Synthesis of 2-(2-hydroxyaroylmethylene)hexahydropyrimidines from 2-trichloromethylchromones and trimethylenediamine

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The reactions of 2-trichloromethylchromones with trimethylenediamine in ethanol at room temperature afford 2-(2-hydroxyaroylmethylene)hexahydropyrimidines. Under analogous conditions, 2-methylchromone gives a mixture of *N,N'*-trimethylenebis[3-amino-1-(2'-hydroxyphenyl)-2-buten-1-one] and *N,N'*-trimethylenebis(imine) of 2-hydroxyacetophenone.

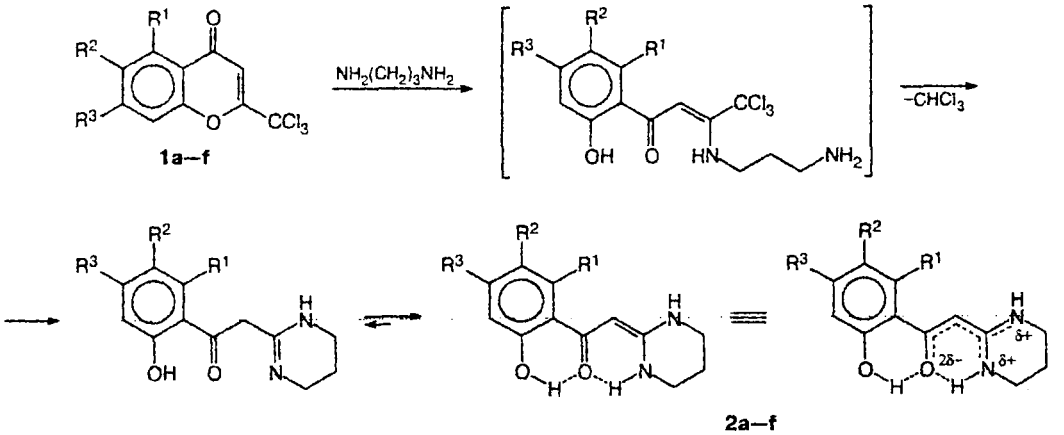
Key words: 2-trichloromethylchromones, 2-methylchromone, trimethylenediamine, 2-(2-hydroxyaroylmethylene)hexahydropyrimidines, *N,N'*-trimethylenebis[3-amino-1-(2'-hydroxyphenyl)-2-buten-1-one], *N,N'*-trimethylenebis(imine) of 2-hydroxyacetophenone.

Unlike 2-mono- and 2,2-disubstituted hexahydropyrimidines, whose preparation and ring-chain tautomerism have been reported recently,[1] data on derivatives of 2-methylenehexahydropyrimidines are scarce.[2] As part of continuing studies of 2-trichloromethylchromones,[3] which react with ethylenediamine to give 2-phenacylideneimidazolidines,[4] we found that the reaction of chromones **1a—f** with trimethylenediamine in alcohol at room temperature afforded 2-phenacylidenehexahydropyrimidines **2a—f** in 50—95% yields (Scheme 1).

The reaction proceeds through intermediate aminoenones containing the 3-aminopropyl group at the nitrogen atom. These intermediates are then involved in addition—elimination stages resulting in intramolecular replacement of the CCl_3 group to form 2-phenacyl-1,4,5,6-tetrahydropyrimidines, which exist as keto-enamine tautomers, *viz.*, 2-phenacylidenehexahydropyrimidines **2a—f**, in DMSO-d_6 and $CDCl_3$ solutions. Due to the strong conjugation between the lone electron pairs of the nitrogen atoms and the carbonyl oxygen atom, these compounds belong to highly delocalized π-systems with equalized bonds. These compounds have been studied intensively in recent years.[5,6]

The ^{1}H NMR spectra of phenacylidenehexahydropyrimidines **2d,e** measured in a DMSO-d_6 solution have a singlet of the vinyl hydrogen atom at δ 5.15 and 5.03, respectively, a broadened two-proton singlet of the protons of the NH group at δ 8.93 and 8.81, respectively,

