Three-component synthesis of partially hydrogenated quinolines from 3-substituted chromones, dimedone, and ammonium acetate

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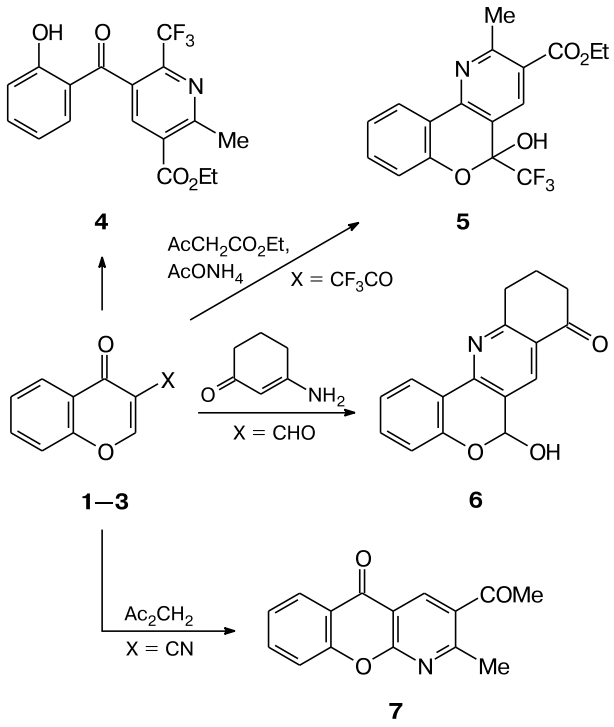
Reaction of 3-R-chromones with dimedone and ammonium acetate leads to 2-(2-hydroxyaryl)-7,7-dimethyl-7,8-dihydroquinolin-5(6*H*)-ones (R = CF_3CO, H), 3-(2-hydroxyaroyl)-7,7-dimethyl-7,8-dihydroquinolin-5(6*H*)-ones (R = CHO), and 8,8-dimethyl-8*H*-chromeno[2,3-*b*]quinoline-10,12(7*H*,9*H*)-diones (R = CN) depending on the nature of substituent R.

Key words: chromones, dimedone, heterocyclization, partially hydrogenated quinolines.

Chromone (4*H*-chromen-4-one, 4*H*-1-benzopyran-4-one) and its derivatives represent an important class of oxygen-containing heterocyclic compounds, which are widely spread in plants[1] and exhibit low toxicity in combination with a wide spectrum of useful properties.[2] Introduction of an electron-withdrawing substituent at position 3 of the chromone system considerably changes reactivity of the pyrone ring with respect to nucleophilic agents and provides vast synthetic possibilities of 3-substituted chromones. Variable properties of these compounds are explained by the fact that they, being actually the highly reactive geminally activated olefins,[3] due to the good leaving group at β-carbon atom (phenoxide anion) are capable of additional transformations involving recyclization of the γ-pyrone ring. Thus, it is known[4—6] that 3-trifluoroacetylchromone **1**, 3-formylchromone **2**, and 3-cyanochromone **3** react with compounds having active methylene group and give rise to heterocycles **4—7** (Scheme 1).

Scheme 1



X = CF_3CO (**1**), CHO (**2**), CN (**3**)

Results and Discussion

During study on the synthesis of new R^F-containing derivatives of nicotinic acid from 3-polyfluoroacylchromones and 1,3-C,N-dinucleophiles, we found that the three-component reaction between 3-trifluoroacetylchromones **1a,b**, dimedone, and ammonium acetate under reflux in ethanol is accompanied by detrifluoroacetylation and leads to the earlier unknown 2-(2-hydroxyaryl)tetrahydroquinolin-5-ones **8a,b** in low yields (23—25%) owing to partial decomposition to 2-hydroxyacetophenones. The structure of quinoline **8a** was confirmed by its synthesis from unsubstituted chromone under similar conditions. The yield of **8a** was only 7% in this case that indicates the favorable role of the 3-CF_3CO group in chromones **1a,b** in the course of the reaction with the *in situ* arising dimedone enamine. 3-Formylchromones **2a—c** under these conditions afford 3-(2-hydroxyaroyl)tetrahydroquinolin-5-ones **9a—c** (34—59% yield), from which **9a** was oxidized under the Dakin reac-

