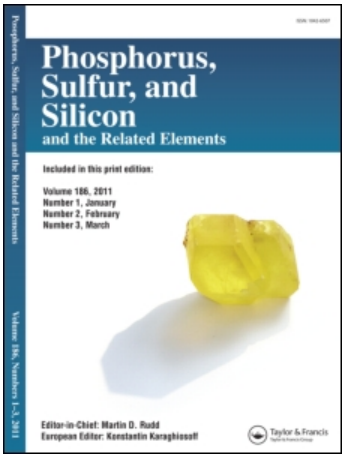

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2-Amino-1,1,3-tricyanopropene in Heterocyclic Synthesis: Novel Synthesis of Thiopyran Pyridinethiones and Nicotinonitrile Derivatives

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2-AMINO-1,1,3-TRICYANOPROPENE IN HETEROCYCLIC SYNTHESIS: NOVEL SYNTHESIS OF THIOPYRAN PYRIDINETHIONES AND NICOTINONITRILE DERIVATIVES

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2-Amino-1,1,3-tricyano-3-bromopropene was obtained from bromination of malononitrile dimer, 2-amino-1,1,3-tricyanopropene with N-bromo-succinimide (NBS). The reactions of this bromo derivative with sodium hydrogen sulfide and thioglycollic acid afforded thiophene and thiopyran derivatives respectively. A novel synthesis of pyridinethione and nicotinonitrile derivatives by using 3-amino-4,4-dicyano-3-butenethioamide as starting material are reported and the synthetic potential of the method is described.

Keywords: Nicotinonitrile; pyridinethiones; thiophene; thiopyran

Pyridinethione and thiophene systems are progressively important derivatives as intermediates for the synthesis of biologically and pharmaceutically active constituents, and are considered as the fundamental key structure units in sulfur containing heterocycles.[1–6]

RESULTS AND DISCUSSION

As a continuation of our program aiming to develop new simple routes to potential biodegradable agrochemicals from laboratory available starting materials,[7–11] we report on the synthesis of thiophene, thiopyran, pyridinethione, and nicotinonitrile derivatives of anticipated biological activity. The key precursors, in such synthetic routes were malononitrile dimmer, 2-amino-1,1,3-tricyanopropene **1**[12] and

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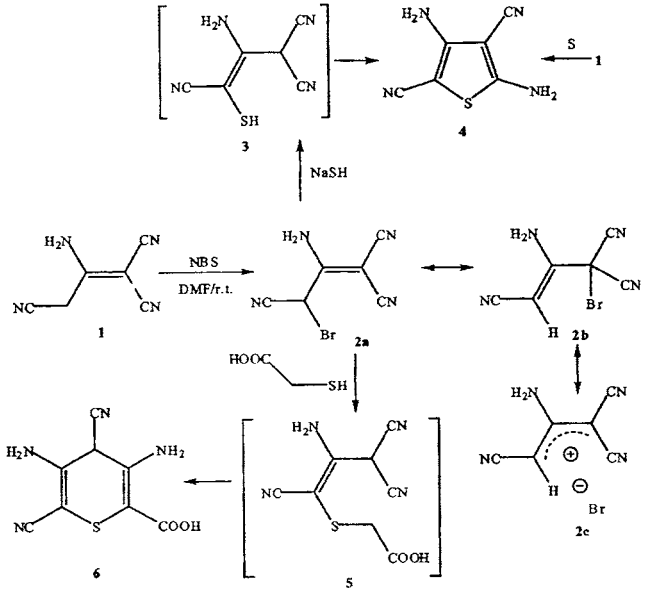
2-amino-1,1,3-tricyano-3-bromo-propene **2**. The interesting structure features of the malaononitrile dimmer **1** have been utilized in a number of transformations. For example, treating of compound **1** with N-bromo-succinimide (NBS) in dimethylformamide (DMF) at room temperature gave the bromoderivative **2** in 68% yield (Scheme 1).



