Diastereospesific 1,3-dipolar cycloaddition reaction of 3-ethyl-3-methyl-4,5-dihydro-3H-bezazepine N-oxide to allyl-N-phenylcarbamate

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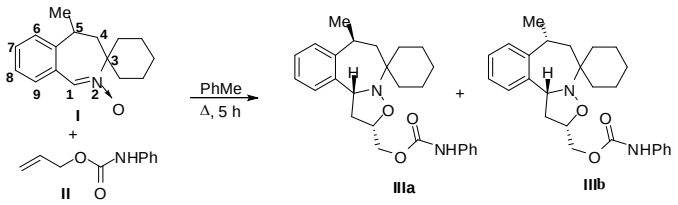
Abstract — **[3+2]-Cycloaddition of 3-ethyl-trimethyl-4,5-dihydro-3H-2-benzazepine N-oxide to allyl-N-phenylcarbamate occurred a regio- and stereo-specifically with formation of single diastereoisomer of (5-ethyl-5,7,7-trimethyl-1,2,5,6,7,11b-hexahydroisoxazolo[3,2-a][2]benzazepine-2-yl)methyl-N-phenylcarbamate, which molecular structure was investigated by X-ray structure analysis.**

Keywords– carbamates; azaheterocycles; 1,3-dipolar cycloaddition; diastereospecific reaction;

I. INTRODUCTION

Wide synthetic opportunities of nitrones, formed at oxidation of secondary amines by per acids of transitive metals of VI group (more often V and W), have provided fast extension of this method in chemistry of heterocyclic compounds [1, 2]. Formed as a result of oxidation cyclic nitrones appear active 1,3-dipoles and enter cycloaddition reaction with a wide set of 1,3-dipolarophiles.

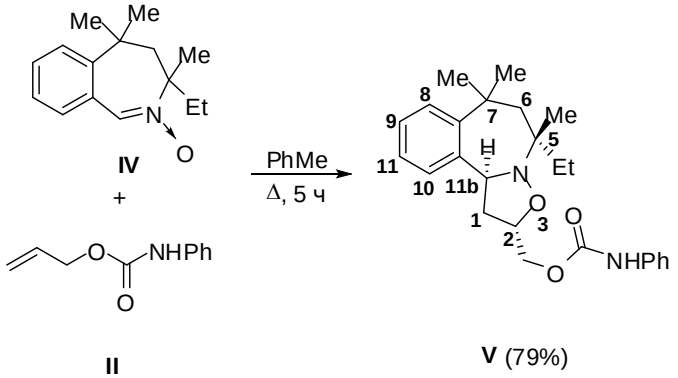
Benz-2-azeine N-Oxides do not concern to accessible compounds, and data on their behaviors in dipolar cycloaddition reactions are extremely limited. So, there are data as about regioselective [3], and regio-oriented [4] addition of styrene to such nitrones. It is shown, that [3+2]-cycloaddition of acrylonitrile [5], ethyl- and methyl- acrylates [6] to 4,5-dihydro-5-methyl-3H-spiro[benz-2-azepine-3,1′-cyclohexane] N-oxide (I) proceeds not stereo- and not regio-specifically, with formation of a mixture of all eight possible diastereoisomers. At the same time cycloaddition of mentioned above nitrone to styrene [7] or allyl-N-phenylcarbamate (II) [8] proceeds regio-selectively and stereo-specifically with formation of two stereoisomers IIIa and IIIb in 80:20 ratio approximately (scheme 1). In the latter case from a mixture of stereoisomers in an individual state it was possible to separate out with use of liquid column chromatography method only major stereoisomer IIIa, which structure has been confirmed with NOESY method.



Thus, it has been earlier shown, that alkyl substituent at position 5 of benz-2-azepine nitrones does not render essential influence on regio-selectivity of [3+2]-cycloaddition to its of activated alkenes. The complex of all possible diastereisomers is formed.

