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Chemistry of Thiazole, I

Synthesis and Properties of 2,3,5,6-Tetrahydro-6-(3-methylbenzofuran-2-yl)imidazo[2,1-*b*]thiazole*)

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Synthese und Eigenschaften von 2,3,5,6-Tetrahydro-6-(3-methylbenzofuran-2-yl)-imidazo[2,1-*b*]thiazol*)

Die Titelverbindung **13** wird auf zwei Wegen ausgehend von 2-Hydroxyacetophenon (**1**) über das Benzofuran-Derivat 7 und die Thiazolidine **9** bzw. **10** erhalten.

In search of new biologically active compounds the synthesis of heterocyclic analogues of tetramisole[1] has been undertaken. The present paper describes the synthesis of the title compound **13** not known in the literature. 2-Bromo-1-(3-methylbenzofuran-2-yl)ethanone (**7**), prepared in two ways, was the key compound. In both methods, 2-hydroxyacetophenone (**1**) was used as the starting substance. **1** reacts with chloroacetone in the presence of anhydrous K_2CO_3 in acetone to yield **4**. In a second way, from the reaction of **1** with ethyl chloroacetate under the same conditions ethyl (2-acetylphenoxy)acetate (**2**) was obtained in 58% yield. Its basic hydrolysis gave (2-acetylphenoxy)acetic acid (**3**). This acid was cyclized in the presence of acetic anhydride and sodium acetate to 3-methylbenzofuran (**5**) in 62% yield. Hydrocarbon **5**, when treated with acetyl chloride in the presence of anhydrous $AlCl_3$ in CS_2, formed **4** (52%), identical with the substance obtained above.

Ethanone **7** was prepared also in two ways. In the first method, ketone **4** was brominated using the complex of bromine and dioxane in anhydrous ether. In the second way, 7 was obtained on direct treating of hydrocarbon **5** with $BrCH_2COCl$ in the presence of anhydrous $AlCl_3$ in CS_2 (52%).

The second component for the preparation of the title compound, i. e. 2-iminothiazolidine (**6**), was obtained from thiourea solution by treating with ethylenimine in 50% H_2SO_4. This compound exists in equilibrium with its tautomeric form 2-amino-2-thiazoline (**6a**).

Condensation of ω-bromoketone **7** with **6** leads to the 3-substituted derivative **8** of thiazolidine as hydrobromide in 96% yield. Hydrobromide **8** was decomposed yielding ketone **9**, the imine function of which was blocked by acetylation to give **12**. Reduction of **12** with $NaBH_4$ in methanol resulted in the formation of the ethanol derivative **14**, which was treated with thionyl chloride in $CHCl_3$. The resulting crude chloride was then cyclized with K_2CO_3 in water and the obtained title compound **13** was purified via its hydrochloride **11**.

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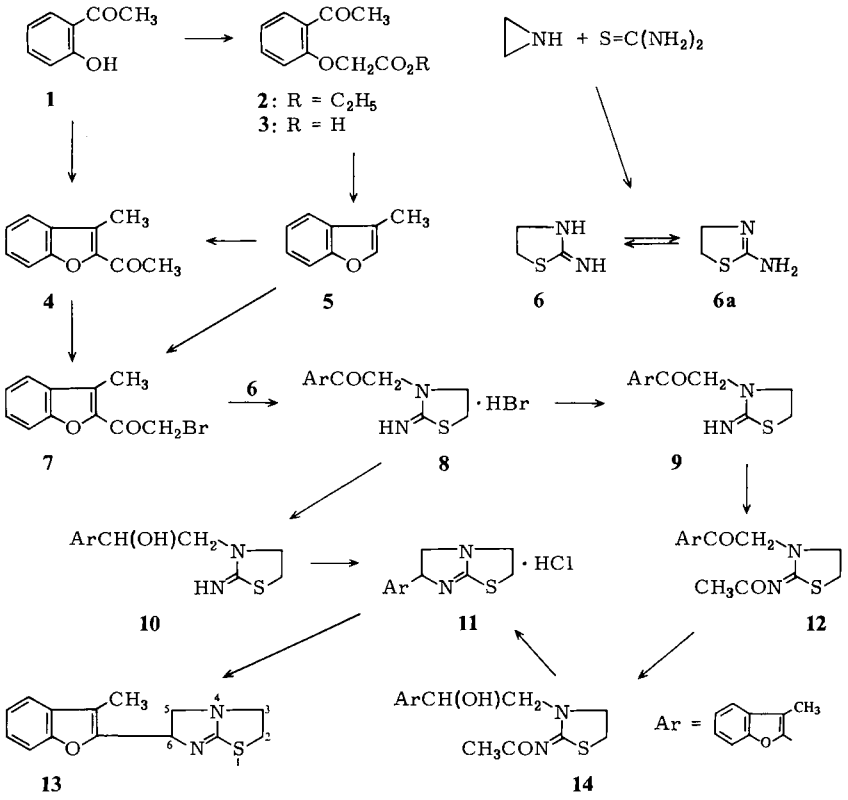

