

NEW PYRAZOLO[3,4-b]PYRIDINE AND PYRAZOLO[3,4-d]PYRIMIDINE DERIVATIVES FROM 4-ACETYL-5-AMINO-1,3-DIPHENYLPYRAZOLE

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Abstract- 4-Acetyl-5-amino-1,3-diphenylpyrazole (1) undergoes cyclization with compounds of the type $R-CH_2X$ ($X=COCH_3$ and/or $COPh$, $R=H$ and CH_3CO ; $X=R=CN$) and with formamide to give new pyrazolo[3,4-b]pyridine and pyrazolo[3,4-d]pyrimidine derivatives, respectively.

Pyrazolo[3,4-b]pyridine and pyrazolo[3,4-d]pyrimidine ring systems have aroused great interest in recent years due to the wide variety of their biological and pharmacological properties.¹⁻⁸

As part of our studies which have dealt with the preparation of difunctionalized pyrazoles as building blocks for condensed heterocycles, we wish now to report the synthesis of some new pyrazolopyridine and -pyrimidine derivatives from 4-acetyl-5-amino-1,3-diphenylpyrazole (1), readily available by alkaline hydrolysis of 3-methyl-4,6-diphenylisoxazolo[3,4-d]pyridazin-7(6H)-one.⁹

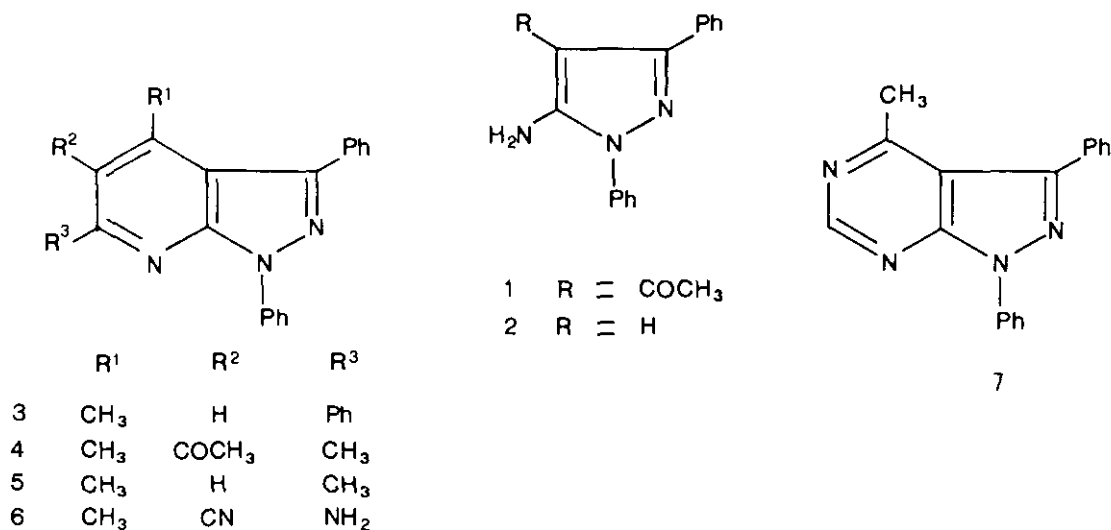
Thus, compound 1 undergoes condensation with acetophenone in the sense of Friedländer's synthesis of quinoline¹⁰ to afford 1,3,6-triphenyl-4-methylpyrazolo[3,4-b]pyridine (3), which was alternatively obtained from the reaction of 1,3-diphenyl-5-aminopyrazole (2) with 1-phenyl-1,3-butanedione.

Following the same approach, compounds 4 and 5¹¹ were obtained by reaction of 1 with ketones such as acetylacetone and acetone, respectively. Moreover, the usefulness of the title compound 1 in preparing pyrazolopyridines is illustrated by the condensation reaction with malononitrile which gives, in good yield, the 5,6-difunctional derivative 6.

Finally, it is noteworthy that, whereas 5-aminopyrazoles with the 4 position free cannot form a pyrimidine ring, compound 1 reacts smoothly e.g. with formamide to

give 1,3-diphenyl-4-methylpyrazolo[3,4-d]pyrimidine (7) (SCHEME)

SCHEME



Structural determination of the new compounds was accomplished on the basis of spectral data and microanalyses (see Tables).

