

This article was downloaded by:

On: 27 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713618290>

A One-Pot Synthesis of Thiophenes and Their Annulated Derivatives With Potential Pharmaceutical Interest

Wagnat Wahba Wardakhan^a

^a National Organization for Drug Control & Research, Cairo, Arab Republic of Egypt

To cite this Article Wardakhan, Wagnat Wahba(2006) 'A One-Pot Synthesis of Thiophenes and Their Annulated Derivatives With Potential Pharmaceutical Interest', *Phosphorus, Sulfur, and Silicon and the Related Elements*, 181: 9, 2051 — 2061

To link to this Article: DOI: 10.1080/10426500600605749

URL: <http://dx.doi.org/10.1080/10426500600605749>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

A One-Pot Synthesis of Thiophenes and Their Annulated Derivatives With Potential Pharmaceutical Interest

Wagnat Wahba Wardakhan

National Organization for Drug Control & Research, Cairo,
Arab Republic of Egypt

The reaction of 2-cyanomethylene benzo[d]imidazole (1) with carbon disulphide in basic DMF solution gave the di-potassium disulphide salt (3). The reaction of the latter with the α -halocarbonyl compounds 4 and 13 afforded the thiophene derivatives 5 and 14, respectively. The latter products were used to synthesize annulated products with potential pharmaceutical interest.

Keywords Benzo[d]imidazole; carbon disulphide; thieno[3,2-b]pyridine; thiophene

INTRODUCTION

Our long-term continuing interest in the chemistry of thiophenes^{1–4} forms a part of our systematic efforts to obtain pyridines, pyrimidines, pyridazines, thiophenes, and their analogues. The importance of such compounds is due to their diverse pharmaceutical activities, including antibacterial,^{5,6} anti-diabetic,⁷ anti-HIV,⁸ antiviral,^{9,10} and analgesic¹¹ activities.

RESULTS AND DISCUSSION

Chemistry

Recently we have reported on the uses of thiophenes to form annulated systems.^{12,13} In continuation to our previous work, we report herein the reaction of 2-cyanomethylenobenzo[d]imidazole with carbon disulphide in basic dimethylformamide. The reaction led to the formation

Received November 14, 2005; accepted December 9, 2005.

The screening antimicrobial tests were recorded by Professor S. A. Ouf and his research group, Department of Botany, Faculty of Science, Botany Department; his efforts were greatly appreciated.

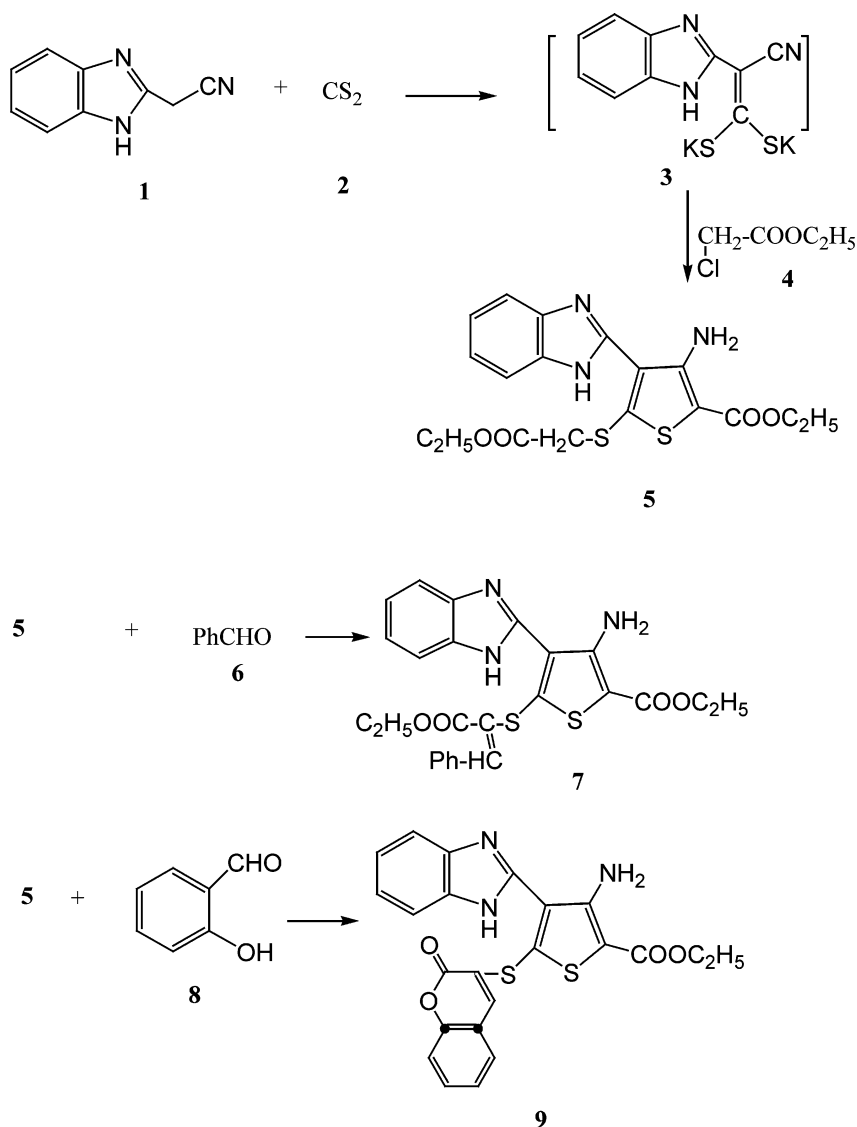
Address correspondence to Wagnat Wahba Wardakhan, National Organization for Drug Control & Research, PO Box 29, Cairo, A. R. Egypt. E-mail: wagnatward@hotmail.com