Scheme 1



2a—f

a: $R^1 = R^2 = R^3 = H$; **b:** $R^1 = R^3 = H$, $R^2 = Me$; **c:** $R^1 = R^3 = H$, $R^2 = Cl$; **d:** $R^1 = R^3 = H$, $R^2 = MeO$; **e:** $R^1 = R^2 = H$, $R^3 = MeO$; **f:** $R^1 = R^3 = Me$, $R^2 = H$

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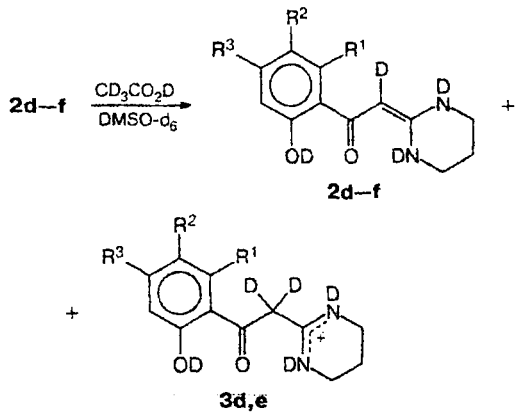
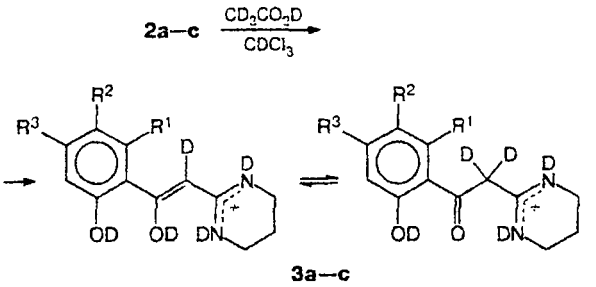
and a singlet of the proton of the phenol hydroxyl group at δ 14.24 and 15.29, respectively, along with signals of the aliphatic and aromatic protons. The spectra of compounds **2d,e** change substantially immediately after addition of CD_3CO_2D. Thus, a new set of signals, which are shifted downfield and belong to the symmetrically delocalized tetrahydropyrimidinium monocation (the contents of cations **3d** and **3e** are 40 and 20%, respectively), appears along with the signals of the initial molecule. In the spectrum of the latter, the intensity of the vinyl proton decreases to 0.2—0.3 H due to the rapid H/D exchange. In addition, the spectra have residual signals at δ 4.2—4.3, 8.9—9.0, and 9.6, the high-field signals belonging to the protons of the CHD groups of the phenacyl substituents in tetrahydropyrimidinium monocations **3d,e** and the low-field signals belonging to the protons of the NH groups, which are involved in intermolecular hydrogen bonding with solvent molecules and which have not managed to be replaced by deuterium. In the ^1H NMR spectrum of compound **2f**, which was also measured in a DMSO-d_6 solution, the signals of the vinyl and hydroxyl protons are shifted upfield (at δ 4.75 and 12.54, respectively), which is associated with a decrease in the deshielding effect of the aryl group and weakening of the intramolecular O—H...O hydrogen bond due to the deviation of the aromatic ring from the plane of the aminoenone fragment. This deviation is caused by unfavorable steric interactions between the *ortho*-methyl group and the hydrogen atom at the double bond. In this case, the addition of CD_3CO_2D also causes a decrease in the intensity of the vinyl hydrogen atom to 0.3 H but does not afford the cationic form.

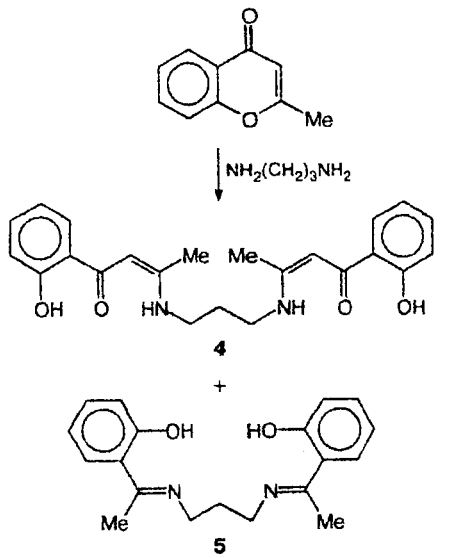


In the ^1H NMR spectra of compounds **2a—c**, measured in $CDCl_3$ solutions, noteworthy is a signal of the vinyl proton at δ 5.00—5.06, which appears as a broadened singlet with the peak half-width of up to 50 Hz. This is indicative of the participation of the vinyl proton in exchange and tautomeric processes. This singlet as well as substantially broadened signals of the protons of the OH and NH groups disappear immediately after addition of CD_3CO_2D and the spectra have only one set of signals corresponding to tetrahydropyrimidinium monocations **3a—c**.



