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THE 3,4-DIHYDRO-N-OXO-3-ETHYL-2,1-BENZOXAZINIUM CATION IN THE SYNTHESIS OF β- AND γ-SUBSTITUTED ARYLBUTANES AND 1-ARYL-2-BUTENES

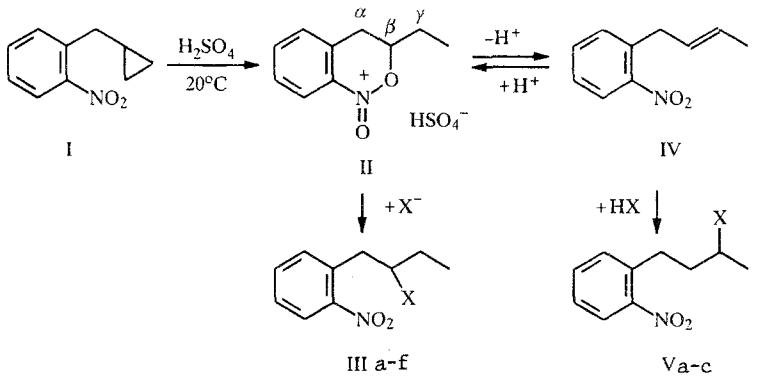
E. V. Trofimova, A. N. Fedotov, S. S. Mochalov, Yu. S. Shabarov, and N. S. Zefirov

The reaction of 3,4-dihydro-N-oxo-3-ethyl-2,1-benzoxazinium salts with reagents with nucleophilic and basic character can be used to obtain β- or γ-substituted arylbutanes and trans-1-aryl-2-butenes. The reactions proceed regiospecifically and are regulated by the nature of the reagents used.

It is known that certain difficulties are encountered in the synthesis of β- or γ-substituted alkylbenzenes and unconjugated alkenylbenzenes.

In the present research we were able to show that 3,4-dihydro-N-oxo-3-ethyl-2,1-benzoxazinium salts II, which are readily formed, for example, from 2-nitrobenzylcyclopropane (I) [1], can serve as convenient synthones for obtaining either β- or γ-substituted butylbenzenes or trans-1-(2-nitrophenyl)-2-butenes.

For example, treatment of a sulfuric acid solution of heterocyclic ion II with nucleophilic reagents such as the bromide ion, methanol, or acetonitrile leads to β-substituted 1-arylbutanes — the corresponding bromide IIIa, ether IIIb, and acetamidobutylbenzene IIIc* — in virtually quantitative yields. The reaction of cyclic ion II with acetonitrile essentially models the Ritter reaction [2].



III aX=B , bX=OMe, c X=NHCOMe, dX=OC_3H_7, eX=OCOMe, f X=OH; V aX=NHCOMe, bX=OC_3H_7-*i*, c X=OH

*In this case, a small amount (≈5%) of γ-substituted isomer Va is formed in addition to the chief reaction product, viz., IIIc.

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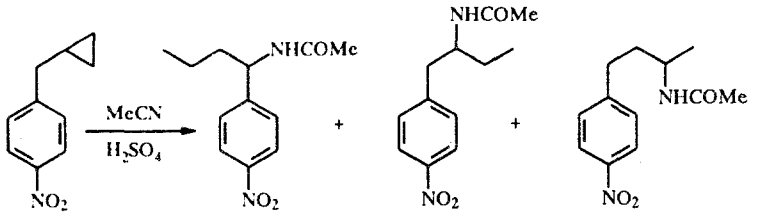
TABLE 1. Physicochemical Characteristics and Yields of IIIa-e, Va, and Vb Obtained by the Reaction of Bisulfate II with Nucleophilic Reagents