of the intermediate di-potassium disulphide salt **3**. The reaction of **3** with α -haloesters was studied. Thus, ethyl α -chloroacetate (**4**) gave the thiophene derivative **5**. The structure of compound **5** was based on analytical and spectral data. Thus, the IR spectrum of the reaction product showed NH and NH₂ stretchings at ν^- 3480–3328 cm⁻¹, and two C=O stretchings at ν^- 1694 and 1685 cm⁻¹. Moreover, the ¹H NMR spectrum showed two triplets at δ 1.13, and 1.18 for two esters CH₃ groups, two quartets at δ 4.24 and 4.26 for two esters CH₂ groups, a singlet at δ 4.88 for a CH₂ group, a singlet (D₂O exchangeable) at δ 5.32 for a NH₂ group, a multiplet at δ 7.28–7.34 for a C₆H₄ group, and a singlet at δ 8.88 (D₂O exchangeable) for a NH group. The reaction of compound **5** with benzaldehyde (**6**) afforded the benzal derivative **7**. However, with salicylaldehyde (**8**), the coumarin derivative **9** was formed¹⁴ (Scheme 1). The analytical and spectral data for compounds **8** and **9** were inconsistent with the assigned structures (see the Experimental section).

The reaction of compound **5** with hydrazine hydrate gave the 5-hydrazino thiophene derivative **11**. The latter product underwent ready cyclization when heated in dimethylformamide solution containing triethylamine to give the benzo[d]imidazo[3,2:2,3]pyrazolo[5,4:2,3]-thiophene derivative **12** through ammonia elimination. The structure of the latter product was based on ¹H NMR spectrum, which showed a triplet at δ 1.16 for ester CH₃, a quartet at δ 4.23 for the ester CH₂ group, a singlet (D₂O exchangeable) at δ 4.89 for a NH₂ group, a multiplet at δ 7.30–7.37 for C₆H₄ protons, and a singlet at δ 9.03 (D₂O exchangeable) for NH a group.

