SYNTHESIS OF PYRIDYLPHENYL KETOXIME O-ESTERS IN CONDITIONS OF PHASE-TRANSFER CATALYSIS

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Alkylation of pyridylphenyl ketoximes with alkyl, allyl, and benzyl halides in conditions of phase-transfer catalysis yields the corresponding O-esters with a good yield. Partial Z,E-isomerization takes place during the reaction.

Hetaryl ketoxime O-esters are of interest as biologically active compounds. Although less popular than hetaryl aldoxime O-esters, they are nevertheless relatively widely used as antiulcer agents [1], photoprotective substances in cosmetic mixtures [2], calcium and calmodulin antagonists, in treatment of ischemic disease (they prevent erythrocyte deformation) [3], and as pesticides in agriculture [4].

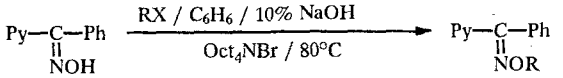
These compounds are either prepared by O-alkylation of the corresponding hetaryl ketoximes in the presence of highly inflammable bases (sodium hydride or alcoholates), or by the reaction of hetaryl ketones with O-alkylhydroxylamines, whose synthesis is a somewhat complex problem [1]. We also know that smooth alkylation of aliphatic and aromatic aldoximes and ketoximes takes place in conditions of phase-transfer catalysis (PTC) in a liquid/liquid system [5], and the regioselectivity of the process is determined by the configuration of the starting oxime: *E*-isomers form O-esters, and *Z*-isomers form nitrones. It was found that *Z,E*-isomerization does not occur in this case.

Alkylation of *E*-pyridyl aldoximes was conducted in [6] in conditions of PTC in the system C_6H_6/10% aqueous solution of NaOH/Oct_4NBr. Pyridine aldoxime O-esters are selectively formed and retain the *E*-configuration of the starting aldoxime.

Data are reported on alkylation of pyridylphenyl ketoximes in conditions of PTC with the method developed in [6].

The starting ketoximes were obtained by the reaction of the corresponding ketones with hydroxylamine hydrochloride in potassium hydroxide in ethanol [7]. The 2- and 3-pyridylphenyl ketoximes (I, II) obtained in this way were a mixture of *Z*- and *E*-isomers in 1:1 ratio, and 4-pyridylphenyl ketoxime (III) was obtained as an *E*-isomer. The isomers were identified with the data from the PMR spectra, and the signals were assigned according to [8, 9] (Table 1).

Pyridylphenyl ketoximes were alkylated in the C_6H_6/10% aqueous NaOH/Oct_4NBr system at the boiling point of the reaction mixture for 2.5-8 h.



I-III I-IIIa-d

I Py = 2-pyridyl, II Py =- 3-pyridyl, III Py = 4-pyridyl; a R = CH_3, b R = C_4H_9, c R = $CH_2CH{=}CH_2$, d R = CH_2Ph

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TABLE 1. Chemical Shifts in PMR Spectra of Pyridylphenyl Ketoximes*

Ketoxime	Stercoisomers, %	Pyridine ring protons					
		2-H	3-H	4-H	5-H	6-H	OH
I	50 (*E*)	—	7,61	7,69	7,28	8,63	8,5
	50 (*Z*)	—	7,31	7,83	7,26	8,67	13,9
II	50 (*E*)	8,70	—	7,79	...	8,67	9,4
	50 (*Z*)	8,77	—	7,79	...	8,60	9,6
III	> 95 (*E*)	8,70	7,27	—	7,27	8,70	8,04
	< 5 (*Z*)	8,55	...	—	...	8,55	...

*The signals of benzene ring protons are a multiplet in the 7.1-7.6 ppm range; the signals overlapped by this multiplet are not indicated.

