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SHORT COMMUNICATIONS

Reaction of Acylpyruvic Acids and Their Esters with *N*-(2-Aminophenyl)acetamide

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Abstract—Acylpyruvic acids and their esters regioselectively reacted with *N*-(2-aminophenyl)acetamide to give acyclic enamines, substituted (*Z*)-2-[(2-acetamidophenyl)amino]-4-oxobut-2-enoates, whose structure was confirmed by X-ray analysis. These compounds were formed as a result of condensation involving the primary amino group of *N*-(2-aminophenyl)acetamide at the most electrophilic C^2=O carbonyl group of acylpyruvic acid or its ester. The obtained enamines underwent thermal heterocyclization to (*Z*)-3-(2-oxoethylidene)-3,4-dihydroquinoxalin-2(1*H*)-ones having no substituent on the N^1 atom rather than expected (*Z*)-1-acetyl-3-(2-oxoethylidene)-3,4-dihydroquinoxalin-2(1*H*)-ones. The heterocyclization involves intramolecular exchange between the amide and carboxylic acid (ester) fragments. The described transformations occur under mild conditions, require no catalyst or other additives, and therefore conform to the "green chemistry" principles. The products may be interesting from the viewpoints of medicinal chemistry, pharmacology, and fine organic synthesis.

Keywords: acylpyruvic acids, enamines, X-ray analysis, quinoxaline, cyclization.

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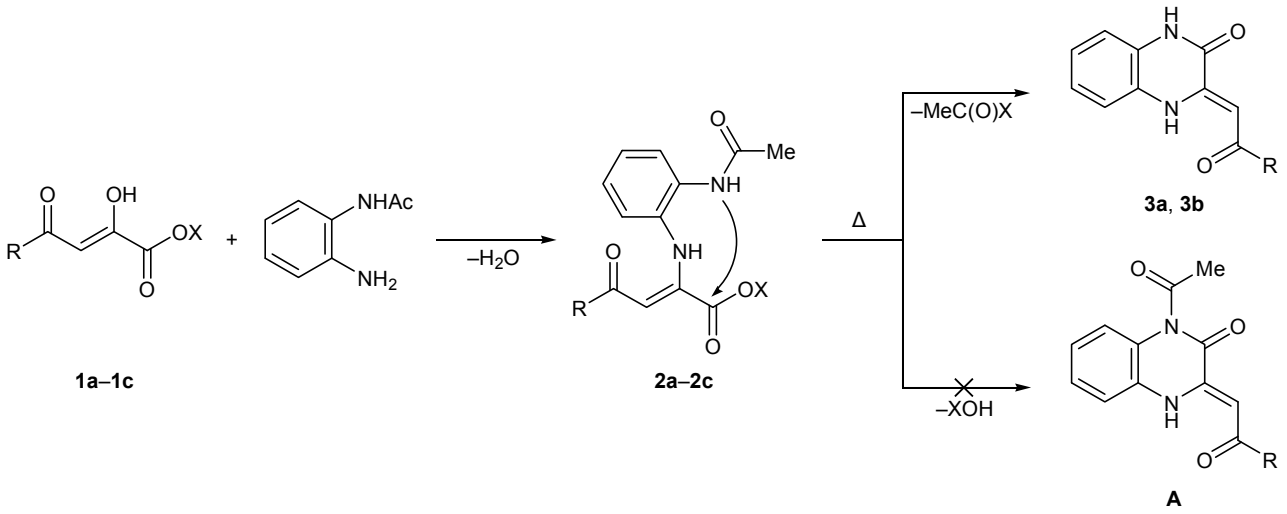
Reactions of acylpyruvic acids and their esters with *o*-phenylenediamine and its derivatives were studied with the goal of obtaining substituted (*Z*)-3-(2-oxoethylidene)-3,4-dihydroquinoxalin-2(1*H*)-ones which exhibit a pronounced biological activity, in particular antioxidant [1], antimicrobial [2, 3], etc. In addition, these compounds are important intermediate products for the synthesis of various heterocyc systems [4–6]. The reactions with N-unsubstituted *o*-phenylenediamine [1–4, 7–10] and *N*-phenyl-*o*-phenylenediamine [3, 11–13] have been studied in most detail. There are no published data on reactions of acylpyruvic acids or their esters with *N*-(2-aminophenyl)acetamide (*N*-acetyl-*o*-phenylenediamine).

