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HALOGENATION OF PROPARGYL ETHERS OF HETERYLALDOXIMES AND KETOXIMES UNDER INTERPHASE CATALYSIS CONDITIONS

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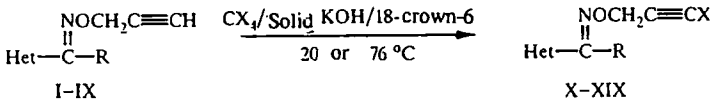
The halogenation of propargyl ethers of heterylaldoximes and ketoximes in interphase catalytic systems CX_4 (X = Cl, Br)/solid KOH/18-crown-6 leads selectively to the formation of the corresponding O-(halopropargyl)oximes.

Halogen-containing O-ethers of heterylaldoximes and ketoximes are of interest as biologically active substances. Halogen-containing derivatives of oximes of the furan and thiophene series have cardiotropic [1], antihypertensive [2], cholesterol-lowering [3], antidepressant [4], analgesic and antiinflammatory [5], and also microbicidal [6], insecticidal [7], fungicidal [8], and pesticidal [9] activity, and are used as plant growth regulators [10]. Halogen-containing O-ethers of pyridine-containing oximes are inhibitors of thrombocyte aggregation [11, 12], they possess antiulcer activity [13], are antidotes for organophosphorus poisoning [14, 15], have insecticidal [16], fungicidal [17-19], pesticidal [20], and herbicidal [21-24] activity. Recently it was shown possible to obtain chlorinated pyridine terminal acetylenes in the interphase catalytic (IPC) system CCl_4/solid KOH/18-crown-6 [25]. However O-(halopropargyl)oximes of heterylaldehydes and ketones have not been studied previously.

We have developed new IPC methods of synthesizing O-chloropropargyl (X)-(XI) and O-bromopropargyl ethers (XII)-(XIX) of heterylketoximes and aldoximes from the corresponding propargyl ethers (I)-(IX) in the systems CCl_4/solid KOH/18-crown-6 and CBr_4/solid KOH/18-crown-6/benzene respectively.



I–IX X–XIX

I,XII Het = 2-furyl, R = H; II,X,XII Het = 2-furyl, R = Me; III,XIV Het = 2-thienyl, R = H; IV,XI Het = 2-thienyl, R = Me; V,XV Het = 5-bromo-2-thienyl, R = Et; VI,XVI Het = 2-pyridyl, R = H; VII,XVII Het = 6-methyl-2-pyridyl, R = H; VIII,XVIII Het = 3-pyridyl, R = H; IX,XIX Het = 4-pyridyl, R = H; X,XI X = Cl; XII-XIX X = Br

The chlorination products of the O-propargyl ethers of 2-acetylfuran and 2-acetylthiophene ketoximes (X) and (XI), isolated by column chromatography, were unstable at elevated temperature. Due to their instability it was not possible to obtain in a pure state the chlorination products of the O-propargyl derivatives of pyridine-containing aldoximes and ketoximes nor the chloro derivatives of the O-propargyloximes of 2-furyl- and 2-thienylcarbaldehydes.

Preliminary experiments showed that the optimum quantity of carbon tetrabromide for brominating O-propargyloximes was 0.75 equivalents for substrates (I)-(III), and (V)-(IX). This may be explained by disproportionation of the initially formed bromoform in the presence of alkali into carbon tetrabromide, prolonging the reaction. The oxime O-halopropargyl ethers were identified by PMR and mass spectroscopy, and also by elemental analysis.

The IPC method developed by us for the synthesis of O-(halopropargyl)oximes (X)-(XIX) from the corresponding propargyloximes is convenient and selective. The reaction products were isolated in yields up to 90%.

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EXPERIMENTAL

The PMR spectra were recorded on a Bruker WH-90/DS spectrometer in $CDCl_3$, internal standard was TMS. The mass spectra were obtained on a Kratos MS 25 chromatograph–mass spectrometer, energy of the ionizing electrons was 70 eV. The GLC analysis was carried out on a Chrom-5 chromatograph with a flame ionization detector and a glass column packed with 5% OV-101 on Chromosorb W-HP (80-100 mesh), analysis temperature was 180-230°C.

