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Synthesis of Heterocyclic Compounds IV[1]
Pyrazol-1′-ylpyridines[2]

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2-Pyrazol-1′-ylpyridines were synthesized by condensation of pyridylhydrazines with 1,3-dicarbonyl compounds or by the *Ullmann* arylation of pyrazoles with halopyridines.

(Keywords: Arylations; Pyrazolylpyridines; Ullmann reaction)

Synthese heterocyclischer Verbindungen, IV. Pyrazol-1′-ylpyridine

2-Pyrazol-1′-ylpyridine wurden über die Kondensation von Pyridylhydrazinen mit 1,3-Dicarbonyl-Verbindungen bzw. mittels *Ullmann*-Arylierung von Pyrazolen mit Halopyridinen dargestellt.

Introduction

Many pyrazole derivatives containing a pyridine ring attached to its carbon atoms have been reported in the literature[3] but there exist only a handful of *N*-pyridylpyrazoles. Some years ago we reported the synthesis of some of these compounds by *Ullmann* arylation method[4]. With the discovery of the new analgesic and anti-inflammatory agent mepirazole[5] a great number of pyrazole derivatives containing diverse type of heterocyclic rings attached to its nitrogen atom have been prepared[6] and as a result of this interest we are starting investigation of the chemistry of such pyrazoles. During these studies we prepared some new 2-pyrazol-1′-ylpyridines either by condensation of appropriate 1,3-dicarbonyl compounds with pyridylhydrazines[3] or by the *Ullmann* arylation method[4,7].

Results and Discussion

The condensations were effected with nitropyridylhydrazines using 1,1,3,3-tetramethoxypropane, 2,4-pentanedione, ethyl acetoacetate and ethyl benzoylacetate. The nitropyridylhydrazines were easily obtained from the reaction of chloronitropyridines with hydrazine.

The arylation of pyrazoles was carried out using halopyridines and copper(II) oxide in pyridine as a solvent. In the reaction of 2-chloro-5-nitropyridine with pyrazole, however, the yields of the arylated products were considerably lower than in the other related arylation reactions using other halopyridines. The considerable decrease in the yield in this reaction, we believe, is due to the participation of the solvent in the competitive process in a reaction similar to that of 2,4-dinitrohalobenzenes with pyridine[8] (A reaction mixture of 2-chloro-5-nitropyridine and pyridine when heated together soon turns red and forms a dark red precipitate). As an alternative the arylation in this case was carried out in dimethylsulfoxide either in the presence of triethylamine[9] or which sodium hydride. Thus various 2-pyrazol-1′-ylpyridines (**1**–**10**) were obtained from the condensation and arylation reactions.

Experimental

The proton magnetic resonance spectra (PMR) were obtained on a Hitachi Perkin-Elmer model R-20 B spectrometer operating at 60 Mc/s (tetramethylsilane as internal standard). The infrared (IR) absorption spectra were taken by the Perkin-Elmer model 727 spectrophotometer and were measured in potassium bromide disks. Melting points (mp) were determined with a Fisher-Johns apparatus and are uncorrected. Elemental analyses were determined on a Perkin-Elmer model 240.

Nitropyridylhydrazines used in this work were obtained by the reaction of hydrazine on chloronitropyridines[10]. Other starting materials were either commercial products or were prepared according to the literature methods.

Condensations

Method A: A mixture of 0.02 mol of a pyridylhydrazine, 1 ml of hydrochloric acid in 15 ml of ethanol was heated under reflux with 0.03 mol of an appropriate 1,3-dicarbonyl compound (1,1,3,3-tetramethoxypropane, 2,4-pentanedione or 1,3-diphenyl-1,3-propanedione). At the end of the reaction period the reaction mixture was cooled, filtered and the product crystallized.

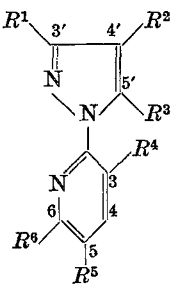
Method B: An equimolar mixture of pyridylhydrazine and ethyl acetoacetate or ethyl benzoylacetate was heated together at 120° and the product was purified by crystallization.

