SYNTHESIS OF 1,2,3,4-TETRAHYDRO-4-PYRIDINONES BY HETEROCYCLIZATION OF β-AMINO-β-ARYLACRYLOYLOXIRANES

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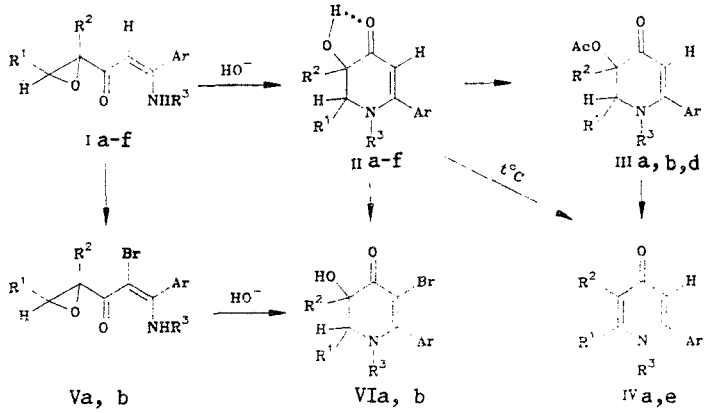
UDC 547.824'447.5'422.07:543.422.25

The heterocyclization of β-alkyl(phenyl)aminocinnamoyloxiranes and their α-bromo derivatives under base-catalysis conditions is a convenient method for the synthesis of 3-hydroxytetrahydro-4-pyridinones.

The presence of a reactive epoxide ring in oxiranyl-β-aminovinyl ketones [1-3] makes it possible to use them in diverse heterocyclization reactions [3-5]. In the present research we studied the cyclization of β-alkyl(phenyl)aminocinnamoyloxiranes to the corresponding 1,2,3,4-tetrahydro-4-pyridinones and examined some chemical transformations of the synthesized compounds.

It was established that β-aminocinnamoyloxiranes Ia-f undergo cyclization to 3-hydroxytetrahydro-4-pyridinones IIa-f in 60-95% yields in the presence of a base (tetrabutylammonium hydroxide or triethylamine). In the IR spectra of IIa-e the band of stretching vibrations of the NH bond at 3270 cm^{-1} vanishes, and a band of an OH group appears at 3470 cm^{-1} the position of which does not change when the solution of the compound in CCl_4 is diluted to 10^{-3} mole/liter; this constitutes evidence for the intramolecular character of the hydrogen bond of the HO and C=O groups.



I, IIa-c,f R^1=H, b, R^1=CH_3; a-f R^2=CH_3; a,b R^3=C_6H_5, c,d R^3=CH_3, e R^3=C_6H_{11}, f R^3=H; a-c, f Ar=C_6H_5, d,e Ar=4-BrC_6H_4; III—VIa R^1=H, R^2=CH_3, R^3=Ar=C_6H_5; IIIb, Vb, VIb R^1=R^2=CH_3, R^3=Ar=C_6H_5; IIId R^1=H, R^2=R^3=CH_3, Ar=4-BrC_6H_4; IVe R^1=H; R^2=CH_3; R^3=C_6H_{11}, Ar=4-BrC_6H_4

In the PMR spectra of tetrahydropyridones IIa-f the 5-H signal is located at stronger field as compared with the signal of the α proton of the amino enone system of Ia-f. It should be noted that the heterocyclization of Ib proceeds stereospecifically. The formation of IIb with cis-oriented methyl groups was confirmed by the change in the chemical shift of the signal of the 2-H proton of tetrahydropyridone IIb and its acetate IIIb. The acetylation of pyridinones IIa, b, d to acetates IIIa, b, d proceeds under the influence of acetyl chloride at room temperature, while pyridones IVa, e are formed by refluxing IIa, e in acetic anhydride.

