

PYRIDAZINE DERIVATIVES AND RELATED COMPOUNDS PART 6.

SYNTHESIS OF TRIAZOLO[3',4':5,1]PYRAZOLO[3,4-*c*]PYRIDAZINE, PYRIDO[2',1':3,2]-[1,2,4]TRIAZOLO[5',1':5,1]PYRAZOLO[3,4-*c*]PYRIDAZINE AND NAPHTHO[2,1-*e*]-PYRIDAZINO[3',4':3,4]PYRAZOLO[5,1-*c*][1,2,4]TRIAZINE DERIVATIVES

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Abstract — 1,2,4-Triazolo[3',4':5,1]pyrazolo[3,4-*c*]pyridazine, pyrido[2',1':3,2]-[1,2,4]triazolo[5',1':5,1]pyrazolo[3,4-*c*]pyridazine, naphtho[2,1-*e*]pyridazino[3',4':3,4]pyrazolo[5,1-*c*][1,2,4]triazine and pyridazino[3',4':3,4]pyrazolo[5,1-*c*][1,2,4]triazin-4(1H)-one were synthesized from 3-amino-1H-pyrazolo[3,4-*c*]pyridazine.

As a continuation of our previous work¹ about the synthesis of fused systems of pyrazolo[3,4-*c*]pyridazine with different nitrogen heterocycles, we report in this paper the synthesis of triazolo[3',4':5,1]pyrazolo[3,4-*c*]pyridazine and pyridazino[3',4':3,4]pyrazolo[5,1-*c*]triazine and some related compounds. Synthesis of these compounds was of interest since some azolo[5,1-*c*][1,2,4]triazines have been reported to have biological and medicinal activities.²

Nitrilimines, usually synthesized in situ by base-catalysed elimination of hydrochloric acid from hydrazonoyl chloride, are reactive intermediates that have found extensive use in heterocyclic synthesis.^{3,4} Thus it has been found that 3-amino-4,5-diphenyl-1H-pyrazolo[3,4-*c*]pyridazine (1)⁵ reacts with *N*-phenylbenzohydrazonoyl chloride in the presence of triethylamine to yield the 1,3,8,9-tetraphenyl-1H-[1,2,4]triazolo[3',4':5,1]pyrazolo[3,4-*c*]pyridazine (2). Based on analytical and spectral data, the formation of compound (2) is assumed to proceed via [2+3] dipolar cycloaddition mechanism.

We previously reported⁶ that 3-amino-4-cynopyrazole reacts with pyridine 1-oxide in boiling dioxane to give 4H,5H-pyrazolo[5',1':2,3][1,2,4]triazolo[1,5-*a*]pyridine-3-carbonitrile. We carried out the reaction of 1 with pyridine 1-oxide in dioxane to give the corresponding 3,4-diphenyl-5H,5aH-pyrido[2',1':3,2][1,2,4]triazolo[5',1':5,1]pyrazolo[3,4-*c*]pyridazine (3). The structure of 3 has been assigned on the basis of analytical and spectral data. The ir spectrum shows an absorption band at 3200 cm⁻¹ due to an NH group, and the ¹H-nmr spectrum shows signals at δ 2.4(s, 1H, H-5a), 6.8(br s, 1H, NH), 7.2-7.4(m, 4H, H-6, H-7, H-8, H-9), and 7.6-7.9(m, 10H, 2Ph).

On the other hand, compound (1) could be converted into a variety of pyridazinopyrazolo-triazine derivatives via diazotization and coupling with active hydrogen reagents. Thus diazotized 1 coupled with β-naphthol to yield arylazo derivative (4). This could be readily cyclized into 5 on treatment with acetic acid.⁷

The structure of 7,8-diphenylnaphtho[2,1-*c*]pyridazino[3',4':3,4]pyrazolo[5,1-*c*][1,2,4]-triazine (5) has been assigned on the basis of analytical and spectral data. The ir spectrum of 5 shows no absorption bands referred to the OH group, and ^1H -nmr spectrum shows signals at δ 7.2-7.6(m, 10H, 2Ph), and 8.0-8.4(m, 6H, H-1, H-2, H-3, H-4, H-13, H-14) ppm.

In the same way diazotized 1 coupled with ethyl acetoacetate to yield directly 3-acetyl-9,10-diphenylpyridazino[3',4':3,4]pyrazolo[5,1-*c*][1,2,4]triazin-4(1H)-one (6). Compound (6) shows in the ir spectrum an absorption band at 1735 cm^{-1} due to acetyl group, and the ^1H -nmr spectrum shows signals at δ 2.4(s, 3H, CH_3), and 7.3-7.6(m, 10H, 2Ph) ppm. The structure of compound (6) was also confirmed by the following chemical transformation, condensation with phenylhydrazine furnished the corresponding 3-methyl-1,6,7-triphenyl-1H-pyrazolo[3,4-*c*]pyridazino[3',4':3,4]pyrazolo[5,1-*c*][1,2,4]triazine (7).

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra (KBr) were recorded on a Unicam SP 1000 Spectrophotometer. ^1H -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.

1,3,8,9-Tetraphenyl-1H-1,2,4-triazolo[3',4':5,1]pyrazolo[3,4-*c*]pyridazine 2.

