PYRIDAZINE DERIVATIVES AND RELATED COMPOUNDS PART 5. PYRAZOLO[3,4-c]PYRIDAZINE: SYNTHESIS AND SOME REACTIONS

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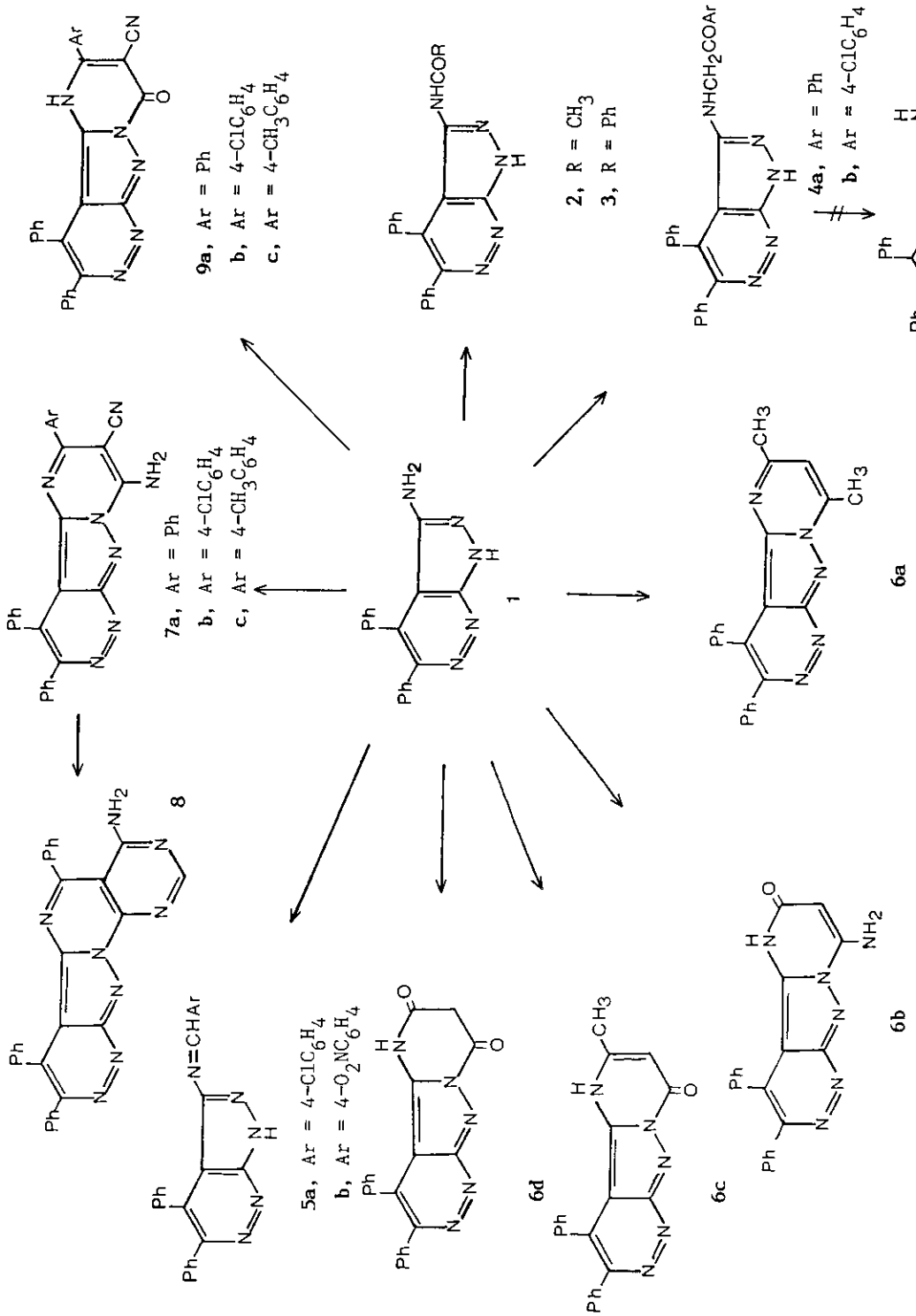
Abstract — This paper describes the synthesis of three pyrimido[1',2':1,5]-pyrazolo[3,4-c]pyridazines (**6,7** and **9**) starting from 3-amino[3,4-c]pyridazine (**1**). Pyrimido[5',4':5,6]pyrimido[1',2':1,5]pyrazolo[3,4-c]pyridazine derivative (**8**) was obtained by condensing **7a** with formamide. Reactions of **1** with acetic anhydride, benzoyl chloride, phenacyl bromide and 4-chlorophenacyl bromide gave 3-substituted amino derivatives.