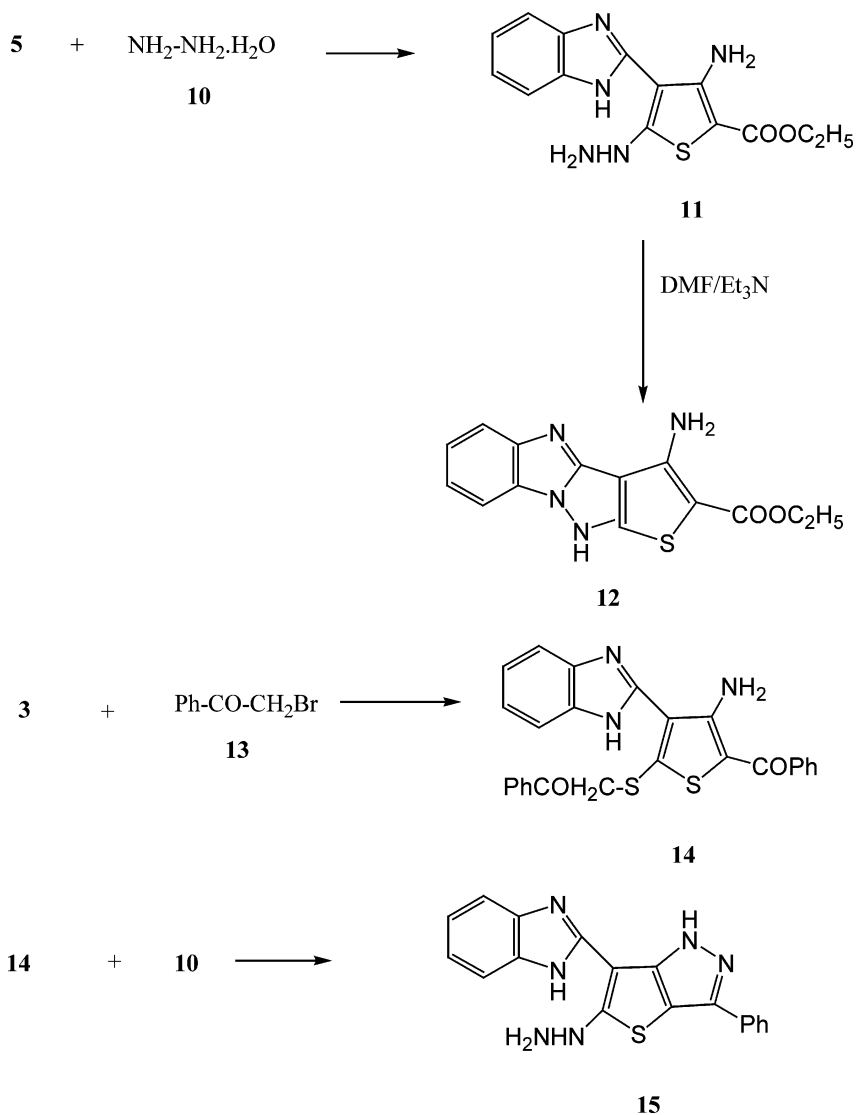
Next, we moved toward studying the reactivity of the intermediate di-potassium disulphide salts **4** toward α -haloketones. Thus, the reaction of **3** with ω -bromoacetophenone (**13**) gave the thiophene derivative **14**. Analytical and spectral data were in agreement with the proposed structure (see the Experimental section). The reaction of **14** with hydrazine hydrate (**10**) gave the 4-hydrazinothieno[3,2-c]pyrazole **15** (Scheme 2).

The reactivity of **14** toward cyanomethylene derivatives was studied in aim to form fused thiophene derivatives with potential pharmaceutical uses. Thus, the reaction of **14** with either malononitrile (**16a**) or ethyl cyanoacetate (**16b**) gave the theino[3,2:b]pyridine derivatives **17a** and **17b**, respectively. The structures of **17a,b** were assigned on the basis of their elemental analyses and spectral data. Thus, the IR spectrum of **17a** indicated the presence of NH₂ and NH groups stretching at ν^- 3487–3345 cm⁻¹, CN groups stretching at ν^- 2225 cm⁻¹, and one C=O group stretching at ν^- 1668 cm⁻¹. The reaction of either **17a** or **17b** with hydrazine hydrate in refluxing 1,4-dioxan solution gave the 5-hydrazinothieno[3,2:b]pyridine derivatives