To a solution of 3-amino-5,6-diphenyl-1H-pyrazolo[3,4-*c*]pyridazine (1) (1.43 g, 5 mmol) in ethanol (20 ml), *N*-phenylhydrazonyl chloride (1.2 g, 5 mmol) and triethylamine (10 ml) were added. The reaction mixture was heated under reflux for 20 h and then evaporated under reduced pressure. The residue was washed with petroleum ether (bp 40-60°C) and triturated with ethanol. The resulting solid product was filtered off to give 1.2 g (50 %), of 2, mp 320°C (ethanol). Anal. Calcd for $\text{C}_{30}\text{H}_{20}\text{N}_6$: C, 77.56; H, 4.34; N, 18.13. Found: C, 77.80; H, 4.00; N, 18.00. ^1H -Nmr: δ 7.0-8.0(m, 20H, 4Ph); ir: 1620, 1500, 1490 cm^{-1} .

3,4-Diphenyl-5H,5aH-pyrido[2',1':3,2][1,2,4]triazolo[5',1':5,1]pyrazolo[3,4-*c*]pyridazine 3.

To a solution of 1 (1.43 g, 5 mmol) in dioxane (20 ml), pyridine 1-oxide (0.5 g, 5 mmol) was added and the reaction mixture was heated under reflux for 18 h. The solvent was evaporated under reduced pressure and the oily residue was washed several times with water, and triturated with ethanol to yield 1.0 g (60 %) of 3, mp 200°C (ethanol). Anal. Calcd for $\text{C}_{22}\text{H}_{16}\text{N}_6$: C, 72.50; H, 4.42; N, 23.06. Found: C, 72.70; H, 4.30; N, 23.20. ^1H -Nmr: δ 2.4(s, 1H, H-5a), 6.8(br s, NH), 7.2-7.4(m, 4H, H-6, H-7, H-8, H-9), 7.6-7.9(m, 10H, 2Ph) ppm; ir: 3200, 1615, 1530 cm^{-1} .

3-(2-Hydroxy-1-naphthylazo)-4,5-diphenyl-1H-pyrazolo[3,4-c]pyridazine 4.

A mixture of **1** (1.43 g, 5 mmol) and 3 ml of 6N hydrochloric acid was cooled to 0°C and treated with sodium nitrite solution (0.3 g, 4 mmol, dissolved in the least amount of water). The reaction mixture was stirred for 30 min and then added to a solution of β -naphthol (0.7 g, 5 mmol) in 20 ml of ethanol containing sodium acetate (2.5 g). The solid product obtained on standing was collected to yield 1.4 g (62 %) of **4**, mp 160°C (ethanol). Anal. Calcd for $C_{27}H_{18}N_6O$: C, 73.29; H, 4.10; N, 18.99. Found: C, 72.90; H, 4.00; N, 19.10. Ir: 3400, 1610, 1600 cm^{-1} .

7,8-Diphenyl[2,1-e]pyridazino[3',4':3,4]pyrazolo[5,1-c][1,2,4]triazine 5.

Compound (**4**) (0.44 g) was heated under reflux in glacial acetic acid (10 ml) for 3 h. The solid obtained on cooling was collected to give 0.2 g (50 %) of **5**, mp 320°C (acetic acid). Anal. Calcd for $C_{27}H_{16}N_6$: C, 76.39; H, 3.80; N, 19.80. Found: C, 76.20; H, 3.50; N, 20.10. 1H -Nmr: δ 7.2-7.6(m, 10H, 2Ph), 8.0-8.4(m, 6H, H-1, H-2, H-3, H-4, H-13, H-14) ppm; ir: 1600, 1500, 1460 cm^{-1} .

3-Acetyl-9,10-diphenylpyridazino[3',4':3,4]pyrazolo[5,1-c][1,2,4]triazin-4(1H)-one 6.

A solution of diazotized **1** (prepared following the above procedure from **1**, 1.43 g 5 mmol) was poured gradually into a solution of ethyl acetoacetate (0.65 g, 5 mmol) in ethanol (20 ml) containing sodium acetate solution (2.5 g in 5 ml water) with continual stirring. The reaction mixture was then stirred at room temperature for 3 h, and the solid product so formed was refluxed in acetic acid (20 ml) for 2 h, then allowed to cool. The solid product was collected to yield 0.9 g (48 %) of **6**, mp 280°C (acetic acid). Anal. Calcd for $C_{21}H_{14}N_6O_2$: C, 65.95; H, 3.69; N, 21.98. Found: C, 66.20; H, 3.79; N, 22.10. 1H -Nmr: δ 2.4(s, 3H, CH_3), 7.3-7.6(m, 10H, 2Ph) ppm; ir: 1735, 1610, 1520 cm^{-1} .

3-Methyl-1,6,7-triphenyl-1H-pyrazolo[3,4-e]pyridazino[3',4':3,4]pyrazolo[5,1-c][1,2,4]-triazine 7.

To a solution of compound (**6**) (0.38 g, 1 mmol) in ethanol (20 ml), phenylhydrazine (0.22 g, 2 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 ethanol and isolated by suction to give 0.17 g (40 %) of **7**, mp 300°C (ethanol). Anal. Calcd for $C_{27}H_{18}N_8$: C, 71.35; H, 3.99; N, 24.66. Found: C, 71.20; H, 4.20; N, 24.80. 1H -Nmr: δ 1.7(s, 3H, CH_3), 7.2-7.9(m, 15H, 3Ph) ppm; ir: 1620, 1570, 1500 cm^{-1} .

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