Synthesis and Biological Activity of New 1,3,4-Thiadiazole Derivatives

A. A. ALY and R. EL-SAYED

Department of Chemistry, Faculty of Science, Benha University, Benha, Egypt
e-mail: ref_at@hotmail.com

Received 5 October 2004; Revised 8 August 2005; Accepted 15 August 2005

The aminothiadiazole (*II*) on treatment with aromatic aldehydes yielded Schiff bases, which cyclized to thiazolidinone derivatives by reaction with thioglycolic acid. Reaction of *II* with phenyl isocyanate and phenyl isothiocyanate afforded the carbamide and carbothiamide derivatives, respectively, which on reaction with malonic acid in acetyl chloride gave barbituric and thiobarbituric acid derivatives. However, reaction of carbon disulfide and methyl iodide with *II* gave dithiocarbamidate derivative which on treatment with ethylenediamine or *o*-phenylenediamine gave the condensed *N*-imidazolylthiadiazolylamine derivatives.

The reported biological activity of many heterocyclic compounds containing thiophene moiety [1—4] as well as thiadiazole derivatives having antifungal and antibacterial effect [5, 6] prompted us by these observations and in continuation of the works [7—10] on the synthesis of biologically active heterocycles. We thought it worthwhile to synthesize new series of benzothiophene, having 1,3,4-thiadiazole moiety, with the objective of obtaining new biologically active compounds.

The reaction of 5-(3-chlorobenzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-ylamine (*II*) with aromatic aldehydes, namely benzaldehyde, 4-chlorobenzaldehyde or 4-methoxybenzaldehyde in refluxing ethanol afforded Schiff bases *IIIa*—*IIIc*, which on condensation with thioglycolic acid yielded 3-[5-(3-chlorobenzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-2-arylthiazolidin-4-ones *IVa*—*IVc* (Scheme 1).

The antibacterial activities of urea derivatives [11] and anticonvulsant activities of thiourea derivatives [12] prompted us to the synthesis of thiadiazolylurea and thiadiazolylthiourea derivatives *VI, VII via* two routes. In the first route the thiadiazole *II* reacted with ethyl chloroformate to give *V*, followed by treatment with aniline, while in the second one *VI* and *VII* was obtained by direct refluxing of *II* with phenyl isocyanate in ethanolic solution. Similarly, *II* was converted to 1-[5-(3-chlorobenzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-3-phenylthiourea (*VII*) by the reaction with phenyl isothiocyanate. The urea derivative *VI* and thiourea derivative *VII* on reaction with malonic acid in the presence of acetyl chloride underwent intermolecular cyclization and yielded 1-[5-(3-chlorobenzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-3-phenyldihydropyrimidine-2,4,6-trione (*VIIIa*) and 3-[5-(3-chlorobenzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-1-phenyl-2-thioxodihydropyrimidine-4,6-dione (*VIIIb*).

