ISSN 1070-4280, Russian Journal of Organic Chemistry, 2007, Vol. 43, No. 3, pp. 449–453. © Pleiades Publishing, Ltd., 2007.
Published in Russian in Zhurnal Organicheskoi Khimii, 2007, Vol. 43, No. 3, pp. 450–454.

Alkylation of Pyridinecarbaldehyde Oximes with Epoxy Compounds*

N. Şen[a], Y. Kar[b], and S. Kurbanov[a]

[a] *University of Selcuk, Department of Chemistry, 42031, Konya, Turkey*

[b] *University of Selcuk, Department of Chemical Engineering, 42031, Konya, Turkey*
e-mail: nsen@selcuk.edu.tr

Received February 28, 2005

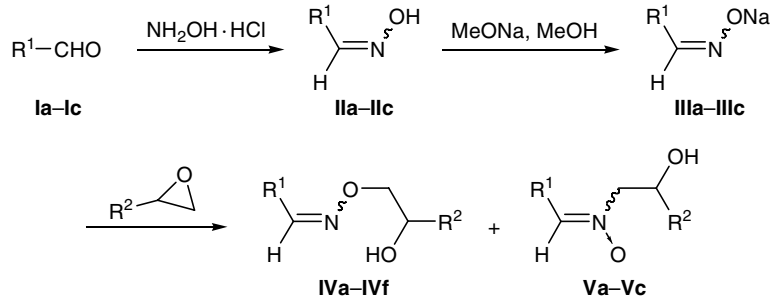
Abstract—O- and N-Alkylation products were obtained by reactions of pyridine-2-, -3-, and -4-carbaldehyde oximes with enantiomerically pure and racemic epoxy compounds (1,2-epoxypropane, 1-phenyl-1,2-epoxyethane, 1-chloro-2,3-epoxypropane, and 1-bromo-2,3-epoxypropane) in the presence of bases and under conditions of phase-transfer catalysis. A series of new amino alcohols was synthesized by condensation of amines with products of O-alkylation of pyridinecarbaldehyde oximes with 1-halo-2,3-epoxypropanes.

DOI: 10.1134/S1070428007030220

Oximes and oxime ethers are important intermediates in organic synthesis. Specifically, they are used for protection, alkylation [1–6], and regeneration of carbonyl compounds [7–10], in the synthesis of hydroxylamines, primary amines [11, 12], nitrones [3–5, 13], nitriles [14–16], and for the preparation of pharmaceuticals [1, 2, 17–20]. Some amino alcohols derived from oximes were found to exhibit properties of β-adrenergic blocking agents *in vitro* [21–23].

In continuation of our previous studies [3, 4, 24], in the present work we synthesized a number of pyridin-2-, -3-, and -4-carbaldehyde *O*- and *N*-alkyl oximes by reactions of the corresponding oximes **IIa**–**IIc** with racemic 1,2-epoxypropane, 1,2-epoxy-1-phenylethane, and 1-chloro-2,3-epoxypropane and enantiomerically pure (*R*)-(+)-1,2-epoxypropane and (*R*)-(+)-1,2-epoxy-1-phenylethane [4, 5]. The alkylation of oximes **IIa**–**IIc** as mixtures of *syn* and *anti* isomers with racemic α-epoxides gave mixtures of isomeric O- and N-alkylation products **IVa**–**IVf** and **Va**–**Vc** [3–5] at a ratio of 92:8 (Scheme 1). In the alkylation of the *anti* isomers, the ratio of the corresponding O- and N-substituted derivatives was 88:12, whereas *syn* isomers gave rise to O- and N-alkylation products at a ratio of 78:22. Compounds **IV** and **V** can readily be separated due to their different solubilities. *O*-Alkyl derivatives **IV** are soluble in diethyl ether, while *N*-alkyl oximes are soluble in chloroform. Therefore, compounds **IVa**–**IVe** were isolated by extraction with diethyl ether, and compounds **Va**–**Vc** were extracted into chloroform. In addition, the O- and N-substituted isomers can be separated by vacuum distillation (the boiling points of

Scheme 1.



I–**V**, R^1 = pyridin-2-yl (**a**, **d**), pyridin-3-yl (**b**, **e**), pyridin-4-yl (**c**, **f**); **IV**, **V**, R^2 = Me (**a**–**c**); **IV**, R^2 = Ph (**d**–**f**).

