Homolytic Alkylation of Chromones in Micellar Solution

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Treatment of an aqueous solution of chromone, the detergent sodium dodecylbenzenesulfonate, silver nitrate and an alkanoic acid, with ammonium peroxydisulfate gives 2-R-chromone [R = *i*-C_3H_7 (47%), R = *t*-C_4H_9 (65%) and R = 1-adamantyl (78%)]. In addition 2-R-4-chromanone [R = *i*-C_3H_7 (40%), R = *t*-C_4H_9 (5%) and R-1-adamantyl (10%)] is formed. It is proposed that the reaction involves as intermediate the relatively stable 2-R-4-chromanon-3-yl radical and that the detergent has a micellar catalytic activity on the free radical alkylation process.

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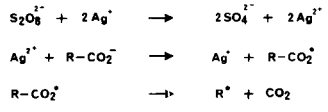
Chromones form a class of compounds, which occur frequently in plants (1). Reactions of chromone and its derivatives have been intensively studied for a long period of time (2a-b). In these studies mainly the reactivity towards electrophiles and nucleophiles has received attention; the behavior of the chromone ring system towards free radicals has been scarcely studied. The chromone ring system consists of an aromatic benzene ring annulated with an oxaheterocycle, which is only slightly aromatic in character (2a-b). Alkyl free radicals do not react very selectively with substituted benzenes but attack aza heteroaromatics preferably on positions of high nucleophilic reactivity (3a-f). In this paper we want to present the results of a study about the regiospecificity of free radical attack in the chromone ring system, with special attention to the application of micellar systems in these radical substitution reactions.

Alkyl radicals can easily be generated by oxidation of alkanoic acids in aqueous solution with ammonium peroxydisulfate, using silver ions as catalyst (4).

Scheme 1

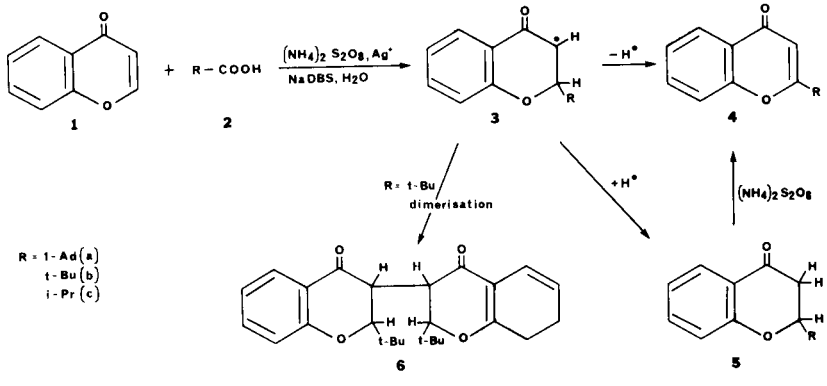


However, due to poor water-solubility of chromone, a pure aqueous solvent system cannot be used. A method, which is frequently applied to overcome this problem, is addition of an organic co-solvent to the aqueous reaction medium. Unfortunately, in free radical alkylations the number of co-solvents applicable is only limited, since alkyl radicals react with many organic co-solvents under the reaction conditions used in these experiments. Acetonitrile has been utilized in some cases but also in this co-solvent side reactions may occur with free radical species (5).

An alternative, more promising, method to solubilize sparingly water-soluble substrates in water is application of surfactants. Surfactants can form micelles in aqueous solution, dissolving easily many poorly water-soluble substrates. Micelles are also capable of catalyzing organic reactions (6). Especially in reactions of water-insoluble organic compounds with water-soluble (inorganic) reagents the use of surfactants can be of considerable interest to synthetic organic chemistry. However, despite their attractive properties, micelles have as yet found limited application in that area (7,8a-b).

In our study the detergent sodium dodecylbenzenesulfonate (NaDBS) was successfully employed to solubilize chromone (**1**). Reaction of **1** in 0.03 *M* NaDBS solution

Scheme 2



with 1-adamantyl, *t*-butyl and isopropyl radicals, generated by oxidation of the corresponding alkanoic acids (**2**) with excess (3 equivalents) of ammonium peroxydisulfate, gave the 2-(1-adamantyl) (**4a**), 2-*t*-butyl (**4b**) and 2-isopropyl (**4c**) chromones in good yields. In all the reactions minor quantities of 2-alkyl-4-chromanones (**5a-c**) were formed. In the reaction with pivalic acid also the dimeric product 3,3'-bis (2-*t*-butyl-4-chromanonyl) (**6**) is formed (Scheme 2).