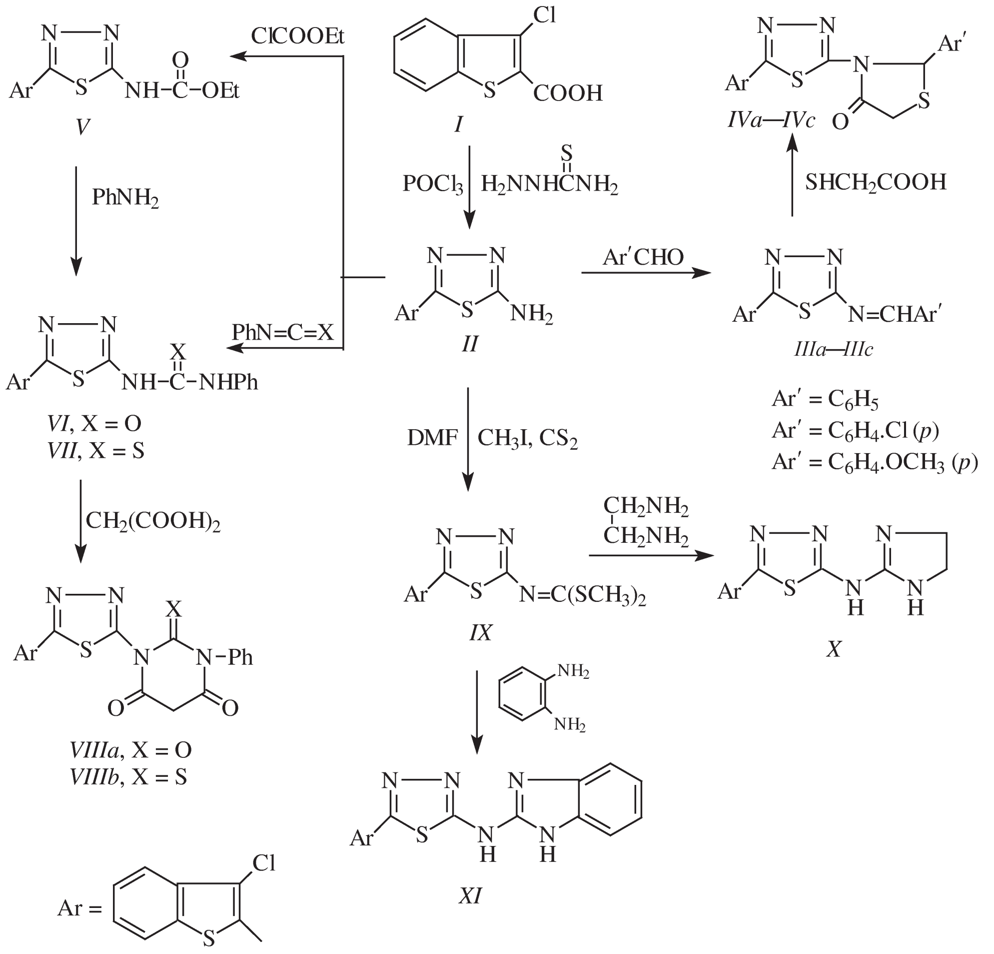
Finally, we reported the reaction of carbon disulfide and methyl iodide with thiadiazole *II* in the presence of concentrated aqueous sodium hydroxide leading to the formation of dimethyl 5-(3-chlorobenzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-ylcarbonodithioimidate (*IX*) which on treatment with binucleophilic reagent such as ethylenediamine and *o*-phenylenediamine afforded *N*-(4,5-dihydro-1*H*-imidazol-2-yl)-5-(3-chlorobenzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-ylamine (*X*) and *N*-[5-(3-chlorobenzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-1*H*-benzo[*d*]imidazol-2-ylamine (*XI*).

The results of the antimicrobial activities are compiled in Table 1. It has been observed that most of the synthesized compounds have remarkable antimicrobial activity towards the selected bacteria and fungi.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were measured on Perkin—Elmer 398 spectrophotometer. The ^{1}H NMR spectra were recorded on Varian Gemini 200 MHz instrument using DMSO-d_6—$CDCl_3$ as solvent and TMS as internal reference. The microanalysis was performed using the Perkin—Elmer 2400 CHN analyzer.

The starting 5-(3-chlorobenzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-ylamine (*II*) was prepared by the condensation of 3-chlorobenzo[*b*]thiophene-2-carboxylic acid (*I*) [13] with thiosemicarbazide using phosphorous oxychloride as condensing agent [14].



Scheme 1

Schiff Bases *IIIa*—*IIIc*

A mixture of *II* (0.01 mol) and aromatic aldehydes (0.01 mol) was refluxed in ethanol containing few drops of Et_3N for 4 h. After cooling, the precipitated solid was collected by filtration.

N-Benzylidene-5-(3-chlorobenzo[b]thiophen-2-yl)-1,3,4-thiadiazol-2-amine (IIIa), yield 1.3 g (65 %) (EtOH), pale yellow, m.p. = 180—182 ℃. IR spectrum ($CDCl_3$), $\tilde{\nu}/cm^{-1}$: 1610—1620 ν(C=N). ^1H NMR spectrum ($CDCl_3$), δ: 7.3—7.8 (m, 9H, H_{arom}), 8.1 (s, 1H, N=CH). For $C_{17}H_{10}ClN_3S_2$ (M_r = 355.86) w_i(calc.): 57.38 % C, 2.83 % H, 11.81 % N; w_i(found): 57.42 % C, 2.86 % H, 11.74 % N.

