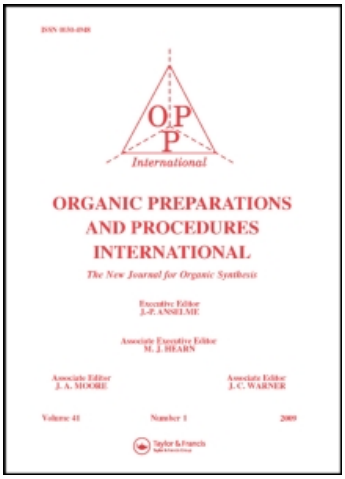


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# SYNTHESIS OF NEW SUBSTITUTED PYRIDINES, PYRANO[2,3-d]IMIDAZOLES AND PYRROLO[2,1-b]QUINAZOLINES

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# SYNTHESIS OF NEW SUBSTITUTED PYRIDINES, PYRANO[2,3-d]IMIDAZOLES AND PYRROLO[2,1-b]QUINAZOLINES†

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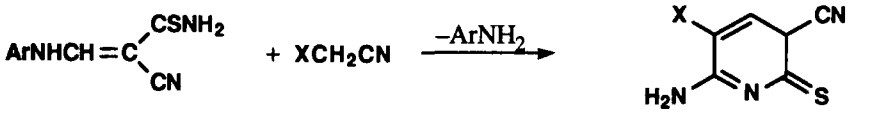
In the course of a program designed to investigate the efficiency of pyridine derivatives as anti-ulcer agents,[1] we needed a simple synthesis of polyfunctionally substituted pyridines. This report deals with the synthesis of such pyridine derivatives as well as related pyrano[2,3-d]imidazoles and pyrrolo[2,1-b]quinazolines.

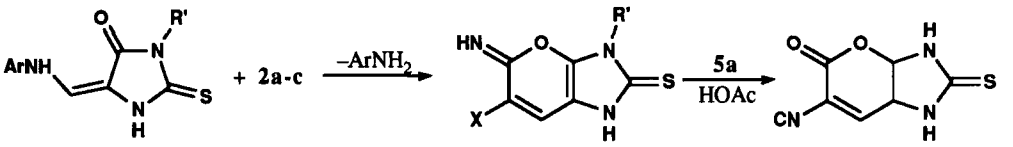
The starting 3-arylamino-2-cyanothioacrylamides (**1a-c**), obtained by treatment of α-cyanothioacetamide with N,N-diarylformamidines, were reacted with malononitrile **2a** in ethanol, using triethylamine as a catalyst; the sole product isolated was 6-amino-3,5-dicarbonitrile-2-pyridothione (**3a**). The formation of **3a** is assumed to proceed *via* an initial Michael addition of the active methylene group of **2a** to the activated double bond of **1a-c**, to yield the acylic intermediates which could then be cyclized to **3a** with elimination of the arylamine. Structure **3a** was established on the basis of elemental analysis and spectral data (see Table 2). Similarly, compounds **1** were treated with ethyl cyanoacetate (**2b**) and benzoylacetonitrile (**2c**) to yield the 2-pyridothione derivatives **3b,c**.




| 1 | 2 | 3 |
|---|---|---|
| a) Ar = $C_6H_5$, X = CN | b) Ar = *p*-$MeC_6H_4$, X = $CO_2Et$ | c) Ar = *p*-$ClC_6H_4$, X = COPh |

Since 2-thiohydantoin derivatives possess anticonvulsant[2] and antiasthmatic[3] activity, compounds having both thiohydantoin and pyrano moieties might be expected to show marked