Reagent	Reaction	Empirical formula	PMR spectrum, δ, ppm	Yield, %
HB	IIIa	$C_{10}H_{12}BrNO_2$	1,08 (3H, t, *J*=7 Hz, CH_3); 1,65...2,25 (2H, m, 3-CH_2); 2,95...3,85 (2H, m, 1-CH_2); 3,90...4,45 (1H, m, CH); 7,10...8,05 (4H, m, HA)	95
CH_3OH	IIIb	$C_{11}H_{15}NO_3$	0,9 (3H, t, *J*=7 Hz, CH_3); 1,15...1,70 (2H, m, 3-CH_2); 2,85...3,40 (6H, m OCH_3, 1-CH_2, CH); 7,10...7,85 (4H, m, HA)	76
CH_3CN	IIIc	$C_{12}H_{16}N_2O_3$	1,0 (3H, t, *J*=7,5 Hz, CH_3); 1,25...1,60 (2H, m, 3-CH_2); 1,85 (3H, s $COCH_3$); 3,0 (2H, d, *J*=5 Hz 1-CH_2); 3,90...4,45 (1H, m, CH); 5,81 (1H, br.d, *J*=10 Hz NH); 7,20...7,95 (4H, m, HAr)	85
CH_3CN	Va	$C_{12}H_{16}N_2O_3$	1,28 (3H, d, *J*=6 Hz CH_3); 1,80...1,95 (2H, m, 2-CH_2); 2,0 (3H, s, $COCH_3$); 2,80...3,20 (2H, m, 1-CH_2); 3,80...4,45 (1H, m, CH); 6,60 (1H, br.d *J*=8,5 Hz NH); 7,20...8,00 (4H, m, HAr)	5
C_3H_7OH**	IIId	$C_{13}H_{19}NO_3$	0,55...1,0 (10H, m, $2CH_2H_5$); 2,80...3,55 (5H, m, OCH_2, 1-CH_2, CH); 7,00...7,95 (4H, m, HAr)	65
i-C_3H_7OH**	Vb	$C_{13}H_{19}NO_3$	0,7 (3H, d, *J*=6 Hz, 4-CH_3); 1,0 (6H, d, *J*=6 Hz, $(CH_3)_2$CHO); 1,15...1,75 (2H, m, 1-CH_2); 2,7...3,7 (4H, m, 2-CH_2, CH, $CH(CH_3)$); 7,25...7,80 (4H, m, HAr)	20
CH_3COOH**	IIIe	$C_{12}H_{15}NO_4$	0,95 (3H, t, *J*=7 Hz, 4-CH_3); 1,65 (2H, m, 3-CH_2); 1,8 (3H, s, $COCH_3$); 2,65...3,55 (2H, m, 1-CH_2); 4,8 (1H, m, CH); 7,3...8,3 (4H, m, HAr)	30

*Compound IIIc had mp 130-132°C, Va had mp 30-31°C, and the remaining compounds were viscous oils.

**In addition to IIId, IIIe, and Vb, 1-(2-nitrophenyl)-2-butene (IV) was isolated in 12%, 51%, and 53% yields, respectively.

The formation of β-substituted butylbenzenes IIIa-c is evidently a consequence of direct attack by the nucleophile at the β-carbon atom of cyclic ion II, in which the nitro group acts as an intramolecular "anchor" that fixes the potential carbonium center. The results of the transformation of p-nitrobenzylcyclopropane (VI) under the adopted conditions serve as an additional confirmation that precisely cyclic ion II plays the decisive role in the formation of β-substituted arylbutanes IIIa-c. It was found that, in contrast to o-nitrobenzylcyclopropane (I), p-nitro isomer VI, in the acid-catalyzed reaction with acetonitrile, forms a mixture of three adducts, the structures of which correspond to the formation of carbonium ions of the α, β, and γ type (in a ratio of 1:3:5, respectively).



VI VII VIII IX

A study of the dependence of the progress of the transformation of ion II on the nature of the nucleophilic reagents showed that steric factors may determine the reaction pathway. Thus two substances — the expected β-propoxybutane IIId and trans-1-(2-nitrophenyl)-2-butene (IV) — are detected in the products of the reaction of ion II when propyl alcohol is used as the reagent. The reaction of ion II with acetic acid also proceeds similarly; in this case the amount of arylbutene IV formed predominates over the amount of substitution product IIIe (Table 1).

In contrast to the examples examined above, in the reaction of ion II with isopropyl alcohol steric factors have such an effect that they completely block the formation of a β-substituted product, and, as a result, γ-substituted nitrophenylbutane Vb is formed; trans-arylbutene IV is also a second reaction product in this case.

Since γ-substituted isopropoxybutane Vb could not have developed directly as a result of the nucleophilic reaction of ion II with isopropyl alcohol, we assumed that it is formed as a consequence of two successive processes — the base-catalyzed conversion of ion II to nitrophenylbutene IV* and the acid-catalyzed addition of the indicated alcohol to the resulting arylalkene IV. The conversion of genuine arylalkene IV on reaction with isopropyl alcohol in the presence of concentrated H_2SO_4 only to γ-isopropoxybutylbenzene Vb, in which some of the arylalkene IV is recovered unchanged, serves as a confirmation of this assumption.

