Monatshefte für Chemie 120, 991 – 995 (1989)

Monatshefte für Chemie
Chemical Monthly

Synthesis of Substituted 4*H*-Thiazolo[4,5-b][1]benzothiopyran-4-ones as Possible Schistosomicidal Agents

Mohamed M. El-Kerdawy[1], **Ali A. El-Emam**[1,*], **Hussein I. El-Subbagh**[1], and **Elie Abushanab**[2]

[1] Department of Medicinal Chemistry, Faculty of Pharmacy, University of Mansoura, Mansoura, Egypt
[2] Department of Medicinal Chemistry, College of Pharmacy, University of Rhode Island, Kingstone, RI 02881, USA

Summary. Interaction of ethyl 2-acetamido-5-bromothiazole-4-carboxylate (**2**) with 2-methyl-5-chlorothiophenol (**3**) afforded the thioether **4**, which was hydrolysed to the corresponding carboxylic acid **5**. Attempted cyclization of **5** to **6** yielded the decarboxylated product **7**. On the other hand, interaction of 2-acetamido-5-bromothiazole (**9**) with thiosalicylic acid (**10**) yielded the thioether **11**, which was cyclized to compound **12**. Acid hydrolysis of **12** yielded the amino derivative **13**, which was reacted with certain selected alkyl halides using sodium hydride to afford compounds **14–18**.

Keywords. 4*H*-Thiazolo[4,5-b][1]benzothiopyran-4-ones.

Synthese von substituierten 4*H*-Thiazolo[4,5-b][1]benzothiopyran-4-onen als mögliche schistosomicide Wirkstoffe

Zusammenfassung. Die Reaktion von Ethyl 2-Acetamido-5-bromthiazol-4-carboxylat (**2**) mit 2-Methyl-5-chlorthiophenol (**3**) ergab den Thioether **4**, der zur entsprechenden Carbonsäure **5** hydrolysiert wurde. Die versuchte Cyclisierung von **5** zu **6** ergab das Decarboxylierungsprodukt **7**. Andererseits ergab die Reaktion von 2-Acetamido-5-bromthiazol (**9**) mit Thiosalizylsäure (**10**) den Thioether **11**, der zu Verbindung **12** cyclisiert werden konnte. Saure Hydrolyse von **12** ergab das Aminoderivat **13**, das mit geeigneten Alkylhalogeniden unter Verwendung von Natriumhydrid zu den Verbindungen **14–18** führte.