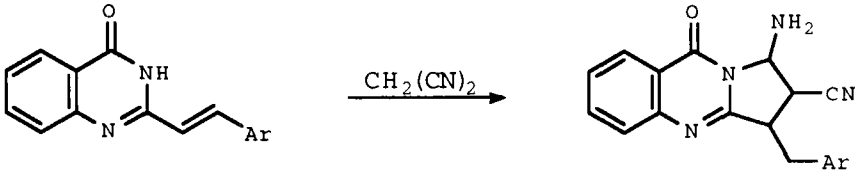
biological Activity. This prompted us to synthesize some fused heterocycles containing the thiohydantoin and pyrano moieties. Thus 5-arylaminomethylene-2-thiohydantoin derivatives (**4a-f**),[4] with **2a-c** under the same conditions, afforded the pyrano[2,3-d]imidazole derivatives **5a-f**. The formation of **5** is assumed to proceed by an initial Michael addition to the double bond of **4** followed by cyclization to **5** with elimination of the arylamine. When compound **5a** is refluxed with glacial acetic acid, the imino group is converted to C=O to give the corresponding oxygen compound **6.** The structure of **6** was confirmed by elemental analysis and spectral data.




**4** **5** **6**

**a)** Ar = $C_6H_5$; R = R' = H; X = CN
**b)** Ar = *p*-$MeC_6H_4$; R = R' = H; X = $CO_2Et$
**c)** Ar = *p*-$ClC_6H_4$ ; R = R'= H; X = COPh
**d)** Ar = R = R' = $C_6H_5$; X = CN
**e)** Ar = *p*-$MeC_6H_4$; R = R' = $C_6H_5$; X = $CO_2Et$
**f)** Ar = *p*-$ClC_6H_4$; R = R' = $C_6H_5$; X = $COC_6H_5$

The work has been further extended to investigate the behavior of 3,4-dihydro-4-oxoquinazoline derivatives (**7a-c**)[5] towards **2a** in order to synthesize new pyrrolo[1,2-a]quinazoline derivatives of potential biological activity. Thus compounds **7** reacted with **2a** to yield the 1:1 adducts **8**. The formation of **8** is assumed to proceed *via* initial Michael addition of **2a** to the activated double bond in **7a-c** to yield the intermediates which then cyclize to the final isolable products 1-amino-2-cyano-3-arylmethylene pyrrolo[1,2-a]quinazoline-9-ones **8a-c**.




7 8

**a)** Ar = $C_6H_5$ **b)** Ar = *p*-$MeC_6H_4$ **c)** Ar = *p*-$ClC_6H_4$

## EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra were recorded on a Pye Unicam SP-1100 spectrophotometer using KBr discs. The $^1H$ NMR spectra were obtained on a Varian EM-390-90 MHz spectrometer using DMSO-$d_6$ as a solvent and TMS as an internal standard. Chemical shifts are expressed as δ ppm units. The microanalyses were performed by the microanalytical center of Cairo University.

**Preparation of 3-Arylamino-2-cyanothioacrylamides (1a-c).**- α-Cyanothioacetamide (5.005 g, 0.05 mole) and the N,N-diarylformamidine (0.055 mole) were mixed well and heated in an oil bath at 140-150° for 40 min. The mixture was left to cool at room temperature, and the solid obtained was collected,

