Three-component condensation of pyridin-2-one, bis(2-chloroethyl)amine hydrochloride, and K_2CO_3 in DMF as a new method for oxazolidinylethylation

V. A. Mamedov, E. A. Khafizova, T. N. Beschastnova, N. A. Zhukova, A. T. Gubaidullin, I. Kh. Rizvanov, E. A. Berdnikov, and I. A. Litvinov*

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Research Center of the Russian Academy of Sciences, 8 ul. Akad. Arbuzova, 420088 Kazan, Russian Federation. Fax: +7 (843 2) 73 1872. E-mail: mamedov@iopc.knc.ru

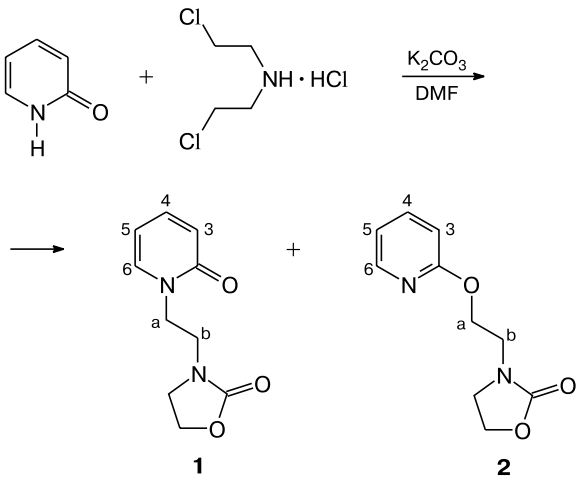
Three-component condensation of pyridin-2-one, bis(2-chloroethyl)amine hydrochloride, and K_2CO_3 in DMF unexpectedly gave *N*- and *O*-oxazolidinylethylation products of pyridin-2-one in the ratio 3 : 2.

Key words: carbamoyl group, pyridin-2-one, oxazolidin-2-one, alkylation, unexpected cyclization.

Oxazolidin-2-ones are used in organic synthesis to obtain compounds for various purposes, including chiral inducers.[1] However, they are of limited application in the synthesis of various oxazolidin-2-one derivatives because known methods involve many steps, hard labor, or expensive reagents.[2—6]

Here we propose a new method for introduction of the oxazolidine ring through an *N*-ethylene spacer into another heterocycle. According to ^{1}H NMR data, a reaction of pyridin-2-one with bis(2-chloroethyl)amine hydrochloride in DMF in the presence of K_2CO_3 yielded two types of compounds for which the ratio of the total integral intensities of the signals for the aromatic protons and the methylene groups was 1 : 2. Either compound contains four magnetically nonequivalent methylene groups (Scheme 1).

Scheme 1



Based on IR, ^{1}H and ^{13}C NMR, and mass spectra, we identified the reaction products as *N*- (**1**) and *O*-oxazolidinylethylated pyridin-2-ones (**2**) in the ratio 3 : 2.

The structure of compound **2** was confirmed by X-ray diffraction analysis (Fig. 1).

Thus, bis(2-chloroethyl)amine acts in this reaction not only as an alkylating reagent but also as a source of a three-atom fragment for a newly constructed oxazolidinone ring. The large difference in the R_f values ($CHCl_3$: EtAc : MeOH, 10 : 2 : 1) allowed easy separation of the mixture of the products. The total yield of the products in a 30-h reaction approaches a quantitative one.

The new way of constructing the oxazolidinone ring we discovered is simpler than known ways to oxazolin-2-ones and uses accessible reagents. Another substantial advantage of this approach is the possibility of simultaneous (*via* a one-pot synthesis) alkylation and introduction of

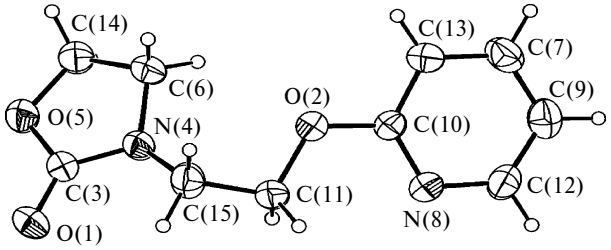


Fig. 1. ORTEP diagram of structure **2** in the crystal. The thermal displacement ellipsoids of the non-hydrogen atoms are shown at 30% probability; the hydrogen atoms are drawn as spheres with an arbitrary radius.