Chromones and 4-chromanones with small alkyl substituents in the 2-position can be prepared by a number of rather laborious cyclization reactions (2a). None of these methods involved the introduction of an alkyl group by direct alkylation. Chromones and 4-chromanones, containing an adamantyl, *t*-butyl, or isopropyl group in the 2-position are hitherto unknown compounds. The method described here is very useful for the introduction of alkyl groups into the 2-position of **1**, making these compounds now easily accessible.

When not an excess, but an equimolar amount of ammonium peroxydisulfate is used as oxidizing agent, the 2-alkyl-4-chromanones (**5a-c**) are the main products. This result suggests that formation of **4** might proceed *via* the chromanones **5**. Indeed, oxidation of **5** with ammonium peroxydisulfate under the same reaction conditions gave **4** in quantitative yield. The important role of the detergent was demonstrated by the fact that when as solvent for the reaction a mixture of acetonitrile-water (1:1) was used, thus in the absence of NaDBS, the yields of **4** and **5** are low.

Besides their advantageous solubilizing effect, micelles may also exert catalytic activity on the free radical alkylation process. The relatively hydrophobic substrate chromone is solubilized in the apolar chore of the micelle. Free alkyl radicals which are generated in the aqueous phase or at the interface of micelle and water are also hydrophobic in character and move to the hydrophobic chore of the micelle, where reaction with **1** can occur. Reaction takes place preferably at the 2-position of chromone, since then the relatively most stable radical **3** is formed. This radical species can react further by three processes: (i) loss of a hydrogen atom from position 2 giving 2-alkyl chromone (**4**); (ii) abstraction of a hydrogen atom, probably from the alkyl chain of the detergent, leading to 2-alkyl-4-chromanone (**5**); (iii) recombination, yielding the dimer compound 3,3'-bis-(2-alkyl-4-chromanonyl) (**6**). The high yields of **5** obtained when only one equivalent of ammonium peroxydisulfate is used suggest that hydrogen abstraction is the most important reaction pathway for radical species **3**. The high yields of **4** by use of excess of ammonium peroxydisulfate indicate a further oxidation of **5** to **4** by this reagent. This is not unusual, since chromanones are known to be oxidized easily to the corresponding chromones (2). The occurrence of dimer **6** as one of the reaction products strongly supports the idea that the addition of radical R to **1** occurs inside the micelle. Only there, a relatively high concentration of radical species **3** may be expected during the reaction, leading to a considerable degree of dimer formation.

EXPERIMENTAL

Melting points were determined on a Kofler hotplate and are uncorrected. The ^{1}H-nmr spectra are recorded on a Varian EM 390 or a Hitachi Perkin Elmer R-24B spectrometer and deuteriochloroform was used as the solvent and TMS (δ = 0) was the internal standard. The gc-ms analysis was carried out on a VG Micromass 7070F spectrometer. Chromone and the alkanoic acids were supplied by the Aldrich Co. Sodium dodecylbenzenesulfonate (85% technical) was purchased from Fluka AG. All reagents were used without further purification.

General Procedure for Alkylation of Chromone (**1**).

A solution of 2.5 g of sodium dodecylbenzenesulfonate in 250 ml of water, 1.46 g (0.01 mole) of **1**, 0.136 g (0.008 mole) of silver nitrate and 0.02 mole of the appropriate alkanoic acid (*vide infra*) was heated to 90° on a water bath. The solution was acidified with sulfuric acid to *p*H = 2.1 and a solution of 13.7 g (0.06 mole) of ammonium peroxydisulfate in 50 ml of water was added dropwise in one hour. During the reaction time the *p*H of the solution was kept on 2.1 with an 1*M* sodium hydroxide solution in a Radiometer automatic burette. After addition, the reaction mixture was neutralized (1*M* sodium hydroxide) and extracted with chloroform. Due to the surfactant, two or more hours were sometimes needed to complete phase separation. Alternatively, the reaction mixture could be extracted in a continuous ether extraction apparatus, also with good results. The extracts were filtered over Chrompack Supercel and the solvent was evaporated *in vacuo*. The residue was subjected to column chromatography on silica gel, using chloroform or toluene as eluent.

