REACTIONS WITH HETEROCYCLIC ENAMINONITRILES: SYNTHESIS OF PYRROLO[2,3-b]PYRIDINE, PYRROLO[2,3-d]PYRIMIDINE AND PYRROLE DERIVATIVES

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Abstract - Synthesis of pyrrolo[2,3-b]pyridine, pyrrolo[2,3-d]pyrimidine and pyrrole derivatives utilizing 1-aryl-2-amino-3-cyano-5-ethoxycarbonyl-4-methylpyrrole derivatives **2** as starting components is reported.

INTRODUCTION

In the course of our investigations on the reactions of dicyanomethylene compounds[1-3] for developing simple, new and efficient procedures for the synthesis of heterocycles, we have found a convenient method for the synthesis of pyrrolo[2,3-b]pyridine, pyrrolo[2,3-d]pyrimidine and pyrrole derivatives involving the use of the enaminonitrile derivatives, namely, 1-aryl-2-amino-3-cyano-5-ethoxycarbonyl-4-methylpyrrole derivatives **2a,b** which were prepared by treatment of ethyl 3-dicyanomethylenebutyrate with aromatic diazonium chlorides and subsequent ring contraction of the resulting pyridazines **1a**[4,5] and **1b** using zinc dust in the presence of acetic acid.

RESULTS AND DISCUSSION

Treatment of **2a** with malononitrile in refluxed pyridine afforded a 1:1 adduct of molecular formula $C_{18}H_{17}N_5O_2$ (M^+ = 335). Two isomeric structures (**3** and **4**) were considered. However, ^1H nmr spectrum could be utilized to rule out structure **3** as it revealed the presence of two NH_2 groups and the absence of the two proton signal for CH_2CN and thus the pyrrolo[2,3-b]-pyridine structure **4a** was established for the reaction product. The formation of **4a** is thus assumed to take place via addition of the active methylene moiety in malononitrile to the nitrile group in **2** followed by cyclization (cf. Chart 1). Analogously, **2b** reacted with malono-nitrile to give **4b**. Compounds **4a,b** were also obtained by conducting the reaction either in ethanolic sodium ethoxide or in the absence of a solvent at 170°C (see experimental section).

