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Reactions of quinoxalin-2-one with β-diketones: a new approach to 6a,7-dihydro-5*H*-pyrido[1,2-*a*]quinoxaline-6,8-diones

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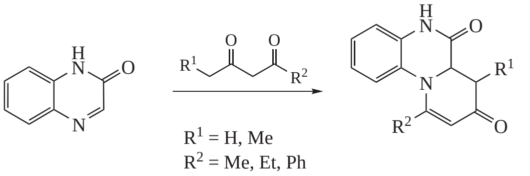
Quinoxalin-2-one on heating with acetylacetone, benzoylacetone or heptane-3,5-dione in trifluoroacetic acid gives 6a,7-dihydro-5*H*-pyrido[1,2-*a*]quinoxaline-6,8-dione derivatives.



Quinoxaline derivatives can possess various types of biological activity,[1,2] *e.g.*, antimicrobial properties of quinoxidine and dioxidine are reported.[3] The synthesis and biological activity of quinoxaline derivatives are reviewed.[4] The reaction of quinoxalinium salts with acetylacetone and ethyl acetoacetate in the presence of amines gives 3a,4,9,9a-tetrahydro-*endo*-furo[2,3-*b*]quinoxalines.[5] Cyclization of 1,3-bis(silyl) enol ethers with quinoxaline affords 6-alkylidene-2,3-benzo-1,4-diaza-7-oxabicyclo[4.3.0]non-2-enes.[6] Hydrogen replacement reactions under mild conditions in the presence of an acid with various C-nucleophiles in the heterocyclic core of quinoxaline to give C–C bonding products were recently reported.[7]

At the same time, no information on reactions of quinoxalin-2-one with β-dicarbonyl compounds is available in the literature.

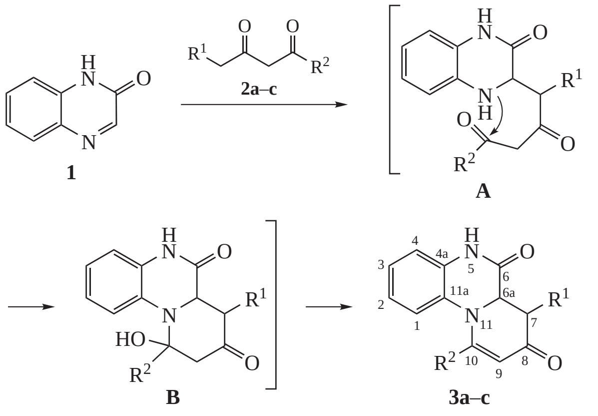
In a search for efficient methods for quinoxalin-2-one functionalization, we studied its reactions with β-diketones under acidic catalysis conditions.

Herein, we report that quinoxalin-2-one **1** reacts with acetylacetone **2a**, benzoylacetone **2b** and heptane-3,5-dione **2c** on heating in trifluoroacetic acid to give 6a,7-dihydropyrido[1,2-*a*]quinoxaline-6,8-dione derivatives **3a–c** (Scheme 1).[†]

The structures of products **3** were determined by ^{1}H and ^{13}C NMR spectroscopy, in paticular, by ^{1}H-^{13}C HSQC, HMBC and ^{1}H-^{15}N HMQC, HMBC 2D experiments for compounds **3a**,**c**.

The ^{1}H NMR spectrum of pyridoquinoxaline **3a** contains signals of four aromatic protons along with singlets of the NH proton at δ 10.74, H^{9} proton at δ 5.05, as well as signals of the ABX-system formed by two non-equivalent protons at C^{7} and a proton at nodal carbon atom C^{6a} [Figure 1(*a*)]. The suggested structure is also confirmed by heteronuclear correlations observed in the ^{1}H-^{13}C HMBC spectrum [Figure 1(*b*)].

Additional arguments in favor of the pyridoquinoxaline structure were obtained from ^{1}H-^{15}N correlation experiments: the HMQC spectrum contains a cross-peak between the NH proton and N^{5} nitrogen (δ_{N} 133.0), while the HMBC spectrum contains cross-peaks between the N^{11} nitrogen (δ_{N} 93.3) and the H^{1},



a R^1 = H, R^2 = Me
b R^1 = H, R^2 = Ph
c R^1 = Me, R^2 = Et

Scheme 1

[†] ^{1}H and ^{13}C spectra were recorded on Bruker Avance-500 and Avance-400 spectrometers relative to TMS internal standards (for ^{1}H) and relative to the solvent signal, δ_{C} 39.5 ppm (for ^{13}C). Mass spectra (EI, 70 eV) were obtained on a MicrOTOF-Q instrument (Bruker Daltonics) at 250 °C.

