SYNTHESIS OF PYRANO, THIOPYRANO, AND PYRIDO[3,2-d]PYRAZOLES

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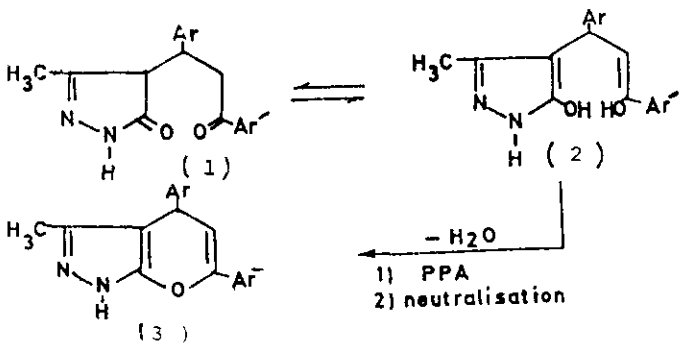
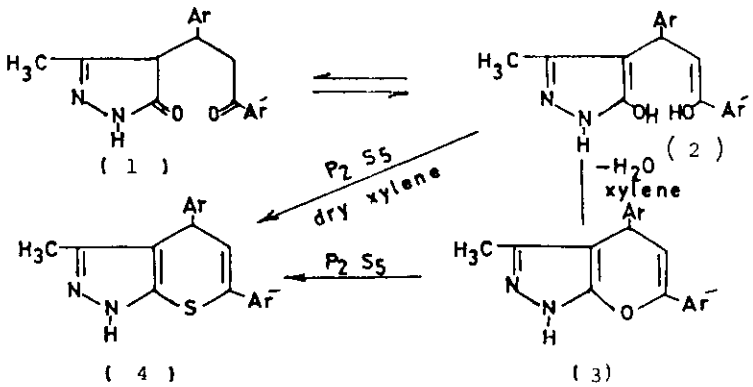
Abstract - The title compounds pyrano[3,2-d]pyrazoles (3) were obtained by the action of polyphosphoric acid on the 3-methyl-4-(1-aryl-3-aryl-3-oxopropyl)-2-pyrazolin-5-one, after neutralisation with sodium bicarbonate. Interaction of phosphorous pentasulphide with the starting compounds (2) in dry xylene gives rise to thiopyrano[3,2-d]pyrazoles (4) but pyrido[3,2-d]pyrazoles (5) were obtained by the action of ammonium acetate on the compound (2) in the presence of glacial acetic acid.

In a previous work[1] we have reported the synthesis of 3-methyl-4(1-aryl-3-aryl)-3-oxopropyl)-2-pyrazolin-5-ones (2) and this encourged us to test such compound for the synthesis of the unknown binuclear heterocyclic compounds: a) 4H-pyrano[3,2-d]-pyrazoles (3), b) thiopyrano[5,4-b]pyrazoles(4) and c) pyrido[3,2-d]pyrazoles (5). The ability of the amidic carbonyl participate in heterocyclisation of oxopropyl-pyrazolones (1) was tested under the influence of different reagents as follows:

a) Action of polyphosphoric acid, followed by neutralisation:

Interaction of the 1,5-diketones (1) with excess polyphosphoric acid at 60-80°C gave after neutralisation and working up the corresponding pyrano 3,2-d pyrazoles (3). The reaction can be represented as follows:





Where

Ar	Ar'
p-$CH_3C_6H_4$	1-naphthyl
p-Cl C_6H_4	1-naphthyl

As a confirmations for a part of the above scheme, we were able to obtain thiopyrans (4) starting from pyrane derivatives (3) by heating with phosphorous pentasulphide in dry xylene. The data for the prepared thiopyranes are indicated in Table 2. The structure of these products was confirmed using elemental as well as IR and mass spectral analyses.