TABLE 2. Conditions of Alkylation of Pyridylphenyl Ketoximes and Physicochemical Properties of the O-Esters Obtained

Compound	Alkylating agent	Duration of reation, h	Reaction product	bp, °C/mm Hg or mp	Yield, %
I	CH_3I	2,5	Ia	130 /1,0	67
	C_4H_9Br	5,0	Ib	141 /1,2	23
	$CH_2{=}CHCH_2Br$	3,5	Ic	131 /1,0	65
	$PhCH_2Br$	5,0	Id	38...42	52
II	CH_3I	4,0	IIa	139 /1,3	71
	C_4H_9Br	8,0	IIb	143 /1,2	35
	$CH_2{=}CHCH_2Br$	3,5	IIc	140 /1,0	68
	$PhCH_2Br$	8,0	IId	40...41	42
III	CH_3I	2,5	IIIa	121 /1,1	64
	C_4H_9Br	4,0	IIIb	139 /1,2	41
	$CH_2{=}CHCH_2Br$	6,0	IIIc	134 /1,0	57
	$PhCH_2Br$	6,0	IIId	36...38	51

The conditions of conducting the reaction and characteristics of the products are reported in Table 2. The chromatographic—mass spectra of the synthesized O-esters are usually a mixture of *E*- and *Z*-isomers. The isomers could be separated chromatographically for compounds Ia and Ic (see Table 3).

The structure of these O-esters was established by PMR spectrometry, and the PMR spectra are reported in Table 4. Dual sets of signals of pyridine ring protons were observed in all compounds obtained, indicating the existence of their *E*- and *Z*-isomers in different ratios.

The signals in the PMR spectra of compounds II and III were assigned based on the known chemical shifts and SSCC of the pyridine ring protons of *E*- and *Z*-isomers of 2-pyridylphenyl (I) and di(2-pyridyl) ketoximes [8]. In addition, it was assumed that the signals of protons in the *ortho* position relative to the oxime group in the *Z*-isomers are shifted to the weaker field in comparison to the signals of protons in the *E*-isomers due to the deshielding effect of the OH group [9].

"Internal" shifts (Δ) of the signals of neighboring pyridine ring protons in the oximes are also characteristic. For compound I, $\Delta_{3,4}$ (i.e., $\delta_{3\text{-}H}\text{-}\delta_{4\text{-}H}$) is 0.5 ppm for the *Z*- and 0.1 ppm for the *E*-isomer, in the spectrum of II, $\Delta_{4,5}$ ($\delta_{4\text{-}H}\text{-}\delta_{5\text{-}H}$) is also equal to 0.5 ppm, and similar internal shifts are observed for benzaldoximes (0.6 and 0.2 ppm, respectively) [10] and 2-furyl ketoximes (0.58 ppm for the *Z*-isomer) [11].

Assignment of the signals in the spectra of pyridylphenyl ketoxime O-esters is facilitated by the fact that there is a significant difference in the concentration of *Z*- and *E*-isomers and the interproton SSCC virtually does not change in most cases. A comparison of the chemical shifts (Tables 1 and 4) shows that in going from ketoximes to the corresponding esters, shielding of the pyridine ring protons in each series varies very little. We can thus conclude that in alkylation of 2-, 3-, and 4-pyridylphenyl ketoximes in conditions of PTC, O-alkylation takes place and nitrones are not formed. In the last case, there should be a sharp increase in the "internal" shifts $\Delta_{3,4}$ and $\Delta_{4,5}$, as in formation of α-phenyl nitrone: Δ = 0.83 ppm [10]. Since the ratio of *E*- and *Z*-isomers of the starting ketoximes and the O-esters obtained do not coincide, partial *E,Z*-isomerization probably takes place in alkylation of ketoximes in conditions of PTC in a liquid/liquid system.