The O-propargyloximes of 2-furancarbaldehyde (I), 2-acetylfuran (II), 2-thiophenecarbaldehyde (III), 2-acetylthiophene (IV), 5-bromo-2-propionylthiophene (V), 2-pyridinecarbaldehyde (VI), 6-methyl-2-pyridinecarbaldehyde (VII), 3-pyridinecarbaldehyde (VIII), and 4-pyridinecarbaldehyde (IX) were obtained from the corresponding carbonyl derivatives [26, 27].

General Procedure for Obtaining O-(Chloropropargyl)oximes (X), (XI). O-(Chloropropargyl)oxime of 2-Acetylfuran (X). Finely powdered KOH (1.40 g: 25 mmole) was added to a solution of the E-isomer of the O-propargyloxime of 2-acetylfuran (0.82 g: 5 mmole) and 18-crown-6 (0.13 g: 0.5 mmole) in carbon tetrachloride (8 ml), the mixture was boiled for 10 h, a second portion (0.70 g: 12.5 mmole) of KOH was added, the mixture boiled for 10 h, then filtered through Al_2O_3. The filtrate was evaporated under reduced pressure, and the residue chromatographed on silica gel (eluent benzene). The yield of E-isomer was 0.48 g (49%). Yellowish oil. PMR spectrum ($CDCl_3$/TMS): 2.07 (3H, s, CH_3); 4.67 (2H, s, CH_2); 6.33 (1H, m, 4-H); 6.56 (1H, m, 3-H); 7.38 ppm (1H, m, 5-H). Mass spectrum, m/z (I_{rel}, %): 197 (24, M^+), 132 (22), 120 (10), 94 (48), 83 (42), 73 (33), 66 (100), 53 (11), 39 (61). Found, %: C 55.74; H 4.44; N 6.59. $C_9H_8ClNO_2$. Calculated, %: C 54.70; H 4.08; N 7.09.

O-(Chloropropargyl)oxime of 2-acetylthiophene (XI) was obtained from the O-propargyloxime of 2-acetylthiophene (ratio of E:Z isomers 80:20) analogously to compound (X). Reaction time was 20 h. Yield was 0.49 g (46%) (mixture of E/Z isomers 80:20) as a yellowish oil. PMR spectrum (E-isomer): 2.13 (3H, s, CH_3); 4.67 (2H, s, CH_2); 6.91 (1H, m, 4-H); 7.20 ppm (2H, m, 3-H and 5-H); (Z-isomer): 2.27 (3H, s, CH_3); 4.73 (2H, s, CH_2); 6.91 (1H, m, 4-H), 7.20 (2H, m, 3-H and 5-H). Mass spectrum, m/z (I_{rel}, %): 213 (29, M^+), 148 (40), 124 (10), 110 (98), 99 (100), 84 (24), 73 (33), 66 (28), 58 (14), 45 (28), 39 (41). Found, %: C 51.30; H 3.68; N 6.40. C_9H_8ClNOS. Calculated, %: C 50.59; H 3.77; N 6.55.

General Procedure for Obtaining O-Bromopropargyloximes (XII)-(XIX). O-Bromopropargyloxime of 2-Furancarbaldehyde (XII). Powdered KOH (0.14 g: 2.515 mmole) was added to a solution of the E-isomer of the O-propargyloxime of 2-furancarbaldehyde (0.075 g: 0.503 mmole), CBr_4 (0.125 g: 0.377 mmole), and 18-crown-6 (0.013 g: 0.05 mmole) in benzene (1 ml) and the mixture stirred for 10 h at room temperature, then filtered through Al_2O_3. The solvent was distilled from the filtrate under reduced pressure and the residue chromatographed on silica gel (eluent was benzene). Yield of E-isomer was 0.06 g (52%) as a yellowish oil. PMR spectrum: 4.78 (2H, s, CH_2); 6.45 (1H, m, 4-H); 6.65 (1H, m, 3-H); 7.47 (1H, m, 5-H); 7.94 ppm (1H, s, CH). Mass spectrum, m/z (I_{rel}, %): 228 (27, M+), 133 (10), 118 (76), 106 (86), 83 (86), 66 (24), 52 (92), 39 (100). Found, %: C 42.13; H 2.83; N 5.71. $C_8H_6BrNO_2$. Calculated, %: C 42.14; H 2.65; N 6.14.

