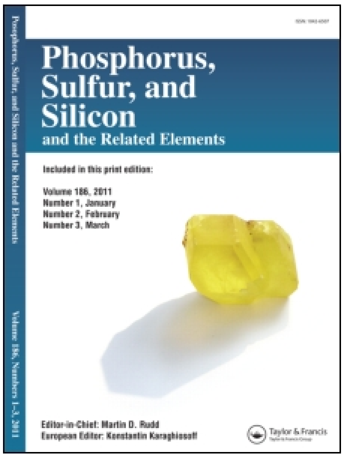

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The Use of Anilinodihydrothiophenes in the Synthesis of Novel Heterocyclic Compounds

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The Use of Anilinodihydrothiophenes in the Synthesis of Novel Heterocyclic Compounds

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*2-Phenylamino-4-oxo-4,5-dihydrothiophenes **1** and **6** were used for the preparation of 2-arylidenethieno[2,3-b]pyridine and benzo[b]thiophene derivatives **3**, **8**, and **11**. The structures of the hitherto unknown ring systems have been confirmed by analytical and spectral methods.*

Keywords Arylidenemalonitriles; heterocycles; thiophenes

INTRODUCTION

The increasing importance of thieno-fused heterocycles as biologically active compounds[1,2] led to the continuing development of new simple procedures for their synthesis. In light of these findings and in continuation of our program in the synthetic importance of the enaminones and synthesis of some functionaly substituted heterocycles,[3–6] the authors investigated the behavior of some thiophenes and of enaminone type-towards cinnamonitriles.

RESULTS AND DISCUSSION

Condensation of the enaminone type 1[7], namely, 2-phenylamino-4-oxo-4,5-dihydrothiophene with arylidenemalononitriles **2a–c**, under refluxing 1-propanol in the presence of a catalytic amount of piperidine, was expected to give the thieno[3,2-b]pyran **4** or the thieno[2,3-b]pyridine 5. However, the product that was obtained was identified on the basis of its analytical and spectral data, as 2-arylidenethieno[2,3-b]pyridine derivatives 3 (Scheme 1). For example, the ^{1}H NMR spectrum of **3b**

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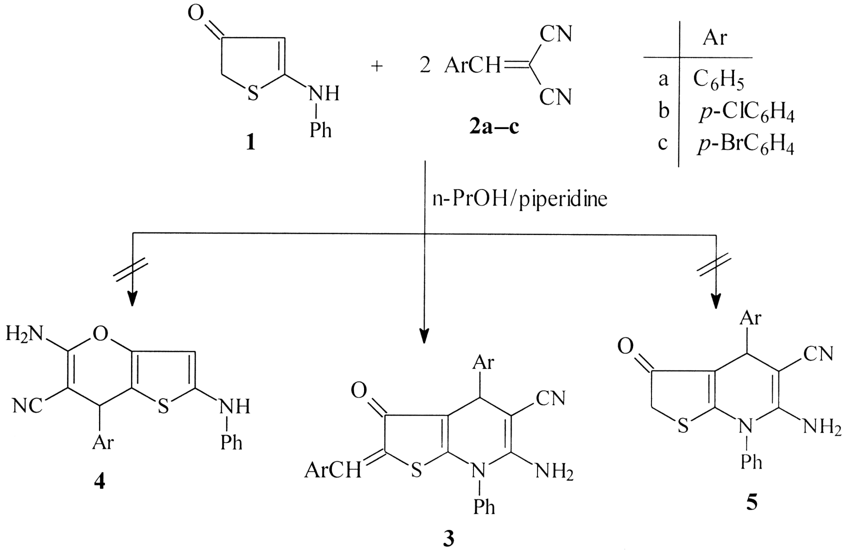
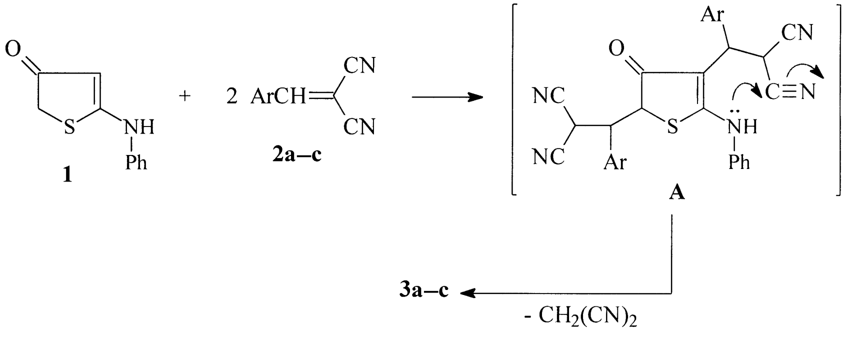
exhibited signals at δ 4.50 for one proton linked to an sp^3 carbon (4H-pyridine), a broad singlet at δ5.72(2H, NH_2), and a complex pattern at δ 7.35–7.65 (14H, aromatic and ylidenic H). The mass spectrum of **3b** showed the molecular ion at m/z 502 (M^+), 391 ($M^+ - C_6H_4Cl$) (base peak), 111 (C_6H_4Cl), and 77 (C_6H_5).



