Chemistry of Heterocyclic Compounds, Vol. 34, No. 2, 1998

SYNTHESIS AND HETEROCYCLIZATION OF OSAZONES OF CARBONYL-SUBSTITUTED GLYOXALS

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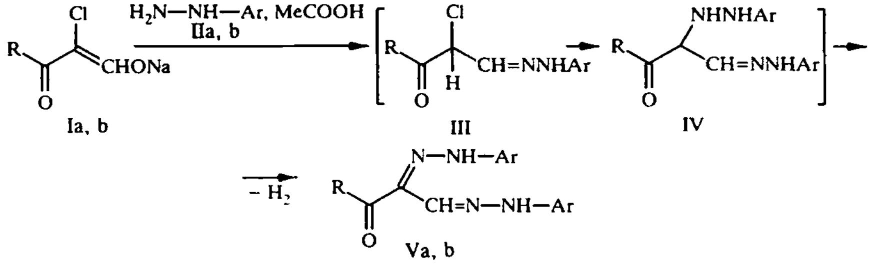
Enolates of α-chloro-β-oxoaldehydes react with arylhydrazines in the presence of acetic acid, forming osazones of carbonyl-substituted glyoxals. The same osazones are obtained by the reaction of β-oxo-α-chlorenamines with arylhydrazines. Under conditions of acid catalysis, these osazones undergo intramolecular heterocyclization to the corresponding functionalized pyrazoles.

We have investigated the reaction of the sodium enolates of β-oxoaldehydes (I) with arylhydrazines (II) in the presence of acetic acid for the purpose of synthesizing functionally substituted hydrazones (III) which, in turn, present interest for the molecular design of heterocyclic systems [1, 2]. In contrast to α-chloroaldehydes, the enolates (I) corresponding to them are more convenient and accessible reagents, which also determined our attention to them.



I a R = Ph, b R = EtO; II a Ar = Ph, b Ar = $C_6H_3(NO_2)_2$-2,4;
V a R = Ph, Ar = $C_6H_3(NO_2)_2$-2,4; b R = EtO, Ar = Ph

It was found that the reaction of the enolates (I) with hydrazines is not completed, as we expected, at the stage of the formation of the hydrazones, but proceeds further, leading to osazones of carbonyl-containing glyoxals (V).

At the first stage of the reaction, the α-chloroaldehydes, which are formed by the neutralization of the enolates (I) with acetic acid, are probably converted to monohydrazones by reaction with the hydrazines (II). Then, owing to the highly reactive CHCl portion in the hydrazone (III), reaction with a second molecule of the hydrazine takes place; this leads to the unstable compounds (IV). Further conversion of the adducts (IV) to osazones may occur as the result either of oxidation or dehydrogenation. The conduction of reactions in an atmosphere of dry nitrogen, as well as the fairly high yields of the compounds (V), probably indicates the dehydrogenation of the intermediate (IV).

In the PMR spectra of the osazones (V), the proton of the CH=N imine group appears in the form of an intense singlet at 8.27-9.03 ppm, and the protons of the NH groups are presented in the form of separate singlets in the region of 10.94-12.01 and 13.00-13.95 ppm.

Taking the example of the β-oxoaldehyde (VI), the stepwise reaction with the arylhydrazine was accomplished successfully, thereby confirming the stages of the formation of osazones. In fact, the condensation of the chloroaldehyde with 2,4-dinitrophenylhydrazine in the solution of ethyl acetate at 60-70°C leads to the formation of the monohydrazone (VII) in quantitative yield. The further reaction of compound (VII) with 2,4-dinitrophenylhydrazine was conducted under milder conditions, in methyl alcohol at room temperature, and led to the synthesis of the bishydrazone (Vc). The possibility of the separation of the reaction stages allows the isolation of mixed osazones of glyoxals (Vc).

Kazan' State Technological University, Kazan' 420015, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 190-193, February, 1998. Original article submitted May 13, 1997.

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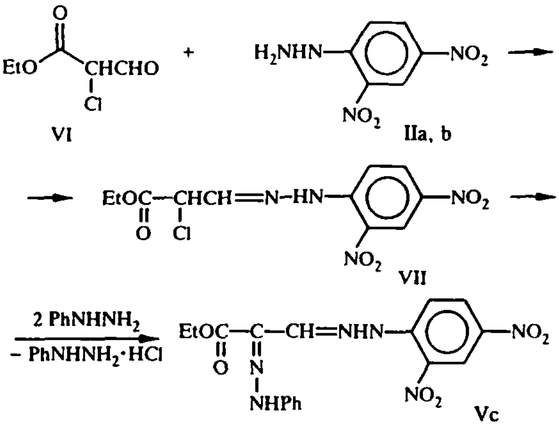
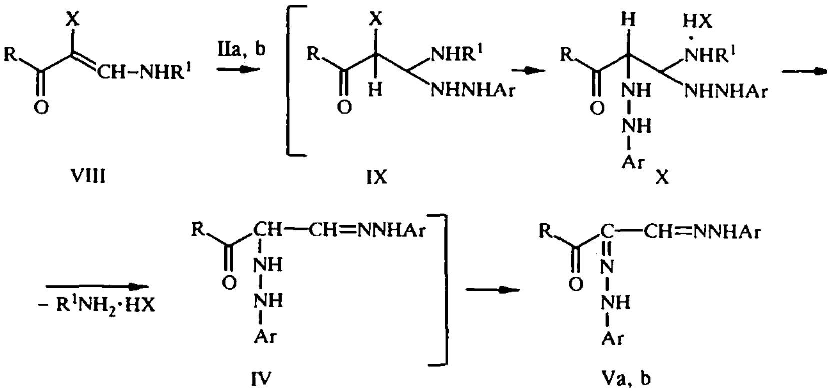


