ISSN 1070-4280, Russian Journal of Organic Chemistry, 2011, Vol. 47, No. 10, pp. 1531–1534. © Pleiades Publishing, Ltd., 2011.
Original Russian Text © R.A. Gadzhily, V.I. Potkin, A.G. Aliev, L.Ya. Gadzhieva, S.K. Petkevich, E.A. Dikusar, 2011, published in Zhurnal Organicheskoi Khimii, 2011, Vol. 47, No. 10, pp. 1504–1507.

Reaction of 3-Alkyl(aryl)-5-chloromethylisoxazoles with Nucleophilic Reagents

R. A. Gadzhily[a], V. I. Potkin[b], A. G. Aliev[a], L. Ya. Gadzhieva[a], S. K. Petkevich[b], and E. A. Dikusar[b]

[a] *Institute of Polymeric Materials, National Academy of Sciences of Azerbaijan, ul. S. Vurguna 124, Sumgait, AZ5004 Azerbaijan*
e-mail: hajili@pochta.ru

[b] *Institute of Physical Organic Chemistry, National Academy of Sciences of Belarus, ul. Surganova 13, Minsk, 220072 Belarus*
e-mail: potkin@ifoch.bas-net.by

Received May 6, 2011

Abstract—Previously unknown 3-alkyl(aryl)isoxazoles containing various functional groups in the 5-position were synthesized by reactions of 3-alkyl(aryl)-5-chloromethylisoxazoles with nucleophiles (2-aminoethanol, methylamine, sodium acetate, and sodium methoxide).

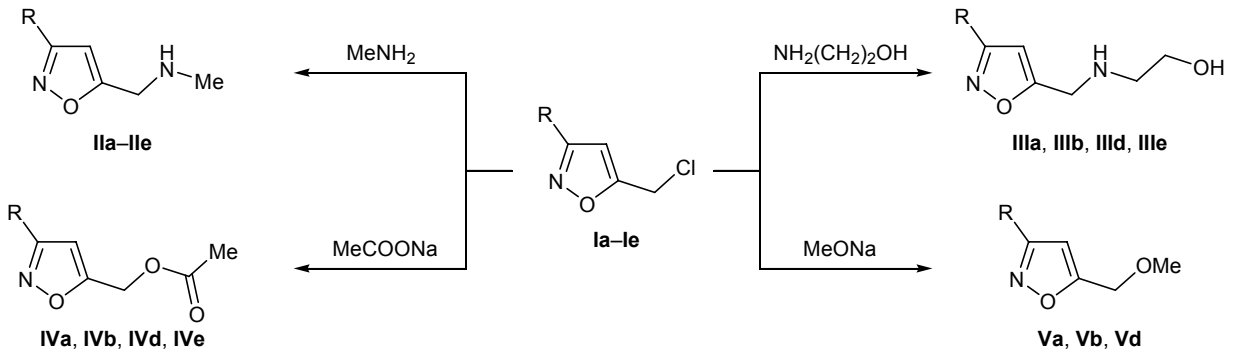
DOI: 10.1134/S1070428011100149

Isoxazole derivatives attract persistent interest due to broad spectrum of biological activity of many compounds of this series [1–3]. Functionalization of isoxazole ring is one of the most rational ways for the preparation of new bioactive products [4, 5]. It was shown previously that condensation of alkyl(aryl)-4-chloro-3-isothiocyanatobut-2-en-1-ones with hydroxylamine hydrochloride leads to the formation of 3-alkyl(aryl)-5-chloromethylisoxazoles **Ia**–**Ie** as promising starting compounds for the synthesis of functionalized isoxazole derivatives. The chlorine atom in molecules **Ia**–**Ie** is highly reactive, and it can readily be replaced by the action of various nucleophiles [6].

The goal of the present work was to develop preparative procedures for the synthesis of previously unknown 3-alkyl(aryl)-5-(2-hydroxyethylaminomethyl, methylaminomethyl, acetoxymethyl, methoxymethyl)-isoxazoles by reactions of isoxazoles **Ia**–**Ie** with nitrogen- and oxygen-centered nucleophiles. The selectivity of the reactions of isoxazoles **Ia**–**Ie** with methylamine and 2-aminoethanol strongly depended on the reactant ratio. When these reactions were performed with equimolar amounts of the reactants in the presence of triethylamine necessary to bind liberated hydrogen chloride, mixtures of amination products were formed. When the nucleophile was taken in excess (30–35°C, 5 h), the corresponding 5-methylaminomethyl- and 5-(2-hydroxyethylamino)-substituted isoxazoles **IIa**–**IIe**, **IIIa**, **IIIb**, **IIId**, and **IIIe** were selectively formed in 71–80 and 63–74% yield, respectively (Scheme 1). By heating isoxazoles **Ia**, **Ib**, **Id**, and **Ie** with 2 equiv of sodium acetate in water over a period of 5 h we obtained 3-alkyl(aryl)-5-acetoxymethylisoxazoles **IVa**, **IVb**, **IVd**, and **IVe** in 67–76% yield. Isoxazoles **Ia**, **Ib**, and **Id** reacted with sodium methoxide in anhydrous methanol at 25–30°C (reaction time 3 h) to produce 68–77% of 3-alkyl(aryl)-5-methoxymethylisoxazoles **Va**, **Vb**, and **Vd**.