Reaction of quinoxalin-2-one with β-diketones **2a–c**. A mixture of quinoxalin-2-one **1** (0.5 mmol) and an appropriate diketone **2** (0.6 mmol) in 2 ml of trifluoroacetic acid was heated for 45–50 h at 110 °C in a sealed tube. The solvent was removed *in vacuo*. The solid residue was dissolved in 2–3 ml of ethanol. The ethanolic solution was treated with 1–2 ml of water. The precipitate of product **3** that formed was filtered and washed with 1.5–2 ml of chloroform.

*10-Methyl-6a,7-dihydro-5*H*-pyrido[1,2-*a*]quinoxaline-6,8-dione* **3a**: yield 60–65%, mp 230–231 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.81 (s, 3H, Me), 2.77 (dd, 1H, H^{7B}, J 16.9, 8.1 Hz), 2.89 (dt, 1H, H^{7A}, J 16.9, 1.3 Hz), 4.42 (dd, 1H, H^{6a}, J 8.1, 1.6 Hz), 5.05 (s, 1H, H^{9}), 7.03 (dd, 1H, H^{4}, J 7.9, 1.4 Hz), 7.08 (td, 1H, H^{2}, J 7.7, 1.4 Hz), 7.27 (td, 1H, H^{3}, J 7.7, 1.4 Hz), 7.47 (dd, H^{1}, J 7.9, 1.4 Hz), 10.74 (s, 1H, NH). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ: 21.11 (Me), 33.41 (C^{7}), 57.28 (C^{6a}), 103.15 (C^{9}), 116.53 (C^{4}), 122.10 (C^{2}), 125.79 (C^{1}), 127.47 (C^{3}), 130.41 (C^{11a}), 133.27 (C^{4a}), 159.57 (C^{10}), 168.34 (C^{6}), 188.45 (C^{8}). ^{15}N NMR (50.7 MHz, DMSO-d_6) δ: 93.3 (N^{11}), 133.0 (N^{5}). MS, m/z (%): 228 [M^{+}] (100), 199 (32), 185 (16), 171 (26), 159 (21), 157 (39), 145 (11), 133 (24), 118 (36). Found (%): C, 68.12; H, 5.40; N, 12.09. Calc. for $C_{13}H_{12}N_{2}O_{2}$ (%): C, 68.41; H, 5.30; N, 12.27.

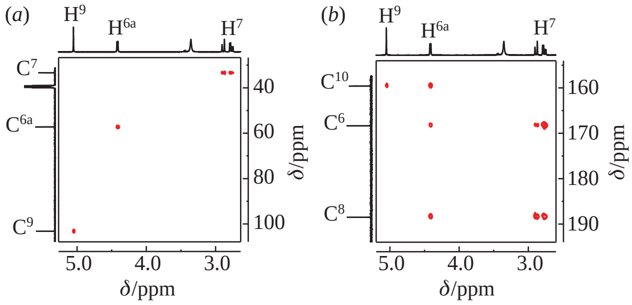


Figure 1 Fragments of the (*a*) ^{1}H-^{13}C HSQC and (*b*) ^{1}H-^{13}C HMBC spectra of compound **3a**.

H^9, and H^{7A} protons, as well as the protons of the methyl group at C^{10}.

The formation of derivatives of the 6a,7-dihydro-5*H*-pyrido[1,2-*a*]quinoxaline-6,8-dione tricyclic system can be represented as a result of sequential stages: (1) attack of the C=N bond in quinoxalin-2-one by the α-carbon atom of the terminal alkyl group of the β-diketone; (2) intramolecular addition–cyclization of intermediate **A** at the C=O group to transform into intermediate **B**; (3) dehydration of **B** to give the end product **3** (see Scheme 1).

A specific feature of the reactions discovered is annulation of the six-membered ring at the C=N bond of the quinoxalone ring upon cyclization with β-diketones. At the same time, the revealed cyclization of quinoxalones with β-diketones is an easy innovative method for synthesizing the 6a,7-dihydro-5*H*-pyrido[1,2-*a*]quinoxaline-6,8-dione derivatives.

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References

1 G. B. Barlin, in *The Chemistry of Heterocyclic Compounds*, eds. G. A. Weissberger and E. C. Taylor, Wiley-Interscience, Chichester, 1982, vol. 41.