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an oxazolidine ring into heterocyclic systems containing an endocyclic carbamoyl function.

The general character of this reaction was verified for compounds containing an endocyclic carbamoyl group. It was demonstrated that quinoxalin-2-ones and their various fused derivatives successfully enter into this reaction, giving *N*- and *O*-oxazolidinylethylation products. These data will be published elsewhere.

Experimental

Melting points were determined on a Boetius hot stage. IR spectra were recorded on a Bruker Vector-22 FTIR spectrometer (Nujol or thin film) in the 400—3600 cm^{-1} range. Mass spectra (EI) were recorded on a ThermoQuest/Finnigan TRACE MS quadrupole mass spectrometer (water-cooled direct inlet probe). ^1H NMR spectra were recorded on a Bruker AVANCE-600 Fourier spectrometer (600.13 MHz) at 25 °C. Chemical shifts are given on the δ scale. The residual signal for $CDCl_3$ (δ_H 7.26) was used as the internal standard.

Condensation of pyridin-2-one with bis(2-chloroethyl)amine hydrochloride in the presence of K_2CO_3 in DMF. Dry K_2CO_3 (11.4 g, 0.08 mol) was added to a solution of pyridin-2-one (1.0 g, 10.5 mmol) in DMF (100 mL). The suspension was stirred for 5—10 min and bis(2-chloroethyl)amine hydrochloride (1.88 g, 10.5 mmol) was added. The reaction mixture was heated to 60 °C. The course of the reaction was monitored by TLC ($CHCl_3$: EtOAc = 3 : 1, Silufol (Kavalier, Chechoslovakia)). The total reaction time was 30 h. The precipitate was filtered off, the solvent was removed *in vacuo*, and the residue was treated with aqueous 20% HCl to pH ≈ 6—7. The product was extracted with chloroform (3×25 mL) and the organic layer was dried over $MgSO_4$ and concentrated. The residue was chromatographed on L 100/160 silica gel (Chemapol) with $CHCl_3$—EtOAc (3 : 1) as an eluent.

1-[2-(2-Oxooxazolidin-3-yl)ethyl]pyridin-2-one (1). The yield was 1.2 g (54.8%), R_f 0.10 ($CHCl_3$: EtOAc : MeOH = 10 : 2 : 1), m.p. 56—57 °C. Found (%): C, 54.61; H, 5.73; N, 13.39. $C_{10}H_{12}N_2O_3$. Calculated (%): C, 54.69; H, 5.81; N, 13.45. IR (Nujol), ν/cm^{-1}: 1730, 1667, 1592, 1540, 1465, 1448, 1427, 1349, 1283, 1269, 1193, 1166, 1148, 1082, 1041, 1017, 974, 762, 529, 477, 439. ^1H NMR (DMSO-d_6), δ: 3.52 (t, 2 H, CH_2N, ^3J = 7.8 Hz); 3.63 (t, 2 H, CH_2N^b, ^3J = 6.0 Hz); 4.17 (t, 2 H, CH_2N^a, ^3J = 6.0 Hz); 4.26 (t, 2 H, CH_2O, ^3J = 7.8 Hz); 6.19 (dd, 1 H, H(5), $^3J_{5,6} = {}^3J_{4,5}$ = 6.5 Hz); 6.56 (d, 1 H, H(3), $^3J_{3,4}$ = 8.9 Hz); 7.30 (dd, 1 H, H(6), $^3J_{6,5}$ = 6.3 Hz, $^4J_{6,4}$ < 0.5 Hz); 8.14 (br.ddd, 1 H, H(4), $^3J_{4,5} = {}^3J_{4,3}$ = 7.6 Hz, $^4J_{4,6}$ < 0.5 Hz). MS, *m/z* (*I* (%)): 208 (2), 122 (44), 121 (16), 120 (67), 114 (49), 113 (69), 109 (13), 108 (65), 100 (66), 97 (25), 96 (97), 95 (90), 93 (15), 80 (37), 79 (42), 78 (76), 70 (67), 69 (100), 68 (62), 67 (66), 66 (10).