Elementary analysis and NMR spectra completely confirmed the structure of compound **13**. A singlet (3H) at $\delta = 2.14$ in the ^{1}H NMR spectrum indicated the presence of a methyl group at an aromatic ring. A triplet (1H) at $\delta = 5.50$ is, on the other hand, the signal of a proton bonded with carbon atom 6. In **13**-hydrochloride in D_2O that proton gives a doublet of doublets (5.61 ppm) with $J_1 = 7.8$ and $J_2 = 11.4$ Hz characteristic of *cis*- and *trans*-coupling.

In a second way, ketone hydrobromide **8** was reduced directly to ethanol derivative **10** in 88% yield. This alcohol was then cyclized with $SOCl_2$ in acetic anhydride to the imidazo-thiazole hydrochloride **11** (= **13** · HCl).

Experimental Part

^{1}H NMR spectra: Tesla BS 487C 80 MHz spectrometer (internal standard HMDSO). – Melting points: Boetius apparatus, without correction.

Ethyl (2-acetylphenoxy)acetate (**2**): A mixture of 110 g (0.80 mol) of 2-hydroxyacetophenone (**1**), 122.5 g (1.0 mol) of ethyl chloroacetate, and anhydrous K_2CO_3 (110.5 g, 0.80 mol) in 600 ml of acetone was refluxed for 58 h. The formed precipitate was filtered off and washed with acetone. The filtrate was distilled and 105 g (58%) of substance was obtained with b. p. 185 °C/5 Torr and m. p. 40–50.5 °C. – ^{1}H NMR ($CDCl_3$, δ): 1.17 t (3H), 2.57 s (3H), 4.14 q (2H), 4.60 s (2H), 6.65–7.70 m (4H).

(2-Acetylphenoxy)acetic acid (**3**): Into the vigorously stirred solution of sodium carbonate (53 g, 0.50 mol) in water (800 ml), ester **2** (100 g, 0.45 mol) was added and the mixture was gently refluxed. After 1 h heating, the solution was cooled to 5 °C and acidified carefully with conc. HCl. The deposited precipitate was filtered off, washed several times with cooled water, and crystallized from hot water. Yield 85 g (97%), m. p. 114 – 114.5 °C (lit.[2] 105 °C). – ^{1}H NMR ($CDCl_3$, δ): 2.57 s (3H), 4.65 s (2H), 6.15 s (1H), 5.70 – 6.75 m (4H).

3-Methylbenzofuran (**5**): A mixture of **3** (77.5 g, 0.40 mol), anhydrous sodium acetate (141 g, 1.7 mol), and acetic anhydride (285 g, 2.8 mol) was heated at 160 °C for 3 h. After cooling, the mixture was poured into 900 ml of water and then extracted with benzene. The combined benzene extracts were washed with 10% Na_2CO_3 solution and then with water and finally dried over $CaCl_2$. The solvent was removed and **5** (32.5 g, 62%) was isolated by distillation. B. p. 65 °C/5 Torr, n_D^{25} = 1.5527 (lit.[3] b. p. 86 °C/20 Torr, n_D^{25} = 1.5533). – ^{1}H NMR ($CDCl_3$, δ): 2.08 s (3H), 7.0 – 7.5 m (5H).

1-(3-Methylbenzofuran-2-yl)ethanone (**4**)

a) A mixture of **1** (136 g, 1.0 mol), K_2CO_3 (138 g, 1.0 mol), chloroacetone (92.5 g, 1.0 mol), and acetone (500 ml) was refluxed for 16 h. Deposited KCl precipitate was filtered off, washed with acetone, and then the solvent was removed to give an oil which was dissolved in ether (500 ml). The ether solution was dried over $MgSO_4$ and, after removing the ether, the residue was distilled in vacuo. The fraction (46.5g, 28%), boiling within the range of 128 – 132 °C/2 Torr, m. p. 25 – 26.5 °C, was collected (lit.[4] b.p. 94 – 98 °C/0.2 Torr, n_D^{25} = 1.5915). – ^{1}H NMR ($CDCl_3$, δ): 2.41 s (3H), 2.45 s (3H), 7.0 – 7.55 m (4H).