2 G. W. N. Cheeseman and R. F. Cookson, in *The Chemistry of Heterocyclic Compounds*, eds. G. A. Weissberger and E. C. Taylor, Wiley-Interscience, New York, 1979, vol. 35.

3 M. D. Mashkovskii, *Lekarstvennye sredstva (Drugs)*, Novaya Volna, Moscow, 2012 (in Russian).

4 G. Sakata and K. Makino, *Heterocycles*, 1988, **27**, 2481.

5 O. N. Chupakhin, V. N. Charushin, N. A. Klyuev, A. I. Rezvukhin and V. A. Semion, *Chem. Heterocycl. Compd.*, 1981, **17**, 1046 (*Khim. Geterotsikl. Soedin.*, 1981, 1392).

6 A. Schmidt, J.-P. Gütlein and P. Langer, *Tetrahedron Lett.*, 2007, **48**, 2067.

7 Yu. A. Azev, M. I. Kodess, M. A. Ezhikova, A. M. Gibor, V. I. Baranov, O. S. Ermakova and V. A. Bakulev, *Chem. Pharm. J.*, 2013, **47**, 498 [*Khim.-Farm. Zh.*, 2013, **47** (9), 46].

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*10-Phenyl-6a,7-dihydro-5*H*-pyrido[1,2-*a*]quinoxaline-6,8-dione* **3b**: yield 70–75%, mp 180–181 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.67 (dd, 1H, H^{7B}, J 17.0, 5.6 Hz), 2.91 (dt, 1H, H^{7A}, J 17.0, 10.5 Hz), 4.68 (dd, 1H, H^{6a}, J 10.5, 5.6 Hz), 5.57 (s, 1H, H^9), 6.26 (dd, 1H, H^4, J 8.2, 1.1 Hz), 6.57 (ddd, 1H, H^2, J 8.0, 7.4, 1.3 Hz), 6.88 (td, 1H, H^3, J 7.6, 1.4 Hz), 6.95 (dd, H^1, J 8.0, 1.4 Hz), 7.34–7.42 (m, 5H, Ph), 10.83 (s, 1H, NH). MS, *m*/*z* (%): 290 [M$^+$] (100), 261 (27), 234 (16), 234 (26), 131 (14), 118 (25), 115 (19), 102 (20). Found (%): C, 74.23; H, 4.90; N, 9.35. Calc. for $C_{18}H_{14}N_2O_2$ (%): C, 74.47; H, 4.86; N, 9.65.

*10-Ethyl-7-methyl-6a,7-dihydro-5*H*-pyrido[1,2-*a*]quinoxaline-6,8-dione* **3c**: yield 50–55%, mp 160–161 °C. ^{1}H NMR (500 MHz, DMSO-d_6–CCl_4) δ: 0.81 (t, 3H, Me, J 7.4 Hz), 1.23 (d, 3H, Me, J 7.6 Hz), 2.00 (dq, 1H, CH*H*, J 14.9, 7.4 Hz), 2.25 (dq, 1H, C*H*H, J 14.9, 7.4 Hz), 2.91 (br. q, 1H, H^7, J 7.6 Hz), 4.00 (d, 1H, H^{6a}, J 1.2 Hz), 4.91 (s, 1H, H^9), 7.03 (dd, 1H, H^4, J 7.9, 1.2 Hz), 7.05 (td, 1H, H^2, J 7.7, 1.2 Hz), 7.25 (td, 1H, H^3, J 7.7, 1.1 Hz), 7.41 (dd, H^1, J 7.8, 1.1 Hz), 10.67 (s, 1H, NH). ^{13}C NMR (125.7 MHz, DMSO-d_6–CCl_4) δ: 11.39 (Me), 15.81 (Me), 25.68 (CH_2), 37.29 (C^7), 63.41 (C^{6a}), 99.66 (C^9), 116.44 (C^4), 121.86 (C^2), 125.54 (C^1), 127.34 (C^3), 130.48 (C^{11a}), 133.68 (C^{4a}), 162.89 (C^{10}), 168.14 (C^6), 192.70 (C^8). MS, *m*/*z* (%): 256 [M$^+$] (100), 227 (23), 213 (16), 199 (21), 188 (32), 171 (15), 159 (68). Found (%): C, 70.33; H, 6.31; N, 10.73. Calc. for $C_{18}H_{14}N_2O_2$ (%): C, 70.29; H, 6.29; N, 10.93.