Table 2. Physical properties of thiopyrano[5,4-b]pyrazole derivatives (4)

Compd. No. (4)	Ar	Ar'	Solvent of crystn.	mp °C	Yield (%)	Molecular Formula	Analysis(Calcd.Found) (%) C	H	N	S	m/z
a	C_6H_5	p-$CH_3C_6H_4$	aq. ethanol	157	94.3	$C_{20}H_{18}N_2S$	75.47 75.30	5.60 5.50	8.80 8.30	10.06 10.40	
b	p-$CH_3C_6H_4$	1-naphthyl	aq. ethanol	162	81.3	$C_{24}H_{20}N_2S$	78.20 77.7	5.40 5.40	7.60 7.30	8.69 8.45	
c	p-ClC_6H_4	1-naphthyl	aq. acetic acid (1:1)	132	78.1	$C_{23}H_{17}ClN_2S$	71.13 71.20	4.38 4.40	7.12 7.10	8.24 7.95	388

c) Reaction of 1,5-diketones with nitrogenous reagents (preparation of 4H-pyrido [3,2-d]pyrazoles (5).

The reactivity of our prepared 1,5-diketones (1) towards nitrogenous reagents was tested by using ammonium acetate/acetic acid as the choiced reagents. The reaction was found to take place smoothly and the pyrido[3,2-d]pyrazoles were isolated by

The structure of pyrano[3,2-d]pyrazoles (3) was confirmed by elemental as well as IR and mass spectral analyses (cf. Table 1).

Table 1. 3-Methyl-4-Ar-6-Ar-4H-pyrano[3,2-d]pyrazole derivatives (3).

Compound No. (3)	Ar	Ar'	mp* °C	Yield (%)	Molecular Formula	Analysis (Calcd./Found) (%) C	H	N	m/z
a	C_6H_5	C_6H_5	204	68.8	$C_{19}H_{16}N_2O$	79.16 79.36	5.55 6.00	9.72 9.59	
b	C_6H_5	(p)CH_3-C_6H_4	228	79.5	$C_{20}H_{18}N_2O$	79.47 79.87	5.96 6.29	3.72 3.66	
c	(p)Cl-C_6H_4	2-naphthyl	233	53.7	$C_{23}H_{17}ClN_2O$	74.19 74.61	4.56 4.70	7.50 7.50	
d	(p)CH_3-C_6H_4	1-naphthyl	258	79.5	$C_{24}H_{20}N_2O$	81.43 81.43	5.20 5.20	7.63 7.63	352

* Crystallised from ethanol.

b) Action of sulphurous reagents:

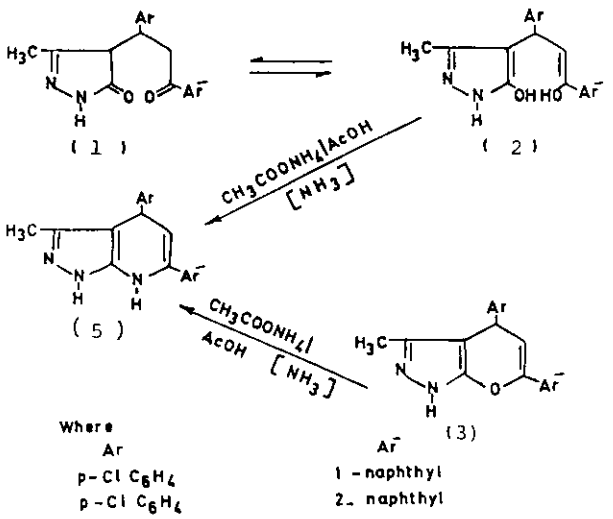
The character of the chemical transformation of 1,5-diarylpentanediones in reactions with nucleophilic reagents has recently been the subject of intensive study[2,3]. In reaction with sulphurous reagents (P_2S_5) thiopyrylium salts are formed via two competitive mechanisms that were determined by the structural peculiarities of the 1,5-dicarbonyl compounds and the reaction conditions[4]. One might have expected that 1,5-dialkyl- or 1-alkyl-5-arylpentadiones would display certain specific characteristics under acid catalysis conditions[5].

Chickenkova et al.[6] found that the starting 1,5-diketones must have no methyl or methylene groups in the α-positions to the carbonyl groups in order sulphurisation to occur. In the presence of such groups carbocyclisation occurred readily, while sulphurisation takes place when such positions are blocked by tert-butyl groups.