In the PMR spectrum of the hydrazone (VII), the signals of the CHCl methine and CH = N imine protons appear in the form of doublets ($^3J_{HH}$ = 7 Hz) in the region of 5.30 ppm and 8.00 ppm correspondingly, and the signal of the proton of the NH group appears at 11.60 ppm.

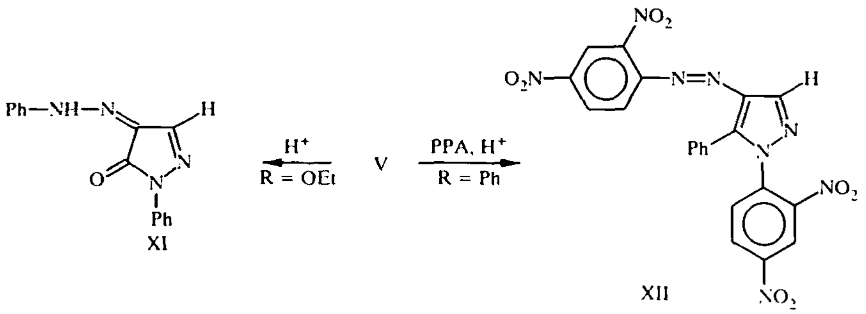
In contrast to the reaction of the enolate with phenylhydrazine, the reaction of the aldehyde (VI) with phenylhydrazine proceeds ambiguously even at low temperature (−8-0°C) and in the solution of ether, and leads to resinification of the reaction mixture, from which only hydrazine hydrochloride was isolated.

We further showed that the carbonyl-substituted enamines (VIII) [3], reacting with arylhydrazines in polar solvents, are also converted to the bishydrazones (V) by analogy with the enolates (I). It can be proposed that the formation of the osazones (V) proceeds through a series of sequential conversions as follows.



VIII a R = Ph, R^1 = p-MeC$_6$H$_4$, X = Cl; b R = Ph, R^1 = C$_6$H$_3$Me$_2$-2,4, X = Br;
c R = EtO, R^1 = Me, X = Cl

Addition of the hydrazine to the enamine (VIII) occurs at the first stage. The resulting adduct (IX), reacting with a second molecule of the hydrazine, is thereby converted to the intermediate (X). Subsequent cleavage of the amine hydrogen halide leads to the unstable product (IV), which is dehydrogenated to the corresponding osazone (V).



In the presence of a catalytic amount of sulfuric acid in the solution of boiling isopropyl alcohol, the osazone (Vb) undergoes intramolecular heterocyclization with the formation of the substituted pyrazole (XI).

TABLE 1. Yields and Characteristics of the Compounds

Compound	Empirical formula	mp, °C	IR spectrum, cm^{-1}	PMR spectrum, ppm	$\frac{\text{Found N, \%}}{\text{Calculated N, \%}}$	Yield,‡ %
Va*	$C_{17}H_{18}N_4O_2$	216...218	3285 (NH) 1670 (C–O) 1597 (C–N)	1,34 (3H, t, Me); 4,18 (2H, q, OCH$_2$); 7,07 (4H, m, H$_{Ph}$); 7,37 (6H, m, H$_{Ph}$); 8,27 (1H, s, CH–); 10,94 (1H, s, NH); 13,24 (1H, s, NH)	$\frac{17,97}{18,05}$	65
Vb	$C_{21}H_{14}N_8O_9$	233...235	3280 (NH) 1705 (C–O) 1590 (C–N)	7,86 (2H, m, H$_{Ar}$); 8,06 (3H, m, H$_{Ph}$); 8,34 (3H, m, 2H$_{Ph}$, H$_{Ar}$); 8,59 (1H, d.d, H$_{Ar}$); 8,96 (2H, d.d, 2H$_{Ar}$); 9,03 (1H, s, CH–); 12,01 (1H, s, NH); 13,95 (1H, s, NH)	$\frac{21,13}{21,45}$	67
Vc	$C_{17}H_{16}N_6O_6$	206...208		1,32 (3H, t, Me); 4,32 (2H, q, OCH$_2$); 7,22 (2H, m, H$_{Ph}$); 7,50 (3H, m, H$_{Ph}$); 7,72 (1H, d, H$_{Ar}$); 8,62 (1H, d.d, H$_{Ar}$); 8,90 (1H, d, H$_{Ar}$); 9,00 (1H, s, CH–); 11,90 (1H, s, NH); 13,00 (1H, s, NH)	$\frac{21,30}{20,99}$	70
VII†	$C_{11}H_{11}ClNO_4$	118...120	3300 (NH) 1640 (C–O) 1600 (C–N)	1,12 (3H, t, Me); 4,20 (2H, q, OCH$_2$); 5,30 (1H, d, CHCl); 8,00 (1H, d, H$_{Ar}$); 8,10 (1H, d, CH–); 8,42 (1H, d.d, H$_{Ar}$); 9,00 (1H, d, H$_{Ar}$); 11,60 (1H, s, NH)	$\frac{17,10}{16,94}$	96
XI	$C_{15}H_{12}N_4O$	143...145	3340 (NH) 1560 (C–N), 1675 (C–O)	7,37 (6H, m, H$_{Ph}$); 7,89 (1H, s, CH–); 8,01 (4H, m, H$_{Ph}$); 13,97 (1H, broad s, NH)	$\frac{21,03}{21,21}$	75