The hypothetical mechanism of the heterocyclization of β-alkyl(phenyl)aminocinnamoyloxiranes to tetrahydro-4-pyridinone includes a step involving the deprotonation of the amino

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 0009-3122/89/2503-0288 $12.50

TABLE 1. Characteristics of IIa-f–VIa,b

Compound	Empirical formula	mp, °C	R^*_f	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm (J, Hz)	Yield, %
IIa	$C_{18}H_{17}NO_2$	154...155	0,40	1600, 1630, 3470	1,30(s, CH_3); 3,90, 4,15 (2H, J_{AB}=11,0; CH_2); 4,26 (s, OH); 5,20 (s, 5-H); 7,10, 7,55 (10H, Ar)	95
IIb	$C_{19}H_{19}NO_2$	174...175	0,49	1600, 1630, 3470	1,20 (s, CH_3); 1,25 (3H, d, J=7,0; CH_3CH); 3,93 (1H, q, J=7,0, 2-H); 4,23 (s, OH); 5,06 (s, 5-H); 6,98; 7,08 (10H, Ar)	97
IIc	$C_{13}H_{15}NO_2$	93...95	0,16	1590, 1640, 3470	1,20 (s, CH_3); 2,86 (s, CH_3); 3,30, 3,40 (2H, J_{AB}=12,0; CH_2); 4,00 (s, OH); 4,66 (s, 5-H); 7,26 (5H, Ar)	74
IId	$C_{13}H_{14}BrNO_2$	166...167	0,16	1590	1,18 (s, CH_3); 2,90(s, CH_3); 3,30, 3,40 (2H, J_{AB}=12,0; CH_2); 4,00 (s, OH); 4,66 (s, 5-H); 7,22, 7,50 (4H, J_{AB}=9,0, Ar)	78
IIe	$C_{18}H_{22}BrNO_2$	167...168	0,43	1600, 1630, 3470	1,15 (s, CH_3); 0,92...1,16 (11H, m, C_6H_{11}); 3,20, 3,40 (2H, J_{AB}=12,0; CH_2); 3,92 (s, OH); 4,48 (s, 5-H); 8,12; 8,42 (4H, J_{AB}=9,0, Ar)	86
IIf	$C_{12}H_{13}NO_2$	158...160	0,10	1600, 1630, 3320, 3470	1,20 (s, CH_3); 3,35, 3,46 (2H, J_{AB}=12,0; CH_2); 3,90(s, OH); 5,10 (d, J=1,0, 5-H); 7,10 (6H, Ar, NH)	56
IIIa	$C_{20}H_{19}NO_3$	112...113	0,56	1660, 1740	1,18 (s, CH_3); 1,80(s, CH_3); 3,80, 4,86 (2H, J_{AB}=12,5; CH_2); 5,18 (s, 5-H); 6,90, 7,10 (10H, Ar)	60
IIIb	$C_{21}H_{21}NO_3$	141...142	0,65	1660, 1740	1,40 (d, J=7,0, CH_3CH); 1,45 (s, CH_3); 1,68 (s, CH_3); 5,00 (1H, q, J=7,00, $CHCH_3$); 5,30 (s, 5-H); 6,80; 7,06 (10H, Ar)	90
IIId	$C_{15}H_{15}BrNO_3$	131...132	0,30	1660, 1740	1,40 (s, CH_3); 1,90 (s, CH_3); 2,84 (s, CH_3); 3,30, 4,30 (2H, J_{AB}=12,5; CH_2); 4,62 (s, 5-H); 7,22, 7,50 (4H, J_{AB}=9,0, Ar)	81
IVa	$C_{18}H_{15}NO$	225...227	0,51	1560, 1630	1,93 (d, J=0,8; 3-CH_3); 6,10 (s, 5-H); 7,15; 7,20, (10H, Ar), 7,62 (1H, q, J=0,8; 2-H)	60
IVe	$C_{18}H_{20}BrNO$	230...231	0,51	1560, 1630	1,86 (s, CH_3); 0,95...2,00 (11H, m, C_6H_{11}); 5,76 (s, 5-H); 7,22, 7,52 (4H, J_{AB}=9,0; Ar); 7,62 (s, 2-H)	90
E-Va	$C_{18}H_{16}BrNO_2$	120...121	0,70	1560, 1590	1,53 (s, CH_3); 2,72; 2,82 (2H, J_{AB}=5,3; CH_2); 6,72; 6,91 (Ar); 7,26 (10H, Ar); 12,85 (s, NH)	65
Z-Va	$C_{18}H_{16}BrNO_2$	Oil	0,81	1630, 1730	1,60 (s, CH_3); 2,88, 3,22 (2H, J_{AB}=5,0; CH_2); 6,74; 7,44 (11H, Ar, NH)	35
E-Vb	$C_{19}H_{18}BrNO_2$	110...111	0,71	1560	1,27 (s, J=6,0; CH_3CH); 1,47 (s, CH_3); 3,05 (1H, q, J=6,0; $CHCH_3$); 6,74; 6,93; 7,28 (10H, Ar); 12,83 (s, NH)	97
VIa	$C_{18}H_{16}BrNO_2$	136...137	0,54	1660, 3480	1,35(s, CH_3); 3,85; 4,08 (2H, J_{AB}=12,6; CH_2); 3,51 (s, OH); 6,99; 7,12 (10H, Ar)	89
VIb	$C_{19}H_{18}BrNO_2$	116...117	0,55	1655, 3480	1,11 (d, J=6,7; CH_3CH); 1,35 (s, CH_3); 3,94 (s, OH); 4,07 (1H, q, J=6,7; $CHCH_3$); 7,00 (10H, Ar)	85

