MIXED ANHYDRIDE OF ACETIC AND FORMIC ACIDS IN THE SYNTHESIS OF CHROMONES. 2.* SYNTHESIS OF 3-ARYLCHROMONES

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A study was carried out on the reaction of α-substituted 2-hydroxyacetophenones with the mixed anhydride of acetic and formic acids in the presence of bases of different strength. Chromones containing a conjugated electron-withdrawing substituent at $C_{(3)}$ are formed in close to quantitative yield in the presence of triethylamine. The preparation of chromones containing an unconjugated substituent under these conditions is recommended only for 5-hydroxychromones.

In previous work [1], we showed that 2-hydroxyacetophenones containing a π-deficient heteroaromatic residue in the α-position react with the mixed anhydride of acetic and formic acids and sodium formate to give chromones in high yield.

In the present work, we attempted to expand the scope of this method for the synthesis of chromones, which either lack a substituent at $C_{(3)}$ or have aryl, alkyl, or other substituents at this position. The solution of this problem reduces to the finding conditions, under which 2-formyloxyphenyl alkyl ketones with reduced CH-acidity of the α-methylene unit will have a greater tendency to undergo cyclization than deformylation, which is the major hindrance in the synthesis of several chromones [1]. Our mechanism for this reaction [1] suggests that the use of a stronger base and lower temperatures should lead to the desired results.

In order to overcome the difficulties arising in the synthesis of 3-arylchromones [1], we studied the reaction of one of the starting compounds, namely, α-phenyl-2,4-dihydroxyacetophenone (Ia) with the mixed anhydride of acetic and formic acids in the presence of bases stronger than sodium formate, namely, N-methylmorpholine, tribenzylamine, trimethylamine, triethylamine, tri-n-butylamine, sodium methylate, and sodium tert-butylate. The mixed anhydride of acetic and formic acids vigorously decomposes upon the action of these bases to give an acetate salt and carbon monoxide. Formate esters of phenols should be more stable under these conditions than the mixed anhydride of acetic and formic acids. Hence, we assumed that it would be desirable initially in the preparation of chromones to perform the formylation of the hydroxy groups of the starting ketone by the mixed anhydride of acetic and formic acids under mild conditions and only then introduce excess base to the formyloxyacetophenone formed. Small amounts of the same base formed upon the addition of the acetate salt to the mixture are conveniently used as the catalyst in the first step. In the case of this order of carrying out the reaction, as found subsequently, the yield of 3-phenyl-7-hydroxychromone is close to quantitative. However, when the sequence of introduction of the reagents is altered (for example, the mixed anhydride of acetic and formic acids is added to a mixture of 2-hydroxyacetophenone and the base [2]), up to 20% of the starting compound remains in the reaction mixture (see method 3 in the Experimental).

*For Communication 1, see [1].

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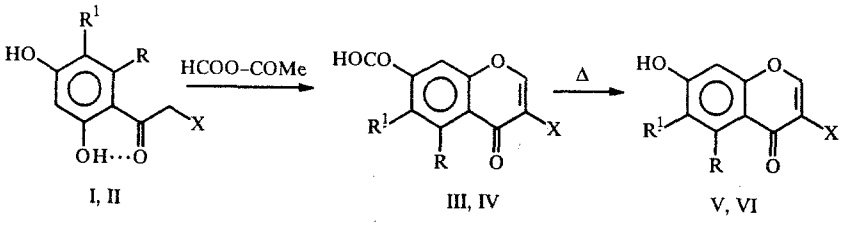

Ia-j, ℓ-q) R = R^1 = H, k) R = H, R^2 = n-Pr, IId-j) R = OH, R^1 = H, IIIk) R = H, R^1 = n-Pr; IVj) R = HCO_2, R^1 = H; Va-j, ℓ-q) R = R^1 = H, k) R = H, R^1 = n-Pr; VId-j) R = OH, R^1 = H; I-VIa) X = Ph, I-VIb) X = 4-HOC_6H_4; I-VIc) X = 4-$O_2NC_6H_4$; I-VId) X = 2-FC_6H_4; I-VIe) 4-FC_6H_4; I-VIf) X = 4-ClC_6H_4; I-VIg) X = 4-BrC_6H_4; I-VIh) X = 4-$MeOC_6H_4$; I-VIi) X = 3,4-$(OCH_2CH_2O)C_6H_3$; I-VIj) X = 5-ethoxycarbonylfur-2-yl; I-VIk) X = benzofur-2-yl; I-VIℓ) X = quinol-7-yl; I-VIm) X = 1-phenylpyrazol-4-yl; I-VIn) X = 4-methoxyphenoxyl; I-VIo) X = F; I-VIp) X = Me; I-VIq) X = H.

