Condensation of 2-hydroxyacetophenones with trichloroacetonitrile as a route to 2-trichloromethylchromones and 4-hydroxycoumarins

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Condensation of 2-hydroxyacetophenones with trichloroacetonitrile in the presence of *N*-methylanilinomagnesium bromide affords hydroxyaryl β-amino-β-trichloromethylvinyl ketones, which are converted into 2-trichloromethylchromones upon treatment with concentrated HCl. The resulting compounds react with alcoholic solutions of NH_3 or KOH to form 3-amino-1-(2-hydroxyaryl)-4,4,4-trichlorobut-2-en-1-ones and 4-hydroxycoumarins, respectively.

Key words: 2-hydroxyacetophenones, trichloroacetonitrile, 3-amino-1-(2-hydroxyaryl)-4,4,4-trichlorobut-2-en-1-ones, 2-trichloromethylchromones, 4-hydroxycoumarins.

Previously,[1] we have described condensation of 2-hydroxyacetophenone with trichloroacetonitrile in the presence of PhN(Et)MgBr, which proceeded through formation of 3-amino-1-(2-hydroxyphenyl)-4,4,4-trichlorobut-2-en-1-one (**1a**) to yield 2-trichloromethylchromone (**2a**). 2-Trichloromethylbenzo[h]chromone,[2] 2-trichloromethylbenzo[f]chromone,[2] and 5,7-dimethyl-2-trichloromethylchromone[3] were synthesized analogously. The reactions of 2-methylchromone and 7-hydroxy-2-methylchromone with thionyl chloride in boiling benzene afforded chromone **2a** and 7-chloro-2-trichloromethylchromone, respectively. These compounds gave 4-hydroxycoumarin (**3a**) and 7-chloro-4-hydroxycoumarin, respectively, in low yields upon treatment with alcoholic alkali.[4] Recently, we have demonstrated that 2-trichloromethylchromones reacted with ethylene- and trimethylenediamines in alcoholic solutions at room temperature to form 2-(2-hydroxyaroylmethylene)imidazolidines[5] and 2-(2-hydroxyaroylmethylene)hexahydropyrimidines.[6] Owing to the high reactivity of 2-trichloromethylchromones, which is manifested in the fact that both the opening of the pyrone ring and the replacement of the trichloromethyl group proceed readily under the action of diamines, these compounds can be considered as synthetic equivalents of difficultly accessible trichloropropynyl ketones and as very attractive initial reagents for preparing partially hydrogenated heterocycles.

Other data on the synthesis and properties of 2-trichloromethylchromones are lacking in the literature. Apparently, this is associated with the fact that trichloroacetic esters undergo haloform-type cleavage under conditions of Claisen condensation with the use of sodium alkoxides to form chloroform[7] and dichlorocarbene.[8] This fact was confirmed by the results of the study,[9] which demonstrated that condensation of methyl dichlorofluoroacetate with acetophenone in the presence of MeONa gave the target product in low yield due to the formation of chlorofluorocarbene, as well as by the fact that ethyl trichloroacetate undergoes haloform-type cleavage even under the action of secondary amines.[10] In this connection, condensation of 2-hydroxyacetophenone with trichloroacetonitrile[1] instead of alkyl trichloroacetates is a very promising procedure for the synthesis of chromones containing the labile trichloromethyl substituent at position 2.

In the present work, we extended this procedure to substituted 2-hydroxyacetophenones with the aim of synthesizing 2-trichloromethylchromones **2a—e** and studied their reactions with alcoholic solutions of NH_3 and KOH.

Condensation of 2-hydroxyacetophenone and 4- and 5-substituted 2-hydroxyacetophenones with trichloroacetonitrile in the presence of PhN(Me)MgBr[1] afforded aminoenones **1a—e** in 33—55% yields. These aminoenones exist as *Z* isomers stabilized *via* two intramolecular O—H...O and N—H...O hydrogen bonds.[2] Treatment of compounds **1a—e** (compounds **1b—e** were prepared for the first time) with concentrated HCl at room temperature for 1 day gave chromones **2a—e** in 77—96% yields.