Table 1. ¹H-nmr data and microanalyses

Compound	Formula	Anal. Calcd. (Found)			¹ H-nmr (δ, ppm, CDCl ₃)
		C	H	N	
3	C ₂₅ H ₁₉ N ₃	83.10 (83.09)	5.26 5.34	11.63 11.42	2.51(s, 3H, 4-CH ₃), 7.21-7.90(m, 12H, Ph, 2×ArH ₂ , and 5-H), 8.05-8.30(m, 2H, ArH ₂), 8.40-8.65(m, 2H, ArH ₂)
4	C ₂₂ H ₁₉ N ₃ O	77.41 (77.22)	5.57 5.55	12.32 12.25	2.35(s, 3H, 4-CH ₃), 2.56(s, 3H, COCH ₃), 2.64(s, 3H, 6-CH ₃), 7.10-7.80(m, 8H, Ph and ArH ₂), 8.20-8.55(m, 2H, ArH ₂)
5	C ₂₀ H ₁₇ N ₃	80.27 (80.10)	5.68 5.70	14.04 13.90	2.38(s, 3H, 4-CH ₃), 2.66(s, 3H, 6-CH ₃), 6.87(s, 1H, 5-H), 7.20-7.85(m, 8H, Ph and ArH ₂), 8.25-8.55(m, 2H, ArH ₂)
6 ^a	C ₂₀ H ₁₅ N ₅	73.84 (74.13)	4.61 4.54	21.53 21.24	2.42(s, 3H, 4-CH ₃), 7.18(exch. br s, 2H, NH ₂), 7.30-7.80(m, 8H, Ph and ArH ₂), 8.20-8.38(m, 2H, ArH ₂)
7	C ₁₈ H ₁₄ N ₄	75.52 (75.33)	4.89 5.04	19.58 19.33	2.71(s, 3H, 4-CH ₃), 7.30-7.90(m, 8H, Ph and ArH ₂), 8.20-8.45(m, 2H, ArH ₂), 9.0(s, 1H, 6-H)

a) Spectrum recorded in DMSO-d₆

Table 2. ^{13}C chemical shifts (δ , ppm) of pyrazolopyridines in CDCl_3

Compound	C-3	C-3a	C-4	C-5	C-6	C-7a	1N-C ₁	3C-C ₁	4-CH ₃	Other resonances
3	151.35	114.6	143.3	116.5	156.6	146.0	139.7	133.85	20.1	139.05 (6-Ph, C-ipso), 129.2 (6-Ph, C-para), 128.6, 128.1 (6-Ph, C-ortho and meta), 129.8, 128.8, 127.4, 121.2 (1- and 3-Ph, C-ortho and meta), 128.4, 125.5 (1- and 3-Ph, C-para)
4	149.8	113.4	138.1	133.0	153.4	146.45	139.3	133.6	16.6	206.4 (CO), 129.8, 128.8, 128.2, 121.4 (1- and 3-Ph, ortho and meta carbons), 128.6, 125.9 (1- and 3-Ph, C-para), 32.55 (COCH_3), 23.4 (6-CH ₃)
5	150.8	113.4	142.5	119.3	158.5	145.7	139.3	133.6	19.4	129.5, 128.5, 127.8, 121.2 (1- and 3-Ph, C-ortho and meta), 128.1, 125.3, (1- and 3-Ph, C-para), 24.3 (6-CH ₃)
6 ^a	151.0 ^b	107.8	150.9 ^b	89.0	159.1	147.1	138.75	132.8	18.3	129.6, 128.9, 128.2, 120.9 (1- and 3-Ph, C-ortho and meta), 128.8, 125.9 (1- and 3-Ph, C-para), 116 (CN)

a) Spectrum recorded in DMSO-d_6 ; b) These assignments may be reversed

In particular, the assignment of ^{13}C resonances was based on chemical shifts and substituent effect consideration,^{12,13} as well as on relaxation data of the quaternary carbons.¹⁴

This procedure may represent a useful route for other condensed pyrazolo heterocycles with potential biological activity; investigations in this field are now in progress and will be shortly reported.

