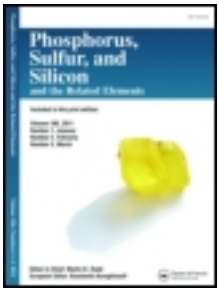

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A One-Pot Synthesis of Thiophenes and Their Annulated Derivatives With Potential Pharmaceutical Interest

Wagnat Wahba Wardakhan [a]
[a] National Organization for Drug Control & Research, Cairo, Arab Republic of Egypt
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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 analogous. 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 analgesic[11] 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 lead to the formation

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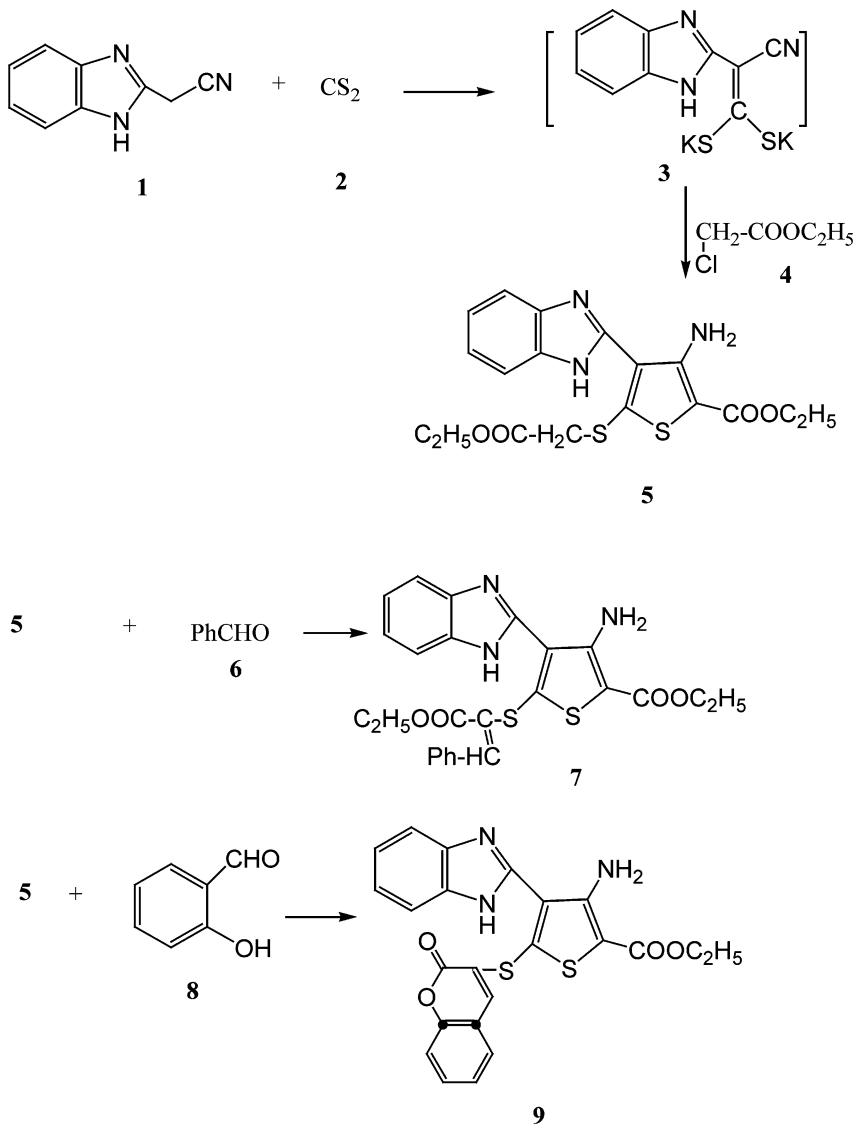
The screening antimicrobial tests were recorded by Professor S. A. Ouf and his research group, Department of Botany, Faculty of Science, Botany Department; his efforts were greatly appreciated.
Address correspondence to Wagnat Wahba Wardakhan, National Organization for Drug Control & Research, PO Box 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 NH_2 stretchings at υ^- 3480–3328 cm^{-1}, and two C=O stretchings at υ^- 1694 and 1685 cm^{-1}. Moreover, the ^1H NMR spectrum showed two triplets at δ 1.13, and 1.18 for two esters CH_3 groups, two quartets at δ 4.24 and 4.26 for two esters CH_2 groups, a singlet at δ 4.88 for a CH_2 group, a singlet (D_2O exchangeable) at δ 5.32 for a NH_2 group, a multiplet at δ 7.28–7.34 for a C_6H_4 group, and a singlet at δ 8.88 (D_2O 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 formed[14] (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 elemination. The structure of the latter product was based on ^1H NMR spectrum, which showed a triplet at δ 1.16 for ester CH_3, a quartet at δ 4.23 for the ester CH_2 group, a singlet (D_2O exchangeable) at δ 4.89 for a NH_2 group, a multiplet at δ 7.30–7.37 for C_6H_4 protons, and a singlet at δ 9.03 (D_2O exchangeable) for NH a group.