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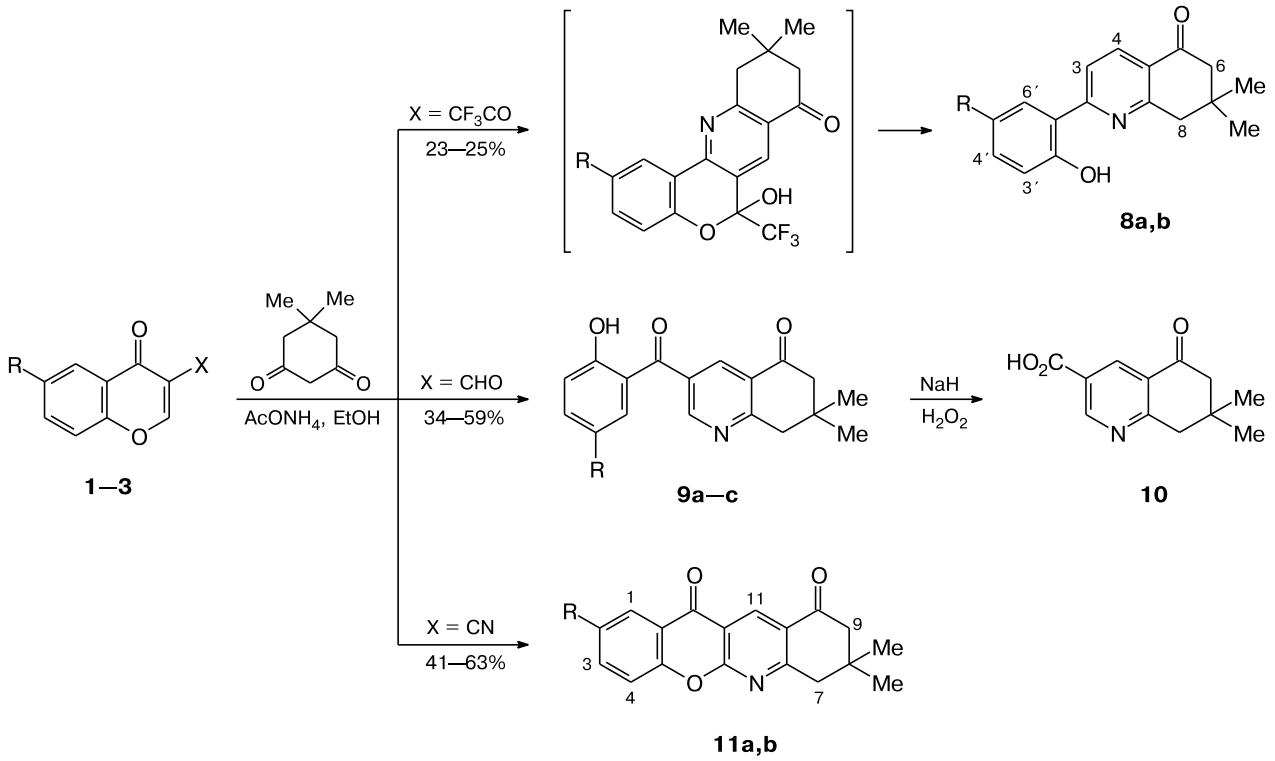
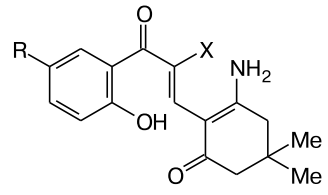
Scheme 2



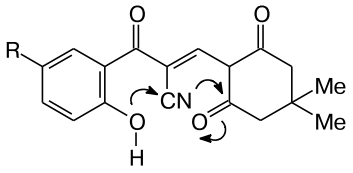
X = CF_3CO (**1**), CHO (**2**), CN (**3**); **8, 9:** R = H (**a**), Me (**b**), Cl (**c**); **11:** R = H (**a**), Cl (**b**)

tion conditions (NaH, H_2O_2)[7] to a new nicotinic acid derivative **10** (50% yield) (Scheme 2).

