SYNTHESIS OF PYRIDAZINE, PYRIDAZIN-3-ONE, 2-AMINOPYRROLE AND 2,5-DIAMINOPYRIDINE DERIVATIVES FROM DICYANOMETHYLENE COMPOUNDS

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Abstract — Aromatic diazonium chlorides react with dicyanomethylene compounds 1-3 and 18 to give the hydrazone derivatives which are readily cyclized into pyridazine 8-10 and pyridazine-3-one 19 respectively. 2-Aminopyrrole 11-13 and dihydropyridazin-3-one 20 are obtained by the reaction of 8-10 and 19 with zinc dust in the presence of acetic acid. Also the reaction of acetoacetanilide with malononitrle in acetic acid and piperidine as a catalyst was studied. The structures of the compounds obtained have been assigned on the basis of elemental analyses and spectral data.

INTRODUCTION

Dicyanomethylene compounds 1-3, readily obtained via the reaction of β-ketoanilide and β-ketoesters with malononitrile and ethyl cyanoacetate[1-4], are verstile reagents and have been extensively utilized as intermediates in heterocyclic synthesis[5-8]. In this communication, we report the synthesis of pyridazine, aminopyrrole and diaminopyridine by the coupling of aromatic diazonium chlorides with dicyanomethylene compounds.

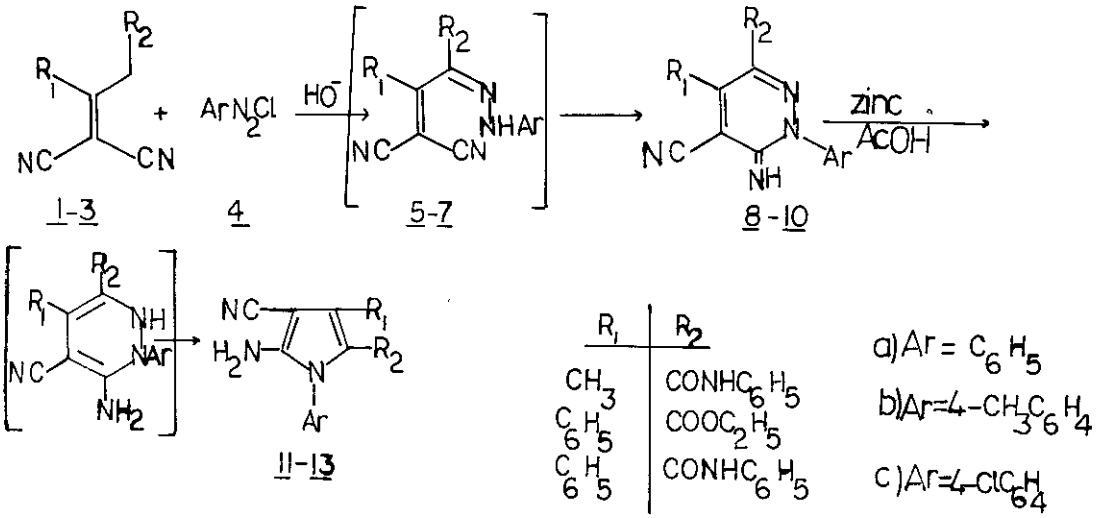
RESULTS AND DISCUSSION

Dicyanomethylene compounds 1-3 couple with aromatic diazonium chlorides in a sodium acetate buffered solution or ethanol to yield the corresponding hydrazone derivatives 5-7 , which are readily cyclized into the pyridazine derivatives 8-10 in the reaction mixture (Scheme 1). The structure of the compound 8-10 was deduced from their elemental analyses and their spectra. Infrared spectrum of compound 8a contained bands of 3310, 2220, and 1670 cm^{-1} due to the NH, CN, and CO groups respectively. Pmr spectrum in dimethyl sulfoxide-d_6 showed a multiplet at δ 7.0-7.8 (H,aromatic and NH) and a singlet at δ 2.4 (3H, CH_3) ppm. Spectral and

analytical data of compounds 8-10 are summarised in Tables 1 and 2.

