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SYNTHESIS OF PYRAZOLES FROM ETHYL-3-DIAZOPYRUVATE

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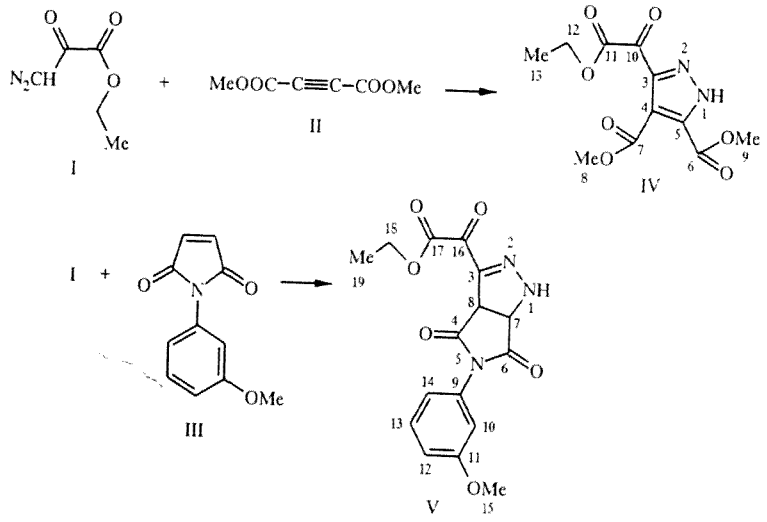
1,3-Dipolar cycloaddition to ethyl-3-diazopyruvate and its hydrazide gives the corresponding polycarbonyl pyrazoles.

In order to obtain polycarbonyl synthons for the preparation of functionally substituted nitrogen heterocycles we have carried out the acylation of diazomethane using ethyloxalyl chloride. The ethyl-3-diazopyruvate product (I) was used in a study of 1,3-dipolar cycloaddition. The dimethyl ester of acetylene-dicarboxylic acid (II) and m-methoxy-N-phenylmaleimide (III) were used as dipolarophiles.



As expected, the presence of an electron acceptor group significantly increased the stability of the diazo compound and lowered the activity of the diazo group towards dipolar cycloaddition. Hence reaction of diazomethane and diazoacetophenone with dipolarophile II occurs readily in ether at room temperature to give the desired products in high yields [1, 2] whereas the reaction between diazo ketone I and dipolarophile II could only be achieved by refluxing the components in methanol for 20 h. The yield of pyrazole IV was 70%. With the lower reactive dipolarophile III a reasonable yield could only be obtained after refluxing for 40 h. Consecutive reactions of diazoketone I with hydrazine and then acetone gave diazoketone VI which was also used to study cycloaddition with dipolarophile II. It was shown that exchange of the ethoxy group in ketone I for the hydrazine fragment had virtually no effect on the reactivity of the diazo group. Pyrazole VII was obtained in 60% yield by refluxing the components in methanol.

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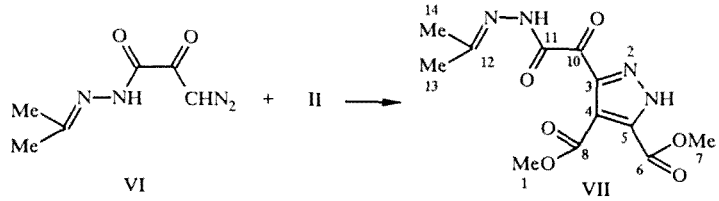
TABLE 1. Yields and Physicochemical Properties of I, IV-VII

Compound	Empirical formula	mp, °C, solvent	PMR spectrum,* δ, ppm, spin coupling (J), Hz	IR spectrum, cm^{-1}	R_f on silufol UV-254	Yield, %
I	$C_5H_6N_2O_3$	73...75, acetone	1,32 (2H, t, J = 7,2, CH_2), 4,29 (3H, q, J = =7,2, CH_3), 6,14 (1H, s, CH)	1702, 2232	0.50, benzene–ethyl acetate, 1:1	70
IV	$C_{11}H_{12}N_2O_7$	131...133	1,29 (3H, t, J = 7,2, CH_3), 3,81 (3H, s, CH_3), 3,87 (3H, s, CH_3), 4,35 (2H, q, J = 7,2, CH_2)	986, 1192, 1242, 1290, 1410, 1520, 1724, 1740, 1756	0.84, methanol–25% ammonia (H_2O), 1:25	70
V	$C_{16}H_{15}N_3O_6$	—	1,34 (3H, t, J = 7,2, CH_3), 3,75 (3H, s, J = =7,6, OCH_3), 4,34 (2H, q, J = 7,2, CH_2), 4,81 (1H, d, J = 11,4, CH), 5,17 (1H, d, J = 11,4, CH), 6,75...7,31 (5H, m, Ph)	1224, 1260, 1330, 1536, 1606, 1620, 1722	0.58, benzene–ethyl acetate, 1:1	60
VI	$C_6H_8N_4O_2$	123...125, ethanol	2,13 (6H, s, $2CH_3$), 6,45 (1H, s, CHN_2), 9,59 (1H, s, NH)	1240, 1418, 1556, 1652, 2232, 3152	0,66, methanol-acetate – methanol, 3 : 1	82
VII	$C_{12}H_{14}N_4O_6$	210 decomp.	2,21 (3H, s, CH_3), 2,28 (3H, s, CH_3), 3,82 (3H, s, OCH_3), 3,89 (3H, s, OCH_3)	1181, 1248, 1292, 1420, 1520, 1652, 1709, 1748, 1771	0.52, benzene–ethyl acetate, 2:1	40