SCHEME 1

The formation of **3** could be explained via (a) the initial double-bond addition of **1** to 2 molecules of **2a–c** to give **A**, (b) the cyclization by the nucleophilic attack of the NH group on the cyano carbon, (c) the tautomerization, and (d) the elimination of a malononitrile. This elimination from such a Michael adduct is in agreement with previously reported cases (Scheme 2).[8,9]



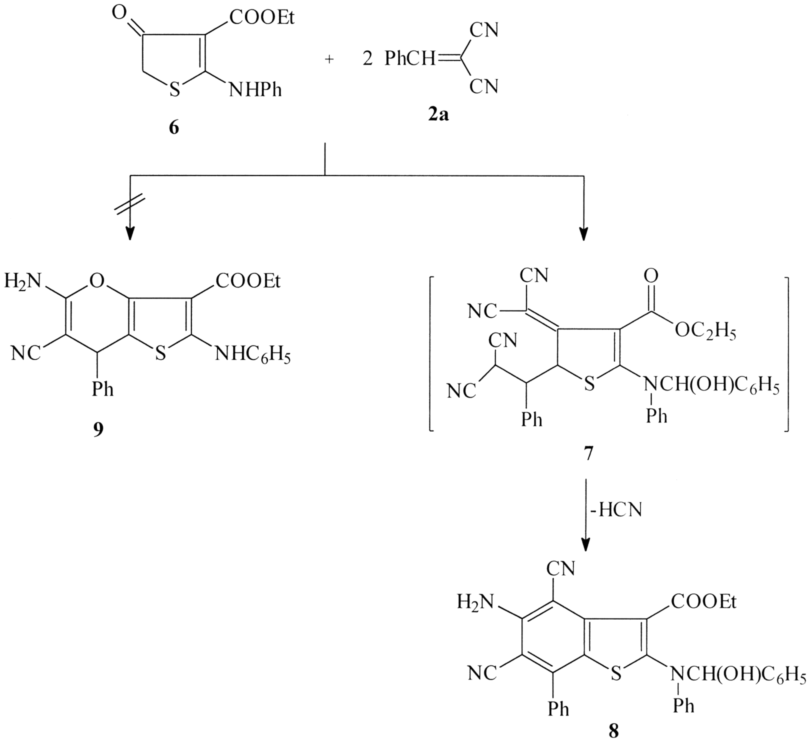
SCHEME 2

The structure proof of **3** was obtained through another route of synthesis by refluxing the appropriate aromatic aldehyde, malononitrile, and compound **1** in a molar ratio of (1:1:1) in 1-propanol in the presence of piperidine.

$$1 + \mathrm{ArCHO} + \mathrm{CH_2(CN)_2} \xrightarrow[\text{Piperidine}]{\text{1-Propanol}} 3 \qquad (1)$$

In this case, formation of **3** is explained by the initial condensation of aldehyde with malononitrile, affording the cyanoolefin **2**, followed by the addition of one molecule of **1** to 2 molecules of **2**, as above.