Acylpyruvic acid derivatives **1a**–**1c** reacted with an equimolar amount of *N*-(2-aminophenyl)acetamide, in boiling ethanol for 1–1.5 h (HPLC monitoring) to give (*Z*)-2-(2-acetamidoanilino)-4-oxobut-2-enoates **2a**–**2c** whose structure was confirmed by X-ray analysis of compound **2b** (Fig. 1). Compound **2b** crystallized in a centrosymmetric space group belonging to the orthorhombic crystal system. The bond lengths and bond angles in molecule **2b** did not differ appreciably from the corresponding reference values. The N^1H^1 hydrogen atom is involved in intramolecular hydrogen bonds N^1–$H^1\cdots O^1$ and N^1–$H^1\cdots O^4$.

Enamines **2a**–**2c** underwent thermal (140–170°C, 1–3 h; HPL monitoring) heterocyclization to 1-unsubstituted (*Z*)-3-(2-oxoethylidene)-3,4-dihydroquinoxalin-2(1*H*)-ones **3a** and **3b** rather than to expected (*Z*)-1-acetyl-3-(2-oxoethylidene)-3,4-dihydroquinoxalin-2(1*H*)-ones **A**. Presumably, enamines **2a**–**2c** are formed via nucleophilic addition of the primary amino group of *N*-(2-aminophenyl)acetamide to the C^2=O carbonyl carbon atom of **1a**–**1c**, which is typical of reactions of acylpyruvic acids and their esters with aromatic amines [14]. Thermally initiated intramolecular exchange between the amide and carboxylic acid (ester) fragments of **2a**–**2c** yields quinoxalinones **3a** and **3b**.

(2*Z*)-2-(2-Acetamidoanilino)-4-oxo-4-phenylbut-2-enoic acid (2a). A mixture of 1.00 g (5.2 mmol) of compound **1a** and 0.78 g (5.2 mmol) of *N*-(2-aminophenyl)acetamide in 10 mL of ethanol was refluxed for 1 h. The mixture was cooled and evaporated by half, and the yellow solid was filtered off. Yield 1.20 g



1, **2**, R = Ph, X = H (**a**), R = Ph, X = Me (**b**), R = EtO, X = Et (**c**); **3**, R = Ph (**a**), EtO (**b**).

(71%), mp 130–132°C (decomp., from EtOH). IR spectrum, ν, cm^{-1}: 3272 (NH, OH), 1715 (C=O). ^1H NMR spectrum, δ, ppm: 2.11 s (3H, Me), 6.38 s (1H, 3-H), 7.07 m (1H, H_{arom}), 7.17 m (2H, H_{arom}), 7.32 m (1H, H_{arom}), 7.49–7.60 m (3H, H_{arom}), 7.96 m (2H, H_{arom}), 9.82 s (1H, NH), 11.61 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 22.8 (Me), 95.3 (C^3); 122.6, 125.1, 125.9, 127.1, 128.2, 128.5, 128.9, 130.3, 131.9, 138.5 (C_{arom}); 151.9 (C^2), 165.2 (COOH), 168.8 (CONH), 189.3 (**C**OPh). Mass spectrum: *m*/*z* 325.15 $[M + H]^+$. Found, %: C 66.59; H 4.87; N 8.44. $C_{18}H_{16}N_2O_4$. Calculated, %: C 66.66; H 4.97; N 8.64. $[M + H]^+$ 325.12.

Compounds **2b** and **2c** were synthesized in a similar way.