Treatment of pyridazine derivatives 8-10 with zinc dust in the presence of acetic acid at 80°C gave aminopyrrole derivatives (Scheme 1). The structure of aminopyrrole 11-13 was established on the basis of analytical and spectroscopic data, for example, compound 12a exhabits 3420, 3320, 3220, 2210 and 1680 cm^{-1} due to NH_2,

Scheme 1.

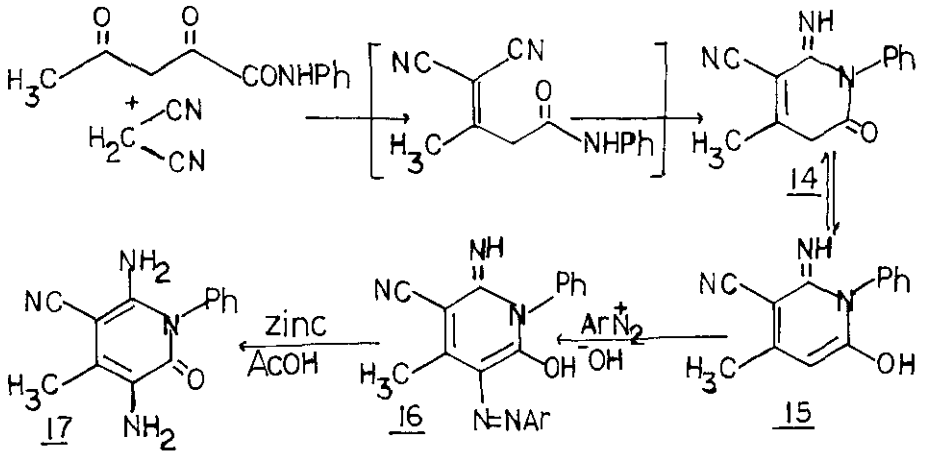


CN, and CO groups respectively. Its pmr spectrum showed δ 0.9 (t,3H); 3.8 (q,2H); 5.8 (s,2H), and 7.3-7.8 (m, 10 H) ppm. The signal at δ 5.8 ppm was disappeared upon shaking with D_2O and another signal appeared at δ 3.7 ppm.

The reaction of acetoacetanilide and malononitrile was mentioned before in non polar solvent[2,3]. But, in this report the reaction was carried in acetic acid, and the isolated product has analytical data consistent with the formula $C_{13}H_{11}N_3O$. Its infrared spectrum reveals bands at 3280 (NH), 2210 (CN), 1670(CO) and 1620(C=C) cm^{-1}. Also, pmr showed signals at δ 2.3 (s,3H), 6.1 (s,1H), and 7.1-7.7 (m, 7H) ppm On the basis of these data, the product was assigned the structure 14 . Compound 14 couples with aromatic diazonium chlorides in a sodium acetate buffered solution to yield the corresponding azo derivatives 16, which were all reduced by zinc dust in acetic acid to give the diaminopyridene derivative 17 (Scheme 2). Infrared spectrum of 17 showed bands at 3460, 3400, 3280 (NH_2), and 2200 (CN) cm^{-1}. Pmr

spectrum of 17 exhibits signals at δ 2.2 (s,3H), 3.3(s,4H), and 7-7.5 (m,5H) ppm.

Scheme 2.