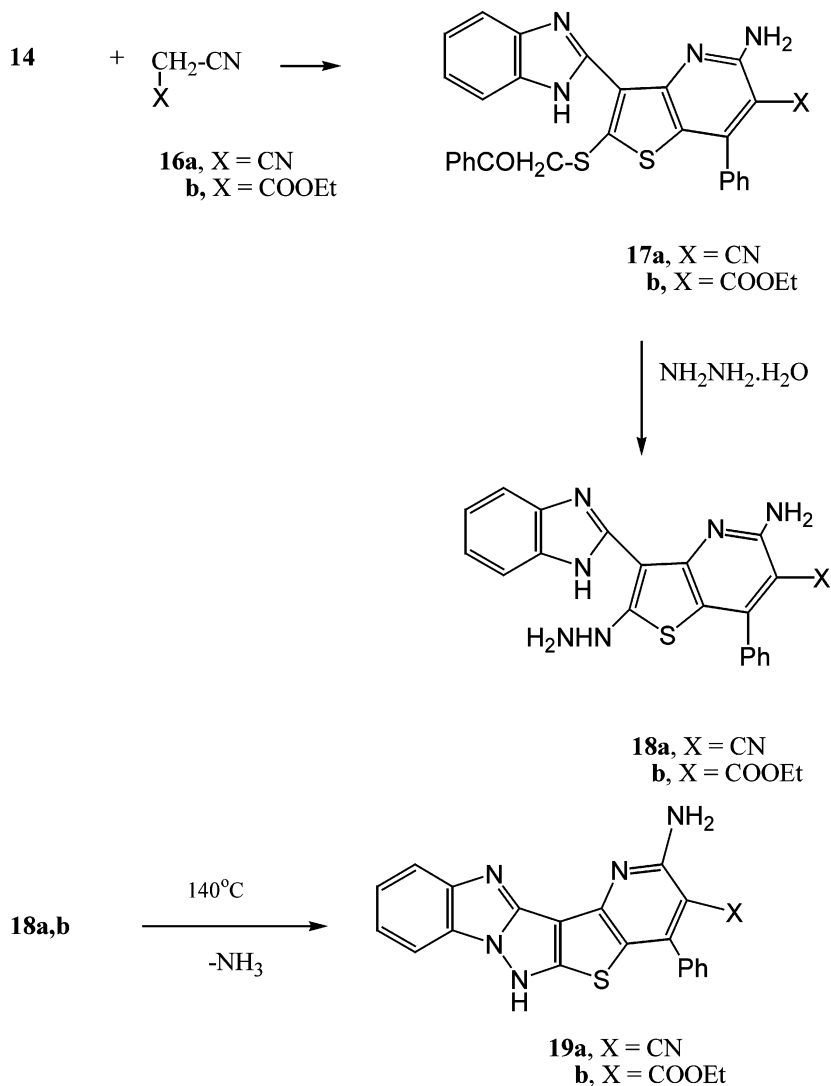
SCHEME 1

18a and **18b**, respectively. Compounds **18a,b** underwent ready cyclization when heated in an oil bath at 140°C to give the annulated products **19a** and **19b**, respectively, through ammonia liberation. The analytical and spectral data of the reaction products were



SCHEME 2

in accordance with the proposed structures (see the Experimental section). The latter reaction constituted a facile and convenient one-pot reaction leading to fused heterocyclic derivatives, which are difficult to access (Scheme 3).



SCHEME 3

SCREENING FOR ANTIMICROBIAL ACTIVITY

Twelve compounds were screened *in vitro* for their antimicrobial activity against two bacterial isolates 1 sapro (*Escherichia coli*), parasitic (*Xanthomonas citi*), 3 fungal isolates, 1 saprophytic (*Aspergillus fumigatus*), 2 phytopathogenic (*Rhizoctonia solani* and *Fusarium*

TABLE I Inhibition Zones in mm for Some of the Synthesized Compounds at a Concentration Level of 25 $\mu\text{g/mL}$

Compound	<i>E. coli</i>	<i>X. citri</i>	<i>A. fumigatus</i>	<i>R. solani</i>	<i>F. oxysporum</i>
5	7	7	10	8	0
7	10	12	7	7	0
9	19	14	6	6	0
11	15	19	15	5	0
12	29	21	8	16	18
15	22	18	17	18	18
17a	35	32	17	16	16
17b	19	22	12	16	8
18a	35	19	15	18	20
18b	20	14	6	10	12
19a	36	14	18	14	16
19b	19	10	10	8	5

oxysporum). The culture medium was the nutrient agar for bacteria and Czapek's Dox agar medium for fungi. The sterile medium was inoculated with the test organism so that each 100 mL of the medium received 1 mL of a 24-h culture of the bacterium or a 7-day-old culture of a spore suspension of the fungus. Solutions of the tested compounds at 25 $\mu\text{g/mL}$ in dimethylformamide (DMF) were placed separately in the cup (8-mm diameter). The plates were incubated at 28°C, and the resulting inhibition zones were measured. DMF as a blank exhibited no antimicrobial activity against any of the tested organisms used.

The recorded inhibition zones are summarized in Table I. The results indicated that most of the prepared compounds were active against the test organisms. The most toxic compounds against bacterial and fungal isolates were **12**, **15**, **17a**, **18a**, and **19a** followed by **17b**, **18b**, and **19b**. Compounds **5**, **7**, **9**, and **11** were less toxic to the test organisms. The bacterial isolates were more susceptible to the synthesized compounds than fungal isolates. The biological investigation was recorded by Professor S. O. Abou Elyazeed, whose efforts are greatly appreciated.

CONCLUSION

The work described in this article showed an easy way for the synthesis of thiophenes and their fused derivatives. Most of the newly synthesized products revealed either high or moderate toxicity.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam Sp-1000 spectrophotometer. ^1H NMR spectra were

obtained on a Varian EM-390 90 MHz spectrometer in DMSO- d_6 as a solvent and TMS as an internal reference. Chemical shifts δ are expressed in ppm.