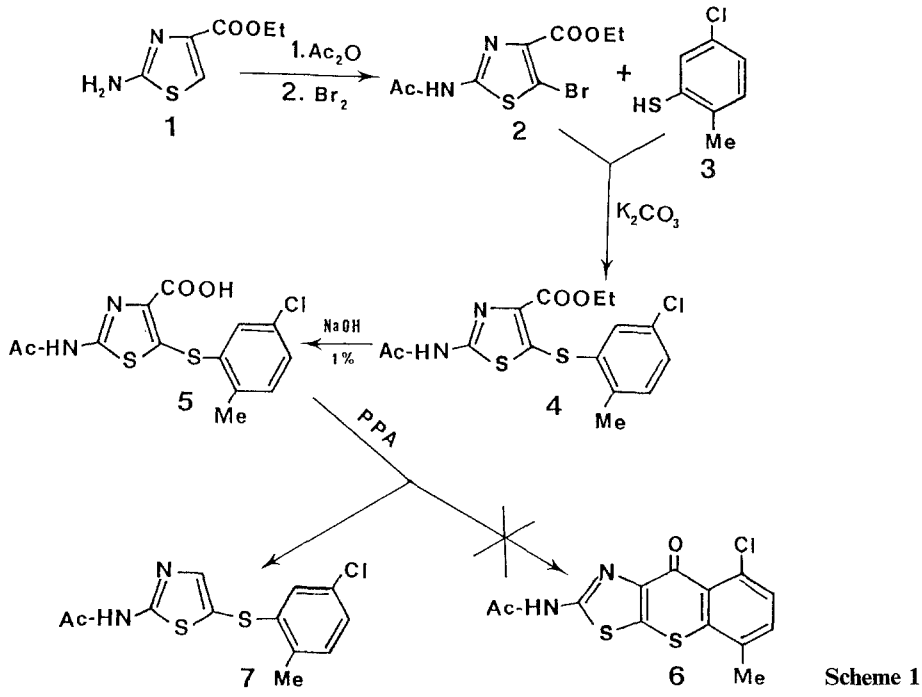
Introduction

Several thiazole derivatives [1–4] were early reported to exert potent schistosomicidal activity. In addition, thioxanthone derivatives [5–10] were the first major compounds to possess schistosomicidal activity. In continuation to our previous work [10], we wish to report the synthesis of certain substituted 4*H*-thiazolo-[4,5-b][1]benzothiopyran-4-ones, which carry the structural features of thiazoles and thioxanthones, as possible schistosomicidal agents.

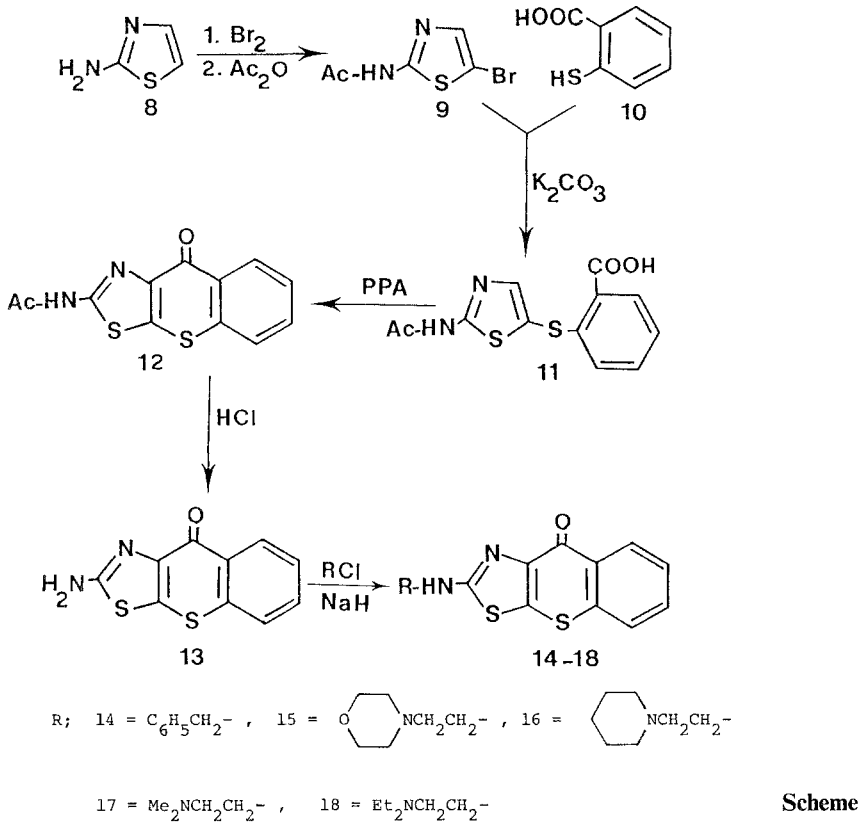
Results and Discussion

Ethyl 2-acetylamino-5-bromothiazole-4-carboxylate (**2**), required as a starting material, was prepared from ethyl 2-aminothiazole-4-carboxylate (**1**) by means of acetylation followed by bromination [11, 12]. Interaction of **2** with 2-methyl-5-chlorothiophenol [13] in presence of anhydrous potassium carbonate in acetone furnished ethyl 2-acetamido-5-[(2-methyl-5-chlorophenyl)thio]thiazole-4-carboxylate (**4**). Hydrolysis of the ester function of compound **4** by refluxing with 1% sodium hydroxide was not selective and led to the cleavage of both the amide and the ester functions. This was evidenced from the ^{1}H-NMR of the product which lacked the typical acetyl signal at 2.1 ppm, elemental analysis also corroborated this finding. Selective hydrolysis of the ester function was successfully achieved by the action of 1% sodium hydroxide at ambient temperature to afford compound **5**. Attempted cyclization of compound **5** to **6** using a variety of cyclizing agents as concentrated sulphuric acid, polyphosphoric acid (*PPA*) or polyphosphoric acid ester (*PPE*) were not successful and resulted in the formation of the decarboxylated product **7**. Structure assignment of **7** was based on elemental analysis and ^{1}H-NMR spectrum, which lacked the carboxylic proton and showed a singlet at 7.7 ppm attributed to the C-4 proton of the thiazole nucleus (Scheme 1).