**TABLE 1.** Yields, mps and Elemental Analysis for **1a-c, 3a-c, 5a-f, 6** and **8a-c**

| Compound | mp. (°C) | Yield (%) | Elemental Analysis Calcd. (Found) C | H | N | S |
|---|---|---|---|---|---|---|
| **1a** | 205 | 88 | 59.09 (59.31) | 4.46 (4.23) | 20.67 (20.50) | 15.78 (15.94) |
| **1b** | 220 | 85 | 60.80 (60.53) | 5.09 (5.30) | 19.33 (19.62) | 14.75 (14.53) |
| **1c** | 233-234 | 81 | 50.53 (50.00) | 3.39 (4.04) | 17.68 (17.52) | 13.49 (13.21) |
| **3a** | 273 | 75 | 47.72 (47.44) | 2.29 (2.12) | 31.80 (32.14) | 18.20 (17.93) |
| **3b** | 245 | 72 | 48.42 (48.23) | 4.06 (4.21) | 18.82 (19.03) | 14.36 (14.00) |
| **3c** | 285-286 | 77 | 61.16 (61.53) | 3.5 5 (3.21) | 16.46 (16.24) | 12.56 (12.73) |
| **5a** | 279 | 76 | 43.75 (43.52) | 2.10 (2.32) | 29.15 (28.91) | 16.68 (16.83) |
| **5b** | 255-256 | 73 | 45.18 (45.01) | 3.79 (3.93) | 17.56 (17.31) | 13.40 (13.52) |
| **5c** | 263 | 70 | 57.56 (57.80) | 3.34 (3.61) | 15.49 (15.71) | 11.82 (11.53) |
| **5d** | 205 | 78 | 66.27 (66.52) | 3.50 (3.24) | 16.27 (16.02) | 9.31 (9.51) |
| **5e** | 220 | 81 | 64.44 (64.21) | 4.37 (1.50) | 10.7 3 (10.93) | 8.19 (8.02) |
| **5f** | 190 | 75 | 70.91 (70.64) | 4.04 (4.32) | 9.92 (10.20) | 7.57 (7.33) |
| **6** | 288 | 72 | 43.52 (43.20) | 1.57 (1.82) | 21.76 (21.51) | 16.58 (16.32) |
| **8a** | 182 | 70 | 72.60 (72.42) | 4.49 (4.61) | 17.82 (17.54) | |
| **8b** | 160-161 | 73 | 69.76 (69.91) | 4.68 (4.53) | 16.27 (16.62) | |
| **8c** | 205 | 71 | 65.43 (65.22) | 3.75 (3.51) | 16.06 (16.24) | |

a) Calcd: Cl, 14.92; Found: 15.21; b) Calcd: Cl, 10.16; Found: 10.50.