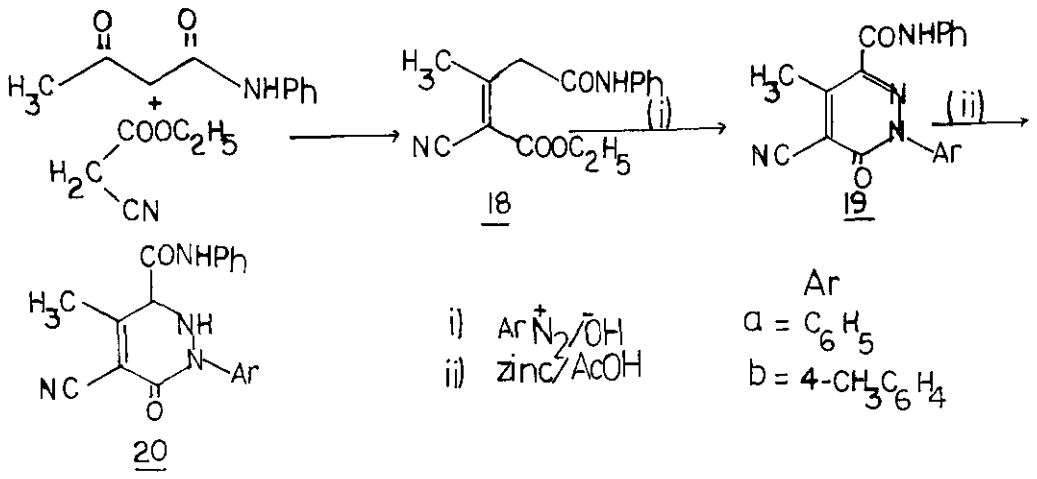


a) Ar = C_6H_5
b) Ar = 4-$CH_3C_6H_4$
c) Ar = 4-ClC_6H_4
d) Ar = 2-$HOOCC_6H_4$
e) Ar = 2-$H_3COOCC_6H_4$

The signal at δ 3.3 ppm disappeared upon shaking with D_2O and δ 3.9 ppm was appeared.

Also, acetoacetanilide reacts with ethyl cyanoacetate in acetic acid in presence of pipieridine as a catalyst to give 18, which coupled with aromatic diazonium chlorides in ethanolic sodium acetate solution to yield the corresponding pyridazine derivatives 19 (Scheme 3). Compounds 19 were converted to dihydropyridazin-3-one derivatives 20 by zinc dust in acetic acid. The structures 19 and 20 were elucidated by elemental analyses and spectral data (see exp.),(Scheme)3.

Scheme 3.



i) $ArN_2^+/\bar{O}H$
ii) zinc/AcOH

Ar
a = C_6H_5
b = 4-$CH_3C_6H_4$

The results of the present work indicate the reaction of aromatic diazonium chlorides with dicyanomethylene compounds, provides the basis of a convenient procedure for the synthesis of pyridazine and aminopyrrole derivatives.

EXPERIMENTAL

Melting points were determined with an electrothermal melting point apparatus (Gallen Kamp) and are uncorrected. The IR spectra (KBr) were measured on a pye-Unicam SP 1000 spectrophotometer. PMR spectra were recorded on a Variam EM-360 instrument at 60 MHz in dimethylsulfoxide-d_6 solution, with tetramethylsilane as the internal standard. Elemental microanalyses were carried out by the Micro-analytical laboratory, University of Cairo, Giza, Egypt. Alkylidene malononitriles 1-3 are obtained as previously prepared in literature[2,3].

4-Cyano-3-imino-5,6-disubistituted 2,3-Dihydropyridazines 8-10. A solution of ylidenenitrile (0.005 mol) in ethanol (50 ml) was stirred for 5 min with sodium acetate (3g) and chilled in an ice-salt bath to 0-5°C. To the resulting cold solution was added the desired diazonium salt (0.005 mol) solution. After the addition was completed, the reaction mixture was stirred for additional 1 h. The crude solid obtained was collected, washed with water and recrystallized from sutable solvent. The dihydropyridazines 8-10 prepared are listed (Table 1 and 2).

2,3-Disubistituted 5-amino-1-Aryl-4-cyanopyrroles 11-13. To a suspension of compounds 8-10 (5 mmol) in acetic acid (20 ml) at 80°C, zinc dust (2g) was added in small portions for 20 min. The reaction mixture was filtered while hot. The filtrate was diluted with 100 ml of water, the crude solid separated was collected and crystallized to give the corresponding 11-13 (Table 1 and 2).