An alternative route was adopted for the synthesis of 2-substituted 4*H*-thiazolo[4,5-b][1]benzothiopyran-4-ones (Scheme 2). Interaction of 2-acetamido-5-bromothiazole (**9**), prepared from 2-aminothiazole (**8**) [12], thiosalicylic acid (**10**) and anhydrous potassium carbonate in dimethylformamide, yielded 2-[(2-acetylamino-5-thiazolyl)thio]benzoic acid (**11**). The chemical shift of the C-4 proton of the thiazole nucleus of compound **11** (7.4 ppm) confirmed the earlier assignment in compound **7**. Compound **11** was successfully cyclized to **12** by the action of



Scheme 1



Scheme 2

polyphosphoric acid (*PPA*). The target compound 2-amino-4*H*-thiazolo[4,5-b][1]benzothiopyran-4-one (**13**), was obtained by hydrolysis of (**12**) using hydrochloric acid. Attempted alkylation of **13** was proved to be difficult, treatment of **13** with a variety of acid chlorides, alkyl halides or aldehydes to get the corresponding amides, alkylamines or Schiff's bases, respectively, was not possible. This was attributed to the reduced basicity of this amino group. It was therefore rationalized that the amino sodium salt (prepared from **13** in NaH/*DMF*) could overcome this problem and lead to the N-alkylated products. However, treatment of this salt with different alkylating agents did not lead to the desired product. When the highly reactive benzyl chloride was used, the corresponding N-benzyl derivative **14** was obtained in a relatively high yield (43%), strongly suggesting that the sodium salt is not nucleophilic enough to be alkylated with less reactive alkyl halides such as in case compounds **15**–**18**, where the yields ranged from 2.5–6%.

Experimental

Melting points (°C) were recorded using a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H-NMR spectra were obtained on a Varian EM 390 90 MHz using *TMS* as an internal standard (Chemical Shift in δ, ppm). Elemental analysis was performed by M-H-W laboratories, Phoenix, Arizona, USA. Analytical data (C, H, N, S) were within $\pm 0.4\%$ of the theoretical values.

Ethyl 2-acetylamino-5-[(2-methyl-5-chlorophenyl)thio]thiazole-4-carboxylate (**4**)

A mixture of ethyl 2-acetylamino-5-bromothiazole-4-carboxylate (**2**) (15 g, 0.05 mol), 2-methyl-5-chlorothiophenol (**3**) (8 g, 0.05 mol), anhydrous potassium carbonate (9 g) in dry acetone (100 ml), was heated under reflux for 10 h. The solvent was then removed in vacuo and the remaining residue was washed with water, filtered, dried and crystallized from ethanol to give 11.4 g (60%) of **4**, m.p. 240–243°. ^{1}H-NMR (*DMSO-d_6*): 1.15–1.35 (t, 3 H, CH_2CH_3), 1.9 (s, 3 H, *Ar*-CH_3), 2.1 (s, 3 H, $COCH_3$), 4.1–4.35 (q, 2 H, CH_2CH_3) and 7.35–7.5 (m, 3 H, *Ar*-H).