SCHEME 1

The IR spectrum of **2** revealed absorption bands at 3430–3250, 2220, 2205, 2195 cm^{-1}, corresponding to NH_2 and CN groups respectively. The ^1H NMR spectrum of compound **2** showed a singlet for NH_2 at 4.20 and two singlets at 4.82 and 4.92 ppm and integrated for (1H). The appearance of two singlets for this proton may be explained by the presence of two geometrical isomers. It can be suggested that the bromination took place on the methylene group of **1** to produce **2a**, which is interchangeable to **2b** via the ion pair **2c**.[13] In support of the foresaid assumption is the fact that both of the geometrical isomers of **2b** are present in solution, which strongly confirms the presence of the ionic form **2c**. Mass spectral measurements and analytical data are in complete agreement with the substitution product **2** (cf. Experimental).

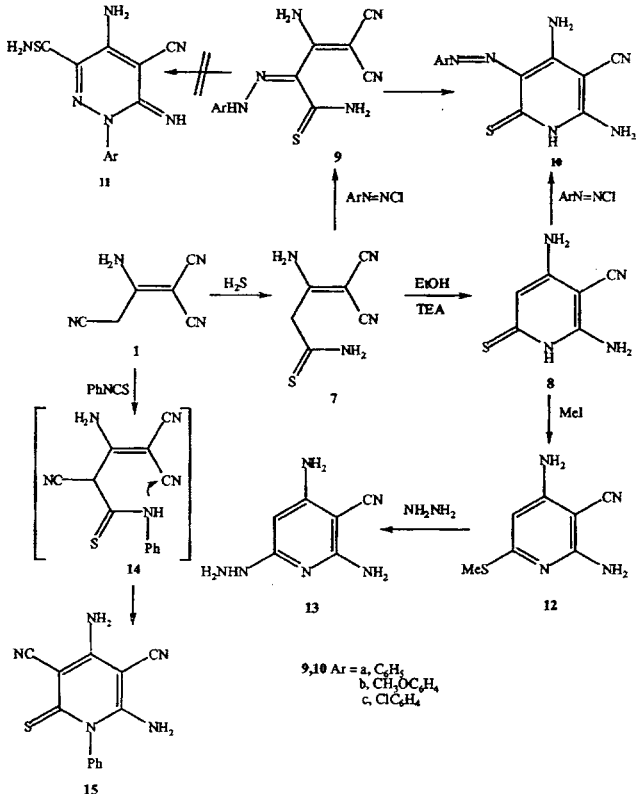
The synthetic potentialities of compound **2** have been explored for other syntheses. Thus compound **2** reacts with sodium hydrogen sulfide in refluxing ethanol to afford 3,5-diaminothiophene-2,4-dicarbonitrile

4. Structure **4** was established based on analytical and spectral data. IR spectrum revealed the presence of stretching mode at 3450–3240 cm^{-1} corresponding to two NH_2 groups and two absorption bands at 2220 and 2210 cm^{-1} attributed to two CN groups. Elemental analysis of this product showed the disappearance of the bromine atom and showed that it is in good agreement with thiophene **4**. It is assumed that the bromine atom in compound **2** is substituted by SH, which brings about cyclization by adding to one of the CN groups. It was found that compound **4** has been previously prepared by the reaction of **1** with elemental sulfur in presence of base.[14]

As expected, the bromo derivative **2** can be converted to thiopyran derivative **6** by the reaction with thioglycollic acid in the presence of a base. Probably, the reactants interact by primary substitution of the bromine atom in **2** by the mercapto group followed by a Dieckmann-Thorpe cyclization of the resulting nonisolable intermediate **5** (Scheme 1). Confirmation of structure **6** was established on their analytical and spectral data.

On the other hand, the reaction of compound **1** with hydrogen sulfide afforded a product of molecular formula $C_6H_6N_4S$. The IR spectrum of the isolated product showed the presence of two NH_2 stretching modes at 3450–3250 cm^{-1} and two CN stretching at 2220, 2205 cm^{-1}, as well as two D_2O exchangeable proton singlets at 2.85 and 4.10 due to two NH_2 protones and a sharp singlet at 2.45 corresponding to methylene protons in ^1H NMR. Based on the above data, the reaction product was identified as 3-amino-4,4-dicycano-3-butenethioamide **7**. Refluxing compound **7** in ethanol in the presence of a catalytic amount of triethylamine afforded the pyridinethione derivative **8**. The formation of **8** is assumed to proceed via Michael addition to yield pyridine-6(1*H*)thione derivative **8**. The structure of **8** was established and confirmed on the basis of elemental analyses and spectral data (cf. Experimental, Scheme 2).