TABLE 3. Chromatographic—Mass Spectra of Compounds I-IIIa-d

Compound	Isomers	m/z ($I_{rel.}$, %)
Ia	Z-	212(23, M^+), 211(70), 181(47), 180(35), 179(12), 167(22), 103(15), 79(64), 78(100), 77(66), 76(20), 52(27), 51(95), 50(26);
	E-	212(36, M^+), 211(94), 181(50), 180(44), 179(22), 166(13), 103(18), 79(69), 78(100), 77(80), 76(22), 52(30), 51(98), 50(30)
Ib	Mixture of E and Z	254(10, M^+), 253(11), 224(14), 223(20), 209(19), 197(30), 181(26), 180(10), 168(33), 167(43), 166(160, 106(14), 105(22), 103(12), 79(100), 78(78), 77(38), 76(12), 57(10), 52(18), 51(56), 50(15), 43(10), 41(41), 39(20), 29(63), 28(10), 27(39)
Ic	E	238(29, M^+), 237(33), 221(32), 208(28), 207(19), 206(13) 197(16), 193(11), 181(19), 180(25), 168(21), 167(25), 166(32), 140(11), 139(18), 103(12), 79(82), 78(100), 77(33), 76(12), 52(15), 51(59), 50(13), 41(35), 39(22), 27(23)
	Z	238(37, M^+), 237(46), 221(46), 208(38), 207(27), 206(18), 197(20), 196(11), 193(15), 181(28), 180(35), 168(28), 167(89), 166(44), 140(14), 139(22), 117(12), 105(12), 104(10), 103(14), 79(99), 78(100), 77(50), 76(15), 52(17), 51(66), 50(16), 41(36), 39(24), 27(20)
Id	Mixture of E and Z	288(7, M^+), 271(10), 106(22), 105(28), 91(100), 79(57), 78(24), 77(51), 52(16), 51(45), 50(20), 39(12);
IIa	Mixture of E and Z	212(40, M^+), 182(18), 181(100), 179(10), 166(12), 154(11), 139(11), 103(10), 79(9), 78(74), 77(97), 76(14), 52(14), 51(99), 50(28), 39(10), 28(10), 27(9).
IIb	Mixture of E and Z	254(6, M^+), 224(20), 223(81), 209(12), 197(24), 182(24), 181(100), 167(12), 166(10), 139(10), 104(10), 78(39), 77(51), 57(15), 52(10), 51(55), 50(14), 41(34), 39(12), 29(49), 27(20).
IIc	Mixture of E and Z	238(441, M^+), 237(100), 221(13), 197(10), 181(18), 169(12), 168(10), 167(45), 166(31), 140(11), 139(32), 78(33), 77(48), 51(64), 50(15), 41(62), 39(17), 27(14).
IId	Mixture of E and Z	288(16, M^+), 182(16), 181(31), 107(12), 106(64), 105(69), 91(100), 79(10), 78(26), 77(87), 52(13), 51(43), 50(20).
IIIa	Mixture of E and Z	212(57, M^+), 181(55), 139(9), 104(10), 103(8), 79(9), 78(66), 77(99), 76(12), 52(11), 51(100), 50(28), 39(8).
IIIb	Mixture of E and Z	254(2, M^+), 224(24), 223(89), 209(13), 197(22), 182(25), 181(66), 170(13), 169(12), 168(18), 167(14), 166(12), 146(10), 139(17), 104(24), 79(13), 78(52), 77(77), 76(11), 57(35), 52(11), 51(100), 50(21), 41(62), 39(18), 29(86), 28(19), 27(25).
IIIb	Mixture of E and Z	254(2, M^+), 224(24), 223(89), 209(13), 197(22), 182(25), 181(66), 170(13), 169(12), 168(18), 167(14), 166(12), 146(10), 139(17), 104(24), 79(13), 78(52), 77(77), 76(11), 57(35), 52(11), 51(100), 50(21), 41(62), 39(18), 29(86), 28(19), 27(25).
IIIc	Mixture of E and Z	238(18, M^+), 237(38), 167(12), 166(11), 139(16), 78(100), 77(36), 51(34), 50(22), 41(50), 39(24).
IIId	Mixture of E and Z	288(14, M^+), 91(100), 77(10), 65(50), 51(12).