$C_{11}H_{10}O_2$ (174.2) Calcd. C 75.84 H 5.78 Found C 75.59 H 5.81

b) $AlCl_3$ (5.4 g, 40 mmol) was added to the solution of **5** (5.3 g, 40 mmol) in CS_2 (150 ml). To that mixture acetyl chloride (3.2 g, 40 mmol), dissolved in CS_2 (25 ml), was dropped in at 5 °C. The mixture was left for 12 h and then treated with dilute HCl. After removing the solvent, the residue was extracted with ether. Further treatment was the same as in a), yield 3.6 g (52%).

2-Bromo-1-(3-methylbenzofuran-2-yl)ethanone (**7**)

a) To the solution of **4** (40 g, 0.23 mol) in anhydrous ether (75 ml) and dioxane (25 ml) bromine (36.8 g, 0.46 mol) was added dropwise during 1 h at 25 – 30 °C. Methanol (10 ml) was added and the mixture was heated for 0.5 h. Then it was poured into water (200 ml). The deposited precipitate was filtered off, washed with water, and crystallized twice from cyclohexane. Yield 39 g (67%), m. p. 108 – 109 °C. – ^{1}H NMR ($CDCl_3$, δ): 2.51 s (3H), 4.39 s (2H), 7.10 – 7.12 m (4H).

$C_{11}H_9BrO_2$ (253.1) Calcd. C 52.20 H 3.58 Br 31.57 Found C 52.10 H 3.51 Br 31.64

b) To the solution of **5** (25 g, 0.19 mol) in CS_2 (100 ml), anhydrous $AlCl_3$ (30 g, 0.22 mol) was added. Then bromoacetyl chloride (31.5 g, 0.20 mol), dissolved in CS_2 (200 ml), was added during 2 h at about 5 °C. The mixture was left for 12 h at room temperature and was then treated with dilute HCl (1 : 1). After removing the solvent, the residue was extracted with chloroform. The combined extracts were washed four times with water, dried over Na_2SO_4, and finally, after removing the solvent, the solid residue was crystallized twice from cyclohexane. Yield 25 g (52%).

2-Iminothiazolidine (**6**): Thiourea (76.1 g, 1.0 mol) was dissolved in 50% H_2SO_4 (110 ml, 1.0 mol). After cooling to 5 °C, ethylenimine (51.0 g, 1.0 mol) was added during 1.5 h and the mixture was refluxed for 2 h. After cooling the reaction mixture was poured into $CHCl_3$ (900 ml) and neutralized with 25% solution of ammonia. The chloroform layer was separated and the water layer was extracted with $CHCl_3$ (900 ml). The combined chloroformic extracts were dried over $MgSO_4$ and then the solvent was removed. The solid residue was crystallized from benzene, yield 67 g (69%), m. p. 79 – 80 °C (lit.[5] 81 °C). – ^{1}H NMR ($CDCl_3$, δ): 3.27 t (2H), 3.79 t (2H), 5.60 s (2H).

2-(2-Imino-3-thiazolidinyl)-1-(3-methylbenzofuran-2-yl)ethanone hydrobromide (**8**): To a vigorously stirred solution of 7 (55.5 g, 0.22 mol) in acetone (300 ml) a solution of **6** (22.5 g, 0.22 mol) in acetone (200 ml) was added during 1 h. The mixture was stirred for about 0.5 h at room temperature. The deposited precipitate was filtered off and washed successively with acetone and chloroform. Yield 74 g (96%), m. p. 293 – 294 °C (sublimating at about 193 °C).

2-(2-Imino-3-thiazolidinyl)-1-(3-methylbenzofuran-2-yl)ethanone (**9**): Fine-powdered **8** (25 g, 70 mmol) was added in small portions to the solution of K_2CO_3 (13.8 g, 100 mmol) in water (200 ml). The mixture was stirred vigorously for about 3 h. The deposited precipitate was filtered off and washed with water; 18.6 g (97%), m. p. 124 – 126 °C (ethanol). – ^{1}H NMR ($CDCl_3$, δ): 2.57 s (3H), 3.21 t (2H), 3.76 t (2H), 3.82 s (2H), 5.51 – 5.78 s (1H), 7.15 – 7.65 m (4H).

$C_{14}H_{14}N_2O_2S$ (274.3) Calcd. C 61.31 H 5.15 N 10.21 Found C 61.40 H 5.18 N 10.22

2-[2-(Acetylimino)-3-thiazolidinyl]-1-(3-methylbenzofuran-2-yl)ethanone (**12**): **9** (17 g, 60 mmol), acetic anhydride (17.3 g, 170 mmol), and $CHCl_3$ (300 ml) were heated for 6 h. The reaction mixture was cooled, neutralized with 20% Na_2CO_3 solution, and washed with water. The chloroformic solution was dried over $MgSO_4$ and the solvent was removed. The crude product was crystallized from methanol; 13.8 g (70%), m. p. 175 °C. – ^{1}H NMR ($CDCl_3$, δ): 2.02 s (3H), 2.50 s (3H), 3.09 t (2H), 3.65 t (2H), 5.00 s (2H), 7.10 – 7.25 m (4H).

