SYNTHETIC UTILIZATION OF N-DIFORMYLMETHYLAZOLES: THE PREPARATION OF 1-HETERYL-4-NITROPYRAZOLES

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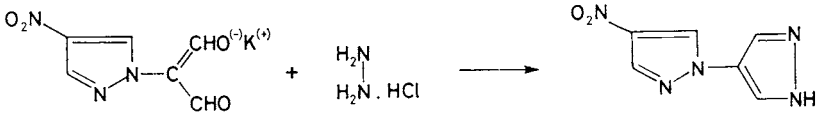
1-Diformylmethyl-4-nitropyrazole serves to show the potential synthetic utilization of N-diformylmethylazoles as suitable synthons for building heterocyclic systems.

The synthetic value of malonaldehyde derivatives for the preparation of heterocyclic compounds is generally known. In our previous papers[1,2] we have described a general synthetic approach to N-diformylmethylazoles and cycloimonium diformyl methylides based on formylation of easily accessible N-heterylacetic acids.

In the present study we show the utilization of these compounds for building bicyclic systems with a C—N bond between the rings. We have chosen 1-diformylmethyl-4-nitropyrazole[3] and its derivatives (*I*–*III*) in order to illustrate the wide scope of reactions with bifunctional nucleophiles (hydrazine, guanidine, urea, thiourea, ethylenediamine and *o*-phenylenediamine), leading to heterobicyclic systems. The ease of the cyclization depends on the character of the bifunctional nucleophile.

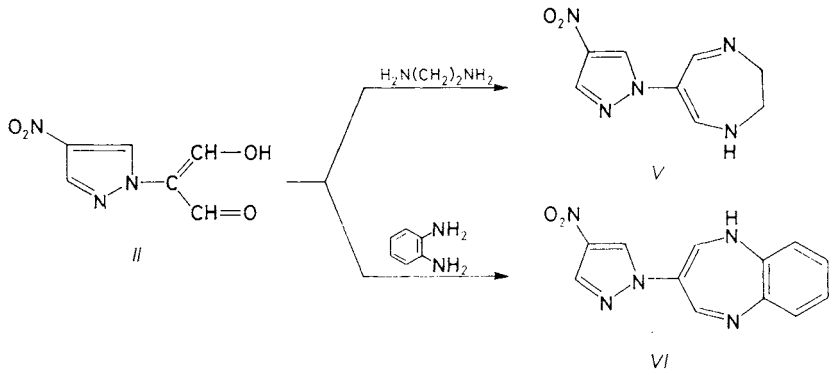
We have observed that potassium salt of 1-diformylmethyl-4-nitropyrazole (*I*) reacts with hydrazine hydrochloride at room temperature to give the corresponding 4-(4'-nitro-1'-pyrazolyl)pyrazole (*IV*) in high yield (Scheme 1).



I *IV*

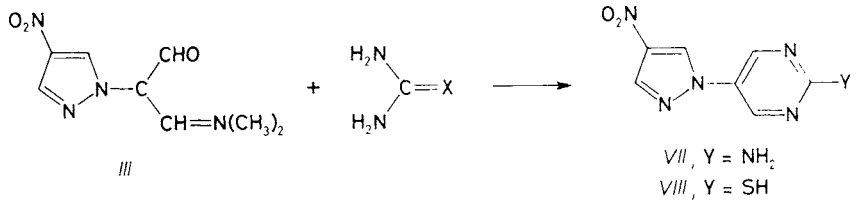
SCHEME 1

Ethylenediamine and *o*-phenylenediamine react with 1-diformylmethyl-4-nitropyrazole (*II*) under formation of the respective diazepine derivatives *V* and *VI*. It is worth notice that ethylenediamine reacts at room temperature whereas the reaction with *o*-phenylenediamine takes place only at elevated temperature (Scheme 2).



