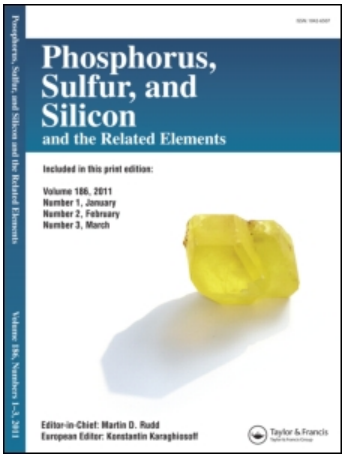


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis of Polyfunctionally Substituted Thiophene, Thieno[2,3-b]pyridine and Thieno[2,3-d]pyrimidine Derivatives

Wagnat W. Wardakhan[a]; Hoda Z. Shams[b]; Hosam E. Moustafa[b]
[a] National Organization for Drug Control & Research, Cairo, Egypt [b] Department of Chemistry, Faculty of Science, Helwan University, Cairo, Egypt

To cite this Article Wardakhan, Wagnat W. , Shams, Hoda Z. and Moustafa, Hosam E.(2005) 'Synthesis of Polyfunctionally Substituted Thiophene, Thieno[2,3-b]pyridine and Thieno[2,3-d]pyrimidine Derivatives', Phosphorus, Sulfur, and Silicon and the Related Elements, 180: 8, 1815 — 1827
To link to this Article: DOI: 10.1080/104265090889422
URL: http://dx.doi.org/10.1080/104265090889422

Phosphorus, Sulfur, and Silicon, 180:1815–1827, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/104265090889422

Taylor & Francis
Taylor & Francis Group

Synthesis of Polyfunctionally Substituted Thiophene, Thieno[2,3-b]pyridine and Thieno[2,3-d]pyrimidine Derivatives

Wagnat W. Wardakhan
National Organization for Drug Control & Research, Cairo, Egypt

Hoda Z. Shams
Hosam E. Moustafa
Department of Chemistry, Faculty of Science, Helwan University, Cairo, Egypt

*The thiophne derivatives **4a–c** were prepared according to the Gewald procedure. Their reactivity towards a variety of chemical reagents was studied to give thienopyridines and pyrimidines. Biological investigations were carried on the newly synthesized products.*

Keywords Bactericidal; fungicidal; thieno[2,3-d]pyrimidine; thienopyridine[2,3-b]-pyridine; thiophene

Recently, there has been an increasing interest in the chemistry of thiophenes because of their biological activities. Many of them have been widely investigated for therapeutic uses, especially as antifungal,[1,2] antibacterial,[3] anti-inflammatory,[4] anticonvulsant,[5] antiasthmatic[6] and analgesic[7] agents. They also were known to show antiHIV,[8] antiproliferative[9] activities. Our research group has studied the reactivity of thiophene derivatives as precursors for the synthesis of a vast variety of fused thiophene derivatives with potential biological activity.[10–13] As a continuation of this study we aimed to design new systems of polyfunctionally substituted thiophene derivatives starting from readily available reagents. The key precursors for such synthetic approach are the aryl thiophene systems **4a–c**.

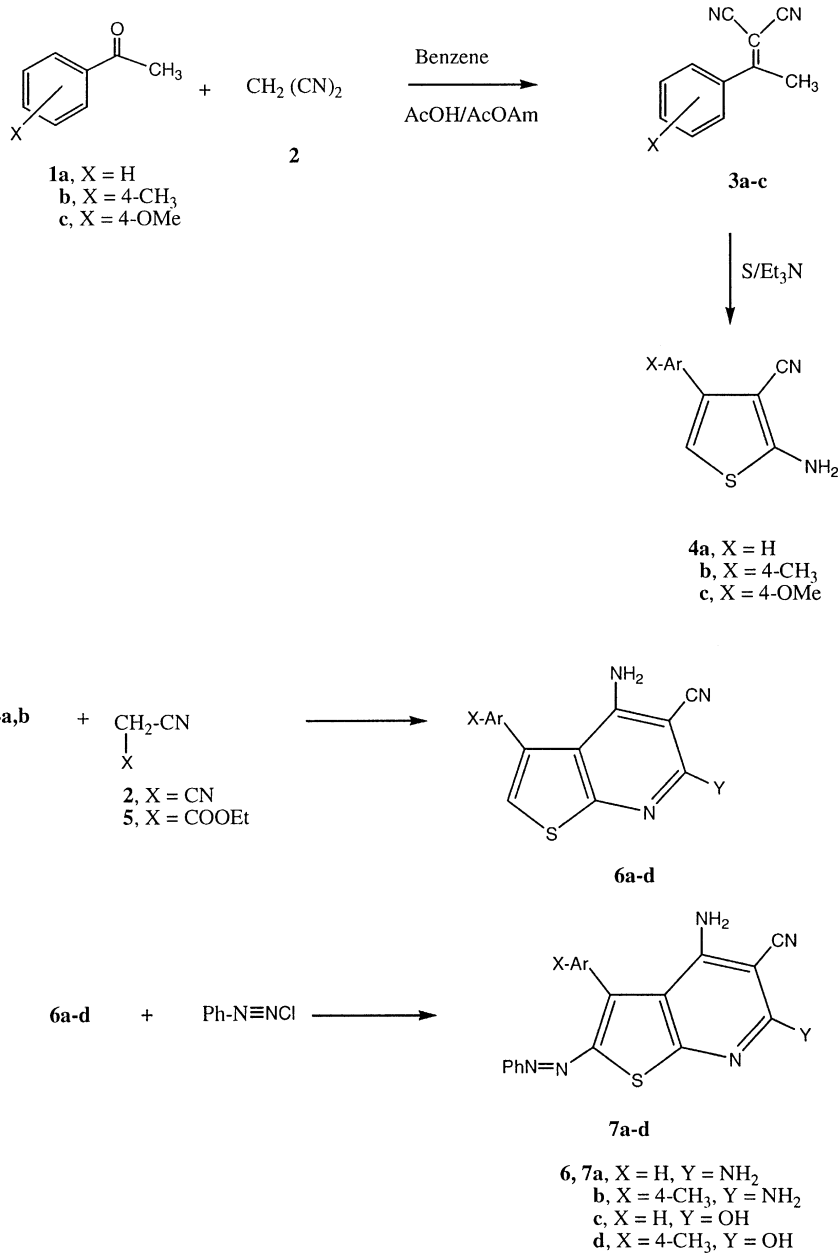
Received June 6, 2004; accepted September 7, 2004.
Address correspondence to Wagnat W. Wardakhan, National Organization for Drug Control & Research, PO Box 29, Cairo, Egypt. E-mail: wagnatward@hotmail.com