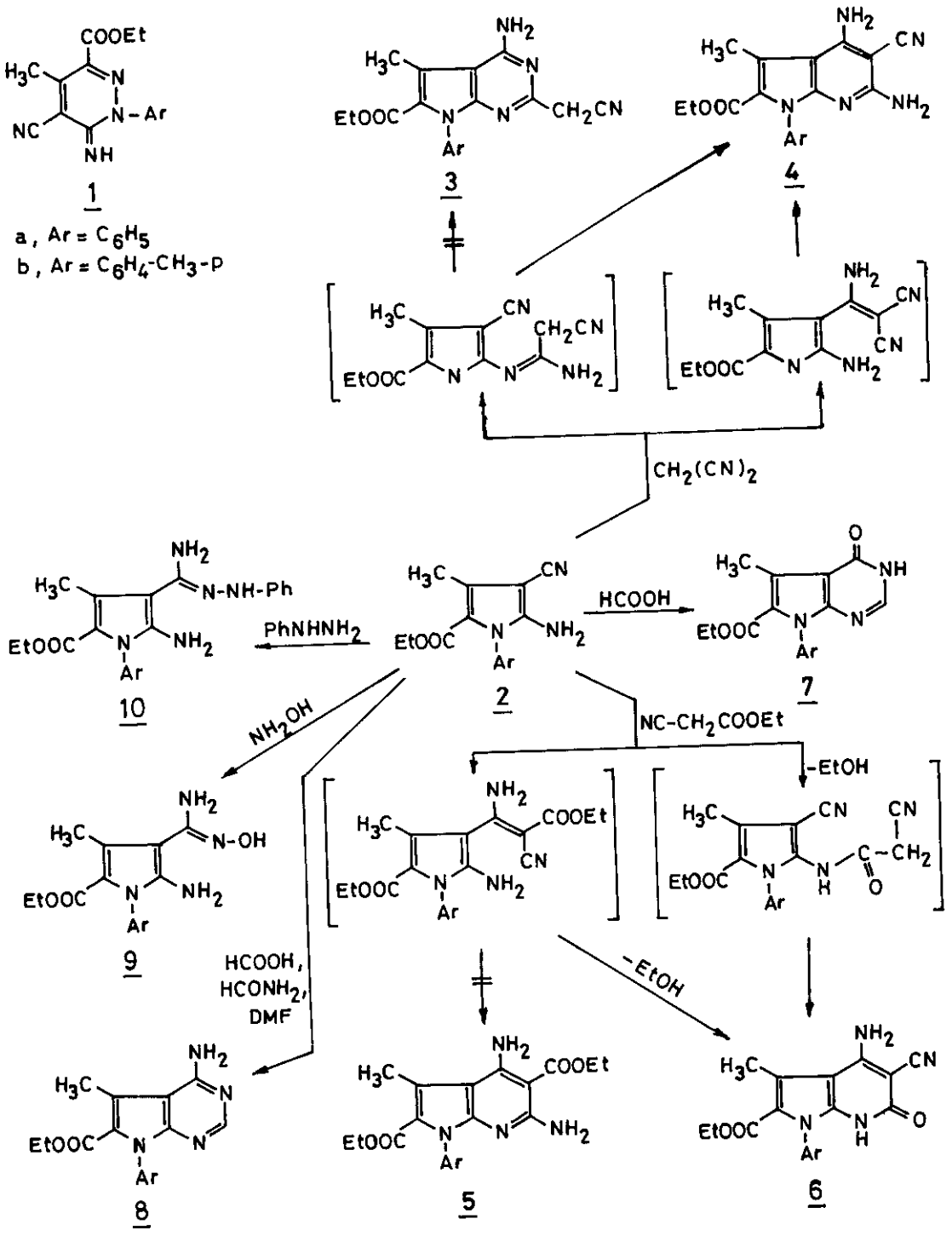
COOEt
H3C
N
N-Ar
NC
NH
1
a, Ar = C6H5
b, Ar = C6H4-CH3-p
NH2
H3C
N
EtOOC
N
N
CH2CN
Ar
3
NH2
CN
H3C
N
EtOOC
N
N
NH2
Ar
4
CH2CN
CN
EtOOC
N
NH2
NH2
CN
CN
EtOOC
N
NH2
CH2(CN)2
NH2
H3C
N-NH-Ph
EtOOC
N
NH2
Ar
10
PhNHNH2
CN
H3C
EtOOC
N
NH2
Ar
2
HCOOH
O
NH
H3C
EtOOC
N
N
Ar
7
NH2OH
NC-CH2COOEt
NH2
H3C
N-OH
EtOOC
N
NH2
Ar
9
NH2
COOEt
H3C
CN
EtOOC
N
NH2
Ar
-EtOH
CN
CN
H3C
EtOOC
N
N
C
CH2
H
O
Ar
HCOOH,
HCONH2,
DMF
NH2
H3C
N
EtOOC
N
N
Ar
8
NH2
COOEt
H3C
EtOOC
N
N
NH2
Ar
5
-EtOH
NH2
CN
H3C
EtOOC
N
N
O
H
Ar
6

Chart 1

Similarly 2a,b reacted with ethyl cyanoacetate to yield a product which may be formulated as 5 or 6. Again structures 5a and 5b were excluded based on ir spectra which revealed the presence of the CN group. The formation of 6a and 6b is assumed to proceed via initial Michael addition to yield acyclic adducts which then cyclized via loss of ethanol, or initial ethanol elimination followed by cyclization (cf. Chart 1). Heating 2a,b with formic acid (85 %) gave the pyrrolo-[2,3-d]pyrimidine derivatives 7a,b respectively. On the other hand, heating 2a,b with a mixture of formic acid, dimethylformamide and formamide resulted in the formation of the pyrrolo[2,3-d]-pyrimidine derivatives 8a,b respectively. Compounds 2a,b reacted with hydroxylamine in refluxed ethanol in the presence of sodium ethoxide to yield the pyrrole derivatives 9a,b respectively. Similarly 2a,b reacted with phenylhydrazine to yield the pyrrole derivatives 10a,b respectively. An attempt of cyclization of 9a,b and 10a,b by refluxing in ethanolic hydrochloric acid was unsuccessful (see experimental section).

