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SYNTHESIS AND PROPERTIES OF AZOLES AND THEIR DERIVATIVES.

10.* SYNTHESIS OF 3,5-DIARYL-4-NITROISOXAZOLES

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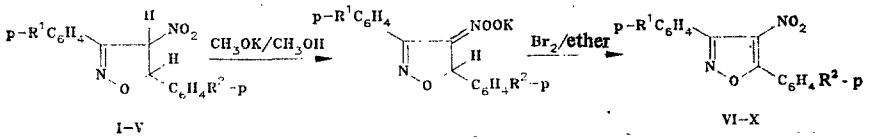
UDC 547.786.1.07:541.634

A method was proposed for the synthesis of 3,5-diaryl-4-nitroisoxazoles entailing the bromination of potassium salts of the corresponding 3,5-diaryl-Δ^2-isoxazolinyl-4-nitronic acids. The method may be used for the conversions of both the trans and cis isomers of 3,5-disubstituted 4-nitro-Δ^2-isoxazolines.

In a continuation of a study of the reactivity of nitro-Δ^2-isoxazolines [2, 3], we investigated the conversion of 3,5-diaryl-4-nitro-Δ^2-isoxazolines (I-V) to the corresponding 3,5-diaryl-4-nitroisoxazoles (VI-X), which hold interest as potentially biologically active compounds. The potassium salts of 3,5-diaryl-Δ^2-isoxazolinyl-4-nitronic acids undergo bromination by molecular bromine and are readily converted to 4-nitroisoxazoles VI-X. The proposed reaction, in contrast to the reported methods for the aromatization of 4-nitro-Δ^2-isoxazoline derivatives [4, 5], proceeds under relatively mild conditions and may be used for either trans or cis isomers of 4-nitro-Δ^2-isoxazolines.



I-V VI-X

The potassium salts of 3,5-diaryl-Δ^2-isoxazolinyl-4-nitronic acids were obtained by the action of potassium methylate on trans and cis isomers of I-V at −5°C. The salts formed were treated with ethereal bromine without isolation at from −15° to −20°C to yield 3,5-diaryl-4-nitroisoxazoles VI-X in 70-80% yields.

Thin-layer chromotographic analysis indicated that the reaction mixtures contained other possible reaction products in addition to VI-X. We should note that this method cannot be used for the aromatization of 5-nitro-Δ^2-isoxazolines since, according to our previous results [2], these derivatives are unstable in alkaline media.

*Communication 9, See [1].

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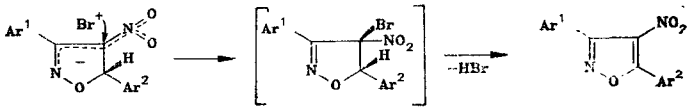
TABLE 1. Characteristics of 3,5-Diaryl-4-nitroisoxazoles VI-X

