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Synthesis of isoxazolo[4,5-*e*][1,4]diazepin-5-ones from 5-acyl-4-(haloacetylamino)isoxazoles

Victor P. Kislyi,[*] Evgenia B. Danilova and Victor V. Semenov

Melting points were measured on a Boetius PHMK05 apparatus at a heating rate of 4°C/min. NMR spectra were determined (unless otherwise states) in DMSO-d_6 at 500.13 MHz with a Bruker DRX-500 and at 300.13 MHz with a Bruker AC-300 instruments. Chemical shifts are recorded in parts per million on the δ scale referenced to the TMS peak as an internal standard. High resolution mass spectra (HRMS) are determined in the positive ion mode with a Bruker mircOTOF II instrument. Ultraviolet (UV) spectra were recorded with a SPECORD UV VIS instrument. Flash chromatography was performed with Merck silica gel (40–200 mesh) accordingly to the procedure[1].

General procedure for acylation with chlorocetylchloride (bromoacetylbromide) in the preparation of **2a–e**.

Dry toluene (2 ml) was added to a mixture of 1.0 mM of aminoisoxazole **1a–d** and 3 equiv. of $ClCH_2COCl$ ($BrCH_2COBr$), and the mixture was stirred at 50–80 °C for 0.5–1 h. Volatiles were removed under vacuum and the residue was washed with water, neutralized, and recrystallized from alcohol.

General procedure for the preparation of iodoacetylisoxazoles **5a–d.**

Anhydrous MeCN (2–4 ml) was added to a mixture of 1 mM of chloroacetylisoxazoles **2a–e** and 1.05–1.1 equiv. of anhydrous NaI, and the mixture was stirred at 60–80°C for 15–30 min. The reaction mixture was cooled, NaCl was filtered off, and the solvent was evaporated *in vacuo*. Yields of **5a–d** were apparent to be quantitative. The resulting solid was used in next stage without purification. For the preparation of the analytical sample, the product was dissolved in EtOAc, inorganic salts were filtered off, and the solvent was removed *in vacuo*. Crystallization from acetonitrile (or ethanol) afforded an analytical sample.

5-Benzoyl-4-(chloroacetylamino)isoxazole-3-carboxamide **2a**. Yield 87%, mp 186–188°C, ^{1}H NMR, *δ*, 4.22 (s, 2H, CH_2Cl), 7.56 (t, *J* 7.2 Hz, 2H, Ar), 7.70 (t, , *J* 7.2 Hz, 1H, Ar), 7.82 (d, *J*

7.2 Hz, 2H, Ar), 8.05 (br.s, 1H, NH_2CO), 8.35 (br.s, 1H, NH_2CO), 10.35 (s, 1H, NHCO). UV (λ, nm(ε)): 295(8600), 262(14000). Found (%): C 50.82, H 3.08, N 13.56. Calc. for $C_{13}H_{10}ClN_3O_4$ (%): C 50.75, H 3.28, N 13.66

*5-Benzoyl-*N*-benzyl-4-(chloroacetylamino)isoxazole-3-carboxamide* **2b**. Yield 89%, mp 155−157°C, ^{1}H NMR, δ, 4.28 (s, 2H, CH_2Cl), 4.50 (d, *J* 7.2 Hz, 2H, $\underline{CH_2}Ph$), 7.28 (t, *J* 7.2 Hz, 2H, Ar), 7.30-7.40 (m, 3H, Ar), 7.60 (t, *J* 7.2 Hz, 2H, Ar), 7.72 (t, *J* 7.2 Hz, 1H, Ar), 7.87 (d, *J* 7.2 Hz, 2H, Ar), 9.70 (t, *J* 7.2 Hz, 1H, BzNHCO), 10.37 (s, 1H, NHCO). UV (λ, nm(ε)): 298(7900), 263(13100). Found (%): C 60.11, H 3.95, N 10.40. Calc. for $C_{20}H_{16}ClN_3O_4$ (%): C 60.38, H 4.05, N 10.56

5-Benzoyl-4-(chloroacetylamino)-3-phenylisoxazole **2c**. Yield 78%, mp 135−137°C, ^{1}H NMR, δ, 4.15 (s, 2H, CH_2Cl), 7.55-7.65 (m, 5H, Ar), 7.72-7.80 (m, 3H, Ar), 7.92 (d, *J* 7.6 Hz, 2H, Ar), 10.40 (s, 1H, NHCO). UV (λ, nm(ε)): 269(16500), 231(20800). Found (%): C 62.86, H 3.83, N 7.88. Calc. for $C_{18}H_{13}ClN_2O_3$ (%): C 63.44, H 3.85, N 8.22