RESULTS AND DISCUSSION

Compounds **4a–c** were synthesized via the condensation of acetophenone derivatives **1a–c** with malononitrile **2** in benzene containing glacial acetic acid and ammonium acetate to give the condensation product **3a–c**. The reaction of compounds **3a–c** with sulfur in ethanol containing a catalytic amount of triethyl amine gave the thiophene derivatives **4a–c** (Scheme 1), according to the Gewald's thiophene synthesis.[14,15] Structures of the latter products were established on the basis of analytical and spectral data. Compound **4a** was previously reported.[16] On the other hand, the IR spectrum of **4b** showed two stretching modes at υ 3577–3476 and 2205 cm^{-1} corresponding to NH_2 and CN groups, respectively. Moreover, it's ^1H NMR spectrum showed a singlet at δ 2.21 corresponding to a CH_3 group, a singlet at δ 4.37 for an NH_2 group, a singlet at δ 6.30 for a thiophene H-5 proton, and a mutiplet at δ 7.25–7.30 for C_6H_4 protons.

The reactivity of **4a**, **b** (as representatives) towards active methylene reagents, namely malononitrile (**2**) and ethyl cyanoacetate (**5**), was studied. Thus, the reaction of **4a**, **b** with either **2** or **5** gave the thieno[2,3-b]pyridine derivatives **6a–d**. Structures of the latter products were established on the basis of analytical and spectral data. Thus, the IR spectra of **6a**, **b** showed the presence of stretching modes at υ 3433, 3205 cm^{-1} region corresponding to NH_2 functions and at 2206 cm^{-1} for CN groups. ^1H NMR spectra displayed singlets at δ 4.19, 5.30 (2H each), and at δ 4.95, 5.82 (2H each), and (D_2O exchangeable) corresponding to NH_2 protons for compounds **6a** and **6b**, respectively. Singlets at δ 6.05, 6.36 (1H each) for thiophene H-2 protons, two multiplets at δ 7.37–7.61 (5H), and at 6.96–7.29 (4H) corresponding to phenyl moieties of **6a** and **6b** respectively are also ditinguished. Compound **6b** exhibited a singlet at δ 3.49 (3H) indicating CH_3 protons. Further confirmation of the assigned thienopyridine structures **6a–d** was achieved via coupling with benzenediazonium chloride to give the corresponding azo derivatives **7a–d** (Scheme 2). The latter products were synthesized using another reaction route. Thus, the reaction of either **4a** or **4b** with benzenediazonium chloride gave the phenylazo derivatives **8a** and **8b**, respectively. The reaction of the latter products with either malononitrile (**2**) or ethyl cyanoacetate (**5**) gave the same products **7a–d** (fingerprint IR, m.p., and mixed m.p., are identical).

The reaction of **8a** with either acetylactone (**9a**) or ethyl acetoacetate (**9b**) gave the thieno[2,3-b]pyridine derivatives **10a** and **10b**, respectively. Structures of the latter products were based on the analytical and spectral data. Thus, the ^1H NMR spectrum of **10a** exhibited