Formation of compounds **8a,b** and **9a—c** proceeds by the mechanism of nucleophilic 1,4-addition with participation of the central C atom of the dimedone enamine and is accompanied by the pyrone ring opening to intermediate **A**. In the case of 3-CF_3CO-chromones **1**, the subsequent heterocyclization of the intermediate **A** proceeds with participation of the aroyl carbonyl and loss of



A



B

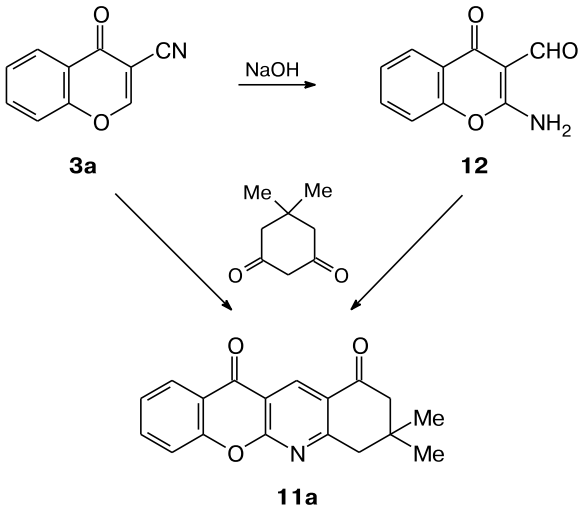
X = CF_3CO, CHO

the trifluoroacetyl group, whereas in 3-CHO-chromones **2**, the aldehyde group turns out to be more active resulting in quinolines **9** in contrast to the reaction of 3-formylchromone **2a** with cyclohexane-1,3-dione enamine described earlier,[5] which leads to chromeno[4,3-*b*]quinoline **6**.

The reaction of 3-cyanochromones **3a,c** with dimedone and ammonium acetate under the same conditions, *i.e.*, in boiling ethanol, led to the expected but earlier unknown 8,8-dimethyl-8*H*-chromeno[2,3-*b*]quinoline-10,12(7*H*,9*H*)-diones **11a,b** in 41—63% yield. In this case, a molecule of dimedone participates in the 1,4-addition step, whereas ammonia only plays the role of a base (intermediate **B**), since the similar reaction of **3a** without ammonium acetate but in the presence of a drop of piperidine[6] gave compound **11a** in 84% yield. In favor of intermediate **B**, cyclizing to chromeno[2,3-*b*]quinolines **11** by the tandem of intramolecular reactions of nucleophilic addition, also speaks the fact that compound **11a** is formed from dimedone and 2-amino-3-formylchromone **12**, to which 3-cyanochromone **3a** is easily transformed under basic conditions[8,9] (Scheme 3). Earlier, 2,3-disubstituted 4-azaxanthones of the type **7** have been obtained from chromones **3** or **12** by the reaction with such methylene-active compounds as acetylacetone and acetoacetic ester.[6,10,11]

The structures of all the heterocycles synthesized are in good agreement with the data of elemental analysis,

Scheme 3



IR spectroscopy, as well as ^{1}H NMR spectroscopy. In the ^{1}H NMR spectra of these compounds, along with the signals for aliphatic and benzene protons there are two doublets for the pyridine protons H(3) and H(4) at δ 8.2 and 8.3 with J_o = 8.6 Hz for **8a,b**, two doublets for the protons H(4) and H(2) at δ 8.5 and 9.0 with J_m = 2.3 Hz for **9a—c** and **10**, and a singlet for the H(11) at δ 8.9 for **11a,b**.