The best results under the conditions obtained were obtained using trimethylamine, triethylamine, and tri-n-butylamine as the catalysts (Table 1). In the presence of these alkylamines, the yield of 3-phenylchromone is close to quantitative, while the consumption of the mixed anhydride of acetic and formic acids and the base (per mole of chromone formed) is minimal. The use of N-methylmorpholine also gave good results. Complete conversion in this case requires greater amounts of the mixed anhydride of acetic and formic acids and amine. In the presence of tribenzylamine, the chromone yield is even lower and the cyclization reaction cannot be brought to completion. Only slight amounts of chromone are formed when sodium methylate is used in the catalysis. The use of sodium tert-butylate leads to a chromone yield of 40-50%. In the latter two cases, the reaction was complicated by the separation of the sodium salts of the phenols formed.

Triethylamine, as the most available and efficient catalyst, was used in our study of the reaction of the mixed anhydride of acetic and formic acids with various α-substituted 2-hydroxyacetophenones (Ia-Iq and IId-IIj). In the presence of this base, all the α-aryl-2-hydroxyacetophenones are converted to the corresponding chromones (Va-Vq and VId-VIj) in close to quantitative yields. The consumption of the mixed anhydride of acetic and formic acids is least in the case of ketones Ic-Ig, which contain electron-withdrawing substituents in the aromatic ring. The thin-layer chromatographic data indicate that resacetophenone (Iq), respropiophenone (Ip), α-fluororesacetophenone (Im), and α-(4-methoxyphenoxy)resacetophenone (In) undergo only 20-30% conversion to the corresponding chromone in the presence of triethylamine.

Hence, the mechanism for chromone formation in our case need not differ from the generally accepted mechanism [1, 3]. Considering the pK_a values of the bases used, we may propose that the strength of the base used along with the CH-acidity of the α-methylene unit plays the determining role in the conversion of 2-formyloxyacetophenones into chromones.

The results obtained using sodium methylate and sodium tert-butylate, which are stronger bases than trialkylamines, may be explained assuming an additional transesterification side-reaction, i.e., migration of the formyl group from the phenolic oxygen atom to the alkoxy oxygen atom with the formation of alkyl formate and a phenolate anion. In the case of sterically hindered tert-butylate, transesterification likely does not proceed as readily. Such a reaction apparently does not occur in the experiments with trialkylamines. In this case, formyloxyacetophenone decomposes to give a hydroxy derivative with carbon monoxide formation along with conversion to the chromone. We should note that less carbon monoxide formation is noted when sodium alcoholates are used.

3-Arylchromones may be obtained by the method described both in the hydroxy form (V and VI) and in formyloxy esters (III and IV). In contrast to 3-hetarylchromones [1], formylated 3-arylchromones separate in low yield due to rapid deformylation even in the cold. However, these products may be readily separated since many of them have low solubility in the reaction solution and, in contrast to hydroxychromones, are readily soluble in chloroform. Formyloxychromones in pure form are rather stable upon storage but rapidly decompose upon heating in ethanol at reflux.

Hence, due to the instability of the mixed anhydride of acetic and formic acids and the formyloxy esters, this method is efficient for the preparation of chromones containing an electron-withdrawing substituent at $C_{(3)}$ (an aromatic or

TABLE 1. Conditions for the Reaction of α-Phenyl-2,4-dihydroxyacetophenone with the Mixed Anhydride of Acetic and Formic Acids in the Presence of Various Bases and the Reaction Product Yields

Base	pK_a of conjugated acid	Conversion to chromone, %*	Chromone yield, %	Base	pK_a of conjugated acid	Conversion to chromone, %*	Chromone yield, %
Tribenzylamine	5,6	50	42	Tri-n-butylamine	11,0	100	95
N-Methylmorpholine	7,4	95	88	Sodium methylate	16,0	~5	—
Trimethylamine	9,8	100	92	Sodium tert-butylate	19,0	50	31
Triethylamine	10,9	100	95				

*According to thin layer chromatographic data.

heteroaromatic system, acetyl or nitro group). In light of the higher yields of 5-hydroxychromones and the specific features of the structure of their precursors [1], we may assume that this method may be extended for the preparation of chromones with substituents at $C_{(3)}$ not possessing an electron-withdrawing effect only in this series.

The structures of the new compounds were supported by IR and PMR spectroscopy (Tables 2 and 3). The chromones obtained using the mixed anhydride of acetic and formic acids were identical to the samples obtained by other methods [4-6].