Adamantylation of Chromone.

Synthesis was carried out by the general procedure using 3.6 g (0.02 mole) of 1-adamantanecarboxylic acid and yielded after column chromatography with chloroform as eluent the following products described below.

2-(1-Adamantyl)chromone (**4a**).

This compound was obtained in a yield of 78%, mp 98-100°; nmr: δ 1.50-2.15 (m, 15H, ad), 6.13 (s, 1H, H-3), 7.10-8.30 (m, 4H, arom); ms: m/e (relative intensity) 281 (20), 280 (100), 135 (14), 121 (23).

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.17; H, 7.04.

2-(1-Adamantyl)-4-chromanone (**5a**).

This compound was obtained in a yield of 10%, mp 74-76°; nmr: δ 1.10 -2.20 (m, 15H, ad), 2.65 (dd, 2H, H-3, J = 6.5 and 10 Hz), 3.90 (dd, 1H, H-2, J = 6.5 and 10 Hz), 6.75-7.95 (m, 4H, arom); ms: m/e (relative intensity) 282 (39), 147 (46), 135 (100).

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.67; H, 8.06.

t-Butylation of Chromone.

The synthesis follows the general procedure, using 2.04 g (0.02 mole) of pivalic acid and gave after column chromatography with chloroform as eluent the following products described below.

2-*t*-Butylchromone (**4b**).

This compound was obtained in a yield of 65%, mp 76-77°; nmr: δ 1.33 (s, 9H, *t*-bu), 6.20 (s, 1H, H-3), 7.10-8.20 (m, 4H, arom); ms: m/e (relative intensity) 202 (100), 187 (48), 161 (27), 159 (51), 121 (51).

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.90; H, 7.00.

2-*t*-Butyl-4-chromanone (**5b**).

This compound was obtained in a yield of 5%, mp 64-65°; nmr: δ 1.05

(s, 9H, *t*-bu), 2.60 (dd, 2H, H-3), J = 7 and 8.5 Hz), 4.00 (dd, 1H, H-2, J = 7 and 8.5 Hz), 6.75-7.90 (m, 4H, arom), ms: m/e (relative intensity) 204 (53), 147 (100), 121 (89), 57 (28).

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.31; H, 8.16.

3,3'-Bis-(2-*t*-butyl-4-chromanonyl) (**6b**).

This compound was obtained in a yield of 10%, mp 209-210°; nmr: δ 0.88 (s, 18H, *t*-bu), 3.12 (s, 2H, H-3,3'), 4.18 (s, 2H, H-2,2'), 6.70-7.75 (m, 8H, arom); ms: m/e (relative intensity) 391 (1), 349 (4), 203 (100), 147 (58), 121 (18).

Anal. Calcd. for $C_{26}H_{30}O_4$: C, 76.82; H, 7.44. Found: C, 76.66; H, 7.69.

In a similar reaction with equimolar amounts of pivalic acid and ammonium peroxydisulfate (0.02 mole) the yields are **4b**, 10%; **5b**, 60% and **6b**, 10%.

Isopropylation of Chromone.

Isobutyric acid (1.76 g, 0.02 mole) was used in a synthesis following the general procedure. Column chromatography with toluene as eluent yields in addition to 10% of polymeric product the following compounds.

2-Isopropylchromone (**4c**).

This compound was obtained in a yield of 47%, bp 103-104° (0.3 mm); nmr: δ 1.30 (d, 6H, *i*-pr), 2.85 (m, 1H, *i*-pr), 6.14 (s, 1H, H-3), 7.10-8.20 (m, 4H, arom); ms: m/e (relative intensity) 188 (100), 173 (30), 145 (40), 121 (35), 120 (33).

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.14; H, 6.62.

2-Isopropyl-4-chromanone (**5c**).

This compound was obtained in a yield of 40%, bp 74-76° (0.2 mm); nmr: δ 1.05 (dd, 6H, *i*-pr), 2.00 (m, 1H, *i*-pr), 2.60 (dd, 2H, H-3, J = 6.5 and 9 Hz), 4.15 (m, 1H,H-2), 6.75-7.90 (m, 4H, arom); ms: m/e (relative intensity) 190 (46), 147 (49), 121 (100), 120 (23).

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.89; H, 7.39.

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