A Novel Synthesis of 2-Trichloromethylchromones and 7-Trichloromethylnorkhellin

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Abstract: The reaction of 2-hydroxyacetophenones with trichloroacetyl chloride in the presence of pyridine at –30 °C followed by treatment of the reaction mixture with potassium tert-butyate affords 2-hydroxy-2-trichloromethylchroman-4-ones. Dehydration then provides the 2-trichloromethylchromones.

Key words: condensation, 2-hydroxyacetophenones, 2-hydroxy-2-trichloromethylchroman-4-ones, 2-trichloromethylchromones

2-Trichloromethylchromones were first synthesized in 1972 by boiling of 2-methylchromones with thionyl chloride in benzene, but the procedure lacked details.† We showed that these compounds can be obtained by the condensation of 2-hydroxyacetophenones with trichloroacetonitrile in the presence of N-methylaminomagnesium bromide followed by acid hydrolysis of the aminoenones.‡ In several cases, formation of aminoenones was accompanied by considerable polymerization of the reaction mixture, impeding the isolation of target products. Till date, this reaction was the only method for obtaining 2-trichloromethylchromones in moderate yields because the Claisen condensation usually used for synthesis of chromones gives unsatisfactory results in the case of trichloroacetic acid esters due to side reactions associated with haloformic splitting and formation of dichlorocarbene.‡ Since 2-trichloromethylchromones contain the labile CCl₃ group and are of interest in the synthesis of hydrogenated nitrogen-containing heterocycles, such as (2-acetyl methyl)-imidazolidines and hexahydropyrimidines, we attempted to make these compounds more accessible from the preparative point of view.

In this work, we wish to report a novel approach to the synthesis of 2-trichloromethylchromones. The approach (Scheme 1) is based on the modified Baker–Venkataraman rearrangement of esters I and allows one to obtain previously unknown 2-hydroxy-2-trichloromethylchroman-4-ones (2) without isolation of intermediate esters 1. It was established that treatment of aryli trichloroacetates 1, formed in the reaction of 2-hydroxyacetophenones with trichloroacetyl chloride in the presence of pyridine, with potassium tert-butyate at –30 °C for 1.5 h leads to the preparation of chromanones 2a–c in good yields. These compounds are the cyclic forms of the corresponding ortho-trichloracetoacetylphenols and are dehydrated when boiling in acetic acid with concentrated HCl for 5 minutes to give 2-trichloromethylchromones 3a–c in high yields. We have earlier used the intramolecular cyclization of esters of aliphatic β-hydroxyketones under the action of lithium hydride to prepare 3,3-dialkyl-2,3-dihydro-6-trifluoromethyl(trichloromethyl)pyran-4-ones.

The condensation of khellinone with trichloroacetonitrile recently allowed us to obtain 7-trichloromethylnorkhellin (4) with an overall yield of 32%. Compound 4 is the chlorinated analog of natural furochromone khellin, an efficient medicinal agent, which is present in the Ammi visnaga L plant known for its curative properties since the ancient Egyptians.‖ We applied the reaction described above to khellinone and synthesized the new khellin derivative, namely furochromanone 5, whose dehydration affords furochromone 4 in 64% yield after two stages (Scheme 2). The improvement of the overall yield from trichloroacetonitrile with this approach rose to about 30%. Note that ring-chain and ketoenol tautomerism (5A:5B:5C = 3:10:87) is observed in a solution of compound 5 in CDCl₃. Under similar conditions, compounds 2a,b contain about 3–9% diketo and ketoenol forms, and 2c exists exclusively in the chromanone form. Thus, we developed a simple and efficient method for the synthesis of 2-hydroxy-2-trichloromethylchroman-4-ones and 2-trichloromethylchromones, including 7-trichloromethylnorkhellin. This method made these compounds accessible for the preparation of heterocyclic systems with pharmacophoric and natural fragments.
1H NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 400.13 MHz in CDCl₃ solutions with TMS as the internal standard. The IR spectra were measured on an IKS-29 instrument as suspensions in vaseline oil. Melting points are uncorrected. All solvents used were dried and distilled per standard procedures.