$C_{16}H_{16}N_2O_3S$ (316.4) Calcd. C 60.37 H 5.70 N 8.80 Found C 60.43 H 5.61 N 8.68

2-(Acetylimino)-α-(3-methylbenzofuran-2-yl)-3-thiazolidineethanol (**14**): Into the vigorously stirred suspension of ketone **12** (12.8 g, 40 mmol) in methanol (100 ml) a solution of 3.0 g (80 mmol) of $NaBH_4$ was added. The reaction mixture was then poured into water (250 ml). The deposited precipitate was filtered off, washed with water, dried, and crystallized from ethanol; 8.9 g (68%), m. p. 160 – 160.5 °C. – ^{1}H NMR ($CDCl_3$, δ): 2.07 s (3H), 2.15 s (3H), 2.85 t (2H), 3.43 t (2H), 3.92 q (2H), 5.15 t (1H), 5.69 s (1H) D_2O, 7.05 – 7.46 m (4H).

$C_{16}H_{18}N_2O_3S$ (318.4) Calcd. C 60.37 H 5.70 N 8.80 Found C 60.43 H 5.61 N 8.68

2-Imino-α-(3-methylbenzofuran-2-yl)-3-thiazolidineethanol (**10**): A suspension of hydrobromide **8** (22.5 g, 0.25 mol) in methanol (250 ml) was treated with $NaBH_4$ (4.8 g, 0.25 mol) in small portions at room temperature. After 1 h the mixture was poured into water (500 ml). The deposited precipitate was filtered off, washed with water and dried. 15.3 g (88%), m. p. 142 – 144 °C. – ^{1}H NMR ($CDCl_3$, δ): 2.17 s (3H), 2.95 t (2H), 3.37 t (2H), 3.75 d (2H), 5.10 t (1H), 6.75 s (2H) D_2O, 6.95 – 7.50 m (4H).

$C_{14}H_{16}N_2O_2S$ (276.3) Calcd. C 60.86 H 5.84 N 10.14 Found C 60.91 H 5.88 N 10.21

2,3,5,6-Tetrahydro-6-(3-methylbenzofuran-2-yl)imidazo[2,1-b]thiazole hydrochloride (**11**)

a) To the solution of **14** (7.5 g, 23 mmol) in $CHCl_3$ (25 ml) $SOCl_2$ (8.7 g, 70 mmol) was added. The mixture was heated for 1 h at 30 °C. Then a solution of K_2CO_3 (9.5 g, 70 mmol) in water (15 ml) was added. The reaction mixture was vigorously stirred for 1 h at room temperature and boiled for 1.5 h. The oily residue was dissolved in isopropyl alcohol (50 ml) and a stream of dry hydrogen chloride was passed through this solution. The deposited precipitate was filtered off, washed with cold acetone and dried to constant weight. 4.0 g (58%), m. p. 219 – 220 °C. – ^{1}H NMR (D_2O, δ): 2.42 s (3H), 3.67 – 4.55 m (6H), 5.61 (1H), 7.37 – 7.87 m (4H).

$C_{14}H_{15}ClN_2OS$ (294.8) Calcd. C 57.04 H 5.12 N 9.56 Found C 57.34 H 4.92 N 9.56

b) Acetic anhydride (250 ml), **10** (25 g, 90 mmol), and $SOCl_2$ (53.5 g, 450 mmol) were mixed and the mixture was heated for 1 h. The excess of thionyl chloride was distilled off below 85 °C. Acetic anhydride was removed in a rotary vacuum evaporator and the crude product was crystallized twice from isopropyl alcohol. Yield 16.4 g (80%).

2,3,5,6-Tetrahydro-6-(3-methylbenzofuran-2-yl)imidazo[2,1-b]thiazole (**13**): To the vigorously stirred suspension of well powdered **11** (3.0 g, 10 mmol) in water (100 ml) K_2CO_3 (15 g, 11 mmol) was added. After 1 h, the precipitate was filtered off, washed with water, dried and crystallized from cyclohexane. 2.85 g (99%), m. p. 93 – 94 °C. – ^{1}H NMR ($CDCl_3$, δ): 2.14 s (3H), 2.90 bis 3.51 m (6H), 5.50 t (1H), 7.00 – 7.40 m (4H).

$C_{14}H_{14}N_2OS$ (246.3) Calcd. C 63.39 H 5.68 N 11.37 Found C 63.35 H 5.77 N 11.43

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