Compounds (XIII)-(XIX) were obtained similarly. The eluent benzene–ethyl acetate, 1:1 was used to separate the pyridine-containing ethers (XVI)-(XIX). Due to their instability and volatility it proved to be impossible to carry out elemental analysis on the O-(bromopropargyl)oximes of 2-acetylfuran (XIII) and of 5-bromo-2-propionylthiophene (XV).

O-Bromopropargyloxime of 2-acetylfuran (XIII) was obtained from the E-isomer of the O-propargyloxime of 2-acetylfuran (II) analogously to compound (XII). Reaction time was 6 h. Yield of E-isomer was 72%. Yellowish oil. PMR spectrum: 2.18 (3H, s, CH_3); 4.74 (2H, s, CH_2); 6.41 (1H, m, 4-H); 6.61 (1H, m, 3-H); 7.45 ppm (1H, m, 5-H). Mass spectrum, m/z (I_{rel}, %): 243 (13), 132 (46), 119 (23), 104 (12), 94 (58), 83 (54), 66 (100), 53 (14), 39 (78).

O-Bromopropargyloxime of 2-thiophenecarbaldehyde (XIV) was obtained from the E-isomer of the O-propargyloxime of 2-thiophenecarbaldehyde (III) analogously to compound (XII). Reaction time was 7 h. Yield of E-isomer was 65%. Yellowish oil. PMR spectrum: 4.72 (3H, s, CH_2); 7.01 (1H, m, 4-H); 7.16 (1H, m, 3-H); 7.34 (1H, m, 5-H); 8.18 ppm (1H, m, CH). Mass spectrum, m/z (I_{rel}, %): 244 (18, M^+), 134 (96), 122 (58), 110 (31), 99 (100), 83 (14), 70 (30), 57 (24), 50 (14), 39 (49). Found, %: C 38.06; H 2.52; N 5.74. C_8H_6BrNOS. Calculated, %: C 39.36; H 2.48; N 5.74.

O-Bromopropargyloxime of 5-Bromo-2-propionyl-thiophene (XV) was obtained from the E-isomer of the O-propargyloxime of 5-bromo-2-propionylthiophene (V) analogously to compound (XII). Reaction time was 8 h. Yield of E-isomer was 90%. Yellowish oil. PMR spectrum: 1.21 (3H, t, CH_3); 2.63 (2H, q, $\underline{CH_2}CH_3$); 4.67 (2H, s, CH_2); 6.9-7.2 ppm (2H, m, 3-H and 4-H). Mass spectrum, m/z (I_{rel}, %): 351 (52, M^+), 242 (25), 215 (18), 203 (71), 189 (69), 177 (98), 161 (31), 149 (21), 133 (20), 123 (100), 108 (44), 82 (77), 69 (43), 57 (22), 38 (66).

