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HETEROCYCLIC NITRO COMPOUNDS

XX.* KETONES OF THE 1,2,4-TRIAZOLE SERIES

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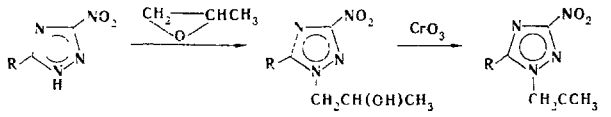
A number of triazolylpropanones were synthesized by oxidation of 1-(2-hydroxypropyl)-3-nitro-5-R-1,2,4-triazoles obtained by condensation of 3-nitro-5-R-1,2,4-triazoles with propylene oxide. Similar triazolylbutanones were obtained by reaction of 3-nitro-5-R-1,2,4-triazoles with methyl vinyl ketone.

It has been previously shown that the reaction of 3-nitro-5-R-1,2,4-triazoles with substituted α-oxides gives secondary alcohols, which can be oxidized with dichromate in sulfuric acid to the corresponding ketones [2, 3]. We obtained a number of 1-(2-oxopropyl)-3-nitro-5-R-1,2,4-triazoles in high yields via this scheme by using milder oxidation conditions (chromic anhydride in acetone):



I-III V-VII VIII-X

I, V, VIII R = NO_2; II, VI, IX R = Br; III, VII, X R = H

Oxidation with dichromate at elevated temperatures gives lower yields of ketones IX and X.

The alkylation of triazoles I-III with propylene oxide to alcohols V-VII occurs under conditions determined by the pK_a value of the starting triazole. A change in the alkylation mechanism and conditions is observed on passing from 3,5-dinitro- and 3-nitro-5-bromo-1,2,4-triazole (pK_a of I 0.66 [4] and of II 3.05 [2]), the acidities of which are sufficient for realization of the process in the absence of external catalysts [2, 3], to the less acidic 3-nitro-1,2,4-triazole (pK_a of III 6.05 [4]). The reaction of triazoles III with propylene oxide proceeds in proton-donor (water and alcohols) and aqueous aprotic solvents (acetonitrile and dioxane) at room temperature only in the presence of bases. The mechanism of the alkylation is similar to that observed for 3,5-dichloro-1,2,4-triazole.

Alcohols VI and VII [2] were obtained as uncrystallizable oils, which were subjected to oxidation without purification.

*See [1] for communication XIX.

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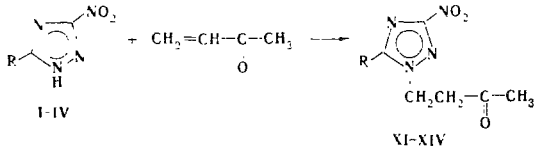
TABLE 1. Triazolyl Ketones VIII-XIV

Compound	mp, °C (crystallization solvent)	Empirical formula	Found, %			Calculated, %			M		PMR spectra,[a] δ, ppm (J, Hz)		IR spectra, cm^{-1}			Yield, %
			C	H	N	C	H	N	found	calc.	CH_2	CH_3	ν_{CO}	ν NO_2	ν ring	
VIII	136—137 (chloroform)	$C_5H_5N_5O_5$	27,6	2,2	33,0	27,9	2,3	32,6	217	215	6,0 s	2,48 s	1735 1175	1580 1320	1525 1450 1350 1140	70
IX	144—145 (ethanol)	$C_5H_5BrN_4O_3$[b]	23,7	2,1	22,4	24,1	2,0	22,5	244	249	5,63 s	2,42 s	1740 1190	1575 1320	1500 1440 1360 1110	81,5
X	100—101 (chloroform)	$C_5H_6N_4O_3$	35,2	3,6	32,8	35,2	3,5	32,9	177	170	5,60 s	2,35 s	1750 1190	1580 1315	1520 1430 1350 1110	70
XI	118—119	$C_6H_7N_7O_3$	31,8	3,0	43,6	32,0	3,10	43,5	217	225	5,03 t (7) 3,36 t (7)	2,20 s	1740 1180	1590 1325	1530 1450 1360 1140	90
XII	66—67 (ethanol)	$C_6H_7BrN_4O_3$[c]	27,3	2,4	21,3	27,4	2,7	21,3	254	264	4,09 t (7) 3,30 t (7)	2,20 s	1720 1170	1560 1305	1490 1450 1370 1120	54,5
XIII	60—61 (aqueous methanol)	$C_6H_8N_4O_3$	38,7	4,1	30,5	39,1	4,3	30,4	183	184	4,61 t (7) 3,28 t (7)	2,20 s	1720 1190	1555 1310	1500 1430 1363 1120	82,5
XIV	65—66 (aqueous ethanol)	$C_7H_{10}N_4O_3$	42,5	5,1	28,4	42,5	5,0	28, 3	205	198	4,46 t (6) 3,35 t (6)	2,13 s 2,61 s	1720 1180	1555 1310	1523 1440 1370 1140	65