The structure of substituted isoxazoles **II**–**V** was confirmed by their IR and ^{1}H NMR spectra and elemental analyses. The IR spectra of **IIa**–**IIe**, **IIIa**, **IIIb**, **IIId**, and **IIIe** contained absorption bands at 3291–3354 cm^{-1} due to stretching vibrations of the NH group, while acetoxy derivatives **IVa**, **IVb**, **IVd**, and **IVe** characteristically displayed carbonyl stretching vibration bands at 1758–1767 cm^{-1}. The ^{1}H NMR spectra of all compounds lacked singlet typical of chloromethyl group in initial isoxazoles **Ia**–**Ie**, but contained a singlet at δ 2.17–2.34 ppm from the MeNH group (**IIa**–**IIe**), a triplet at δ 3.47–3.64 ppm from the CH_2N group (**IIIa**, **IIIb**, **IIId**, **IIIe**), a singlet at δ 1.70–2.31 ppm from the acetyl methyl protons (**IVa**, **IVb**, **IVd**, **IVe**), or a singlet at δ 3.17–3.25 ppm from the methoxy protons (**Va**, **Vb**, **Vd**).

Scheme 1.



R = Me (**a**), Et (**b**), Pr (**c**), Ph (**d**), 4-MeC_6H_4 (**e**).

EXPERIMENTAL

The IR spectra were recorded from thin films on a Nicolet Protégé-460 spectrometer with Fourier transform. The ^{1}H NMR spectra were measured on a Bruker Avance-500 spectrometer using $CDCl_3$ as solvent and tetramethylsilane as reference. The purity of the isolated compounds was checked by TLC on Silufol UV-254 plates using methanol–chloroform–25% aqueous ammonia (3:1:2) as eluent; spots were visualized by treatment with iodine vapor.

Initial 3-alkyl(aryl)-5-chloromethylisoxazoles **Ia–Ie** were synthesized according to the procedures reported in [6].

3-Alkyl(aryl)-5-(methylaminomethyl)isoxazoles IIa–IIe and 3-alkyl(aryl)-5-(2-hydroxyethylaminomethyl)isoxazoles IIIa, IIIb, IIId, and IIIe (*general procedure***).** A solution of 0.1 mol of compound **Ia–Ie** in 30 ml of benzene was added dropwise under stirring at 20–25°C to a mixture of 0.12 mol of 25% aqueous methylamine or 2-aminoethanol and 0.1 mol of triethylamine in 100 ml of benzene. The mixture was stirred for 5 h at 30–35°C, cooled, and washed with an aqueous solution of sodium carbonate. The aqueous phase was treated with diethyl ether, the extract was combined with the organic phase, dried over $MgSO_4$, and evaporated, and the residue was distilled under reduced pressure in a stream of nitrogen.

***N*-Methyl(3-methylisoxazol-5-yl)methanamine (IIa).** Yield 80%, bp 86–87°C (3 mm), R_f 0.56, n_D^{20} = 1.4720, d_4^{20} = 0.9981. IR spectrum, ν, cm^{-1}: 3340 (NH), 3142 (=C–H), 1615, 1580 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm: 1.17 s (3H, 3-CH_3), 2.28 s (3H, NCH_3), 2.49 s (1H, NH), 2.64 s (2H, NCH_2), 5.90 s (1H, 4-H). Found, %: C 57.45; H 7.48; N 22.75. $C_6H_{10}N_2O$. Calculated, %: C 57.14; H 7.94; N 22.22.

(3-Ethylisoxazol-5-yl)-*N*-methylmethanamine (IIb). Yield 78%, bp 101–102°C (3 mm), R_f 0.63, n_D^{20} = 1.4710, d_4^{20} = 0.9850. IR spectrum, ν, cm^{-1}: 3350 (NH), 3140 (=C–H), 1618, 1610 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm: 1.15 t (3H, $CH_2C\mathbf{H}_3$), 2.55 q (2H, CH_2), 2.17 s (3H, NCH_3), 3.40 s (2H, NCH_2), 5.37 s (1H, NH), 6.12 s (1H, 4-H). Found, %: C 60.45; H 8.17; N 20.48. $C_7H_{12}N_2O$. Calculated, %: C 60.00; H 8.57; N 20.00.