N-(4-Chlorobenzylidene)-5-(3-chlorobenzo[b]thiophen-2-yl)-1,3,4-thiadiazol-2-amine (IIIb), yield 1.5 g (62 %) (EtOH), yellow, m.p. = 190—192℃. IR spectrum ($CDCl_3$), $\tilde{\nu}/cm^{-1}$: 1610—1625 ν(C=N). ^1H NMR spectrum ($CDCl_3$), δ: 7.33—7.92 (m, 8H, H_{arom}), 8.4 (s, 1H, N=CH). For $C_{17}H_9Cl_2N_3S_2$ (M_r = 390.32) w_i(calc.): 52.31 % C, 2.32 % H, 10.77 % N; w_i(found): 52.26 % C, 2.27 % H, 10.68 % N.

N-(4-Methoxybenzylidene)-5-(3-chlorobenzo[b]thiophen-2-yl)-1,3,4-thiadiazol-2-amine (IIIc), yield 1.4 g (66 %) (benzene), yellow, m.p. = 167—169℃. IR spectrum ($CDCl_3$), $\tilde{\nu}/cm^{-1}$: 1615—1621 ν(C=N). ^1H NMR spectrum ($CDCl_3$), δ: 3.73 (s, 3H, OCH_3), 8.2 (s, 1H, N=CH), 6.8—7.8 (m, 8H, H_{arom}). For $C_{18}H_{12}ClN_3OS_2$ (M_r = 385.90) w_i(calc.): 56.03 % C, 3.13 % H, 10.89 % N; w_i(found): 56.12 % C, 3.18 % H, 10.77 % N.

3-[5-(3-Chlorobenzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-2-arylthiazolidin-4-ones *IVa*—*IVc*

A mixture of individual derivative *IIIa*—*IIIc* (0.01 mol) and thioglycolic acid (0.01 mol) was refluxed in absolute ethanol (30 cm^3) for 4 h. After cooling the reaction mixture, the precipitated solid was filtered off and crystallized from ethanol.

3-[5-(3-Chlorobenzo[b]thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-2-phenylthiazolidin-4-one (IVa), yield 1.7 g (63 %), brown, m.p. = 140—142℃. IR spectrum ($CDCl_3$), $\tilde{\nu}/cm^{-1}$: 1680 ν(C=O), 1615—1620 ν(C=N). ^1H NMR spectrum (DMSO-d_6), δ: 3.38 (s, 2H, CH_2), 5.92 (s, 1H, CH), 7.06—7.91 (m, 9H, H_{arom}). For $C_{19}H_{12}ClN_3OS_3$ (M_r = 429.97) w_i(calc.): 53.08 % C, 2.81 % H, 9.77 % N; w_i(found): 53.00 % C, 2.75 % H, 9.86 % N.

Table 1. Response of Various Microorganisms to Synthesized Derivatives *in vitro*

Compound	*Bacillus cereus*		*Escherichia coli*		*Aspergillus niger*		*Penicillium notatum*	
	A	{MIC}	A	{MIC}	A	{MIC}	A	{MIC}
II	+	250	+	250	+	250	++	125
IIIa	++	125	+	250	++	125	+	250
IIIb	++	250	++	250	++	250	++	125
IIIc	++	125	+	250	+	250	+	250
IVa	++	250	++	250	+	250	++	250
IVb	+	250	+	250	+	250	+	125
IVc	+	250	+	250	+	250	+	250
V	+	250	++	250	+	125	+	125
VI	++	125	++	250	+++	125	++	125
VII	+	250	+	250	+	250	+	250
VIIIa	++	125	+	250	++	125	+	250
VIIIb	+	250	++	250	+	125	+	125
IX	+++	125	++	250	++	125	+++	250
X	++	125	+	250	+	250	+	250
XI	++	125	++	250	+++	125	++	125

A: antimicrobial activity of tested compounds; the width of the zone of inhibition indicates the potency of antimicrobial activity, - no antimicrobial activity, + weak activity with diameter equal to 0.5—0.7 cm, ++ moderate activity with the diameter zone equal to 1.0—1.2 cm, +++ marked activity with the diameter zone equal to 1.6—1.8 cm.
MIC: minimum inhibition concentration/(μg cm^{-3}).

