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Synthesis of 5-Bromomethylisoxazoles and Their Reactions with Secondary Amines

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Abstract—Treating R-3-chloro-4-bromo-2-buten-1-ones with hydroxylamine hydrochloride afforded 3-alkyl(aryl, furyl)-5-bromomethylisoxazoles. By reaction of the latter with secondary amines new previously unknown aminoisoxazoles were synthesized.

Among the numerous known methods of haloisoxazole synthesis [1–4] the most common procedures are based on reactions between β-chlorovinyl ketones and hydroxylamine hydrochloride that as a rule afford a mixture of two isomers [2, 3]. It is known however [3, 4] that a reaction of chloromethyl β-chlorovinyl ketone gives rise to a pure 5-chloromethylisoxazole.

The target of theis study was investigation applying the procedure described in [3, 4] of reaction between analogs of chloromethyl β-chlorovinyl ketone, easily available synthons widely used in organic synthesis, R-3-chloro-4-bromo-2-buten-1-ones, and hydroxylamine hydrochloride.

In reaction of R-3-chloro-4-bromo-2-buten-1-ones **Ia–Id** (R = Alk) with hydroxylamine hydrochloride we failed to obtain in a pure state 3-R-5-bromomethylisoxazoles **IIa–IId**. Compounds obtained were a mixture of substances **IIa–IId** and their isomers 5-R-3-bromomethylisoxazoles **IIIa–IIId**.

The attempt to separate these isomers was unsuccessful due to the similarity in the boiling points. The formation of a mixture of compounds **IIa** and **IIIa** was proved by the corresponding ^{1}H NMR spectrum, δ, ppm: 2.12 s and 2.26 s [6H, CH_3 (**IIa**) and CH_3 (**IIIa**)], 4.42 s and 5.59 s [4H, CH_2 (**IIa**) and CH_2 (**IIIa**)], 6.05 s and 6.19 s [2H, CH (**IIa**) and CH (**IIIa**)]. The most probable cause of isomeric mixture formation is the reaction of the hydroxylamine hydrochloride with two reaction sites: a carbonyl group and a chlorine atom in the position *3* of the molecule of alkyl 3,4-dihaloketones **Ia–Id**. We formerly observed that the greatest mobility characterized the halogen atom located at the β-carbon in ketones **Ia–Ig** [5].

Unlike alkyl-3-chloro-4-bromo-2-buten-1-ones **Ia–Id** the reaction of aryl(furyl)-3-chloro-4-bromo-2-buten-1-ones **Ie–Ig** with hydroxylamine hydrochloride is more unambiguous and results in a single isomer, namely, 3-aryl-(furyl)-5-bromomethylisoxazole **IIe–IIg**. This result is caused apparently by the electron-withdrawing effect of aryl and furyl substituents enhancing the electrophilicity of the carbonyl reaction site.

Taking into account the practical importance of isoxazoles [6–8] with the goal to find an efficient procedure for preparation of 5-bromo-methylisoxazoles **IIa–IIg** we investigated in this study the reaction of ketones **Ia–Ig** with hydroxylamine. The reaction of ketones **Ia–Ig** with an equimolar amount of hydroxylamine hydrochloride in a water solution in the presence of potassium hydroxide readily afforded isoxazoles **IIa–IIg** in 53–85% yields.

In weak alkaline or neutral media the hydroxylamine apparently first reacts with the carbonyl group to furnish an intermediate oxime. Thereafter occurs essentially intramolecular cyclization resulting in a single product, 3-R-5-bromomethylisoxazole **IIa–IIg**.

We found that at treating isoxazoles **IIa–IIg** with a double amount of a secondary amine in the presence of triethylamine easily occurred a replacement of bromine atom by amino group to give in a high yield the corresponding aminoisoxazoles **IVa–IVf**, **Va–Vg**, and **VIa–VIf**.

