A New Metal Complex Promoted System for Highly Selective Synthesis of 4*H*-Chromen-4-ones (Chromones)

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Co^{III}(salpr)(OH), a six coordinate cobalt Schiff base complex, promotes the highly selective conversion of 1-(*o*-hydroxyaryl)-1,3-diketones to 4*H*-chromen-4-ones under neutral conditions.

It has been shown that the interesting catalytic activity of cobalt(II) Schiff base complexes Co^{II}(SB) in model dioxygenase reactions is attributed to the base catalytic activity of hydroxocobalt(III) species Co^{III}(SB)(OH) produced in an early stage of the reaction.[1] Examples of such base catalytic function of Co^{III}(salpr)(OH) have been demonstrated in the conversion of 2'-hydroxychalcones to flavanones in methanol[2] and in the reaction of the hydroxocobalt(III) complex with *o*-hydroxydibenzoylmethanes in methanol giving rise to a mixture of retro-Claisen reaction products.[3]

We now wish to report here that Co^{III}(salpr)(OH) promotes the exclusive formation of 4*H*-chromen-4-ones (chromones) **3** including flavones from 1-(*o*-hydroxyaryl)-1,3-diketones **2** in 2,2,2-trifluoroethanol (TFE) under neutral conditions (Scheme 1).

Conventional methods for the synthesis of chromones include the cyclodehydration of diketones **2** or equivalent intermediates catalyzed by strong acid or strong bases, where the yield of chromones are not always good.[4-8] Thus, the present results provide a new excellent and convenient method for the synthesis of **3**.

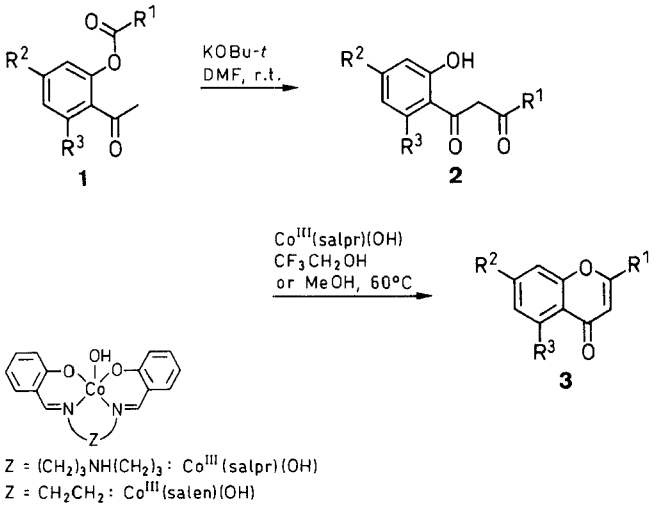
The starting compounds **2** can be conveniently synthesized by the potassium *tert*-butoxide-catalyzed rearrangement of *o*-acyloxyacetophenones **1** in dimethylformamide (Scheme 1) (Table 1). Compounds **1** are obtained readily by conventional acylation of the parent acetophenone derivatives with appropriate acyl chlorides. Compounds **2a–2h** and **2k** are obtained as a tautomeric mixture of the diketo **K** and ketoenol forms **E**, whereas **2i** and **2j** are a mixture of **K**, **E** and cyclic **C** isomers (Scheme 2). Similar results are reported with other samples.[6]

Similar results were obtained when the reaction was carried out with Co^{II}(salpr) under air in place of Co^{III}(salpr)(OH) under nitrogen. Since Co^{II}(salpr) is rapidly oxidized with molecular oxygen in trifluoroethanol to give Co^{III}(salpr)(OCH_2CF_3),[9] this alcoholatocobalt(III) complex should be the primary reactive species in the present reaction.

The fact that retro-Claisen reaction products are formed in methanol[3] strongly suggests the generation of a free methoxide anion in situ under the action of the cobalt catalyst. Trifluoroethanol is a stronger acid than methanol. Therefore, the weaker nucleophilicity of the trifluoroethanolate ($CF_3CH_2O^-$), produced by the dissociation of Co^{III}(salpr)(OCH_2CF_3), would result in constraint of the retro-Claisen reaction. Thus, a substrate anion **4** produced under the reaction conditions in trifluoroethanol undergoes exclusively the intramolecular cyclization giving rise to chromones **3**.

An electron-withdrawing group such as the nitro group in **2a** accelerated the reaction (Table 2), where the retro-Claisen reaction also takes place even in trifluoroethanol to give 2,2,2-trifluoroethyl 4'-nitrobenzoate.

