Arch. Pharm. (Weinheim) *315*, 791–797 (1982)

Reactions with Heterocyclic Amidines, X[1]: Synthesis of Some New Azolylthiourea Derivatives

Sherief M. Fahmy, Mohamed K. A. Ibraheim, Khalid Abouhadid and Mohamed H. Elnagdi*

Chemistry Department, Faculty of Science, Cairo University, Giza, A.R. Egypt

Hikmat H.S. Alnima

Chemistry Department, College of Education, Sullaimaniyah University, Sullaimaniyah, Iraq
Eingegangen am 23. September 1981

A variety of azolylthiourea derivatives were prepared by the reaction of heterocyclic amidines with ethoxycarbonyl isothiocyanate or benzoyl isothiocyanate. The synthesized azolylthioureas were converted into polycyclic derivatives by treatment with alkali and hydrazines.

Reaktionen mit heterozyklischen Amidinen, 10. Mitt.: Synthese einiger neuer Azolylthioharnstoff-Derivate

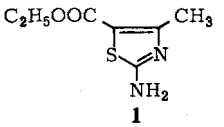
Einige Azolylthioharnstoff-Derivate werden durch Reaktion von heterozyklischen Amidinen mit Ethoxycarbonyl-isothiocyanat und Benzoylisothiocyanat hergestellt. Die erhaltenen Azolylthioharnstoffe werden durch Umsetzung mit Hydrazin und Alkali in polyzyklische Verbindungen umgewandelt.

In previous papers it has been shown that heterocyclic amidines react with ethoxycarbonyl and with benzoylisothiocyanate to yield azolylthiourea derivatives[1-4]. The latter derivatives were found to be useful intermediates for the synthesis of azoloazoline derivatives[5,6]. The latter derivatives are interesting for potential biological activity studies. In continuation of this work we report here the synthesis of several other azolylthioureas as well as some of the chemistry of these compounds.

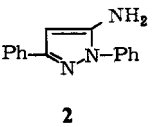
It has been found that 2-amino-4-methyl-5-ethoxycarbonylthiazole **(1)**, 1,3-diphenyl-5-aminopyrazole **(2)** and 3,5-diamino-1-phenyl-1,2,4-triazole **(3)** react with ethoxycarbonyl and with benzoylisothiocyanates to yield the corresponding azolylthiourea derivatives **4a,b, 5a,b**, and **6a,b**. The structure of the derivatives **4a,b** and **6a,b** was inferred from analytical, IR and ^{1}H-NMR data which excludes possible formation of ring N adducts in the case of **1** and **3** and C-4 adduct in the case of **2** (cf. experimental). The ^{1}H-NMR spectra also excludes possible formation of adduct resulting from addition of the thiocyanate to the 5-amino group of **3** as it revealed the two ortho protons of the ring N-C_6H_5 at the same field as that observed for the starting **3**.

Attempts to effect cyclisation of **4a, b** into thiazolo-[3,4]-1,3,5-triazine derivatives by the action of acetic anhydride have led to the loss of the thiocarbonyl moiety and the acetylthiazole derivative **7** was the only isolable product. This is in parallelism to the