**Chromanones 2a–c and 5; General Procedure**

Metallic potassium (2.9 g, 0.074 mol) was dissolved in boiling tBuOH, which initially was diluted with anhyd THF (25 mL) and then was added over 15 min to the obtained soln of tBuOK in tBuOH (50 mL, H₂O content 0.1%) with stirring in a round-bottom flask with a reflux condenser. A soln of aryl trichloroacetate (0.029 mol) and anhyd pyridine (2.6 mL, 2.7 g, 0.034 mol) in anhyd AcOH (3.2 mL, 5.3 g, 0.029 mol) was added with stirring to a soln of the corresponding 2-hydroxyacetophenone (0.029 mol) in anhyd pyridine (2.6 mL, 2.7 g, 0.034 mol) in anhyd THF (20 mL). Then the mixture was heated to boiling and left for 1 h at ~20 °C. The pyridinium hydrochloride precipitate was filtered off and washed with a minor amount of anhyd THF, and the filtrate was added to the residue, the precipitate of chromanone was formed during stirring for 1.5 h at –30 °C, after which HOAc (6 mL) was added to the mixture. The solvate was evaporated, H₂O (100 mL) was added to the residue, the precipitate of chromanone was filtered off, dried, and recrystallized from toluene. In the case of 2a, the crude product was as an oil and solidified after addition of hexane–toluene, 2:1 (20 mL).

**2-Hydroxy-2-trichloromethylchroman-4-one (2a)**

Yield 40%, colorless substance; mp 100 °C.

IR: 3430 (OH), 1690, 1680 (C=O), 1610, 1580 (Ar) cm⁻¹.

1H NMR (400 MHz, CDCl₃): 2.33 (s, 3 H, Me (7)), 2.62 (s, 3 H, Me (5)), 3.25 (d, 1 H, CHH, J = 16.7), 3.43 (d, 1 H, CHH, J = 16.7, both peaks in the low-field part of the AB spectrum are broadened), 3.74 [dd, 1 H, OH (3), Jₐ = 7.2, 10.62 (s, Jₐ = 7.2)], 4.00 (br s, 1 H, OH), 4.07 (s, 3 H, Me), 4.10 (s, 3 H, Me), 6.91 [d, 1 H, H (3), J = 2.3], 7.52 [d, 1 H, H (2), J = 2.3].

5B (10%); 4.05 (s, 3 H, Me), 4.17 (s, 3 H, Me), 4.78 (s, 2 H, CH₂), 6.91 [d, 1 H, H (3), J = 2.3], 7.52 [d, 1 H, H (2), J = 2.3], 12.54 (s, 1 H, OH).

5A (3%); 4.08 (s, 3 H, Me), 4.09 (s, 3 H, Me), 6.88 [d, 1 H, H (3), J = 2.2], 7.41 (s, 1 H, =CH), 7.52 [d, 1 H, H (2), J = 2.2], 10.62 (s, 1 H, OH).

Anal. Calcd for C₁₄H₁₁Cl₃O₆: C, 44.07; H, 2.91. Found: C, 44.08; H, 2.94.

**Chromones 3a–c; General Procedure**

A mixture of chromanone 2 (3.2 mmol), HOAc (8 mL), and concd HCl (5 drops) was boiled for 5 min, then the mixture was cooled and diluted by H₂O (50 mL). The crystalline product was filtered off, washed with EtOH, and dried. Yields of 3a–c were 83–87%, as colorless needle-like crystals.

**3a**

Mp 120 °C (Lit. 3 118–119 °C).

**3b**

Mp 159–160 °C (Lit. 3 159–160 °C).

**3c**

Mp 173–174 °C (Lit. 3 174–175 °C).
7-Trichloromethylnorkhellin (4)
A mixture of chromanone 5 (1.5 g, 3.9 mmol), HOAc (5 mL), and concd HCl (3 drops) were heated for 5 min, then mixed with EtOH (7 mL), and cooled to 0 °C. The crystalline product was filtered off, washed with EtOH, and dried. Yield 1.22 g (85%), yellow needles; mp 169–170 °C (Lit.12 172–173 °C).

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