Ethyl 3-Amino-4-(benzo[d]imidazo-2-yl)-5-ethoxycarbonylmethyl-sulfanylthiophen-2-carboxylate (5) and 3-Amino-2-benzoyl-4-(benzo[d]imidazo-2-yl)-5-benzoylmethylsulfanylthiophene (14)

General Procedure

To a solution of the 2-cyanomethylbenzo[d]imidazole (1) in dimethylformamide (1.57 g, 0.01 mol) containing potassium hydroxide (0.56 g, 0.01 mol), carbon disulphide (0.76 g, 0.01 mol) was added. The reaction mixture was stirred at r.t. overnight, and then either ethyl α -chloroacetate (4) or ω -bromoacetophenone (13) was added; the whole mixture was left at r.t. for another night with continuous stirring. The reaction mixture was poured onto ice/water containing hydrochloric acid (until pH 5–6), and the formed solid product, in each case, was collected by filtration.

5: Orange crystals (from ethanol), yield 67% (2.71 g), m.p. 88°C. IR ν (cm^{-1}) = 3480–3328 (NH_2 , NH), 3057 (CH aromatic), 2987, 2880 (CH_3 , CH_2), 1694, 1685 (2 C=O), 1660 (C=N), 1642 (C=C). ^1H NMR δ = 1.13, 1.18 (2t, 6H, J = 4.56, 6.72 Hz, 2CH_3), 4.24, 4.26 (2q, 4H, J = 4.56, 6.72 Hz 2CH_2), 4.88 (s, 2H, CH_2), 5.32 (s, 2H, NH_2), 7.28–7.34 (m, 4H, C_6H_4), 8.88 (s, 1H, NH). $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_4\text{S}_2$ (405.49): Calcd.: C, 53.32; H, 4.72; N, 10.36; S, 15.82. Found: C, 53.06; H, 5.18; N, 10.07; S, 15.65.

14: Yellow crystals (from ethanol), yield 72% (3.37 g), m.p. 111°C. IR ν (cm^{-1}) = 3480–3321 (NH_2 , NH), 3060 (CH aromatic), 2890 (CH_2), 1688, 1683 (2 C=O), 1657 (C=N), 1634 (C=C). ^1H NMR δ = 5.21 (s, 2H, CH_2), 5.38 (s, 2H, NH_2), 7.30–7.38 (m, 14H, $2\text{C}_6\text{H}_5$, C_6H_4), 8.92 (s, 1H, NH). $\text{C}_{26}\text{H}_{19}\text{N}_3\text{O}_2\text{S}_2$ (469.09): Calcd.: C, 66.50; H, 4.08; N, 8.95; S, 13.66; Found: C, 66.26; H, 4.18; N, 9.31; S, 13.83.

Ethyl 3-Amino-4-(benzo[d]imidazo-2-yl)-5-ethoxycarbonybenzallmeth-yidinosulfanylthiophen-2-carboxylate (7) and Ethyl 3-Amino-4-(benzo[d]imidazo-2-yl)-5-coumarin-3-yl-sulfanylthiophen-2-carboxylate (9)

General Procedure

To a solution of compound 5 (4.05 g, 0.01 mol) in 1,4-dioxan (40 mL) containing piperidine (0.5 g), either benzaldehyde (1.06 g, 0.01 mol) or salicylaldehyde (1.22 g, 0.01 mol) was added. The reaction mixture,

in each case, was heated under reflux for 4 h and then poured onto ice/water containing a few drops of hydrochloric acid. The solid product, formed in each case, was collected by filtration.

7: Orange crystals (from ethanol), yield 78% (3.84 g), m.p. 180°C. IR ν (cm^{-1}) = 3472–3318 (NH_2 , NH), 3045 (CH aromatic), 2980, 2894 (CH_3 , CH_2), 1692, 1687 (2 C=O), 1655 (C=N), 1640 (C=C). ^1H NMR δ = 1.13, 1.16 (2t, 6H, J = 6.43, 6.77 Hz, 2CH_3), 4.23, 4.27 (2q, J = 6.43, 6.77 Hz, 4H, 2CH_2), 5.36 (s, 2H, NH_2), 6.89 (s, 1H, $\text{CH}=\text{C}$), 7.31–7.37 (m, 9H, C_6H_5 , C_6H_4), 9.02 (s, 1H, NH). $\text{C}_{25}\text{H}_{23}\text{N}_3\text{O}_4\text{S}_2$ (493.60): Calcd.: C, 60.83; H, 4.70; N, 8.51; S, 12.99. Found: C, 60.62; H, 5.03; N, 8.89; S, 13.34.

