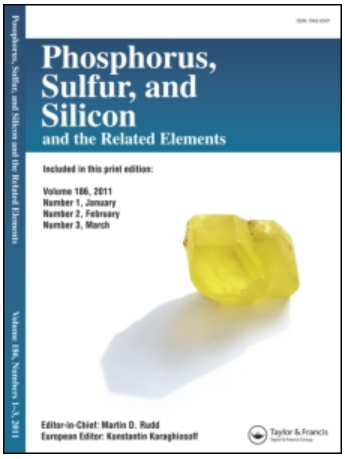

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Nitriles in Organic Synthesis: A Convenient Route to Some Heterocycles Incorporating a Benzothiazole Moiety

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*2-(Benzo[d]thiazol-2-yl)-4-chloro-3-oxobutanenitrile (**2**) was utilized for the synthesis of several new benzothiazole derivatives. Compound **2** reacted with aniline, hydrazine hydrate, ethanolamine, and ethyl glycinate hydrochloride to yield benzothiazole derivatives **3–6**, respectively.*

Keywords Benzothiazole; chloroactyl chloride; 2-cyanomethylbenzothiazole

INTRODUCTION

Benzothiazole derivatives have attracted a great deal of interest due to their antiviral,[1,2] antibacterial,[3] antimicrobial,[4] and fungicidal activites.[5] They are also useful as antiallergic,[6] anti-inflammatory[7] and anthelmintic[8] agents and as appetite depressants,[9] antihypertensives,[10] antineurodegenerative diseases,[11] for treatment circulatory organ diseases,[12] intermediates for dyes,[13–16] plant protectants,[17] histamine H2 antagonists,[18] and photographic sensitizers.[19] In continuation of our interest in the synthesis of heterocycles containing a benzothiazole moiety,[20,21] we report here on a facile route to the synthesis of some new benzothiazole derivatives.

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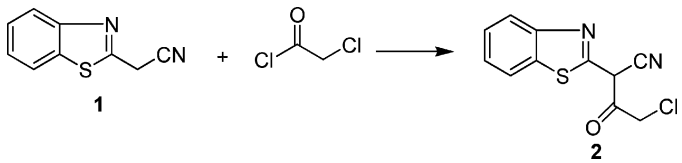
RESULTS AND DISCUSSION

As a part of a program aimed at the synthesis of novel benzothiazole derivatives, which could be useful for biological and pharmacological screening, we have investigated the possible utility of 2-cyanomethylbenzothiazole **(1)** for the synthesis of some heterocyclic compounds. It has been found that the reaction of **1** with chloroacetyl chloride in the presence of triethylamine afforded 2-(benzo[d]thiazol-2-yl)-4-chloro-3-oxobutanenitrile (**2**) in a high yield (Scheme 1).[22] The structure of **2** was established based on both elemental and spectral data.