*The R_f values were determined on Silufol plates; the eluents were ether and chloroform–methanol (2.5:1) (for IVa, e).

group under the influence of the strong base and subsequent stereospecific cyclization of the intermediate with the participation of the epoxide ring. This reaction pathway is confirmed by the effect of the substituent attached to the nitrogen atom on the rate of heterocyclization: the cyclization of anilino enones Ia, b takes place in 0.5 h, while heating for 3 h at 90-100°C is necessary for unsubstituted and alkyl-substituted amino enones Ic-f.

Similar cyclization also occurs in the case of α-bromo derivatives Va, b; in addition to 5-bromotetrahydro-4-pyridinones VIa, b, aminovinyl epoxy ketones Ia, b, the formation of which confirms the proposed cyclization mechanism, were isolated as side products. The starting α-bromo ketones Va, b are formed in quantitative yields in the form of mixtures of E and Z isomers in the reaction of ketones Ia, b with N-bromosuccinimide (NBS) in CCl_4 or $CHCl_3$; the Z-bromoalkene undergoes isomerization to the E isomer during isolation and during storage. The utilization of NBS as the reagent for the introduction of bromine into the α position of the amino enone is preferable as compared with the use of cyanogen bromide, which was recently proposed for this purpose [6]. 5-Bromotetrahydro-4-pyridinones VIa, b can also be obtained in 85-90% yields by bromination of tetrahydro-4-pyridinones IIa, b in the heterocyclic ring with NBS.

EXPERIMENTAL

The IR spectra of solutions of the compounds in CCl_4 and $CHCl_3$ (10^{-1} and 10^{-3} mole/liter) were recorded with a Specord IR-75 spectrometer; the layer thicknesses were 0.01 cm and 1 cm. The PMR spectra of solutions of the compounds in D_6-acetone and D_6-DMSO were measured with a Tesla BS 467 A spectrometer (60 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The course of the reaction was monitored by means of TLC on Silufol plates in ether–hexane (1:1).

The characteristics of the synthesized compounds are presented in Table 1. The results of elementary analysis for C, H, and N were in agreement with the calculated values.

The synthesis of Ia, b was accomplished by the method described in [3], while Ic, d were synthesized by the method in [1].

5-Amino(cyclohexylamino)-2-methyl-5-aryl-1,2-epoxy-4-penten-3-ones Ie, f. A 20-mmole sample of cyclohexylamine or a solution of ammonia in ether was added to 10 mmole of 2-methyl-5-aryl-1,2-epoxy-4-penten-3-one [7] in 40-60 ml of ether. After 4 h, the ether was evaporated, and If was isolated in the form of an oil; ketone Ie was recrystallized from hexane and had mp 106-107°C (88% yield).