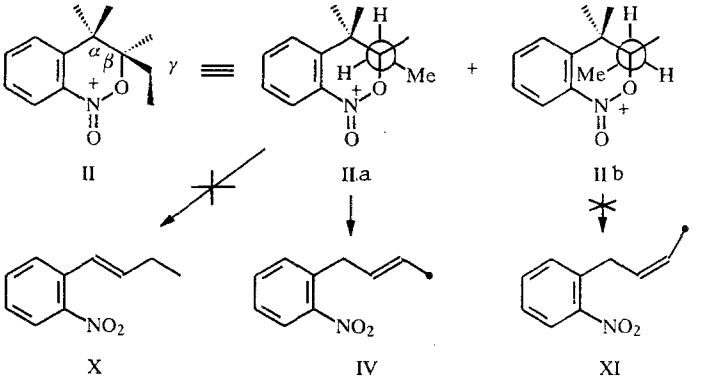
The absence of the β-substituted isomer in the case of the direct reaction of arylalkene IV with isopropyl alcohol proves that in the acid-catalyzed addition of isopropyl alcohol to the double bond of o-nitrophenyl-2-butene IV intramolecular attack by the spatially close nitro group on the β-carbon atom of the protonated double bond of the substrate is realized in preference to external attack by isopropyl alcohol.

It is interesting to note that if arylalkene IV is not previously converted to cyclic ion II (the latter on treatment with water gives only β-substituted nitrophenylbutanol IIIf [1]) but is subjected directly to acid-catalyzed hydrolysis, then, in contrast to the transformation in isopropyl alcohol, two addition products, viz., nitrophenylbutanols IIIf and Vc, are formed, and the amount of the β-substituted product predominates in this case (IIIf:Vc = 4:1). This result once again shows that the structural factors of the nucleophilic reagents play a decisive role in the reaction of the latter with the II ion.

It should be emphasized that, despite the ambiguous course of the reactions of the II ion with propyl and isopropyl alcohols, as well as with acetic acid, they still can be carried out regiospecifically virtually completely if one takes into account, on the one hand, the fact that the arylalkene IV isolated in each case can again be quantitatively converted to cyclic ion II [1] and, on the other, the fact that the indicated arylalkene reacts regioselectively with the corresponding nucleophile.

As regards the reasons for the regio- and stereoselectivity of the formation of unconjugated nitrophenylbutene IV in the examined reactions and the impossibility of the formation of the more stable conjugated isomer X, they become understandable when the following two conditions are assumed: 1) alkene IV is formed directly from cyclic ion II; 2) the reaction proceeds via a mechanism of the bimolecular-pseudoelimination type.

It is known that bimolecular elimination requires a trans orientation of the eliminated fragments in the starting molecule or in the transition state. As demonstrated by an analysis of molecular models of the various conformers of the II ion, due to the rigid fixation of the atoms of the heterocyclic fragment the α-hydrogen atoms in conformer IIa (or IIb) exist in space in an orientation that does not favor the formation of a double bond between the α- and β-carbon atoms via a bimolecular mechanism.



At the same time, a conformation that is convenient for pseudoelimination can be realized easily with the participation of the fragments attached to the β- and γ-carbon atoms, and conformation IIa, which is responsible for the formation of precisely trans-alkene IV, is energically more favorable.

The result of the dehydrobromination of 1-(2-nitrophenyl)-2-bromobutane (IIIa) by the action of potassium hydroxide in alcohol also constitutes convincing evidence in favor of the proposed explanation for the formation of trans-alkene IV. The only product in this case was an arylalkene of the conjugated type X. Thus, in the absence of steric limitations for the

*Isopropyl alcohol acts as a base in this case.

formation of a double bond between the α- and β-carbon atoms or the β- and γ-carbon atoms of the side chain, the formation of conjugated arylalkene X is a more favorable process.

EXPERIMENTAL

The IR spectra of films or suspensions in mineral oil were recorded with a Specord IR-75 spectrometer. The PMR spectra of solutions in CCl_4 or $CDCl_3$ were obtained with Bruker XL-100 and Varian spectrometers with operating frequencies of 100 and 60 MHz with tetramethylsilane (TMS) as the internal standard.