9: Orange crystals (from ethanol), yield 86% (3.30 g), m.p. 222–225°C. IR ν (cm^{-1}) = 3469–3331 (NH_2 , NH), 3052 (CH aromatic), 2983, 2877 (CH_3 , CH_2), 1689, 1683 (2 C=O), 1658 (C=N), 1639 (C=C). ^1H NMR δ = 1.15 (t, 3H, J = 7.03 Hz, CH_3), 4.25 (q, H, J = 7.03 Hz, CH_2), 5.32 (s, 2H, NH_2), 6.99 (s, 1H, coumarin H-4), 7.26–7.34 (m, 8H, $2\text{C}_6\text{H}_4$), 8.92 (s, 1H, NH). $\text{C}_{23}\text{H}_{17}\text{N}_3\text{O}_4\text{S}_2$ (463.53): Calcd.: C, 59.60; H, 3.70; N, 9.07; S, 13.84. Found: C, 60.02; H, 4.09; N, 9.45; S, 13.32.

Ethyl 3-Amino-4-(benzo[d]imidazolo-2-yl)-5-hydrazinothiophen-2-carboxylate (**11**) and 4-Hydrazino-5-(benzo[d]imidazolo-2-yl)-3-phenylthieno[3,2-c]pyrazole (**15**)

General Procedure

To a solution of either **5** (4.05 g, 0.01 mol) or **14** (4.69 g, 0.01 mol) in ethanol (40 mL), hydrazine hydrate (0.50 mL, 0.01 mol) was added. The reaction mixture was heated under reflux for 4 h and then poured onto ice/water. The solid product, formed in each case, was collected by filtration.

11: Pale yellow crystals (from 1,4-dioxan), yield 78% (3.84 g), m.p. 180°C. IR ν (cm^{-1}) = 3466–3323 (2NH_2 , 2NH), 3060 (CH aromatic), 2983, 2890 (CH_3 , CH_2), 1677 (C=O), 1654 (C=N), 1633 (C=C). ^1H NMR δ = 1.15 (t, 3H, J = 6.89 Hz, CH_3), 4.26 (q, 2H, J = 6.89 Hz, CH_2), 4.88, 5.33 (2s, 4H, 2NH_2), 7.32–7.40 (m, 4H, C_6H_4), 8.23, 8.93 (2s, 2H, 2NH). $\text{C}_{14}\text{H}_{15}\text{N}_5\text{O}_2\text{S}$ (317.37): Calcd.: C, 52.98; H, 4.76; N, 22.07; S, 10.10. Found: C, 52.59; H, 4.56; N, 22.07; S, 9.78.

15: Pale yellow crystals (from ethanol), yield 70% (2.33 g), m.p. 189–192°C. IR ν (cm^{-1}) = 3468–3313 (2NH_2 , NH), 3055 (CH aromatic), 2894 (CH_2), 1682 (C=O), 1660 (C=N), 1630 (C=C). ^1H NMR δ 5.66 (s, 2H, NH_2), 7.32–7.35 (m, 9H, C_6H_5 , C_6H_4), 8.67, 9.21–9.26 (3s, 3H, 3NH). $\text{C}_{18}\text{H}_{14}\text{N}_6\text{S}$ (346.10): Calcd.: C, 62.41; H, 4.07; N, 24.26; S, 9.26. Found: C, 62.46; H, 4.34; N, 24.85; S, 10.02.

Ethyl 3-Aminobenzo[d]imidazo[3,2:2,3]pyrazolo[5,4:2,3]-thiophen-2-carboxylate (12)

A solution of **11** (3.17 g, 0.01 mol) in dimethylformamide (40 mL) containing triethylamine (0.5 mL) was heated under reflux for 8 h and then evaporated in vacuum. The remaining product was triturated in diethyl ether, and the solidified product was collected by filtration.

12: Pale yellow crystals (from AcOH), yield 80% (2.40 g), m.p. 112°C. IR ν (cm⁻¹) = 3445–3312 (NH₂, NH), 3056 (CH aromatic), 2980, 2893 (CH₃, CH₂), 1682 (C=O), 1651 (C=N), 1636 (C=C). ¹H NMR δ = 1.16 (t, 3H, J = 7.02 Hz, CH₃), 4.23 (q, 2H, J = 7.02 Hz, CH₂), 4.89 (s, 2H, NH₂), 7.30–7.37 (m, 4H, C₆H₄), 9.03 (s, 1H, NH). C₁₄H₁₂N₄O₂S (300.34): Calcd.: C, 55.99; H, 4.03; N, 18.65; S, 10.68. Found: C, 56.31; H, 4.40; N, 18.31; S, 11.09.

2-Amino-5-benzoylmethylsulfanyl-3-cyano-6-benzo[d]imidazo-2-ylthieno-[3,2-c]pyridine (17a) and Ethyl 2-Amino-5-benzoylmethyl-sulfanyl-6-benzo[d]imidazo-2-ylthieno-[3,2-c]pyridine-3-carboxylate (17b)**General Procedure**

To a solution of **14** (4.69 g, 0.01 mol) in 1,4-dioxan (40 mL) containing triethylamine (0.5 mL), either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 6 h and then evaporated under vacuum. The remaining product was triturated with toluene, and the solidified product was collected by filtration.