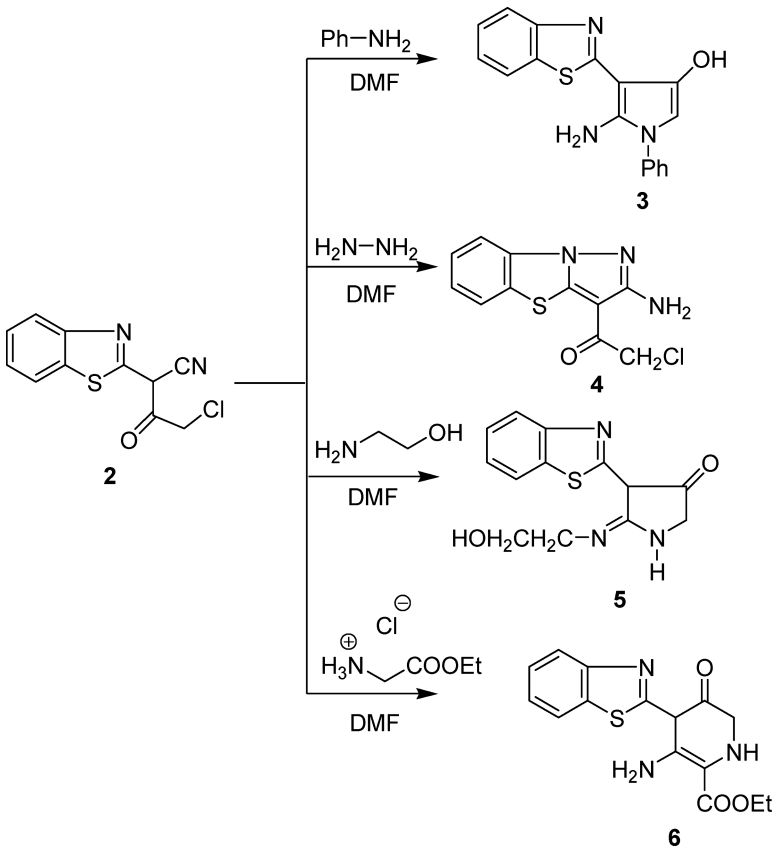
SCHEME 1

The IR spectrum showed strong absorption bands at 2199 cm^{-1} and 1625 cm^{-1} due to CN and (C=N), respectively. The ^1H NMR spectrum of **2** revealed two singlet signals at δ 4.50 and 4.72 ppm of CH_2 and CH respectively, and an aromatic multiplet at δ 7.45–8.22 ppm, while its mass spectroscopic measurement showed m/z: 250 (M^+), 215, 201 (100% base peak), 189, 173, 147, 108, and 107.

The latter 2-(benzo[d]thiazol-2-yl)-4-chloro-3-oxobutanenitrile (**2**) allowed a fruitful, one step synthesis of several heterocyclic rings via its reaction with aniline, hydrazine hydrate, ethanolamine, and ethyl glycinate hydrochloride to yield 5-amino-4-(benzo-[d]thiazol-2-yl)-1-phenyl-1H-pyrrol-3-ol (**3**), 2-amino-3-chloroacetyl pyra zollo[5,1-b]benzothiazole **(4)**, 4-(benzo[d]thiazol-2-yl)-5-(2-hydroxyethylimino)pyrrolidin-3-one (**5**), and ethyl 3-amino-4-(benzo[d]thiazol-2-yl)-5-oxo-1,4,5,6-tetrahydropyridine-2-carboxylate (**6**), respectively, in high yield, as shown in Scheme **2**.

The reaction of compound **2** with aniline in refluxing dimethylformamide afforded a single product **3**.[23] The structure of the compound was established on the basis of both the elemental analysis and IR spectrum of the reaction product.

The IR spectrum showed absorption bands at 3339 and 3406 cm^{-1} due to the NH_2 group, in addition to bands at 3381 and 3163 cm^{-1} due to the OH and tautomeric NH groups, respectively, it and showed no bands in the region of cyano group around 2200 cm^{-1}. However, ^1H-NMR spectroscopy together with the mass fragmentation pattern provided conclusive evidence of the proposed structure. Thus, a broad



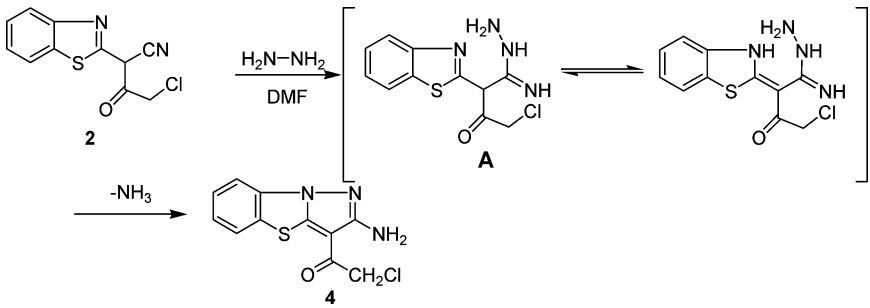
SCHEME 2

signal D_2O-exchangeable proton observed at δ 4.48 ppm was attributed to the amino group, a singlet signal at δ 8.5 ppm due to an OH proton, and a multiplet at δ 7.3–8.1 ppm for aromatic protons.