2-Acetylamino-5-[(2-methyl-5-chlorophenyl)thio]thiazole-4-carboxylic Acid (**5**)

Compound **4** (0.4 g, 0.001 mol), was added to a solution of 1% sodium hydroxide (30 ml) and the mixture was stirred at ambient temperature for 7 h. The mixture was then acidified with 10% hydrochloric acid. The separated product was filtered, washed with water, dried and crystallized from aqueous-methanol to yield 0.21 g of **5** (57%), m.p. 267–268°. ^{1}H-NMR (*DMSO-d_6*): 2.1 (s, 3 H, CH_3) 2.3 (s, 3 H, $COCH_3$), 7.39–7.52 (m, 3 H, *Ar*-H).

2-Acetylamino-5-[(2-methyl-5-chlorophenyl)thio]thiazole (**7**)

A mixture of compound **5** (0.5 g) and polyphosphoric acid (10 g) was heated under reflux at 120° for 3 h. On cooling the reaction mixture was poured onto crushed ice (50 g). The precipitated crude product was filtered, washed with dilute ammonium hydroxide, dried and crystallized from aqueous-dimethylformamide to give 0.13 g of **7** (30%), m.p. 180–182°. ^{1}H-NMR (*DMSO-d_6*): 2.15 (s, 3 H, *Ar*-CH_3), 6.75 (s, 1 H, *Ar*-H), 7.17 (s, 2 H, *Ar*-H) and 7.7 (s, 1 H, *Ar*-H).

2-[(2-Acetylamino-5-thiazolyl)thio]benzoic Acid (**11**)

A suspension of **9** (4.5 g, 0.02 mol), thiosalicylic acid (3 g, 0.02 mol) and anhydrous potassium carbonate (5.5 g) in *DMF* (50 ml), was heated under reflux for 5 h. On cooling, the solvent was distilled in vacuo and the remaining residue was dissolved in water (150 ml) and extracted with ether. The aqueous layer was acidified with hydrochloric acid, the precipitated product was filtered, washed with methanol, dried and crystallized from acetic acid to yield 3.5 g of **11** (60%), m.p. 305–307°. ^{1}H-NMR (CF_3COOH): 2.0 (s, 3 H, $COCH_3$), 6.5–7.2 (m, 3 H, *Ar*-H and NH), 7.4 (s, 1 H, *Ar*-H) and 7.6–7.8 (m, 1 H, *Ar*-H).

2-Acetylamino-4H-thiazolo[4,5-b][1]benzothiopyran-4-one (**12**)

A mixture of **11** (3 g, 0.01 mol) and polyphosphoric acid (30 g) was heated under reflux at 120° for 5 h. On cooling, the mixture was poured onto crushed ice (100 g), the separated crude product was filtered, washed with dilute ammonium hydroxide, dried and crystallized from dimethylformamide to yield 2.4 g of **12** (86%), m.p. 280–282°. ^{1}H-NMR (CF_3COOH): 2.2 (s, 3 H, $COCH_3$), 7.3–7.6 (m, 4 H, *Ar*-H and NH) and 8.2–8.5 (m, 1 H, *Ar*-H).

2-Amino-4 H-thiazolo[4,5-b][1]benzothiopyran-4-one (**13**)

Compound **12** (2.8 g, 0.01 mol) was suspended in concentrated hdrochloric acid (50 ml) and the mixture was heated under reflux for 8 h. The hydrochloride salt, which was precipitated on cooling, was filtered, dried and crystallized from methanol (m.p. 324°). The free base **13** was obtained by suspending the hydrochloride salt in concentrated ammonium hydroxide (20 ml) while warming and stirring for 2 h. The precipitated free base was then filtered, dried and crystallized from dimethylformamide to yield 1.7 g (73%) of **13**, m.p. 280–282°. ^{1}H-NMR (CF_3COOH): 7.3–7.6 (m, 3 H, *Ar*-H) and 7.8–8.4 (m, 3 H, *Ar*-H and NH_2).

2-Substituted Amino-4 H-thiazolo[4,5-b][1]benzothiopyran-4-ones (**14–18**)

Sodium hydride (0.1 g) was added to an ice-cooled dimethylformamide (25 ml) while stirring under nitrogen. Compound **13** (0.5 g, 0.002 mol) was added portionwise over a period of 30 min, followed by the appropriate halide (0.002 mol) and the mixture was heated under reflux at 80° for 4 h. The solvent was then removed in vacuo and the remaining residue was dissolved in chloroform, suspended on a silica gel column and eluted with a mixture of ethanol : chloroform : ethyl acetate (5 : 2 : 3) to yield compounds **14–18**.