Compound Ie, $C_{18}H_{22}BrNO_2$. PMR spectrum: 1.32 (3H, s, CH_3); 0.80-1.80 (11H, m, C_6H_{11}); 2.60 (2H, s, CH_2); 4.92 (1H, s, 4-H); 7.15, 7.42 (4H, AB system, J_{AB} = 9.0 Hz, Ar); 10.70 ppm (1H, d, J = 9.0 Hz, N–H).

Compound If, $C_{12}H_{13}NO_2$. PMR spectrum: 1.35 (3H, s, CH_3), 2.55 (2H, s, CH_2), 5.36 (1H, s, 4-H), 7.20 (6H, m, Ar, NH), 9.80 ppm (1H, S, N–H).

3-Hydroxy-6-aryl-1,2,3,4-tetrahydro-4-pyridinones IIa-f. A) A 10-mmole sample of Ia, b was allowed to stand with 0.3-0.5 g of tetrabutylammonium hydroxide in 10 ml of dioxane for 0.5 h at 18-20°C, or 10 mmole of Ic-f was allowed to stand with 0.5-1.0 g of tetrabutylammonium hydroxide in 10-20 ml of dioxane for 3 h at 90-100°C. After evaporation of the dioxane, the oily residue was filtered through a layer of silica gel (1 cm) to separate the base using ether (100-150 ml) as the eluent. After evaporation of the ether solution, IIa, b were crystallized from ether, while IIc-f were crystallized from ether–petroleum ether (1:1).

B) A 1-ml sample of triethylamine was added to a solution of 10 mmole of amino ketone Ia, b in 10 ml of isopropyl alcohol, and the mixture was refluxed for 1 h. After evaporation of the alcohol, Ia, b were isolated as described in experiment A.

3-Acetoxy-1-phenyl(methyl)-(2),3-(di)methyl-6-aryl-1,2,3,4-tetrahydro-4-pyridinones IIIa, b, d. A solution of 2 ml of acetyl chloride in 5 ml of acetic acid was added to 5 mmole of IIa, b, d. After 12 h, the reaction mixture was diluted with a tenfold volume of ice water, and the aqueous mixture was neutralized with sodium carbonate and extracted with ether. The ether solution was washed with sodium carbonate solution and water and dried over sodium sulfate. The ether was evaporated, and IIIa, b, d were crystallized from ether–hexane (1:2).

2-Methyl-6-aryl-4-pyridones IVa, e. A 10-mmole sample of IIa, e was refluxed in 10 ml of acetic anhydride for 1 h, after which the reaction mixture was diluted with water, washed with sodium carbonate solution, and extracted with ether. Compounds IVa, e crystallized after partial evaporation of the ether.

4-Bromo-2-methyl-5-phenyl-1,2-epoxy-4-penten-3-one (Va) and 5-Bromo-3-methyl-6-phenyl-3,2-epoxy-5-hexene-4-one (Vb). A 2.93-g sample of N-bromosuccinimide (NBS) was added in portions to 10 mmole of amino ketone Ia, b in 10 ml of chloroform. After 0.5 h, the chloroform was evaporated, and the residue was filtered through a layer of silica gel by elution with ether–hexane (1:2). The E isomers of Va, b crystallized after partial evaporation of the solvent; Z-bromoalkene Va was isolated in the form of an oil, which underwent isomerization to the E isomer on standing for 14 days.

5-Bromo-3-hydroxy-1,6-diphenyl-1,2,3,4-tetrahydro-4-pyridinones VIa, b. A) A 0.2-0.5 g sample of tetrabutylammonium hydroxide was added to 5 mmole of E-bromoalkenes IIa, b in 20 ml of dioxane. After 0.5 h, the solvent was evaporated, and the residue was filtered through a layer of silica gel by elution with ether. Compounds VIa, b were crystallized from ether. Compounds Ia, b were identified by means of TLC. The yields of tetrahydro-4-pyridinones were 40-49%.

B) A 1.47-g sample of NBS was added to 5 mmole of pyridones IIa, b in 20 ml of chloroform. After evaporation of the solvent, VIa, b were isolated as described in experiment A. The yields ranged from 85% to 89%.

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