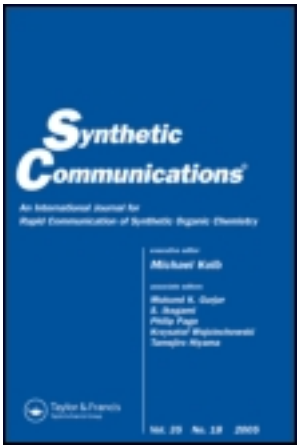


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Heterocyclic Synthesis with Nitriles: Synthesis of Some New Thiophene, Pyridazine, Oxazine, Thiopyran, Pyrrole, and Pyrrolo[1,2-b]pyridazine Derivatives

Fathy M. Abdelrazek [a]

[a] Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt

Version of record first published: 18 Aug 2006

To cite this article: Fathy M. Abdelrazek (2005): Heterocyclic Synthesis with Nitriles: Synthesis of Some New Thiophene, Pyridazine, Oxazine, Thiopyran, Pyrrole, and Pyrrolo[1,2-b]pyridazine Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 35:17, 2251-2258

To link to this article: http://dx.doi.org/10.1080/00397910500184727

Synthetic Communications®, 35: 2251–2258, 2005

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500184727

Heterocyclic Synthesis with Nitriles: Synthesis of Some New Thiophene, Pyridazine, Oxazine, Thiopyran, Pyrrole, and Pyrrolo[1,2-b]pyridazine Derivatives

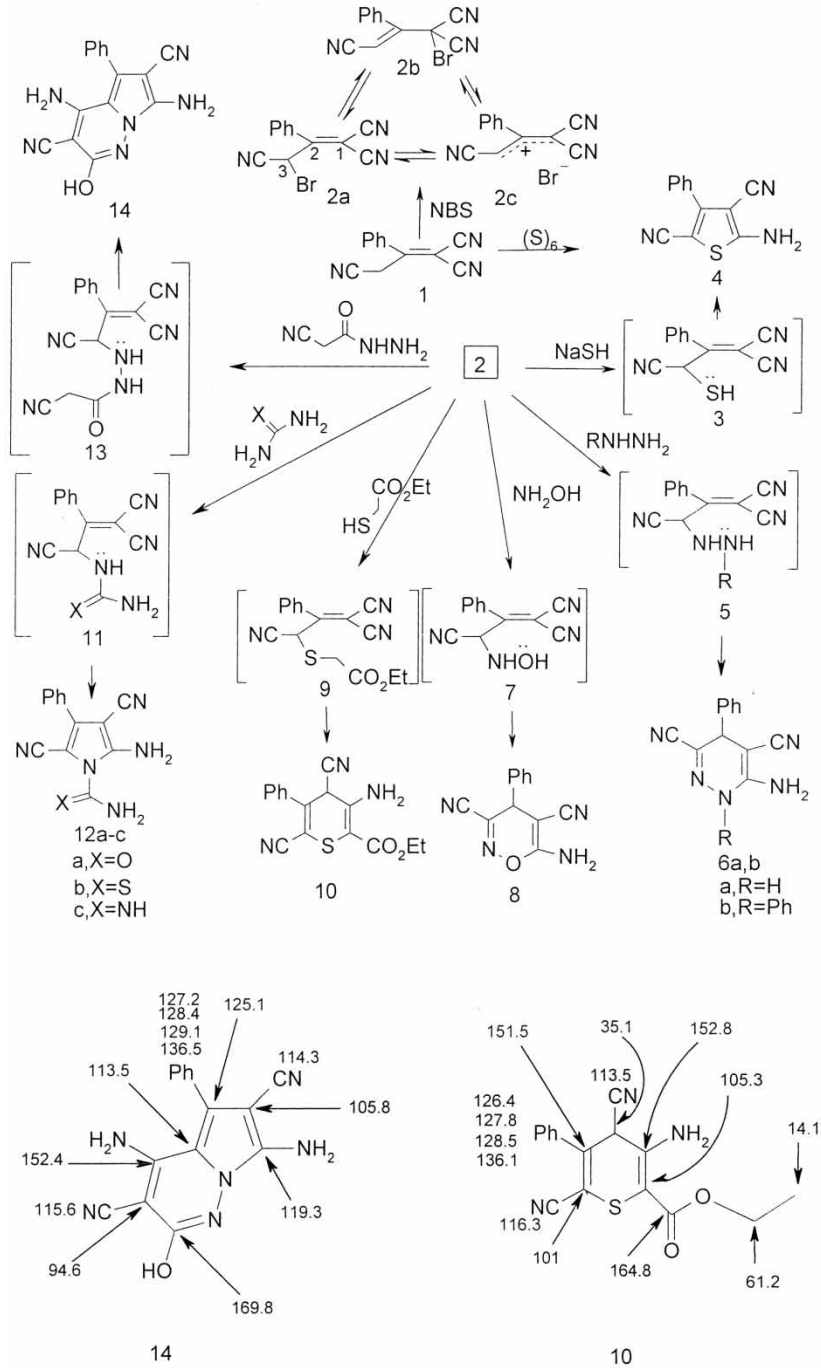
Fathy M. Abdelrazek
Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt

Abstract: 2-Phenyl-1,1,3-tricyanopropene[α-(cyanomethyl)benzylidene-malononitrile] undergoes bromination with N-bromosuccinimide (NBS) to afford 2-phenyl-1,1,3-tricyano-3-bromopropene: [α(bromocyanomethyl)benzylidene malononitrile]. This bromo derivative undergoes reactions with sodium hydrogen sulfide, hydrazine hydrate, phenyl hydrazine, hydroxylamine hydrochloride, ethyl thioglycollate, urea derivatives, and cyanacetohydrazide to afford thiophene, 4H-pyridazines, 4H-oxazine and 4H-thiopyran, N-substituted pyrrole, and pyrrolo[1,2-b]pyridazine derivatives respectively.

Keywords: Thiophene, pyridazine, oxazine, thiopyran, pyrrole derivatives

In the past few years we have been involved in a program aiming to develop new, simple procedures for the synthesis of functionally substituted heterocycles of anticipated biological activity that can be used as biodegradable agrochemicals, from available laboratory starting materials.[1–4] In the context of this program some new functionally substituted pyridazine, pyrrole, and pyrrolo-fused derivatives were required. α-(Cyanomethyl) benzylidenemalononitrile **1**[5] (Scheme 1) seemed to be a good candidate to fulfill our objective via

Received in the UK December 8, 2004
This work has been presented at the 9th Ibn Sina international conference on pure and applied heterocyclic chemistry, held 11–14 December, 2004 at Sharm El Sheikh, Egypt, and organized by the Egyptian Society of Heterocyclic Chemistry, Conference Book p. 194.
Address correspondence to Fathy M. Abdelrazek, Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt. E-mail: prof_fmrazek@yahoo.com



Scheme 1.

brominating and then reacting the bromo derivative with suitable reagents. Thus, compound **1** was allowed to react with N-bromosuccinimide in dimethylformamide (DMF) at room temperature to afford the bromo derivative **2** (Scheme 1) in 70% yield. The IR spectrum of **2** showed absorption bands at ν_{max} 2215, 2207, and 2198 cm^{-1}, corresponding to CN groups, respectively. The ^1H NMR spectrum of this bromo derivative revealed an aromatic multiplet (5H) at $\delta = 7.10-7.35$ and two singlets at $\delta = 4.95$ and 5.10 ppm integrated for (1H). The appearance of these two singlets for this proton may be attributed to the presence of two position isomers. These data can only be interpreted in terms of the allylic rearrangement product **2b**. It can be assumed that the bromination took place on the methylene group of **1** to afford **2a**. In solution, structure **2a** seems to be interchangeable with **2b** via the ion pair **2c** and both structures (**2a** and **2b**) are present in a state of dynamic equilibrium. In support of this assumption is the fact that both of the position isomers **2a** and **2b** are present in solution (from the ^1H NMR and ^{13}C NMR data; see the experimental section). Furthermore, all nucleophilic substitution products of **2** show that the attack is on C-3, which agrees with an SN_1 mechanism in which the Br^- is lost in the first step, leaving the allyl cation, which is then attacked by the nucleophile. The direction of attack is apparently controlled by the steric factors, which favor the attack on C-3. Mass spectral measurements and analytical data are in complete agreement with structures **2a and 2b** (see the experimental section). Analogous behavior of a similar bromo derivative has been previously observed.[6]