5-Acetyl-4-(chloroacetylamino)-3-phenylisoxazole **2d**. Yield 82%, mp 111−114°C, ^{1}H NMR, δ, 2.60 (s, 3H, CH_3), 4.32 (s, 2H, CH_2Cl), 7.55 (m, 3H, Ar), 7.70 (m, 2H, Ar), 10.35 (s, 1H, NHCO). UV (λ, nm(ε)): 266(6100), 230(20600). Found (%): C 55.84, H 4.04, N 9.80. Calc. for $C_{13}H_{11}ClN_2O_3$ (%): C 56.03, H 3.98, N 10.05.

*5-Benzoyl-*N*-benzyl-4-(bromoacetylamino)isoxazole-3-carboxamide* **2e**. Yield 88%, mp 154−156°C, ^{1}H NMR, δ, as mixture 24:6 of (E/Z)-isomers of the bromoacetamide fragment**[2,3]**: 3.85 s (min)+ 4.07 s(maj) (2H, CH_2Br), 4.51 (d, *J* 6.13, 2H, CH2N), 7.25-7.85 (m, 10H, Ph+Ph), 9.65 t(*J* 6.11 Hz, maj) + 9.75t(*J* 6.11 Hz, min)(1H, BnNH), 10.15 s(min)+10.30 s(maj)(1H, $N\underline{H}COCH_2$). HRMS: 444.0359. Calc. for $C_{20}H_{16}BrN_3O_4{+}H^+$ 444.0377; HRMS: 466.0177. Calc. for $C_{20}H_{16}BrN_3O_4{+}Na^+$ 466.0197.

*5-Chloromethyl-7-methyl-3-phenylisoxazolo[4,5-*d*]pyrimidine* **4d**. To 1mM of *5-acetyl-4-(chloroacetylamino)-3-phenylisoxazole* **2d** was added 6 ml of 5% methanolic ammonia, and the mixture was stirred for 3 h. After 2 days, solvent was evaporated under vacuum, and the residue was recrystallized from ethanol. Yield 71%, mp 122−124°C, ^{1}H NMR, δ, 2.87 (s, 3H, CH_3), 5.03(s, 2H, CH_2Cl), 7.69 (m, 2H, Ph), 8.41 (m, 2H, Ph). UV (λ, nm(ε)): 296(11400), 224(19400). Found (%): C 59.82, H 3.68, N 15.85. Calc. for $C_{13}H_{10}ClN_3O$ (%): C 60.13, H 3.88, N 16.18.

5-Benzoyl-4-(iodoacetylamino)isoxazole-3-carboxamide **5a**. Yield 92%, mp 210−212°C, ^{1}H NMR, *δ*, 3.82 (s, 2H, CH_2I), 7.56 (t, *J* 7.2 Hz, 2H, Ar), 7.70 (t, *J* 7.2 Hz, 1H, Ar), 7.82 (d, *J* 7.2 Hz, 2H, Ar), 8.00 (br.s, 1H, NH_2CO), 8.29 (br.s, 1H, NH_2CO), 10.30 (s, 1H, NHCO). HRMS: 399.9799, Calcd. for $C_{13}H_{10}IN_3O_4$+H$^+$ 399.9789.

N-*Benzyl-5-benzoyl-4-(iodoacetylamino)isoxazole-3-carboxamide* **5b**. Yield 95%, mp 189−191°C, ^{1}H NMR, *δ*, 3.85 (s, 2H, CH_2I), 4.50 (d, *J* 6.15, 2H, $\underline{CH_2}NH$), 7.35-7.45 (m, 5H, Ph), 7.60 (t, 2H,Ph), 7.72 (t, 1H, Ph), 7.85 (d, 2H, Ph), 9.62 (t, *J* 6.25, 1H, $\underline{NH}CH_2$), 10.3 (s, 1H, NHCO). HRMS: 490.0238 Calcd. for $C_{20}H_{16}IN_3O_4$+H$^+$ 490.0258; HRMS: 512.0064 Calcd. for $C_{20}H_{16}IN_3O_4$+Na$^+$ 512.0078.

