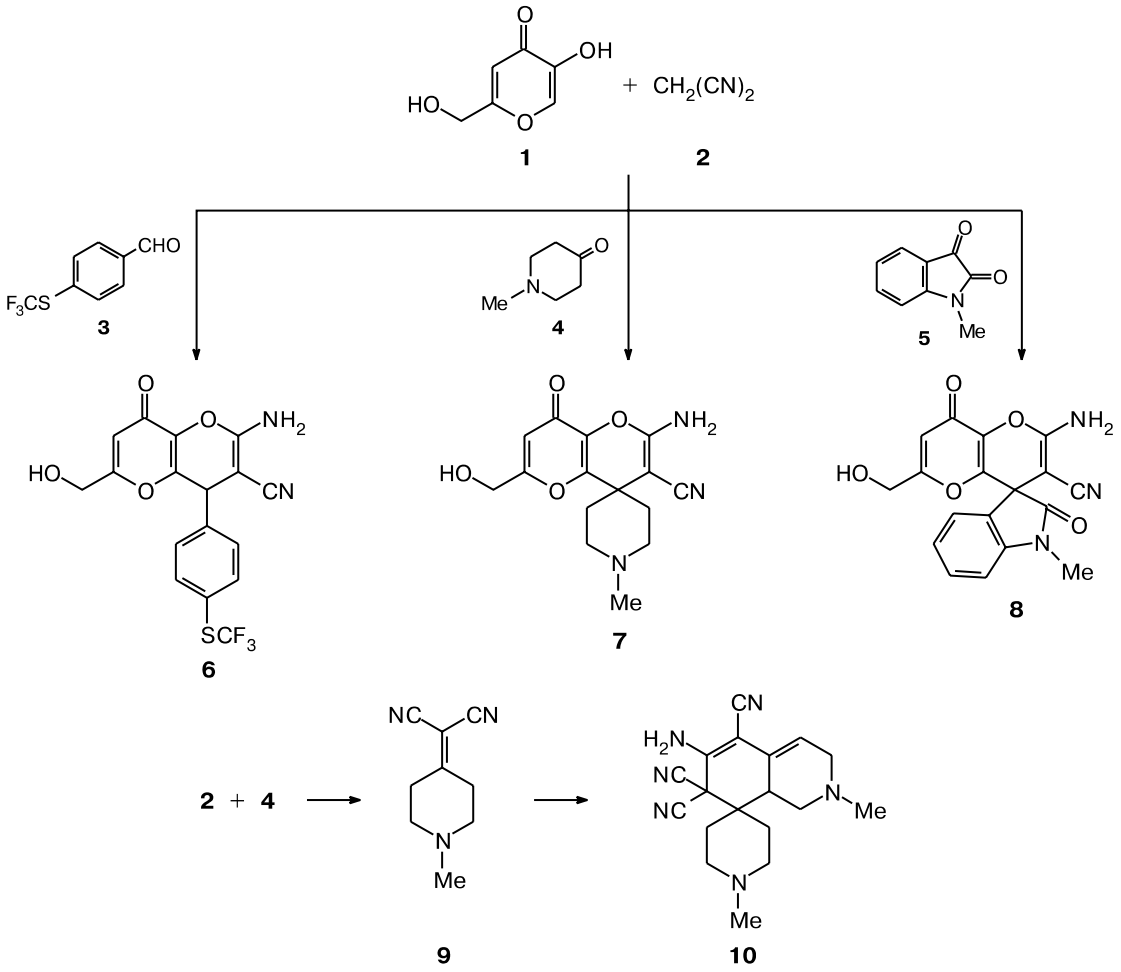
One-step synthesis of substituted 4,8-dihydropyrano[3,2-*b*]pyran-4-ones

*A. A. Shestopalov, L. A. Rodinovskaya, A. M. Shestopalov, and V. P. Litvinov**

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (095) 135 5328. E-mail: vpl@ioc.ac.ru

Kojic acid, which was first isolated from *Aspergillus oryzae*, was used in reactions with arylidenemalononitriles for the preparation of substituted 6-amino-8-aryl-2-hydroxymethyl-4,8-dihydropyrano[3,2-*b*]pyran-4-ones as analogs of human immunodeficiency virus (HIV) protease inhibitors.[1—3] In continuation of studies of the cross-reactions of carbonyl compounds with cyanoacetic acid derivatives with the aim of developing convenient one-step methods for the synthesis of functionalized carbo- and heterocycles,[4,5] we studied the reactions of kojic acid (**1**) with malononitrile (**2**) and carbonyl compounds **3—5** and developed a one-step procedure for the preparation of substituted 4,8-dihydropyrano[3,2-*b*]pyran-4-ones **6—8**.

Compounds **6—8** were prepared in one step without the preliminary synthesis and isolation of unsaturated nitriles by briefly refluxing equimolar amounts of the starting reagents **1** and **2** and the corresponding carbonyl compounds **3—5** in ethanol in the presence of catalytic amounts of Et_3N.



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In the present study, spiro-fused heterocycles **7** and **8** were prepared for the first time. The advantage of the new method is that it allows one to prepare compounds **6—8** in high yields (83—97%). It should also be stressed that compound **7** can only be synthesized by the three-component reaction, since the attempted preparation of unsaturated nitrile **9** from malononitrile **2** and piperidin-4-one **4** afforded ultimately isoquinoline **10**.[5]

The ^{1}H NMR spectra were recorded on a Bruker DRX 500 spectrometer (500.13 MHz) in DMSO-d_6 with Me_4Si as the internal standard. The IR spectra were measured on a Perkin-Elmer 577 instrument in KBr pellets. Elemental analysis was carried out on a Perkin-Elmer C,H,N-analyzer.