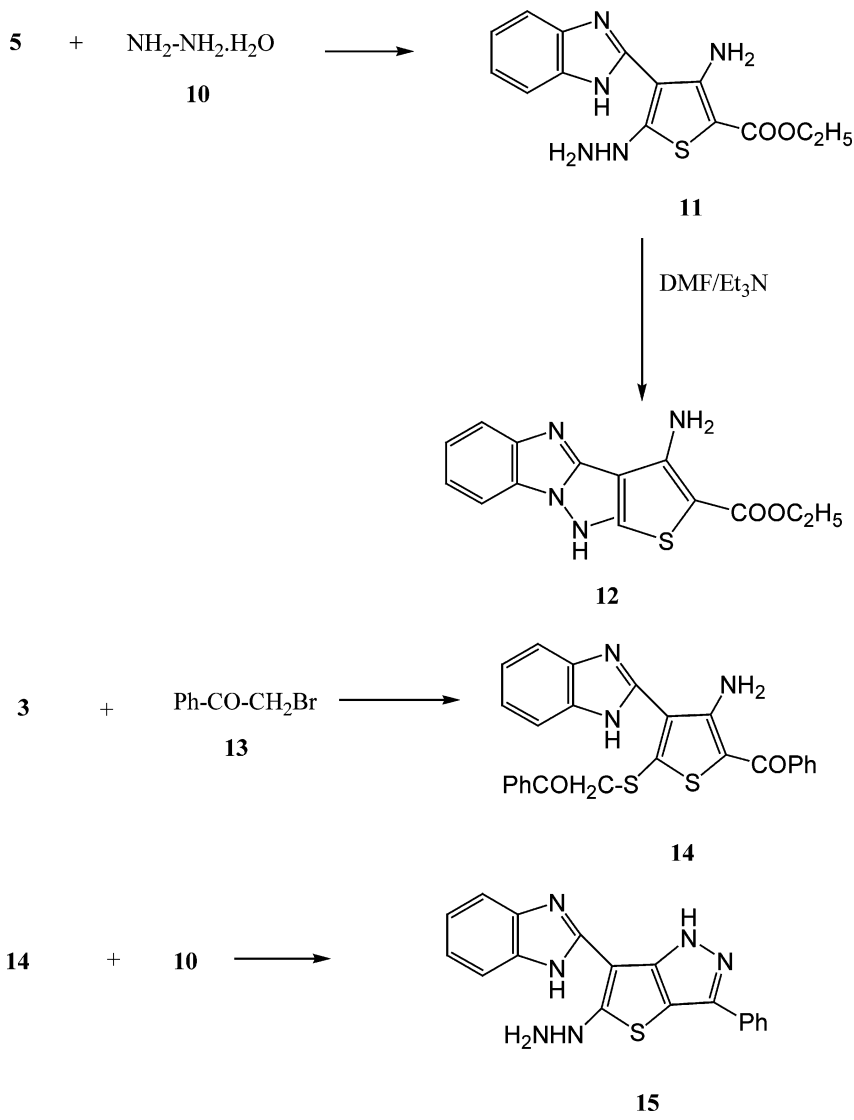
Next, we moved toward studying the reactivity of the intermediate di-potassium disulphide salts **4** toward α-haloketones. Thus, the reaction of **3** with ω-bromoacetophenone (**13**) gave the thiophene derivative **14**. Analytical and spectral data were in agreement with the proposed structure (see 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 NH_2 and NH groups stretching at υ^- 3487–3345 cm^{-1}, CN groups stretching at υ^- 2225 cm^{-1}, and one C=O group stretching at υ^- 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