The structure of isoxasoles **II–VI** was confirmed by IR, UV, and ^{1}H NMR spectra, and also by elemental analysis and independent synthesis by reaction of 3-R-5-chloromethylisoxazoles with the mentioned secondary

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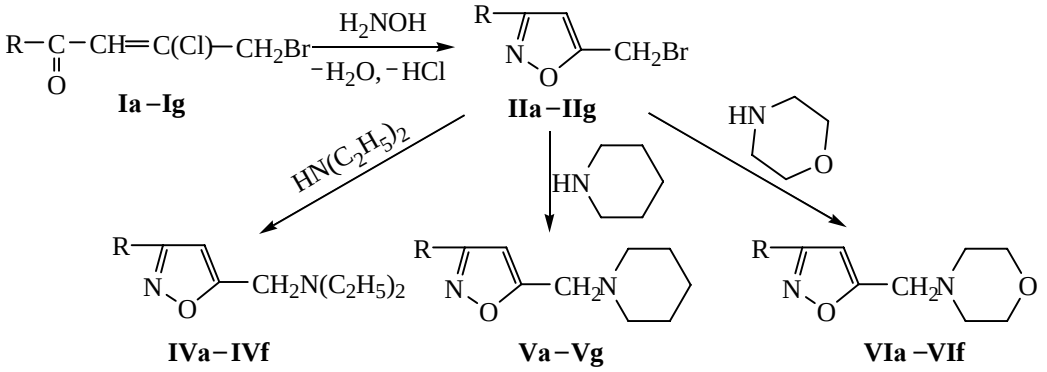

R = CH_3 (**a**), C_2H_5 (**b**), C_3H_7 (**c**), *iso*-C_3H_7 (**d**), C_6H_5 (**e**), *para*-$CH_3C_6H_4$ (**f**), furyl (**g**).

amines. The spectral characteristics of aminoisoxazoles **IV–VI** obtained by both procedures were identical.

EXPERIMENTAL

IR spectra of compounds were recorded from thin films on spectrophotometers UR-20 and Specord M-80, UV spectra were measured on a spectrophotometer Specord UV-Vis from methanol solutions. ^{1}H NMR spectra were registered from 5–10% solutions of compounds in CCl_4, $CDCl_3$, or CD_3OD on a spectrometer Tesla BS-487B (operating frequency 80 MHz). The purity of compounds obtained was checked by TLC on Silufol UV-254 plates, eluent methanol–chloroform – 25% aqueous ammonia, 3:2:1, development in the iodine vapor. Initial R-3-chloro-4-bromo-2-buten-1-ones were prepared as described in [9].

3-Alkyl(aryl,furyl)-5-bromomethylisoxazoles IIa–IIg. To a solution of 14 g (0.2 mol) of hydroxylamine hydrochloride in 80 ml of methanol or ethanol at 10–15°C was added dropwise while stirring 12 g (0.2 mol) of potassium hydroxide dissolved in 180 ml of water, and then at the same temperature was added dropwise a solution of 0.2 mol of ketone **I** in 40 ml of MeOH (EtOH). Then the reaction mixture was heated at 65–70°C for 6 h [in the absence of potassium hydroxide formed two isomers: 3-alkyl-5-bromo-methyl- (**IIa–IId**) and 5-alkyl-3-bromomethylisoxazoles (**IIIa–IIId**)]. Compounds **IIe–IIg** were prepared without potassium hydroxide. On cooling the reaction products were separated, washed several times with a saturated water solution of potassium or sodium carbonate till neutral washings, combined with ether or benzene extracts from the water layer, dried over $MgSO_4$, and on removing the solvent they were distilled in a vacuum in a nitrogen flow.