17a: Pale yellow crystals (from 1,4-dioxan), yield 77% (3.98 g), m.p. 267–270°C. IR ν (cm⁻¹) = 3487–3345 (NH₂, NH), 3062 (CH aromatic), 2886 (CH₂), 2225 (CN), 1668 (C=O), 1656 (C=N), 1641 (C=C). ¹H NMR δ = 5.21 (s, 2H, CH₂), 5.59 (s, 2H, NH₂), 7.32–7.40 (m, 14H, 2C₆H₅, C₆H₄), 8.87 (s, 1H, NH). C₂₉H₁₉N₅OS₂ (517.63): Calcd.: C, 67.29; H, 3.70; N, 13.53; S, 12.39. Found: C, 67.06; H, 4.16; N, 13.31; S, 11.96.

17b: Pale brown crystals (from 1,4-dioxan), yield 63% (3.55g), m.p. 147–149°C. IR ν (cm⁻¹) = 3480–3323 (NH₂, NH), 3056 (CH aromatic), 2987, 2886 (CH₃, CH₂), 1702, 1680 (2 C=O), 1661 (C=N), 1633 (C=C). ¹H NMR δ = 1.14 (t, 3H, J = 4.66 Hz, CH₃), 4.25 (q, 2H, J = 4.66 Hz, CH₂), 5.23 (s, 2H, CH₂), 5.49 (s, 2H, NH₂), 7.31–7.36 (m, 14H, 2C₆H₅, C₆H₄), 8.89 (s, 1H, NH). C₃₁H₂₄N₄O₃S₂ (564.68): Calcd.: C, 65.94; H, 4.28; N, 9.92; S, 11.36. Found: C, 65.76; H, 4.26; N, 10.25; S, 11.65.

2-Amino-5-hydrazino-3-cyano-6-benzo[d]imidazo-2-ylthieno-[3,2-c]pyridine (18a) and Ethyl 2-Amino-5-hydrazino-6-benzo[d]imidazo-2-ylthieno-[3,2-c]pyridine-3-carboxylate (18b)

General Procedure

Equimolar amounts of either **17a** (5.17 g, 0.01 mol) or **17b** (5.64 g, 0.01 mol) and hydrazine hydrate (0.5 g, 0.01 mol) in 1,4-dioxan (50 mL) was heated under reflux for 5 h. The solid product formed, in each case, upon pouring onto ice/water containing few drops of hydrochloric acid was collected by filtration.

18a: Yellow crystals (from 1,4-dioxan), yield 70% (2.77 g), m.p. 203–206°C. IR ν (cm⁻¹) = 3460–3321 (2NH₂, 2NH), 3052 (CH aromatic), 2221 (CN), 1648 (C=N), 1633 (C=C). ¹H NMR δ =s 4.78, 5.53 (2s, 4H, 2NH₂), 7.28–7.35 (m, 9H, C₆H₅, C₆H₄), 8.69, 9.03 (2s, 2H, 2NH). C₂₁H₁₅N₇S (397.11): Calcd.: C, 63.46; H, 3.80; N, 24.67; S, 8.07. Found: C, 63.25; H, 4.22; N, 24.43; S, 7.89.

18b: Pale brown crystals (ethanol), yield 83% (3.68 g), m.p. 188–190°C. IR ν (cm⁻¹) = 3497–3334 (2NH₂, 2NH), 3055 (CH aromatic), 2992, 2880 (CH₃, CH₂), 1684 (C=O), 1666 (C=N), 1639 (C=C). ¹H NMR δ = 1.16 (t, 3H, J = 5.89 Hz, CH₃), 4.24 (q, 2H, J = 5.89 Hz, CH₂), 4.92, 5.49 (2s, 4H, 2NH₂), 7.33–7.38 (m, 9H, C₆H₅, C₆H₄), 8.78, 9.21 (2s, 2H, 2NH). C₂₃H₂₀N₆O₂S (444.51): Calcd.: C, 62.15; H, 4.54; N, 18.91; S, 7.21. Found: C, 62.45; H, 4.87; N, 18.22; S, 7.07.

2-Amino-3-cyano-4-phenylbenzo[d]imidazolo[3,2:2,3]-thieno[4,5:2,3]-pyrazole (19a) and Ethyl 2-Amino-3-cyano-phenylbenzo[d]imidazolo-[3,2:2,3]thieno-[4,5:2,3]-pyrazol-3-carboxylate (19b)

General Procedure

A dry solid of either **18a** (3.97 g, 0.01 mol) or **18b** (4.44 g, 0.01 mol) was heated in an oil bath at 140°C for 1 h and then left to cool. The remaining product was triturated with diethyl ether, and the formed solid product was collected by filtration.