In the IR spectra of the chromones, the band at 1660 cm^{-1} (for the 5-hydroxychromones) or at 1625-1635 cm^{-1} (for all the other chromones) corresponds to the stretching vibrations of the C=O bond of the chromone system, while the band at 1610-1635 cm^{-1} is related to stretching vibrations of the C=C bond. The OH bond stretching vibrations appear as a strong, broad peak at 3400 cm^{-1}. This band is lacking in the IR spectra of the formyloxychromones, but the $\nu_{C=O}$ band for the formyloxy group appears at 1740 cm^{-1}.

The existence of a chromone system in IIIk, IVj, Va-Vi, and VId-VIj is also indicated by a one-proton PMR singlet at 8.3-8.7 ppm, which appears instead of the singlets of the 2-OH group (12.5 ppm) and α-methylene unit (~4.5 ppm), which are found in the spectra of the starting ketones, The proton of the formyloxy group in formylated derivatives IIIk and IVj also appears as a singlet in the vicinity of 8.3 ppm.

EXPERIMENTAL

The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates using 9:1 or 85:15 chloroform—methanol or 95:5 benzene—ethanol as the eluents. The PMR spectra were taken on ZKR-60 and Bruker CXP-200 spectrometers. The IR spectra were taken on a Specord IR-71 spectrometer for KBr pellets. The melting points were determined on a PTP instrument.

Starting 2-hydroxyacetophenones Ia-Iq and IId-IIj were prepared according to reported procedures [5, 7]. All these compounds as well as chromones Va-Vc, Ve-Vj, VIe, VIf, VIh, and VIi (except for the compounds given in Table 2) have been described [4-6]. Pure-grade samples of the liquid trialkylamines were initially dried over potassium hydroxide. Tribenzylamine, sodium methylate, and sodium tert-butylate were dried at 60-100°C and 10 mm Hg for 5 h. The mixed anhydride of acetic and formic acids was used without purification. Analysis of the reaction mixture for chromone and starting ketone was carried out according to our procedure [1].

3-Phenyl-7-hydroxychromone(Va) [8]. A. A sample of 1 g (3.5 mmoles) tribenzylamine was added with stirring to a suspension of 1.14 g (5 mmoles) Ia in 1 ml (11 mmoles) mixed anhydride of acetic and formic acids and 5 ml dry chloroform and, after 10 min and additional 8 g (28 mmoles) tribenzylamine was added. Twice at 30 min intervals, 1 ml mixed anhydride of acetic and formic acids was added. The mixture was stirred at room temperature for 1 h, maintained at 80-100°C for 15 min, and poured into water. The precipitate formed was filtered off and thrice crystallized from benzene to give 0.5 g (42%) Va.

B. A sample of 0.7 ml (15.2 mmoles) N-methylmorpholine was added with stirring over 20 min to a suspension of 1.14 g (5 mmoles) ketone Ia in 1.1 ml (12 mmoles) mixed anhydride of acetic and formic acids at 0°C. After 30 min, 0.7 ml (8 mmoles) mixed anhydride of acetic and formic acids and 1.3 ml (11.5 mmoles) N-methylmorpholine were added at the same temperature. After an additional 30 min, the same amounts of these reagents were added. Chromone Va was separated analogously to the previous procedure. Recrystallization from benzene gave 1.05 g (88%) Va.

TABLE 2. Characteristics of I and II

Compound	Chemical formula	Mp, °C	IR spectrum, ν, cm⁻¹		PMR spectrum in DMSO-d_6, δ, ppm*						
			C=O ketone	OH	2-OH	3-H	4-OH	5-H	6-R	α-CH_3	X
Id	$C_{14}H_{11}FO_3$	138	1630	3350	12,20	6,37	10,63	6,46	7,86	4,41	7,17 (4H, m, 3-H...6-H)
Iℓ	$C_{17}H_{13}NO_3$	226	1625	3430	12,28	6,27	10,40	6,37	7,93	4,55	8,75 (1H, d.d, 2-H); 7,37 (1H, d.d, 3-H); 8,19 (1H, d.d, 4-H); 7,82 (1H, d 5-H); 7,42 (1H, d.d, 6-H); 7,89 (1H, d, 8-H)
In	$C_{15}H_{14}O_5$	179	1630	3300	11,90	6,45	10,75	6,50	7,86	5,42	6,91 (4H, m, 2-H, 3-H, 5-H, 6-H); 3,75 (H, 4-OCH_3)
IId	$C_{14}H_{11}FO_4$	182	1640	3500	12,06	5,88	10,06	5,88	12,06	4,42	7,10 (4H, m, 3-H...6-H)
IIg	$C_{14}H_{11}BrO_4$	231	1640	3420	12,19	5,87	10,41	5,87	12,19	4,37	7,16 (2H, d, 2-H, 6-H); 7,47 (2H, d 3-H, 5-H)

*Spectrum of In was taken in acetone-D_6.