In conclusion, a direction of three-component condensation of 3-substituted chromones with dimedone and ammonium acetate is defined by the nature of the substituent at position 3 and leads to the synthesis of new derivatives of partially hydrogenated quinoline.

Experimental

IR spectra were recorded on a Perkin-Elmer Spectrum BX-II spectrometer in KBr pellets. ^{1}H NMR spectra were recorded on a Bruker DRX-400 spectrometer in DMSO-d_6 or $CDCl_3$ (400.1 MHz, internal standard, Me_4Si). Chromones **1—3** and **12** were obtained according to procedures described earlier.[8,12,13]

2-(2-Hydroxyphenyl)-7,7-dimethyl-7,8-dihydroquinolin-5(6*H*)-one (8a). A solution of chromone **1a** (250 mg, 1.0 mmol), dimedone (360 mg, 2.6 mmol), and ammonium acetate (1.1 g, 14.3 mmol) in ethanol (5 mL) was refluxed for 4 h. Then, the reaction mixture was concentrated to dryness and the residue was recrystallized from methanol to obtain compound **8a** (60 mg, 23%) as colorless crystals with m.p. 142—143 °C. Found (%): C, 76.23; H, 6.47; N, 5.34. $C_{17}H_{17}NO_2$. Calculated (%): C, 76.38; H, 6.41; N, 5.24. IR, ν/cm^{-1}: 1686, 1585, 1562, 1507, 1472. ^{1}H NMR (DMSO-d_6), δ: 1.08 (s, 6 H, 2 Me); 2.60 (s, 2 H, C(6)H_2); 3.09 (s, 2 H, C(8)H_2); 6.94—6.98 (m, 2 H, H(3′), H(5′)); 7.39 (ddd, 1 H, H(4′), J_o = 8.3 Hz, J_o = 7.2 Hz, J_m = 1.6 Hz); 8.08 (dd, 1 H, H(6′), J_o = 8.5 Hz, J_m = 1.6 Hz); 8.22 (d, 1 H, H(3), J_o = 8.6 Hz); 8.31 (d, 1 H, H(4), J_o = 8.6 Hz); 13.98 (s, 1 H, OH).

Compound **8a** was also obtained by alternative synthesis from unsubstituted chromone, dimedone, and ammonium acetate under similar conditions in 7% yield.

2-(2-Hydroxy-5-methylphenyl)-7,7-dimethyl-7,8-dihydroquinolin-5(6*H*)-one (8b) was obtained similarly to compound **8a** from chromone **1b** in 25% yield as colorless crystals with m.p. 193—194 °C. Found (%): C, 76.64; H, 6.74; N, 4.87. $C_{18}H_{19}NO_2$. Calculated (%): C, 76.84; H, 6.81; N, 4.98. IR, ν/cm^{-1}: 1686, 1618, 1582, 1563, 1492, 1455. ^{1}H NMR (DMSO-d_6), δ: 1.07 (s, 6 H, 2 Me); 2.30 (s, 3 H, Me); 2.60 (s, 2 H, C(6)H_2); 3.08 (s, 2 H, C(8)H_2); 6.87 (d, 1 H, H(3′), J_o = 8.3 Hz); 7.20 (dd, 1 H, H(4′), J_o = 8.3 Hz, J_m = 1.8 Hz); 7.89 (d, 1 H, H(6′), J_m = 1.8 Hz); 8.21 (d, 1 H, H(3), J_o = 8.6 Hz); 8.30 (d, 1 H, H(4), J_o = 8.6 Hz); 13.72 (s, 1 H, OH).