2-Aryl-4-cyano-5-methyl-3-oxo-2,3-dihydropyridazin-6-phenylcarboxanilide 19. A solution of compound 18 (0.005 mol) in ethanol (50 ml) was stirred for 5 min with sodium acetate (3g) at 0-5°C. To the resulting cold solution was added arene diazonium chloride (0.005 mol) solution, the reaction mixture was stirred at 0°C for 30 min. The crude product was collected and crystallized from acetic acid. The 3-oxo-dihydropyridazine 19 prepared are listed (Table 1 and 2).

2-Aryl-4-cyano-5-methyl-6-oxo-1,2,3,6-tetrahydropyridazine-3-phenylcarboxanilides 20 To a suspension of compound 19 (5 mmol) in acetic acid (20 ml) at 80°C, zinc dust (3g) was added in small portions for 15-20 min. The reaction mixture was filtered

while hot. The filtrate was diluted with 70 ml of water. The solid was collected and crystallized from dilute acetic acid to give the corresponding 20 (Table 1 & 2).

2-Imino-4-methyl-6-hydroxy-3-carbonitrile-N-phenyl-pyridine 14 . A mixture of 1.8 g (0.01 mol acetoacetanilide, 0.7g (0.01 mol) of malonoitrile, one drop of piperedine and 20 ml of acetic acid was heated under reflux for 3 h. Colorless plates, mp 217°C Anal. $C_{13}H_{11}N_3O$, calcd. (found):C,69.19 (69.21); H,4.91(4.70), N,18.62 (18.73)%.

4-Arylazo-2-imino-4-methyl-6-hydroxy-3-carbonitrile-N-phenylpyridines 16.
A solution of compound 14 (0.005 mol) in ethanol (50 ml) was stirred for 5 min with sodium acetate (3g) at 0°C. To the resulting cold solution was added arene diazonium chloride (0.005 mol) solution, the reaction mixture was stirred at 0°C for 30 min. The crude product was collected and crystallized from acetic acid. The compounds 16 prepared are listed in Tables 1 and 2.

2,5-Diamino-1,6-dihydro-4-methyl-6-oxo-1-phenylpyridine-3-carbonitrile 17. To a suspension of compound 16a (5 mmole) in acetic acid (20 ml) at 80°C, zinc dust(2g) was added in small portions. The reaction mixture was filtered while hot. The filtrate was diluted with water. The crude solid was collected and crystallized from acetic acid to give the corresponding 17. When the reaction was repeated for 16b-16e the compounds obtained were identical in all respects with compound 17.

Table 1:
List of the newly synthesised heterocyclic derivatives 8-13, 16, 17, 19 and 20.

Compound No	R_1	R_2	Ar	M.P.°C	Molecular formula	C% Calcd. (found)	H% Calcd. (found)	N% Calcd. (found)
8a	CH_3	$CONHC_6H_5$	C_6H_5	160	$C_{19}H_{15}N_5O$	69.28 (69.30)	4.59 (4.31)	21.26 (21.12)
8b	CH_3	$CONHC_6H_5$	$P\text{-}CH_3C_6H_4$	180	$C_{20}H_{17}N_5O$	69.96 (69.75)	4.99 (5.01)	20.39 (19.90)
9a	C_6H_5	$COOC_2H_5$	C_6H_5	193	$C_{20}H_{16}N_4O_2$	69.75 (69.40)	4.68 (4.81)	16.27 (16.43)
9c	C_6H_5	$COOC_2H_5$	$P\text{-}ClC_6H_4$	50[S]	$C_{20}H_{15}N_4ClO_2$	63.41 (63.10)	3.99 (4.08)	14.79 (14.96)
10a	C_6H_5	$CONHC_6H_5$	C_6H_5	155	$C_{24}H_{17}N_5O$	73.64 (73.30)	4.37 (4.31)	17.89 (17.91)
10b	C_6H_5	$CONHC_6H_5$	$P\text{-}CH_3C_6H_4$	230	$C_{25}H_{19}N_5O$	74.05 (73.92)	4.72 (4.81)	17.27 (16.83)