* The text was submitted by the authors in English.

Table 1. Yields and melting points of compounds **IVa**–**IVf**, **Va**–**Vc**, and **VIIa**–**VIIc**

Comp. no.	R^1	R^2	Yield, %	mp, °C	Formula
IVa	2-Pyridyl	CH_3	38	78–79	$C_9H_{12}N_2O_2$
Va	2-Pyridyl	CH_3	7	93–94	$C_9H_{12}N_2O_2$
IVb	3-Pyridyl	CH_3	42	106	$C_9H_{12}N_2O_2$
Vb	3-Pyridyl	CH_3	6.5	128	$C_9H_{12}N_2O_2$
IVc	4-Pyridyl	CH_3	34	105	$C_9H_{12}N_2O_2$
Vc	4-Pyridyl	CH_3	8.5	118	$C_9H_{12}N_2O_2$
IVd	2-Pyridyl	C_6H_5	36	101–102	$C_{14}H_{14}N_2O_2$
IVe	3-Pyridyl	C_6H_5	39	108	$C_{14}H_{14}N_2O_2$
IVf	4-Pyridyl	C_6H_5	44	115	$C_{14}H_{14}N_2O_2$
VIIa	(*E*)-2-Pyridyl	C_4H_8O (R^2R^3)	45[a]	112–113	$C_{13}H_{19}N_3O_3$
VIIb	(*E*)-3-Pyridyl	C_5H_{10} (R^2R^3)	35[b]	64	$C_{14}H_{21}N_3O_2$
VIIc	(*E*)-4-Pyridyl	*iso*-C_3H_7	48[c]	134–136	$C_{12}H_{19}N_3O_2$

[a] Method *B*; yield 12 % (*A*), 27 % (*C*).
[b] Method *B*; yield 7 % (*A*), 8.5 % (*C*).
[c] Method *B*; yield 32 % (*A*), 14 % (*C*).

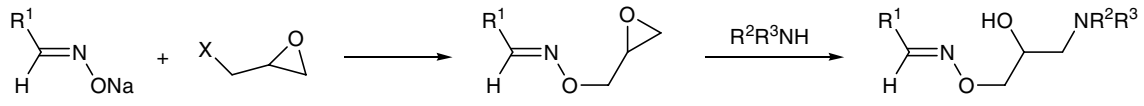
the latter range from 80 to 100°C) or by preparative thin-layer chromatography on aluminum oxide (eluent chloroform–diethyl ether, 5:1; R_f 0.46 and 0.78 for the O- and N-substituted isomers, respectively).

The IR spectra of compounds **IVa**–**IVf** and **Va**–**Vc** characteristically contained absorption bands at 920–930 and 1260–1270 cm^{-1}, belonging to vibrations of the N–O and N→O bonds, respectively. The *E* configuration of oximes **IIa**–**IIc** is confirmed by a color test (red–brown color) with iron(II) salts and formation of green chelates with copper(II) ions [24]. In the ^1H NMR spectra of **IVa**–**IVf**, the difference between the chemical shifts of the OH and CH=N protons was 3.1 ppm, which is typical of *E* isomers [24, 25]; the corresponding difference in the spectra of (*Z*)-oximes **IIa** and **IId** is 3.9 ppm [26, 27].

The yield of the alkylation products strongly depended on the solvent nature and catalyst. As a rule, poor yields were obtained on treatment of the oxime sodium salts with 1-chloro-2,3-epoxypropane in heterogeneous medium. Only in the reaction of **IIa** with (*R*)-(+)-1,2-epoxypropane and (*R*)-(+)-1,2-epoxy-1-phenylethane in anhydrous tetrahydrofuran (method *A*) the corresponding O-alkylated products **IVd** and **IVe** were isolated in a good yield (Scheme 1).