SCHEME 2

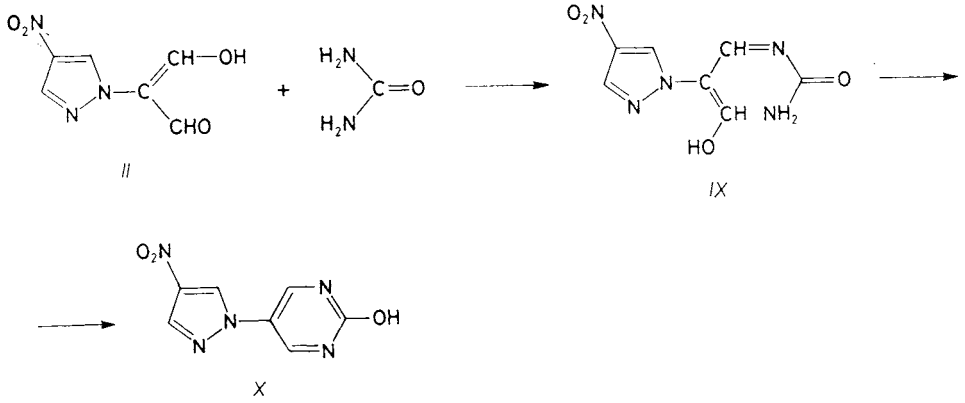
Guanidine and thiourea do not react with the starting dialdehydes *I* and *II*. To obtain the bicyclic system linked by a C—N bond we used the more reactive acrylaldehyde derivative *III* (Scheme 3).



SCHEME 3

Concerning the condensation mechanism, we assume that the products *IV*–*VIII* are formed stepwise: the bifunctional nucleophile reacts first with one formyl group and then the product is cyclized to give the bicyclic system. This reaction course has been confirmed in the case of condensation of dialdehyde *II* with urea where we first isolated the product of reaction at one formyl group (*IX*, Scheme 4); its cyclization led to the final product *X*.

The newly prepared compounds were characterized using IR, ^{1}H NMR and mass spectra and their composition was confirmed by elemental analysis. The pertinent data are summarized in Table I.



SCHEME 4

The described novel synthesis of bicyclic systems, in which 4-nitropyrazole is linked with five-, six- and seven-membered nitrogen heterocyclic compounds by

TABLE I

Characteristics of the new compounds

Compound	M.p., °C (mass spectrum)	^{1}H NMR spectrum	Formula (mol. w.)	Calculated/found		
				% C	% H	% N
IV[a]	192–193 (179)	8·13 s, 2 H; 8·38 s, 1 H; 9·30 s, 1 H	$C_6H_5N_5O_2$ (179·2)	40·22 40·11	2·79 2·64	39·11 39·21
V	219–221 (207)	—	$C_8H_9N_5O_2$ (207·2)	46·38 46·25	4·35 4·28	33·82 33·69
VI	260 (decomp.) (255)	—	$C_{12}H_9N_5O_2$ (255·2)	56·47 56·41	3·53 3·59	27·45 27·39
VII[b]	198–200 (206)	3·30 s (NH_2); 8·35 s, 2 H; 8·76 s, 1 H; 8·88 s, 1 H	$C_7H_6N_6O_2$ (206·2)	40·78 40·73	2·91 2·96	40·77 40·81
VIII[c]	188–190 (223)	8·53 s, 2 H; 9·05 s, 1 H; 9·40 s, 1 H	$C_7H_5N_5O_2S$ (223·2)	37·67 37·71	2·24 2·19	31·39 31·45
X[d]	184–185 (207)	8·58 s, 2 H; 9·06 s, 1 H; 9·50 s, 1 H	$C_7H_5N_5O_2$ (207·2)	46·37 46·31	2·41 2·37	33·81 33·69

[a] IR spectra of *IV*–*X* exhibit characteristic bands of aromatic nitro group at 1 660–1 670 cm^{-1} and 1 355–1 365 cm^{-1}; [b] IR spectrum (cm^{-1}): 1 630, 3 420 (NH_2); [c] calculated: 14·35% S, found: 14·31% S; [d] IR spectrum (cm^{-1}): 3 230 (OH).