[a] Abbreviations: s is singlet and t is triplet.
[b] Found: Br 32.0%. Calculated: Br 32.2%.
[c] Found: Br 30.7%. Calculated: Br 30.3%.

The 3-nitro-5-R-1,2,4-triazoles are active in the Michael reaction and give 1-(3-oxobutyl)-3-nitro-5-R-triazoles on condensation with methyl vinyl ketone:



I-IV XI-XIV

XI R = NO_2; XII R = Br; XIII R = H; IV, XIV R = CH_3

As in the case of the alkylation of triazoles with α-oxides, the factor that determines the reaction conditions is the acidity of the substrate. Thus 3,5-dinitro-1,2,4-triazole gives ketone XI in high yield on condensation with methyl vinyl ketone in ether in the absence of a catalyst. The conversion of 3-nitro-5-bromo-1,2-4-triazole to ketone XII under the same conditions does not exceed 8-10%, and triazoles III and IV do not react at all with methyl vinyl ketone in the absence of bases. In the presence of catalytic amounts of triethylamine, triazoles II-IV give the corresponding ketones in high yields both in aprotic (acetone) and proton-donor solvents (methanol and ethanol).

Two methylene triplets at 3-5 ppm are characteristic for the PMR spectra of ketones XI-XIV. The stability of the signal at ~ 3.3 ppm makes it possible to assign it to the CH_2 group bonded to the carbonyl group. The signal at weaker field (4-5 ppm) consequently belongs to the methylene group situated in the triazole ring, and this constitutes evidence for the considerable acceptor effect of the latter. In the spectra of ketones VIII-X the signal of the CH_2 group is shifted to 5.6-6 ppm as a result of the overall acceptor effect of the carbonyl group and the triazole ring.

EXPERIMENTAL

The PMR spectra of deuteroacetone solutions of the compounds were recorded with a Perkin–Elmer R-12 spectrometer (60 MHz) with hexamethadisiloxane as the internal standard. The IR spectra of films of the compounds were recorded with a UR-20 spectrometer.

1-(2-Hydroxypropyl)-3-nitro-1,2,4-triazole (VII). A solution of 1.06 g (26 mmole) of sodium hydroxide in 10 ml of water and 26 ml (252 mmole) of propylene oxide were added to a solution of 20 g (158 mmole) of triazole III [6] in 100 ml of ethanol, and the mixture was allowed to stand in a sealed container with periodic monotoring of the pH of the medium. When the pH reach 7.5-8.0, the mixture was diluted to twice its volume with water, the ethanol was evaporated, and the residue was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, the solvent was removed, and the residue was subjected to oxidation.

1-(2-Oxopropyl)-3-nitro-5-R-1,2,4-triazoles (VIII-X). A previously prepared solution of 7 g of chromic anhydride in sulfuric acid (14 ml of water and 6.1 ml of concentrated H_2SO_4) was added dropwise with stirring at 25-30° to a solution of 75 mmole of alcohols V [3], VI [2], and VII in 190 ml of acetone, and the mixture was then stirred at 25° for 1.5 h. A few drops of isopropyl alcohol were added, and the mixture was filtered. The solid material was washed with acetone. The filtrate was stirred with 10 g of sodium bicarbonate and filtered, and the acetone was evaporated from the filtrate. The residue was purified by crystallization.