19a: Pale yellow crystals (from 1,4-dioxan), yield 66% (2.50 g), m.p. > 300°C. IR ν (cm⁻¹) = 3442–3321 (NH₂, NH), 3059 (CH aromatic), 2218 (CN), 1658 (C=N), 1640 (C=C). ¹H NMR δ = 5.33 (s, 2H, NH₂), 7.25–7.33 (m, 9H, C₆H₅, C₆H₄), 9.04 (s, 1H, NH). C₂₁H₁₂N₆S (380.43): Calcd.: C, 66.30; H, 3.18; N, 22.09; S, 8.43; Found: C, 66.81; H, 2.87; N, 21.85; S, 8.02.

19b: Buff crystals (ethanol), yield 56% (2.39 g), m.p. 240–243°C. IR ν (cm⁻¹) = 3477–3341 (NH₂, 2NH), 3052 (CH aromatic), 2988, 2887 (CH₃,

CH₂), 1688 (C=O), 1660 (C=N), 1630 (C=C). ¹H NMR δ = 1.14 (t, 3H, J = 7.22 Hz, CH₃), 4.22 (q, 2H, J = 7.22 Hz, CH₂), 5.39 (s, 2H, NH₂), 7.30–7.33(m, 9H, C₆H₅, C₆H₄), 9.09 (s, H, NH). C₂₃H₁₇N₅O₂S (427.48): Calcd.: C, 64.62; H, 4.01; N, 16.38; S, 7.50. Found: C, 64.45; H, 3.88; N, 16.05; S, 7.33.

REFERENCES

- [1] R. M. Mohareb, H. F. Zohdi, S. M. sherif, and W. W. Wardakhan, *Tetrahedron*, **50**, 5807 (1994).
- [2] R. M. Mohareb, W. W. Wardakhan, and F. Z. El-Ablack, *J. Chem. Research* (S), 126 (1994); (M), 0747 (1994).
- [3] H. F. Zohdi, R. M. Mohareb, and W. W. Wardakhan, *Phosphorus, Sulfur, and Silicon*, **101**, 179 (1995).
- [4] H. F. Zohdi, W. W. Wardakhan, S. H. Doss, and R. M. Mohareb, *J. Chem. Research* (S), 440 (1996); (M), 2526 (1996).
- [5] M. Bakonyi, M. N. Csatari, L. Molnar, Z. Makovi, P. Jobb, and T. Bai, *PCT Int. Appl. WO*, **51**, 681 (1998); *Chem. Abstr.*, **130**, 24963 (1999).
- [6] N. J. Broom, J. S. Elder, P. C. Hannan, J. E. Pons, P. J. O'Hanlon, G. Walker, J. Wilson, and P. Woodall, *J. Antibiotics*, **48**, 1336 (1995).
- [7] A. Magni, G. Signorelli, and G. Bocchiola, *Arzeneim-Forsch J. Drug Res.*, **44**, 1420 (1994).
- [8] R. Pontikis, R. Benhida, A. M. Aubertin, D. S. Grierson, and C. Monneret, *J. Med. Chem.*, **40**, 1845 (1997).
- [9] G. D. Nanteuil, Y. Herve, J. Duhault, J. Espinal, M. Boulanger, and D. Ravel, *Arzeneim-Forsch J. Drug Res.*, **45**, 1175 (1995).
- [10] J. F. C. Albuquerque, A. Albuquerque, C. C. Azevedo, F. Thomasson, L. S. Galdino, J. Chante-Grel, M. T. J. Catanho, R. Pitta, and C. Luu-Due, *Pharmazie*, **50**, 387 (1995).
- [11] R. E. Boyd, J. B. Press, C. R. Rasmussen, R. B. Raffa, E. E. Codd, C. D. Connelly, Q. S. Li, R. P. Martinez, M. A. Lewis, and B. Almond, *J. Med. Chem.*, **44**, 863 (2001).
- [12] W. W. Wardakhan, G. A. Elmegeed, and F. M. Manhi, *Phosphorus, Sulfur, and Silicon*, **180**(1), 125 (2005).
- [13] G. A. Elmegeed, W. W. Wardakhan, M. Younis, and N. A. Louca, *Arch. Pharm. Med. Chem.*, **337**, 140 (2004).
- [14] R. M. Mohareb, H. Z. Shams, and M. H. Elnagdi, *Gazzeta Chimica Ital.*, **41**, 122 (1992).