Compound	R^1	R^2	M_p, °C[a]	Mass spectrum, m/z (peak intensities in % of maximum peak)[b]	IR spectrum, cm^{-1}			Found, %		Chemical formula	Calc., %		Yield, %[c]
					νNO_2	$\nu C=N$	β-ring	C	H		C	H	
VI	H	H	174—176[d] (dec.)	267 (10,6), 266 (60,7), 189 (7,0), 145 (20,8), 143 (7,0), 119 (42,1), 105 (100), 103 (10,1), 91 (9,7), 89 (35,9), 78 (9,6), 77 (81,1), 76 (11,8)	1525, 1370	1620	835	67,6	3,7	$C_{15}H_{10}N_2O_3$	67,7	3,8	76 (A), 73 (B)
VII	H	Cl	161—163 (dec.)	302 (12,0), 301 (7,5), 300 (37,0), 145 (11,5), 141 (33,3), 140 (8,5), 139 (100), 125 (6,4), 123 (16,8), 119 (39,3), 113 (14,0), 111 (37,0), 103 (14,1), 91 (6,4), 77 (28,1), 76 (12,6), 75 (21,9)	1540, 1370	1620	830	60,0	2,9	$C_{15}H_9ClN_2O_3$	59,9	3,0	78 (A), 80 (B)
VIII	H	Br	163—165 (dec.)	347 (6,8), 346 (38,7), 345 (7,1), 344 (38,7), 185 (97,3), 184 (7,9), 183 (100), 182 (10,8), 169 (14,1), 167 (14,5), 161 (8,4), 157 (37,5), 155 (38,8), 145 (18,6), 143 (6,7), 139 (14,5), 119 (62,6), 111 (6,3), 103 (11,7), 91 (10,4), 88 (8,6), 77 (40,0), 76 (31,8), 75 (26,1)	1540, 1370	1625	830	52,1	2,6	$C_{15}H_9BrN_2O_3$	52,2	2,6	78 (A), 76 (B)
IX	H	CH_3	133—134	281 (17,1), 280 (86,5), 145 (14,1), 143 (5,5), 135 (17,8), 120 (18,3), 119 (100), 103 (25,9), 91 (86,7), 89 (9,2), 77 (31,2)	1515, 1370	1625	830	68,9	4,5	$C_{16}H_{12}N_2O_3$	68,6	4,3	71 (A)
X	CH_3	H	152—153	281 (18,1), 280 (98,1), 203 (5,2), 159 (18,0), 134 (7,8), 133 (83,2), 132 (12,8), 117 (8,2), 116 (93,0), 107 (7,6), 106 (13,3), 105 (100), 91 (35,2), 90 (11,4), 89 (59,7), 78 (11,1), 77 (72,8), 76 (7,9)	1515, 1570	1620	835	68,8	4,6	$C_{16}H_{12}N_2O_3$	68,6	4,3	78 (A)

[a] Recrystallization solvents: VI from 2-propanol; VII, IX, and X from methanol; and VIII from ethanol.
[b] Peaks given with intensity ≥5%.
[c] The isomer of the starting 4-nitro-Δ^2-isoxzoline is given in parentheses: A indicates the trans isomer, while B indicates the cis isomer.
[d] mp 175-176°C [5].

The mechanism for the conversion of 4-nitro-Δ^2-isoxazolines to 4-nitroisoxazoles, in all likelihood, involves the reaction of the anion of the nitro compound with a bromine cation leading to 4-bromo-4-nitro-Δ^2-isoxazolines which, under the reaction conditions, undergo syn elimination of a hydrogen bromide molecule.* Since significant amounts of 3,5-diaryl-4-bromoisoxazoles were not found in the reaction mixture, we may assume that the electrophilic attack of the bromine cation occurs exclusively trans to the substituent at C-5 of the heterocyclic ring.

Attack of an electrophilic species form the opposite side which would lead to 3,5-diaryl-4-bromoisoxazoles is apparently hindered sterically by the aryl group at C-5 of the Δ^2-isoxazoline ring.



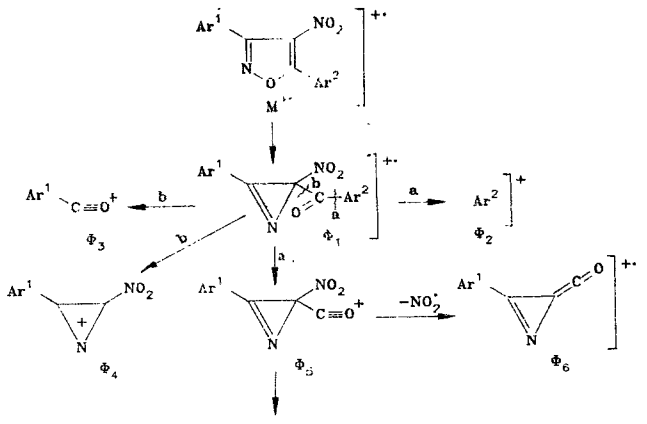
The compositions of products VI-X were established by elemental analysis and their structures were confirmed by spectral methods. The IR spectra isoxazoles VI-X (Table 1) have strong bands at 1540-1515 cm^{-1} for asymmetric stretching vibrations of the nitro groups attached to the heteroaromatic fragment [10, 11]. The bands at 1625-1620 and 835-830 cm^{-1} should be assigned to the C=N bond stretching vibrations and in-plane deformation vibrations of the isoxazole ring [11], respectively. As expected, the PMR spectra of these compounds show an aromatic proton multiplet for the aryl substituents at 7.3-8.0 ppm and, in the case of IX and X, methyl group singlets at 2.5 and 2.4 ppm, respectively.

