Cyclization Reactions of Hydrazones XXV[#]: Synthesis and Study of Reactivity of some Derivatives of [1]benzothieno[2,3-e]1,2,4-triazine

Jakub Stýskala*, Jan Slouka

Department of Organic Chemistry, Palacky University, Tr. Svobody 8, 771 46 Olomouc, Czech Republic

E-mail: styskala@risc.upol.cz

Abstract: By coupling of diazonium salts with ethyl N-(2-benzo[b]thienyl)-carbamate **1** were obtained corresponding 3-arylazocompounds **2**, wchich are tautomeric with their hydrazono form **3**. These ones were thermally cyclized to the corresponding 2-aryl-2,3-dihydro-[1]benzothieno[2,3-e]1,2,4-triazin-3-ones **4**. By basic hydrolysis of these compounds, the thiophene ring is opened with formation of corresponding 1-aryl-5-(o-mercaptophenyl)-6-azauracils **5**. The longterm acidic hydrolysis, howewer, causes the splitting of the 1,2,4-triazine ring and the corresponding 3-arylhydrazono-2,3-dihydro-benzo[b]thiophen-2-ones **6** were thus obtained. The mercapto-compounds **5** are very easily oxidised to the corresponding disulphides **7**.

Introduction

The previous synthesis of [1]benzothieno[2,3-e]1,2,4-triazine derivatives were based on two principles. The first principle concerns the cyclization of amidinohydrazone of the 2,3-dihydro-benzo[b]thiophen-2,3-dione (1), the second principle is based on closure of thiophene ring of the 5-(2-mercaptophenyl)-6-azauracil (2).

In this communication the syntheses of some derivatives of 2-aryl-2,3-dihydro-benzo[b]thieno[2,3-e]1,2,4-triazin-3-ones **4** are described, based on the third principle, which was successfully verified at the synthesis of the analogues [1]benzofuro[2,3-e]1,2,4-triazine derivatives (3).

Results

By coupling of diazonium salts with ethyl N-(2-benzo[b]thienyl)-carbamate **1** in pyridine medium corresponding 3-arylazocompounds **2** were prepared in good yields. Unlike analogous azocompounds of the benzo[b]furan series, which easily changes to tautomeric hydrazones (3), we found azocompounds **2** which are stable at room temperature, according to the results of the IR spectroscopy of the compound **2a** in

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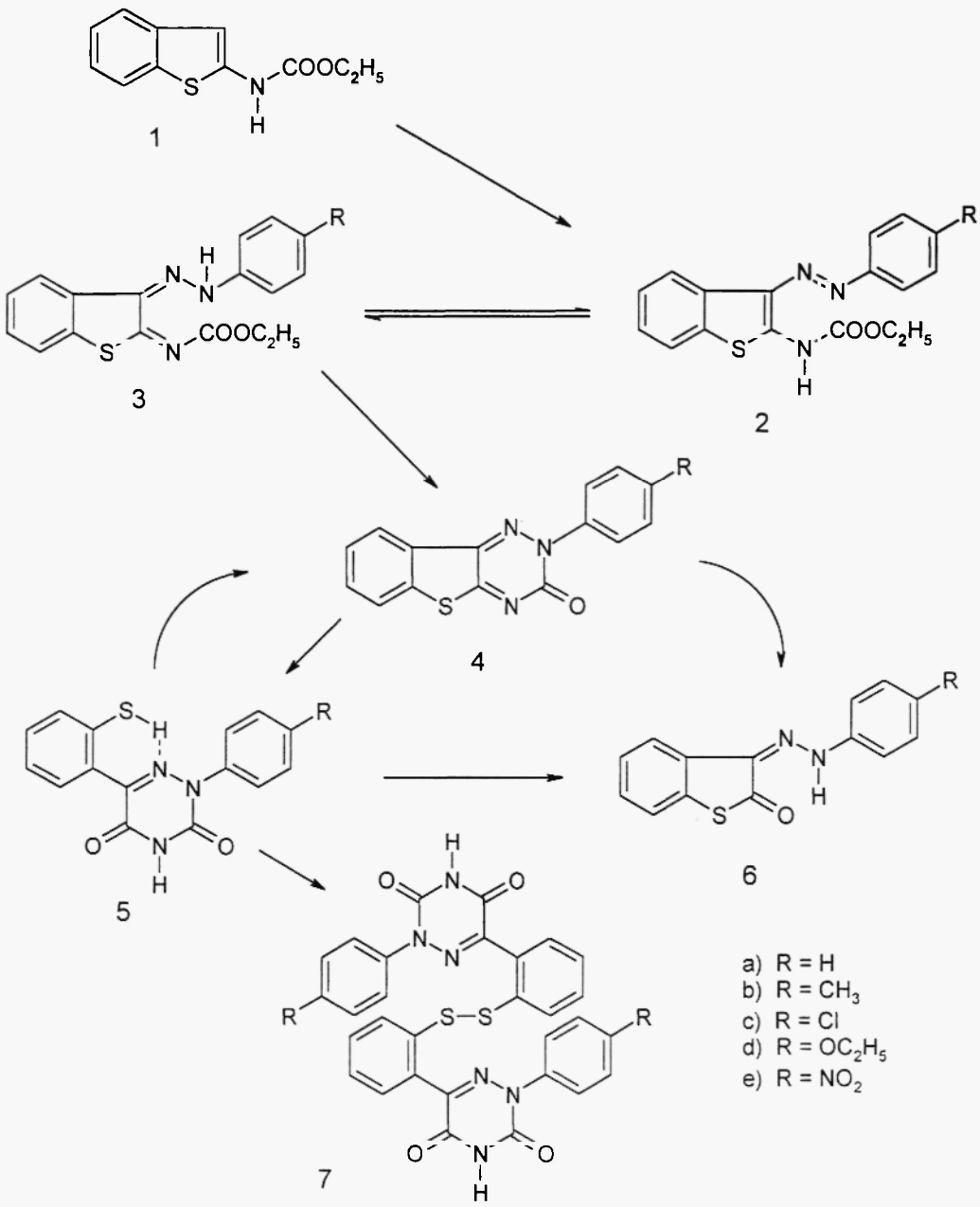
[#]Part XXIV: see ref.[3]