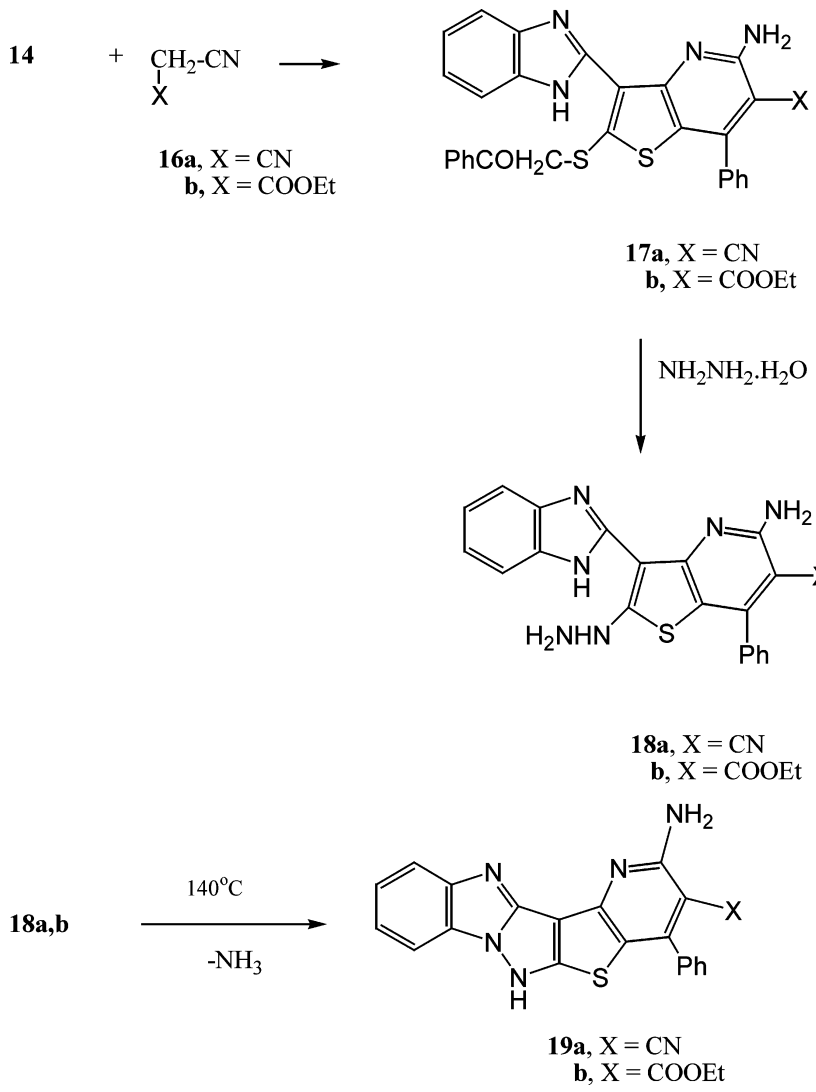
SCHEME 1

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 μg/mL

Compound	*E. coli*	*X. citri*	*A. fumigatus*	*R. solani*	*F. oxysporum*
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 μg/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. ^{1}H 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]imidazolo-2-yl)-5-ethoxycarbonylmethyl-sulfanylthiophen-2-carboxylate (5) and 3-Amino-2-benzoyl-4-(benzo[d]imidazolo-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 υ (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). ^{1}H 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). $C_{18}H_{19}N_3O_4S_2$ (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 υ (cm^{-1}) = 3480–3321 (NH_2, NH), 3060 (CH aromatic), 2890 (CH_2), 1688, 1683 (2 C=O), 1657 (C=N), 1634 (C=C). ^{1}H NMR δ = 5.21 (s, 2H, CH_2), 5.38 (s, 2H, NH_2), 7.30–7.38 (m, 14H, $2C_6H_5$, C_6H_4), 8.92 (s, 1H, NH). $C_{26}H_{19}N_3O_2S_2$ (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]imidazolo-2-yl)-5-ethoxycarbonybenzallmeth-yidinosulfanylthiophen-2-carboxylate (7) and Ethyl 3-Amino-4-(benzo[d]-imidazolo-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 salicyaldehyde (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 υ (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). ^{1}H 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, CH=C), 7.31–7.37 (m, 9H, C_6H_5, C_6H_4), 9.02 (s, 1H, NH). $C_{25}H_{23}N_3O_4S_2$ (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 υ (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). ^{1}H 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, $2C_6H_4$), 8.92 (s, 1H, NH). $C_{23}H_{17}N_3O_4S_2$ (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 υ (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). ^{1}H 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). $C_{14}H_{15}N_5O_2S$ (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 υ (cm^{-1}) = 3468–3313 ($2NH_2$, NH), 3055 (CH aromatic), 2894 (CH_2), 1682 (C=O) 1660 (C=N), 1630 (C=C). ^{1}H 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). $C_{18}H_{14}N_6S$ (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 υ (cm^{-1}) = 3445–3312 (NH_2, NH), 3056 (CH aromatic), 