7,7-Dimethyl-3-salicyl-7,8-dihydroquinolin-5(6*H*)-one (9a). A solution of chromone **2a** (1.0 g, 5.7 mmol), dimedone (2.0 g, 14.4 mmol), and ammonium acetate (6.3 g, 82.0 mmol) in ethanol (35 mL) was refluxed for 2 h. Then, the solution was half concentrated and cooled, the crystals formed were filtered off, dried, and recrystallized from aqueous ethanol (1 : 1) to obtain compound **9a** (1.0 g, 59%) as colorless crystals with m.p. 132—133 °C. Found (%): C, 73.42; H, 5.60; N, 4.61. $C_{18}H_{17}NO_3$. Calculated (%): C, 73.20; H, 5.80; N, 4.74. IR, ν/cm^{-1}: 3457, 1691, 1625, 1590, 1484, 1463. ^{1}H NMR ($CDCl_3$), δ: 1.17 (s, 6 H, 2 Me); 2.63 (s, 2 H, C(6)H_2); 3.15 (s, 2 H, C(8)H_2); 6.92 (ddd, 1 H, H(5′), J_o = 8.0 Hz, J_o = 7.3 Hz, J_m = 1.1 Hz); 7.11 (dd, 1 H, H(3′), J_o = 8.5 Hz, J_m = 1.1 Hz); 7.51 (dd, 1 H, H(6′), J_o = 8.0 Hz, J_m = 1.6 Hz); 7.56 (ddd, 1 H, H(4′), J_o = 8.5 Hz, J_o = 7.3 Hz, J_m = 1.6 Hz); 8.54 (d, 1 H, H(4), J_m = 2.3 Hz); 9.01 (d, 1 H, H(2), J_m = 2.3 Hz); 11.80 (s, 1 H, OH).

3-(2-Hydroxy-5-methylbenzoyl)-7,7-dimethyl-7,8-dihydroquinolin-5(6*H*)-one (9b) was obtained similarly to compound **9a** from chromone **2b** in 34% yield as colorless crystals with m.p. 164—165 °C. Found (%): C, 73.46; H, 6.22; N, 4.36. $C_{19}H_{19}NO_3$. Calculated (%): C, 73.77; H, 6.19; N, 4.53. IR, ν/cm^{-1}: 3178, 1681, 1638, 1613, 1590, 1480, 1461. ^{1}H NMR ($CDCl_3$), δ: 1.17 (s, 6 H, 2 Me); 2.27 (s, 3 H, Me); 2.63 (s, 2 H, C(6)H_2); 3.16 (s, 2 H, C(8)H_2); 7.01 (d, 1 H, H(3′), J_o = 8.5 Hz); 7.26 (br.s, 1 H, H(6′), J_m = 1.5 Hz); 7.38 (dd, 1 H, H(4′), J_o = 8.5 Hz, J_m = 2.1 Hz); 8.54 (d, 1 H, H(4), J_m = 2.3 Hz); 8.99 (d, 1 H, H(2), J_m = 2.3 Hz); 11.62 (s, 1 H, OH).

3-(5-Chloro-2-hydroxybenzoyl)-7,7-dimethyl-7,8-dihydroquinolin-5(6*H*)-one (9c) was obtained similarly to compound **9a** from chromone **2c** in 57% yield as colorless crystals with m.p. 160—161 °C. Found (%): C, 65.59; H, 4.81; N, 4.24. $C_{18}H_{16}ClNO_3$. Calculated (%): C, 65.56; H, 4.89; N, 4.25. IR, ν/cm^{-1}: 3445, 1684, 1633, 1613, 1592, 1570, 1551, 1457. ^{1}H NMR ($CDCl_3$), δ: 1.18 (s, 6 H, 2 Me); 2.64 (s, 2 H, C(6)H_2); 3.17 (s, 2 H, C(8)H_2); 7.08 (d, 1 H, H(3′), J_o = 8.9 Hz); 7.46 (d, 1 H, H(6′), J_m = 2.6 Hz); 7.51 (dd, 1 H, H(4′), J_o = 8.9 Hz, J_m = 2.6 Hz); 8.54 (d, 1 H, H(4), J_m = 2.3 Hz); 8.99 (d, 1 H, H(2), J_m = 2.3 Hz); 11.68 (s, 1 H, OH).