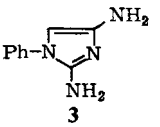
0365-6233/82/0909–0791 $ 02.50/0



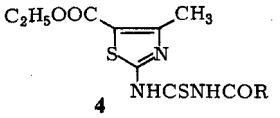
1



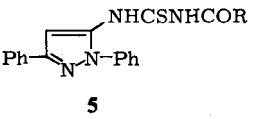
2



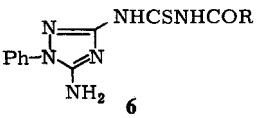
3



4



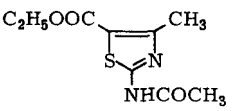
5



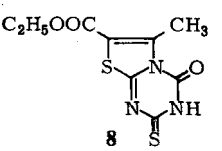
6

4-6a: R = OC_2H_5
4-6b: R = C_6H_5

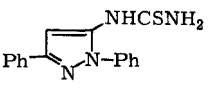
reported reversibility of the reaction of isothiocyanates with cyclic amidines and the observed formation of acyl derivatives when pyrazol-5-ylthioureas were treated with acetic anhydride. Compound **4** could be smoothly cyclised into the thiazolo[2,3-a]triazine derivative **8** on treatment with 3 % of sodium ethoxide solution. The ^{1}H-NMR spectra of **8** revealed methyl group resonance at almost the same field as that observed for **4a b**. This indicates that the methyl protons are unaffected by the anisotropy of the triazine CO group. Compound **4** was recovered almost unaffected when treated with the same reagent under the same conditions. On the other hand compound **5** decomposed into the thiourea derivative **9** on treatment with ethanolic methyl amine. In the same manner the thiourea derivatives **6a, b** decomposed into **10** on treatment with ethanolic sodium ethoxide.



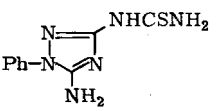
7



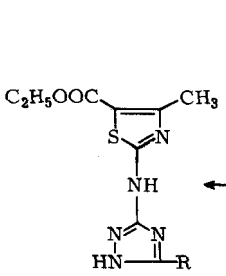
8



9

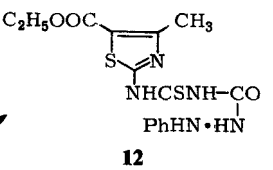


10

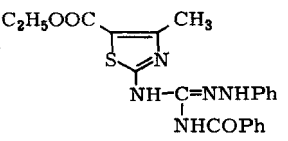


11a: R = OH
b: R = Ph

4a,b



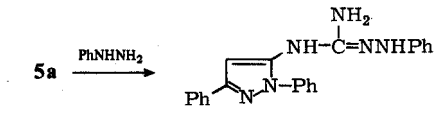
12



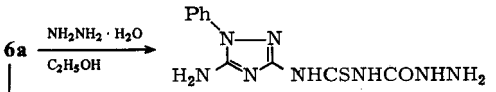
13

Compounds **4a, b** reacted with hydrazine hydrate to yield the thiazol-2-yl-1,2,4-triazole derivatives **11a, b**. On the other hand compound **4a** reacted with phenylhydrazine to the phenylhydrazide **12**. Attempted cyclisation of this compound into a thiazol-2-yl-1,2,4-triazole derivative under a variety of conditions were unsuccessfull. Compound **4b** reacted with phenylhydrazine to yield the amidrazone derivative **13** as the sole isolable reaction product.

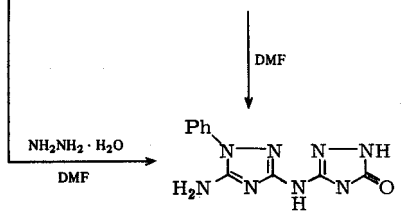
Compounds **5a, b** did not react with hydrazines after long reflux in ethanolic solutions. However, when **5** was heated at 100 °C with phenylhydrazine in the absence of a solvent the amidrazone **14** was obtained. Compound **6a** reacted with hydrazine in boiling ethanol to yield the hydrazide **15**. On the other hand when **6a** was treated with hydrazine hydrate in boiling DMF the triazolyltriazole derivative **16** was formed. Compound **16** was also obtained on heating **15** in DMF solution under reflux.