TABLE 3. Characteristics of III-VI

Compound	Chemical formula	Mp, °C	IR spectrum, ν, cm⁻¹		PMR spectrum, δ, ppm					
			C = O, C = C chromone	OH	2-H, s***	5-R**	6-R^1**	7-OH**, (s, CH)	8-H, d***	X
IIIk	$C_{21}H_{16}O_5$	172	1650; 1620	1740***	8,64	8,17 s	0,97 (3H, t, CH_3); 1,71 (2H, m, CH_2); 2,70 (2H, t, CH_2)	8,39***	7,31	7,79 (1H, s, 3-H); 7,14...7,68 (4H, m, 4-H...6-H)
IVj	$C_{18}H_{12}O_9$	178	1650; 1615	1737***	8,66	8,32 d	7,40 d.d	8,36***	7,23	7,01 (1H, d, 3-H); 7,40 (1H, d, 4-H); 4,25 (2H, q, CH_2); 1,43 (3H, t, CH_3)
Vd	$C_{15}H_9FO_3$	224	1630; 1610	3320	8,33	8,01 d	7,02 d.d	10,77	6,95	7,37 (4H, m, 3-H...6-H)
Vℓ	$C_{18}H_{11}NO_3$	288	1630; 1610	3420	8,40	7,88 d	6,85 d.d	10,52	6,78	8,75 (1H, d.d, 2-H); 7,37 (1H, d.d, 3-H); 8,19 (1H, d.d, 4-H); 7,88 (1H, d, 5-H); 7,65 (1H, d.d, 6-H); 8,01 (1H, d, 8-H)
Vk	$C_{20}H_{16}O_4$	254	1640; 1625	3220	8,73	7,89 s	0,98 (3H, t, CH_3); 1,69 (2H, m, CH_2); 2,69 (2H, t, CH_2)	10,83	6,99	7,73 (1H, s, 3-H); 7,15...7,74 (4H, m, 4-H...6-H)
VId	$C_{15}H_9FO_4$	177	1660; 1635	3100	8,38	12,58 s	6,27 d	10,92	6,43	7,33 (4H, m, 3-H...6-H)
VIg	$C_{15}H_9BrO_4$	245	1660; 1635	3100	8,45	12,84 s	6,26 d	—	6,40	7,58 (4H, m, 2-H, 3-H, 5-H, 6-H)
VIj	$C_{16}H_{12}O_7$	262	1650; 1625	3400	8,65	12,42 s	6,26 d	10,85	6,42	7,20 (1H, d, 3-H); 7,30 (1H, d, 4-H); 4,35 (2H, q, CH_2—C_2H_5); 1,36 (3H, t, CH_3)

*Spectra of Vd, Vℓ, Vk, VId, VIg, and VIj were taken in DMSO-d_6, while the spectra of IIIm and IVj were taken in $CDCl_3$.

**Chromone fragment.

C. Dry gaseous trimethylamine obtained by adding 2.2 ml (30 mmoles) 50% aqueous KOH to trimethylammonium chloride was passed through a suspension of 1.14 g (5 mmoles) ketone Ia in 1.1 ml (12 mmoles) mixed anhydride of acetic and formic acids under the conditions described in Procedure A. After 10 min, 0.7 ml (8 mmoles) mixed anhydride of acetic and formic acids was added and the indicated amount of trimethylamine was again introduced. The product was isolated as in Procedure B to give 1.1 g (92%) Va.

D. A sample of 3.5 ml (14.8 mmoles) tri-n-butylamine was added to a suspension of 1.14 g (5 mmoles) ketone Ia in 1.1 ml (12 mmoles) mixed anhydride of acetic and formic acids under the conditions of Procedure B. After stirring for 20 min, a sample of 1.1 ml (12 mmoles) mixed anhydride of acetic and formic acids and 3.5 ml (14.8 mmoles) tri-n-butylamine were added to the lower layer of the two-layer mixture. Separation according to Procedure B gave 1.13 g (95%) Va.

E. A sample of 2 ml (14.3 mmoles) triethylamine was added under the conditions of Procedure B to a suspension of 1.14 g (5 mmoles) ketone Ia in 1.1 ml (12 mmoles) mixed anhydride of acetic and formic acids. After 10 min, 0.7 ml (8 mmoles) mixed anhydride of acetic and formic acids and 1.1 ml (8 mmoles) triethylamine were added consecutively. Separation gave 1.13 g (95%) Va.