3-[5-(3-Chlorobenzo[b]thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-2-(4-chlorophenyl)thiazolidin-5-one (*IVb*), yield 1.2 g (58 %), reddish yellow, m.p. = 151—153 ℃. IR spectrum (CDCl$_3$), $\tilde{\nu}$/cm^{-1}: 1675 ν(C=O), 1610—1618 ν(C=N). ^{1}H NMR spectrum (DMSO-d_6), δ: 3.28 (s, 2H, CH$_2$), 5.92 (s, 1H, CH), 7.0—7.9 (m, 9H, H$_{\text{arom}}$). For $C_{19}H_{11}Cl_2N_3OS_3$ (M_r = 464.42) w_i(calc.): 49.14 % C, 2.39 % H, 9.05 % N; w_i(found): 49.05 % C, 2.42 % H, 9.09 % N.

3-[5-(3-Chlorobenzo[b]thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-2-(4-methoxyphenyl)thiazolidin-4-one (IVc), yield 1.4 g (56 %), reddish yellow, m.p. =161—163 ℃. IR spectrum (CDCl$_3$), $\tilde{\nu}$/cm^{-1}: 1672 ν(C=O), 1612—1620 ν(C=N). ^{1}H NMR spectrum (DMSO-d_6), δ: 3.4 (s, 3H, OCH$_3$), 4.21 (s, 2H, CH$_2$), 5.11 (s, 1H, CH), 7.3—7.85 (m, 9H, H$_{\text{arom}}$). For $C_{20}H_{14}ClN_3O_2S_3$ (M_r = 459.99) w_i(calc.): 52.22 % C, 3.07 % H, 9.13 % N; w_i(found): 52.16 % C, 2.99 % H, 9.22 % N.

Ethyl 5-(3-Chlorobenzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-ylcarbamate (*V*)

A mixture of *II* (0.01 mol) and ethylchloroformate (0.012 mol) in pyridine (20 cm^3) containing Et$_3$N (1 cm^3) was refluxed for 3 h, then poured into dilute HCl (50 %) and the formed solid was crystallized from ethanol. Yield 1.9 g (63 %), white yellow, m.p. = 211—213 ℃. IR spectrum (CDCl$_3$), $\tilde{\nu}$/cm^{-1}: 3240 ν(NH), 1726 ν(C=O), and 1610—1620 ν(C=N). ^{1}H NMR spectrum (CDCl$_3$), δ: 1.3 (t, 3H, CH$_3$), 4.12 (q, 2H, CH$_2$), 7.3—7.9 (m, 4H, H$_{\text{arom}}$), 8.0 (s, 1H, NH, exchangeable). For $C_{13}H_{10}ClN_3O_2S_2$ (M_r = 339.82) w_i(calc.): 45.95 % C, 2.97 % H, 12.37 % N; w_i(found): 45.88 % C, 2.86 % H, 12.26 % N.

1-[5-(3-Chlorobenzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-3-phenylurea (*VI*)

Method A

A mixture of *V* (0.01 mol) and aniline (0.01 mol) was refluxed for 15 h in ethanol (20 cm^3). After cooling the mixture, the precipitated solid was filtered off and crystallized from ethanol.

Method B

A mixture of *II* (0.01 mol) and phenyl isocyanate (0.01 mol) was refluxed in ethanol (30 cm^3) for 8 h. The separated solid was filtered off and crystallized. Yield 1.7 g (45 %), brown, m.p. = 196—198 ℃. IR spectrum (CDCl$_3$), $\tilde{\nu}$/cm^{-1}: 3200—3300 ν(NH), 1670 ν(C=O), 1615—1620 ν(C=N). ^{1}H NMR spectrum (DMSO-d_6), δ: 7.0—7.9 (m, 9H, H$_{\text{arom}}$), 6.0 (s, 2H, NH, exchangeable). For $C_{17}H_{11}ClN_4OS_2$ (M_r = 386.88) w_i(calc.): 52.78 % C, 2.87 % H, 14.48 % N; w_i (found): 52.70 % C, 2.79 % H, 14.22 % N.