Compounds **IVa**–**IVf** were also prepared in good yields using a liquid–solid heterophase system (acetonitrile) in the presence of 2-(2-methoxyethoxy)ethanamine as phase-transfer catalyst (method *B*). Compounds **IVa**–**IVf** and **Va**–**Vc** were isolated as mixtures of *anti* and *syn* isomers. [28]. Oxime sodium salts **IIIa**–**IIIc** (*E* isomers) were converted into ethers **VIa**–**VIc** by treatment with 1-halo-2,3-epoxy-propanes in anhydrous ether in the presence of a base (Scheme 2). Depending on the conditions, the reaction involved replacement of the halogen atom or opening of the oxirane ring [22, 25]. The use of 2-(2-methoxyethoxy)-ethanamine ensured better results as compared to tetrabutylammonium bromide (TBAB) (method *C*). Ethers **VIa**–**VIc** were treated (without additional purification) with amines (morpholine, piperidine, or isopropylamine) in a phosphate buffer (pH 7.3) to obtain amino alcohols **VIIa**–**VIIc** (Scheme 2, Table 1). The absolute configuration of chiral compounds **IVc** and **Vc** was not determined because of the lack of the corresponding optically pure enantiomers with known configuration.

Scheme 2.



(*E*)-**IIIa**–(*E*)-**IIIc** (*E*)-**VIa**–(*E*)-**VIc** (*E*)-**VIIa**–(*E*)-**VIIc**

VI, **VII**, R^1 = pyridin-2-yl (**a**), pyridin-3-yl (**b**), pyridin-4-yl (**c**); **VII**, R^2R^3N = morpholino (**a**), piperidino (**b**); R^2 = *i*-Pr, R^3 = H (**c**).

Table 2. IR and ^{1}H NMR spectra of compounds **IVa–IVf**, **Va–Vc**, and **VIIa–VIIc**