These results suggest that the proton acceptor from the substrate should be $CF_3CH_2O^-$ produced in situ by the reaction of Co^{III}(salpr)(OH) with trifluoroethanol.



1–3	R^1	R^2	R^3	1–3	R^1	R^2	R^3
a	4-$NO_2C_6H_4$	H	H	**g**	Ph	H	$MeOCH_2O$
b	4-ClC_6H_4	H	H	**h**	Ph	OH	H
c	Ph	H	H	**i**	Me	H	H
d	4-MeC_6H_4	H	H	**j**	Et	H	H
e	4-$MeOC_6H_4$	H	H	**k**	*i*-Pr	H	H
f	Ph	MeO	H				

Scheme 1

Table 1. Compounds **2** Prepared

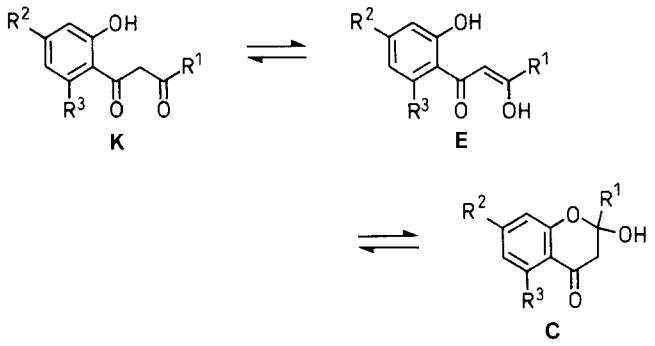
Product	Yield (%)	mp (°C)	Molecular Formula[a] or Lit. mp (°C)
2a	54	199.5–201.5	200–201[7]
2b	71	120.0–121.5	124–125[10]
2c	83	122	118[10]
2d	72	107.0–110.5	109–110[10]
2e	89	110–111	108–109[10]
2f	74	99.5–100.5	101–102[5]
2g	87	74.5–76.0	$C_{17}H_{16}O_5$ (300.3)
2h	58	157–160	162[4]
2i	71	oil	$C_{10}H_{10}O_3$ (178.2)
2j	83	oil	$C_{11}H_{12}O_3$ (192.2)
2k	85	oil	$C_{12}H_{14}O_3$ (206.2)

[a] Satisfactory microanalyses obtained: C ±0.30, H ±0.25.

Table 2. Co^{III}(salpr)(OH) Promoted Conversion of **2** to **3**[a]

Starting Material	Solvent[b]	Reaction Time (h)	Conversion (%)	Selectivity (%)	Product	mp (°C)	Molecular Formula[c] or Lit. mp (°C)
2a	A	8	100	91[d]	**3a**	243–244	240[7]
2b	A	12	87	100	**3b**	185–188	189–190[7]
2c	A	13	77	100	**3c**	97	93–94[8]
	B	5	86	100			
2d	A	17.5	81	100	**3d**	112.5–114	113.5–114.5[7]
2e	A	29	74	100	**3e**	158–160	160–162[7]
2f	A	53.5	84	100	**3f**	104–106	105–106.5[7]
2g	A	53	70	100	**3g**[e]	123–124	$C_{17}H_{14}O_4$ (283.3)
2h	A	26	0	–	–	–	–
2i	C	1	100	94[f]	**3i**	70.0–70.5	69–70[8]
	B	2	100	100			
2j	C	1	100	92[f]	**3j**	oil	oil[8]
2k	C	1	100	100	**3k**	oil	oil[8]

[a] Reaction conditions: 2 (0.5 mmol), Co^{III}(salpr)(OH) (0.5 mmol), solvent; 60 °C.
[b] A = CF_3CH_2OH (10 ml), $ClCH_2CH_2Cl$ (5 ml).
B = CF_3CH_2OH (15 ml).
C = MeOH (15 ml).
[c] Satisfactory microanalyses obtained: C ±0.45, H ±0.30.
[d] 4-$NO_2C_6H_4CO_2CH_2CF_3$ was obtained in addition in addition in 9% yield.
[e] ^1H NMR ($CDCl_3$): δ = 3.56 (s, 3H), 5.35 (s, 2H), 6.70 (s, 1H), 6.9–8.1 (m, 8H). MS: m/z = 282, 267, 251, 238.
[f] *o*-Hydroxyacetophenone was obtained in the reactions of **2i** and **2j** in 6 and 8% yield, respectively.