1a, X = H
b, X = 4-CH_3
c, X = 4-OMe

2

3a-c

4a, X = H
b, X = 4-CH_3
c, X = 4-OMe

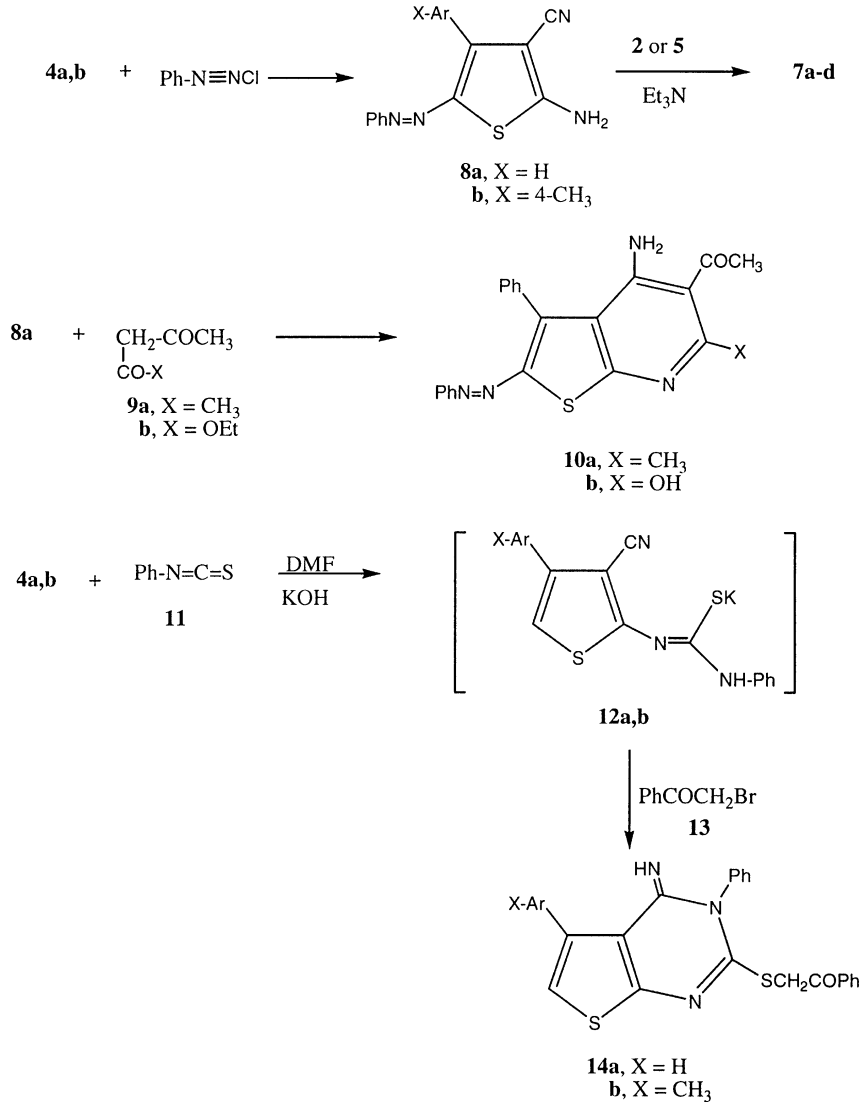
2, X = CN
5, X = COOEt

6a-d

7a-d

6, 7a, X = H, Y = NH_2
b, X = 4-CH_3, Y = NH_2
c, X = H, Y = OH
d, X = 4-CH_3, Y = OH

SCHEME 1



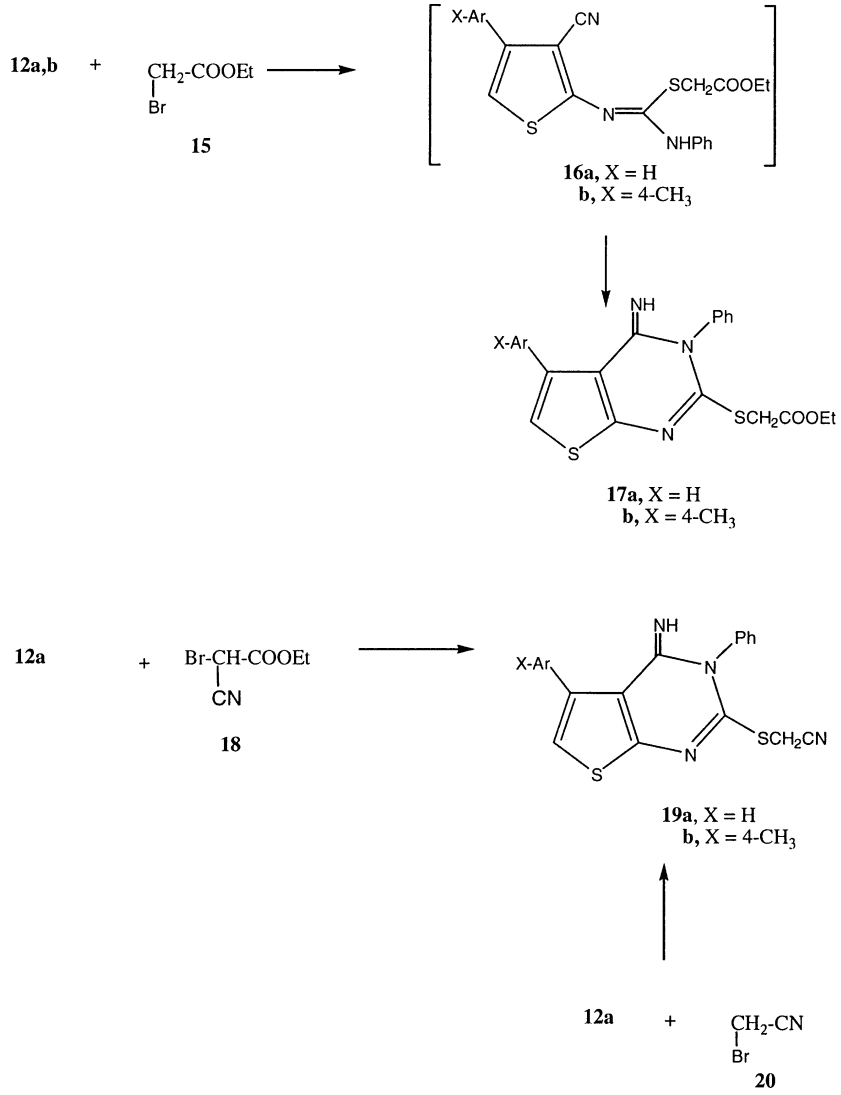
SCHEME 2

two singlets at δ 2.51 and 3.36 (3H each) corresponding to two methyl groups and a D_2O exchangeable singlet at δ 5.67 (2H) for resonating NH_2 groups. The ^1H NMR spectrum of **10b** showed a singlet at δ 2.63 (3H) corresponding to methyl function, a D_2O exchangeable singlet at δ 5.55 (2H), 7.98 corresponding to resonating NH_2, and a singlet at δ 10.31 (1H) corresponding to OH proton.