Condensation of the enaminone type **6**, namely ethyl 2-phenylamino-4-oxo-4,5-dihydrothiophene-3-carboxylate,[7] with benzylidenemalononitriles **2a** resulted in the formation of benzo[b]thiophen derivative **8**. It might be expected that the presence of a substituent in the 3-position of **1** prevents its reaction as enaminone at C-3. However, when **6** was reacted with **2a** in refluxing 1-propanol in the presence of a catalytic amount of piperidine, the benzo[b]thiophene derivative **8** was obtained, instead of the expected thieno[3,2-b]pyran **9** (Scheme 3). The ^{1}H NMR



SCHEME 3

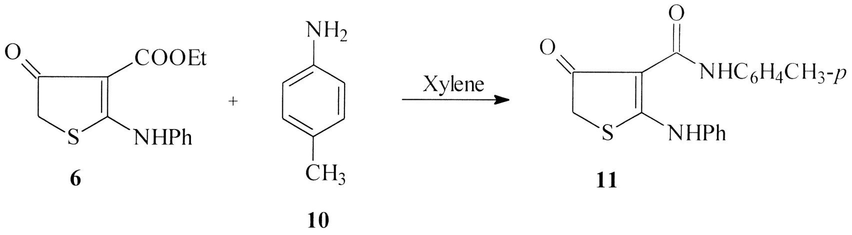
of **8** exhibited 3 protons triplet at δ 1.25 (CH_3-ester), 2 protons quartet at δ 4.15 (CH_2-ester), 2 protons singlet at δ 5.05 (NH_2), 1 proton at δ 5.50 (CH-benzyl), 1 proton singlet at δ 5.60 (OH), and 15 protons multiplet at δ 7.19–7.45 (aromatic).

The formation of **8** could be explained by the addition of two molecules of **2** to **6** to form the intermediate **7**, followed by the cyclization and elimination of hydrogen cyanide.

This reaction represents an interesting method for the construction and functionalization of the benzo[b]thiophene ring systems. In addition, this method has the advantages of ready accessibility of the reagents, good yields, and experimental simplicity.

The increasing importance of thiophene derivatives as intermediates to biologically active compounds[10] and in organic synthesis has led to the continuing development of new simple procedures for their synthesis.

In view of this and in connection with the present work, aiming to explore the synthetic importance of enaminones, the authors studied the conversion of **6** into some new substituted thiophene derivatives. The heterocyclic enaminone **6** has been condensed with *p*-toluidine **10** in refluxing xylene to give the expected compound **11** (Scheme 4). The product **11** was characterized by analytical and spectral data (c.f. Experimental section).



SCHEME 4

EXPERIMENTAL

Melting points C° (uncorrected) were taken on a Fisher electric melting point apparatus. Elemental analyses were carried out in the Microanalytical Unit, Faculty of Science, Mansoura and Cairo Universities. Infrared spectra were recorded on a SP-2000 Pye-Unicam Spectrometer. ^{1}H-NMR spectra were obtained with Varian-Gemini 200 MHz and Brucker 250 MHz TMS (Internal standard, $\delta = 0$ ppm). Mass spectra were recorded on a GCMS QP1000EX Schimadzu mass spectrometer at 70 eV. The purity of the synthesized compounds were tested by thin layer chromatography (TLC, EtOH: pyridine 2:1; EtOH: ethyl acetate 2:1), and no by products were noticed in all cases.

Synthesis of 6-Amino-4-aryl-2-arylidene-5-Cyano-3-Oxo-7-phenyl-2,3,4,7-tetrahydrothieno[2,3-b]pyridines 3a–c

Method A

A mixture of **1** (0.0025 mole) and the appropriate arylidienemalononitriles **2a–c** (0.0025 mole) in 1-propanol (25 mL) and piperidine (0.1 mL) was refluxed for 15 min. The solid products that deposited during reflux were filtered off and recrystallized from acetic acid to give yellow crystals of **3a–c**.

Method B

A mixture of **1**(0.0025 mole) and the appropriate aldehyde (0.0025 mole), malononitrile (0.0025 mole) in 1-propanol (25 mL), and piperidine (0.1 mL) was refluxed for 15 min. The solid products that separated were filtered off and recrystallized from acetic acid to give compounds **3a–c**.

6-Amino-4-phenyl-2-benzylidene-5-cyano-3-oxo-7-phenyl-2,3,4,7-tetrahydrothieno[2,3-b]pyridine (3a)

m.p. 260–261°C; Yield: 83%. IR (KBr) (υ, cm^{-1}): 3430, 3300 (NH_2), 2182 ($C \equiv N$) and 1630 (C=O). ^{1}H NMR (DMSO) δ_H: 4.50 (s, 1H, 4H-pyrimidine), 5.71 (br,s, 2H, NH_2) and 7.2–7.75 (complex pattern, 15H, aromatic and ylidenic). Found: C, 75.03; H, 4.63; N, 9.89%. $C_{27}H_{19}N_3OS$ (433.4) requires C, 74.82; H, 4.42; N, 9.70%.