Our investigation was extended to study the reaction of **7** with diazotized aromatic amines in ethanol containing sodium acetate to afford the corresponding hydrazoderivatives **9a–c**. Analytical and spectral data of **9a–c** were in complete agreement with the proposed structures. The cyclization of **9a–c** were conducted by refluxing in 10% ethanolic sodium hydroxide solution to afford 5-arylazopyridine-6(1*H*)thione derivatives compounds **10a–c** not the pyridazinimine derivatives structure **11**. The structures of **10a–c** were further proved via its alternative synthesis. Thus, compound **8** couples smoothly with diazotized aromatic amines to give the corresponding azo derivatives **10a–c**, Compounds **10a–c** prepared via, this route were found to be identical in all respects with those prepared as described before.



SCHEME 2

Compound **8** bearing latent functional substituents were found to be useful for the synthesis of pyridine derivatives. Thus, compound **8** reacted with methyl iodide in sodium ethoxide to afford the corresponding S-substituted derivative **12**. When compound **12** was treated with hydrazine the 2-hydrazino derivatives **13** was obtained. The structures of **12** and **13** were established on basis of their elemental analyses and spectral data.

Subjecting compound **1** to react with phenylisothiocyanate, the corresponding pyridine-2-thione **15** was obtained in reasonable yield. The reaction was assumed to proceed via the intermediacy of the expected acyclic intermediate **14** which readily underwent intramolecualr cyclization to afford the isolated product **15**.

Assignment of structure **15** was based on their consistency with the data obtained from elemental analyses and spectral data. The IR spectrum or **15** showed strong NH_2 stretching modes at 3495–3200 cm^{-1}

corresponding to two NH_2 groups, as well as two typical CN stretching at 2225 and 2215 cm^{-1}. Also, its ^{1}HNMR spectrum exhibited two D_2O exchangeable singlet at 2.76 (2H) and 3.22 (2H) ppm, corresponding to two NH_2 groups, in addition to the aromatic protons 7.05–7.55. from the forgoing results the reaction product was formulated as the 4,6-diamino-1-phenyl-2-thioxo-1,2-dihydro-pyridine-3,5-dicarbonitrile **15** (Scheme 2).

EXPERIMENTAL

General

Melting points were determined on an electrothermal (9100) apparatus and are uncorrected. The IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer. The ^{1}H-NMR spectra were taken on a VXR 300 MHz spectrometer in DMSO-d_6 using TMS as internal standard. Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (70 ev). Elemental analyses were carried out by the Microanalytical Center at Cairo University. 2-Amino-1,1,3-tricycanopropene **1** was prepared as described in the literature.[12,14]

2-Amino-1,1,3-tricyano-3-bromopropene 2

To a solution of 13.2 g of **1** (100 mmol) in 75 mL of dry DMF was added 17.8 g (100 mmol) of NBS. The reaction mixture was stirred for 24 h at room temperature. The mixture was then poured on ice-cold water and acidified with a few drops of HCl whereupon precipitated appeared which was filtered off and recrystallized from ethanol to afford the title compound. (14.35 g, 68%), m.p. 125–127°C (EtOH); [Found: C, 34.10; H, 1.50; N, 26.50; Br, 37.90. $C_6H_3BrN_4$ requires C, 34.15; H, 1.43; N, 26.55; Br, 37.87.; ν_{max} (KBr) 3430–3250 (NH_2), 2220, 2205, 2195 (CN); δ_H (300 MHz, DMSO-d_6) 4.20 (s, 2H, NH_2, D_2O-exchangable), 4.82, 4.92 (2s,1H). m/e, 210, 212.

3,5-Diaminothiophene-2,4-dicarbonitrile 4

Method A: Compound **4** was prepared through coupling of compound **1** with elemental sulfur as described in the literature,[14] m.p. 252–254°C.

Method B: To a solution of **2** (2.11 g, 10 mmol) in 25 mL of ethanol was added 0.56 g (10 mmol) of sodium hydrogen sulfide. The reaction mixture was heated on water bath for 1 h. After cooling, the mixture was poured on ice-cold water, the solid product was collected by filtration and recrystallized from ethanol. (1.31 g, 80%), m.p. 250–252°C (EtOH);

[Found: C, 44.10; H, 2.60; N, 34.20; S, 19.60. $C_6H_4N_4S$, requires C, 43.89; H, 2.46; N, 34.12; S, 16.53.; ν_{max} (KBr) 3490–3350 (NH_2), 2220, 2200 (CN); δ_H (300 MHz, DMSO-d_6) 4.20 (s, 2H, NH_2, D_2O-exchangable), 5.40 (s, 2H, NH_2, D_2O-exchangable). m/e, 164.