TABLE 4. Chemical Shifts in the PMR spectra of Pyridylphenyl Ketoxime O-Esters*

Product of the reaction	Stereoisomers	Pyridine ring					R
		2-H	3-H	4-H	5-H	6-H	
Ia	80 (E)	—	8,07	7,78	...	8,73	3,98 (OCH_3)
	20 (Z)	—	7,58	7,90	...	8,77	4,04 (OCH_3)
Ib	50 (E)	—	...	7,68	...	8,59	4,24 (OCH_2); 1,50 and 1,33 (CH_2CH_2); 0,90 (CH_3)
	50 (Z)	—	...	7,76	...	8,72	4,18 (OCH_2); 1,54 and 1,39 (CH_2CH_2); 0,92 (CH_3)
Ic	75 (E)	—	7,72	7,68	7,25	8,60	6,04 (CH=); 5,29 and 5,20 ($=CH_2$); 4,75 (OCH_2)
	25 (Z)	—	7,53	7,78	7,23	8,72	6,01 (CH=); 5,26 and 5,18 ($=CH_2$); 4,69 (OCH_2)
Id	50 (E)	—	...	7,71	...	8,59	5,24 (OCH_2); 7,1—7,6 (Ph)
	50 (Z)	—	...	7,76	...	8,73	5,30 (OCH_2); 7,1—7,6 (Ph)
IIa	70 (E)	8,61	—	7,69	...	8,64	3,99 (OCH_3)
	30 (Z)	8,70	—	7,80	...	8,59	4,00 (OCH_3)
IIb	60 (E)	8,64	—	8,62	7,68	7,21	4,20 (OCH_2); 1,67 and 1,35 (CH_2CH_2); 0,85 (CH_3)
	40 (Z)	8,64	—	8,57	7,79	7,29	4,21 (OCH_2); 1,67 and 1,35 (CH_2CH_2); 0,89 (CH_3)
IIc	65 (E)	8,63	—	7,71	7,37	8,64	6,01 (CH=); 5,27 and 5,21 ($=CH_2$); 4,70 (OCH_2)
	35 (Z)	8,69	—	7,79	7,25	8,58	6,02 (CH=); 5,29 and 5,21 ($=CH_2$); 4,70 (OCH_2)
IId	70 (E)	8,62	—	7,68	7,36	8,63	5,23 (OCH_2); 7,1—7,6 (Ph)
	30 (Z)	8,68	—	7,75	7,23	8,57	5,24 (OCH_2); 7,1—7,6 (Ph)
IIIa	64 (E)	8,70	7,23	—	7,23	8,70	3,97 (OCH_3)
	36 (Z)	8,57	7,37	—	7,37	8,57	4,01 (OCH_3)
IIIb	45 (E)	8,70	7,24	—	7,24	8,70	4,19 (OCH_2); 1,3—1,75 (CH_2CH_2); 0,91 (CH_3)
	55 (Z)	8,57	7,37	—	7,37	8,57	4,22 (OCH_3); 1,3—1,75 (CH_2CH_2); 0,92 (CH_3)
IIIc	70 (E)	8,71	7,26	—	7,26	8,71	5,9—6,1 (CH=); 5,2—5,3 ($=CH_2$); 4,69 (OCH_2)
	30 (Z)	8,57	7,37	—	7,37	8,57	5,9—6,1 (CH=); 5,2—5,3 ($=CH_2$); 4,72 (OCH_2)
IIId	70 (E)	8,70	7,23	—	7,23	8,70	5,23 (OCH_2); 7,3 (Ph)
	30 (Z)	8,57	...	—	...	8,57	5,26 (OCH_2); 7,3 (Ph)

*The signals of benzene ring protons are a multiplet in the 7.1-7.6 ppm range; the signals whose chemical shifts are not indicated were masked by this multiplet.

EXPERIMENTAL

The PMR spectra were recorded for 5-7% solutions of the compounds in $CDCl_3$ at a sample temperature of 303 K on a WM-360 (360 MHz) spectrometer with TMS as the internal standard. The chromatographic-mass spectra were made on a Kratos MS-25 GC/MC (70 eV). The GLC analysis was conducted on a Chrom-5 chromatograph using a flame-ionization detector in a glass column (1.2 m × 3 mm) packed with 5% OV-17 phase on Chromosorb W-HP (80-100 mesh). Helium was the carrier gas (50 cm^3/min), and the column temperature was 200-250°C. The melting point was determined on a Boetius stage.

The starting 2- and 3-benzoylpyridines, methyl iodide, butyl chloride, allyl bromide (from Reakhim), 4-benzylpyridine (Aldrich Europe), and Oct_4NBr (Fluka) were used without additional purification.

4-Benzoylpyridine was synthesized by oxidation of 4-benzylpyridine with potassium permanganate by PTC according to [12].

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