Methyl (2*Z*)-2-(2-acetamidoanilino)-4-oxo-4-phenylbut-2-enoate (2b). Yield 1.28 g (73%), mp 167–168°C (decomp., from EtOH). IR spectrum, ν, cm^{-1}: 3172 br (NH), 1731 (C^1=O), 1663 (C^4=O, $C^{1'}$=O). ^1H NMR spectrum, δ, ppm: 2.10 s (3H, **Me**CONH), 3.66 s (3H, OMe), 6.47 s (1H, 3-H), 6.95 m (1H, H_{arom}), 7.19 m (2H, H_{arom}), 7.32 m (1H, H_{arom}), 7.52 m (2H, H_{arom}), 7.60 m (1H, H_{arom}), 7.98 m (2H, H_{arom}), 9.85 s (1H, NH), 11.51 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 22.8 (**Me**CONH), 52.7 (OMe), 96.3 (C^3); 122.6, 125.4, 125.8, 126.0, 127.1, 128.3, 128.5, 130.6, 132.1, 138.2 (C_{arom}); 149.3 (C^2), 164.2 (**C**OOMe), 168.8 (**C**ONH), 189.4 (COPh). Mass spectrum: *m*/*z* 339.18 $[M + H]^+$. Found, %: C 67.53; H 5.33; N 8.15. $C_{19}H_{18}N_2O_4$. Calculated, %: C 67.45; H 5.36; N 8.28. $[M + H]^+$ 339.13.

Diethyl (2*Z*)-2-(2-acetamidoanilino)but-2-enedioate (2c). Yield 1.15 g (69%), mp 99–101°C (decomp., from EtOH). IR spectrum, ν, cm^{-1}: 3182 br (NH), 1739 (C^1=O, C^4=O), 1664 ($C^{1'}$=O). ^1H NMR spectrum, δ, ppm: 0.96 t (3H, CH_2**Me**, *J* = 7.1 Hz), 1.23 t (3H, CH_2**Me**, *J* = 7.1 Hz), 2.08 s (3H, **Me**CONH), 4.02 q (2H, OCH_2, *J* = 7.1 Hz), 4.14 q (2H, OCH_2, *J* = 7.1 Hz), 5.22 s (1H, 3-H), 6.81 m (1H, H_{arom}), 7.13 m (2H, H_{arom}), 7.26 m (1H, H_{arom}), 9.40 s (1H, NH), 9.88 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.2 (CH_2**Me**), 14.1 (CH_2**Me**), 22.8 (**Me**CONH), 59.3 (OCH_2), 61.5 (OCH_2), 93.4 (C^3); 122.6, 124.8, 125.1, 125.7, 130.6, 135.1 (C_{arom}); 148.0 (C^2), 163.8 (C^4), 167.4 (C^1), 168.7 (Me**C**ONH). Mass spectrum: *m*/*z* 321.14 $[M + H]^+$. Found, %: C 60.03; H 6.37; N 8.65. $C_{16}H_{20}N_2O_5$. Calculated, %: C 59.99; H 6.29; N 8.74. $[M + H]^+$ 321.15.

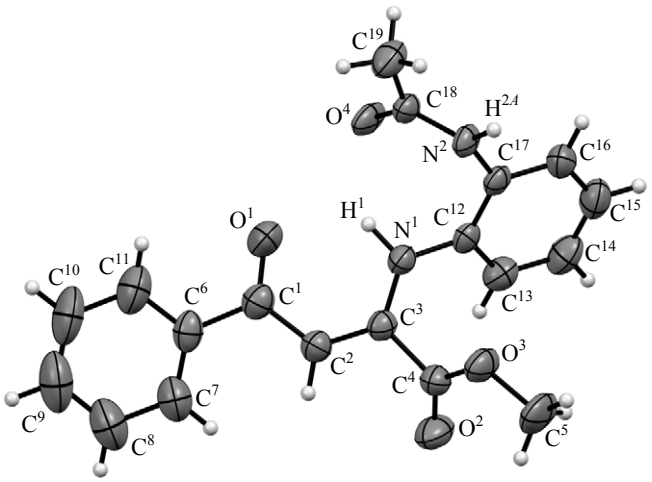


Fig. 1. Structure of the molecule of methyl (2*Z*)-2-(2-acetamidoanilino)-4-oxo-4-phenylbut-2-enoate (**2b**) according to the X-ray diffraction data. Non-hydrogen atoms are shown as thermal vibration ellipsoids with a probability of 50%.