Scheme 2

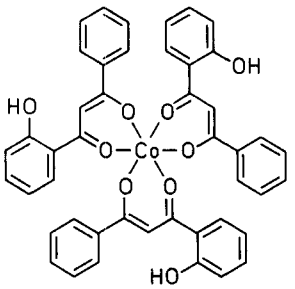
$$Co^{III}(salpr)(OH) + CF_3CH_2OH \rightarrow Co^{III}(salpr)(OCH_2CF_3)$$

$$Co^{III}(salpr)(OCH_2CF_3) \rightleftharpoons [Co^{III}(salpr)]^+ + CF_3CH_2O^-$$

$$2 + CF_3CH_2O^- \rightleftharpoons \mathbf{4} + CF_3CH_2OH$$

Scheme 3

On the other hand, when R^1 is a phenyl substituent bearing an electron-releasing group at the para position, the reaction was slow and only flavones were obtained without completion of the reaction (Table 2). The incompleteness of the reaction is due to the formation of some nonreactive cobalt(III) species including those coordinating the substrate **2** as a bidentate ligand. Among the nonreactive species, a green complex identified as tris[1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedionato]-cobalt(III) (**5**), was actually isolated (2% yield) from the reaction mixture of **2c**. Complex **5** was absolutely inactive for the conversion of **2** to **3**.



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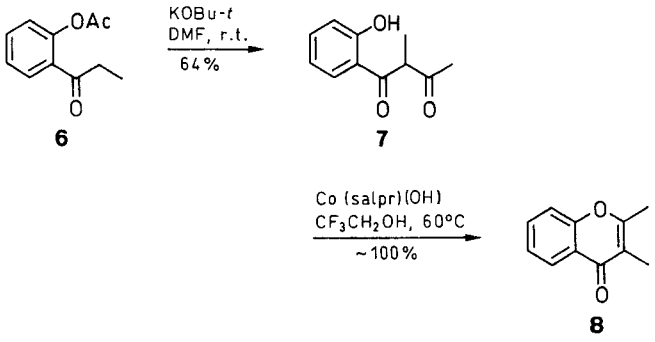
The reactions of **2i–2k** were very fast even in methanol and gave **3i–3k** predominantly together with a small amount of retro-Claisen reaction products (Table 1). When trifluoroethanol was employed as the solvent, the reaction of **2i** became slow but **3i** was obtained in nearly quantitative yield.

The reaction rate was influenced also by the nature of the axial anionic ligand X in Co^{III}(salpr)(X): the weaker nucleophilicity of X results in the slower reaction: that is, the reaction rate increased in the order of X = OAc < OCH_2CF_3 < OH.

Coordinately saturated structure of the cobalt(III) complex is essential for the catalytic activity. No reaction took place with coordinately unsaturated Co^{III}(salen)(OH). In this case, a catalytically inactive Co^{III}(salen) species coordinating the substrate as a bidentate ligand was formed. These results also support the base type catalytic function of Co^{III}(salpr)(OH) as discussed above. The present method can be generally extended to the synthesis

of 2,3-dialkylchromones. For example, 2,3-dimethylchromone (**8**) was obtained quantitatively from the reaction of 1-(*o*-hydroxyphenyl)-2-methylbutane-1,3-dione (**7**), prepared from the base promoted rearrangement of *o*-acetoxypropiophenone (**6**).



6 **7** **8**

The detailed mechanism of the present reaction is currently under investigation by means of electrochemical technique.

1-(2-Hydroxyphenyl)-1,3-diketones (2); General Procedure:
To a solution of *o*-acyloxyacetophenone **1** (0.1 mol), prepared by the conventional acylation of *o*-hydroxyacetophenone in DMF (80 mL) was added a solution of *t*-BuOK (22.4 g, 0.2 mol) in DMF (50 mL) under N_2 at r.t. (with cooling if necessary, because of exothermic reaction). The mixture was allowed to cool at r.t. for about 1 h. The mixture was poured into ice-cooled 3% aq HCl to give solid product, which was collected by filtration washed with water, and dried in vacuo. Recrystallization from EtOH gave the corresponding **2** in excellent yield (Table 1).

The ^{1}H NMR and MS values of new compounds **2g, 2i, 2j** and **2k** are given below.

2g:

^{1}H NMR ($CDCl_3$), **K**-form: δ = 3.15 (s, 3 H), 4.67 (s, 2 H), 4.87 (s, 2 H), 6.4–8.3 (m, 8 H), 12.89 (s, 1 H).

E-form: δ = 3.53 (s, 3 H), 5.31 (s, 2 H), 6.4–8.3 (m, 9 H), 12.27 (s, 1 H). No signal for another OH group was detected (too broad).