***N*-Methyl(3-propylisoxazol-5-yl)methanamine (IIc).** Yield 76%, bp 102–103°C (3 mm), R_f 0.67, n_D^{20} = 1.4690, d_4^{20} = 0.9685. IR spectrum, ν, cm^{-1}: 3348 (NH), 3145 (=C–H), 1618, 1600 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm: 0.85 t (3H, CH_3), 1.54 m (2H, CH_2), 2.38 t (2H, CH_2), 2.19 s (3H, NCH_3), 3.46 s (2H, NCH_2), 5.30 s (1H, NH), 6.18 s (1H, 4-H). Found, %: C 62.78; H 9.54; N 18.47. $C_8H_{14}N_2O$. Calculated, %: C 62.34; H 9.09; N 18.18.

***N*-Methyl(3-phenylisoxazol-5-yl)methanamine (IId).** Yield 73%, bp 134–136°C (2 mm), n_D^{20} = 1.5310, d_4^{20} = 1.0937. IR spectrum, ν, cm^{-1}: 3340 (NH), 3134 (=C–H), 3070 (C–H_{arom}), 1630, 1618, 1578 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm: 2.31 s (3H, NCH_3), 3.70 s (2H, NCH_2), 5.47 s (1H, NH), 7.00–7.58 m (5H, H_{arom}), 6.12 s (1H, 4-H). Found, %: C 70.71; H 6.58; N 14.43. $C_{11}H_{12}N_2O$. Calculated, %: C 70.21; H 6.38; N 14.89.

***N*-Methyl[3-(4-methylphenyl)isoxazol-5-yl]-methanamine (IIe).** Yield 71%, bp 130–133°C (1 mm), R_f 0.58, n_D^{20} = 1.5440, d_4^{20} = 1.0975. IR spectrum, ν, cm^{-1}: 3354 (NH), 3118 (=C–H), 3075 (C–H_{arom}), 1612, 1590, 1580 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm: 2.28 s (3H, CH_3), 2.34 s (3H, NCH_3), 3.81 s (2H, NCH_2), 5.91 s (1H, NH), 6.60 s (1H, 4-H), 7.10 d and 7.60 d (2H each, H_{arom}). Found,

%: C 71.75; H 6.48; N 13.97. $C_{12}H_{14}N_2O$. Calculated, %: C 71.29; H 6.93; N 13.86.

2-(3-Methylisoxazol-5-ylmethylamino)ethanol (IIIa). Yield 74%, bp 126–127°C (3 mm), R_f 0.70, n_D^{20} = 1.5180, d_4^{20} = 1.1020. IR spectrum, ν, cm^{-1}: 3430 (OH), 3340 (NH), 3248 (=C–H), 1619, 1570 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 2.10 s (3H, CH_3), 2.63 t (2H, OCH_2), 3.53 t (2H, NCH_2), 3.70 s (2H, 5-CH_2), 3.90 s (1H, OH), 5.36 (1H, NH), 5.90 s (1H, 4-H). Found, %: C 53.41; H 7.99; N 17.53. $C_7H_{12}N_2O_2$. Calculated, %: C 53.85; H 7.69; N 17.95.

2-(3-Ethylisoxazol-5-ylmethylamino)ethanol (IIIb). Yield 71%, bp 136–137°C (3 mm), R_f 0.68, n_D^{20} = 1.5090, d_4^{20} = 1.0980. IR spectrum, ν, cm^{-1}: 3435 (OH), 3337 (NH), 3250 (=C–H), 1625, 1590 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 1.19 t (3H, CH_3), 2.50 m (2H, CH_2), 2.70 t (2H, OCH_2), 3.59 t (2H, NCH_2), 3.84 s (2H, 5-CH_2), 3.35 s (1H, OH), 5.34 s (1H, NH), 5.96 s (1H, 4-H). Found, %: C 56.98; H 8.74; N 16.91. $C_8H_{14}N_2O_2$. Calculated, %: C 56.47; H 8.24; N 16.47.