Recently, our research group was interested in studying the reactions of active methylene reagents with phenyl isothiocyanate in basic dimethylformamide followed by a reaction with α-halocarbonyl compounds to give either thiophene or thiazole derivatives.[17,18] As an extension of this work, we studied the reactivity of **4a**, **b** towards phenyl isothiocyanate to give the intermediate potassium sulfide salts **12a**, **b**. The latter products underwent heterocyclization through reaction with phenacyl bromide **13** to give the thiophene derivatives **14a** and **14b**, respectively (Scheme 2). Structures of the latter products were confirmed on the basis of analytical and spectral data (see Experimental section). Similarly, the reaction of **12a**, **b** with ethyl bromoacetate (**15**) gave the thieno[2,3-b]pyrimidine derivatives **17a** and **17b**, respectively. Formation of the latter products took place via the intermediate formation of **16a** and **16b**, respectively (Scheme 3). Structures of **17a** and **17b** were based on analytical and spectral data. Thus the ^{1}H NMR spectra of **17a** and **17b** exhibited the ethyl ester CH_3 triplets at δ 1.22; 1.26 (3H each) and CH_2 quartets at δ 4.23, 4.28 (2H each); singlets at δ 5.35 and 5.22 (2H each) due to methylene sulfide moiety; singlets at δ 6.91 and 6.26 (1H each) exhibiting thieno H-6 protons, and D_2O exchangeable singlets at δ 8.23 and 8.09 (1H each) corresponding to imino functions. Compound **17b** showed a singlet at δ 2.36 (3H) revealing a methyl group in the aromatic moiety. In a similar manner, the reaction of **12a** with ethyl bromocyanoacetate (**18**) gave the thieno[2,3-d]pyrimidine derivative **19**. The latter product is formed through the hydrolysis of the ethyl carboxylate group and cyclization. Structure of the latter product was confirmed on the basis of analytical and spectral data (see Experimental section). Further confirmation was obtained through the synthesis of **19** via another reaction route. Thus, the reaction of **12a** with bromoacetonitrile (**20**) gave the product **19** (finger print IR, m.p., & mixed m.p.).

Antimicrobial Activity

The diverse biological activities of azole and azine derivatives prompted us to test and study the biological activities of some of the newly synthesized products.[19,20] 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-hour culture of bacterium or a 7-day-old culture of spore suspension of the fungus. The solutions of the tested compounds at 25 μg/mL in dimethylformamide (DMF) were placed separately in the cup (8 mm diameter) through the disc and the compound diffused from the disc into the medium. The culture was examined for areas of



SCHEME 3

no growth around the disc (zones of inhibition) after overnight incubation. Growth of bacterial strains sensitive to a compound was inhibited at certain distances from the center of the disc whereas resistant stains grew up to the edge of the disc.

The results showed in Table I indicated that most of the prepared compounds were active against the test organisms. The most toxic

TABLE I *In Vitro* Bactericidal and Fungicidal Activity of Some of the Newly Synthesized Compounds[a]

Compound no.	*Bacillus cereus* (Gram positive)	*Staph. Aureus* (Gram positive)	*E. Coli* (Gram negative)	*K. Pneumonia* (Gram negative)
4a	+	+++	++	–
4b	++	++	+++	+++
6a	+++	+++	+++	++
6b	++	++	++	++
7a	+++	–	++	+++
8a	++	++	+	+
8b	++	+++	+++	+
10a	++	++	+++	+
10b	+++	+	++	+
14a	++	+++	+	+++
14b	+	++	+++	++
17a	+	++	+++	+
17b	+	++	+	++
19a	++	+++	++	++

[a]Slight inhibition, +; moderate inhibition, ++; Strong inhibition, + + +; rating percent control: no inhibition, 0; slight inhibition, 10, 20, 30; moderate inhibition, 40, 50, 60; strong inhibition, 70, 80, 90; complete inhibition, 100.

compounds against bacterial and fungal isolates were **4b**, **6a**, **8b**, and **14a** followed by **6b**, **8a**, **10a**, **10b**, **17a**, **19a**, and **14b**. Compounds **4a**, **7a**, and **17b** were less toxic to the test organisms.

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 spectrophotometer in DMSO-d_6 as solvent and TMS as internal reference. Chemical shifts δ are expressed in ppm.

2-Amino-3-cyano-4-phenylthiophene (4a), 2-Amino-3-cyano-4-(4-methyl- phenyl)thiophene (4b) and 2-Amino-3-cyano-4-(4-methoxy-phenyl)thiophene (4c)

General Procedure

Equimolar amount of α-cyano-β-phenyl crotononitrile (**3a**) (1.68 g, 0.01 mol), or α-cyano-β-(4-methylphenyl) crotononitrile (**3b**) (1.82 g, 0.01 mol) or α-cyano-β-(4-methoxyphenyl) crotnonitrile (**3c**) (1.98 g, 0.01 mol) and sulfur (0.32 g, 0.01 mol) in absolute ethanol

(20 mL) containing triethylamine (0.5 mL) were heated under reflux for 3 h. The solid product, in each case, thus formed upon dilution with water containing few drops of hydrochloric acid, which was collected by filtration.

4a. Yellow crystals (from ethanol), yield 80% (3.19 g), m.p. 96–100°C. IR υ (cm^{-1}) = 3855–3567 (NH_2), 3050 (CH aromatic), 2205 (CN), 1626 (C=C). ^1H NMR δ = 4.94 (s, 2H, NH_2, D_2O exchangeable), 6.35 (s, 1H, thiophene H-5), 7.40–7.65 (m, 5H, C_6H_5). Anal. Calcd. for $C_{11}H_8N_2S$ (M/e = 200): C, 65.97; H, 4.03; N, 13.98; S, 16.01; found: C, 66.08; H, 3.88; N, 14.06; S, 15.88%.