**TABLE 2.** IR and $^1$H NMR Spectral Data of **1, 3, 5, 6** and **8**

| Compound | IR ($cm^{-1}$) | $^1$H NMR ($\delta$ ppm) |
|---|---|---|
| **1a** | 3400, 3330, 3190, 2200 and 1200 | 14.5 (s, br., 2H, $NH_2$); 11.4 (s, 1H, NH) exchangeable with $D_2O$); 6.2 (s, 1H, C H=C) and 7.2-7.4 (m, 5H, ArH). |
| **1b** | 3380, 3340, 3220, 2210 and 1205 | 2. 1 (s, 3H, $CH_3$ ); 4.7 (s, br, 2H, $NH_2$); 11.2 (s, 1H, NH); 6.1 (s, 1H, CH=C) and 7.1-7.3 (m, 4H, ArH). |
| **1c** | 3410, 3350, 3280, 2220 and 1210 | 5.6 (s, br, 2H, $NH_2$); 11.7 (s, 1H, NH); 6.3 (s, 1H, CH=C) and 7.3-7.5 (m, 4H, ArH). |
| **3a** | 3380, 3320, 2225, 2220, 1640 and 1205 | 3.2 (d, 1H, CH-CN); 6.2 (d, 1H, CH=C) and 9.2 (s, br, 2H, $NH_2$ exchangeable with $D_2O$). |
| **3b** | 3360, 3330, 2200, 1730, 1630 and 1200 | 1. 3 (t, 3H, $CH_3$); 3.5 (d, 1H, CH-CN);4.3 (q, 2H, $CH_2$); 6.3 (d, 1H, CH=C) and 9.4 (s, br, 2H, $NH_2$). |
| **3c** | 3400, 3320, 2220, 1680, 1630 and 1200. | 3.3 (d, 1H, CH-CN); 6.1 (d, 1H, CH=C); 7.2-7.4 (m, 5H, ArH) and 8.7 (s, br, 2H, $NH_2$). |
| **5a** | 3370, 3330, 3280, 2210, 1640 and 1200 | 6.1 (s, 1H, CH=C); and 9.1, 9.7, 10.8 (3s, 3H, 3NH these peaks removed by addition of $D_2O$). |
| **5b** | 3380, 3350, 3190, 1725, 1630 and 1200 | 1.5 (t, 3H, $CH_3$); 4.5 (q, 2H, $CH_2$); 6.2 (s, 1H) CH=C) and 8.9, 9.5, 10.9 (3s, 3H, 3NH). |
| **5c** | 3360, 3310, 3170, 1670, 1630 and 1210 | 6.2 (s, 1H, CH=C); 7.2-7.5 (m, 5H, ArH); 9.1, 9.6, 11.1 (3s, 3H, 3NH). |
| **5d** | 3360, 2200, 1630 and 1200 | 6.2 (s, 1H, CH=C); 7.2-7.6 (m, 10H, ArH); and 10.9(s, 1H, NH exchangeable with $D_2O$). |
| **5e** | 3380, 1730, 1640 and 1200 | 1.4 (t, 3H, $CH_3$); 4.2 (q, 2H, $CH_3$); 6.1 (s, 1H, CH=C);7.1-7.4 (m, 10H, ArH) and 11.1 (s, 1H, NH). |
| **5f** | 3390, 1680, 1630 and 1205 | 6.2 (s, 1H, CH=C); 7.2-7.6 (m, 15H, ArH) and 11.3 (s, 1H, NH). |
| **6** | 3360, 3320, 2220, 1720, and 1205 | 6.3 (s, 1H, C H=C) and 9.4, 9.3 (2s, 2 H, 2NH exchangeable with $D_2O$). |
| **8a** | 3370, 3320, 2200, 1690, and 1640 | 3.3 (d, 2H, $CH_2$); 4.6 (t, 1H, CH); 6.2 (s, br, 2H, NH) exchangeable with $D_2O$) and 7.2-7.5 (m,9H, ArH). |
| **8b** | 3360, 3280, 2220, 1680, and 1630 | 3.5 (d, 2H, $CH_2$); 4.0 (s, 3H, $OCH_3$); 4.7 t, 1H, (CH); 6.5 (s, 2H, $NH_2$) and 7.1-7.4 (m, 8H, ArH). |
| **8c** | 3390, 3300, 2210, 1690, and 1640 | 3.6 (d, 2H $CH_2$); 4.8 (t, 1H, CH); 6.3 (s, br, 2H, $NH_2$) and 7.2-7.6 (m, 8H, ArH). |

washed with ethyl alcohol and crystallized from ethanol to yield yellow crystals of **1a-c** (Tables 1 and 2).

**General Procedure for the Reaction of 1 and of 4 with the Activated Nitriles (2).**- A solution of **2** (0.01 mole) and **1** or **4** (0.01 mole) in absolute ethanol (50 mL) and triethylamine (0.5 mL) was heated under reflux for 4 hrs. The solids thus obtained, were collected and crystallized from ethanol to give yellow crystals of **3** or **5** respectively (Tables 1 and 2).

**Acid Hydrolysis of 5a.**- A solution of **5a** (1 g) in glacial acetic acid (20 mL) was refluxed for 30 min. The solid yellow product obtained on cooling was collected and crystallized from acetone to give yellow crystals of **6**.

**General Procedure for the Synthesis of 1-Amino-2-cyano-3-arylmethylene pyrrolo[1,2-a]quinazoline-9-ones (8).**- Malononitrile **2a** (0.66 g, 0.01 mole) was added to solutions of styryl derivatives **7** (0.01 mole) in pyridine (30 mL) and the mixtures heated under reflux for 6 hrs. The reaction mixtures were evaporated to half volume and diluted with water (15 mL). The solid products which formed on standing, were collected and crystallized from ethanol to give brown crystals of **8a-c** (Tables 1 and 2).

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