II. CYCLOADDITION OF 3-ETHYL-3,5,5-TRIMETHYL-4,5-DIHYDRO-3H-2-BENZAZEPINE N-OXIDE TO ALLYL-N-PHENYLCARBAMATE

Developing these researches in the present work, we have studied interaction of allyl-N-phenylcarbamate (II) with nitrone asymmetrically substituted on position 3 of benz-2-azepine. As the last has been chosen accessible in two synthetic stages 3-ethyl-3,5,5-trimethyl-4,5-dihydro-3H-2-benzazepine N-oxide (IV) (it is received by a procedure similar [9]).



Cycloaddition reaction carried out by heating equimolar amounts of the reactants in boiling toluene for 5 h (scheme 2). Target cycloaddition adduct (V) has been isolated as only single of diastereoisomer with 79 % yield. On the basis of 1H NMR spectroscopy and thin-layer chromatography of a

reactionary mixture can be asserted, that in this case 1,3-dipolar cycloaddition proceeds regio- and stereo-specifically (other products are not found out). As a result of reaction two new asymmetric center (C-11b, C-2) are formed, thus, most likely, diastereoselectivity of reactions are supervised with steric remoteness of the most bulk substituent's at atoms C-11b and C-5 in a transient state (Et-5 cis-orientated in relation to H-11b).

The spatial structure of isoxazolidine V has been established by X-ray diffraction analysis method with use of synchrotron radiations (fig. 1).

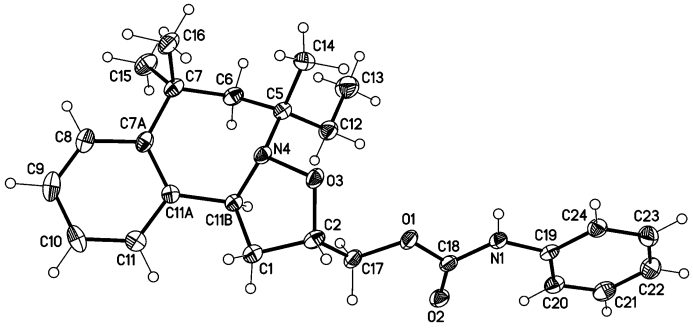


Figure 1. Molecular structure of isoxazolidine V on data X-ray diffraction analysis (one of two crystallographic independent molecules is represented).

The molecule of compound V contains three asymmetric centers at C2, C5 and C11B atoms. The crystal of compound V represents racemate and will consist from enantiomer pairs with the following relative configuration of chiral centers: rac-2S *, 5S *, 11BS*.

Length of C1-C11B bond in isoxazolidine cycle of compound V same as in 3,4,5-substituted isoxazolidine [10], at the same time N4-O3 bond is extended on 0.044 Å, and N4-C11B, O3-C2 and C1-C2 bonds are shortened, accordingly, on 0.048, 0.017 and 0.011 Å. Thus in comparison with 3,4,5-trisubstituted isoxazolidine reduction of N4-C11B-C1 valence angle on 2° is observed, and other valence angles practically do not change.

Thus, in the present work for the first time it is shown, what even small distinctions in steric volume of substituents in position 3 of benz-2-azepine nitrones of some considerably raise diastereoselectivity of [3+2]-cycloaddition to its of alkenes.

III. Experimental part

^{1}H NMR spectra were recorded on a Bruker DRX-500 (500 MHz) spectrometer from solutions in DMSO-d_6. IR spectra are measured on a Specord M82 spectrophotometer in wavenumber range 4000-400 sm^{-1} from sample prepared as KBr pellets. The purity of the product was checked by TLC on Silufol UV-254 plates in ethyl acetate - petroleum-ether (1:3).