2-(3-Phenylisoxazol-5-ylmethylamino)ethanol (IIId). Yield 67%, bp 175–177°C (3 mm), n_D^{20} = 1.5670, d_4^{20} = 1.1650. IR spectrum, ν, cm^{-1}: 3418 (OH), 3328 (NH), 3241 (=C–H), 1615, 1585 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 2.70 t (2H, OCH_2), 3.64 t (2H, NCH_2), 3.80 s (2H, 5-CH_2), 3.98 s (1H, OH), 5.36 s (1H, NH), 5.96 s (1H, 4-H), 7.10–7.40 m (5H, H_{arom}). Found, %: C 66.50; H 6.89; N 12.35. $C_{12}H_{14}N_2O_2$. Calculated, %: C 66.05; H 6.42; N 12.84.

2-[3-(4-Methylphenyl)isoxazol-5-ylmethylamino]ethanol (IIIe). Yield 63%, bp 172–173°C (3 mm), n_D^{20} = 1.5730, d_4^{20} = 1.1620. IR spectrum, ν, cm^{-1}: 3422 (OH), 3291 (NH), 3238 (=C–H), 1620, 1575 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 2.59 t (2H, OCH_2), 3.47 t (2H, NCH_2), 3.56 s (2H, 5-CH_2), 3.85 s (1H, OH), 5.30 s (1H, NH), 5.85 s (1H, 4-H), 7.16 d and 7.68 d (2H each, H_{arom}). Found, %: C 67.70; H 6.59; N 12.39. $C_{13}H_{16}N_2O_2$. Calculated, %: C 67.24; H 6.70; N 12.07.

3-Alkyl(aryl)-5-acetoxymethylisoxazoles IVa, IVb, IVd, and IVe (*general procedure*). Isoxazole **Ia**, **Ib**, **Id**, or **Ie**, 0.1 mol, was added dropwise under stirring to a solution of 16.4 g (0.2 mol) of sodium acetate in 150 ml of water. The mixture was heated for 5 h under reflux, cooled, and extracted with diethyl ether. The extract was washed with water, dried over $MgSO_4$, and evaporated, and the residue was distilled under reduced pressure in a stream of nitrogen.

3-Methylisoxazol-5-ylmethyl acetate (IVa). Yield 76%, bp 106–108°C (3 mm), n_D^{20} = 1.4650, d_4^{20} = 1.1146. IR spectrum, ν, cm^{-1}: 3150 (=C–H), 1760 (C=O), 1626, 1540 (C=C, C=N), 1203 (C–O). ^1H NMR spectrum, δ, ppm: 1.98 s (3H, 3-CH_3), 2.17 s (3H, $COCH_3$), 4.96 s (2H, OCH_2), 6.02 s (1H, 4-H). Found, %: C 54.72; H 5.50; N 9.55. $C_7H_9NO_3$. Calculated, %: C 54.19; H 5.81; N 9.03.

3-Ethylisoxazol-5-ylmethyl acetate (IVb). Yield 73%, bp 120–122°C (3 mm), n_D^{20} = 1.4620, d_4^{20} = 1.0830. IR spectrum, ν, cm^{-1}: 3144 (=C–H), 1758 (C=O), 1620, 1560 (C=C, C=N), 1205 (C–O). ^1H NMR spectrum, δ, ppm: 1.65 t (3H, CH_3), 1.97 s (3H, $COCH_3$), 2.60 q (2H, $CH_3C\mathbf{H}_2$), 4.99 s (2H, OCH_2), 6.10 s (1H, 4-H). Found, %: C 57.32; H 6.25; N 8.79. $C_8H_{11}NO_3$. Calculated, %: C 57.83; H 6.63; N 8.43.

3-Phenylisoxazol-5-ylmethyl acetate (IVd). Yield 68%, bp 157–159°C (4 mm), n_D^{20} = 1.5090, d_4^{20} = 1.1195. IR spectrum, ν, cm^{-1}: 3147 (=C–H), 3081 (C–H_{arom}), 1767 (C=O), 1618, 1579, 1573 (C=C, C=N), 1208 (C–O). ^1H NMR spectrum, δ, ppm: 1.70 s (3H, $COCH_3$), 4.60 s (2H, OCH_2), 6.15 s (1H, 4-H), 7.10–7.85 m (5H, H_{arom}). Found, %: C 66.74; H 5.27; N 6.87. $C_{12}H_{11}NO_3$. Calculated, %: C 66.34; H 5.07; N 6.45.