14



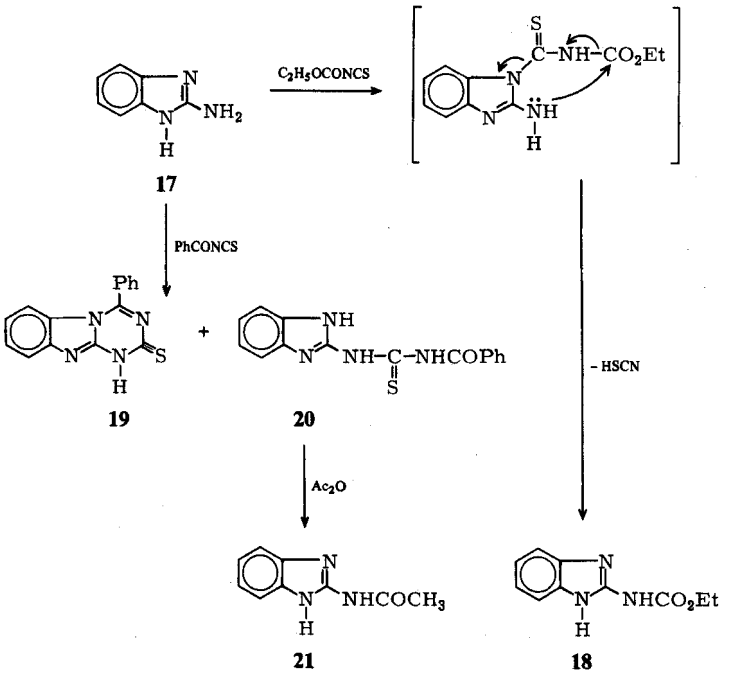
15



16

The reaction of 2-aminobenzimidazole **(17)** with ethoxycarbonyl isothiocyanate has been reported to afford the corresponding ethoxycarbonyl aminobenzimidazole derivative **(18)**. On the other hand benzoyl isothiocyanate reacted with **17** to yield **19**[7]. In our laboratory **17** reacted with the same product to yield **18** as the sole isolable product. On the other hand from reaction of **17** with benzoyl isothiocyanate we could isolate in addition to **19** the benzoylthiourea derivative **20** in 20 % yield. Compound **20** did not cyclise into **19** under a variety of conditions indicating that **20** is not an intermediate for the formation of **19**. Thus, it may be assumed that **17** reacts with benzoyl isothiocyanate via two mechanistic pathways which take place simultaneously. Cyclo addition of the reagent affords directly **19**, where as addition to the exocyclic amino group affords the benzimidazoyl thiourea **20**. Products resulting from addition involving ring nitrogen in a way similar to that reported for reaction of **17** with ethoxycarbonyl isothiocyanate, thus leading to benzoyliminobenzimidazole were not formed.

Thus **20** was recovered almost unaffected on reflux with ethanolic sodium ethoxide or in 3 % ethanolic sodium hydroxide. Attempted cyclisation of **20** to **19** by the action of acetic anhydride has resulted in the formation of the 2-acetylaminobenzimidazole derivative **21**.



H.H. Alnima is gratefull to the Department of Pharmaceutical Technology and Biochemistry at the Technical University of Gdansk in Poland for facilities provided during a leave of absence from Sullaimaniyah University which helped in completing this work. The financial support of Sullaimaniyah University of this work is highly appreciated.

Experimental

MP: uncorr. *IR spectra:* (KBr) Pye Unicum SP 1100. ^{1}*H-NMR spectra:* Bruker NH-9o in DMSO, TMS int. stand., chemical shifts: δ (ppm).

Reaction of **1–3** *with isothiocyanates*

General procedure: A solution of **1–3** in 100 ml acetone with ethoxycarbonyl isothiocyanate or benzoyl isothiocyanate (prepared from 0.1 mol of NH_4SCN as has been previously described[3]) was refluxed for 3 h and then evaporated i. vac. The remaining product was triturated with water and the resulting solid product was crystallised from the proper solvent.

1-Ethoxycarbonyl-3-(5-ethoxycarbonyl-4-methylthiazol-2-yl)thiourea **(4a)** formed yellow crystals from ethanol, m.p. 140 °C; yield 62 %. IR: 3200, (CH_3), 1725 and 1750 cm^{-1} (ester). ^{1}H-NMR: δ (ppm) = 1.4 (t, 1H, CH_3), 2.7 (s, 3H, CH_3), 4.2 (q, 2H, CH_2) and a wide band at 8.5 for 2H, (NH). $C_{11}H_{15}N_3O_4S_2$ (317.25) Calcd. C 41.6 H 4.8 N 13.3 S 20.2; Found C 41.4 H 4.8 N 13.3 S 19.8.

1-Benzoyl-3-(5-ethoxycarbonyl-3-methylthiazol-2-yl)thiourea **(4b)** formed pale yellow crystals from DMF-water, m.p. 160 °C; yield 85 %. IR: 3320 (NH), 3000, 2920 (CH_3 and CH), 1700 (ester CO) and 1680 cm^{-1} (benzoyl CO). $C_{15}H_{15}N_3O_3S_2$ (349.29) Calcd. C 51.5 H 4.2 N 12.0 S 18.3; Found C 51.6 H 4.0 N 11.8 S 18.3.