3,5-Diamino-4,6-dicyano-4H-thiopyran-2-carboxylic acid 6

To a stirred solution of **2** (2.11 g, 10 mmol) and thioglycollic acid (10 mmol) in 30 mL pyridine was heated under reflux for 3 h. The solid product was collected by filtration and recrystallized from ethanol. (1.62 g, 73%), m.p. 210–212°C (EtOH); [Found: C, 43.30; H, 2.80; N, 25.10; S, 14.50. $C_8H_6N_4O_2S$, requires C, 43.24; H, 2.72; N, 25.21; S, 14.43.; ν_{max} (KBr) 3420–3250 (NH_2), 2215, 2205 (CN), 1685 (CO); δ_H (300 MHz, DMSO-d_6) 2.90 (s, 2H, NH_2), 3.35 (s, 2H, NH_2), 4.52 (s, 1H, H4), 10.00 (s, 1H, COOH).

3-Amino-4,4-dicyano-3-butenethioamide 7

Hydrogen sulfide gas was bubbled at a constant stream in a solution of **1** (100 mmol) in absolute ethanol containing a catalytic amount of piperidine for 3 h. The solid product which precipitated was collected by filtration and crystallized from EtOH-DMF to afford **7**. (14.10 g, 85%), m.p. 280–284°C (EtOH-DMF); [Found: C, 43.40; H, 3.80; N, 33.60; S, 19.20. $C_6H_6N_4S$, requires C, 43.36; H, 3.64; N, 33.71; S, 19.29.; ν_{max} (KBr) 3450–3250 (NH_2), 2220, 2205 (CN), 1550 (CS); δ_H (300 MHz, DMSO-d_6) 2.45 (s, 2H), 2.85 (s, 2H, NH_2, D_2O-exchangable), 4.10 (s, 2H, NH_2, D_2O-exchangable); m/e, 166.

2,4-Diamino-6-thioxo-1,6-dihydropyridine-3-carbonitrile 8

A solution of **7** (10 mmol) in 25 mL ethanol containing catalytic amount of triethylamine was refluxed for 4 h. The solid product obtained was collected by filtration and crystallized from ethanol and few drops of DMF to afford **8**. (1.44 g, 87%), m.p. 190–192°C (EtOH); [Found: C, 43.50; H, 3.60; N, 33.80; S, 19.30. $C_6H_6H_4S$, requires C, 43.36; H, 3.64; N, 33.71; S, 19.29.; ν_{max} (KBr) 3430, 3350–3200 (NH_2, NH), 2210 (CN), 1540 (CS); δ_H (300 MHz, DMSO-d_6) 2.95 (s, 2H, NH_2), 3.47 (s, 2H, NH_2), 4.82 (s, 1H), 5.88 (br, 1H, NH).

3-Amino-4,4-dicyano-2-arylhydrazono-3-butenethioamide 9a–c

General Procedure. A solution of **7** (10 mmol) in 35 mL of ethanol containing sodium acetate 2.5 g was cooled to 0°C and then treated gradually with a cold solution of aryldiazonium chloride [prepared from arylamines (aniline, p-anisidine and p-chloroaniline, 10 mmol) and the

appropriate quantity of HCl and $NaNO_2$]. The solid product formed was collected by filtration, washed with cold water, dried, and recrystallized from the appropriate solvent.

9a: (1.75 g, 65%), m.p. 290–294°C (EtOH-DMF); [Found: C, 53.50; H, 3.70; N, 31.00; S, 11.90. $C_{12}H_{10}N_6S$, requires C, 53.32; H, 3.73; N, 31.09; S, 11.86.; ν_{max} (KBr) 3540–3280 (NH_2 NH), 2225, 2208 (CN), 1550 (CS); δ_H (300 MHz, DMSO-d_6) 2.81 (s, 2H, NH_2), 3.35 (s, 2H, NH_2), 6.95–7.38 (m, 6H, Ar-H, NH).