The structure of **3** was confirmed also by its mass spectroscopic measurement, which showed m/z the molecular ion peak at 307 (M^+, base peak).

We thought to extend this synthetic approach by allowing **2** to react with hydrazine hydrate to yield a compound that was identical with product **4,** where the elemental analysis and mass spectroscopy confirmed that the product **4** was formed by a loss of ammonia.[24]

This derivative was thus assumed to be formed via an initial addition of a hydrazine molecule to the cyano group in compound **2** to yield the intermediate (**A**) that cylices into product **4** by a loss of ammonia molecule, as shown in Scheme 3.



SCHEME 3

The structure of **4** was established by chemical tests and spectral data. The element test showed the presence of a chlorine atom, indicating that chlorine was not involved in the reaction. The IR spectrum showed no absorption band of a cyano group around the region 2150–2300 cm^{-1}, indicating that the cyano group was involved in the reaction. In addition, the IR spectrum showed a band at 1718 cm^{-1} due to the carbonyl group. Moreover the ^1H NMR showed a singlet signal at δ 4.52 ppm assigned to the CH_2 and a D_2O-exchangable broad signal at δ 5.64 ppm assignable to NH_2besides an aromatic multiplet at δ 7.20–8.01 ppm. The mass spectrum showed a molecular ion peak at m/e 266 (7%), which indicated that the intermediate was cyclized by a loss of an ammonia molecule.

The mass spectrum also showed the fragments 189 (15%), 173 (13%), 157 (10%), and 73 (100% base peak).

In a different manner to the behavior of aniline and hydrazine, ethanol amine reacted with **2** in refluxing dimethylformamide to yield **5**.

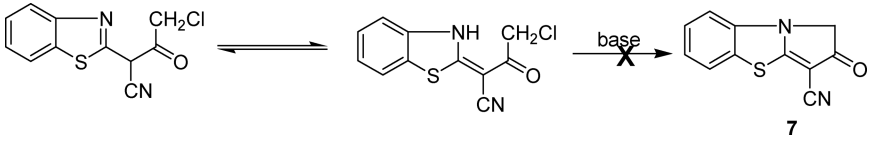
The structure of **5** was determined on the basis of its spectral data as well as the elemental analysis. The element test showed the absence of a chlorine atom, indicating that it was lost during the cyclization step. Thus, the mass spectrum of **5** revealed a molecular ion peak at m/z = 275 with 100% relative abundance corresponding to the molecular formula $C_{13}H_{13}N_3O_2S$. Its IR spectrum showed absorption peaks corresponding to the presence of OH and NH functions at 3896 and 3128, respectively, besides the disappearance of absorption bands due the NH_2 and C≡N groups.

In its ^1H NMR spectrum (DMSO-d_6), two types of D_2O-exchangeable protons at δ 8.3 (s, 1H) and 8.68 (s, 1H) ppm corresponding to NH and OH functions, respectively, were detected in addition to the aromatic multiplet. Also, the ^1H NMR showed a multiplet band for four protons (—CH_2CH_2—) at δ 3.6–3.7, a singlet at δ 4.0 for two protons (—CH_2—), and a singlet band at δ 5.06 for the CH proton.

2 reacts with ethyl glycinate hydrochloride in DMF to yield the pyridine derivatives **6**. The structure of **6** was confirmed by its IR spectrum, which showed the absence of a spectrum band in the region of 2220 cm^{-1}, which indicated that, the CN group was involved in the cyclization process; it also showed bands at 1715 cm^{-1} (—COOEt), 3189, and 3416 cm^{-1} due to NH and OH (enolized), respectively, and at 3252 and 3398 cm^{-1} due to the NH_2 function. The ^1H NMR (DMSO-d_6) showed a triblet band at δ 1.2 ppm due to CH_3 protons, a singlet at δ 2.8 ppm due to CH_2 protons, a quartet broad band in the region 3.5–3.85 ppm due to CH_2 and NH_2 protons, a singlet band at δ 4.6 ppm due to NH, and a multiplet band at δ 7.4–8.4 ppm due to aromatic protons.