6-Amino-7-cyano-2-hydroxymethyl-8-[(4-trifluoromethylthio)phenyl]-4,8-dihydropyrano[3,2-*b*]pyran-4-one (6). A mixture of kojic acid **1** (0.71 g, 0.005 mol), malononitrile (**2**) (0.33 g, 0.005 mol), aldehyde **3** (1.03 g, 0.005 mol), and Et_3N (0.14 mL, 0.001 mol) in EtOH (20 mL) was refluxed for 15 min and kept at 4 °C for 12 h. The precipitate that formed was filtered off and washed with ethanol and hexane. After recrystallization from EtOH, compound **6** was obtained in a yield of 1.92 g (97%) as colorless crystals, m.p. 224—226 °C. Found (%): C, 51.29; H, 2.62; N, 6.85. $C_{17}H_{11}F_3N_2O_4S$. Calculated (%): C, 51.52; H, 2.80; N, 7.07. IR, ν/cm^{-1}: 3498, 3385, 3264, 3167 (OH, NH_2); 2193 (CN); 1672 (CO); 1637 (δ NH_2). ^{1}H NMR, δ: 4.12 (dd, 1 H, CH_2, J = 15.0 Hz, J = 6.2 Hz); 4.21 (dd, 1 H, CH_2, J = 15.0 Hz, J = 6.2 Hz); 4.85 (s, 2 H, NH_2); 5.52 (t, 1 H, OH, J = 6.2 Hz); 6.37 (s, 1 H, C(3)H); 7.24 (s, 2 H, NH_2); 7.46 (d, 2 H, C_6H_4, J = 7.1 Hz); 7.75 (d, 2 H, C_6H_4, J = 7.1 Hz).

6-Amino-7-cyano-2-hydroxymethyl-1′-methyl-4,8-dihydrospiro[pyrano[3,2-*b*]pyran-8,4′-piperidine]-4-one (7) was prepared analogously. The yield was 83%, white powder, m.p. 248—250 °C (from nitromethane). Found (%): C, 59.73; H, 5.84; N, 13.97. $C_{15}H_{17}N_3O_4$. Calculated (%): C, 59.40; H, 5.65; N, 13.85. IR, ν/cm^{-1}: 3492, 3376, 3284, 3153 (OH, NH_2); 2188 (CN); 1687 (CO); 1625 (δ NH_2). ^{1}H NMR, δ: 1.86—2.07 (m, 4 H, C(3′)H_2, C(5′)H_2); 2.24 (s, 3 H, Me); 2.42—2.73 (m, 4 H, C(2′)H_2, C(6′)H_2); 4.32 (dd, 1 H, CH_2, J = 15.2 Hz, J = 6.4 Hz); 4.38 (dd, 1 H, CH_2, J = 15.2 Hz, J = 6.4 Hz); 5.68 (t, 1 H, OH, J = 6.4 Hz); 6.47 (s, 1 H, C(3)H); 6.94 (s, 2 H, NH_2).

6-Amino-7-cyano-2-hydroxymethyl-1′-methylindane-4,2′-dioxo-4,8,2′,3′-tetrahydrospiro[pyrano[3,2-*b*]pyran-8,3′-indole] (8) was prepared analogously. The yield was 89%, white powder, m.p. 223—224 °C (from nitromethane). Found (%): C, 61.31; H, 3.54; N, 11.68. $C_{18}H_{13}N_3O_5$. Calculated (%): C, 61.54; H, 3.73; N, 11.96. IR, ν/cm^{-1}: 3486, 3369, 3265, 3148 (OH, NH_2); 2192 (CN); 1680, 1672 (CO); 1627 (δ NH_2). ^{1}H NMR, δ: 3.28 (s, 3 H, CH_3); 3.98 (dd, 1 H, CH_2, J = 15.6 Hz, J = 6.5 Hz); 4.10 (dd, 1 H, CH_2, J = 15.6 Hz, J = 6.5 Hz); 5.43 (t, 1 H, OH, J = 6.5 Hz); 6.34 (s, 1 H, C(3)H); 7.15 (d, 1 H, C(7′)H, J = 7.9 Hz); 7.18 (t, 1 H, C(6′)H, J = 7.9 Hz, J = 7.7 Hz); 7.27 (d, 1 H, C(4′)H, J = 8.2 Hz); 7.32 (s, 2 H, NH_2); 7.39 (t, 1 H, C(5′)H, J = 7.7 Hz, J = 8.2 Hz).

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References

1. *The Merck Index*, Eds V. J. O´Neil, Merck and Co., Inc., Whitehouse Station, NJ, 2001, 951 p.
2. M.-Z. Piao and K. Imafuku, *Tetrahedron Lett.*, 1997, **38**, 5301.
3. S. Wang, G. W. A. Milne, X. Yang, I. J. Posey, M. C. Nicklaus, L. Graham, and W. G. Rice, *J. Med. Chem.*, 1996, **39**, 2047.
4. V. P. Litvinov and A. M. Shestopalov, *Zh. Org. Khim.*, 1997, **33**, 975 [*Russ. J. Org. Chem.*, 1997, **33**, 926 (Engl. Transl.)].
5. A. M. Shestopalov, Y. M. Emeliyanova, A. A. Shestopalov, L. A. Rodinovskaya, Z. I. Niazimbetova, and D. H. Evans, *Tetrahedron*, 2003, **59**, 7491.

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