9b: (1.65 g, 55%), m.p. > 300°C (DMF); [Found: C, 52.10; H, 4.20; N, 27.90; S, 10.60. $C_{13}H_{12}N_6OS$, requires C, 51.99; H, 4.03; N, 27.98; S, 10.68.; ν_{max} (KBr) 3560–3190 (NH_2, NH), 2215, 2205 (CN), 1540 (CS); δ_H (300 MHz, DMSO-d_6) 2.80(s, 2H, NH_2), 3.24 (s, 2H, NH_2), 3.80 (s, 3H, OCH_3), 7.10–7.45 (m, 5H, Ar-H, NH); m/e, 300.

9c: (2.13 g, 70%), m.p. 265°C (EtOH-DMF); [Found: C, 47.30; H, 2.90; N, 27.50; Cl, 11.60; S, 10.40. $C_{12}H_9N_6ClS$, requires C, 47.29; H, 2.98; N, 27.58; Cl, 11.63; S, 10.52.; ν_{max} (KBr) 3520, 3410–3270 (NH_2, NH), 2220, 2205 (CN), 1540 (CS); δ_H (300 MHz, DMSO-d_6) 3.15 (s, 2H, NH_2), 4.10 (s, 2H, NH_2), 6.90–7.44 (m, 4H, Ar-H), 7.65 (br, 1H, NH).

2,4-Diamino-5-Arylazo-6-thioxo-1,6-dihydropyridine-3-carbonitrile 10a–c

Method A: To a solution of each of **9a–c** (10 mmol) in 20 mL of ethanol was added 5 mL of 10% sodium hydroxide solution. The reaction mixture was refluxed in each case for 3 h then left to cool over night. The solid products formed were collected by filtration, washed with cold water, and crystallized from a proper solvent to afforde the corresponding 5-aylazopyridine-6(1*H*)thione derivatives **10a–c**.

Method B: A cold solution of diazotized aromatic amine prepared as previously described, were added to a cold solution of **8** in ethanol (30 mL) and anhydrous sodium acetate (3.0 g) portionwise during aperiod of 30 min. The reaction mixture was stirred for further 1 h in an ice bath. After stirring was completed, the solid product obtained was filtered off, washed with cold water, and crystallized from the proper solvent to give **10a–c**.

10a: (2.0 g, 73%), m.p. 225°C (EtOH-DMF); [Found: C, 53.40; H, 3.90; N, 31.20; S, 11.80. $C_{12}H_{10}N_6S$, requires C, 53.32; H, 3.73; N, 31.09; S, 11.86.; ν_{max} (KBr) 3640, 3480–3190 (NH_2, NH), 2215 (CN), 1545 (CS); δ_H (300 MHz, DMSO-d_6) 3.10 (s, 2H, NH_2), 3.90 (s, 2H, NH_2), 7.20–7.55 (m, 5H, Ar-H), 7.95 (s, 1H, NH).

10b: (1.92 g, 64%), m.p. 245–247°C (AcOH); [Found: C, 52.00; H, 4.10; N, 28.10; S, 10.60. $C_{13}H_{12}N_6OS$, requires C, 51.99; H, 4.03; N, 27.98; S, 10.68.; ν_{max} (KBr) 3560–3190 (NH_2, NH), 2212 (CN), 1540 (CS).

10c: (2.0 g, 68%), m.p. 238–240°C (EtOH-DMF); [Found: C, 47.40; H, 3.10; N, 27.60; Cl, 11.70 S, 10.60. $C_{12}H_9N_6ClS$, requires C, 47.29; H, 2.98; N, 27.58; Cl, 11.63; S, 10.52.; ν_{max} (KBr) 3530, 3390–3250 (NH_2, NH), 2210 (CN), 1540 (CS).

2,4-Diamino-6-methylsulfanyl nicotinnitrile 12

To a solution of sodium ethoxide (prepared by dissolving sodium metal [10 mmol] in absolute ethanol [10 mL]), the equivalent amount of **8** dissolved in 10 mL DMF were added. The reaction mixture was refluxed for 15 min, cooled and then methyl iodide (12 mmol) was added. The solution was stirred for 1 h at room temperature and allowed to stand overnight. The product was isolated by neutralizating the reaction mixture with dil. HCl and crystallizing from dioxane. (1.19 g, 66%), m.p. 175°C (Dioxane); [Found: C, 46.80; H, 4.60; N, 31.00; S, 17.90. $C_7H_8N_4S$, requires C, 46.65; H, 4.47; N, 31.09; S, 17.79. ν_{max} (KBr) 3350–3190 (NH_2), 2215 (CN); δ_H (300 MHz, DMSO-d_6) 2.44 (s, 3H, CH_3), 4.62 (s, 2H, NH_2), 5.55 (s, 2H, NH_2), 6.84 (s, 1H, H5).