*Spectra of I, V, VI recorded in $CDCl_3$, IV, VII in $(CD_3)_2SO$

TABLE 2. ^{13}C NMR Spectra of IV, V, VII

Compound	Chemical shift, δ, ppm, spin coupling (J), Hz
IV	13,45 ($C_{(13)}$), 51,12, 51,61, 52,46 ($C_{(3)}$, $C_{(4)}$, $C_{(5)}$), 60,72 ($C_{(8)}$), 62,26 ($C_{(9)}$), 89,50 ($C_{(12)}$), 140,61, 141,51, 162,94, 169,45 ($C_{(6)}$, $C_{(7)}$, $C_{(10)}$, $C_{(11)}$)
V	13,95 ($C_{(19)}$), 49,65, 55,48, 62,50, 64,62 ($C_{(3)}$, $C_{(7)}$, $C_{(8)}$, $C_{(15)}$), 112,06, 115,14, 118,42 (Ph), 129,97 ($C_{(18)}$), 160,16, 163,06 ($C_{(4)}$, $C_{(6)}$), 170,06, 172,00 ($C_{(17)}$, $C_{(16)}$)
VII	28,16, 32,28 ($C_{(13)}$, $C_{(14)}$), 51,44, 52,96, 53,10 ($C_{(3)}$, $C_{(4)}$, $C_{(5)}$), 54,12 ($C_{(12)}$), 61,10, 63,40 ($C_{(7)}$, $C_{(9)}$), 150...160 ($C_{(6)}$, $C_{(8)}$, $C_{(10)}$, $C_{(11)}$)



The structure of pyrazoles IV, V, and VII were proved by IR, PMR and ^{13}C NMR spectroscopy and their composition confirmed by elemental analysis (see Tables 1 and 2).

It was not possible to carry out a further synthesis of pyrazole VII from pyrazole IV and acetone hydrazone, evidently because of the presence in the pyrazole molecule of active carbonyl groups which also take part in reactions with hydrazine under these conditions to give a complex mixture of products. It was also found that addition of diazoketones I and VI to dimethylazodicarboxylate or N-phenyltriazolinedione did not occur under the conditions studied.

EXPERIMENTAL

NMR spectra were recorded on a Bruker AC-200 instrument at 200 MHz using $CDCl_3$ or DMSO-D_6 solvent and TMS internal standard. IR spectra were taken on a Specord IR-75 instrument in Vaseline oil and TLC carried out on Silufol UV-254 plates.

Ethyl-3-pyruvate (I). Ethyloxalyl chloride (4.92 ml, 44 mmole) in absolute ether (50 ml) was added over 30 min with stirring and cooling to 5°C to an ether solution (200 ml) containing diazomethane (5.54 g, 132 mmole). The mixture stood at room temperature for 2 h and the ether was evaporated off. The residue was chromatographed on a silica gel column collecting the fraction with R_f 0.50 (benzene–ethyl acetate, 1:1) to give the yellowish crystalline diazoketone I (4.3 g, 70%) with mp 73-75°C (acetone).

Acetone 3-Diazopyruvylhydrazone (VI). Hydrazine hydrate (300 mg, 6 mmole) in ethanol (5 ml) was added with stirring to a solution of ethyl-3-pyruvate (568 mg, 4 mmole) in ethanol (5 ml). The white crystalline precipitate was filtered and washed with ethanol. The product was dissolved in acetone (15 ml) and refluxed for 20 min until disappearance of the precipitate. Evaporation of acetone gave the product (550 mg, 82%).

Pyrazoles IV, V, VII (general method). The diazocarbonyl compound (3 mmole) and the corresponding dipolarophile (3 mmole) were refluxed in methanol (15 ml) for 20 h (40 h for pyrazoline V). The product was separated chromatographically. R_f and yields are given in Table 1.

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