Mass spectrum showed m/z at 317 (M^+), 245 (19.8% M^+-COOEt), 214 (15.6%), 213 (5.9%), 201 (18.3%), 174 (100%), 134, and 108 (31.5%).

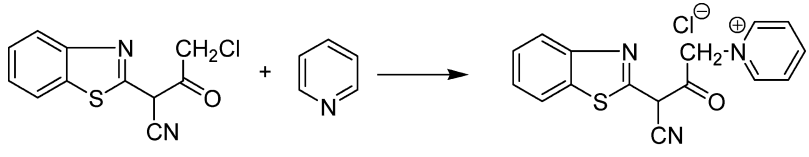
All attempts to cyclize compound **5** by heating in it DMF in the presence of different bases to obtain the pyrrolo[2,1-b]benzothiazole derivative (**7**) failed.



7

SCHEME 4

On the other hand, it was found that refluxing compound **2** in boiling pyridine yielded a single product, which analyzed correctly for $C_{16}H_{12}N_3SOCl$. This product was formulated as 1-[3-cyano-3-(benzothiazol-2-yl]acetonyl]-pyridinium chloride (**8**).



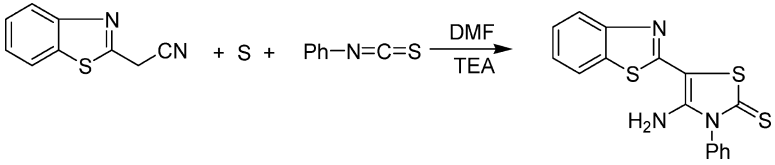
8

SCHEME 5

The structure of **8** was proved by IR and ^1H NMR spectra. Its ^1H NMR (DMSO-d_6) spectrum revealed a singlet band at δ 4.7 ppm due to a CH proton, δ 5.8 ppm attributable to the CH_2 protons, and a multiplet band at δ 7.1–7.8 ppm for four aromatic protons of benzothiazole ring, in addition to a multiplet at δ 8.2–9.0 ppm due to aromatic protons of the pyridine ring.

In addition, its IR spectrum showed absorption frequency at 2220 cm^{-1} due to the C≡N group while the carbonyl absorption function was not observed, which may explain that compound **8** may be exist in the enol form in a solid state.

The thiazoline heterocyclic ring incorporating a benzothiazole moiety was prepared directly from compound **1**. Thus, the treatment of **1** with sulfur metal and phenylisothiocyanate in the presence of an excess of triethylamine[25–26] afforded the corresponding 4-amino-5-(benzo[d]thiazol-2-yl)-3-phenylthiazole-2(3H)-thione (**9**).



9

SCHEME 6

The structure of **9** could be established for the reaction product based on the IR spectrum, which showed absorption bands at 3482 and 3395 cm^{-1} (NH_2). Its ^1H NMR (DMSO-d_6) spectrum revealed a D_2O-exchangable proton at δ 6.12 ppm due to NH_2 protons besides a multiplet at δ 7.22–8.16 ppm due to 9 aromatic protons.

EXPERIMENTAL

Melting points were uncorrected. Elemental analysis was carried out in the Microanalytical Unit Faculty of Science, Cairo University, Cairo, Egypt. IR spectra were recorded on a Pye Unicam SP-1000 cm^{-1} spectrometer using a KBr wafer technique. ^1H NMR spectra were determined on Varian Gemini 200 MHz NMR spectrometers using TMS as an internal standard with $\delta = 0$ ppm. Mass spectra were determined on a GC-MS.QP-100 EX Schimadzye (Japan).