1-Ethoxycarbonyl-3-(1,3-diphenylpyrazol-5-yl)-thiourea **(5a)** formed pale yellow crystals, m.p. 154 °C; yield 85 %. IR: 3200, 3080, 3000 (NH), and 1735 cm^{-1} (ester CO). ^{1}H-NMR: δ (ppm) = 1.22 (t, 3H, CH_3) 4.13 (q, 2H, CH_2), 7.13 (s, 1H, pyrazole C-4 proton), 7.36, 8.03 (m, 10 H, $2C_6H_5$) and 11.50 (d, 2H, lost after D_2O exchange, NH). $C_{19}H_{18}N_4O_2S$ (366.37) Calcd. C 62.2 H 4.9 N 15.3 S 8.7; Found C 62.2 H 4.8 N 15.1 S 8.7.

1-Benzoyl-3-(1,3-diphenylpyrazol-5-yl)-thiourea **(5b)** formed colourless crystals, m.p. 214 °C; yield 95 %. IR: Two bands at 3350, 3180 (NH), 1690 (benzoyl CO) and 1615 cm^{-1} (C≡N). ^{1}H-NMR: δ (ppm) = 5.5 (s, pyrazole CH) and 7.4, 8,0 m (phenyl and NH protons). $C_{23}H_{18}N_4OS$ (398.41) Calcd. C 69.3 H 4.5 N 14.0 S 8.0. Found C 69.6 H 4.3 N 14.1 S 7.8.

2-Acetylamino-5-ethoxycarbonyl-4-methylthiazole **(7)**

A solution of each of 2.0 g **4a** and **4b** in 40 ml acetic anhydride was refluxed for 4 h. The solvent was poured onto water. The solid product, obtained on standing, was crystallised from ethanol. Compound **7** formed colourless crystals, m.p. 222 °C; yield 70 %. IR: 3210 (NH), 1720 (ester CO) and 1670 cm^{-1} (acetyl CO). $C_9H_{12}O_3N_2S$ (228.20) Calcd. C 47.3 H 5.3; Found 47.2 H 5.1 %.

3-Ethoxycarbonyl-2-methyl-7-thioxothiazolo[2,3-a]-1,3,5-triazine **(8)**

A solution of 2.0 g **4a** in 100 ml 3 % ethanolic sodium hydroxide was refluxed for 30 min and then evaporated i. vac. The remaining product was triturated with water and neutralised. The solid product, so formed, was crystallised from DMF-water. Compound **8** formed colourless crystals, m.p. 215 °C; yield 90 %. IR: 3300 (NH), 1730 (ester CO) and 1715 cm^{-1} (ring CO). ^{1}H-NMR: δ (ppm) = 1.4 (t, 3H, CH_3), 2.7 (s, 3H, CH_3) 4.2 (q, 2H, CH_2). $C_9H_9O_3N_3S_2$ (271.19) Calcd. C 39.9 H 3.4 N 15.5. Found C 39.8 H 3.3 N 15.5.

1-(1,5-diphenylpyrazol-5-yl) thiourea **(9)**

A solution of 5.0 g **5b** in 100 ml ethanol was treated with 3.0 ml 24 % methyl amine. The reaction mixture was refluxed for 10 h and then evaporated i. vac. The remaining product was triturated with water and the resulting solid product was crystallised from ethanol. Compound **9** formed colourless crystals, m.p. 160 °C; yield 60 %. IR: 3290 (NH) and 1630 cm^{-1}. $C_{16}H_{14}N_4S$ (294.30) Calcd. C 65.3 H 4.7 N 19.0 S 10.8; Found C 65.2 H 4.8 N 18.7 S 10.6.