Monitoring of the purity of the starting compounds and the individuality of the products isolated and analysis of the reaction mixtures were carried out by both GLC and by chromatography on Silufol plates. Analysis by GLC was accomplished with an LKhM-8MD chromatograph with a 3-m long column with a diameter of 4 mm; the stationary phase was 5% SE-30 siloxane elastomer on a Chromaton N-AW-DMCS support, and the carrier gas was helium. Silpearl silica gel was used for column chromatography, and the eluent was ether—pentane (1:3).

The results of elementary analysis of the compounds obtained for C, H, and N were in agreement with the calculated values.

2-Nitrobenzylcyclopropane (I). This compound was obtained by nitration of benzylcyclopropane by the method in [3] and had bp 103-104°C (1 mm) and n_D^{20} 1.5452.

3,4-Dihydro-N-oxo-3-ethyl-2,1-benzoxazinium Bisulfate (II). A 3.54-g (20 mmole) sample of 2-nitrobenzylcyclopropane (I) was added gradually with stirring to 15 ml of concentrated H_2SO_4 (cooled to −20°C), after which the mixture was maintained for 1 h at the same temperature, and the resulting solution was used in reactions with the nucleophilic reagents.

Transformations of 3,4-Dihydro-N-oxo-3-ethyl-2,1-benzoxazinium Bisulfate (II) by the Action of Nucleophilic Reagents (General Method). A solution of the II ion prepared as described above was added slowly to the cooled (to 0°C) corresponding reagent (50 ml), and the reaction mixture was stirred for 4 h and then diluted with 150 ml of water. The aqueous mixture was extracted with chloroform (3 × 20 ml), and the extract was washed with water and dried with magnesium sulfate. The solvent was evaporated, and the residue was chromatographed with a column. The yields and characteristics of the products obtained are presented in Table 1.

1-(2-Nitrophenyl)-2-butanol (IIIf) and 1-(2-Nitrophenyl)-3-butanol (Vc). A 50-ml sample of 5% H_2SO_4 was added to 1.77 g (10 mmole) of 1-(2-nitrophenyl)-2-butene (IV), and the mixture was stirred for 1 h. The organic compounds were extracted with chloroform (2 × 25 ml), and the extract was washed with water and dried with magnesium sulfate. The solvent was evaporated, and the residue was chromatographed with a column to give 1.01 g (52%) of 1-(2-nitrophenyl)-2-butanol (IIIf), the spectral characteristics of which were in agreement with those presented in [1], and 0.25 g (13%) of 1-(2-nitrophenyl)-3-butanol (Vc). IR spectrum of Vc: 1530, 1350 (NO_2); 3390 cm^{-1} (OH). PMR spectrum of Vc: 1.35 (3H, d, J = 7 Hz, CH_3), 1.5-2.05 (2H, m, 3-CH_2), 2.45 (1H, s, OH), 2.75-3.30 (2H, m, CH_2Ar), 3.61-4.10 (1H, m, CH), 7.15-8.20 ppm (4H, m, HAr). Also obtained was 0.37 g (21%) of starting butene IV.

Isopropyl 1-(2-Nitrophenyl)-3-butyl Ether (Vb). A 2-ml sample of concentrated H_2SO_4 was added to a solution of 1.77 g (10 mmole) of 1-(2-nitrophenyl)-2-butene (IV) in 25 ml of isopropyl alcohol, and the mixture was stirred for 1 h. The alcohol was then evaporated, and the residue was chromatographed to give 0.92 g (39%) of Vb and 0.85 g (48%) of starting butene IV.

1-(2-Nitrophenyl)-1-butene (X). A solution of 1.12 g of potassium hydroxide in 10 ml of methanol was added gradually with stirring at 20°C to a solution of 2.6 g (10 mmole) of 1-(2-nitrophenyl)-2-bromobutane (IIIa) in 10 ml of methanol, and the reaction mixture was stirred for 1 h and then poured into 150 ml of cold water. The organic substances were extracted with ether, and the extract was washed with water and dried with magnesium sulfate. The solvent was evaporated, and the residue was chromatographed with a column to give 1.56 g (88%) of X in the form of a viscous oil. IR spectrum: 1525, 1350 (NO_2); 1650, 960 cm^{-1} (CH=CH). PMR spectrum: 1.31 (3H, t, J = 6.3 Hz, CH_3), 2.01-2.61 (2H, m, CH_2), 5.90-7.01 (2H, m, —CH=CH—), 7.11-8.01 ppm (4H, m, HAr).

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