O-Bromopropargyloxime of 2-pyridinecarbaldehyde (XVI) was obtained from the E-isomer of the O-propargyloxime of 2-pyridinecarbaldehyde (VI) analogously to compound (XII). Reaction time was 4 h. Yield of E-isomer was 59%, mp 107-110°C. PMR spectrum: 4.83 (2H, s, CH_2); 7.15-7.35 (1H, m, 5-H); 7.55-7.89 (2H, m, 3-H and 4-H); 8.19 (1H, s, CH); 8.54-8.67 ppm (1H, m, 6-H). Mass spectrum, m/z (I_{rel}, %): 239 (10, M^+), 237 (10), 210 (30), 209 (10), 208 (20), 131 (12), 129 (44), 119 (32), 117 (34), 104 (10), 79 (19), 78 (100), 66 (16), 64 (12), 63 (16), 52 (20), 51 (44), 50 (15), 39 (14), 38 (25). Found, %: C 45.40; H 2.91; N 11.49. $C_9H_7BrN_2O$. Calculated, %: C 45.22; H 2.95; N 11.72.

O-Bromopropargyloxime of 6-methyl-2-pyridine-carbaldehyde (XVII) was obtained from the E-isomer of O-propargyloxime of 6-methyl-2-pyridinecarbaldehyde analogously to compound (XII). Reaction time was 6 h. Yield of E-isomer was 52%. Yellowish oil. PMR spectrum: 2.58 (3H, s, CH_3); 4.78 (2H, s, CH_2); 7.0-7.6 (2H, m, 3-H and 4-H); 8.11 ppm (1H, s, CH). Mass spectrum, m/z (I_{rel}, %): 253 (9, M^+), 224 (13), 159 (10), 143 (100), 117 (41), 104 (10), 92 (91), 80 (37), 65 (80), 53 (17), 39 (42). Found, %: C 47.10, H 3.31; N 11.59. $C_{10}H_9BrN_2O$. Calculated, %: C 47.41; H 3.58; N 11.07.

O-Bromopropargyloxime of 3-pyridinecarbaldehyde (XVIII) was obtained from the E-isomer of the O-propargyloxime of 3-pyridinecarbaldehyde analogously to compound (XII). Reaction time was 4 h. Yield of E-isomer was 64%, mp 61-63°C. PMR spectrum: 4.76 (2H, s, CH_2); 7.13-7.36 (1H, m, 5-H), 7.91 (1H, d t, J_1 = 7.6, J_2 = 1.6 Hz, 4-H); 8.07 (1H, s, CH); 8.54 (1H, d d, J_1 = 6.0, J_2 = 1.6 Hz, 6-H); 8.67 ppm (1H, d, 2-H). Mass spectrum, m/z (I_{rel}, %): 239 (46, M^+), 238 (12), 237 (48), 159 (13), 131 (27), 130 (11), 129 (72), 119 (92), 117 (100), 106 (11), 105 (20), 104 (27), 103 (12), 91 (15), 79 (12), 77 (17), 76 (12), 66 (23), 64 (36), 63 (49), 52 (27), 51 (74), 50 (35), 39 (23), 38 (48), 37 (16). Found, %: C 45.40; H 2.95; N 11.49. $C_9H_7BrNO_2$. Calculated, %: C 45.22; H 2.95; N 11.72.

O-Bromopropargyloxime of 4-pyridinecarbaldehyde (XIX) was obtained from the E-isomer of the O-propargyloxime of 4-pyridinecarbaldehyde analogously to compound (XII). Reaction time was 4 h. Yield of E-isomer was 42%, mp 129-131°C. PMR spectrum: 4.76 (2H, s, CH_2); 7.38 (2H, d d, J_1 = 6.2, J_2 = 2.0 Hz, 3-H and 5-H); 7.97 (1H, s, CH); 8.56 ppm (2H, d d, J_1 = 6.2, J_2 = 2.0 Hz, 2-H and 6-H). Mass spectrum, m/z (I_{rel}, %): 239 (13, M^+), 237 (13), 131 (30), 130 (15), 129 (100), 119 (84), 117 (90), 105 (16), 104 (21), 78 (44), 77 (12), 66 (15), 64 (18), 63 (29), 52 (14), 51 (66), 50 (33), 39 (26), 38 (29), 37 (12). Found, %: C 45.47; H 2.89; N 11.63. $C_9H_7BrN_2O$. Calculated, %: C 45.22; H 2.95; N 11.71.

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