As an extension of our previous investigations[1,2] directed toward the synthesis of heterocyclic-annelated pyridazines as building blocks for the preparation of potential biologically active compounds, the 3-amino-1H-pyrazolo[3,4-c]pyridazine system became an object of interest. Various biological activities, e.g. an interesting chemotherapeutic activity[3,4] has been observed with derivatives of 1H-pyrazolo[3,4-c]-pyridazines. Synthesis of this ring system is usually achieved by cyclization reaction of 3-chloropyridazine derivatives substituted with such groups as cyano, ethoxycarbonyl and hydroxymethyl in the 4-position with hydrazine.[5] 3-Amino-5,6-diphenyl-1H-pyrazolo[3,4-c]pyridazine (**1**) was synthesized following the literature by reaction of 3-chloro-5,6-diphenylpyridazine-4-carbonitrile with hydrazine.[6]

Compound (**1**) was treated with benzoyl chloride in presence of pyridine to afford an 85 % yield of 3-acetylamino and 3-benzoylamino derivatives (**2**) and (**3**). The characteristic amide band appears in the ir at 1710 cm^{-1}. Similarly compound (**1**) reacted with phenacyl bromide and with 4-chlorophenacyl bromide to yield 3-phenacyl and 3-(4-chloro)-phenacylamino derivatives (**4a,b**). The ir spectrum revealed absorption at 1680 cm^{-1} for C=O group. An attempted cyclization reaction for compounds (**4a,b**) was failed to provide 3,8,9-triphenyl-1H-imidazolo[2',3':5,1]pyrazolo[3,4-c]pyridazine.

Condensation of **1** with aromatic aldehyde such as 4-chloro- and 4-nitrobenzaldehyde furnished the corresponding anils (**5a,b**).

In accord to the well known cyclocondensation of 5-aminopyrazoles with ß-bifunctional reagents to yield pyrazolo[1,5-a]pyrimidines,[7] compound (**1**) reacted with acetylacetone, ethyl cyanoacetate, ethyl acetoacetate and diethyl malonate to yield pyrimido[1',2':1,5]-pyrazolo[3,4-c]pyridazine derivatives (**6a-d**). The structure of the tricyclic derivatives (**6a-d**) was inferred from the analytical and spectroscopic data. The ^{1}H-nmr spectrum of **6a** showed signals at δ 2.7(s, 3H, CH_3-2), 3.8(d, J = 7 Hz, 3H, CH_3-4), 7.4-7.8(m, 10H, 2Ph) and 8.8(m, 1H, H-3).


9a, Ar = Ph
b, Ar = 4-ClC6H4
c, Ar = 4-CH3C6H4
2, R = CH3
3, R = Ph
4a, Ar = Ph
b, Ar = 4-ClC6H4
7a, Ar = Ph
b, Ar = 4-ClC6H4
c, Ar = 4-CH3C6H4
1
6a
8
5a, Ar = 4-ClC6H4
b, Ar = 4-O2NC6H4
6d
6c
6b

Compound (**1**) was also subjected to the reaction with arylidene compounds. It was found that **1** reacts with arylidenemalononitriles to give derivatives (**7a-c**), whose structures were assigned on the basis of analytical and spectral data. The ir spectrum revealed absorption at 3400, 3320 cm^{-1} (NH_2) and 2240 cm^{-1} (CN). Structure of compound (**7a**) was also confirmed by the following chemical transformation. Cyclodehydration with formamide furnished the corresponding pyrimido[5',4':5,6]pyrimido[1',2':1,5]pyrazolo[3,4-c]pyridazine derivative (**8**). Compound (**1**) is also capable of a similar condensation reaction with ethyl arylidenecyanoacetate to give (**9a-c**).