1-(2-Oxobutyl)-3-nitro-5-R-triazoles (XI-XIV). A 4.5-ml (54 mmole) sample of methyl vinyl ketone and 1 ml of triethylamine were added at room temperature to a solution of 44 mmole of triazole II [6], III [6], or IX [6] in 100 ml of methanol, and the mixture was allowed to stand in a closed volume for 2 days, after which the solvent was evaporated, and the residue was purified by crystallization.

1-(2-Oxobutyl)-3,5-dinitro-1,2,4-triazole (XI). A solution of 5 g of the sodium salt of 3,5-dinitro-1,2,4-triazole [5] in 15 ml of water was added to 60 ml of 10% H_2SO_4, and triazole III was extracted with five 50-ml portions of ether. The extract was dried over anhydrous magnesium sulfate. Methyl vinyl ketone [2.5 ml (30 mmole)] was added to the ether solution, and the mixture was allowed to stand at room temperature for 24 h. The precipitated ketone was removed by filtration. An additional amount of the ketone was obtained after evaporation of the filtrate. The product was purified by crystallization.

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TRANSAMINATION OF AZOMETHINES WITH o-ALKYLISOUREAS AS A METHOD FOR THE SYNTHESIS OF 1,2-DIHYDRO-sym-TRIAZINES

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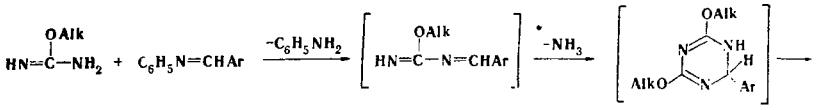
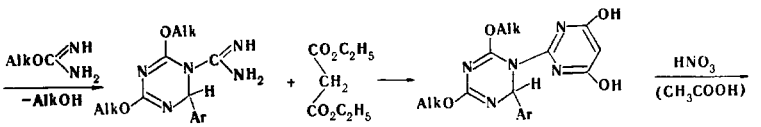
The reaction of o-alkylisoureas with azomethines leads to the formation of 4,6-dialkoxy-2-aryl-1-N-amidino-1,2-dihydro-sym-triazines. 4,6-Dialkoxy-2-phenyl-1-N-(4,6-dihydroxy-2-pyrimidinyl)-1,2-dihydro-sym-triazines were obtained by cyclization of these compounds with malonic ester.

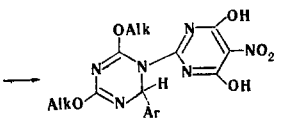
The transamination of azomethines with carboxylic acid amidines, which gives 1,2-dihydro-sym-triazines, was previously studied in [1]. In the present paper we describe the transamination of azomethines with O-alkylisoureas, which can be considered to be analogs of amidines. Instead of the expected dihydro-sym-triazines (I), we obtained 4,6-dialkoxy-2-aryl-1-N-amidino-1,2-dihydro-sym-triazines (II).



I



II III a-d



IV a-d

II—IV a Alk=CH_3, Ar=C_6H_5; b Alk=CH_3, Ar=p-$(CH_3)_2NC_6H_4$; c Alk=CH_3, Ar=p-$O_2NC_6H_4$; d Alk=C_2H_5, Ar=C_6H_5; e Alk=C_2H_5, Ar=p-$(CH_3)_2NC_6H_4$

The reaction evidently proceeds in the same way with acid amidines, but the resulting dihydro-sym-triazines (I) undergo further reaction as nucleophiles with O-alkylisoureas to give II (Table 1).

Compounds II are colorless crystalline substances that are unstable in air. Like amidines, aqueous solutions of II give a strongly alkaline reaction.

Absorption bands of NH and NH_2 groupings at 3200-3500 and 1550-1590 cm^{-1}, which confirm the presence of an amidine grouping, are observed in the IR spectra of 4,6-dialkoxy-2-aryl-1-N-amidino-1,2-dihydro-sym-triazines II. The same bands are also present in the spectrum of benzamidine.

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