The structures of the newly synthesized derivatives were established on the basis of analytical and spectroscopic data (Tables 1 and 2).

EXPERIMENTAL

Melting points are uncorrected. Ir spectra were recorded (KBr) on a Pye Unicam SP-1000. ^{1}H nmr spectra were obtained on an EM-360 MHz spectrometer in DMSO-d_6 using TMS as internal standard and chemical shifts are expressed as δ ppm. Analyses were performed by the micro-analytical unit, Cairo University.

Ethyl 3-dicyanomethylenebutyrate was prepared according to the reported procedure[6].

Ethyl 4-cyano-3-imino-5-methyl-2-aryl-2,3-dihydro-pyridazin-6-carboxylate (1). A solution of ethyl 3-dicyanomethylenebutyrate (1.68 g, 0.01 mol) in ethanol (50 ml) was stirred for 5 min with sodium acetate (3 g) and chilled in an ice-salt bath to 0-5°C. To the resulting cold solution was added the desired aryldiazonium chloride solution (0.01 mol). After the addition was completed, the reaction mixture was stirred for additional 1 h. Ammonia solution (3 ml, 25 %) was added to the reaction mixture. The separated solid product was collected by filtration, washed with water and crystallized from ethanol to give 1. 1a, mp 136-137°C [5]. 1b (cf. Tables 1 and 2).

Ethyl 5-Amino-1-aryl-4-cyano-3-methyl-pyrrol-2-carboxylate (2). To a suspension of 1 (5 mmol) in acetic acid (20 ml) at 80°C, zinc dust (2 g) was added in small portions in a period of 20 min. The reaction mixture was filtered hot. The filtrate was diluted with 100 ml of water, the resulting crude solid was collected and crystallized from ethanol to give 2 (cf. Tables 1 and 2).

Synthesis of Pyrrolo[2,3-b]pyridine Derivatives 4 and 6. Method (A). An equimolecular mixture of 2, malononitrile or ethyl cyanoacetate and sodium ethoxide in absolute ethanol (20 ml) was refluxed for 3h. The solvent was removed under reduced pressure and the residue was triturated

with water. The so-formed solid was collected and crystallized from ethanol to give **4** and **6**, respectively (cf. Tables 1 and 2).

Method (B). An equimolecular mixture of **2** and malononitrile or ethyl cyanoacetate in pyridine (20 ml) was refluxed for 2h. The solvent was evaporated under reduced pressure and the residue was triturated with water. The so-formed solid was collected to give **4** and **6**, respectively.

Method (C). An equimolecular mixture of **2** and malononitrile or ethyl cyanoacetate in dry test tube was heated at 170°C (bath temp.) for 2 h. The so-formed solid was collected and crystallized from ethanol to give **4** and **6**, respectively.

The products obtained in method "B" and method "C" were identical in all respects with those obtained from method "A" (mp, mixed mp and spectra).

Synthesis of Pyrrolo[2,3-d]pyrimidinone Derivatives 7. The appropriate **2** (1.0 g) was refluxed in formic acid (25 ml, 85 %) for 7-9 h. The so-formed solid after cooling was collected and crystallized to give **7** (cf. Tables 1 and 2).

Synthesis of Amino-pyrrolo[2,3-d]pyrimidine Derivatives 8. The appropriate **2** (1.0 g) was refluxed in a mixture of formic acid, formamide and dimethylformamide (5 ml. of each) for 9-10 h. The reaction mixture was cooled and diluted with water. The so-formed solid was collected and crystallized to give **8** (cf. Tables 1 and 2).

Synthesis of Pyrrolo Derivatives 9. Hydroxylamine hydrochloride (0.01 mol) was treated with sodium ethoxide (0.01 mol) in absolute ethanol and stirred for 20 min. The appropriate **2** (0.01 mol) was added to the resulting solution. Then, the reaction mixture was refluxed for 3 h. The reaction mixture was diluted with water. The so-formed solid was collected and crystallized to give the pyrrole derivatives **9** (cf. Tables 1 and 2).