Comp. no.	IR spectrum, ν, cm^{-1}			^{1}H NMR spectrum, δ, ppm
	C=N	N–O or N→O	OH	
IVa	1670	965	1080, 3450	8.60 d (1H, 3-H, *J* = 6 Hz), 7.91 d (1H, 5-H, *J* = 6 Hz), 7.69 d (1H, 6-H, *J* = 6 Hz), 7.53 s (1H, CH=N), 7.40 d (1H, 4-H, *J* = 6 Hz), 6.20 s (1H, OH), 4.15–3.93 m (2H, OCH_2), 3.05–2.85 m (1H, C**H**CH_3), 1.10 s (3H, CH_3)
Va	1635, 1175	1265	1075, 3400	8.50 d (1H, 3-H, *J* = 6 Hz), 7.96 d (1H, 5-H, *J* = 6 Hz), 7.52 d (1H, 6-H, *J* = 6 Hz), 6.84 s (1H, CH=N$^+$O$^-$), 6.55 d (1H, 4-H, *J* = 6 Hz), 6.10 s (1H, OH), 3.44–3.23 m (2H, CH_2N^+), 2.70–2.57 m (1H, C**H**CH_3), 1.3 s (3H, CH_3)
IVb	1630	930	1070, 3450	8.79 d (1H, 2-H, *J* = 6 Hz), 8.62 d (1H, 4-H, *J* = 6 Hz), 8.10 d (1H, 6-H, *J* = 6 Hz), 7.58 d (1H, 5-H, *J* = 6 Hz), 7.44 s (1H, CH=N), 5.90 s (1H, OH), 4.11–3.94 m (2H, OCH_2), 3.08–2.82 m (1H, C**H**CH_3), 1.02 s (3H, CH_3)
Vb	1620	935	1065, 3400	8.70 d (2H, 2-H, 4-H, *J* = 6 Hz), 7.86 d (1H, 6-H, *J* = 6 Hz), 7.38 s (1H, CH=N$^+$O$^-$), 7.32 d (1H, 5-H, *J* = 6 Hz), 6.14 s (1H, OH), 3.40–3.21 m (2H, CH_2N^+), 2.68–2.53 m (1H, C**H**CH_3), 1.3 s (3H, CH_3)
IVc	1640	930	1070, 3450	8.80 d (2H, 3-H, 5-H, *J* = 6 Hz), 8.10 d (2H, 2-H, 6-H, *J* = 6 Hz), 7.70 s (1H, CH=N), 6.23 s (1H, OH), 4.16–3.98 m (2H, OCH_2), 3.10–2.80 m (1H, C**H**CH_3), 1.0 s (3H, CH_3)
Vc	1615, 1175	1265	1075, 3400	8.60 d (2H, 3-H, 5-H, *J* = 6 Hz), 7.10 d (2H, 2-H, 6-H, *J* = 6 Hz), 6.85 s (1H, CH=N$^+$O$^-$), 6.02 s (1H, OH), 3.41–3.18 m (2H, CH_2N^+), 2.73–2.61 m (1H, C**H**CH_3), 1.1 s (3H, CH_3)
IVd	1630	960	1080, 3480	8.65 d (1H, 3-H, *J* = 6 Hz), 8.12 d (1H, 5-H, *J* = 6 Hz), 7.75 d (1H, 6-H, *J* = 6 Hz), 7.48 s (1H, CH=N), 7.35–7.24 m (5H, H_{arom}), 7.22 d (1H, 4-H, *J* = 6 Hz), 6.12 s (1H, OH), 4.23–3.95 m (2H, OCH_2), 3.58–3.31 m (1H, PhC**H**)
IVe	1640	930	1050, 3450	8.72 d (1H, 2-H, *J* = 6 Hz), 8.60 d (1H, 4-H, *J* = 6 Hz), 8.12 d (1H, 6-H, *J* = 6 Hz), 7.58 d (1H, 5-H, *J* = 6 Hz), 7.44 s (1H, CH=N), 7.30–7.21 m (5H, H_{arom}), 5.98 s (1H, OH), 4.21–3.92 m (2H, OCH_2), 3.54–3.29 m (1H, PhC**H**)
IVf	1630	920	1030, 3440	8.80 d (2H, 3-H, 5-H, *J* = 6 Hz), 8.10 d (2H, 2-H, 6-H, *J* = 6 Hz), 7.70 s (1H, CH=N), 7.28–7.24 m (5H, H_{arom}), 6.14 s (1H, OH), 4.19–3.91 m (2H, OCH_2), 3.451–3.26 m (1H, PhC**H**)
VIIa	1645	920	1075, 3400	8.63 d (1H, 3-H, *J* = 6 Hz), 8.05 d (1H, 5-H, *J* = 6 Hz), 7.71 d (1H, 6-H, *J* = 6 Hz), 7.55 s (1H, CH=N), 7.44 d (1H, 4-H, *J* = 6 Hz), 6.20 s (1H, OH), 3.86–3.63 m (2H, OCH_2), 3.65–3.46 m (1H, C**H**CH_2N), 3.61 t (4H, O**C**H_2CH_2, *J* = 6 Hz), 2.65–2.51 m (2H, CHC**H**$_2$N), 2.43–2.29 m (4H, CH_2N)
VIIb	1670	935	1080, 3450	8.72 d (1H, 2-H, *J* = 6 Hz), 8.63 d (1H, 4-H, *J* = 6 Hz), 7.95 d (1H, 6-H, *J* = 6 Hz), 7.55 d (1H, 5-H, *J* = 6 Hz), 7.46 s (1H, CH=N), 6.47 s (1H, OH), 3.83–3.68 m (2H, OCH_2), 3.62–3.42 m (1H, C**H**CH_2N), 2.63–2.48 m (2H, CHC**H**$_2$N), 2.33–2.21 m (4H, CH_2N), 1.65–1.40 m (6H, CH_2)
VIIc	1660	920	1055, 3430	8.65 d (2H, 3-H, 5-H, *J* = 6 Hz), 8.35 d (2H, 2-H, 6-H, *J* = 6 Hz), 7.53 s (1H, CH=N), 6.42 s (1H, OH), 6.13 s (1H, CH_2N**H**), 3.83–3.68 m (2H, OCH_2), 3.60–3.39 m (1H, C**H**CH_2NH), 2.63–2.48 m (2H, CHC**H**$_2$NH), 2.85 s [1H, C**H**$(CH_3)_2$], 1.12 s (6H, CH_3)

EXPERIMENTAL

The melting points were determined on a Buchi capillary melting point apparatus and were not corrected. The IR spectra were recorded on a Pye Unicam SP 1025 spectrometer. The ^{1}H NMR spectra were measured on a Bruker Avance DPX 400 instrument using $CDCl_3$ as solvent and tetramethylsilane as internal reference. The elemental analyses were obtained on a Carlo Erba 1106 automatic analyzer; the experimental values coincided with the calculated ones within ±0.4% (unless otherwise stated). The solvents and reagents used were commercial products (Aldrich or Merck). Thin-layer chromatography was performed using Kieselgel 60 F254 plates (Merck); spots were visualized under UV light. Silica gel Kieselgel 60 (0.040–0.063 mm, Merck) was used for preparative chromatography. The yields, melting points, and spectral parameters of the newly synthesized compounds are given in Tables 1 and 2.