1-[5-(3-Chlorobenzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-3-phenylthiourea (*VII*)

A mixture of *II* (0.01 mol) and phenyl isothiocyanate (0.01 mol) was refluxed in ethanol (30 cm^3) for 8 h. The separated solid was filtered off and crystallized from benzene. Yield 1.1 g (59 %), reddish yellow, m.p. = 186—188 ℃. IR spectrum (CDCl$_3$), $\tilde{\nu}$/cm^{-1}: 3220—3300 ν(NH), 1473 ν(C=S), 1610—1615 ν(C=N). ^{1}H NMR spectrum (CDCl$_3$), δ: 6.46—7.91 (m, 9H, H$_{\text{arom}}$), 4.0 (s, 2H, NH, exchangeable). For $C_{17}H_{11}ClN_4S_3$ (M_r = 402.94) w_i(calc.): 50.67 % C, 2.75 % H, 13.90 % N; w_i(found): 50.55 % C, 2.65 % H, 13.69 % N.

1-[5-(3-Chlorobenzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-3-phenyldihydropyrimidine-2,4,6-trione (*VIIIa*)

A mixture of *VI* (0.01 mol) and malonic acid (0.01 mol) was refluxed in acetyl chloride (30 cm^3) for 3 h. After cooling the obtained solid was filtered off and crystallized from benzene. Yield 1.6 g (71 %), brown, m.p. = 210—212 ℃. IR spectrum ($CDCl_3$), $\tilde{\nu}/cm^{-1}$: 1670—1680 ν(C=O), 1610—1620 ν(C=N). ^1H NMR spectrum (DMSO-d_6), δ: 3.12 (s, 2H, CH_2), 7.0—7.8 (m, 9H, H_{arom}). For $C_{20}H_{11}ClN_4O_3S_2$ (M_r = 454) w_i(calc.): 52.81 % C, 2.44 % H, 12.32 % N; w_i(found): 52.84 % C, 2.47 % H, 12.35 % N.

3-[5-(3-Chlorobenzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-1-phenyl-2-thioxodihydropyrimidine-4,6-dione (*VIIIb*)

A mixture of *VII* (0.01 mol) and malonic acid (0.01 mol) was refluxed in acetyl chloride (30 cm^3) for 3 h. After cooling the obtained solid was filtered off and crystallized from benzene. Yield 1.4 g (63 %), brown, m.p. = 220—222 ℃. IR spectrum ($CDCl_3$), $\tilde{\nu}/cm^{-1}$: 1600 ν(C=S), 1600—1610 ν(C=N). ^1H NMR spectrum (DMSO-d_6), δ: 3.12 (s, 2H, CH_2), 7.00—7.91 (m, 9H, H_{arom}). For $C_{20}H_{11}ClN_4O_2S_3$ (M_r = 470.98) w_i(calc.): 51.00 % C, 2.35 % H, 11.90 % N; w_i(found): 51.11 % C, 2.39 % H, 11.98 % N.

N-Di(methylthio)methylene-[5-(3-chlorobenzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-amine (*IX*)

To stirred cold solution of *II* (0.05 mol) in DMF (25 cm^3), 20 M-NaOH (5 cm^3), carbon disulfide (8 cm^3), and methyl iodide (0.05 mol) were added and the stirring was continued for additional 4 h. The mixture was poured into cold water and the formed solid was crystallized from benzene. Yield 1.8 g (62 %), pale yellow, m.p. = 170—172 ℃. IR spectrum ($CDCl_3$), $\tilde{\nu}/cm^{-1}$: 1605—1620 ν(C=N). ^1H NMR spectrum ($CDCl_3$), δ: 2.0 (s, 6H, 2CH_3), 6.89—7.95 (m, 4H, H_{arom}). For $C_{13}H_{10}ClN_3S_4$ (M_r = 371.95) w_i(calc.): 41.98 % C, 2.71 % H, 11.30 % N; w_i(found): 42.05 % C, 2.78 % H, 11.38 % N.