3-Methyl-5-bromomethylisoxazole (IIa). Yield 85%, bp 67–68°C (2 mm Hg), R_f 0.60, n_D^{20} 1.5090, d_4^{20} 1.4838. IR spectrum, ν, cm^{-1}: 3148 (CH), 1640 (C=C, C=N), 570 (C–Br). ^{1}H NMR spectrum, δ, ppm: 2.24 s (3H, CH_3), 4.59 s (2H, CH_2), 6.09 s (1H, CH). UV spectrum, λ_{max}, nm (ε): 240 (7900). Found, %: C 34.69; H 3.91; Br 46.45; N 7.38. C_5H_6BrNO. Calculated, %: C 34.09; H 3.41; Br 45.45; N 7.95.

3-Ethyl-5-bromomethylisoxazole (IIb). Yield 84%, bp 77–78°C (2 mm Hg), R_f 0.58, n_D^{20} 1.5070, d_4^{20} 1.4346. IR spectrum, ν, cm^{-1}: 3140 (CH), 1660 (C=C, C=N), 620 (C–Br). ^{1}H NMR spectrum, δ, ppm: 1.15 t and 2.55 q (5H, CH_3CH_2), 4.39 C (2H, CH_2), 6.15 C (1H, CH). UV spectrum, λ_{max}, nm (ε): 230 (9900). Found, %: C 37.44; H 4.57; Br 42.28; N 7.11. C_5H_8BrNO. Calculated, %: C 37.89; H 4.21; Br 42.10; N 7.37.

3-Propyl-5-bromomethylisoxazole (IIc). Yield 80%, bp 96–98°C (2 mm Hg), R_f 0.54, n_D^{20} 1.4950, d_4^{20} 1.3548. IR spectrum, ν, cm^{-1}: 3130 (CH), 1650 (C=C, C=N), 520 (C–Br). ^{1}H NMR spectrum, δ, ppm: 0.92 t, 1.62 m and 2.48 t [7H, $CH_3(CH_2)_2$], 4.74 s (2H, CH_2), 6.60 s (1H, CH). UV spectrum, λ_{max}, nm (ε): 229 (10800). Found, %: C 41.37; H 4.59; Br 39.70; N 7.00. $C_7H_{10}BrNO$. Calculated, %: C 41.17; H 4.90; Br 39.22; N 6.86.

3-Isopropyl-5-bromomethylisoxazole (IId). Yield 76%, bp 92–93°C (2 mm Hg), R_f 0.55, n_D^{20} 1.4970, d_4^{20} 1.3620. IR spectrum, ν, cm^{-1}: 3140 (CH), 1660 (C=C, C=N), 620 (C–Br). ^{1}H NMR spectrum, δ, ppm: 1.08 d and 2.67 m [7H, $CH(CH_3)_2$], 4.07 s (2H, CH_2), 6.61 s (1H, CH). UV spectrum, λ_{max}, nm (ε): 235 (9500). Found, %: C 41.48; H 4.63; Br 39.51; N 6.48. $C_7H_{10}BrNO$. Calculated, %: C 41.17; H 4.9; Br 39.22; N 6.86.

3-Phenyl-5-bromomethylisoxazole (IIe). Yield 70%, bp 143–145°C (2 mm Hg), R_f 0.61, n_D^{20} 1.5890, d_4^{20}

1.4780. IR spectrum, ν, cm^{-1}: 3144 (CH), 1670 (C=C, C=N), 580 (C–Br). ^{1}H NMR spectrum, δ, ppm: 7.30 m and 8.00 m (5H, H_{arom}), 4.20 s (2H, CH_2), 6.40 s (1H, CH). UV spectrum, λ_{max}, nm (ε): 239 (7500). Found, %: C 50.85; H 3.71; Br 33.84; N 5.28. $C_{10}H_8BrNO$. Calculated, %: C 50.42; H 3.36; Br 33.61; N 5.88.