F. Under the conditions of Procedure B, a sample of 0.75 g (14 mmoles) sodium methylate was added in portions over 20 min to a suspension of 1.14 g (5 mmoles) ketone Ia in 1.1 ml (12 mmoles) mixed anhydride of acetic and formic acids and 5 ml dry benzene. After stirring, the indicated amounts of the mixed anhydride of acetic and formic acids and sodium methylate were again added. The reaction product was separated as in Procedure B. The filtered precipitate was starting Ia containing up to 5% chromone Va.

G. Under the conditions of Procedure B, 0.34 g (5 mmoles) sodium formate was added to a suspension of 1.14 g (5 mmoles) ketone Ia in 1.1 ml (12 mmoles) mixed anhydride of acetic and formic acids. After the precipitate entered solution (30 min), 1.44 g (15 mmoles) sodium tert-butylate and 5 ml dry, vacuum-distilled DMF were added to the mixture. The reaction mixture was maintained for 1 h at room temperature and heated for 1 h with 50 ml 10% aqueous hydrochloric acid at reflux. The precipitate formed was filtered off and crystallized from benzene to give 0.38 g (38%) chromone Va.

H. A sample of 5 ml ethereal mixed anhydride of acetic and formic acids containing 2.2 ml (25 mmoles) reagent was added to a solution of 1.14 g (5 mmoles) ketone Ia in 25 ml dry benzene and 3 ml (21.5 mmoles) triethylamine. The reaction mixture was stirred at about 0°C for 1 h. Then, 1.5 ml (10.8 mmoles) triethylamine and 5 ml mixed anhydride of acetic and formic acids in ether were added dropwise. The mixture was maintained at room temperature for 1 h. The solvent was distilled off and 100 ml water was added to the residue. The precipitate formed contained 70-80% chromone Va and 20-30% ketone Ia. Separation of the precipitate and crystallization from benzene gave 0.89 g (75%) Va.

7-Hydroxychromones Vb-Vi were obtained analogously to chromone Va according to Procedure E with yields not less than 90%.

7-Hydroxychromones Vn-Vm were synthesized according to Procedure E but the chromones were not separated from the mixture with the starting reagents In-Iq. Their content in the mixture was determined by thin-layer chromatography [1].

3-(2-Benzofuryl)-6-propyl-7-formyloxychromone (IIIk). A sample of 20 ml (143 mmoles) triethylamine was added with stirring over 30 min to a suspension of 19.5 g (63 mmoles) ketone Ia in 22.6 ml (251 mmoles) mixed anhydride of acetic and formic acids and 20 ml dry chloroform. After 30 min, the reaction mixture was diluted with 100 ml dry acetone. The precipitate was filtered off and recrystallized from 1:5 chloroform—acetone to give 19 g (86%) IIIk.

3-(2-Benzofuryl)-6-propyl-7-hydroxychromone (Vk). A solution of 1.74 g (5 mmoles) formate IIIk in 10 ml ethanol was heated at reflux until the starting compound completely disappeared (3-5 h). After cooling to room temperature, the precipitate formed was filtered off. The mother liquor was evaporated to a third of its original volume and additional chromone Vk was extracted. The total yield of Vk was 1.57 g (98%).

3-(5-Ethoxycarbonyl-2-furyl)-5,7-diformyloxychromone (IVj). A sample of 2 ml (14.3 mmoles) triethylamine was added to a suspension of 1.45 g (5 mmoles) ketone IIj in 1.5 ml (17 mmoles) mixed anhydride of acetic and formic acids. After 10 min, 0.7 ml (8 mmoles) mixed anhydride of acetic and formic acids, 1.1 ml (8 mmoles) triethylamine, and 0.7 ml mixed anhydride of acetic and formic acids were added consecutively. The reaction mixture was poured onto ice. The precipitate formed was filtered off, dried, and crystallized from 1:5 chloroform—acetone to give 1 g (64%) formate IVj.

3-(4-Chlorophenyl)-5,7-dihydroxychromone (VIf). A sample of 3 ml (21.5 mmoles) triethylamine was added under the conditions described for Procedure B to a suspension of 1.4 g (5 mmoles) IIf in 1.6 ml (18 mmoles) mixed anhydride of acetic and formic acids. After 10 min, 1.1 ml acetic anhydride and 1.1 ml triethylamine were added. Separation of the reaction product and recrystallization from methanol gave 1.44 g (99%) VIf.

5,7-Dihydroxychromones VId-VIe and VIg-VIj were obtained analogously to VIf with yields not less than 90%.

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