Interaction of 2-trichloromethylchromones with ethylenediamine. A simple synthesis of 2-(2-hydroxyaroylmethylene)imidazolidines

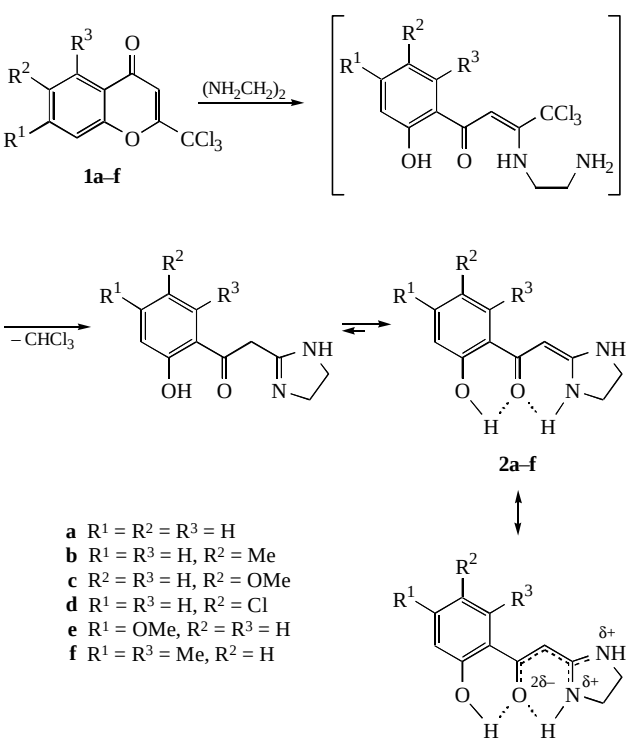
Vyacheslav Ya. Sosnovskikh* and Valentin A. Kutsenko

Department of Chemistry, A. M. Gor'ky Urals State University, 620083 Ekaterinburg, Russian Federation. Fax: +7 3432 61 5978; e-mail: Vyacheslav.Sosnovskikh@usu.ru

Reactions of 2-trichloromethylchromones with ethylenediamine at room temperature give 2-(2-hydroxyaroylmethylene)imidazolidines in high yields.

It is well known that 2-acetonylideneimidazolidine[1] and its analogues substituted at the acetyl group[2] can be prepared by the interaction of ethylenediamine with β-dialkylaminoethynyl ketones and β-amino-β-trichloromethylvinyl ketones, respectively. 2-Phenacylideneimidazolidines were obtained by a reaction that involves desulfurization of phenacylthioimidazolines with triphenylphosphine as a thiophilic reagent.[3] Here we report a synthesis of 2-phenacylideneimidazolidines by the interaction of 2-trichloromethylchromones **1a**–**f** with ethylenediamine.

Previously, chromone **1a** was prepared by a reaction of 2-methylchromone with thionyl chloride in boiling benzene[4] or by condensation of 2-hydroxyacetophenone with trichloroacetonitrile followed by treatment of the condensation product (3-amino-4,4,4-trichloro-1-phenylbut-2-en-1-one) with concentrated HCl.[5] Using the latter method,[5] we obtained 2-trichloromethylchromones **1a**–**f** and found that the interaction of ethylenediamine with **1a**–**f** is a simple and convenient method for synthesising 2-(2-hydroxyaroylmethylene)imidazolidines **2a**–**f**. The reaction proceeded in ethanol or without solvent at room temperature in 3–5 h and afforded compounds **2a**–**f** in 63–94% yields.†

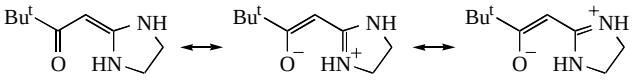


Scheme 1

Most probably, the reaction begins with an attack of an ethylenediamine NH_2 group on the C(2) atom of the chromone system resulting in pyrone ring opening and formation of an intermediate aminoenone with a 2-aminoethyl group at the nitrogen atom. Next, intramolecular replacement of the trichloromethyl group proceeds *via* addition–elimination steps, and 2-phenacyl-Δ^2-imidazolines are formed. The last-mentioned compounds occur in the more stable ketoenamine form of 2-phenacylideneimidazolidines, which were the only species detected by ^{1}H NMR spectroscopy.