Hence, as expected, exchange and salt-formation processes in a basic solvent, such as DMSO-d_6, proceed more slowly than those in $CDCl_3$, which allows one to observe both the neutral and cationic forms of phenacylidenehexahydropyrimidines in acidic DMSO-d_6 solutions.

It should be noted that 2-trifluoromethylchromones are decomposed under the action of trimethylenediamine in alcohol to form 2-hydroxyacetophenones, which then react with trimethylenediamine to give the corresponding Schiff's bases.[7] In this connection, it was of interest to compare the behavior of 2-trihalomethylchromones and 2-methylchromone in the reactions with trimethylenediamine. It was found that 2-methylchromone under analogous conditions gave a mixture of bis(aminoenone) (**4**) and bis(imine) (**5**) in a ratio of 70 : 30, which were not separated, but the ratio of the products was established based on the ^1H NMR spectral data.



Therefore, unlike the reactions of 2-trifluoromethyl- and 2-methylchromones with trimethylenediamine, which are accompanied by decomposition of the

chromone system to 2-hydroxyacetophenones, the reaction of 2-trichloromethylchromones **1a—f** with this diamine is a simple and convenient method for the synthesis of previously difficultly accessible 2-phenacylidenehexahydropyrimidines **2a—f**.

Experimental

The IR spectra were obtained on an IKS-29 instrument as Nujol mulls. The ^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer in $CDCl_3$ and DMSO-d_6 operating at 250 MHz with Me_4Si as the internal standard.

2-(2-Hydroxybenzoylmethylene)hexahydropyrimidine (2a). Trimethylenediamine (200 mL, 177 mg, 2.39 mmol) was added to a solution of chromone **1a** (200 mg, 0.76 mmol) in ethanol (3 mL) and the reaction mixture was kept at ~20 °C for 3 h. The crystals that precipitated were filtered off on a Schott filter, washed with water and ethanol, and dried. The yield was 90%, m.p. 193—194 °C. Found (%): C, 66.09; H, 6.68; N, 12.85. $C_{12}H_{14}N_2O_2$. Calculated (%): C, 66.04; H, 6.47; N, 12.84. IR, ν/cm^{-1}: 3250, 3150 (NH); 1620 (C=O); 1605, 1580, 1550 (C=C, NH). ^{1}H NMR ($CDCl_3$), δ: 1.98 (m, 2 H, CH_2); 3.39 (m, 4 H, 2 CH_2N); 5.06 (br.s, 1 H, =CH); 4.50—5.50 (br.s, 1 H, NH); 6.73 (m, 1 H, H(5)); 6.86 (d, 1 H, H(3), J = 8.1 Hz); 7.26 (m, 1 H, H(4)); 7.48 (m, 1 H, H(6)); 9.50—11.50 (br.s, 1 H, NH...O); 14.16 (br.s, 1 H, OH); immediately after addition of CD_3CO_2D: **3a**, 2.01 (m, 2 H, CH_2); 3.45 (s, 4 H, 2 CH_2N); 6.90 (t, 1 H, H(5), J = 7.4 Hz), 6.94 (d, 1 H, H(3)); 7.48 (t, 1 H, H(4)); 7.71 (d, 1 H, H(6)). Compounds **2b—e** were prepared analogously to compound **2a**. In the case of compound **2f**, the reaction time was 3 days.