14: M.p. 208–210° (*n*-hexane), 6% yield. ^{1}H-NMR ($CDCl_3$): 4.2 (s, 2 H, CH_2), 7.0–7.6 (m, 8 H, *Ar*-H) and 8.1–8.3 (m, 2 H, *Ar*-H and NH).

15: M.p. 165–167° (*n*-hexane-chloroform), 2.5% yield. ^{1}H-NMR ($CDCl_3$): 2.25–2.6 (m, 6 H, CH_2), 3.0–3.3 (m, 2 H, CH_2), 3.4–3.8 (m, 4 H, CH_2), 7.3–7.6 (m, 3 H, *Ar*-H), 7.9–8.2 (m, 1 H, NH) and 8.4–8.6 (m, 1 H, *Ar*-H).

16: M.p. 172–175° (petrol ether-chloroform), 2.5% yield. ^{1}H-NMR ($CDCl_3$): 1.1–1.7 (m, 6 H, CH_2), 2.2–3.9 (m, 8 H, CH_2), 7.3–7.6 (m, 3 H, *Ar*-H), 7.9–8.2 (m, 1 H, NH) and 8.4–8.6 (m, 1 H, *Ar*-H).

17: M.p. 158–160° (*n*-hexane-chloroform), 2.5% yield. ^{1}H-NMR ($CDCl_3$): 2.2 (s, 6 H, CH_3), 2.5–2.8 (m, 2 H, CH_2), 3.1–3.3 (m, 2 H, CH_2), 5.5 (s, 1 H, NH), 7.3–7.7 (m, 3 H, *Ar*-H) and 8.3–8.5 (m, 1 H, *Ar*-H).

18: M.p. 130–132 (petrol ether-chloroform), 3.2% yield. ^{1}H-NMR ($CDCl_3$): 0.5–1.5 (m, 6 H, CH_2CH_3), 2.0–3.5 (m, 8 H, CH_2), 7.0–7.6 (m, 4 H, *Ar*-H and NH) and 8.5–8.7 (m, 1 H, *Ar*-H).

References

[1] Schmidt P., Wilhelm M. (1966) Angew. Chem. Int. Ed. **5**: 857
[2] Werbel L. M., Battaglia J. R. (1971) J. Med. Chem. **14**: 10
[3] Lin Y., Hulbert P. B., Bueding E., Robinson C. H. (1974) J. Med. Chem. **17**: 835
[4] Islip P. J., Closier M. D., Neville M. C. (1974) J. Med. Chem. **17**: 207
[5] Kikuth W., Gonnert R. (1948) Ann. Trop. Med. Parasitol. **42**: 256
[6] Rosi D., Peruzotti G., Dennis D. A., Berberian D. A., Freele H., Archer S. (1965) Nature (London) **208**: 1005
[7] Archer S., Rochester L. B., Jackman M. (1954) J. Am. Chem. Soc. **76**: 588
[8] Elslager E. F. (1975) Ger. Offen 2,433,998; (1975) Chem. Abstr. **83**: 43318 r
[9] Elslager E. F., Worth D., Donald E. (1976) U.S. Pat. 3,904,631; (1976) Chem. Abstr. **84**: 44151 p
[10] El-Kerdawy M. M., El-Emam A. A., El-Subbagh H. I. (1986) Arch. Pharm. Res. **9**: 25
[11] Sprague J. M., Lincoln R. M., Ziegler C. (1946) J. Am. Chem. Soc. **68**: 266
[12] Beyerman H. C., Berben P. H., Bontekoe J. S. (1954) Rec. Trav. Chim. **73**: 325
[13] Sharp T. M. (1951) J. Chem. Soc.: 2961

Received December 29, 1988. Accepted March 27, 1989