Analysis of the mass spectra of VI-X revealed several common features for the dissociative ionization of these molecules, which are characteristic for isoxazole derivatives [12-15]. The agreement of the m/z values for the molecular ion peaks (Table 1) with the molecular mass confirms the proposed structures for isoxazoles VI-X.

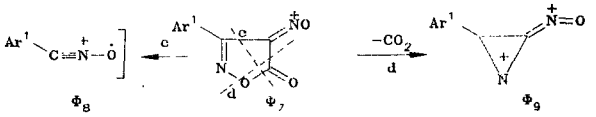
The major directions for the fragmentation are given in Scheme 1. We should note, however, more special features of this process.

The molecular ions formed upon electron impact for VI-X eliminate the nitro group only with difficulty (the intensity of the $[M - NO_2]^+$ ion peaks does not exceed 2% of the maximum peak). The intensity of the $[M - NO]^+$ ion peaks is also low (0.4-0.2%). These findings indicate the low probability of a nitro–nitrite rearrangement which is characteristic for many nitroheteroaromatic compounds [16]. An important feature is the rearrangement of the Φ_5 fragment ion (see Scheme 1) related to the migration of a nitro group oxygen atom and opening of the small ring, leading to Φ_7 ions with 5-isoxazolone structure. Evidence for this process may be found for the presence of a metastable ion peak related to the elimination of a CO_2 molecule from the Φ_5 ion and a strong peak for the Φ_8 ion [17]. The elemental composition of the fragment ions Φ_1–Φ_9 of 3,5-diphenyl-4-nitroisoxazole (VI) was confirmed by high-resolution mass spectroscopy.

Scheme 1



*The possibility of thermal syn elimination of small molecules from Δ^2-isoxazoline derivatives has been noted in our previous work [2, 3, 6, 8] and by Vita-Finzi [7] and Sasaki [9].



EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer in KBr pellets. The PMR spectra were taken on a Tesla BS-487C spectrometer at 80 MHz in $CDCl_3$ with TMS as the internal standard. The mass spectra were taken on an LKB-9000S spectrometer with 70 eV ionizing energy, 250°C ion source temperature, and 35-65°C sample injection temperature. The reaction course and purity of the compounds obtained were monitored using thin-layer chromatography on Merck Kieselgel HF 254 plates.

General Method for the Preparation of 3,5-Diaryl-4-nitroisoxazoles (VI-X). A solution of 5 mmoles potassium methylate in 5 ml absolute methanol was added dropwise with rapid stirring to a suspension of 5 mmoles trans- or cis-3,5-diaryl-4-nitro-Δ^2-isoxazoline (I-V) in 15 ml absolute methanol at −5°C. The solvent was removed at reduced pressure and the potassium salt obtained was suspended in 60 ml dry ether, cooled to −15 to −20°C. A solution of 6 mmoles bromine in 10 ml dry ether was then added dropwise to this solution with rapid stirring. After introduction of the entire amount of bromine, the reaction mixture was stirred for 1 h at 20°C and evaporated to dryness at reduced pressure. The residue was washed several times with cold water, dried, and crystallized from a suitable solvent (see Table 1).

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