Compound **2** reacts with sodium hydrogen sulfide in refluxing ethanol to afford a dark yellowish-brown solid product. The IR spectrum of this product revealed the presence of amino and cyano absorption bands at ν 3450–3350 (NH_2) and 2215 and 2208 (CN) cm^{-1}. Elemental analysis of this product showed the disappearance of the bromine atom and showed that it is in good agreement with structure **4** (Scheme 1). It is assumed that the bromine atom in compound **2** is substituted by SH to afford the intermediate **3**, which brings about cyclization by addition to one of the CN groups under these basic conditions to afford the thiophene derivative **4**. Mass spectral measurements and the ^1H NMR spectrum are consistent with structure **4**. Compound **4** could also be obtained by reacting **1** with elemental sulphur in presence of a basic catalyst according to the literature methods.[7] The identity of the two products was inferred from mp, TLC analysis, and analytical data.

Compound **2** reacts with hydrazine hydrate, phenyl hydrazine, hydroxylamine hydrochloride, and ethyl thioglycollate in the presence of sodium acetate to afford dark-colored solid products. Structures **6a, 6b**, **8**, and **10** were assigned to these products respectively on the basis of their analytical and spectral data (experimental section). The formation of these products is assumed to proceed via the initial elimination of HBr to afford the acyclic intermediates **5**, **7**, and **9** respectively, followed by either a Michael or a Thorpe-Ziegler[8] cyclization to afford the final isolable products (Scheme 1). This behavior is similar to a previously reported work on related systems.[6,9–11]

Pyrroles and fused pyrrole derivatives have recently received considerable attention because of their synthetic and pharmaceutical importance, and different approaches for their synthesis have been developed.[12,13] In the past few years we have reported several syntheses of pyrrole derivatives.[14,15] In the present work we explore the synthetic potentialities of **2** to obtain some novel N-substituted pyrroles and pyrrolo-fused pyridazine. Thus, compound **2** was allowed to react with either urea, thiourea, or guanidine to afford pyrrole N-amide, N-thioamide, or N-amidine derivative **12a–c** respectively presumably via the acyclic intermediates **11.** The reaction of **2** with cyanoacetohydrazide apparently follows the same pathway to afford the nonisolable acyclic intermediate **13** but in this case a further cyclization took place via the addition of the active methylene to the CN group to afford the pyrrolo[1,2-b]pyridazine derivative **14**. Elemental analyses and spectral data are in complete agreement with the proposed structures **12a–c** and **14** (see the experimental section).

EXPERIMENTAL

Melting points were determined on an electrothermal (9100) apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin-Elmer 1430 spectrophotometer. The ^{1}HNMR and ^{13}CNMR spectra were taken on a Varian Gemini 300-MHz spectrometer in DMSO-d_6 using TMS as internal standard and chemical shifts are expressed in δ (ppm) values. Assignments were made by correlation of the off-resonance decoupled ^{13}CNMR spectra and determination of the ^{1}H chemical shifts. 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, Egypt.

Bromination of l: Preparation of 2-Phenyl-1,1,3-tricyano-3-bromopropene 2

To a solution of 1.93 g (0.01 mol) of **1** in 25 mL of dry DMF was added 1.78 g (0.01 mol) of NBS. The reaction mixture was stirred for 4 h at room temperature and then left overnight. The mixture was then poured on ice-cold water and acidified with a few drops of HC1 whereupon a solid precipitate appeared, which was filtered off and recrystallized from ethanol to afford 1.9 g, (70%) of **2** as reddish-violet crystalline solid, mp 185–187°C. Found: C, 52.65; H, 2.45; Br, 29.20; N, 15.40. $C_{12}H_6BrN_3$ (m/e 271 and 273) requires C, 52.97; H, 2.22; Br, 29.37; N, 15.44. ν_{max} 2215, 2207, 2198 (CN) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 4.95, 5.10 (2s, 1H), 7.10–7.35 (m, 5H, phenyl H). δ C 35.45 (d), 92.8 (d) (C-3), 114.90, 116.45, 117.20 (CN groups), 126.85–134.20 (arom. C), 134.45 (s), 43.42 (s) (C-1), 172.28 (s), 163.5 (s) (C-2).