Taking into account the information stated above, as well as the interest in thiopyrans and thiopyrylium salts in connection with their extensive practical importance[7], we subject our 1,5-diketones to sulphurisation. This was done by heating the diketones with phosphorous pentasulphide in dry xylene. The reaction products was proved to be thiopyrans and no carbocyclisation occurred even the starting compounds possesses one methylene group in an α-position to one of the ketonic groups.

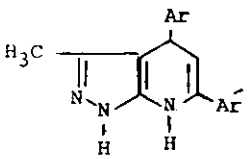
In our case the question is still open for the formation of thiopyran derivatives (4) via pyran precursors (3) by substitution of oxygen with sulphur[8]. The reaction mechanism can be indicated by the following scheme:

neutralisation. The scheme of this reaction can be represented as follows:



As in case of thiopyrans (4), pyrido[3,2-d]pyrazoles (5) were prepared separately by the action of ammonium acetate/acetic acid reagent on pyrano-pyrazoles (3). The results are listed in Table 3.

Table 3. Physical properties of 4H-pyrido[3,2-d]pyrazole derivatives (5)



Compound No. (5)	Ar	Ar'	mp °C	Crystallized from	Yield (%)	Molecular formula	Analysis(Calcd./Found) C	H	N	m/z
a	C_6H_5	p-$CH_3C_6H_4$	227	toluene	83.0	$C_{20}H_{19}N_3$	79.70 79.20	6.30 6.30	13.90 13.8	
b	p-$CH_3OC_6H_4$	1-naphthyl	215	ethyl alcohol	81.9	$C_{24}H_{20}N_3O$	78.6 78.1	5.4 5.5	11.4 11.6	
c	p-ClC_6H_4	2-naphthyl	230	ethyl alcohol	91.0	$C_{23}H_{18}N_3Cl$	74.39 74.40	4.85 4.95	11.32 11.60	371,373

EXPERIMENTAL

All mps were uncorrected and determined either on a sulphuric acid apparatus or on a Kofler melting point apparatus. Infrared spectra were determined with a Beckman IR 20 infrared spectrophotometer using KBr Wafer technique. Mass spectra

were obtained using an AET MS-9 mass spectrometer operating at 70-eV.

Elemental analyses and all the above analyses were carried out at institute of organic chemistry, TH-Darmstadt, West Germany. 3-Methyl-4(1-aryl-3-aryl-3-oxopropyl)-2-pyrazolin-5-ones were prepared according to the literature procedures[1].

Syntheses of 3-Methyl-4-Ar-6-Ar-4H-pyrano[3,2-d]pyrazoles(3): General Procedure:

A mixture of 3-methyl-4(1-Ar-3-oxopropyl)-2-pyrazolin-5-one (0.01 mol.), polyphosphoric acid and phosphorous pentoxide (0.01 mol) was heated on water bath at 60-80°C for 1-2 h. after which the excess polyphosphoric acid was decomposed with water. The precipitated material was separated by filtration. Sodium bicarbonate solution was added to the precipitate with stirring until the bubbles ceased to evolve. The product was collected, and recrystallised from the proper solvent. The results are summarised in Table 1.

Synthesis of 3-Methyl-4-Ar-6-Ar-4H-thiopyrano[3,2-d]pyrazoles (4): General Procedure:

3-Methyl-4-(1-Ar-3-Ar-3-oxopropyl)-2-pyrazolin-5-one (0.01 mol.) and phosphorous pentasulphide (0.011 mol.) were dissolved in dry xylene (30 ml) and refluxed on a hot plate for 3 h. After cooling the precipitated product was coolected by filtration and recrystallised from the proper solvent. The results are listed in Table 2.

Synthesis of 3-Methyl-4-Ar-6-Ar-4H-pyrido[3,2-d]pyrazoles (5): General Procedure:

A mixture of 3-methyl-4(1-Ar-3-Ar-3-oxopropyl)-2-pyrazolin-5-one, (0.01 mol.) ammonium acetate (0.15 mol.) and acetic acid (25 ml) were refluxed on a hot plate for 5 h. The colour of the reaction mixture was darkened. The product was isolated by concentration of the reaction mixture followed by dilution with water. The product was collected, filterated, dried and crystallised from proper solvent. The results are summarised in Table 3.

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