X-ray structure analysis of compound V. Crystals of compound **V** ($C_{25}H_{32}N_2O_3$, M = 408.53) triclinic, spatial group $P\ \bar{1}$, at T = 100 K: a = 11.362(1), b = 11.597(1), c = 18.012(1) Å, α = 94.88(1), β = 91.93(1), γ = 114.25(1), V = 2149.9(3) $Å^3$, Z = 4, d = 1.262 g/sm^3, μ = 0.083 mm^{-1}. Diffraction experiment is received on a MAR225 diffractometer (synchroton radiation, λ = 0.90500, BL14.2, PSF, BESSY, Berlin, Germany, monochromator Cu(113), CCD method of measurement of diffraction pattern, $2\theta_{max}$ = 65.2°, 27227 measured reflections, 7872 independent reflections, R_{int} = 0.095). The structure is deciphered by direct method under program SHELXS-97 [11] and specified by full-matrix method of least-squares on F^2 in anisotropic approximation for non-hydrogen atoms under program SHELXL-97 [12]. Hydrogen atoms, which position are designed geometrically, included in specification in isotropic approximation with fixed item (model of "horseman") and thermal parameters. Final values of divergence factors are equal R_1 = 0.071 for 4690 reflections with $F^2 > 2\sigma(I)$ and wR_2 = 0.192 for all independent reflections. Tables of atom coordinates, bond lengths of compound, valent and torsion angles and parameters of anisotropic shift for compound **V** are deposited in the Cambridge Bank of the Structural Data (CCDC 860100, 12 Union Road, Cambridge CB2 1EZ, UK).

(5-Ethyl-5,7,7-trimethyl-1,2,5,6,7,11*b*-hexahydroisoxazolo[3,2-*a*][2]benzazepine-2-yl)methyl-N-phenylcarbamate (V). A mixture of 1.5 g (8.45 mmol) of allyl-N-phenylcarbamate (I)**,** 1.94 g (8.45 mmol) of 3-ethyl-3,3,5-trimethyl-4,5-dihydro-3*H*-2-benzazepine N-oxide (IV) in 100 ml of toluene was heated for 5 h. The solvent was removed under reduced pressure. To the residue was added 15 ml of ether, and the mixture was left to stand for 24 h for crystallization. The formed precipitate was filtered and washed out diethyl ether. Recrystallization of the product from ethyl acetate - petroleum-ether (1: 2) gave 2,7 g (79%) of compound (V), colorless crystals, m.p. 171-172 °C. R_f 0.41 (Silufol UV-254, ethyl acetate - petroleum-ether, 1:3). IR, ν, sm^{-1}: 3415 (NH), 1715 (C=O), 1610, 1585, 1520 (C—$C_{arom.}$). ^{1}H NMR, δ, ppm: 9.71 br. s (1H, NH), 7.48 d (2H, $H^{2'}$, $H^{6'}$, J 8.0 Hz), 7.27 t (2H, $H^{3'}$, $H^{5'}$, J 8.0 Hz), 7.23-7.13 m (4H, H^8 - H^{11}), 6.95 t (1H, $H^{4'}$, J 8.0 Hz), 4.65 d. t (1H, H^{11b}, J 8.0, 27.0 Hz), 4.27 d. d (1H, OCH_2^A, J 4.0, 12.0 Hz), 4.14-4.08 m (1H, H^2), 4.05 d. d. (1H, OCH_2^B, J 4.0, 12.0 Hz), 2.60-2.72 m (1H, H^{1A}), 2.44-2.56 m (1H, H^{1B}), 1.82 d (1H, H^{6a}, J 14.7 Hz), 1.76 d (1H, H^{6b}, J 14.7 Hz), 1.61 q (2H, CH_2CH_3, J 7.4 Hz), 1.27 s (3H, CH_3 at C^5 atom), 1.12 s (3H, CH_3 at C^7 atom), 1.08 s (3H, CH_3 at C^7 atom), 0.87 t (3H, $CH_2C\underline{H}_3$, J 7.4 Hz).

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