6-Amino-4-(*p*-chlorophenyl)-2-(*p*-chlorobenzylidene)-5-cyano-3-oxo-7-phenyl-2,3,4,7-tetrahydrothieno-[2,3-b]pyridine (3b)

m.p. 269–271°C; Yield: 86%. IR (KBr) (υ, cm^{-1}): 3470, 3314 (NH_2), 2184 ($C\equiv N$) and 1626 (C=O). MS (m/z) (%); 502 (M^+) (10), 391 (M^+ - C_6H_4Cl) (base Peak) (100), 111 (C_6H_4Cl) (2) and 77 (C_6H_5) (38), ^{1}H NMR (DMSO); δ_H 4.50 (s, 1H, 4H-pyridine), 5.72 (br s, 2H, NH_2) and 7.35–7.65 (complex pattern, 14H, aromatic and ylidenic). Found: C, 64.31; H, 3.51; N, 8.52%. $C_{27}H_{17}N_3OSCl_2$ (502.30) requires C, 64.56; H, 3.40; N, 8.37%.

6-Amino-4-(*p*-bromophenyl)-2-(*p*-bromobenzylidene)-5-cyano-3-oxo-7-phenyl–2,3,4,7-tetrahydrothieno-[2,3-b]pyridine (3c)

m.p. 278–280°C; Yield: 85%. IR (KBr) (υ, cm^{-1}): 3469, 3315 (NH_2), 2185 ($C{\equiv}N$) and 1629 ($C{=}O$). MS (m/z)(%); 435($M^+ - C_6H_4Br$) (base Peak) (100), 156 (C_6H_4Br) (12) and 77 (C_6H_5) (95). Found: C, 54.67; H, 2.95; N, 7.23%. $C_{27}H_{17}N_3OSBr_2$ (591.3) requires C, 54.84; H, 2.90; N, 7.11%.

Synthesis of Ethyl-5-amino-7-phenyl-4,6-dicyano-2-(α-hydroxyphenylamino)benzo[b]thiophene-3-carboxylate (8)

A mixture of **6** (0.003 mole) and the benzylidinemalononitrile **2** (0.006 mole) in 1-propanol (30 mL) and piperidine (0.1 mL) was refluxed for 8 hs. The solid product that was obtained after cooling was filtered off and recrystallized from ethanol to give **8** as yellow crystals.

m.p. > 300°C; Yield: 54%. IR (KBr) (υ, cm^{-1}): 3372 (OH), 3305, 3215 (NH_2), 2218 ($C{\equiv}N$) and 1642 ($C{=}O$). MS (m/z) (%): 286 [M^+ -($CO_2C_2H_5$+ C_6H_5+ C_6H_5CHOH +H)] (4.3), 284 (286-2H) (base peak) (100), 257 (base peak-HCN)(15.5), 193 (base peak-C_6H_5N) (4), 165 [257- (C_6H_5N + H)] (20.4) and 92 (C_6H_5NH) (2.5). Found: C, 70.34; H, 4.61; N, 10.17%. $C_{32}H_{24}N_4O_3S$ (544.6) requires C, 70.57; H, 4.44; N, 10.29%.

4-Oxo-2-phenylaminothiophene-3-(P-tolyl)carboxamide (11)

A mixture of **6** (0.003 mole) and *p*-toluidine **10** (0.003 mole) in xylene (15 mL) was refluxed for 6 h. The solid product that was obtained after concentration and cooling was filtered off and recrystallized from ethanol to give **11** as golden yellow crystals.

m.p. 160–162°C; Yield: 59%. IR (KBr) (υ, cm^{-1}): 3389 (NH) 1645 ($C = O$) and 1599 ($C{=}O$ amide). MS (m/z) (%): 324 (M^+) (25), 218 ($M^+ - C_7H_8N$), 190 (218-CO) (2), 107 (C_7H_8N + H) (base peak) (100), 92 (base peak – CH_3) (3) and 77 (92-NH) (17). Found: C, 66.75; H, 5.12; N, 8.71%. $C_{18}H_{16}N_2O_2S$ (324.4) requires C, 66.64; H, 4.97; N, 8.64%.

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