Table 1. List of the newly synthesized compounds

Compound*	Mp (°C)	Yield (%)	Mol. Formula	C % Calcd (Found)	H % Calcd (Found)	N % Calcd (Found)
1b	157	80	$C_{16}H_{16}N_4O_2$	64.85 (64.70)	5.44 (5.10)	18.90 (19.20)
2b	180	65	$C_{16}H_{17}N_3O_2$	67.82 (67.50)	6.04 (5.70)	14.83 (14.50)
4a	172	62	$C_{18}H_{17}N_5O_2$	64.46 (64.80)	5.11 (4.80)	20.88 (21.10)
4b	160	72	$C_{19}H_{19}N_5O_2$	65.31 (65.60)	5.48 (5.70)	20.04 (19.60)
6a	195	75	$C_{18}H_{16}N_4O_3$	64.27 (64.50)	4.79 (5.10)	16.65 (17.00)
6b	190	70	$C_{19}H_{18}N_4O_3$	65.13 (64.80)	5.17 (5.30)	15.99 (16.20)
7a	205	90	$C_{16}H_{15}N_3O_3$	64.63 (64.90)	5.08 (4.80)	14.13 (14.50)
7b	210	85	$C_{17}H_{17}N_3O_3$	65.58 (65.10)	5.50 (5.70)	13.49 (14.00)

Table (1) Contd

Compound*	Mp (°C)	Yield (%)	Mol. Formula	C % Calcd (Found)	H % Calcd (Found)	N % Calcd (Found)
8a	255	65	$C_{16}H_{16}N_4O_2$	64.85 (64.40)	5.44 (5.10)	18.90 (19.20)
8b	210	60	$C_{17}H_{18}N_4O_2$	65.79 (65.80)	5.84 (5.90)	18.05 (18.50)
9a	165	78	$C_{15}H_{18}N_4O_3$	59.59 (60.20)	6.00 (5.70)	18.53 (19.00)
9b	155	81	$C_{16}H_{20}N_4O_3$	60.74 (61.10)	6.37 (5.90)	17.70 (17.90)
10a	148	78	$C_{21}H_{23}N_5O_2$	66.82 (67.20)	6.14 (6.30)	18.55 (18.10)
10b	158	72	$C_{22}H_{25}N_5O_2$	67.49 (67.10)	6.43 (6.70)	17.88 (17.60)

*•All compounds are crystallized from ethanol except 8a,b which were crystallized from pet. ether (40-60°C). All compounds are pale yellow except 1b which is orange.

Table 2. IR and ^{1}H NMR data of compounds listed in Table 1.