3-(4-Methylphenyl)isoxazol-5-ylmethyl acetate (IVe). Yield 67%, bp 150–152°C (3 mm), n_D^{20} = 1.5060, d_4^{20} = 1.1086. IR spectrum, ν, cm^{-1}: 3154 (=C–H), 3090 (C–H_{arom}), 1760 (C=O), 1610, 1584, 1570 (C=C, C=N), 1195 (C–O). ^1H NMR spectrum, δ, ppm: 1.36 s (3H, CH_3), 2.31 s (3H, $COCH_3$), 4.10 s (2H, OCH_2), 6.51 s (1H, 4-H), 7.17 d and 7.58 d (2H each, H_{arom}). Found, %: C 67.98; H 5.79; N 6.58. $C_{13}H_{13}NO_3$. Calculated, %: C 67.53; H 5.63; N 6.06.

3-Alkyl(aryl)-5-(methoxymethyl)isoxazoles Va, Vb, and Vd (*general procedure*). Metallic sodium, 2.3 g (0.1 mol), was dissolved in 50 ml of anhydrous methanol cooled to –5°C, a solution of 0.1 mol of isoxazole **Ia**, **Ib**, or **Id** in 20 ml of anhydrous methanol was added dropwise at 20–25°C, and the mixture was stirred for 3 h at 25–30°C and treated with a saturated aqueous solution of sodium carbonate. The organic phase was separated and washed with water, the aqueous phase was extracted with diethyl ether, the extract was combined with the organic phase, dried over $MgSO_4$, and evaporated, and the residue was subjected to vacuum distillation in a stream of nitrogen.

5-Methoxymethyl-3-methylisoxazole (Va). Yield 77%, bp 61–62°C (3 mm), R_f 0.70, n_D^{20} = 1.4560,

d_4^{20} = 1.0621. IR spectrum, ν, cm^{-1}: 3138 (=C–H), 1603, 1570 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 1.10 s (3H, CH_3), 3.20 s (3H, OCH_3), 4.30 s (2H, OCH_2), 6.03 s (1H, 4-H). Found, %: C 56.89; H 7.65; N 11.48. $C_6H_9NO_2$. Calculated, %: C 56.69; H 7.09; N 11.02.

3-Ethyl-5-methoxymethylisoxazole (Vb). Yield 73%, bp 70–72°C (3 mm), R_f 0.67, n_D^{20} = 1.4530, d_4^{20} = 1.0248. IR spectrum, ν, cm^{-1}: 3145 (=C–H), 1609, 1578 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 1.17 t (3H, CH_3), 2.55 q (2H, CH_2), 3.25 s (3H, OCH_3), 4.37 s (2H, OCH_2), 6.05 s (1H, 4-H). Found, %: C 60.01; H 7.45; N 9.48. $C_7H_{11}NO_2$. Calculated, %: C 59.57; H 7.80; N 9.93.

5-Methoxymethyl-3-phenylisoxazole (Vd). Yield 68%, bp 136–137°C (3 mm), R_f 0.71, n_D^{20} = 1.5280, d_4^{20} = 1.2350. IR spectrum, ν, cm^{-1}: 3140 (=C–H), 3074 ($C–H_{arom}$), 1608, 1578, 1575 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 3.17 s (3H, OCH_3), 4.23 s (2H, OCH_2), 6.20 s (1H, 4-H), 7.00–7.64 m (5H, H_{arom}). Found, %: C 69.32; H 5.41; N 7.91. $C_{11}H_{11}NO_2$. Calculated, %: C 69.83; H 5.86; N 7.40.

This study was performed under financial support by the Belarussian Republican Foundation for Basic Research and by the National Academy of Sciences of Azerbaijan (project no. Kh10Az-001).

REFERENCES

1. Yamamoto, T., Fujita, K., Asari, S., Chiba, A., Kataba, Y., Ohsumi, K., Ohmuta, N., Iida, Y., Ijichi, C., Iwayama, S., Fukuchi, N., and Shoji, M., *Bioorg. Med. Chem. Lett*., 2007, vol. 17, p. 3736.
2. Wankhede, K.S., Vaidya, V.V., Sarang, P.S., Salunkhe, M.M., and Trivedi, G.K., *Tetrahedron Lett*., 2008, vol. 49, p. 2649.
3. Dallanoce, C., Frigerio, F., De Amici, M., Dorsch, S., Klotz, K.N., and De Micheli, C., *Bioorg. Med. Chem*., 2007, vol. 15, p. 2533.
4. Khripach, V.A., Zhabinskii, V.N., Ol'khovik, V.K., Zavadskaya, M.I., Drachenova, O.A., and Khripach, N.B., *Russ. J. Org. Chem*., 1996, vol. 32, p. 805.
5. Potkin, V.I., Petkevich, S.K., and Zalesskaya, E.G., *Russ. J. Org. Chem*., 2009, vol. 45, p. 879.
6. Gadzhily, R.A. and Aliev, A.A., *Russ. J. Org. Chem*., 2002, vol. 38, p. 415.