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra (KBr) were recorded on a Unicam SP 1000 Spectrophotometer. ^{1}H-Nmr spectra in DMSO-d_6 were recorded on a Varian A-60 Spectrometer using tetramethylsilane as an internal reference. Elemental analyses were carried out at the Microanalytical Center at the University of Cairo, Egypt.

3-Acetylamino-4,5-diphenyl-1H-pyrazolo[3,4-c]pyridazine 2.

A mixture of 3-amino-5,6-diphenyl-1H-pyrazolo[3,4-c]pyridazine (**1**) (1.43 g, 5 mmol) and pyridine (5 ml, 0.06 mol) was heated under reflux in acetic anhydride (20 ml, 196 mmol) for 5 h. The reaction mixture was allowed to cool to room temperature, then poured into 50 ml of 6N hydrochloric acid. The precipitate was filtered. The yield was 1.35 g (85 %), mp 179°C (ethanol). Anal. Calcd for $C_{19}H_{15}N_5O$: C, 69.28; H, 4.59; N, 21.26. Found: C, 69.00; H, 4.61; N, 21.30. ^{1}H-Nmr: δ 2.8(s, 3H, CH_3), 7.0-7.8(m, 10H, 2Ph), 8.1-8.4(br s, 2H, 2NH); ir: 3250, 1710, 1610 cm^{-1}.

3-Benzoylamino-4,5-diphenyl-1H-pyrazolo[3,4-c]pyridazine 3.

A mixture of compound (**1**) (1.43 g, 5 mmol) and pyridine (5 ml, 60 mmol) was heated under reflux in benzoyl chloride (10 ml, 70 mmol) for 5 h. The reaction mixture was allowed to cool to room temperature, then poured into 50 ml of 6N hydrochloric acid. The precipitate was filtered. The yield was 1.5 g (85 %), mp 165°C (ethanol). Anal. Calcd for $C_{24}H_{17}N_5O$: C, 73.63; H, 4.38; N, 17.89: Found: C, 73.50; H, 4.20; N, 17.60. Ir: 3270, 1710, 1610 cm^{-1}.

Reaction of 1 with Phenacyl Bromide or 4-Chlorophenacyl Bromide.

To a solution of compound (**1**) (1.43 g, 5 mmol) in acetic acid (30 ml), phenacyl bromide (1 g, 5 mmol) or 4-chlorophenacyl bromide (1.16 g, 5 mmol) was added. The reaction mixture was heated under reflux for 7 h (the progress of the reaction was followed by tlc). The reaction mixture was concentrated to give 3-phenacylamino-4,5-diphenyl-1H-pyrazolo-[3,4-c]pyridazine (**4a**) or 3-(4-chlorophenacyl)amino-4,5-diphenyl-1H-pyrazolo[3,4-c]-pyridazine (**4b**).

4a: 1.2 g (60 %), mp 195°C (acetic acid). Anal. Calcd for $C_{25}H_{19}N_5O$: C, 74.05; H, 4.72; N, 17.27. Found: C, 73.86; H, 4.20; N, 17.40. ^{1}H-Nmr: δ 4.2(d, J = 9 Hz, 2H, CH_2), 7.6-8.0(m, 15H, 3Ph), 8.2-8.5(br s, 2H, 2NH); ir: 3250, 1680, 1620 cm^{-1}.

4b: 1.7 g (70 %), mp 189°C (acetic acid). Anal. Calcd for $C_{25}H_{18}N_5OCl$: C, 68.25; H, 4.12; N, 15.92. Found: C, 67.92; H, 3.90; N, 15.79. Ir: 3170, 1680, 1620 cm^{-1}.

Reaction of 1 with 4-Chloro- or 4-Nitrobenzaldehyde.

To a solution of compound (**1**) (1.43 g, 5 mmol) in n-butanol (30 ml), 4-chlorobenzaldehyde (0.7 g, 5 mmol) or 4-nitrobenzaldehyde (0.75 g, 5 mmol) was added. The reaction mixture was heated under reflux for 5 h (the progress of the reaction was followed by tlc). The solvent was evaporated under reduced pressure. The solid residue was digested with n-butanol and the products (**5a,b**) were isolated and recrystallized.