2-(2-Hydroxy-5-methylbenzoylmethylene)hexahydropyrimidine (2b). The yield was 95%, m.p. 194—195 °C. Found (%): C, 67.12; H, 6.89; N, 12.01. $C_{13}H_{16}N_2O_2$. Calculated (%): C, 67.22; H, 6.94; N, 12.06. IR, ν/cm^{-1}: 3320, 3150 w (NH); 1630 (C=O); 1600, 1550 (C=C, NH). ^{1}H NMR ($CDCl_3$), δ: 1.95 (quintet, 2 H, CH_2, J = 5.8 Hz); 2.23 (s, 3 H, Me); 3.35 (t, 4 H, 2 CH_2N); 5.05 (br.s, 1 H, =CH); 4.50—5.50 (br.s, 1 H, NH); 6.75 (d, 1 H, H(3), J = 8.3 Hz); 7.03 (d, 1 H, H(4)); 7.23 (s, 1 H, H(6)); 9.50—11.50 (br.s, 1 H, NH...O); 14.02 (br.s, 1 H, OH); immediately after addition of CD_3CO_2D: **3b**, 1.95 (m, 2 H, CH_2); 2.23 (s, 3 H, Me); 3.40 (t, 4 H, 2 CH_2N, J = 5.8 Hz); 6.81 (d, 1 H, H(3), J = 8.4 Hz); 7.24 (d, 1 H, H(4)); 7.45 (s, 1 H, H(6)).

2-(5-Chloro-2-hydroxybenzoylmethylene)hexahydropyrimidine (2c). The yield was 88%, m.p. 219—220 °C. Found (%): C, 57.21; H, 5.20; N, 11.22. $C_{12}H_{13}ClN_2O_2$. Calculated (%): C, 57.04; H, 5.19; N, 11.09. IR, ν/cm^{-1}: 3280, 3150 w (NH); 1620 (C=O); 1575, 1550 (C=C, NH). ^{1}H NMR ($CDCl_3$), δ: 2.01 (quintet, 2 H, CH_2, J = 5.4 Hz); 3.41 (s, 4 H, 2 CH_2N); 5.00 (br.s, 1 H, =CH); 4.50—5.50 (br.s, 1 H, NH); 6.79 (d, 1 H, H(3), J = 8.7 Hz); 7.15 (dd, 1 H, H(4), J = 2.5 Hz); 7.39 (d, 1 H, H(6)); 9.80—11.40 (br.s, 1 H, NH...O); 14.16 (br.s, 1 H, OH); immediately after addition of CD_3CO_2D: **3c**, 2.04 (m, 2 H, CH_2); 3.47 (t, 4 H, 2 CH_2N, J = 5.8 Hz); 6.92 (d, 1 H, H(3), J = 9.2 Hz); 7.41 (dd, 1 H, H(4), J = 2.4 Hz); 7.69 (d, 1 H, H(6)).

2-(2-Hydroxy-5-methoxybenzoylmethylene)hexahydropyrimidine (2d). The yield was 77%, m.p. 176—177 °C. Found (%): C, 62.64; H, 6.75; N, 11.33. $C_{13}H_{16}N_2O_3$. Calculated (%): C, 62.89; H, 6.50; N, 11.28. IR, ν/cm^{-1}: 3320, 3180 (NH); 1630 (C=O); 1590, 1555 (C=C, NH). ^{1}H NMR (DMSO-d_6), δ: 1.85 (quintet, 2 H, CH_2, J = 5.7 Hz); 3.28 (m, 4 H, 2 CH_2N); 3.68 (s, 3 H, MeO); 5.15 (s, 1 H, =CH); 6.62 (d, 1 H, H(3), J = 8.7 Hz); 6.83 (dd, 1 H, H(4), J = 2.9 Hz); 6.90 (d, 1 H, H(6)); 8.93 (br.s, 2 H, 2 NH); 14.24 (s, 1 H, OH); a new set of signals belonging to tetrahydropyrimidinium monocation **3d** (the content was 40%) appeared along with signals of compound **2d** immediately after addition of CD_3CO_2D: 1.85 (m, 2 H, CH_2); 3.40 (s, 4 H, 2 CH_2N); 3.74 (s, 3 H, MeO); 4.27 (s, 0.4 H, CHD); 6.99 (d, 1 H, H(3), J = 8.7 Hz); 7.18 (dd, 1 H, H(4), J = 2.8 Hz); 7.25 (d, 1 H, H(6)).