Compound	IR [cm^{-1}] Selected bands	^{1}H NMR (δ ppm) [DMSO-d_6]
1b	3350 (NH); 2220 (CN); 1700 (CO); 1620 (C=N); 1600 (C=C).	1.1 (t,3H,ester CH_3); 2.4 (s,3H,CH_3); 2.7 (s, 3H,CH_3); 4.1 (q,2H,ester CH_2); 7.2-7.8 (m, 5H, C_6H_4 and NH).
2b	3430, 3330, 3320 (NH_2); 2200 (CN); 1680 (CO); 1600 (C=C).	1.1 (t,3H,ester CH_3); 2.4 (s,3H,CH_3); 2.67(s, 3H,CH_3); 4.1(q,2H,ester CH_2); 4.3 (s,2H,NH_2); 7.2-7.6 (m, 4H,C_6H_4).
4a	3440, 3350, 3280 (NH_2); 2220 (CN); 1680 (CO); 1640 (C=N); 1600 (C=C)	1.1 (t, 3H, ester CH_3); 2.4 (s, 3H,CH_3); 4.1 (q, 2H, ester CH_2); 5.5 (s, br.,4H, two NH_2); 7.2-7.5 (m, 5H, C_6H_5).
4b	3440, 3350, 3290 (NH_2); 2220 (CN); 1680 (CO); 1640 (C=N); 1600 (C=C)	1.1 (t, 3H,ester CH_3); 2.3 (s,3H,CH_3); 2.7 (s, 3H, CH_3); 4.1 (q, 2H, ester CH_2); 5.6 (s, 4H, two NH_2); 7.2-7.6 (m, 4H, C_6H_4).
6a	3440, 3340, 3220 (NH_2); 2200 (CN); 1690, 1670 (CO); 1620 (C=N); 1600 (C=C).	1.2 (t, 3H,ester CH_3); 2.4 (s,3H,CH_3); 4.1 (q, 2H,ester CH_2); 5.2 (s, 2H,NH_2); 7.2-8 (m, 6H, C_6H_5 and NH).
6b	3440, 3340, 3220 (NH_2); 2200 (CN); 1680, 1670 (CO); 1620 (C=N); 1600 (C=C).	1.1 (t, 3H,ester CH_3); 2.4 (s, 3H,CH_3); 2.7 (s,3H,CH_3); 4.1 (q, 2H,ester CH_2); 5.2 (s, 2H,NH_2); 7.2-8 (m,5H,C_6H_4 and NH).
7a	3450 (NH); 1690, 1680 (CO); 1620 (C=N); 1600 (C=C).	1.1 (t, 3H,ester CH_3); 2.4 (s, 3H, CH_3); 4.1 (q, 2H, ester CH_2); 7.2-8.1 (m, 7H,C_6H_5, NH and pyrimidine H-2).
7b	3440 (NH); 1690, 1680 (CO); 1630 (C=N); 1600 (C=C).	1.1 (t,3H,ester CH_3); 2.4 (s,3H,CH_3);2.7 (s, 3H, CH_3); 4.2(q,2H,ester CH_2); 7.2-8 (m, 6H, C_6H_4, NH and pyrimidine H-2).

Table (2) Contd.

Compound	IR [cm^{-1}] Selected bands	^1H NMR (δ ppm) [DMSO-d_6]
8a	3440, 3340, 3250 (NH_2); 1680 (CO); 1620 (C=N); 1600 (C=C).	1.1 (t, 3H,ester CH_3); 2.4 (s,3H,CH_3); 4.1 (q, 2H, ester CH_2); 5.6 (s,br., 2H, NH_2); 7.2-7.5 (m, 6H,C_6H_5 and pyrimidine H-2).
8b	3450, 3380, 3250 (NH_2); 1680 (CO); 1630 (C=N); 1600 (C=C).	1.1 (t, 3H, ester CH_3); 2.4 (s,3H,CH_3); 2.8 (s, 3H,CH_3); 4.2 (q,2H,ester CH_2); 5.5 (s,br., 2H, NH_2); 7.2-7.8 (m, 5H, C_6H_4 and pyrimidine H-2).
9a	3450, 3380, 3300-3220 br. (NH_2 and OH); 1680 (CO); 1620 (C=N); 1600 (C=C).	1.1 (t, 3H,ester CH_3); 2.4 (s,3H,CH_3); 4.1 (q, 2H, ester CH_2); 7.2-8.8 (m, 9H, C_6H_5 and two NH_2); 11.3 (s, 1H, OH).
9b	3440, 3380, 3310-3220 (NH_2) and OH); 1680 (CO); 1620 (C=N); 1600 (C=C).	1.2 (t,3H, ester CH_3); 2.4 (s, 3H,CH_3); 2.7 (s, 3H, CH_3); 4.1 (q,2H,ester CH_2); 7.2-8.1 (m, 8H,C_6H_4 and two NH_2); 11.5 (s, 1H,OH).
10a	3440, 3340, 3250 (NH_2); 1680 (CO); 1620 (C=N); 1600 (C=C).	1.1 (t,3H,ester CH_3); 2.4 (s,3H,CH_3); 4.1 (q,2H, ester CH_2); 5.6 (s,br., 4H, two NH_2); 7.2-8.1 (m, 11H, aromatic and NH).
10b	3450, 3330, 3270 (NH_2); 1680 (CO); 1620 (C=N); 1600 (C=C).	1.1 (t, 3H,ester CH_3); 2.4 (s, 3H, CH_3); 2.7 (s, 3H, CH_3); 4.1(q, 2H, ester CH_2); 5.5 (s,br.,4H, two NH_2); 7.2-8.2(m, 10H, aromatic and NH).

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