5a: 1.1 g (55 %), mp 204°C (n-butanol). Anal. Calcd for $C_{24}H_{16}N_5Cl$: C, 70.32; H, 3.93; N, 17.25. Found: C, 70.20; H, 3.62; N, 17.00. ^{1}H-Nmr: δ 3.8(s, 1H, =CHAr), 7.3-7.6(m, 10H, 2Ph), 7.8-7.9(m, 4H, ArH), 8.6(s, 1H, NH); ir: 3250, 1590, 1510 cm^{-1}.

5b: 1.2 g (57 %), mp 300°C (n-butanol). Anal. Calcd for $C_{24}H_{16}N_6O_2$: C, 68.56; H, 3.83; N, 19.99. Found: C, 68.40; H, 4.00; N, 20.10. Ir: 3250, 1590, 1510 cm^{-1}.

6,8-Dimethyl-3,4-diphenylpyrimido[1',2':1,5]pyrazolo[3,4-c]pyridazine 6a.

To a solution of compound (**1**) (1.43 g, 5 mmol) in ethanol (30 ml), acetylacetone (0.52 g, 6 mmol) was added. The reaction mixture was heated under reflux for 7 h. The solvent was evaporated under reduced pressure. The solid residue was digested with ethanol and filtered to yield 1.57 g (90 %), mp 210°C (toluene). Anal. Calcd for $C_{22}H_{17}N_5$: C, 75.17; H, 4.70; N, 19.93. Found: C, 75.17; H, 4.70; N, 19.80. ^{1}H-Nmr: δ 2.7(s, 3H, CH_3-2), 3.8(d, J = 7 Hz, 3H, CH_3-4), 7.4-7.8(m, 10H, 2Ph), 8.8(m, 1H, H-3); ir: 3150, 1629, 1375 cm^{-1}.

8-Amino-3,4-diphenylpyrimido[1',2':1,5]pyrazolo[3,4-c]pyridazin-6(5H)-one 6b.

A mixture of compound (**1**) (1.43 g, 5 mmol) and ethyl cyanoacetate (0.6 g, 5 mmol) was heated at 180°C in an oil bath for 3 h. The hot reaction mixture was allowed to cool, before it was treated with ethanol and filtered to yield 0.8 g (45 %), mp 320°C (n-butanol). Anal. Calcd for $C_{20}H_{14}N_6O$: C, 67.78; H, 3.98; N, 23.70. Found: C, 67.50; H, 3.98; N, 23.50. ^{1}H-Nmr: δ 5.0(s, 2H, NH_2), 7.4-7.8(m, 10H, 2Ph), 8.7(s, 1H, H-3); ir: 3430, 3330, 1670 cm^{-1}.

6-Methyl-3,4-diphenylpyrimido[1',2':1,5]pyrazolo[3,4-c]pyridazin-8(5H)-one 6c.

To a solution of compound (**1**) (1.43 g, 5 mmol) in acetic acid (20 ml), ethyl acetoacetate (0.95 g, 5 mmol) was added. The reaction mixture was heated under reflux for 5 h. The solvent was evaporated under reduced pressure. The solid residue was digested with acetic acid and isolation by suction to yield 1.1 g (63 %), mp 360°C (acetic acid). Anal. Calcd for $C_{21}H_{15}N_5O$: C, 71.37; H, 4.27; N, 19.82. Found: C, 71.10; H, 4.50; N, 19.60. ^{1}H-Nmr:

δ 2.9(s, 3H, CH_3), 7.5-7.8(m, 10H, 2Ph), 8.6(s, 1H, H-3); ir: 3100, 1680, 1580 1560 cm^{-1}.

3,4-Diphenylpyrimido[1',2':1,5]pyrazolo[3,4-c]pyridazine-6,8(5H,7H)-dione 6d.

A mixture of compound (**1**) (1.43 g, 5 mmol) and diethyl malonate (0.8 g, 5 mmol) was heated at 180°C in an oil bath for 1 h, the reaction mixture was then cooled and triturated with ethanol. The solid product of **6d** was collected by suction and recrystallized from toluene, mp 270°C, yield 0.79 g (45 %). Anal. Calcd for $C_{20}H_{13}N_5O_2$: C, 67.59; H, 3.50; N, 19.71. Found: C, 67.40; H, 3.50; N, 19.60. Ir: 3100, 1690, 1660 cm^{-1}.