4b. Canary-yellow crystals (from ethanol), yield 85% (1.81 g), m.p. 95°C. IR υ (cm^{-1}) = 3577–3476 (NH_2), 3055 (CH aromatic), 2987 (CH_3), 2210 (CN), 1638 (C=C). ^1H NMR δ = 2.21 (s, 3H, CH_3), 4.37 (s, 2H, NH_2, D_2O exchangeable), 6.30 (s, 2H, thiophene H-5), 7.25–7.30 (m, 4H, C_6H_5). Anal. Calcd for $C_{12}H_{10}N_2S$ (M/e = 214): C, 67.26; H, 4.70; N, 13.07; S, 14.96; found: C, 67.09; H, 4.90; N, 12.89; S, 15.35%.

4c. Yellowish brown crystals (from ethanol/dioxane), yield 85% (1.95 g), m.p. 105°C. IR υ (cm^{-1}) = 3567–3436 (NH_2), 3052 (CH aromatic), 2988 (CH_3), 2215 (CN), 1632 (C=C). ^1H NMR δ = 2.88 (s, 3H, CH_3), 4.43 (s, 2H, NH_2, D_2O), 6.30 (s, 1H, thiazole H-5), 7.21–7.35 (m, 4H, C_6H_4). Anal. Calcd. for $C_{12}H_{10}N_2OS$ (230.28): C, 62.58; H, 4.37; N, 12.16; S, 13.92; found: C, 62.81; H, 4.53; N, 11.88; S, 14.30%.

4,6-Diamino-5-cyano-3-phenylthieno[2,3-b]pyridine (6a), 4,6-Diamino-5-cyano-3-(4-methylphenyl)thieno[2,3-b]pyridine (6b), 4-Amino-5-cyano-6-hydroxy-3-phenylthieno[2,3-b] pyridine (6c) and 4-Amino-5-cyano-6-hydroxy-3-(4-methylphenyl) Thieno[2,3-b]pyridine (6d)

General Procedure

To a solution of either **4a** (2.00 g, 0.01 mol) or **4b** (2.14 g, 0.01 mol) in absolute ethanol (25 mL) containing a catalytic amount of triethylamine (0.5 mL) either malononitrile (**2**) (0.66 g, 0.01 mol) or ethyl cyanoacetate (**5**) (1.13 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 2 h then poured onto ice water mixture containing a few drops of hydrochloric acid. The solid product, formed in each case, was collected by filtration.

6a. Yellowish brown crystals (from ethanol), yield 70% (1.82 g), m.p. 85°C. IR υ (cm^{-1}) = 3426, 3205 (2 NH_2), 3048 (CH aromatic), 2206 (CN), 1627 (C=C). ^1H NMR δ = 4.19, 5.30 (m, 4H, $2NH_2$, D_2O exchangeable), 6.05 (s, 1H, thiophene H-5), 7.37–7.61 (m, 5H, C_6H_5). Anal. Calcd. for

$C_{14}H_{10}N_4S$ (266.32): C, 63.14; H, 3.78; N, 21.04; S, 12.04; found: C, 63.00; H, 3.45; N, 21.41; S, 11.87%.

6b. Brown crystals (from ethanol/dioxane), yield 65% (1.82 g), m.p. 130°C. IR υ (cm^{-1}) = 3433, 3209 (2 NH_2), 3065 (CH aromatic), 2854 (CH_3), 2206 (CN), 1655 (C=N). ^1H NMR δ = 3.49 (s, 3H, CH_3), 4.95, 5.82 (2s, 4H, $2NH_2$, D_2O exchangeable), 6.36 (s, 1H, thiophene H-5), 6.96–7.29 (m, 4H, C_6H_4). Anal. Calcd. for $C_{15}H_{12}N_4S$ (280.35): C, 64.26; H, 4.31; N, 19.98; S, 11.44; found: C, 64.09; H, 3.95; N, 19.62; S, 11.80%.

6c. Brown crystals (from ethanol), yield 65% (1.73 g), m.p. 133°C. IR υ (cm^{-1}) = 3597, 3303 (NH_2, OH), 3055 (CH aromatic), 2206 (CN), 1626 (C=C). ^1H NMR δ = 4.97 (s, 2H, NH_2, D_2O exchangeable), 6.35 (s, 1H, thiophene H-2), 7.35–7.59 (m, 5H, C_6H_5), 10.42 (s, 1H, OH). Anal. Calcd. for $C_{14}H_9N_3OS$ (267.31): C, 62.90; H, 3.39; N, 15.72; S, 11.99; found: C, 62.84; H, 3.55; N, 15.43; S, 11.71%.

6d. Yellow crystals (from acetic acid), yield 80% (2.24 g), m.p. 180–2°C. IR υ (cm^{-1}) = 3582, 3315 (NH_2, OH), 3050 (CH aromatic), 2880 (CH_3), 2215 (CN), 1634 (C=C). ^1H NMR δ = 4.82 (s, 2H, NH_2, D_2O exchangeable), 6.30 (s, 1H, thiophene H-2), 7.32–7.49 (m, 5H, C_6H_5), 10.29 (s, 1H, OH). Anal. Calcd. for $C_{15}H_{11}N_3OS$ (281.34): C, 64.04; H, 3.94; N, 14.93; S, 11.39; found: C, 63.88; H, 3.65; N, 15.35; S, 11.52%.