2-[2-(2-Oxooxazolidin-3-yl)ethoxy]pyridine (2). The yield was 0.78 g (35.6%), R_f 0.45 ($CHCl_3$: EtOAc : MeOH = 10 : 2 : 1), m.p. 98—99 °C. Found (%): C, 54.55; H, 5.75; N, 13.42. $C_{10}H_{12}N_2O_3$. Calculated (%): C, 54.69; H, 5.81; N, 13.45. IR (thin film), ν/cm^{-1}: 3479, 2989, 2960, 2917, 1739, 1661, 1597, 1571, 1481, 1435, 1372, 1313, 1271, 1208, 1160, 1095, 1043, 988, 976, 912, 784, 764, 696, 662, 626, 530, 436. ^1H NMR (DMSO-d_6), δ: 3.67 (t, 2 H, CH_2N^b, ^3J = 5.2 Hz); 3.72 (t, 2 H, CH_2N, ^3J = 7.8 Hz); 4.31 (t, 2 H, CH_2O, ^3J = 7.9 Hz); 4.50 (t, 2 H, CH_2O^a, ^3J = 5.2 Hz); 6.74 (dd, 1 H, H(3), $^3J_{3,4}$ = 8.4 Hz, $^4J_{3,5}$ < 0.3 Hz); 6.89 (ddd, 1 H, H(5), $^3J_{5,4}$ = 7.7 Hz, $^3J_{5,6}$ = 5.0 Hz, $^4J_{5,3}$ < 0.3 Hz); 7.58 (ddd, 1 H, H(4), $^3J_{4,3}$ = 8.4 Hz, $^3J_{4,5}$ = 7.7 Hz, $^4J_{4,6}$ = 1.3 Hz); 8.14 (dd, 1 H, H(6), $^3J_{6,5}$ = 5.0 Hz, $^4J_{6,4}$ = 1.3 Hz). MS, *m/z* (*I* (%)): 208 (3), 122 (5), 120 (16), 109 (3), 108 (5), 100 (9), 96 (62), 95 (19), 93 (6), 81 (9), 80 (43), 78 (27), 69 (73), 68 (34), 67 (19), 66 (6), 65 (5), 61 (6), 57 (4), 56 (95), 55 (15), 54 (100), 53 (54), 52 (16), 51 (21), 50 (7), 42 (40), 41 (34), 40 (14), 39 (40).

X-ray diffraction analysis of compound 2 was carried out on a Nonius B.V. CAD-4 automatic X-ray diffractometer. The crystals of compound **2**, $C_{10}H_{12}N_2O_3$, are monoclinic. At 20 °C, a = 12.297(6) Å, b = 7.218(5) Å, c = 12.686(6) Å, β = 115.45(5)°, V = 1017(1) Å^3, d_{calc} = 1.36 g cm^{-3}, Z = 4, space group $P2_1/c$. The unit cell parameters and the intensities of 2116 reflections (1381 reflections with $I \geq 2\sigma$) were measured at 20 °C (graphite monochromator, λ-Cu-Kα, ω scan mode, $\theta \leq 74.59°$). The intensities of three reference reflections did not drop during the experiment; no absorption correction was applied (μCu 8.52 cm^{-1}). The structure was solved by the direct method with the SIR program[7] and refined first in the isotropic and then anisotropic approximations with the SHELXL program.[8] The coordinates of hydrogen atoms were calculated from stereochemical criteria and refined in the rider model. Final residuals were R = 0.0619 and R_w = 0.1675 for 1381 reflections with $F^2 \geq 4\sigma$. All calculations were performed with the MolEN[9] and WinGX programs.[10] The molecule was depicted with the PLATON program.[11] X-ray diffraction data for compound **2** have been deposited with the Cambridge Crystallographic Data Center (CCDC # 626759).

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