2-Amino-4-phenylthiophene-3,5-dicarbonitrile 4

To a solution of 2.72 g (0.01 mol) of **2** in 25 mL of ethanol was added 0.56 g (0.01 mol) of sodium hydrogen sulfide and the reaction mixture was heated on a water bath for 1 h. The mixture was allowed to cool down, then poured on ice-cold water and acidified with HC1 unntil neutral. The dark greenish-brown precipitate that had formed was filtered off and recrystallized from ethanol to afford 1.5 g (67%) of **4**, mp 242–244°C. Found: C, 64.10; H, 3.20; N, 18.40; S, 14.20. $C_{12}H_7N_3S$ (m/e = 225) requires C, 63.98; H, 3.13; N, 18.65; S, 14.23. ν_{max} (KBr) 3450 and 3350 (NH_2), 2208, 2215 (CN) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 5.5 (s, 2H, NH_2, exch.), 7.18–7.50 (m, 5H, arom. H). This compound was found to be identical with an authentic sample obtained from the reaction of **1** with elemental sulfur as described in the literature.[7]

Reaction of 2 with Hydrazine Hydrate and Phenyl Hydrazine (General Procedure)

To a solution of 2.72 g (0.01 mol) of **2** in 25 mL of ethanol was added an excess of hydrazine hydrate (~2 mL) or 1.08 g (0.01 mol) of phenyl hydrazine, and the reaction mixture was refluxed for 2 h in each case, after which it was left overnight. The solid precipitates that formed were filtered off and recrystallized from EtOH/DMF (1 : 1) to afford **6a** and **6b** respectively.

6-Amino-4-phenyl-1,4-dihydropyridazine-3,5-dicarbonitrile **6a**

Brown crystalline solid, mp 201–203°C (EtOH/DMF) (1.7 g, 75%). Found: C, 64.50; H, 4.10; N, 31.50. $C_{12}H_9N_5$ (m/e = 223) requires C, 64.56; H, 4.06; N, 31.37. ν_{max} (KBr) 3450–3255 (NH and NH2), 2222, 2217 (CN). δ_H (300 MHz, DMSO-d_6) 3.95 (s, 1H,4-H), 4.4 (s, 2H, NH_2, D_2O exch.), 7.1–7.4 (m, 5H, arom. H), 8.1 (bs, 1H, NH, exch).

6-Ammo-1,4-diphenyl-1,4- dihydropyridazine-3,5-dicarbonitrile **6b**

Coffee-brown crystalline solid, mp 232–233°C (EtOH/DMF) (2.3 g, 76%). Found: C, 72.50; H, 4.50; N, 23.60. $C_{18}H_{13}N_5$ (m/e = 299), requires C, 72.23; H, 4.38; N, 23.40. ν_{max} (KBr) 3400–3200 (NH_2), 2215 and 2205 (CN) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 4.0 (s, 1H, 4-H), 6.52–7.65 (2 m, 10H, arom. H), 7.80 (s, 2H, NH_2, exch).

6-Amino-4-phenyl-4H-1,2-oxazine-3,5-dicarbonitrile 8

To a mixture of 2.72 g (0.01 mol) of **2** and 0.7 g (0.01 mol) of hydroxylamine hydrochloride in 30 mL of ethanol was added a solution of potassium carbonate (2.76 g; 0.02 mol in a minimum amount of water), and the reaction

mixture was refluxed for 2 h. The mixture was left to cool to room temperature, then poured on crushed ice and neutralized with HC1. The brownish precipitate that appeared was filtered off and recrystallized from ethanol to give 1.5 g (70%) of **8**, mp 169–170°C (EtOH). Found: C, 64.50; H, 3.75; N, 25.10. $C_{12}H_8N_4O$ (m/e = 224) requires C, 64.28; H, 3.60; N, 24.99. ν_{max} (KBr) 3441–3220 (NH_2), 2225 and 2209 (CN) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 4.16 (s, 1H, 4-H), 7.05–7.25 (m, 5H, arom. H), 7.84 (s, 2H, NH_2).