N-(4,5-Dihydro-1*H*-imidazol-2-yl)-5-(3-chlorobenzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-ylamine (*X*)

A mixture of *IX* (0.03 mol) and ethylenediamine (0.06 mol) in DMF (25 cm^3) was stirred at room temperature for 1 h and then it was maintained at 100 ℃ for 8 h. After cooling the reaction mixture was poured into cold water and the formed solid was crystallized from benzene. Yield 1.3 g (57 %), reddish brown, m.p. = 217—219 ℃. IR spectrum ($CDCl_3$), $\tilde{\nu}/cm^{-1}$: 3320—3350 ν(NH), 1610—1625 ν(C=N). ^1H NMR spectrum (DMSO-d_6), δ: 1.6 (t, 2H, CH_2), 2.7 (t, 2H, CH_2), 7.3—7.9 (m, 4H, H_{arom}), 2.0, 4.0 (2s, 2H, NH, exchangeable). For $C_{13}H_{10}ClN_5S_2$ (M_r = 335.84) w_i(calc.): 46.49 % C, 3.00 % H, 20.85 % N; w_i(found): 46.39 % C, 2.88 % H, 20.89 % N.

N-[5-(3-Chlorobenzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-1*H*-benzo[*d*]imidazol-2-ylamine (*XI*)

A mixture of *IX* (0.04 mol) and *o*-phenylenediamine (0.04 mol) in DMF (30 cm^3) was refluxed for 8 h. After cooling, the formed solid was crystallized from ethanol. Yield 1.6 g (55 %), brown, m.p. = 230—232 ℃. IR spectrum ($CDCl_3$), $\tilde{\nu}/cm^{-1}$: 3340—3350 ν(NH), 1605—1620 ν(C=N). ^1H NMR spectrum (DMSO-d_6), δ: 7.26—7.92 (m, 9H, H_{arom}), 4.0, 5.0 (2s, 2H, NH, exchangeable). For $C_{17}H_{10}ClN_5S_2$ (M_r = 383.88) w_i(calc.): 53.19 % C, 2.63 % H, 18.24 % N; w_i(found): 53.25 % C, 2.68 % H, 18.27 % N.

Antimicrobial Activities

The antimicrobial activities of the synthesized compounds were determined *in vitro* using hole plate and filter paper disc method [15]. Different species of gram-positive and gram-negative bacteria in addition to some fungal plant pathogens were used (see Table 1). The considered compounds were dissolved in 10 % acetone, different concentrations have been chosen (125, 250, 500 $\mu g\ cm^{-3}$). Agar plates were surface-inoculated uniformly from fresh broth culture of microorganisms. The discs were incubated at 28 ℃ for 24 h. The formed inhibition zones were measured in mm.

Acknowledgements. All strains were kindly supplied from the Department of Botany, Faculty of Science, Benha University, for biological screening.

REFERENCES

1. Kumar, S., *J. Org. Chem. 67*, 8842 (2002).
2. Ram, V. J., Pandey, H. K., and Vlietinck, A. T., *J. Heterocycl. Chem. 18*, 1277 (1981).
3. Chakrabarti, J. K., Horman, L., Hotten, T. M., Pullar, I. A., Tupper, D. E., and Wright, F. C., *J. Med. Chem. 23*, 878 (1980).
4. Sudabeh, P. J. and Raymond, C., *J. Heterocycl. Chem. 23*, 1571 (1986).
5. Singh, H. and Yadav, L. S., *Agric. Biol. Chem. 40*, 759 (1976).
6. Chaaban, I. and Oji, O. O., *J. Indian Chem. Soc. 61*, 523 (1984).
7. Aly, A. A., *Phosphorus, Sulfur Silicon Relat. Elem. 178*, 2415 (2003).
8. Aly, A. A., *Chin. J. Chem. 21*, 339 (2003).
9. Amine, M. S., Eissa, A. M. F., Shaaban, A. F., El-Sawy, A. A., and El-Sayed, R., *Indian J. Chem. 37B*, 1153 (1998).

10. Amine, M. S., Eissa, A. M. F., Shaaban, A. F., El-Sawy, A. A., and El-Sayed, R., *Indian J. Chem. 129*, 19 (1998).
11. Feiberg, I., Fien, G., and Walker, J. M., *Science 198*, 847 (1977).
12. Lien, E. J. and Hussain, M., *J. Med. Chem. 14*, 138 (1971).
13. Wright, W. B. and Brabander, H. J., *J. Org. Chem. Soc. 19*, 711 (1971).
14. Kokila, D. and Boxi, A. J., *J. Indian Chem. Soc. 69*, 212 (1992).
15. Leifert, C., Chidbouree, S., Hampson, S., Workman, S., Sigee, D., Epton, H. A., and Harbour, A., *J. Appl. Bacteriol. 78*, 97 (1995).