It should be noted that condensation of 2-hydroxyacetophenones in the conditions under study was successfully performed only with activated nitriles (CCl_3CN or R^FCN). Therefore, the above-described procedure for the synthesis of 2-trichloromethylchromones is also applicable to 2-polyfluoroalkylchromones[1] but it is not suitable for the preparation of 2-alkylchromones and flavones because aliphatic nitriles do not enter into this reaction and benzonitrile reacts with 2-hydroxy-

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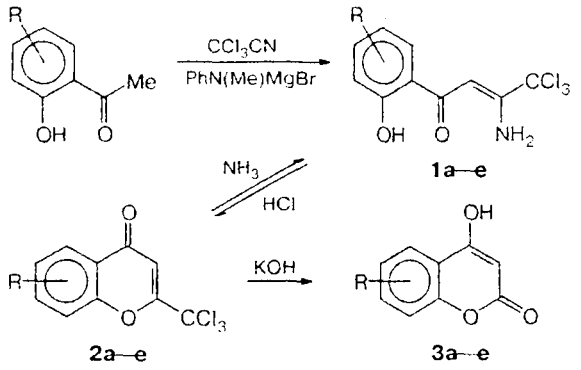

R = H (**1a**—**3a**); 5-Me (**1b**), 6-Me (**2b**, **3b**); 5-Cl (**1c**), 6-Cl (**2c**, **3c**); 5-MeO (**1d**), 6-MeO (**2d**, **3d**); 4-MeO (**1e**), 7-MeO (**2e**, **3e**)

acetophenone to form 3-amino-1-(2-hydroxyphenyl)-3-phenyl-2-propen-1-one (**4**) in low yield (Table 1).

It is known[11—13] that 2-methylchromones are cleaved under the action of amines to form β-aminovinyl ketones containing the 2-hydroxyaryl substituent at the carbonyl group. Previously,[14] we have found that the structures of the products of the reactions of 2-trifluoromethylchromones with ammonia and primary amines are governed by the steric factor. Thus, if the chromone system contains a substituent at position 5, the reaction is terminated at the stage of nucleophilic addition at the C(2) atom, whereas if such substituent is absent, the reaction proceeds further and is accompanied by the opening of the pyrone ring to form the corresponding β-aminovinyl ketones.

We found that 2-trichloromethylchromones **2a**—**e**, like 2-trifluoromethylchromones, which do not contain

Table 1. Physicochemical characteristics of aminoenones **1a**—**e** and **4**

Compound	Yield (%)	M.p./°C	Molecular formula	Found / Calculated (%)			^{1}H NMR (CDCl$_3$, δ, J/Hz)	IR, ν/cm^{-1}
				C	H	N		
1a	36	88—89	$C_{10}H_8Cl_3NO_2$	42.70 42.81	2.56 2.87	5.10 4.99	6.66 (s, 1 H, =CH); 6.80—7.00 (m, 2 H, H(5), H(3)); 7.42 (td, 1 H, H(4), J_o = 8.6, J_m = 1.5); 7.73 (dd, 1 H, H(6), J_o = 8.6, J_m = 1.5); 7.9 (br.s, 2 H, NH$_2$)); 12.74 (s, 1 H, OH)	3400, 3290, 1620, 1580, 1530
1b	49	150—151	$C_{11}H_{10}Cl_3NO_2$	44.80 44.85	3.60 3.42	4.51 4.76	2.31 (s, 3 H, Me); 6.64 (s, 1 H, =CH); 6.86 (d, 1 H, H(3), J_o = 8.5); 7.23 (dd, 1 H, H(4), J_o = 8.5, J_m = 2.1); 7.48 (d, 1 H, H(6), J_m = 2.1); 7.8 (br.s, 2 H, NH$_2$); 12.53 (s, 1 H, OH)	3360, 3180, 1625, 1590, 1525
1c	48	156—157	$C_{10}H_7Cl_4NO_2$	38.09 38.13	2.19 2.24	4.30 4.45	6.56 (s, 1 H, =CH); 6.92 (d, 1 H, H(3), J_o = 8.9); 7.36 (dd, 1 H, H(4), J_o = 8.9, J_m = 2.6); 7.66 (d, 1 H, H(6), J_m = 2.6); 7.9 (br.s, 2 H, NH$_2$); 12.66 (s, 1 H, OH)	3360, 3180, 1620, 1575, 1530
1d	55	123—124	$C_{11}H_{10}Cl_3NO_3$	42.39 42.54	3.15 3.25	4.22 4.51	3.80 (s, 3 H, MeO); 6.60 (s, 1 H, =CH); 6.90 (d, 1 H, H(3), J_o = 8.5); 7.07 (dd, 1 H, H(4), J_o = 8.5, J_m = 2.8); 7.20 (d, 1 H, H(6), J_m = 2.8); 7.9 (br.s, 2 H, NH$_2$); 12.24 (s, 1 H, OH)	3360, 3190, 1625, 1590, 1530
1e	33	107—108	$C_{11}H_{10}Cl_3NO_3$	42.83 42.54	3.20 3.25	4.34 4.51	3.82 (s, 3 H, MeO); 6.55 (s, 1 H, =CH); 6.42 (d, 1 H, H(3), J_m = 2.5); 6.43 (dd, 1 H, H(5), J_o = 9.6, J_m = 2.5); 7.64 (d, 1 H, H(6), J_o = 9.6); 7.7 (br.s, 2 H, NH$_2$); 13.25 (s, 1 H, OH)	3500, 3290, 1615, 1580, 1520
4	8	101—102	$C_{15}H_{13}NO_2$	75.04 75.30	5.47 5.48	5.63 5.85	5.6 (br.s, 1 H, NH); 6.12 (s, 1 H, =CH); 6.73—6.97 (m, 2 H, CH arom.); 7.23—7.83 (m, 7 H, CH arom.); 10.1 (br.s, 1 H, NH...O); 13.46 (s, 1 H, OH)	3430, 3210, 1615, 1580, 1530