5-Benzoyl-4-(iodooacetylamino)-3-phenylisoxazole **5c**. Yield 88%, mp 170−172°C, ^{1}H NMR, *δ*, 3.7 (s, 2H, CH_2I), 7.55-7.65 (m, 5H, Ar), 7,75-7.8 (m, 3H, Ar), 7.92 (d, *J* 8.45 Hz, 2H, Ar). HRMS: 433.0019, Calcd. for $C_{18}H_{13}IN_2O_3$+H$^+$ 433.0044; HRMS: 454.9840, Calcd. for $C_{18}H_{13}IN_2O_3$+Na$^+$ 454.9863.

5-Acetyl-4-(iodoacetylamino)-3-phenylisoxazole **5d**. Yield 94%, mp 159−161°C, ^{1}H NMR, *δ*, 3.85 (s, 2H, CH_2I), 7.55 (m, 3H, Ph), 7.72 (m, 2H, Ph), 10.4 (s, 1H, NHCO). HRMS: 370.9890, Calcd. for $C_{13}H_{11}IN_2O_3$+H$^+$ 370.9890.

*5-Oxo-8-phenyl-5,6-dihydroisoxazolo[4,5-*e*][1,4]diazepine-3-carboxamide* **3a**. Yield 56%, mp 221−222°C, ^{1}H NMR, *δ*, 4.50 (s, 2H, CH_2CO), 7.52 (t, 2H, Ph), 7.60 (t, 1H, Ph) 7.75 (d, *J* 7.60 Hz, 2H, Ph), 8.15 s + 8.45 s (2H, NH_2CO), 10.2 (s, 1H, NHCO); UV (*λ*, nm(*ε*)): 321(5800), 275(12700). HRMS: 271.0825 Calcd. for $C_{13}H_{10}N_4O_3$+H$^+$ 271.0826; HRMS: 293.0647 Calcd. for $C_{13}H_{10}N_4O_3$+Na$^+$ 293.0645.

N-*Benzyl 5-oxo-8-phenyl-5,6-dihydroisoxazolo[4,5-*e*][1,4]diazepine-3-carboxamide* **3b**. Yield 62%, mp 210−212°C, ^{1}H NMR, *δ*, 4.50 (m, 4H, NCH_2CO+$NH\underline{CH_2}$), 7.37-7.45 (m, 5H, $\underline{Ph}CH_2$), 7.52-7.60 (m, 3H, Ph), 7.78 (d, *J* 7.62, 2H, Ph), 9.62 (t, *J* 6.06, 1H, Bn$\underline{NH}$), 10.35 (s, 1H, NHCO). UV (*λ*, nm(*ε*)): 320(5400), 274(11600). Found (%): C 66.42, H 4.36, N 15.47. Calc. for $C_{20}H_{16}N_4O_3$ (%): C 66.66, H 4.48, N 15.55; HRMS: 361.1297 Calcd. for $C_{20}H_{16}N_4O_3$+H$^+$ 361.1295.

*5-Oxo-3,8-diphenyl-5,6-dihydroisoxazolo[4,5-*e*][1,4]diazepine* **3c**, *solvate with ½ MeOH and H_2O*. Yield 75%, mp 110−112°C, ^{1}H NMR, *δ*, 4.55 (s, 2H, CH_2CO), 7.52-7.62 (m, 6H, Ph+Ph), 7.80-7.88 (m, 4H, Ph+Ph), 10.5 (s, 1H, NHCO); 1/2MeOH: 3.18 (d, *J* 5.23 Hz, 1.5H), 4.1 (q, *J* 5.24 Hz, 0.5H). UV (λ, nm(ε)): 316(5040), 272(12300), 222(29000). HRMS: 304.1088, Calcd. for $C_{18}H_{13}N_3O_2$+H^+ 304.1081. Found (%): C 67.92, H 4.76, N 12.55. Calc. for $[(C_{18}H_{13}N_3O_2)_2$*MeOH*$H_2O]$ (%): C 67.67, H 4.91, N 12.81.

*8-Methyl-5-oxo-3-phenyl-5,6-dihydroisoxazolo[4,5-*e*][1,4]diazepine* **3d**. Yield 70%, mp 175−177°C, ^{1}H NMR, δ, 2.43 (s, 3H, CH_3) 4.30 (s, 2H, CH2CO), 7.58 (m, 3H,Ph), 7.80 (m, 2H, Ph), 10.7 (s, 1H, NHCO).). UV (λ, nm(ε)): 318(510), 274(6900), 224(29200). HRMS: 242.0927, Calcd. for $C_{13}H_{11}N_3O_2$+H^+ 242.0924.

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