4,6-Diamino-5-cyano-2-phenylazo-3-phenylthieno[2,3-b]pyridine (7a), 4,6-Diamino-5-cyano-2-phenylazo -3-(4-methylphenyl)thieno[2,3-b]pyridine (7b), 4-Amino—5-cyano-6-hydroxy-2-phenylazo-3-phenylthieno[2,3-b]-pyridine (7c), 4-Amino-5-cyano-6-hydroxy-2-phenylazo-3-(4-methylphenyl)thieno[2,3-b]pyridine (7d), 2-Amino-3-cyano-4-(4′-methylphenyl)-5-phenylazothiophene (8a) and 2-Amino-3-cyano-4-phenyl-5-phenylazo-thiophene (8b)

General Procedure

To a cold solution (0–5°C) of either **6a** (2.66 g, 0.01 mol), **6b** (2.80 g, 0.01 mol), **6c** (2.67 g, 0.01 mol), **6d** (2.81 g, 0.01 mol), **4a** (2.0 g, 0.01 mol), or **4b** (2.14 g, 0.01 mol) in ethanol (50 mL) containing sodium acetate (5.0 g), benzenediazonium chloride (0.01 mol) [prepared by adding a cold solution of sodium nitrite (0.7 g, 0.01 mol) to a solution of aniline (0.94 g, 0.01 mol) in hydrochloric acid (5 mL) with continuous stirring] was added. The reaction mixture, in each case, was left at room temperature for 2 h with stirring and the formed a solid product which was collected by filtration.

7a. Orange crystals (from acetic acid), yield 80% (2.96 g), m.p. 195–7°C. IR υ (cm^{-1}) = 3426, 3222 (2 NH_2), 3053 (CH aromatic), 2220 (CN), 1633 (C=C). ^1H NMR $\delta = 4.20$ (m, 4H, $2NH_2$, D_2O exchangeable), 7.31–7.52 (m, 10H, $2C_6H_5$). Anal. Calcd. for $C_{20}H_{14}N_6S$ (370.44): C, 64.84; H, 3.81; N, 22.68; S, 8.65; found: C, 64.64; H, 4.27; N, 22.41; S, 8.45%.

7b. Orange crystals (from acetic acid), yield 78% (2.99 g), m.p. 232–4°C. IR υ (cm^{-1}) = 3445, 3222 (2 NH_2), 3053 (CH aromatic), 2220 (CN), 1633 (C=C). ^1H NMR $\delta = 2.89$ (s, 3H, CH_3), 4.20 (m, 4H, $2NH_2$, D_2O exchangeable), 7.28–7.46 (m, 9H, C_6H_4, C_6H_5). Anal. Calcd. for $C_{21}H_{16}N_6S$ (384.46): C, 65.60; H, 4.19; N, 21.86; S, 8.34; found: C, 65.47; H, 4.38; N, 22.01; S, 8.28%.

7c. Yellow crystals (from 1,4-dioxane), yield 69% (2.55 g), m.p. 236–8°C. IR υ (cm^{-1}) = 3546–3230 (OH, NH_2), 3045 (CH aromatic), 2215 (CN), 1634 (C=C). ^1H NMR $\delta = 4.36$ (m, 2H, NH_2, D_2O exchangeable), 7.32–7.47 (m, 10H, $2C_6H_5$), 10.20 (s, 1H, OH). Anal. Calcd for $C_{20}H_{13}N_5OS$ (371.41): C, 64.67; H, 3.53; N, 18.85; S, 8.63; found: C, 64.88; H, 3.87; N, 18.67; S, 8.57%.

7d. Orange-red crystals (ethanol), yield 66% (2.54 g), m.p. 280–3°C. IR υ (cm^{-1}) = 3450–3211 (OH, NH_2), 3051 (CH aromatic), 2209 (CN), 1629 (C=C). ^1H NMR $\delta = 2.88$ (s, 3H, CH_3), 4.30 (m, 2H, NH_2, D_2O exchangeable), 7.28–7.45 (m, 9H, C_6H_4, C_6H_5), 10.15 (s, 1H, OH). Anal. Calcd. for $C_{21}H_{15}N_5OS$ (385.44): C, 65.44; H, 3.92; N, 18.17; S, 8.32; found: C, 64.28; H, 4.09; N, 18.04; S, 8.46%.

8a. Red crystals (from ethanol), yield 80% (2.43 g), m.p. 240–4°C. IR υ (cm^{-1}) = 3493, 2434 (NH_2), 3058 (CH aromatic), 2212 (CN), 1638 (C=C). ^1H NMR $\delta = 4.23$ (m, 2H, NH_2, D_2O exchangeable), 7.36–7.44 (m, 10H, $2C_6H_5$). Anal. Calcd. for $C_{17}H_{12}N_4S$ (304.42): C, 67.07; H, 3.97; N, 18.42; S, 10.53; found: C, 66.87; H, 4.17; N, 18.28; S, 10.46%.

8b. Yellow crystals (from ethanol), yield 75% (2.38 g), m.p. 184–6°C. IR υ (cm^{-1}) = 3490, 3380 (NH_2), 3056 (CH aromatic), 2985 (CH_3), 2209 (CN), 1645 (C=C). ^1H NMR $\delta = 2.27$ (s, 3H, CH_3), 4.48 (m, 2H, NH_2, D_2O exchangeable), 6.86–7.33 (m, 9H, C_6H_4, C_6H_5). Anal. Cald. for $C_{18}H_{14}N_4S$ (318.40): C, 67.90; H, 4.43; N, 17.59; S, 10.07; found: C, 67.77; H, 4.33; N, 17.68; S, 9.93%.