3-Toluyl-5-bromoethylisoxazole (IIf). Yield 69%, bp 140–141°C (2 mm Hg), R_f 0.65, n_D^{20} 1.5930, d_4^{20} 1.4550. IR spectrum, ν, cm^{-1}: 3146 (CH), 1670 (C=C, C=N), 580 (C–Br). ^{1}H NMR spectrum, δ, ppm: 2.50 s (3H, CH_3), 7.40 m and 7.88 m (4H, H_{arom}), 3.8 s (2H, CH_2), 6.57 s (1H, CH). UV spectrum, λ_{max}, nm (ε): 239 (7500). Found, %: C 52.75; H 3.48; Br 31.28; N 5.87. $C_{11}H_{10}BrNO$. Calculated, %: C 52.38; H 3.97; Br 31.75; N 5.55.

3-Furyl-5-bromomethylisoxazole (IIg). Yield 53%, bp 138–139°C (3 mm Hg), n_D^{20} 1.5820, d_4^{20} 1.4780. Found, %: C 42.29; H 2.87; Br 35.17; N 6.29. $C_8H_6BrNO_2$. Calculated, %: C 42.10; H 2.63; Br 35.09; N 6.14.

3-Alkyl(aryl, furyl)-5-dialkylaminomethylisoxazoles IVa–IVf, Va–Vg, and VIa–VIf. To a solution of 0.2 mol of a secondary amine (diethylamine, piperidine, morpholine) and 0.2 mol of triethylamine in 150 ml of benzene was added dropwise at stirring 0.1 mol of 3-alkyl(aryl, furyl)-5-bromomethylisoxazole **II** dissolved in 30 ml of benzene at 30–35°C. Then the mixture was heated to 50–60°C and stirred at this temperature for 5 h. On cooling the reaction mixture was diluted with 100 ml of saturated water solution of potassium or sodium carbonate, washed till neutral washings, combined with ether or benzene extracts from the water layer, dried over $MgSO_4$, and on removing the solvent the products were distilled in a vacuum in a nitrogen flow.

3-Methyl-5-diethylaminomethylisoxazole (IVa). Yield 89%, bp 77–78°C (1 mm Hg), R_f 0.70, n_D^{20} 1.4666, d_4^{20} 0.9880. IR spectrum, ν, cm^{-1}: 3150 (CH), 1630 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm: 0.97 t and 2.45 q [10H, $(CH_2CH_3)_2$], 2.13 s (3H, CH_3), 6.60 s (1H, CH). UV spectrum, λ_{max}, nm (ε): 225 (8500). Found, %: C 64.70; H 9.91; N 16.21. $C_9H_{16}N_2O$. Calculated, %: C 64.29; H 9.52; N 16.67.

3-Ethyl-5-diethylaminomethylisoxazole (IVb). Yield 84%, bp 89–90°C (3 mm Hg), R_f 0.63, n_D^{20} 1.4650, d_4^{20} 0.9698. IR spectrum, ν, cm^{-1}: 3138 (CH), 1603 (C=C, C=N). UV spectrum, λ_{max}, nm (ε): 220 (6700). Found, %: C 65.40; H 9.21; N 15.70. $C_{10}H_{18}N_2O$. Calculated, %: C 65.93; H 9.89; N 15.38.

3-Propyl-5-diethylaminomethylisoxazole (IVc). Yield 82%, bp 100–102°C (1 mm Hg), R_f 0.57, n_D^{20}1.463, d_4^{20} 0.9496. IR spectrum, ν, cm^{-1}: 3130 (CH), 1600 (C=C, C=N). UV spectrum, λ_{max}, nm (ε): 218 (5800). Found, %: C 67.74; H 10.73; N 14.77. $C_{11}H_{20}N_2O$. Calculated, %: C 67.35; H 10.20; N 14.29.

3-Isopropyl-5-diethylaminomethylisoxazole (IVd). Yield 80%, bp 98–99°C (1 mm Hg), R_f 0.60, n_D^{20} 1.4610, d_4^{20} 0.9480. IR spectrum, ν, cm^{-1}: 3140 (CH), 1608 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm: 1.03 t and 2.45 d [10H, $(CH_2CH_3)_2$], 1.25 quintet [7H, $CH(CH_3)_2$], 3.62 s (2H, CH_2), 5.95 s (1H, CH). UV spectrum, λ_{max}, nm (ε): 220 (7300). Found, %: C 67.24; H 10.31; N14.98. $C_{11}H_{20}N_2O$. Calculated, %: C 67.35; H 10.20; N 14.29.