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*The ^{13}C NMR spectrum (DMSO-D$_6$) is as follows: 14.26 ppm (CH$_3$), 60.54 ppm (OCH$_2$), 112.14 ppm, 114.46 ppm (o-C$_{Ph}$), 120.22 ppm, 123.04 ppm (p-C$_{Ph}$), 124.96 ppm (C=N), 129.57 ppm, 129.67 ppm (m-C$_{Ph}$), 132.81 ppm (CH=N), 142.72 ppm, 143.60 ppm (N-C$_{Ph}$), and 164.15 ppm (C=O).

†Found, %: Cl 10.35. Calculated, %: Cl 10.47.

‡The yields of the compounds (Va, b) are presented according to the method B.

On the basis of the data of IR spectroscopy and NMR, it was established that, even under drastic conditions — prolonged heating at 180-190°C in the presence of polyphosphoric acid, the benzoyl-containing osazone (Va) is only partially converted to the pyrazole (XII), which could not be isolated in discrete form.

The structure of the compounds (Va-c), (VII), and (XI) synthesized was shown by the methods of IR spectroscopy and ^{1}H and ^{13}C NMR, and was confirmed by the data of the elemental analysis (Table 1).

Therefore, convenient preparative methods for the synthesis of previously unknown carbonyl-substituted osazones of glyoxals were developed by utilizing accessible starting reagents, and their intramolecular heterocyclization was accomplished.

EXPERIMENTAL

The IR spectra of suspensions of the samples in mineral oil were taken on the UR-20 spectrometer. The PMR spectra of solutions in DMSO-D$_6$ were taken on the Tesla BW-567 spectrometer (100 MHz) with HMDS as the internal standard. The ^{13}C NMR spectra were recorded on the Bruker WP-80 spectrometer.

Bishydrazones of Carbonyl-Substituted Glyoxals (Va-c). A. To the mixture of 0.08 mole of the enolate (I), 50 ml of glacial CH_3COOH, and 50 ml of diethyl ether is added, with stirring at −5-0°C, 0.24 mole of the hydrazine (II). The reaction mixture is held for 30 min with cooling, and for 3 h at room temperature. The residue is filtered off, and the precipitated crystals of the osazones (Va, b) are separated, washed with the 1:1 mixture of water−alcohol, and dried.

B. The mixture of 0.03 mole of the enamine (VIII), 0.06 mole of the hydrazine (II), and 50 ml of ethyl acetate is boiled for 5 h, and the mixture is cooled. The residue is filtered off, and the filtrate is evaporated to 1/3 vol. The precipitated crystals of the osazones (Va, b) are separated and dried.

C. To the suspension of 2.75 mmole of the hydrazone (VII) in 15 ml of methanol are added, dropwise with stirring at 20°C, 5.5 mmole of phenylhydrazine. The reaction mixture is held at room temperature for 12 h. The precipitated crystals of the osazone (Vc) are filtered off, washed with the 1:1 mixture of water−alcohol, and dried.

The physicochemical characteristics of the compounds obtained by the methods A and B are identical.

Ethoxycarbonylchloroacetaldehyde 2,4-Dinitrophenylhydrazone (VII). The mixture of 0.1 mole of 2,4-dinitrophenylhydrazine and 50 ml of ethyl acetate is heated to 60-70°C prior to the addition, dropwise with stirring, of 0.1 mole of the aldehyde (VI). The reaction mixture is cooled and held at room temperature for 5 h. The solvent is removed, and the precipitated crystals of (VII) are filtered off and dried.

1-Phenyl-2-pyrazoline-4,5-dione 4-Phenylhydrazone (XI). The mixture of 9.68 mmole of the osazone (Vb), 50 ml of isopropyl alcohol, and 8-10 drops of concentrated H_2SO_4 is boiled for 18 h. The precipitated bright orange crystals of compound (XI) are filtered off, washed with isopropyl alcohol, and dried.

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