The Synthesis of 2-(Benzo[d]thiazol-2-yl)-4-chloro-3-oxobutanenitrile (2)

In a mixture of 1 (0.01 mole) in absolute ethanol (25 mL) containing a catalytic amount of triethylamine (6 drops) and chloroacetyl chloride (0.01 mole), the mixture was heated over a water bath for 10 min. The obtainable solid product was collected by filtration and crystallized from chloroform-ethanol (1:1) to give compound **2**. Compound **2**: Light brown crystals; yield (96%); m.p. 249°C; IR(cm^{-1})(KBr) 1625 (C=N),

2199 (CN); ^{1}H NMR: (DMSO-d_6): δ=4.5 (s, 2H, CH_2), 4.72 (s, 1H, CH) and 7.45–8.22 (m, 4H, Ar-H); MS: m/z 250 (M^+), 215, 201 (100% base peak), 189, 173, 147, 108, 107. Anal. calcd. for $C_{11}H_7N_2OSCl$: C, 52.45; H, 2.78; N, 11.03. Found: C, 52.70; H, 2.81; N, 11.17.

The Synthesis of 5-Amino-4-(benzo[d]thiazol-2-yl)-1-phenyl-1H-pyrrol-3-ol (3)

To a solution of **2** (0.01 mole) in dimethylformamide (25 mL) a freshly distillated aniline (0.01 mole) was added. The reaction mixture was refluxed for 4 and left to cool at r.t., and poured onto ice cold water (100 mL). The solid product was collected by filtration and recrystallized from dimethylformamide-ethanol (1:1) to obtain (**3**). Compound **3**: white crystals; yield (65%); m.p. 230°C; IR(cm^{-1})(KBr) 3339, 3406 (NH_2), 3381(OH) and 3163 (NH); ^{1}H NMR: (DMSO-d_6): δ = 4.48 (br, 2H, NH_2), 7.3–8.1 (m, 10H, Ar-H), 8.5 (s, 1H, OH); MS: m/z 307 (M^+, base peak), 306, 279, 230, 174, 173, 106. Anal. calcd. for $C_{17}H_{13}N_3OS$: C, 66.45; H, 4.12; N, 13.43. Found: C, 66.43; H, 4.26; N, 13.67.

The Synthesis of 2-Amino-3-chloroacetyl Pyrazolo[5,1-b]benzothiazole (4)

A mixture of **5** (0.01 mole) and hydrazine hydrate (0.012 mole) in dimethylformamide (20 mL) was refluxed for 3 hs. The reaction mixture after cooling was evaporated under reduced pressure, and the residue was triturated with ethanol. The resulting material was collected by filtration and recrystallized from ethanol to give (**4**). Compound **4**: white crystals; yield (48%); mp 165°C; IR(cm^{-1})(KBr) 3339, 3406 (NH_2), 1718 (C=O), 3345, 3478 (NH_2); ^{1}H NMR: (DMSO-d_6): δ = 4.52 (s, 2H, CH_2), 5.64 (br, 2H, NH_2) 7.20–8.01 (m, 4H, Ar-H),; MS: m/z 266 (M^+). Anal. calcd. for $C_{11}H_8ClN_3OS$: C, 49.64; H, 2.98; N, 15.76. Found: C, 49.72; H, 3.03; N, 15.81.

The Synthesis of 4-(benzo[d]thiazol-2-yl)-5-(2-hydroxyethylimino)pyrrolidin-3-one (5)

To a solution of **2** (0.01 mol) in dimethylformamide (20 mL) ethanolamine (0.6 mL, 0.01 mole) was added. The reaction mixture was refluxed for 5 h, left to cool at r.t., and poured onto ice cold water. The solid product was collected by filtration and recrystallized from dimethylformamide-ethanol (1:2) to give (**5**). Compound **5**: orange crystals; yield (74%); mp 244°C; IR(cm^{-1})(KBr) 1704(C=O), 3128, 3896

(NH and OH respectively); ^{1}H NMR: (DMSO-d_6):$\delta = 3.6$–3.7 (m, 4H, CH_2CH_2), 4.0 (s, 2H, CH_2), 5.06 (s, 1H, CH), 7.0–8.0 (m, 4H, Ar-H), 8.3(br, 1H, NH) and 8.68 (s, 1H, OH): MS ($M^+ = 275$). Anal. calcd. for $C_{13}H_{13}N_3O_2S$: C, 57.01; H, 4.69; N, 15.16. Found: C, 56.71; H, 4.76; N, 15.26.