7,7-Dimethyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylic acid (10) was obtained from pyridine **9a** according to the procedure described in Ref. 7. The yield was 50%, colorless crystals with m.p. 215—216 °C. Found (%): C, 66.08; H, 6.20; N, 6.12. $C_{12}H_{13}NO_3$. Calculated (%): C, 65.74; H, 5.98; N, 6.39. IR, ν/cm^{-1}: 2460, 1703, 1689, 1603, 1563, 1575, 1465. ^{1}H NMR (DMSO-d_6), δ: 1.04 (s, 6 H, 2 Me); 2.62 (s, 2 H, C(6)H_2); 3.09 (s, 2 H, C(8)H_2); 8.54 (d, 1 H, H(4), J_m = 2.2 Hz); 9.17 (d, 1 H, H(2), J_m = 2.2 Hz); 13.4—13.8 (br.s, 1 H, OH).

8,8-Dimethyl-8*H*-chromeno[2,3-*b*]quinoline-10,12(7*H*,9*H*)-dione (11a). A solution of chromone **3a** (200 mg, 1.2 mmol), dimedone (410 mg, 2.9 mmol), and ammonium acetate (1.3 g,

16.9 mmol) in ethanol (7 mL) was refluxed for 1 h. Then, the reaction mixture was cooled, the crystals formed were filtered off and washed with cold ethanol to obtain compound **11a** (140 mg, 41%) as colorless crystals with m.p. 241—242 °C. When piperidine (1 drop)[6] was used instead of ammonium acetate under similar conditions, the yield of compound **11a** was 84%. 2-Amino-3-formylchromone **12** in the reaction with dimedone in the presence of piperidine[6] gives **11a** in 57% yield. Found (%): C, 73.35; H, 4.98; N, 4.87. $C_{18}H_{15}NO_3$. Calculated (%): C, 73.71; H, 5.15; N, 4.78. IR, ν/cm^{-1}: 1684, 1653, 1597, 1553, 1473. ^{1}H NMR (DMSO-d_6), δ: 1.08 (s, 6 H, 2 Me); 2.67 (s, 2 H, C(9)H_2); 3.13 (s, 2 H, C(7)H_2); 7.56 (ddd, 1 H, H(2), J_o = 8.0 Hz, J_o = 7.2 Hz, J_m = 1.0 Hz); 7.76 (dd, 1 H, H(4), J_o = 8.6 Hz, J_m = 0.8 Hz); 7.95 (ddd, 1 H, H(3), J_o = 8.6 Hz, J_o = 7.2 Hz, J_m = 1.7 Hz); 8.19 (dd, 1 H, H(1), J_o = 7.9 Hz, J_m = 1.7 Hz); 8.88 (s, 1 H, H(11)).

2-Chloro-8,8-dimethyl-8*H*-chromeno[2,3-*b*]quinoline-10,12(7*H*,9*H*)-dione (11b) was obtained similarly to compound **11a** from chromone **3c** in the presence of ammonium acetate in 63% yield after recrystallization from toluene—butanol (2 : 1), colorless crystals with m.p. 249—250 °C. Found (%): C, 64.43; H, 4.16; N, 4.08. $C_{18}H_{14}ClNO_3 \cdot 0.5H_2O$. Calculated (%): C, 64.20; H, 4.49; N, 4.16. IR, ν/cm^{-1}: 1686, 1668, 1596, 1551, 1472. ^{1}H NMR (DMSO-d_6), δ: 1.08 (s, 6 H, 2 Me); 2.67 (s, 2 H, C(9)H_2); 3.13 (s, 2 H, C(7)H_2); 7.83 (d, 1 H, H(4), J_o = 8.9 Hz); 7.99 (dd, 1 H, H(3), J_o = 8.9 Hz, J_m = 2.7 Hz); 8.11 (d, 1 H, H(1), J_m = 2.6 Hz); 8.87 (s, 1 H, H(11)).

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