3-Phenyl-5-diethylaminomethylisoxazole (IVe). Yield 75%, bp 132–133°C (2 mm Hg), R_f 0.54, n_D^{20} 1.5660, d_4^{20} 1.0970. IR spectrum, ν, cm^{-1}: 3150 (=CH), 1630 (C=C, C=N). UV spectrum, λ_{max}, nm (ε): 210 (8300). Found, %: C 73.41; H 7.51; N 12.67. $C_{14}H_{18}N_2O$. Calculated, %: C 73.04; H 7.83; N 12.17.

3-Toluyl-5-diethylaminomethylisoxazole (IVf). Yield 70%, bp 129–131°C (2 mm Hg), n_D^{20} 1.5610, d_4^{20} 1.0925. Found, %: C 73.20; H 8.91; N 11.05. $C_{15}H_{20}N_2O$. Calculated, %: C 73.77; H 8.20; N 11.74.

3-Methyl-5-piperidinomethylisoxazole (Va). Yield 84%, bp 120–121°C (3 mm Hg), R_f 0.57, n_D^{20} 1.4924, d_4^{20} 1.0098. IR spectrum, ν, cm^{-1}: 3150 (=CH), 1620 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm: 2.21 s (3H, CH_3), 1.84 m and 2.75 t [10H, $(CH_2)_5$], 4.08 s (2H, CH_2), 5.35 s (1H, CH). UV spectrum, λ_{max}, nm (ε): 210 (5700). Found, %: C 66.24; H 9.00; N 15.79. $C_{10}H_{16}N_2O$. Calculated, %: C 66.67; H 8.89; N 15.56.

3-Ethyl-5-piperidinomethylisoxazole (Vb). Yield 80%, bp 130–132°C (3 mm Hg), n_D^{20} 1.4910, n_D^{20} 0.9928. Found, %: C 68.34; H 9.70; N 14.78. $C_{11}H_{18}N_2O$. Calculated, %: C 68.04; H 9.28; N 14.43.

3-Propyl-5-piperidinomethylisoxazole (Vc). Yield 81%, bp 135–136°C (2 mm Hg), R_f 0.57, n_D^{20} 1.4890, d_4^{20} 1.9832. IR spectrum, ν, cm^{-1}: 3140 (CH), 1620 (C=C, C=N). UV spectrum, λ_{max}, nm (ε): 218 (5800). Found, %: C 69.54; H 9.04; N 13.85. $C_{12}H_2N_2O$. Calculated, %: C 69.23; H 9.28; N 13.46.

3-Isopropyl-5-piperidinomethylisoxazole (Vd). Yield 78%, bp 130–131°C (2 mm Hg), R_f 0.67, n_D^{20} 1.4850, d_4^{20} 0.9832. IR spectrum, ν, cm^{-1}: 3150 (CH), 1610 (C=C, C=N). UV spectrum, λ_{max}, nm (ε): 220 (7200). Found, %: C 69.70; H 9.21; N 13.99. $C_{12}H_{20}N_2O$. Calculated, %: C 69.23; H 9.61; N 13.46.

3-Phenyl-5-piperidinomethylisoxazole (Ve). Yield 74%, bp 140–141°C (2 mm Hg), R_f 0.57, n_D^{20} 1.5740, d_4^{20} 1.1030. IR spectrum, ν, cm^{-1}: 3150 (CH), 1630 (C=C, C=N). UV spectrum, λ_{max}, nm (ε): 210 (8200). Found, %: C 74.78; H 7.88; N 11.05. $C_{15}H_{18}N_2O$. Calculated, %: C 74.38; H 7.44; N 11.70.