(3*Z*)-3-(2-Oxo-2-phenylethylidene)-3,4-dihydroqunoxalin-2(1*H*)-one (3a). *a*. Compound **2a**, 0.50 g (1.5 mmol), was heated for 1 h at 140°C. The product was recrystallized from 1,4-dioxane. Yield 0.30 g (68%), mp 266–267°C (decomp., from 1,4-dioxane).

b. Compound **2b**, 0.50 g (1.5 mmol), was heated for 2 h at 170°C. The product was recrystallized from 1,4-dioxane. Yield 0.30 g (71%), mp 266–267°C (decomp., from 1,4-dioxane) [4].

Ethyl (2*Z*)-2-(3-oxo-3,4-dihydroquinoxalin-2(1*H*)-ylidene)acetate (3b). Compound **2c**, 0.50 g (1.6 mmol), was heated for 3 h at 140°C. The product was recrystallized from 1,4-dioxane. Yield 0.24 g (71%), mp 208–210°C (decomp., from 1,4-dioxane); published data [3]: mp 206–208°C (from EtOH).

X-Ray analysis of compound 2b. The X-ray diffraction data for compound **2b** were obtained on an Xcalibur Ruby single-crystal diffractometer with a CCD detector according to standard procedure [Mo K_α radiation, 295(2) K, ω-scanning with a step of 1°]. A correction for absorption was applied empirically by SCALE3 ABSPACK algorithm [15]. Orthorhombic crystal system, space group *Pbca*; $C_{19}H_{18}N_2O_4$, M 338.35; unit cell parameters: a = 13.736(3), b = 9.3940(17), c = 27.201(8) Å; V = 3509.9(14) Å^3; Z = 8, d_{calc} = 1.281 g/cm^3; μ = 0.091 mm^{-1}. The structure was solved by the direct method (SHELXS) [16] and was refined against F^2 by the full-matrix least-squares method in anisotropic approximation for all non-hydrogen atoms (SHELXL) [17] using OLEX2 graphical interface [18]. Hydrogen atoms of the NH groups were refined independently in isotropic approximation. The positions of the other hydrogens were refined according to the riding model. Final divergence factors: R_1 = 0.0562, wR_2 = 0.1306 [for 2384 reflections with $I > 2\sigma(I)$]; R_1 = 0.1071, wR_2 = 0.1537 (for 4195 independent reflections); goodness of fit S = 1.024. The X-ray diffraction data for compound **2b** were deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 1866129) and are available at *www.ccdc.cam.ac.uk/data_request/cif*.

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD 400 spectrometer at 400 and 100 MHz, respectively, using DMSO-d_6 as solvent and hexamethyldisiloxane as internal standard. The IR spectra were recorded on a Perkin Elmer Spectrum Two spectrometer from samples dispersed in mineral oil. The elemental compositions were determined using a Vario MICRO cube analyzer. The melting points were measured in open capillaries with a Mettler Toledo MP90 melting point apparatus. The reaction conditions were optimized by UHPLC (Waters Acquity UPLCI-Class; Acquity UPLC BEH C18 column, grain size 1.7 μm; eluent acetonitrile–water, flow rate 0.6 mL/min; Acquity UPLC PDA el diode array detector, λ 230–780 nm; XevoTQD mass-selective detector, positive electrospray ionization, ion source temperature 150°C, capillary voltage 3500–4000 V, cone voltage 20–70 V, vaporizer temperature 150–300°C) and HPLC (Hitachi Chromaster; Nucleodur C18 Gravity column, 5 μm; eluent acetonitrile–water, flow rate 1.5 mL/min; Hitachi Chromaster 5430 diode array detector, λ 210–750 nm). The purity of the isolated compounds was checked by TLC on Silicagel 60 F_{254} plates (Merck); eluent toluene, ethyl acetate, or toluene–ethyl acetate (5:1); spots were visualized by treatment with iodine vapor or under UV light (λ 254 nm).

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CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

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