tetrachloromethane solution. Spectrum of this compound in the region over 3000 cm^{-1} is quite identical with spectrum of the derivative **2a** with isotopical labeled nitrogen atom, which was prepared from aniline with ^{15}N. The band at 3388 cm^{-1} thus corresponds to the carbamate N-H stretching vibration of the azo- tautomer. The band of the hydrazono-tautomer **3** with ^{15}N would be shifted by 7 cm^{-1} toward lower wawenumbers. This azo form of compounds **2** was unambiguously confirmed by ^{1}H, ^{13}C and ^{15}N NMR spectroscopy. Hydrazones **3** are formed from the corresponding azocompounds **2** most probably at high temperature and this fact



makes the ring closure difficult. Contrary to the ethyl N-(3-arylazo-benzo[b]furan-2-yl)-carbamates, which are completely cyclized by 1 hour boiling in decaline (3), azocompounds **2** cyclize to the corresponding 2-aryl-2,3-dihydro-[1]benzothieno[2,3-e]1,2,4-triazine-3-ones **4** only in 5% yield under the same conditions. The reaction temperature had to be rised to 250-255 °C. Under these conditions the ring closure of compounds **2a-2d** is completed during 15 minutes. The cyclization of derivative **2e**, howewer, was not successful due to the –M effct of the nitro-group.

The stability of compounds **4** towards hydrolytic splitting might be of interest. Contrary to the analogues of [1]benzofuro[2,3-e]1,2,4-triazine derivatives, which are susceptible to hydrolytic splitting in acidic, neutral and basic mediums (3), compounds **4** opened their thiophene ring in basic medium only to give corresponding 1-aryl-5-(2-mercaptophenyl)-6-azauracils **5**. These compounds **5** are very susceptible to oxidation and give corresponding disulphides **7** by standing on air oxygen or oxidation by iodine.

In acidic medium compounds **5** are transformed back to 1,2,4-triazines **4**. If the boiling of compounds **4** or **5** is prolonged in acidic medium for 2 days then the 1,2,4-triazine ring is splitted affording the corresponding 3-arylhydrazono-2,3-dihydro-benzo[b]thiophen-2-ones **6**.

Apparatus and methods

The melting points were determined on a Boetius stage and are uncorrected. The infrared spectra were recorded in KBr wafers and scanned on an ATI Unicam Genesis FTIR instrument. The NMR spectra were registered in $(CD_3)_2SO$ on a Bruker AMX-360 spectrometer (360 MHz); the chemical shifts are reported in ppm. Elemental analyses were performed with an EA 1108 Elemental Analyser (Fison Instrument).