4-Amino-6-methyl-5-acetyl-2-phenylazo-3-phenylthieno[2,3-b]pyridine (10a) and 4-Amino-6-hydroxy-5-acetyl-2-phenylazo-3-phenylthieno[2,3-b]pyridine (10b)

General Procedure

To a solution of **8a** (3.04 g, 0.01 mol) in absolute ethanol (50 mL) containing triethylamine (0.5 mL), either acetylacetone (1.0 g, 0.01 mol) or ethyl acetoacetate (1.30 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 3 h and then left to cool. The solid product that was formed; in each case upon pouring onto water containing few drops of hydrochloric acid, was collected by filtration.

10a. Yellowish brown crystals (from 1,4-dioxane), yield 75% (2.98 g), m.p. 240–2°C. IR υ (cm^{-1}) = 3297, 3178 (NH_2), 3051 (CH aromatic), 1639 (C=N), 1511 (N=N). ^1H NMR $\delta = 2.51$, 3.36 (2s, 6H, $2CH_3$), 5.67 (s, 2H, NH_2, D_2O exchangeable), 7.34–7.72 (2m, 10H, $2C_6H_5$). Anal. Calcd. for $C_{22}H_{18}N_4OS$ (386.47): C, 68.37; H, 4.69; N, 14.49; S, 8.29; found: C, 68.02; H, 4.37; N, 14.68; S, 8.37%.

10b. Yellowish brown crystals (from ethanol), yield 75% (3.0 g), m.p. 247–9°C. IR υ (cm^{-1}) = 3630–3298 (OH, NH_2), 3056 (CH aromatic), 2926 (CH_3), 1639 (C=N), 1511 (N=N). ^1H NMR $\delta = 2.63$ (s, 3H, CH_3), 5.55 (s, 2H, NH_2, D_2O exchangeable), 7.20–7.33 (m, 10H, $2C_6H_5$), 10.31 (s, 1H, OH). Anal. Calcd. for $C_{21}H_{16}N_4O_2S$ (388.47): C, 64.93; H, 4.15; N, 14.42; S, 8.24; found: C, 65.35; H, 4.29; N, 14.58; S, 8.51 %.

2-(Benzoylmethylthio)-4-imino-3,5-diphenylthieno[2,3-d]-pyrimidine (14a), 2-(Benzoylmethylthio)-4-imino-5-(4-methylphenyl)-3-phenylthieno[2,3-d]-pyrimidine (14b), 2-(α-ethyl acetatothio)-4-imino-3,5-diphenylthien-o[2,3-d]pyrimidine (17a) 2-(α-ethyl acetatothio)-4-imino-5-(4-methylphenyl)-3-phenylthieno[2,3-d]pyrimidine (17b) 2-(α-acetonitrilo-thio)-4-imino-3,5-diphenylthieno[2,3-d]pyrimidine 2-(α-acetonitrilo-thio)-4-imino-5-(4-methylphenyl)-3-phenylthieno[2,3-d]-pyrimidine (19b)

General Procedure

To a solution of either **4a** (2.00 g, 0.01 mol) or **4b** (2.14 g, 0.01 mol) in dimethyl formamide (20 mL), phenylisothiocyanate (1.35 g, 0.01 mol) and potassium hydroxide (0.57 g, 0.01 mol) were added. The reaction mixture, in each case, was heated under reflux on a boiling water bath for 1 h, then either phenacyl bromide (**13**) (1.99 g, 0.01 mol), ethyl bromoacetate (**15**) (1.67 g, 0.01 mol), or ethyl bromocyanoacetate (**18**) was

added. The reaction mixture, in each case, was left stirring at room temperature overnight. The solid product which was formed in each case upon pouring into ice/water containing hydrochloric acid, was collected by filtration.

14a. Yellow crystals (from acetic acid), yield 73% (3.30 g), m.p. 228–30°C. IR υ (cm^{-1}) = 3390–3317 (NH), 3055 (CH aromatic), 1728–1695 (CO), 1540 (C=N). ^1H NMR δ = 4.41 (s, 2H, CH_2), 6.84 (s, 1H, thiophene H-5), 7.14–7.77 (m, 15H, $3C_6H_5$), 7.99 (s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{26}H_{19}N_3OS_2$ (453.59): C, 68.85; H, 4.22; N, 9.26; S, 14.14; found: C, 68.72; H, 4.44; N, 9.56; S, 14.38%.

14b. Yellowish-brown crystals (from acetic acid), yield 70% (3.26 g), m.p. 180–182°C. IR υ (cm^{-1}) = 3395–3320 (NH), 3050 (CH aromatic), 1720–1695 (CO), 1542 (C=N). ^1H NMR δ = 2.29 (s, 3H, CH_3), 4.38 (s, 2H, CH_2), 6.81 (s, 1H, thiophene H-5), 7.28–7.57 (m, 14H, $2C_6H_5$, C_6H_4), 7.96 (s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{27}H_{21}N_3OS_2$ (467.61): C, 69.37; H, 4.53; N, 8.98; S, 13.71; found: C, 69.58; H, 4.50; N, 9.27; S, 14.09%.

17a. Yellowish crystals (from ethanol), yield 65% (2.73 g), m.p. 76°C. IR υ (cm^{-1}) = 3340–3305 (NH), 3055 (CH aromatic), 1695 (CO), 1634 (C=C). ^1H NMR δ = 1.22 (t, 3H, CH_3), 4.23 (q, 2H, CH_2), 5.35 (s, 2H, CH_2), 6.91 (s, 1H, thiophene H-5), 7.30–7.44 (m, 10H, $2C_6H_5$), 8.23 (s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{22}H_{19}N_3O_2S_2$ (421.54): C, 62.68; H, 4.54; N, 9.97; S, 15.21; found: C, 62.79; H, 4.44; N, 9.56; S, 14.86%.