a substituent at position 5,[14] reacted with an alcoholic solution of ammonia at room temperature with the opening of the pyrone ring to form aminoenones **1a—e**. In this case, the replacement of the CCl_3 group, which was observed in the reactions with ethylene-[5] and trimethylenediamines,[6] did not occur.

The reactions of chromones **2a—e** with a methanolic solution of KOH upon refluxing for 0.5 h proceeded differently. In these cases, 4-hydroxycoumarins **3a—e**, which have been described previously,[15—17] were obtained in 45—74% yields. As mentioned above, the transformations of chromone **2a** and 7-chloro-2-trichloromethylchromone into the corresponding 4-hydroxycoumarins have been described for the first time in Ref. 4, but the procedure for the synthesis was not reported and coumarin **3a** was isolated in low yield. The reaction mechanism suggested by the authors does not take into account the ability of the CCl_3 group to be replaced under the action of nucleophiles and is based on the assumption that the trichloromethyl group initially undergoes hydrolysis to form the carboxyl group. The authors believed[4] that the subsequent opening of the pyrone ring of chromone-2-carboxylic acid affords α,γ-dioxo acid, whose decarbonylation gives β-oxo acid. The latter undergoes cyclization to coumarin **3a**. Since no evidence for this mechanism was reported in Ref. 4 and taking into account the fact that we did not observe the formation of 4-hydroxycoumarins upon treatment of chromone-2-carboxylic acid with an alcoholic solution of KOH (only the initial acid was isolated), it is believed that the preparation of coumarins **3a—e** from chromones **2a—e** is accompanied by the replacement of the CCl_3 group by the hydroxy group without destruction of the pyrone ring. As a result, 2-hydroxychromones are formed. The most stable tautomeric form of the latter are 4-hydroxycoumarins **3a—e**, which are widely used in production of drugs, owing to their biological properties.

The most important procedures for the preparation of compounds **3a—e** involve condensation of 2-hydroxyacetophenones with diethyl carbonate as well as of phenols with malonic acid.[16] Compared to the latter procedure, the above-described approach to the synthesis of 4-hydroxycoumarins is unlikely to be of practical use. However, this approach is of interest from the viewpoint of the chemical properties of 2-trichloromethylchromones, in which the trichloromethyl substituent is replaced by the hydroxy group rather than undergoing hydrolysis to form the carboxyl group, as was observed in the case of refluxing of 2-trichloromethyl-4-quinolones with a 10% aqueous solution of NaOH over a short period, resulting in 4-hydroxyquinaldic acids (kynurenic acids).[18]

The structures of the resulting aminoenones **1a—e** and 2-trichloromethylchromones **2a—e** accord well with the results of ^1H NMR and IR spectroscopy (Tables 1 and 2). The IR spectra of coumarins **3b—e** have a band of the α-pyrone C=O group at 1695—1715 cm^{-1}, while the IR spectrum of coumarin **3a** shows ν(OH) and ν(C=O) bands at 3380 and 1650 cm^{-1}, respectively, which indicates that the latter compound exists as 2-hydroxychromone in the crystalline state. An analogous conclusion has been made previously.[19]