a C—N bond, illustrates wide possibilities of utilizing N-diformylmethylazoles and cycloimonium diformyl methylides for the synthesis of many groups of heterocyclic compounds, obtainable hitherto only with difficulty.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. ^{1}H NMR spectra were obtained with a Tesla BS 467 (60 MHz) instrument in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. IR spectra were recorded on a Zeiss UR 20 spectrometer in KBr pellets. Analytical samples were dried over phosphorus pentoxide at 25°C/25 Pa overnight. The starting compounds *I*—*III* were prepared according to the literature[2]. The conditions for the condensation reactions were studied using our previous results[4].

4-(4′-Nitro-1′-pyrazolyl)pyrazole (*IV*)

Hydrazine hydrochloride (0·25 g; 3·2 mmol) was added to a solution of *I* (0·663 g; 3 mmol) in water (10 ml). After stirring at room temperature for 1 h and standing overnight, the separated product was collected and washed with water to give 0·47 g (87%) of compound *IV*.

6-(4′-Nitro-1′-pyrazolyl)-1*H*-2,3-dihydro-1,4-diazepine (*V*)

Ethylenediamine (0·3 ml; 4·5 mmol) in ethanol (5 ml) was added to a solution of *II* (0·73 g; 4 mmol) in ethanol (15 ml). The mixture was stirred at room temperature for 4 h and the separated product was filtered and washed with ether; yield 0·79 g (95%) of *V*.

6-(4′-Nitro-1′-pyrazolyl)-1*H*-2,3-dihydrobenzo-1,4-diazepine (*VI*)

o-Phenylenediamine (0·49 g; 4·5 mmol) was added to compound *II* (0·73 g; 4 mmol) in ethanol (30 ml), the mixture was stirred at room temperature for 10 min and then at 70°C for 1·5 h. After cooling, the product *VI* was collected (0·95 g; 93%) and washed with ether.

5-(4′-Nitro-1′-pyrazolyl)-2-aminopyrimidine (*VII*)

Guanidine carbonate (0·45 g; 2·5 mmol) in a mixture of glacial acetic acid (1 ml) and ethanol (5 ml) was added to acrylaldehyde *III* (0·42 g; 2 mmol) in ethanol (10 ml). The reaction mixture was heated to 70°C with stirring for 3 h and set aside at −10°C for 4 h. The separated product was filtered and washed with ether; yield 0·26 g (62%) of compound *VII*.

5-(4′-Nitro-1′-pyrazolyl)-2-mercaptopyrimidine (*VIII*)

A solution of thiourea (0·19 g; 2·5 mmol) in glacial acetic acid was added to acrylaldehyde *III* (0·42 g; 2 mmol) in ethanol (10 ml). After refluxing for 3 h and standing at −10°C for 4 h, the product *VIII* was filtered and washed with ether; yield 0·29 g (66%).

5-(4′-Nitro-1′-pyrazolyl)-4-hydroxypyrimidine (*X*)

A) Urea (0·25 g; 4 mmol) was added to dialdehyde *II* (0·73 g; 4 mmol) in ethanol (20 ml) and the mixture was refluxed for 12 h. After cooling, the product was filtered and washed with ether; yield 0·72 g (80%) of *IX*. ^{1}H NMR spectrum: 7·03 bs (NH_2); 8·18 s, 1 H; 8·52 s, 1 H; 9·03 s, 1 H; 9·32 s, 1 H. Mass spectrum, *m/z*: 225 ($M^{+\cdot}$).

B) A solution of *IX* (0·675 g; 3 mmol) in 20% HCl in ethanol (10 ml) was refluxed for 6 h. After standing at −10°C for 4 h, the separated *X* (0·45 g; 73%) was collected and washed with ether.

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