Arylations

Method C: An equimolar mixture of a pyrazole, halopyridine, anhydrous potassium carbonate and catalytic amounts of copper(II) oxide in a sufficient volume of pyridine was heated under reflux for a period of 24 h. The reaction mixture was allowed to cool down and was filtered. The solid was extracted with chloroform and the solvent was removed from the combined extracts and the filtrate. The residue thus obtained was purified by crystallization from a suitable solvent.

The 2-pyrazol-1′-ylpyridines (**1**–**10**) prepared by these methods A, B, and C are presented in Table 1 and their spectral characteristics in Table 2.

Table 1. *2-Pyrazol-1'-ylpyridines*



	*R*1	*R*2	*R*3	*R*4	*R*5	*R*6
1	H	H	H	NO_2	H	H
2	H	H	H	H	NO_2	H
3	*Me*	H	*Me*	H	NO_2	H
4	*Ph*	H	*Ph*	H	NO_2	H
5	*Me*	H	OH	H	NO_2	H
6	*Ph*	H	OH	H	NO_2	H
7	H	NO_2	H	H	H	H
8	H	NO_2	H	H	NO_2	H
9	H	H	H	H	H	*Me*
10	*Ph*	H	*Ph*	H	H	H

Compd. No.	Method of prepn.	Reaction time (h)	yield (%)	m.p.° (from)	Molecular formula[a]
1	A	1.5	38	94-95 (50% *Et*OH)	$C_8H_6N_4O_2$
2[b]	A	1.5	82	195 ($CHCl_3$)	$C_8H_6N_4O_2$
3	A	3	62	104-105 (50% *Et*OH)	$C_{10}H_{10}N_4O_2$
4	A	5	78	179-179.5 (*Ac*OH)	$C_{20}H_{14}N_4O_2$
5	B	2	86	225-226 (*Ac*OH)	$C_9H_8N_4O_3$
6	B	2	94	215-216 (*Ac*OH)	$C_{14}H_{10}N_4O_3$
7	C	24	48	160-160.5 ($CHCl_3$)	$C_8H_6N_4O_2$
8	C	24	47	206-207 (*Et*OH)	$C_8H_5N_5O_4$
9	C	24	20	c	$C_9H_9N_3$
10	C	24	58	114-115 (*Et*OH)	$C_{20}H_{15}N_3$

[a] Elemental analyses are in full agreement with the calculated values.

[b] Also obtained by Method C in 18% yield; arylation using triethylamine (24.5% yield); and arylation using sodium hydride in *DMSO* over a period of 4 h and room temp. (60% yield).

[c] Liquid bp. 180°/760 mm, purified by chromatography on alumina (benzene as the eluting solvent).