To summarize, condensation of 2-hydroxyacetophenones with trichloroacetonitrile is a simple and convenient procedure for the synthesis of 2-trichloromethylchromones. The reactions of the latter with am-

Table 2. Physicoshemical sharacteristics of 2-trichloromethylchromones **2a—e**

Compound	Yield (%)	M.p./°C	Molecular formula	Found / Calculated (%)		^1H NMR ($CDCl_3$, δ, J/Hz)	IR, ν/cm^{-1}
				C	H		
2a	95	118—119*	$C_{10}H_5Cl_3O_2$	45.82 / 45.58	1.90 / 1.91	7.00 (s, 1 H, =CH); 7.31—7.88 (m, 3 H, CH arom.); 8.18 (dd, 1 H, H(5), J_o = 8.0, J_m = 1.6)	3060, 1655, 1635, 1610, 1580
2b	96	149—150	$C_{11}H_7Cl_3O_2$	47.50 / 47.61	2.64 / 2.54	2.48 (s, 3 H, Me); 6.99 (s, 1 H, =CH); 7.46 (d, 1 H, H(8), J_o = 8.7); 7.58 (dd, 1 H, H(7), J_o = 8.7, J_m = 1.9); 7.98 (d, 1 H, H(5), J_m = 1.9)	3080, 1660, 1620
2c	77	136—137	$C_{10}H_4Cl_4O_2$	40.49 / 40.31	1.35 / 1.35	7.02 (s, 1 H, =CH); 7.55 (d, 1 H, H(8), J_o = 8.9); 7.72 (dd, 1 H, H(7), J_o = 8.9, J_m = 2.4); 8.14 (d, 1 H, H(5), J_m = 2.4)	3100, 1655, 1605, 1575
2d	95	99—100	$C_{11}H_7Cl_3O_3$	45.01 / 45.01	2.38 / 2.40	3.91 (s, 3 H, MeO); 7.00 (s, 1 H, =CH); 7.33 (dd, 1 H, H(7), J_o = 9.2, J_m = 2.8); 7.54 (d, 1 H, H(8), J_o = 9.2); 7.55 (d, 1 H, H(5), J_m = 2.8)	1660, 1620, 1590
2e	84	159—160	$C_{11}H_7Cl_3O_3$	44.98 / 45.01	2.33 / 2.40	3.93 (s, 3 H, MeO); 6.94 (s, 1 H, =CH); 6.96 (d, 1 H, H(8), J_m = 2.2); 7.01 (dd, 1 H, H(6), J_o = 8.8, J_m = 2.2); 8.08 (d, 1 H, H(5), J_o = 8.8)	1650, 1630, 1605, 1570

* Lit. data[4]: m.p. 118 °C.

monia result in the opening of the pyrone ring, and the reactions with potassium hydroxide lead to the replacement of the CCl_3 group to form 4-hydroxycoumarins.

Experimental

The IR spectra were measured on an IKS-29 instrument in Nujol mulls. The ^1H NMR spectra were recorded on a Tesla BS-567A instrument operating at 100 MHz and on a Bruker WM-250 instrument in $CDCl_3$ and DMSO-d_6 with Me_4Si as the internal standard.

The yields, the melting points, the data of elemental analysis, and the results of IR and ^1H NMR spectroscopy of aminoenones **1a—e** and **4** and of 2-trichloromethylchromones **2a—e** are given in Tables 1 and 2, respectively. Chromone-2-carboxylic acid was prepared according to a known procedure.[20]

3-Amino-4,4,4-trichloro-1-(2-hydroxyphenyl)but-2-en-1-one (1a). A solution of *N*-methylaniline (6.4 g, 0.06 mol, 6.5 mL) in ether (10 mL) was added dropwise with stirring and cooling with ice water to a solution of ethylmagnesium bromide, which was prepared from magnesium (1.5 g, 0.062 mol) and bromoethane (7.6 g, 0.07 mol, 5.2 mL), in anhydrous ether (40 mL). An ethereal solution of a mixture of 2-hydroxyacetophenone (4.1 g, 0.03 mol, 3.6 mL) and trichloroacetonitrile (4.3 g, 0.03 mol, 3.0 mL) was added dropwise to the resulting Grignard—Colonge reagent for 15 min. The reaction mixture was stirred at ~20 °C for 3 h and then decomposed with a saturated aqueous solution of NH_4Cl. The ethereal layer was washed with water and dried with Na_2SO_4. The solvent was distilled off and crystalline product **1a** was filtered off and recrystallized from ethanol. Aminoenones **1b—e** and **4** were prepared analogously.