Reactions of pyridine-2-, -3-, and -4-carbaldehyde oximes IIa–IIc with α-epoxides. *Method A*. Pyridinecarbaldehyde oxime **IIa**–**IIc**, 0.025 mol, was added to a solution of sodium methoxide, prepared from 0.025 mol of metallic sodium and 25 ml of anhydrous methanol, and the mixture was heated for 1.5 h under reflux. The solvent was removed under reduced pressure, the residue was dissolved in acetonitrile, DMF, or DMSO, 1.75 ml (0.025 mol) of 1,2-epoxypropane or 2.85 ml (0.025 mol) of 1,2-epoxy-1-phenylethane was added, and the mixture was stirred for 4.5 h at 15–20°C. The solvent was removed under reduced pressure, and the residue was treated with water and extracted with diethyl ether or chloroform (3×30 ml). The organic extract was dried over anhydrous calcium chloride and evaporated, and the oily residue was purified by chromatography on aluminum oxide using methanol as eluent.

Method B. Pyridinecarbaldehyde oxime **IIa** or **IIb**, 0.025 mol, was added to a solution of sodium ethoxide, prepared from 0.025 mol of metallic sodium and 25 ml of anhydrous ethanol, and the mixture was heated for 1 h under reflux. The solvent was removed under reduced pressure, the residue was dissolved in 40 ml of acetonitrile containing 0.1 ml of 2-(2-methoxyethoxy)ethanamine, 2 ml (2.3 g, 0.025 mol) of 1-chloro-2,3-epoxypropane was added, and the mixture was stirred for 16–18 h at 20°C. The solvent was removed under reduced pressure, and the residue was extracted with diethyl ether or chloroform. The extract was dried over $MgSO_4$ and evaporated, and the residue (compound **VIa** or **VIb**) was recrystallized from ethyl acetate and additionally purified by thin-layer chromatography using methanol–chloroform (5:1) as eluent.

Method C. Pyridinecarbaldehyde oxime **IIa**–**IIc**, 0.025 mol, was added over a period of 35 min to a mixture of 1.2 g (0.030 mol) of NaOH, 6 ml of H_2O, 15 ml of benzene or toluene, 1.1 g (0.0012 mol) of tetrabutylammonium bromide, and 0.025 mol of 1-chloro-2,3-epoxypropane or 1-bromo-2,3-epoxypropane under stirring at 60–65°C. The mixture was stirred for 1.5 h at 70–75°C and extracted with diethyl ether, the extract was dried over anhydrous sodium sulfate and evaporated, and the residue was recrystallized from ethyl acetate and additionally purified by column chromatography on aluminum oxide (CH_2Cl_2–MeOH, 3:1).

1-Amino-3-(pyridylmethylideneaminooxy)-propan-2-ols VIIa–VIIc (*general procedure*). Oxime **IIa**–**IIc**, 0.032 mol, was added to a solution of sodium methoxide, prepared from 0.032 mol of metallic sodium and 25 ml of anhydrous methanol, and the mixture was heated for 1 h under reflux. The solvent was removed under reduced pressure, the residue was dissolved in 40 ml of acetonitrile containing 0.1 ml of 2-(2-methoxyethoxy)ethanamine, 0.048 mol of 1-chloro- or 1-bromo-2,3-epoxypropane was added, the mixture was stirred for 22 h, the precipitate of NaCl or NaBr was filtered off, and the filtrate was evaporated under reduced pressure to leave crude epoxy derivative **VIa**–**VIc** as an oily substance. The crude product was dissolved in 15 ml of a phosphate buffer (pH 7.2) containing 10 ml of the corresponding amine (as a solution in acetone), and the mixture was left to stand for 22 h at room temperature. The solvent was removed under reduced pressure, the residue was diluted with water and extracted with ethyl acetate, and the extract was dried over Na_2SO_4, filtered, and evaporated to dryness. Compounds **VIIa**–**VIIc** were recrystallized from chloroform.