1-(5-Amino-1-phenyl-1,2,4-triazol-3-yl)-thiourea **(10)**

A solution of sodium ethoxide (prepared from 2.3 g of sodium metal and the appropriate quantity of ethanol (ca. 70 ml) was treated with **6a** or **6b** (0.1 mol of each). The reaction mixture was then refluxed for 4 h and evaporated i. vac. The remaining product was triturated with water and neutralised with diluted hydrochloric acid. The solid product, was crystallised from DMF-water mixture. Compound **10** formed colourless crystals, m.p. 267 °C, yield 80 %, IR: 3340, 3180 (NH and NH_2) and 1630 cm^{-1} (NH_2 deformation). $C_9H_{10}N_6S$ (234.22) Calcd. C 46.1 H 4.2 Found C 45.5 H 4.1.

5-Ethoxycarbonyl-4-methyl-(5-substituted-1,2,4-triazol-3-yl)-2-aminothiazoles **(11a, b)**:

A solution of each of 0.01 mol. **4a**, **b** in 100 ml ethanol was treated with 0.01 mol hydrazine hydrate. The reaction mixture was boiled under reflux for 3 h and then evaporated i. vac. The remaining

product was triturated with water and the resulting solid product was crystallised from the proper solvent. Compound **11a** formed colourless crystals from DMF-water, m.p. 240 °C, yield 80 %, IR: 1720, 1730 (ring and ester CO), 3200 (NH), and 3000 cm^{-1} (CH_3). $C_9H_{11}O_3N_5S$ (269.22) Calcd. C 40.1 H 4.1 S 11.9 Found C 40.4 H 4.0 S 11.5. Compound **11b** formed yellow crystals from ethanol; m.p. 206 °C IR: 1730 (ester CO), 3410 (NH) and 3000 cm^{-1} (CH_3). $C_{15}H_{15}O_2N_5S$ (329.31) Calcd. C 54.7 H 4.6. Found C 54.8 H 4.9.

Reaction of **4a, b** *with phenylhydrazine*

A mixture of each of 2.0 g **4a, b** and 1.5 ml phenylhydrazine was heated at 100 °C (bath-temp.) for 2 h. The reaction mixture was then allowed to cool and then triturated with ethanol. The solid product was crystallised from ethanol. Compound **12** formed yellow crystals, m.p. 265 °C, yield 70 %. IR: 3260 (NH), 1710 (thiazole CO) and 1650 cm^{-1} (C=N). ^{1}H-NMR: δ (ppm) = 1.2 (t, 3H, CH_3), 2.0 (s, 3H, CH_3), 3.2 (q, 2H, CH_2) and a wide band at 7.3 (NH and Ph protons). $C_{15}H_{17}O_3N_5S_2$ (379.33) Calcd. C 47.5 H 4.4 S 16.8; Found C 47.2 H 4.2 S 16.5. Compound **13** formed yellow crystals, m.p. 166–167 °C; yield 40 %. ^{1}H-NMR: δ (ppm) = 1.2 (t, 3H, CH_3), 2.3 (s, 3H, CH_3) 3.3 (q, 2H, CH_2) and a broad band from 7.7–7.8 (aromatic and NH protons). $C_{21}H_{21}O_3N_5S$ (423.42) Calcd. C 59.5 H 4.9 N 16.5; Found C 59.5 H 4.9 N 16.1.

Action of phenylhydrazine on **5b**

A suspension of 0.01 mol **5b** in 0.015 mol phenylhydrazine was left at 140 °C (bath temp.) for 5 h, triturated with ethanol and crystallised from ethanol. Compound **14** formed pale yellow crystals, m.p. 195 °C, yield 40 %. $C_{22}H_{20}N_6$ (368.43) Calcd. C 71.7 H 5.4 N 22.8; Found C 71.5 H 5.2 N 22.5.

Reaction of **6a** *with hydrazine hydrate*

a) In ethanol: The experimental procedure described previously for the reaction of **4a** with hydrazine hydrate was utilised and the resulting product was crystallised from ethanol. Compound **15** formed colourless crystals, m.p. 223 °C. $C_{10}H_{12}ON_8S$ (292.26) Calcd. C 41.1 H 4.0 S 10.9; Found C 40.6 H 4.0 S 11.2.

b) In DMF solution: A solution of **6a** in 50 ml DMF was treated with 0.1 mol hydrazine hydrate then boiled under reflux for 6 h. The reaction mixture was then poured into water and the resulting solid product crystallised from ethanol. Compound **16** formed colourless crystals, m.p. 285 °C; yield 60 %. $C_{10}H_8ON_8$ (256.23) Calcd. C 46.5 H 3.5; Found C 46.8 H 3.1.