2980, 2893 (CH_3, CH_2), 1682 (C=O), 1651 (C=N), 1636 (C=C). ^1H NMR δ = 1.16 (t, 3H, J = 7.02 Hz, CH_3), 4.23 (q, 2H, J = 7.02 Hz, CH_2), 4.89 (s, 2H, NH_2), 7.30–7.37 (m, 4H, C_6H_4), 9.03 (s, 1H, NH). $C_{14}H_{12}N_4O_2S$ (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 υ (cm^{-1}) = 3487–3345 (NH_2, NH), 3062 (CH aromatic), 2886 (CH_2), 2225 (CN), 1668 (C=O), 1656 (C=N), 1641 (C=C). ^1H NMR δ = 5.21 (s, 2H, CH_2), 5.59 (s, 2H, NH_2), 7.32–7.40 (m, 14H, $2C_6H_5$, C_6H_4), 8.87 (s, 1H, NH). $C_{29}H_{19}N_5OS_2$ (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 υ (cm^{-1}) = 3480–3323 (NH_2, NH), 3056 (CH aromatic), 2987, 2886 (CH_3, CH_2), 1702, 1680 (2 C=O), 1661 (C=N), 1633 (C=C). ^1H NMR δ = 1.14 (t, 3H, J = 4.66 Hz, CH_3), 4.25 (q, 2H, J = 4.66 Hz, CH_2), 5.23 (s, 2H, CH_2), 5.49 (s, 2H, NH_2), 7.31–7.36 (m, 14H, $2C_6H_5$, C_6H_4), 8.89 (s, 1H, NH). $C_{31}H_{24}N_4O_3S_2$ (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 υ (cm^{-1}) = 3460–3321 ($2NH_2$, 2NH), 3052 (CH aromatic), 2221 (CN), 1648 (C=N), 1633 (C=C). ^1H NMR δ =s 4.78, 5.53 (2s, 4H, $2NH_2$), 7.28–7.35 (m, 9H, C_6H_5, C_6H_4), 8.69, 9.03 (2s, 2H, 2NH). $C_{21}H_{15}N_7S$ (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 υ (cm^{-1}) = 3497–3334 ($2NH_2$, 2NH), 3055(CH aromatic), 2992, 2880 (CH_3, CH_2), 1684 (C=O), 1666 (C=N), 1639 (C=C). ^1H NMR δ = 1.16 (t, 3H, J = 5.89 Hz, CH_3), 4.24 (q, 2H, J = 5.89 Hz, CH_2), 4.92, 5.49 (2s, 4H, $2NH_2$), 7.33–7.38 (m, 9H, C_6H_5, C_6H_4), 8.78, 9.21 (2s, 2H, 2NH). $C_{23}H_{20}N_6O_2S$ (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 υ (cm^{-1}) = 3442–3321 (NH_2, NH), 3059 (CH aromatic), 2218 (CN), 1658 (C=N), 1640 (C=C). ^1H NMR δ = 5.33 (s, 2H, NH_2), 7.25–7.33 (m, 9H, C_6H_5, C_6H_4), 9.04 (s, 1H, NH). $C_{21}H_{12}N_6S$ (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 υ (cm^{-1}) = 3477–3341 (NH_2, 2NH), 3052 (CH aromatic), 2988, 2887 (CH_3,

CH_2), 1688 (C=O), 1660 (C=N), 1630 (C=C). ^{1}H NMR $\delta = 1.14$ (t, 3H, J = 7.22 Hz, CH_3), 4.22 (q, 2H, J = 7.22 Hz, CH_2), 5.39 (s, 2H, NH_2), 7.30–7.33(m, 9H, C_6H_5, C_6H_4), 9.09 (s, H, NH). $C_{23}H_{17}N_5O_2S$ (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.

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