Compound No.	R_1	R_2	Ar	M.P.°C	Molecular formula	C% Calcd (Found)	H% Calcd (Found)	N% Calcd (Found)
11a	CH_3	$CONHC_6H_5$	C_6H_5	265	$C_{19}H_{16}N_4O$	72.13 (71.82)	5.09 (4.81)	17.70 (17.90)
11b	CH_3	$COOC_2H_5$	$P\text{-}CH_3C_6H_4$	270	$C_{20}H_{18}N_4O$	72.70 (72.61)	5.49 (5.52)	16.95 (17.21)
12a	C_6H_5	$COOC_2H_5$	C_6H_5	194	$C_{20}H_{17}N_3O_2$	72.49 (72.60)	5.17 (5.23)	12.68 (12.82)
13a	C_6H_5	$CONHC_6H_5$	C_6H_5	262	$C_{24}H_{18}N_4O$	76.17 (75.90)	4.79 (4.91)	14.80 (15.00)
13b	C_6H_5	$CONHC_6H_5$	$P\text{-}CH_3C_6H_4$	270	$C_{25}H_{20}N_4O$	76.51 (76.30)	5.14 (4.91)	14.27 (14.42)
16a	-	-	C_6H_5	212	$C_{19}H_{15}N_5O$	69.28 (69.21)	4.59 (4.63)	21.26 (21.56)
16b	-	-	$P\text{-}CH_3C_6H_4$	265	$C_{20}H_{17}N_5O$	69.95 (70.12)	4.99 (5.30)	20.39 (20.70)
16c	-	-	$P\text{-}ClC_6H_4$	264	$C_{19}H_{14}N_5ClO$	62.72 (62.41)	3.88 (3.80)	19.25 (18.92)
16d	-	-	$O\text{-}HOOCC_6H_4$	264	$C_{20}H_{15}N_5O_3$	64.33 (64.12)	4.05 (3.91)	18.76 (19.10)
16e	-	-	$O\text{-}H_3COOCC_6H_4$	259	$C_{21}H_{17}N_5O_3$	65.11 (64.91)	4.42 (4.50)	18.08 (18.21)
17	-	-	-	245	$C_{13}H_{12}N_4O$	64.98 (64.70)	5.03 (5.11)	23.32 (23.11)
19a	-	-	C_6H_5	230	$C_{19}H_{14}N_4O_2$	69.08 (69.11)	4.27 (4.13)	16.96 (17.20)
19b	-	-	$P\text{-}CH_3C_6H_4$	220	$C_{20}H_{16}N_4O_2$	69.76 (69.41)	4.68 (4.84)	16.26 (15.83)
20a	-	-	C_6H_5	220	$C_{19}H_{16}N_4O_2$	68.66 (68.41)	4.85 (5.00)	16.85 (17.11)
20b	-	-	$P\text{-}CH_3C_6H_4$	185	$C_{20}H_{18}N_4O_2$	69.53 (69.01)	5.24 (5.32)	16.47 (16.70)

S : Sublimation

Table 2: IR Spectra (KBr) of some compounds under study.

Compound No	IR cm^{-1}
8b	3380(NH); 3090(CH); 2980(CH_3), 2240(CN); 1660(CO); 1620(C=N) and 1600(C=C)

Compound No	IR cm^{-1}
9a	3290(NH); 3020(CH); 2980(CH_3); 2220(CN); 1710(CO) and 1625(C=N).
10b	3450, 3320(NH); 2200(CN) and 1650(CO).
11b	3460, 3360, 3320(NH_2); 2220(CN); 1660(CO) and 1630(C=N).
12a	3420, 3320, 3220(NH_2); 2210(CN); 1680(CO); and 1620(C=C).
13b	3400, 3360, 3330(NH_2); 2220(CN); 1660(CO) and 1600(C=C).
16b	3310(NH); 220(CN); 1650(CO) and 1590(C=N).
17	3400, 3280, 3190(NH_2) & 2200(CN) and 1650(CO).
19b	3320(NH); 2220(CN) and 1690, 165(CO).
20b	2220(CN); 1690(CO); and 1620(C=N), 3300(NH); 2210(CN); and 1680(CO).

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