It was found previously that substituted chromone-2-carboxylic acid esters afforded 3-(2-hydroxyaroylmethylene)piperazin-2-ones[6,7] by the reaction with ethylenediamine in ethanol. It is also well known that 2-methylchromones undergo ring opening under the action of ethylenediamine in an alcoholic solution at room temperature to form *N*,*N*′-ethylenebis[3-amino-1-(2-hydroxyaryl)but-2-en-1-ones],[8] and 2-trifluoromethylchromones form 5-(2-hydroxyaryl)-7-trifluoromethyl-2,3-dihydro-1*H*-1,4-diazepines[9] under the specified conditions. As for the properties of 2-trichloromethylchromones, the above reaction is the first example of a reaction of these compounds, except for the reaction of chromone **1a** with an alcoholic alkali solution to form 4-hydroxycoumarin.[4]

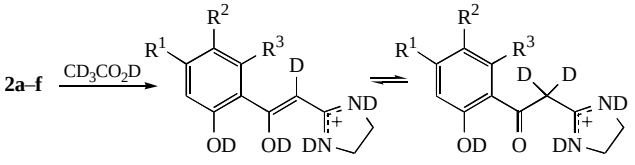
According to X-ray diffraction analysis data,[10] the structure of 2-pivaloylmethyleneimidazolidine, which was described previously,[2] can be considered as the superposition of a ketoenamine tautomer and resonance charge-transfer structures.



Scheme 2

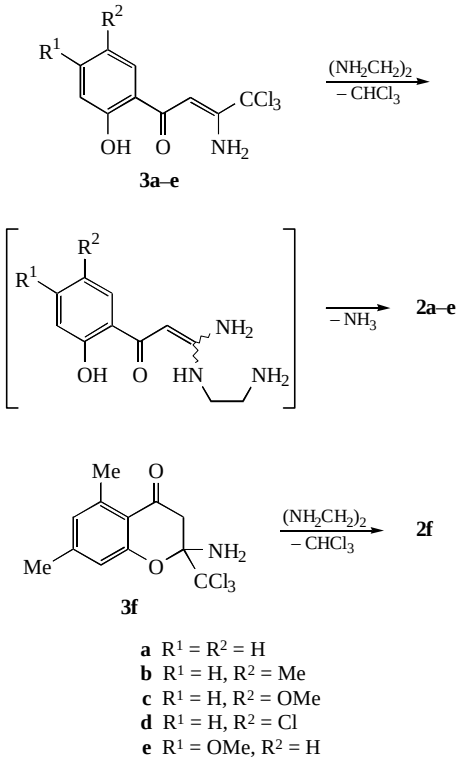
Because both of the hydrogen atoms are localised at nitrogen atoms, the iminoenol form was rejected. Taking into account these data and the possibility of forming an intramolecular hydrogen bond between hydroxyl and carbonyl groups, which stabilises the ketoenamine form relative to the iminoenol form, we believe that products **2a**–**f** also exhibit the structure of ketoenamines with delocalised bonds. The electron-density delocalization is due to strong conjugation of lone electron pairs of nitrogen atoms with carbonyl oxygen, which is favoured by the second intramolecular hydrogen bond N–H···O responsible for flattening the ketoenamine fragment. Thus, 2-phenacylideneimidazolidines **2a**–**f** can be considered as highly delocalised π-systems with a short strong hydrogen bond the nature of which has been studied intensively in recent years.[11]

The exchange of not only OH and NH protons, but also vinyl hydrogen atoms for deuterium occurred immediately after addition of CD_3CO_2D to solutions of compounds **2a**–**f** in $CDCl_3$. This is because of rapid H/D exchange due to an equilibrium between enol and keto forms of the phenacyl substituent of the symmetrically delocalised imidazolinium monocation, which is formed in an acidic medium. In this case, the AA′BB′ multiplet of the ethylene unit becomes a singlet, as was the case in aliphatic analogues.[2]



Scheme 3

Enamino ketones **3a**–**e**, acid hydrolysis of which gave chromones **1a**–**e**, also react with ethylenediamine to form 2-phenacylideneimidazolidines **2a**–**e**. However, in this case, the reaction proceeded at a lower rate (for 3–5 days); the yields of products were lower (25–40%); and analytically pure samples can be obtained only by chromatography. In spite of the fact that the product of 2-hydroxy-4,6-dimethylacetophenone condensation with CCl_3CN occurs as cyclic species **3f**,[12] it also reacts with ethylenediamine to form imidazolidine **2f**, suggesting that the CCl_3 group at the hemiaminal carbon atom can be replaced.



a $R^1 = R^2 = H$
b $R^1 = H$, $R^2 = Me$
c $R^1 = H$, $R^2 = OMe$
d $R^1 = H$, $R^2 = Cl$
e $R^1 = OMe$, $R^2 = H$

Scheme 4

The reduced reactivity of β-amino-β-trichloromethylvinyl ketones in comparison with 2-trichloromethylchromones can be explained by the fact that in aminoenones the CCl_3 group is primarily replaced,[13] and cyclization of ketene aminal intermediates is difficult because of the poor leaving capability of the NH_2 group. Chromones **1a**–**f** are free from this disadvantage, because first the phenol unit [O(1)–C(2) bond rupture] and then the trichloromethyl substituent‡ play the role of the leaving groups in these compounds. Thus, they can readily react not only with ethylenediamine, but also with trimethylenediamine. In the latter case, 2-phenacylidenehexahydropyrimidines are formed in good yields.