Ethyl 3-Amino-4,6-dicyano-5-phenyl -4H-thiopyran-2-carboxylate 10

To a mixture of 2.72 g (0.01 mol) of **2** and 1.20 g (0.01 mol) of ethyl thioglycollate in 30 mL of ethanol was added 1.64 g (0.02 mol) of sodium acetate. The mixture was stirred at room temperature for 4 h, and then was poured on crushed ice and neutralized with HC1. The dark-colored precipitate thus formed was filtered off and recrystallized to afford 2 g (65%) of **10**, brown crystalline solid, mp 185–187°C. Found: C, 61.50; H, 3.90; N, 13.40; S, 10.20. $C_{16}H_{13}N_3O_2S$ (m/e = 311) requires C, 61.72; H, 4.21; N, 13.50; S, 10.30. ν_{max} (KBr) 3425–3255 (NH2), 2199 and 2210 (CN), 1705 (C═O) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 1.35 (t, $J = 7$ Hz, 3H, Me), 4.05 (s, 1H, 4-H), 4.2 (q, $J = 7$ Hz, 2H, CH_2), 7.10–7.35 (m, 5H, arom. H), 8.4 (s, 2H, NH_2); δ C; 14.1(q), 35.1(d), 61.2(t), 101(s), 105.3(s), 113.5(s), 116.3(s), 126.4(d), 127.8(d), 128.5(d), 136.1(s), 152.8(s), 164.8(s) (cf. Scheme 1).

Reaction of 2 with Urea Derivatives and Cyanoacetohydrazide (General Procedure)

To a solution of **2** (2.72 g; 0.01 mol) in 30 ml of DMF was added 0.01 mol of urea, thiourea, guanidine nitrate, or cyanoacetohydrazide followed by a catalytic amount of triethylamine (0.01 mol of the same reagent in the case of guanidine nitrate). The respective reaction mixtures were refluxed for 3 h, left to cool, poured on cold water, and neutralized with HC1. The precipitates were filtered off and recrystallized to afford the following.

2-Amino-3,5-dicyano-4-phenylpyrrole-N-carboxamide **12a**

Grey crystalline solid, mp 215–217°C (EtOH/DMF) (1.76 g, 70%). Found: C, 62.50; H, 3.50; N, 27.60. $C_{13}H_9N_5O$ (m/e = 251) requires C, 62.15; H, 3.61; N, 27.87. ν_{max} (KBr) 3400–3220 (NH_2), 2212 and 2200 (CN), 1660 (C═O) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 4.8 (s, 2H, NH_2), 7.12–7.56 (m, 5H, arom. H), 8.32 (s, 2H, NH_2, exch).

2-Amino 3,5-dicyano-4-phenylpyrrole-N-thiocarboxamide **12b**

Reddish-brown crystalline solid, mp 187–189°C (EtOH/DMF) (1.9 g, 72%. Found: C, 58.50; H, 3.50; N, 26.60; S, 12.40. $C_{13}H_9N_5S$ (m/e = 267)

requires C, 58.41; H, 3.39; N, 26.20; S, 12.00. ν_{max} (KBr) 3390–3210 (NH_2), 2210 and 2200 (CN) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 5.1 (s, 2H, NH_2), 7.15–7.55 (m, 5H, arom. H), 8.30 (s, 2H, NH_2, exch).

2-Amino-3,5-dicyano-4-phenylpyrrole-N-carboxamidine **12c**

Yellowish-brown crystalline solid, mp 267–268°C (EtOH/DMF) (1.85 g, 74%). Found: C, 62.60; H, 4.30; N, 33.60. $C_{13}H_{10}N_6$ (m/e = 250) requires C, 62.39; H, 4.03; N, 33.58. ν_{max} (KBr) 3380–3185 (NH_2 and NH), 2215 and 2205 (CN) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 4.9 (s, 2H, NH_2), 7.1–7.5 (m, 5H, arom. H), 8.2 (s, 2H, NH_2), 8.65 (s, 1H, NH).

4,7-Diamino-2-hydroxy-5-phenylpyrrolo[1,2-6b]pyridiazine-3,6-dicarbonitrile **14**

Brown crystalline solid, mp 292–293°C (EtOH/DMF) (2.0 g, 69%. Found: C, 62.20; H, 3.50; N, 28.60. $C_{15}H_{10}N_6O$ (m/e = 290) requires C, 62.06; H, 3.47; N, 28.95. ν_{max} (KBr) 3460–3220 (NH_2 and OH), 2220 and 2205 (CN) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 4.8 (s, 2H, NH_2), 6.2 (s,1H, OH), 7.2–7.6 (m, 5H, arom. H), 8.32 (s, 2H, NH_2, exch.); δ C; 94.6(s), 105.8(s), 113.5(s), 114.3(s), 115.6(s), 119.3(s), 125.1(s), 127.2(d), 128.4(d), 129.1(d), 136.5(s), 152,4(s), 169.8(s) (cf. Scheme 1).