EXPERIMENTAL

All melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Unless otherwise stated, ir spectra were measured for nujol mulls with a Perkin-Elmer 337 spectrometer. ^1H -nmr spectra were recorded with either a Varian EM-360 or a Perkin-Elmer R32 spectrometers and ^{13}C -nmr spectra with a Varian FT-80A instrument; chemical shift are reported in ppm from internal tetramethylsilane. Silica-gel plates (Merck F₂₅₄) and silica-gel 60 (Merck 70-230 mesh) were used for analytical t.l.c. and for column chromatography, respectively.

4-Methyl-1,3,6-triphenylpyrazolo[3,4-b]pyridine (3): i) Sodium ethoxide (5 mmoles) in absolute ethanol (4.5 ml) was added to a suspension of 1 (2 mmoles) and acetophenone (5 mmoles) and the mixture was refluxed for 20 h. After cooling, compound 3 was filtered off as a white solid (y 57%); mp 172°C (from ethanol); ii) compound 1 (3.6 mmoles) and acetophenone (20 mmoles) were heated at 130°C for 24 h with catalytic amounts of ZnCl_2 . Treatment of the reaction mixture with ethanol precipitated compound 3 (y 47.2%).

Compound 3 was also obtained by heating 2 (3.4 mmoles) with 1-phenyl-1,3-butandione (6 mmoles) at 110°C for 24 h, in the presence of catalytic amounts of ZnCl_2 (y 62.7%).

5-Acetyl-4,6-dimethyl-1,3-diphenylpyrazolo[3,4-b]pyridine (4): Compound 1 (1.5 g; 5.4 mmoles) and acetylacetone (1.9 ml; 18 mmoles) in acetic acid (9 ml) were refluxed for 70 h. Dilution with water (120 ml) precipitated a solid (0.780 g) mainly containing the acetyl derivative 4 together a small amount of 5 and unreacted 1 (0.150 g). An analytical sample of 4 was obtained by column chromatography (cyclohexane-ethyl acetate 2:1 v/v) and crystallization from ethanol (y 32%); white crystals, mp 154°C; ir 1700 cm^{-1} (CO).

4,6-Dimethyl-1,3-diphenylpyrazolo[3,4-b]pyridine (5): i) Compound 5 was obtained as by-product (y 6%) in the synthesis of 4; ii) a mixture of 1 (1 mmole) and acetone (3 ml) in acetic acid (5 ml) was refluxed for 24 h in the presence of ZnCl_2 (catalytic amounts). The solid (y 41.3%) isolated after dilution with water (50

ml), was purified by column chromatography (cyclohexane-ethyl acetate 2:1 v/v);
 iii) sodium methoxide (5 mmoles) in dry methanol (3 ml) was added to a suspension of 1 (1.8 mmoles) in acetone (2 ml) and the mixture was refluxed for 2 h. After dilution with water (70 ml), compound 5 was filtered off as a white solid (y 32.2%) mp 112°C (from ethanol) [lit.¹¹ mp 111°C (from ethanol)].

6-Amino-5-cyano-4-methyl-1,3-diphenylpyrazolo[3,4-b]pyridine (6): Compound 1 (5.4 mmoles) and malononitrile (32 mmoles) in pyridine (15 ml) were heated, under nitrogen, at 105°C for 80 h. Dilution of the reaction mixture with water (200 ml) afforded compound 6 (y 64.3%) as white crystals, mp 225°C (from ethanol); ir 2218 cm^{-1} (C \equiv N).

4-Methyl-1,3-diphenylpyrazolo[3,4-d]pyrimidine (7): Compound 1 (7.2 mmoles) and formamide (0.4 moles) were heated at 130°C for 24 h in the presence of catalytic amounts of ZnCl_2 . The solid formed (y 55.1%) was separated by filtration and purified by column chromatography (cyclohexane-ethyl acetate 2:1 v/v), mp 120°C (after sublimation at 90°C and 0.05 mmHg); ^{13}C -nmr (CDCl_3) δ : 163.9 (C-4), 155.3 (C-6), 153.0 (C-3 or C-7a), 146.7 (C-7a or C-3), 138.5 (1N, C-ipso), 132.3 (3C, C-ipso), 129.6, 129.0, 128.4, 121.5 (1- and 3-phenyl, C-ortho and meta), 129.1, 126.5 (1- and 3-phenyl, C-para), 113.6 (C-3a), 23.3 (4- CH_3).

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Received, 17th June, 1985