3-Toluyl-5-piperidinomethylisoxazole (Vf). Yield 70%, bp 137–138°C (3 mm Hg), n_D^{20} 1.5790, d_4^{20} 1.1071. Found, %: C 75.21; H 7.40; N 10.21. $C_{16}H_{20}N_2O$. Calculated, %: C 75.00; H 7.81; N 10.94.

3-Furyl-5-piperidinomethylisoxazole (Vg). Yield 68%, bp 168–169°C (2 mm Hg). Found, %: C 67.71; H 6.12; N 12.18. $C_{13}H_{16}N_2O_2$. Calculated, %: C 67.24; H 6.89; N 12.07.

3-Methyl-5-morpholinomethylisoxazole (VIa). Yield 87%, bp 118–120°C (2 mm Hg), R_f 0.67, n_D^{20} 1.4990, d_4^{20} 1.1119. IR spectrum, ν, cm^{-1}: 3140 (CH), 1608 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm: 2.11 s (3H, CH_3), 2.34 t and 3.50 t [8H, $(CH_2)_4$], 3.46 s (2H, CH_2), 5.88 s (1H, CH). UV spectrum, λ_{max}, nm (ε): 225 (6800). Found, %: C 59.48; H 7.97; N 15.01. $C_9H_{14}N_2O_2$. Calculated, %: C 59.34; H 7.69; N 15.38.

3-Ethyl-5-morpholinomethylisoxazole (VIb). Yield 85%, bp 129–131°C (2 mm Hg), n_D^{20} 1.4960, d_4^{20} 1.0883. Found, %: C 61.78; H 8.51; N 14.99. $C_{10}H_{16}N_2O_2$. Calculated, %: C 61.22; H 8,16; N 14.29.

3-Propyl-5-morpholinomethylisoxazole (VIIc). Yield 84%, bp 136–137°C (2 mm Hg), n_D^{20} 1.4920, d_4^{20} 1.0640. Found, %: C 62.07; H 8.12; N 13.78. $C_{11}H_{18}N_2O_2$. Calculated, %: C 62.86; H 8.57; N 13.33.

3-Isopropyl-5-morpholinomethylisoxazole (VId). Yield 80%, bp 134–135°C (2 mm Hg), R_f 0.70, n_D^{20} 1.4910, d_4^{20} 1.0498. IR spectrum, ν, cm^{-1}: 3150 (CH), 1620 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm: 1.23 d and 3.20 q [7H, $CH(CH_3)_2$], 2.40 t and 3.58 t [8H, $(CH_2)_4$], 3.54 s (2H, CH_2), 5.97 s (1H, CH). UV spectrum, λ_{max}, nm (ε): 219 (7100). Found, %: C 62.48; H 8.21; N 13.97. $C_{11}H_{18}N_2O_2$. Calculated, %: C 62.86; H 8.57; N 13.33.

3-Phenyl-5-morpholinomethylisoxazole (VIe). Yield 75%, bp 145–146°C (2 mm Hg), n_D^{20} 1.5760, d_4^{20} 1.237. Found, %: C 68.85; H 6.97; N 11.73. $C_{14}H_{16}N_2O$. Calculated, %: C 68.85; H 6.56; N 11.48.

3-Toluyl-5-morpholinomethylisoxazole (VIf). Yield 76%, bp 138–139°C (2 mm Hg), R_f 0.64, n_D^{20} 1.582, d_4^{20} 1.1093. IR spectrum, ν, cm^{-1}: 3150 (CH), 1625 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm: 2.37 s (3H, CH_3), 2.47 t and 3.60 t [8H, $(CH_2)_4$], 3.57 s (2H, CH_2), 6.32 s (1H, CH), 7.19 m and 7.60 m (4H, H_{arom}). UV spectrum, λ_{max}, nm (ε): 217 (6100). Found, %: C 69.21; H 6.17; N 10.20. $C_{15}H_{18}N_2O_2$. Calculated, %: C 69.77; H 6.97; N 10.85.

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