The Synthesis of Ethyl 3-Amino-4-(benzo[d]thiazol-2-yl)-5-oxo-1,4,5,6-tetrahydropyridine-2-carboxylate (6)

A mixture of **2** (0.01 mole), ethyl glycinate hydrochloride (0.01 mol), and sodium acetate (0.82 g, 0.01 mole) in dimethylformamide (25 mL) was refluxed for 6 h. The reaction mixture was left to cool at r.t., and then poured onto ice cold water (100 mL). The precipitated product was collected by filtration and crystallized from dimethylformamide-ethanol (1:1) to yield (**6**). Compound **6**: white crystals; yield (62%); mp 247°C; IR(cm^{-1}) (KBr) 1715 (-COOEt), 3189, 3416 (NH, OH respectively) and 3252, 3398 (NH_2); ^{1}H NMR: (DMSO-d_6):$\delta = 1.2$ (t, 3H, CH_3), 2.8 (s, 2H, CH_2), 3.5–3.8 (br, q, 4H, CH_2 and NH_2), 5.3 (s, 1H, CH), 7.4–8.4 (m, 4H, Ar-H). Anal. calcd. for $C_{15}H_{15}N_3O_3S$: C, 56.76; H, 4.80; N, 13.19. Found: C, 56.77; H, 4.76; N, 13.24.

The Synthesis of 1-[3-Cyano-3-(benzothiazol-2-yl)-acetonyl]pyridium Chloride (8)

Compound **2** (0.01 mol) was refluxed for 30 min in dry pyridine. The resulting solid product was separated as white crystals, collected by filtration, dried well, and recrystallized from pyridine to give (**8**). Compound **8**: white crystals; yield (89%); mp 272°C; IR(cm^{-1})(KBr); 2220 (CN) ^{1}H NMR: (DMSO-d_6):$\delta = 4.7$(s, 1H, CH), 5.8 (s, 2H, CH_2), 2.8 (s, 2H), 7.1–7.8 (m, 4H, benzene-H), 8.2–9.0 (m, 4H, pyridine-H); MS 317 (M^+, 12%), 245 (M^+-COOEt), 214 (15.6%), 213 (5.9%), 201 (18.3%), 174 (100%), 134, 108 (31.5%).

Anal. calcd. for $C_{16}H_{12}ClN_3OS$: C, 58.27; H, 3.67; N, 12.74. Found: C, 58.42; H, 3.59; N, 12.68.

The Synthesis of 4-Amino-5-(benzo[d]thiazol-2-yl)-3-phenylthiazole-2(3H)-thione (9)

A stirred mixture of **1** (0.01 mol), elementary sulfur (0.32 g, 0.01 mol) and phenylisothiocyanate (1.2 mL, 0.01 mol) in dimethylformamide (6.0 mL) was added to triethylamine (6.0 mL) dropwise at 50°C. The reaction mixture was stirred at this temperature for 3 h, and then

cooled to r.t. The resulting crystals were obtained by the addition of a water-acetone mixture (5:1), collected by filtration, and recrystallized from acetic acid to give (**9**). Compound **9**: brown crystals; yield (58%); mp 226°C; IR(cm^{-1})(KBr); 3482, 3395 cm^{-1} (NH_2); ^{1}H NMR: (DMSO-d_6):δ = 6.12 (br, 2H, NH_2), 7.22–8.16 (m, 9H, Ar-H); MS ($M^+ = 341$). Anal. calcd. for $C_{16}H_{11}N_3S_3$: C, 56.09; H, 3.10; N, 12.29. Found: C, 56.28; H, 3.25; N, 12.31.