ACKNOWLEDGMENT

The author thanks the Alexander von Humboldt Foundation (Germany) for granting a fellowship, and the hospitality of Professor P. Metz, Institut für Organische Chemie, TU Dresden, is also highly appreciated.

REFERENCES

1. Abdelrazek, F. M. Heterocyclic synthesis with nitriles: A novel synthesis of some thiophene and thieno[2,3-d]pyrimidine derivatives. *Z. Naturforsch.* **1989**, *44b*, 488–492.
2. Abdelrazek, F. M.; Salah, A. M. Heterocyclic synthesis with nitriles: Synthesis of some new mercapto-substituted heterocycles from alkylidenemalononitrile. *Bull. Chem. Soc. Jpn.* **1993**, *66* (6), 1722–1726.
3. Abdelrazek, F. M.; Metwally, N. H. The reaction of ethyl benzoylacetate with ortho-substituted anilines. *Afinidad* **2004**, *61* (510), 134–138.
4. Abdelrazek, F. M.; Metz, P.; Farrag, E. K. Synthesis and molluscicidal activity of 5-oxo-5,6,7,8-tetrahydro-4H-chromene derivatives. *Arch. Pharm. Pharm. Med. Chem.* (Weinheim). **2004**, *337* (9), 482–485.
5. Kandeel, Z. E.; Farag, A. M.; Abdelrazek, F. M. Facile synthesis of some novel pyrrole and pyridazinoquinazolone derivatives. *Heteroatom Chem.* **1995**, *6* (3), 281–285.

6. Abdelrazek, F. M. Heterocyclic synthesis with nitriles: Synthesis of some new thiocyanato-substituted heterocycles from alkylidenemalononitrile. *Heteroatom Chem.* **1995**, *6* (3), 211–214.
7. Kandeel, Z. E. Nitriles in heterocyclic synthesis: Synthesis of some thieno[2,3-d]pyrimidine and thieno[2,3-b]pyridine derivatives. *Heteroatom Chem.* **1996**, *7* (1), 29–33.
8. Gewald, K.; Schaefer, H.; Bellmann, P.; Hain, U. The synthesis of 3-aminopyrroles through Thorpe–Ziegler cyclization. *J. Prakt. Chem. Chem. Zeitung* **1992**, *334*, 491–496.
9. Schollberg, K.; Schäfer, H.; Gewald, K. A simple preparation of α-chloro- and β-chloro-α-cyanocinnamonitriles. *J. Prakt. Chem.* **1983**, *325* (5), 876–879.
10. Hartmann, H.; Liebscher, J. A simple method for the synthesis of 5-aryl-3-amino-2-ethoxycarbonylthiophenes. *Synthesis (Commun.)* **1984**, 275–276.
11. Hartmann, H.; Liebscher, J. A facile synthesis of 5-aminopyrazoles by the reaction of β-chlorocinnamonitriles with hydrazine hydrate. *Synthesis (Commun.)* **1984**, 276–277.
12. Baccolini, G.; Sandali, C. Synthesis of pyrroles under mild conditions using PCl_3, ketones, and alkylhydrazines. *J. Chem. Soc. Chem. Commun.* **1987**, 788–789.
13. Toja, E.; Depaoli, A.; Tuan, G.; Kettenring, J. Synthesis of 2-amino-3-ethoxycarbonylpyrroles. *Synthesis* **1987**, 272–274.
14. Abdelrazek, F. M.; Kandeel, Z. E.; Salah, A. M. Some reactions with ω-bromoacetophenone: Synthesis of $\Delta^{\alpha,\beta}$-butenolide and its transformation into pyrrole derivatives. *Heteroatom Chem.* **1995**, *6* (1), 77–80.
15. Metwally, N. H.; Abdelrazek, F. M. Heterocyclic synthesis with nitriles: Synthesis of some novel pyrrolo[2,1-b]thiadiazoline, pyrrolo[2,1-b]thiadiazolo[3,2-a]pyrimidine and pyridine derivatives. *J. Prakt. Chem. Chem Zeitung* **1998**, *340*, 676–678.