Reaction of **17** with benzoyl isothiocyanate

The experimental procedure described previously for the reaction of **1–3** with isothiocyanates was utilised. The resulting product was a mixture of compounds **19** and **20**. **19** and **20** were separated by fractional crystallization from ethanol. Compound **19**, formed yellow crystals, m.p. 304 °C, lit. m.p. 304 °C[7]. Yield 50 %. Compound **20**, formed pale yellow crystals; m.p. 182 °C; yield 20 %. $C_{15}H_{12}ON_4S$ (296.28) Calcd. C 60.8 H 4.0; Found C 61.2 H 4.1.

Reaction of **20** *with acetic anhydride*

A suspension of 2.0 g **20** in 30 ml acetic anhydride was refluxed for 40 min. The solvent was then evaporated. The resulting product was triturated with water. The solid product was identified as **21**. Mol. wt. 175.02, M^+: 175.07.

References

1 Part IX: H.M. Fahmy, M.H. Elnagdi and L.I. Ibrahim, Indian J. Chem. *196*, 644 (1980).
2 M.H. Elnagdi, M.R.H. Elmoghayar, D.H. Fleita, E.A. Hafez and S.M. Fahmy, J. Org. Chem. *41*, 3781 (1976).
3 M.H. Elnagdi, E.M. Kandeel and K.U. Sadek, Z. Naturforsch. *32b*, 311 (1977).
4 M.H. Elnagdi, S.M. Fahmy, M.R.H. Elmoghayar and E.M. Kandeel, J. Heterocycl. Chem. *16*, 61 (1979).
5 M.H. Elnagdi, E.M. Zayed, E.M. Kandeel and S.M. Fahmy, Z. Naturforsch. *32b*, 430 (1977).
6 M.H. Elnagdi, E.M. Kandeel and K.U. Sadek, Z. Naturforsch. *34b*, 275 (1979).
7 L. Capuano and H.J. Schrepfer, Chem. Ber. *104*, 3039 (1971).

[Ph 500]

Arch. Pharm. (Weinheim) *315*, 797–801 (1982)

Derivate des 2-Amino-1,2,3,4-tetrahydronaphthalins, 7. Mitt.[1)]

Aroylester des *cis*- und *trans*-2-Dimethylamino-3-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalins

Kristina Christova**, Damjan Dantschev*, Liliana Rainova und Duschka Staneva

Pharmazeutische Fakultät der Medizinischen Akademie, Dunav Str. 2, 1000 Sofia, Bulgarien, Lehrstuhl für Pharmazeutische und Organische Chemie und Lehrstuhl für Pharmakologie und Toxikologie
Eingegangen am 29. September 1981

Durch Acylierung von *cis*- und *trans*-2-Dimethylamino-3-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalin **(2)** mit den Chloriden einiger aromatischer Säuren wurden ihre Aroylester **1** erhalten. Die neuen Verbindungen zeigten spasmolytische und lokalanästhetische Wirkung.

Derivatives of 2-Amino-1,2,3,4-tetrahydronaphthalene, VII: Aroyl Esters of *cis*- and *trans*-2-Dimethylamino-3-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalenes

By acylation of *cis*- and *trans*-2-dimethylamino-3-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene **(2)** with the chlorides of some aromatic acids, the aroyl esters **1** were obtained. The new compounds show spasmolytic and local anesthetic activities.

Bekannt sind O-Acylderivate des *trans*-2-Dialkylamino-3-hydroxy-1,2,3,4-tetrahydronaphthalins[2,3)], sowie analoge Derivate des *cis*- und *trans*-1-Hydroxy-2-dimethylaminotetralins[4–7)]. Manche dieser Verbindungen weisen eine lokalanästhetische Aktivität[2,4,7)] auf.

In der vorliegenden Arbeit werden einige Aroylester (**1a–1d**, Tab. 2) der von uns synthetisierten[1)] *cis*- und *trans*-2-Dimethylamino-3-hydroxy-5,8-dimethoxytetraline **2** beschrieben.

0365-6233/82/0909–0797 $ 02.50/0