2-Trichloromethylchromone (2a). Concentrated HCl (10 mL) was added to aminoenone **1a** (1.0 g) and the reaction mixture was kept at ~20 °C for 1 day. Crystals of chromone **2a** were filtered off and recrystallized from ethanol. Chromones **2b—e** were prepared analogously.

4-Hydroxycoumarin (3a). A solution of chromone **2a** (0.2 g, 0.76 mmol) in methanol (5 mL) was added to a solution of KOH (0.2 g, 3.6 mmol) in methanol (5 mL). The reaction mixture was refluxed for 0.5 h and then neutralized with a 5% HCl solution. The crystals that precipitated were filtered off and recrystallized from ethanol; the yield was 80 mg (65%), m.p. 211—212 °C (lit. data[15]: m.p. 210—211 °C). IR, ν/cm^{-1}: 3380 (OH); 1650 (C=O); 1620, 1605, 1560, 1530 sh. (C=C, arom.). ^1H NMR (DMSO-d_6), δ: 5.60 (s, 1 H, =CH); 7.30—7.37 (m, 2 H, H(7), H(8)); 7.60—7.67 (m, 1 H, H(6)); 7.80—7.84 (m, 1 H, H(5)); 12.38 (br.s, 1 H, OH). 4-Hydroxycoumarins **3b—e** were prepared analogously.

4-Hydroxy-6-methylcoumarin (3b). The yield was 71%, m.p. 258—260 °C (methanol) (lit. data[16]: 261—264 °C). IR, ν/cm^{-1}: 1695 (C=O); 1635, 1610, 1575, 1510 (C=C, arom.). ^1H NMR ($CDCl_3$), δ: 2.40 (s, 3 H, Me); 5.76 (s, 1 H, =CH); 7.18 (d, 1 H, H(8), J_o = 8.5 Hz); 7.33 (dd, 1 H, H(7), J_o = 8.5 Hz, J_m = 0.9 Hz); 7.65 (d, 1 H, H(5), J_m = 0.9 Hz); 11.38 (br.s, 1 H, OH).

6-Chloro-4-hydroxycoumarin (3c). The yield was 45%, m.p. 267—269 °C (lit. data[16]: 266—268 °C). IR, ν/cm^{-1}: 1715 (C=O); 1665 w, 1615, 1565 (C=C, arom.). ^1H NMR (DMSO-d_6), δ: 5.59 (s, 1 H, =CH); 7.32 (d, 1 H, H(8), J_o = 8.6 Hz); 7.56 (dd, 1 H, H(7), J_o = 8.6 Hz, J_m = 2.5 Hz); 7.74 (d, 1 H, H(5), J_m = 2.5 Hz); 12.43 (br.s, 1 H, OH).

4-Hydroxy-6-methoxycoumarin (3d). The yield was 74%, m.p. 268—270 °C (lit. data[16]: 271—272 °C). IR, ν/cm^{-1}: 1700 (C=O); 1660 w, 1620, 1590, 1560, 1515 w (C=C, arom.). ^1H NMR (DMSO-d_6), δ: 3.82 (s, 3 H, MeO); 5.59 (s, 1 H, =CH); 7.12 (dd, 1 H, H(7), J_o = 8.8 Hz, J_m = 3.2 Hz); 7.21 (d, 1 H, H(8), J_o = 8.8 Hz); 7.21 (d, 1 H, H(5), J_m = 3.2 Hz); 12.22 (br.s, 1 H, OH).

4-Hydroxy-7-methoxycoumarin (3e). The yield was 54%, m.p. 248—250 °C (aqueous ethanol) (lit. data[17]: 249—253 °C; lit. data[16]: 258—260 °C). IR, ν/cm^{-1}: 1695 (C=O), 1660, 1615, 1560, 1515 (C=C, arom.). ^1H NMR (DMSO-d_6 and CCl_4), δ: 3.85 (s, 3 H, MeO); 5.41 (s, 1 H, =CH); 6.78—6.90 (m, 2 H, H(6), H(8)); 7.68 (d, 1 H, H(5), J_o = 9.4 Hz); the signal for OH was not observed.

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