REFERENCES

1. Markova, Y.W., *Chem. Pharm. J*., 1969, vol. 3, p. 13.
2. Wolfgang, K., *Justus Justus Liebigs Ann. Chem.,* 1970, vol. 733, p. 192.
3. Güler, E., Şen, N., Sırıt, A., Kurbanov, S., and Mirzaoğlu, R., *Org. Prep. Proced. Int*., 1998, vol. 30, p. 195.
4. Kurbanov, S., Sırıt, A., and Şen, N., *Org. Prep. Proced. Int*., 1999, vol. 31, p. 681.
5. Kurbanlı, S., Şen, N., Güler, E., and Koçak, A., *Synth. Commun*., 2004, vol. 34, p. 1663.

6. Gawley, R.E. and Nagy, T., *Tetrahedron Lett*., 1984, vol. 25, p. 263.
7. Yasuo, K., Ryoko, O., and Yasuhisa, A., *Arch. Microbiol*., 1998, vol. 170, p. 85.
8. Zhou, J.F., Tu-Shu, J., and Feng, J.C., *Synth. Commun*., 2002, vol. 32, p. 959.
9. Varkar, P., Rathore, R., and Chandrase-Karan, S., *J. Org. Chem*., 1986, vol. 51, p. 3063.
10. Curran, D.P., Brill, J.F., and Rakiewicz, D.M., *J. Org. Chem*., 1984, vol. 49, p. 1654.
11. Hidlicky, M., *Reduction in Organic Chemistry*, Chichester: Ellis Horwood, 1984, p. 132.
12. Cohen, J.H., Abdel-Magid, A.F., Almond, H.R., and Maryanoff, C.A., *Tetrahedron Lett*., 2002, vol. 43, p. 1977.
13. Norman, A.L. and Balasubramanian, N., *Tetrahedron Lett*., 1985, vol. 26, p. 4331.
14. Ghiaci, M. and Bakhtiari, K., *Synth. Commun*., 2001, vol. 31, p. 1803.
15. Hekmatshoar, R., Heravi, M.M., Beheshtiha, Y.S., and Asadolah, K., *Monatsh. Chem*., 2002, vol. 133, p. 111.
16. Iranpoor, N., Firouzabadi, H., and Aghapour, G., *Synth. Commun*., 2002, vol. 32, p. 2535.
17. Mitcher, L.A., *The Organic Chemistry of Drug Synthesis*, New York: Wiley, 1980, vol. 2.
18. Desideri, N., Sestili, I., Manarini, S., Cerletti, C., and Stein, M.L., *Eur. J. Med. Chem*., 1991, vol. 26, p. 455.
19. Steven, A.R. and Richard, J.K.T., *Tetrahedron Lett*., 2000, vol. 41, p. 10357.
20. Leclerc, G., Mann, A., and Wermuth, C.G., *J. Med. Chem*., 1977, vol. 20, p. 1657.
21. Manna, F., Bolasco, A., Bizzari, B., and Lena, R., *Farmaco*, 1996, vol. 51, p. 579.
22. Arena, F., Manna, F., Pizza, C., Stein, M.L., and Grifantini, M., *J. Med. Chem*., 1975, vol. 18, p. 1147.
23. Kurbanova, R.A., Mirzaoğlu, R., Kurbanov, S., Karataş, İ., Pamuk, V., Ozcan, E., Okudan, A., and Guler, E., *J. Adhesion Sci. Technol*., 1997, vol. 11, p. 105.
24. Kleinspehn, G.G., Jung, J.A., and Studniarz, S.A., *J. Org. Chem*., 1967, vol. 32, p. 460.
25. Ginsburg, S. and Wilson, I.B., *J. Am. Chem. Soc*., 1957, vol. 79, p. 481.
26. Brown, D.S., Gallogher, P.T., Lightfoot, A.P., Moody, C.J., Slwin, A.M.Z., and Swann, E., *Tetrahedron*, 1995, vol. 51, p. 11473.
27. Cativiela, C., D. Diaz-de-Villegas, M., and Galvez, J.A., *Tetrahedron: Asymmetry*, 1996, vol. 7, p. 529.
28. McClure, D.E., Arison, B.H., and Baldwin, J.J., *J. Am. Chem. Soc*., 1979, vol. 101, p. 3666.