2-(2-Hydroxy-4-methoxybenzoylmethylene)hexahydropyrimidine (2e). The yield was 83%, m.p. 198—199 °C. Found (%): C, 62.73; H, 6.73; N, 11.33. $C_{13}H_{16}N_2O_3$. Calculated (%): C, 62.89; H, 6.50; N, 11.28. IR, ν/cm^{-1}: 3270 (NH); 1620 (C=O); 1585, 1550 (C=C, NH). ^{1}H NMR (DMSO-d_6), δ: 1.84 (quintet, 2 H, CH_2, J = 5.6 Hz); 3.29 (m, 4 H, 2 CH_2N); 3.72 (s, 3 H, MeO); 5.03 (s, 1 H, =CH); 6.21 (d, 1 H, H(3), J = 2.3 Hz); 6.29 (dd, 1 H, H(5), J = 8.8 Hz); 7.29 (d, 1 H, H(6)); 8.81 (br.s, 2 H, 2 NH); 15.29 (s, 1 H, OH); a new set of signals belonging to tetrahydropyrimidinium monocation **3e** (the content was 20%) appeared along with the signals of compound **2e** immediately after addition of CD_3CO_2D: 1.84 (m, 2 H, CH_2); 3.38 (s, 4 H, 2 CH_2N); 3.82 (s, 3 H, MeO); 4.22 (br.s, 0.5 H, CHD); 6.56 (m, 2 H, H(3), H(5)); 7.80 (d, 1 H, H(6), J = 8.6 Hz).

2-(2-Hydroxy-4,6-dimethylbenzoylmethylene)hexahydropyrimidine (2f). The yield was 50%, m.p. 224—225 °C. Found (%): C, 67.98; H, 7.39; N, 11.09. $C_{14}H_{18}N_2O_2$. Calculated (%): C, 68.27; H, 7.37; N, 11.37. IR, ν/cm^{-1}: 3310 (NH); 1620 (C=O); 1600, 1565 (C=C, NH). ^{1}H NMR (DMSO-d_6), δ: 1.85 (quintet, 2 H, CH_2, J = 5.7 Hz); 2.15 (s, 3 H, Me); 2.34 (s, 3 H, Me); 3.29 (m, 4 H, 2 CH_2N); 4.75 (s, 1 H, =CH); 6.36 (s, 1 H, H(5)); 6.40 (s, 1 H, H(3)); 9.08 (br.s, 2 H, 2 NH); 12.54 (br.s, 1 H, OH). Immediately after addition of CD_3CO_2D, the chemical shifts of the aliphatic protons remained unchanged, the signal of the aromatic protons appeared as a singlet at δ 6.41, the intensity of the signal of the vinyl proton decreased to 0.3 H, and a broadened singlet of residual NH protons, which had not managed to be replaced by deuterium, was observed at δ 9.14. Judging from these data, the tetrahydropyrimidinium monocation of compound **2f** did not form.

***N,N'*-Trimethylenebis(3-amino-1-(2'-hydroxyphenyl)-2-buten-1-one) (4) and *N,N'*-trimethylenebis(imine) of 2-hydroxyacetophenone (5).** A mixture of compounds **4** and **5** was prepared in a ratio of 70 : 30 from 2-methylchromone and trimethylenediamine under the conditions described for hexahydropyrimidine **2a**. IR, ν/cm^{-1}: 3200 w, 1615, 1580, 1555, 1520. ^{1}H NMR (80 MHz, $CDCl_3$), δ: **4**, 2.00—2.30 (m, 2 H, CH_2); 2.09 (s, 3 H, Me); 2.11 (s, 3 H, Me); 3.40—3.70 (m, 4 H, 2 CH_2N); 5.67 (s, 1 H, =CH); 5.70 (s, 1 H, =CH); 6.60—7.70 (m, 8 H, 2 C_6H_4)); 11.10 (br.s, 2 H, 2 NH); 13.38 (s, 1 H, OH); 13.46 (s, 1 H, OH); **5**, 2.00—2.30 (m, 2 H, CH_2); 2.36 (s, 6 H, 2 Me); 3.60—3.80 (m, 4 H, 2 CH_2N); 6.60—7.60 (m, 8 H, 2 C_6H_4).

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