Thus, unlike trichloromethylarenes[14] and 2-trichloromethyl-4-quinolones,[15] which are synthetic equivalents of corresponding carboxylic acids, and also trichloromethyl ketones,[16,17] which are selective acylating agents, 2-trichloromethylchromones behave as synthetic equivalents of inaccessible trichloropropynyl ketones in the reactions with aliphatic diamines and are of interest as new highly reactive synthons for preparing partially hydrogenated heterocycles.

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† *2-(2-Hydroxybenzoylmethylene)imidazolidine* **2a**. Chromone **1a** (200 mg, 0.76 mmol) and ethylenediamine (200 μl, 180 mg, 3.0 mmol) were dissolved in 3 ml of ethanol. The reaction mixture was kept for 5 h at room temperature. The resulting crystals of imidazolidine **2a** were washed with ethanol and recrystallised from C_6H_6 and ethanol, yield 110 mg (71%), mp 183–184 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 3.74 (m, 4H, CH_2CH_2), 4.79 (br. s, 1H, NH), 5.38 (s, 1H, =CH), 6.74 [t, 1H, H(5), J_{ortho} 7.2 Hz], 6.88 [d, 1H, H(3), J_{ortho} 8.3 Hz], 7.26 [m, 1H, H(4)], 7.51 [d, 1H, H(6)], 9.19 (br. s, 1H, NH···O), 14.22 (br. s, 1H, OH); after addition of CD_3CO_2D: 3.96 (s, 4H, CH_2CH_2), 6.95 [m, 2H, H(3), H(5)], 7.48 [m, 1H, H(4)], 7.70 [m, 1H, H(6)]. IR (Vaseline oil, ν/cm^{-1}): 3360, 3200 (br., NH), 1615 (C=O), 1585, 1570, 1515. Found (%): C, 64.80; H, 6.12; N, 13.78. Calc. for $C_{11}H_{12}N_2O_2$ (%): C, 64.69; H, 5.92; N, 13.72.

2-(2-Hydroxy-5-methylbenzoylmethylene)imidazolidine **2b**. Yield 89%, mp 195–196 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.27 (s, 3H, Me), 3.63 (m, 2H, CH_2), 3.79 (m, 2H, CH_2), 4.75 (br. s, 1H, NH), 5.41 (s, 1H, =CH), 6.80 [d, 1H, H(3), J_{ortho} 8.1 Hz], 7.09 [dd, 1H, H(4), J_{meta} 2.0 Hz], 7.32 [d, 1H, H(6)], 9.20 (br. s, 1H, NH···O), 13.98 (br. s, 1H, OH); after addition of CD_3CO_2D: 2.27 (s, 3H, Me), 3.84 (s, 4H, CH_2CH_2), 6.84 [d, 1H, H(3), J_{ortho} 8.4 Hz], 7.23 [m, 1H, H(4)], 7.42 [m, 1H, H(6)]. IR (Vaseline oil, ν/cm^{-1}): 3350, 3200 (br., NH), 1615 (C=O), 1570, 1515. Found (%): C, 66.02; H, 6.63; N, 12.70. Calc. for $C_{12}H_{14}N_2O_2$ (%): C, 66.04; H, 6.47; N, 12.84.

2-(2-Hydroxy-5-methoxybenzoylmethylene)imidazolidine **2c**. Yield 84%, mp 165–166 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 3.70 (m, 4H, CH_2CH_2), 3.75 (s, 3H, MeO), 4.87 (br. s, 1H, NH), 5.33 (s, 1H, =CH), 6.81 [d, 1H, H(3), J_{ortho} 8.8 Hz], 6.90 [dd, 1H, H(4), J_{meta} 3.1 Hz], 7.03 [d, 1H, H(6)], 9.17 (br. s, 1H, NH···O), 13.67 (br. s, 1H, OH); after addition of CD_3CO_2D: 3.74 (s, 3H, MeO), 3.83 (s, 4H, CH_2CH_2), 6.84 [d, 1H, H(3), J_{ortho} 9.1 Hz], 7.01 [dd, 1H, H(4)], 7.07 [d, 1H, H(6), J 2.5 Hz]. IR (Vaseline oil, ν/cm^{-1}): 3350, 3220 (br., NH), 1615 (C=O), 1570. Found (%): C, 61.48; H, 6.06; N, 12.07. Calc. for $C_{12}H_{14}N_2O_3$ (%): C, 61.53; H, 6.02; N, 11.96.

