254 (12), 252 (13), 228 (46), 226 (46), 173 (16), 147 (14), 120 (7), 108 (6), 57 (18)

Acknowledgment. *We wish to thank Dr B. Vogler from Hohenheim University (Stuttgart, Germany) for the NMR spectra. Thanks are also due to our colleagues Dr I. Kozekov and Dr. L. Nechev from Vanderbilt University (Nashville, Tennessee) for numerous helpful suggestions.*

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Received on September 15, 2003.