2,4-Diamino-6-hydrazinonicotinonitrile 13

An equivalent mixture of **12** and hydrazine hydrate (10 mmol) was stirred in ethanol 20 mL for 1 h. The product that separated on cooling was filtered and recrystallized from DMF-EtOH. (0.92 g, 56%), m.p. 265°C (EtOH-DMF); [Found: C, 44.10; H, 5.00; N, 51.30. $C_6H_8N_6$, requires C, 43.90; H, 4.91; N, 51.19.; ν_{max} (KBr) 3640, 3460–3190 (NH_2, NH), 2210 (CN); m/e, 164.

4,6-Diamino-1-phenyl-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile 15

To a solution of **1** (10 mmol) in DMF 20 mL, a catalytic amount of triethylamine was added phenylisothiocyanate (10 mmol) and the reaction mixture was refluxed for 2 h. The precipitated solid obtained on cooling was filtered off and recrystallized from AcOH. (2.14 g, 80%), m.p. 250–252°C (AcOH); [Found: C, 58.30; H, 3.40; N, 26.20; S, 11.80. $C_{13}H_9N_5S$, requires C, 58.41; H, 3.39; N, 26.20; S, 12.00.; ν_{max} (KBr) 3495–3210 (NH_2), 2225, 2215 (CN), 1550 (CS); δ_H (300 MHz, DMSO-d_6) 2.76 (s, 2H, NH_2, D_20-exchangable), 3.22 (s, 2H, NH_2, D_2O-exchangable), 7.05–7.55 (m, 5H, Ar-H); m/e, 267.

REFERENCES

[1] A. Esnu, Ger. 3,433,403 (1986); *Chem. Abstr.*, **105,** 115047 (1986).
[2] C. S. Schneider, K. H. Weber, H. Daniel, W. D. Bechtel, and D. Boeke, *J. Med. Chem.*, **27,** 1150 (1984).

[3] E. C. Taylor, C. C. Palmert, T. J. George, S. R. Fletcher, C. P. Tseng, P. J. Harrington, and G. P. Beardsley, *J. Org. Chem.*, **48,** 4852 (1983).
[4] C. C. Cheng, *Progress in Midicinal Chemistry*, edited by G. P. Ellis and G. B. West (Amsterdam, The Netherlands, 1989), vol. 25, p. 25.
[5] G. D. Madding and M. D. Thompson, *J. Heterocyl. Chem.*, **24,** 581 (1987).
[6] C. J. Shishoo, M. B. Devani, V. S. Bhadti, K. S. Jain, and S. Anathan, *J. Heterocycl. Chem.*, **27,** 119 (1990).
[7] F. M. Abdelrazek, A. M. Salah, and Z. E. Elbazza, *Arch. Pharm.* (*Weinheim*), **325,** 301 (1992).
[8] F. M. Abdelrazek and A. M. Salah, *Bull. Chem. Soc. Jpn.*, **66,** 1722 (1993).
[9] F. M. Abdelrazek, A. M. Salah El-Din, and A. E. Mekky, *Tetrahedron*, **57,** 1813 (2001).
[10] F. M. Abdelrazek, A. M. Salah El-Din, and A. E. Mekky, *Tetrahedron*, **57,** 6787 (2001).
[11] A. M. Salah El-Din, *Sulfur Letters*, **26,** 35 (2003).
[12] R. A. Gabroni, D. D. Coffman, and E. G. Howard, *J. Amer. Chem. Soc.*, **80,** 2838 (1958).
[13] F. M. Abdelrazek and M. S. Bahbouh, *Phosphorus, Sulfur and Silicon*, **116,** 235 (1996).
[14] K. Gewald, M. Kleinert, B. Thiele, and M. H. Entschel, *J. Prakt. Chem.*, **314,** 303 (1972).