REFERENCES

[1] M. A. El-Sherbeny, *Arzeneim. Forsch*., **50,** 848 (2000).
[2] S. Shigeta, M. Hosoya, and S. Mochizuki, *Ciba*, *Tokkyo Yakugak Zasshi*, **108,** 856 (1988).
[3] F. Russo and M. Santagati, *Farmaco, Ed. Sci*., **31,** 41 (1976).
[4] K. M. Ghoneim, S. El-Basil, A. N. Osaman, M. M. Said, and S. A. Megahed, *Rev. Roum. Chim*., **36,** 1355 (1991).
[5] S. P. Singh and S. Segal, *Indian J. Chem*., **27B,** 941 (1988).
[6] J. H. Musser, R. E. Brown, B. Love, K. Baily, H. Jones, R. Kahen, F. Haung, A. Khandwala, and M. Leibowitz, *J. Med. Chem*., **27,** 121 (1984).
[7] S. N. Sawhney and O. P. Bansal, *Indian J. Chem*., **15B,** 121 (1977).
[8] H. D. Brown, *US Pat*., **3,** 278, 547 (1966).
[9] Takeda Chemical Industries, Ltd., *Jpn. Kokai Tokkyo Toho*, **532**; *J. Chin. Chem. Soc.,* **47,** 2000 (1984).
[10] H. Okujima, T. Niifuku, H. Betsushor, A. Kyonor, J. Hayashi, A. Tobe, and M. Kobayashi, *Jpn-Kokai Tokkyo Koho*, Jp 05, **59,** 003 (1993).
[11] K. Kato, S. Miki, K. Naruo, and H. Takahashi, *Eur. Pat. Appl. Ep.*, **737,** 671, (1996).
[12] T. Goto, Y. Manome, M. Murata, S. Suzuki, and K. Kojo, *Jpn. Koki Tokkyo Koho Jp*, **11,** 80 155 (1999).
[13] H. Hagen and R. D. Kohler, *Ger. Pat*., **3,** 528, 230 (1987).
[14] M. Lorenz and K. W. Wanken, *Eur. Pat. Appl. Ep.*, **684,** 289 (1995).
[15] M. Lorenz, *Eur. Pat. Appl. Ep.*, **811,** 662 (1997).
[16] O. S. Wolfbeis, I. Trummer, and A. Knierzinger, *Liebigs Ann. Chem.*, **5,** 811 (1981).
[17] T. Papenfuhs, *Ger. Offen*. DE, **3,** 528, 032 (1987).
[18] H. Takasugi, Y. Katsura, Y. Inoue, S. Nishino, and T. Takaya, *Eur. Pat. Appl. Ep.*, **356,** 234 (1990).
[19] J. D. Kendall, R. H. J. Waddington, and G. F. Duffin, *Brit. Pat*., **867,** 592 (1961).
[20] A. A. Fadda, F. A. Amer, M. E. A Zaki, and K. Samir, *Phosphorus, Sulfur, and Silicon*, **155,** 59 (1999).
[21] M. E. A Zaki, A. A. Fadda, K. Samir, and F. A. Amer, *Chemistry of Heterocyclic Compounds,* **39,** 1413 (2003).
[22] V. K. Ahluwahia, P. Sharma, and B. Goyal, *Indian Journal of Chemistry*, **36B,** 920 (1997).
[23] E. V. Resnyanskaya, A. V. Tverdokhlebov, Yu. M. Volovenko, and T. V. Shokol, *Russ. J. Org. Chem*., **40,** 368 (2004).
[24] A. K. El-Shafai and A.M. El-Sayed, *Gazz. Chem. Ital.*, **117,** 385 (1987).
[25] K. Gewald and U. Hain, *East Ger. Pat*., DD, **273,** 441 (1989).
[26] R. M. Mohareb, W. W. Wardakhan, and F. Z. El-Ablack, *J. Chem. Research (S),* **126,** (1994); *J. Chem. Research (M)*, 747 (1994).