4,5-DIHYDRO-6H-OXAZINE N-OXIDE IN THE 1,3-DIPOLAR CYCLOADDITION REACTION

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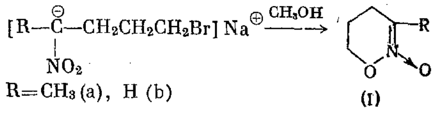
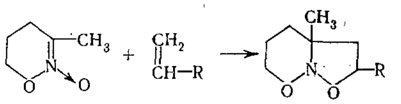
Previously the 1,3-cycloaddition reaction with cyclic and linear nitronic esters could be accomplished only in the case of 1,3-dipoles, containing either functional or aromatic substituents attached to the carbon atom [1]. In the present paper an attempt was made to synthesize cyclic nitronic esters with alkyl substituents or the hydrogen atom attached to the carbon atom of the 1,3-system, and to study their behavior in the 1,3-cycloaddition reaction. The nitronic esters were synthesized according to the scheme:



(Ia) is a very unstable compound: when stored at ~20° without a solvent it decomposes completely in 1 day, but in solutions its stability increases. (Ia) proved to be very active in the 1,3-cycloaddition reaction. Thus, when (Ia) is kept for 15-20 h with methyl acrylate or styrene at ~20° the yield of the adducts exceeds 80%. When (Ia) is reacted with a less active dipolarophile, like allyl chloride, the adduct could not be obtained in a yield exceeding 10%.

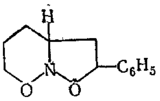


(II)

R = $COOCH_3$(a); C_6H_5(b); CH_2Cl(c)

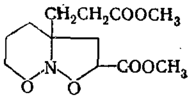
As a result, (Ia) in its reactivity approaches 3-carbomethoxy-4,5-dihydro-6H-1,2-oxazine N-oxide, and far surpasses 3-phenyl-4,5-dihydro-6H-1,2-oxazine N-oxide [2].

Compound (Ib) proved to be so unstable that it could not be isolated in the pure state. However, the existence of (Ib) was proved by preparing the adduct with styrene. For this a solution of the Na salt of 1-nitro-4-chlorobutane in anhydrous dimethylformamide (DMF) was kept with excess styrene for 3 days, and after the appropriate workup we isolated the adduct of (Ib) with styrene.



(IId)

When methyl acrylate was used in this reaction we were unable to obtain a product with the structure



(IIe)

in a yield exceeding 2%.

The formation of (IIe) can be explained by the following scheme

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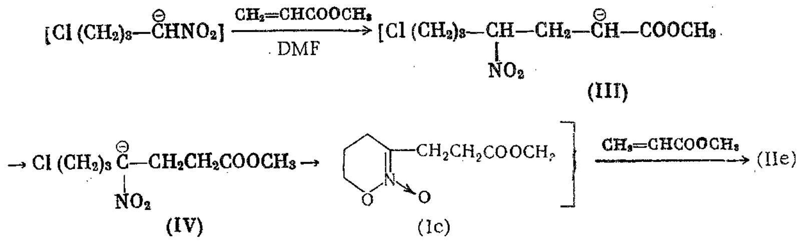
N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 11, pp. 2641-2643, November, 1970. Original article submitted March 18, 1970.



The first step consists of the usual addition according to the Michael reaction, but since the reaction is run in an aprotic medium, anion (III) undergoes rearrangement to the more stable (IV) anion, which then cyclizes to (Ic). The low yield of (IIe) is explained by the fact that (III) and (IV) can react with excess methyl acrylate, and this excludes the formation of (Ic). In support of such an interpretation of the mechanism for the formation of (IIe) is the fact that, if to a solution of the Na salt of 1-nitro-4-chlorobutane in DMF is first added an equimolar amount of methyl acrylate, and only after holding for 2.5 h is another 3-fold excess of methyl acrylate added, then the yield of (IIe) increases 17 times.

The NMR spectra of all of the (II) compounds contain signals that are characteristic for the ABX system of protons (fragment $-\mathrm{O}-\overset{\mathrm{CH_2}}{\overset{|}{\mathrm{CH}}}-\mathrm{R}$ of a 5-membered ring), in which connection the signals of the X part lie in the 4.7-4.9 ppm (R = $COOCH_3$), 5.4-5.7 ppm (R = C_6H_5) and 4.57 ppm (R = CH_2Cl) regions. These values of the chemical shifts exclude the presence of the alternative system $-\mathrm{O}-\mathrm{CH_2}-\overset{|}{\mathrm{CH}}-\mathrm{R}$. As a result, in the case of (Ia – c) a strict structural directivity of the 1,3-cycloaddition reaction is corroborated, which is characteristic for the previously studied nitronic esters [1]. It should be mentioned that in some cases the analytically pure (II) compounds have ill-defined melting points. It is possible that this is associated with the presence of the cis – trans isomers of R with respect to the substituent in the bridgehead, but as yet we have been unable to establish the presence of such isomerism either by chromatography on Al_2O_3 or by the NMR method.