17b. Pale yellow crystals (from ethanol), yield 60% (2.52 g), m.p. 89°C. IR υ (cm^{-1}) = 3325–3120 (NH), 3060 (CH aromatic), 1728 (CO), 1660 (C=N). ^1H NMR δ = 1.26 (t, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.28 (q, 2H, CH_2), 5.22 (s, 2H, CH_2), 6.26 (s, 1H, thiophene H-5), 7.16–7.48 (m, 9H, C_6H_5, C_6H_4), 8.09 (s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{23}H_{21}N_3O_2S_2$ (435.57): C, 63.42; H, 4.86; N, 9.65; S, 14.72; found: C, 62.99; H, 4.74; N, 9.68; S, 14.91%.

19a. Yellow crystals (from ethanol), yield 65% (2.43 g), m.p. 128°C. IR υ (cm^{-1}) = 3317–3209 (NH), 3055 (CH aromatic), 2222 (CN), 1656 (C=N). ^1H NMR δ = 5.21 (s, 2H, CH_2), 7.03 (s, 1H, thiophene H-5), 7.19–7.45 (m, 10H, $2C_6H_5$), 8.49 (s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{20}H_{14}N_4S_2$ (374.48): C, 64.14; H, 3.76; N, 14.96; S, 17.12; found: C, 64.00; H, 4.08; N, 14.82; S, 16.78%.

19b. Orange crystals (from ethanol), yield 70% (2.71 g), m.p. 223–225°C. IR υ (cm^{-1}) = 3332–3197 (NH), 3062 (CH aromatic), 2215 (CN), 1660 (C=N). ^1H NMR δ = 2.24 (s, 3H, CH_3), 5.18 (s, 2H, CH_2), 7.04 (s,

1H, thiophene H-5), 7.22–7.39 (m, 9H, C_6H_5, C_6H_4), 8.49 (s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{21}H_{16}N_4S_2$ (388.51): C, 64.92; H, 4.15; N, 14.42; S, 16.50; found: C, 65.36; H, 4.22; N, 14.02; S, 16.37%.

REFERENCES

[1] F. Bracher and T. Papke, *Pharmazie*, **50,** 525 (1995).
[2] P. Nussbaumer, G. Petranyi, and A. Stutz, *J. Med. Chem.*, **34,** 65 (1991).
[3] N. J. Broom, J. S. Elder, P. C. Hannan, J. E. Pons, P. J. O'Hanlon, G. Walker, J. Wilson, and P. J. Woodall, *Antibiotics*, **48,** 1336 (1995).
[4] M. Nakanishi, H. Imamura, Y. Maruyama, and H. Hoshino, *J. Pharm. Soc. Jpn.*, **90,** 272 (1970).
[5] D. Briel, *Pharmazie*, **45,** 236 (1995).
[6] M. Yamaguchi, N. Maruyama, T. Koga, K. Kamei, M. Akima, T. Kuroki, M. Hamana, and N. Ohi, *Chem. Pharm. Bull.*, **43,** 236 (1995).
[7] 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. J. Almond, *J. Med. Chem.*, **44,** 863 (2001).
[8] R. Pontikis, R. Benhida, A. M. Aubertin, D. S. Grieson, and C. Monneret, *J. Med Chem.*, **40,** 1845 (1997).
[9] P. Diana, P. Barraja, A. Lauria, A. M. Almerico, G. Cirrincione, C. Minnei, S. Longu, D. Congiu, C. Musiu, and R. La Colla, *Anticancer Res*, **19,** 2127 (1999).
[10] H. Z. Shams, Y. M. Elkholy, R. A. Azzam, R. M. Mohareb, *Phosphorus, Sulfur, & Silicon*, **155,** 215 (1999).
[11] S. M. Sherif, R. M. Mohareb, H. Z. Shams, and H. M. Gaber, *J. Chem. Research (s)*, 434 (1995).
[12] R. M. Mohareb, Y. M. Elkholy, N. I. Abdel-Sayed, and H. Z. Shams, *J. Chin. Chem. Soc.*, **39,** 181 (1992).
[13] R. M. Mohareb, H. Z. Shams, and Y. M. Elkholy, *Phosphorus Sulfur & Silicon*, **72,** 93 (1992).
[14] K. Gewald, E. Schinke, and H. Bottcher, *Chem. Ber.*, **94,** 99 (1966).
[15] H. Schafer, H. Jablohoff, M. Hentschel, and K. Gewald, *J. Prakt. Chemie.*, **326,** 916 (1984).
[16] K. Gewald, *Chem. Ber.*, **98,** 3571 (1965).
[17] R. M. Mohareb, H. F. Zohdi, S. M. Sherif, and W. W. Wardakhan, *Tetrahedron*, **50,** 5807 (1994).
[18] R. M. Mohareb, W. W. Wardakhan, and F. Z. El-Ablack, *J. Chem. Research (s)*, 126 (1994); *J. Chem. Research (M)*, 0747 (1994).
[19] Y. Z. Gutter, *Pflanzenkr Pflanzenschutz*, **89,** 332 (1982); *Chem. Abstr.*, **97,** 143345 (1982).
[20] Y. Shachnai, M. N. Gutter, and A. Dinoor, *Bull Merkaz Volcano Minhol Ha-Merchkar (bet Dogan, Isr.)*, **189,** 64 (1981); *Chem. Abstr.*, **97,** 143345 (1982).