8-Amino-6-aryl-3,4-diphenylpyrimido[1',2':1,5]pyrazolo[3,4-c]pyridazine-7-carbonitriles 7a-c (General Procedure).

A mixture of compound (**1**) (1.43 g, 5 mmol) and arylidenemalononitrile (benzylidene, 4-chlorobenzylidene and 4-methoxybenzylidene, 5 mmol) was heated under reflux for 8-10 h, in n-butanol (30 ml) and 1 ml of piperedine. The reaction mixture was then allowed to cool to room temperature, poured into crushed ice (200 g) and neutralized with conc. HCl. The precipitate was isolated by suction and recrystallized.

7a: Yield 1.1 g (50 %), mp 340°C (ethanol). Anal. Calcd for $C_{27}H_{17}N_7$: C, 73.78; H, 3.90; N, 22.31. Found: C, 73.50; H, 4.10; N, 22.10: ^{1}H-Nmr: δ 4.3(br s, 2H, NH_2), 7.3-7.5(m, 15H, 3Ph); ir: 3400, 3320, 2240 cm^{-1}.

7b: Yield 0.94 g (40 %), mp 365°C (ethanol). Anal. Calcd for $C_{27}H_{16}N_7Cl$: C, 68.42; H, 3.40; N, 20.69. Found: C, 68.30; H, 3.50; N, 20.40. Ir: 3410, 3320, 2245 cm^{-1}.

7c: Yield 1.0 g (43 %), mp 330°C (ethanol). Anal. Calcd for $C_{28}H_{19}N_7O$: C, 71.62; H, 4.07; N, 20.88. Found: C, 71.40; H, 4.20; N, 20.50. Ir: 3410, 3310, 2235 cm^{-1}.

4-Amino-5,7,8-triphenylpyrimido[5',4':5,6]pyrimido[1',2':1,5]pyrazolo[3,4-c]pyridazine 8.

A mixture of compound (**7a**) (0.4 g, 1 mmol) and formamide (5 ml, 0.1 mol) was heated at 120°C in an oil bath for 1 h, the reaction mixture was then cooled and poured into ice-water (100 ml). The precipitated product was isolated by suction to yield 0.19 g (45 %), mp 203°C (toluene). Anal. Calcd for $C_{28}H_{18}N_8$: C, 72.08; H, 3.88; N, 24.02. Found: C, 71.80; H, 3.90; N, 24.20. ^{1}H-Nmr: δ 4.4(br s, 2H, NH_2), 7.5-7.7(m, 15H, 3Ph), 8.8(s, 1H, H-2); ir: 3420, 3320, 1610 cm^{-1}.

6-Aryl-7-cyano-3,4-diphenylpyrimido[1',2':1,5]pyrazolo[3,4-c]pyridazin-8(5H)-ones 9a-c (General Procedure).

A mixture of compound (**1**) (1.43 g, 5 mmol), ethanol (30 ml), ethyl arylidenecyanoacetate (benzylidene, 4-chlorobenzylidene and 5-mrthoxybenzylidene, 5 mmol) and piperidine (1 ml) was heated under reflux for 7-10 h (the progress of the reaction was followed by tlc). The reaction mixture was then allowed to cool to room temperature, poured into crushed ice (200 g) and neutralized with conc. HCl. The precipitate was isolated and recrystallized.

9a: Yield 0.7 g (32 %), mp 350°C (ethanol). Anal. Calcd for $C_{27}H_{16}N_6O$: C, 73.62; H, 3.66; N, 19.08. Found: C, 73.90; H, 3.80; N, 19.20. Ir: 3100, 2240, 1680 cm^{-1}.
9b: Yield 1.06 g (45 %), mp 320°C (ethanol). Anal. Calcd for $C_{27}H_{15}N_6OCl$: C, 68.28; H, 3.18; N, 17.69. Found: C, 68.00; H, 3.00; N, 17.80. Ir: 3100, 2230, 1680 cm^{-1}.
9c: Yield 0.89 g (42 %), mp 335°C (ethanol). Anal. Calcd for $C_{28}H_{18}N_6O_2$: C, 71.47; H, 3.85; N, 17.86. Found: C, 71.30; H, 3.60; N, 17.60. Ir: 3210, 2235, 1685 cm^{-1}.

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