EXPERIMENTAL METHOD

2-Nitro-5-bromopentane (V) was obtained in 50% yield by treating 2-nitro-5-pentanol [3] with PBr_3, in absolute benzene, bp 68-70° (1.5 mm); n_D^{20} 1.4786. 1-Nitro-4-chlorobutane (VI) was obtained in 59% yield by treating 1-nitro-4-butanol [4] with PCl_5 in absolute benzene, bp 48-50° (1 mm); n_D^{20} 1.4584.

Preparation of (Ia). To a solution of 4.85 g of (V) in 10 ml of absolute methanol was added a solution of sodium methylate (from 0.69 g of Na in 15 ml of absolute methanol), the methanol was vacuum-distilled at a temperature not exceeding 40°, the residue was extracted with benzene, the NaBr was filtered, and the benzene was vacuum-distilled at the same temperature as before. We obtained 3.19 g (93%) of (Ia); n_D^{20} 1.5125. Found: C 51.60; 51.76; H 7.87; 7.97; N 12.10; 12.21%. $C_5H_9NO_2$. Calculated: C 52.17; H 7.83; N 12.17%.

Preparation of (IIa-c). Freshly prepared (Ia) was covered with a 5-fold excess of the olefin, the mixture was kept at room temperature for ~20 h, the excess olefin was distilled off, and the (IIa-c) were isolated. (IIa) was obtained in 85% yield, mp 50-54° (from a 1:1 hexane – CCl_4 mixture). Found: C 53.96; 54.04; H 7.65; 7.75; N 7.23; 7.09%. $C_9H_{15}NO_4$. Calculated: C 53.73; H 7.46; N 6.97%. (IIb) was obtained in 80.5% yield, mp 66-67° (from alcohol). Found: C 71.14; 71.35; H 7.68; 7.81; N 6.54; 6.47%. $C_{17}H_{17}NO_2$. Calculated: C 71.23; H 7.76; N 6.39%. (IIc) was obtained in 10% yield, mp 45-46° (from hexane). Found: C 50.01; 49.95; H 7.23; 7.25; Cl 18.35; 18.70%. $C_8H_{14}ClNO_2$. Calculated: C 50.13; H 7.13; Cl 18.53%.

Preparation of (IId). To 5.06 g of (VI) in 10 ml of absolute methanol was added a solution of sodium methylate (from 0.85 g of Na in 20 ml of absolute methanol), the alcohol was vacuum-distilled, the remaining salt was dissolved in 70 ml of anhydrous DMF, and 10 ml of styrene was added. After 3 days the reaction mixture was poured into cold water, extracted with benzene, and the benzene layer was dried over $MgSO_4$. After distilling off the benzene we obtained 1.63 g (21.5%) of (IId), mp 96-103° (from hexane). Found: C 70.24; 70.09; H 7.35; 7.45; N 6.66; 6.73%. $C_{12}H_{15}NO_2$. Calculated: C 70.24; H 7.32; N 6.83%.

Preparation of (IIe). To a solution of 1.72 g of the salt (obtained the same as in the preceding experiment) in 60 ml of anhydrous DMF was added in drops, with vigorous stirring, 0.95 ml of methyl acrylate, after which the reaction mixture was kept at 20° for 2.5 h, and then another 3 ml of methyl acrylate was added. After holding for 2 days the reaction mixture was poured into cold water, extracted with benzene, and the benzene extract was dried over $MgSO_4$. After distilling off the benzene we obtained 1 g (34%) of (IIe), mp 85-86° (from a 1:1 hexane – CCl_4 mixture). Found: C 52.80; 52.51; H 6.96; 6.92; N 5.47; 5.53%. $C_{12}H_{19}NO_6$. Calculated: C 52.75; H 6.96; N 5.13.

CONCLUSIONS

The 3-H-, 3-methyl-, and 3-(β-carbomethoxyethyl)-4,5-dihydro-6H-oxazine N-oxides enter into the 1,3-cycloaddition reaction with unsaturated compounds by the usual scheme.

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