Experimental

Ethyl N-(3-arylazo-2-benzo[b]thienyl)-carbamates **2a–2e**.

General Procedure:

A solution of corresponding aromatic amine (2.00 mmol) in a mixture of ice water (10 ml) and 37% hydrochloric acid (1.2 ml) was diazotized with a solution of sodium nitrite (2.00 mmol) in ice water (6 ml). The mixture was stirred in ice bath for 15 min and then added portionwise to a solution of ethyl N-(2-benzo[b]thienyl)-carbamate (2.01 mmol) in pyridine (40 ml), which was cooled to 0–5 °C. The mixture was left to stand at 0–5 °C for 24 h and then slowly diluted with ice water to a total volume of 300 ml. The next day the precipitated orange solid was collected, washed with water, dried, and recrystallized from ethanol-benzene mixture.

For further details, see tables 1-2.

2-aryl-2,3-dihydro-[1]benzothieno[2,3-e]1,2,4-triazin-3-ones **4a–4d**.

General procedure:

Method a: by cyclization of azo-carbamates **2**.

Corresponding azocarbamate **2** (1.5 mmol) was heated at 250-255 °C in a metal bath for 15 min. After cooling the crude product was finely pulverized, recrystallized from toluene and dried at 120 °C.

Method b: by cyclization of compounds **5**.

A suspension of 6-azauracil **5** (0.1 mmol) in 37% hydrochloric acid (4 ml) was refluxed for 60 min. After cooling, undissolved compound was filtered off, washed with water and dried. The sample for analysis was obtained by recrystallization from ethanol.

For further details, see tables 1-2.

1-aryl-5-(2-mercaptophenyl)-6-azauracils **5a–5d**.

General procedure:

The corresponding compound **4** (0.5 mmol) was dissolved in a solution of 1M-NaOH (15 ml) and sodium disulphite (7 mg) and refluxed under nitrogen atmosphere for 15 min.The clear solution so obtained was cooled by immersing the flask in ice water and neutralization by dilute acetic acid. Precipitated colourless compound **5** was collected, washed with water and dried over NaOH under oxygen free conditions. Prepared compounds **5** are very sussceptible to air oxygen and it was not possible to prepare them in pure form, due to the presence of traces of disulphide. This is the reason why we could not determine a melting point of these compounds.

For further details, see tables 1-2.

3-arylhydrazono-2,3-dihydro-benzo[b]thiophen-2-ones **6a–6d**.

General procedure:

Corresponding compound **4** (0.1 mmol) in a mixture of ethanol (10 ml) and 37% hydrochloric acid (6ml) was refluxed for 36 hours. After this time ethanol was distilled off under vacuum. The reaction mixture was cooled for one day and precipitated crystalline substance was filtered off, washed with water and recrystallized from ethanol-water mixture with using charcoal.

For further details, see tables 1-2.

2,2′-bis-(1-aryl-6-azauracil-5-yl)-diphenyl-disulphides **7a–7d**.

General procedure:

To the solution of compound **5** (0.1 mmol) in ethanol (10 ml) was dropwise added solution of iodine (1% solution) in ethanol until the colour of the solution was permanent light brown. During this period the oxidized product started to precipitate from solution. This one was filtered off, washed with ethanol and water and recrystallized from larger amount of ethanol.

For further details, see tables 1-2.

References:

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Table 1

Characteristic data of compounds **2-7** *

Compound	M.p. (°C) Yield (%)	Formula M.w.	IR spectroscopic data (cm^{-1})
2a	127-129 90	$C_{17}H_{15}N_3O_2S$ 325.39	3062, 2984, 1720, 1543, 1462, 1198, 752
2b	150-152 87	$C_{18}H_{17}N_3O_2S$ 339.41	3070, 2978, 1720, 1540, 1458, 1196, 762
2c	192-194 86	$C_{17}H_{14}N_3O_2S$ 359.83	3061, 2978, 1721, 1539, 1193, 764
2d	145-147 76	$C_{19}H_{19}N_3O_3S$ 369.45	3066, 2987, 1723, 1546, 1458, 1274, 1204, 762
2e	205-207 86	$C_{17}H_{14}N_4O_4S$ 370.38	3079, 2980, 1726, 1683, 1544, 1519, 1335, 1251, 1067, 751
4a	244-245 97 [a]; 88 [b]	$C_{15}H_9N_3OS$ 297.32	3062, 1680, 1580, 1514, 1056, 688
4b	203-205 98 [a]; 85 [b]	$C_{16}H_{11}N_3OS$ 393.34	3028, 1684, 1584, 1512, 1053, 723
4c	266-268 99 [a]; 84 [b]	$C_{15}H_8N_3OSCl$ 313.76	3065, 1673, 1578, 1489, 1058, 731
4d	203-205 98 [a]; 80 [b]	$C_{17}H_{13}N_3O_2S$ 323.38	3075, 2981, 1676, 1580, 1510, 1250, 1053, 728
5a	- 80	$C_{15}H_{11}N_3O_2S$ 297.35	3062, 1692, 1490, 1296, 758
5b	- 84	$C_{16}H_{13}N_3O_2S$ 311.36	3063, 1697, 1511, 1297, 760
5c	- 86	$C_{15}H_{10}N_3O_2SCl$ 331.78	3065, 1696, 1491, 1297, 758
5d	- 83	$C_{17}H_{15}N_3O_3S$ 341.39	3067, 2981, 1697, 1511, 1250, 760
6a	164-166; 165-6 [c] 43	$C_{14}H_{10}N_2OS_2$ 254.31	1634, 1538, 1477, 1262, 1044, 751
6b	261-264 40	$C_{15}H_{12}N_2OS$ 268.34	1632, 1535, 1474, 1258, 1044, 756
6c	207-210 52	$C_{14}H_9N_2OSCl$ 288.76	1637, 1543, 1476, 1256, 1047, 756
6d	143-145 43	$C_{16}H_{14}N_2O_2S$ 298.37	1627, 1533, 1474, 1239, 1043, 757

Table 1, continuation			
7a	295-296 88	$C_{30}H_{20}N_6O_4S_2$ 592.66	3045, 1692, 1491, 1293, 750, 596
7b	265-267 81	$C_{32}H_{24}N_6O_4S_2$ 620.71	3044, 2924, 1697, 1511, 1294, 756, 590
7c	231-233 85	$C_{30}H_{18}N_6O_4S_2Cl$ 661.55	3062, 1696, 1491, 1296, 759, 586
7d	229-232 86	$C_{34}H_{28}N_6O_6S_2$ 680.77	3063, 2981, 1698, 1510, 1250, 759, 593

* Analyses were given as suplementary data; experimental values are within ± 0,04% of the calculated ones.

[a] by method a [b] by method b [c] ref. (5)

Table 2

NMR spectral data of compounds **2a, 4a, 5a and 7a**

Compound/ nucleus	NMR spectrum (ppm)
2a ^1H	1.39 (t, 3H, CH_3), 4.38 (q, 2H, CH_2), 7.41 (t, 1H, H_{arom}), 7.49 (m, 2H, H_{arom}), 7.60 (t, 2H, H_{arom}), 7.69 (d, 1H, H_{arom}), 8.15 (d, 2H, H_{arom}), 8.69 (d, 1H, H_{arom}), 11.87 (br s, 1H, NH)
2a ^{13}C	14.43 (CH_3), 62.59 (CH_2), 122.02, 122.51, 122.64, 124.94, 126.41, 129.25, 169.69, 130.08, 130.75, 132.54, 149.38, 152.10, 154.19
2a ^{15}N	66.97 (s, 1N, ^{15}N=N)
4a ^1H	1.39 (t, 3H, CH_3), 4.38 (q, 2H, CH_2), 7.41 (t, 1H, H_{arom}), 7.49 (m, 2H, H_{arom}), 7.60 (t, 2H, H_{arom}), 7.69 (d, 1H, H_{arom}), 8.15 (d, 2H, H_{arom}), 8.69 (d, 1H, H_{arom}), 11.87 (br s, 1H, NH)
5a ^1H	7.25 (t, 1H, H_{arom}), 7.35 (t, 1H, H_{arom}), 7.44 (t, 1H, H_{arom}), 7.54 (m, 4H, H_{arom}), 7.63 (m, 2H, H_{arom}) acidic hydrogens did not appear here
7a ^1H	7.42 (m, 6H, H_{arom}), 7.54 (t, 4H, H_{arom}), 7.63 (t, 6H, H_{arom}), 7.72 (d, 2H, H_{arom}), 12.65 (br s, 2H, NH)

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