2-(2-Hydroxy-5-chlorobenzoylmethylene)imidazolidine **2d**. Yield 94%, mp 238–239 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 3.65 (m, 2H, CH_2), 3.81 (m, 2H, CH_2), 4.73 (br. s, 1H, NH), 5.31 (s, 1H, =CH), 6.82 [d, 1H, H(3), J_{ortho} 8.7 Hz], 7.19 [dd, 1H, H(4), J_{meta} 2.6 Hz], 7.46 [d, 1H, H(6)], 9.17 (br. s, 1H, NH···O), 14.17 (br. s, 1H, OH); after addition of CD_3CO_2D: 4.02 (s, 4H, CH_2CH_2), 6.96 [d, 1H, H(3), J_{ortho} 8.9 Hz], 7.45 [dd, 1H, H(4), J_{meta} 2.4 Hz], 7.73 [d, 1H, H(6)]; after addition of CF_3CO_2D: 4.11 (s, 4H, CH_2CH_2), 7.02 [d, 1H, H(3), J_{ortho} 9.1 Hz], 7.55 [dd, 1H, H(4), J_{meta} 2.3 Hz], 7.64 [d, 1H, H(6)]. IR (Vaseline oil, ν/cm^{-1}): 3350, 3210 (br., NH), 1615 (C=O), 1570, 1515. Found (%): C, 55.31; H, 4.45; N, 11.82. Calc. for $C_{11}H_{11}ClN_2O_2$ (%): C, 55.36; H, 4.65; N, 11.74.

2-(2-Hydroxy-4-methoxybenzoylmethylene)imidazolidine **2e**. Yield 83%, mp 192–193 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 3.75 (m, 4H, CH_2CH_2), 3.79 (s, 3H, MeO), 4.64 (br. s, 1H, NH), 5.28 (s, 1H, =CH), 6.32 [d, 1H, H(5), J_{ortho} 8.5 Hz], 6.38 [s, 1H, H(3)], 7.42 [d, 1H, H(6)], 9.05 (br. s, 1H, NH···O), 14.60 (br. s, 1H, OH); after addition of CD_3CO_2D: 3.83 (s, 3H, MeO), 3.99 (s, 4H, CH_2CH_2), 6.40 [d, 1H, H(3), J_{meta} 2.0 Hz], 6.49 [dd, 1H, H(5), J_{ortho} 8.7 Hz], 7.67 [d, 1H, H(6)]. IR (Vaseline oil, ν/cm^{-1}): 3360, 3210 (br., NH), 1610 (C=O), 1550, 1520. Found (%): C, 61.26; H, 5.94; N, 11.82. Calc. for $C_{12}H_{14}N_2O_3$ (%): C, 61.53; H, 6.02; N, 11.96.

2-(2-Hydroxy-4,6-dimethylbenzoylmethylene)imidazolidine **2f**. Yield 63%, mp 202–203 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.23 [s, 3H, Me(4)], 2.42 [s, 3H, Me(6)], 3.59 (m, 2H, CH_2), 3.74 (m, 2H, CH_2), 4.80 (br. s, 1H, NH), 5.01 (s, 1H, =CH), 6.47 [d, 1H, H(5), J_{meta} 0.7 Hz], 6.56 [d, 1H, H(3)], 9.41 (br. s, 1H, NH···O), 11.6–11.7 (br. s, 1H, OH); after addition of CD_3CO_2D: 2.23 [s, 3H, Me(4)], 2.35 [s, 3H, Me(6)], 3.76 (s, 4H, CH_2CH_2), 6.49 [s, 1H, H(5)], 6.60 [s, 1H, H(3)]. IR (Vaseline oil, ν/cm^{-1}): 3350 (NH), 1610 (C=O), 1570. Found (%): C, 67.25; H, 7.08; N, 11.91. Calc. for $C_{13}H_{16}N_2O_2$ (%): C, 67.22; H, 6.94; N, 12.06.

‡ According to our unpublished data, 2-trichloromethylchromones form corresponding 3-amino-4,4,4-trichloro-1-(2-hydroxyaryl)but-2-en-1-ones upon treatment with an alcoholic solution of ammonia at room temperature. These reactions demonstrate that pyrone ring opening primarily takes place in reactions of 2-trichloromethylchromones with N-nucleophiles, and next the intramolecular replacement of the CCl_3 group occurs with the use of binucleophiles.

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