Table 2. *IR and PMR Spectra of 2-Pyrazol-1′-ylpyridines*

Compd. No.	IR (cm^{-1})	PMR δ (J in Hz)	Solvent
1	3150, 3140, 3080, 1595, 1575, 1525 (NO_2), 1470, 1395, 1360, 1338 (NO_2), 945, 855, 770, 755.	6.40 (1 H, t, $J_{3',4'} = J_{4',5'} = 2$, H-4′), 7.25 (1 H, dd, $J_{4,5} = 8$, $J_{5,6} = 5$, H-5), 7.63 (1 H, d, $J_{3',4'} = 2$, H-3′), 7.95 (1 H, dd, $J_{4,5} = 8$, $J_{4,6} = 1$, H-4), 8.30 (1 H, d, $J_{4',5'} = 2$, H-5′), 8.48 (1 H, dd, $J_{4,6} = 1$, $J_{5,6} = 5$, H-6).	$CDCl_3$
2	3150, 3128, 3095, 1602, 1575 1515 (NO_2), 1470, 1432, 1342 (NO_2), 1335, 1040, 932, 850, 780.	6.52 (1 H, t, $J_{3',4'} = J_{4',5'} = 1.7$, H-4′), 7.80 (1 H, d, $J_{3',4'} = 1.7$, H-3′), 8.10 (1 H, d, $J_{3,4} = 9$, H-3), 8.40-8.70 (2 H, m, H-4 and H-5′), 9.26 (1 H, d, $J_{4,6} = 3$, H-6).	$CDCl_3$
3	3125, 3080, 1600, 1580, 1520 (NO_2), 1480, 1405, 1340 (NO_2), 1280, 1130, 975, 840, 765.	2.28 (3 H, s, *Me*-3′), 2.66 (3 H, s, *Me*-5′), 6.00 (1 H, s, H-4′), 7.98 (1 H, d, $J_{3,4} = 9$, H-3), 8.40 (1 H, dd, $J_{3,4} = 9$, $J_{4,6} = 2.5$, H-4), 9.12 (1 H, d, $J_{4,6} = 2.5$, H-6).	$CDCl_3$
4	3130, 3085, 3060, 1598, 1580, 1520 (NO_2), 1475, 1440, 1340 (NO_2), 1280, 1112, 953, 840, 765.	6.82 (1 H, s, H-4′), 7.38 (10 H, s, *Ph*-3′ and *Ph*-5′), 8.08 (1 H, d, $J_{3,4} = 9$, H-3), 8.54 (1 H, dd, $J_{3,4} = 9$, $J_{4,6} = 2.5$, H-4), 8.98 (1 H, d, $J_{4,6} = 2.5$, H-6).	$CDCl_3$
5	3200-2900 (OH), 1640 (C=O), 1595, 1582, 1520 (NO_2), 1470, 1405, 1350 (NO_2), 1340, 1120, 850, 785, 630.	—[a]	
6	3130, 3080, 1640 (C=O), 1585, 1528 (NO_2), 1480, 1415, 1345 (NO_2), 1285 1110, 945, 840, 765.	5.60 (1 H, br., OH), 6.16 (1 H, s, H-4′), 7.20-8.00 (5 H, m, *Ph*), 8.26 (1 H, d, $J_{3,4} = 9$, H-3), 8.76 (1 H, dd, $J_{3,4} = 9$, $J_{4,6} = 2.5$, H-4), 9.32 (1 H, d, $J_{4,6} = 2.5$, H-6).	*DMSO*-d_6
7	3130, 3080, 3030, 1585, 1510 (NO_2), 1500, 1410, 1330 (NO_2), 940, 800, 750.	7.30 (1 H, dd, $J_{4,5} = 7$, $J_{5,6} = 5$, H-5), 7.70-8.10 (2 H, m, H-3 and H-4), 8.20 (1 H, s, H-3′), 8.45 (1 H, d, $J_{5,6} = 5$, H-6), 9.23 (1 H, s, H-5′).	$CDCl_3$

8	3160, 3125, 3095, 1615, 1585, 1530 (NO_2), 1480, 1405, 1350 (NO_2), 1325, 1118, 948, 821, 755.	8.00-8.80 (3 H, m, H-3′, H-3, H-4), 9.20 (1 H, br., H-6), 9.35 (1 H, s, H-5′).	CD_3COCD_3
9	3160, 3110, 3040, 1603, 1580, 1470, 1420, 1393, 1042, 949, 795, 760.	2.48 (3 H, s, *Me*), 6.37 (1 H, t, $J_{3',4'} = J_{4',5'} = 2$, H-4′), 6.85 (1 H, dd, $J_{3,5} = 1$, $J_{4,5} = 5$, H-5), 7.35-7.85 (3 H, m, H-3′, H-3 and H-4), 8.54 (1 H, d, $J_{4',5'} = 2$, H-5′).	$CDCl_3$
10	3120, 3065, 3040, 1585, 1575, 1480, 1445, 1360, 975, 785, 760, 699.	6.80 (1 H, s, H-4′), 7.00-8.00 (3 H, m, H-3, H-4 and H-5), 7.29 (10 H, s, *Ph*), 8.30 (1 H, d, $J_{5,6} = 5$, H-6).	$CDCl_3$

[a] Not very soluble in usual NMR solvents at room temperature.

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