MS: *m/z* = 300, 105.

2i:

^{1}H NMR ($CDCl_3$), **K**-form: δ = 2.33 (s, 3 H), 4.11 (s, 2 H), 6.6–8.1 (m, 4 H), 11.99 (s, 1 H).

E-form: δ = 2.13 (s, 3 H), 6.20 (s, 1 H), 6.6–8.1 (m, 4 H), 12.03 (s, 1 H), 14.97 (br s, 1 H).

C-form: δ = 1.77 (s, 3 H), 2.93 (s, 2 H), 3.33 (br s, 1 H), 6.6–8.1 (s, 1 H).

MS: *m/z* = 178, 121.

2j:

^{1}H NMR ($CDCl_3$), **K**-form: δ = 1.23 (t, 3 H, *J* = 8 Hz), 4.13 (s, 2 H), 6.9–8.1 (m, 4 H), 11.94 (s, 1 H).

E-form: δ = 1.23 (t, 3 H, *J* = 8 Hz), 6.20 (s, 1 H), 6.9–8.1 (m, 4 H), 12.06 (s, 1 H), 15.00 (br s, 1 H).

C-form: δ = 1.23 (t, 3 H, 8.0 Hz), 2.88 (s, 2 H), 3.13 (br s, 1 H), 6.9–8.1 (m, 4 H).

The CH_2 group in the ethyl moiety shows multiplet signals around δ = 1.3–2.8 due to the mixture of the three forms.

MS: *m/z* = 192, 163.

2k:

^{1}H NMR ($CDCl_3$), **K**-form: δ = 1.32 (d, 3 H, *J* = 6.8 Hz), 4.13 (s, 2 H), 6.7–8.0 (m, 4 H), 11.98 (s, 1 H).

E-form: δ = 1.32 (d, 6 H, *J* = 6.8 Hz), 2.59 (septet, 1 H, *J* = 6.8 Hz), 6.19 (s, 1 H), 6.7–8.0 (m, 4 H), 12.07 (s, 1 H), 15.11 (br s, 1 H).

MS: *m/z* = 206, 103.

4*H*-Chromen-4-ones 3; General Procedure:
A homogeneous mixture including diketone **2** (0.5 mmol) and Co^{III}(salpr)(OH) (207 mg, 0.5 mmol) TFE (10 mL) and 1,2-dichloroethane (5 mL) was warmed at 60 °C. The time required for completion of the reaction depended on the nature of the solvent as well as that of the substrate **2** employed. The mixture was evaporated and the resulting residue was dissolved in CH_2Cl_2 and chromatographed on a short column of silica gel so that the metal complex was removed. Evaporation of the CH_2Cl_2 eluent gave the appropriate chromone **3** (Table 2).

TLC separation (silica gel, CH_2Cl_2) of a mixture obtained from the reaction of Co^{III} (salpr) (OH) with **2c** gave the diamagnetic **5** as green crystals; yield: 20%.

5

$C_{45}H_{33}O_9Co$	calc.	C 69.59	H 4.28
(776.6)	found	69.54	4.16

^{1}H NMR ($CDCl_3$): δ = 6.8–8.1 (m, 30 H), 10.73 (s, 1 H), 10.81 (s, 1 H), 10.94 (s, 1 H).

The same compound **5** was also obtained from the reaction of $Co^{III}(acac)_3 \cdot 2H_2O$ with **2c** as follows:

A solution of **2c** (0.2417 g, 1 mmol) and $Co^{III}(acac)_3 \cdot 2H_2O$ (0.0985 g, 0.336 mmol) in TFE (10 mL) and 1,2-dichloroethane (5 mL) containing *tert*-butyl hydroperoxide (0.3 mL) was heated at 60 °C with stirring for 1 h. Compound **5** was deposited as green crystals, which were collected by filtration, washed with water, and dried; yield: 0.14 g (52%).

1-(*o*-Hydroxyphenyl)-2-methylbutan-1,3-dione (7) and 2,3-Dimethyl-4*H*-chromen-4-one (8):
To a stirred solution of **6** (5 g, 26 mmol) in DMF (10 mL) was added dropwise a solution of *t*-BuOK (4.2 g, 37 mmol) in DMF (40 mL) at r.t.. After 30 min the resulting solution was treated with ice-cooled 3% aq. HCl (70 mL) and extracted with Et_2O. The Et_2O extract was washed with water, dried (Na_2SO_4), and evaporated to give **7**, which was purified by vacuum distillation; yield: 3.2 g (64%). To a solution of **7** (0.097 g, 0.5 mmol) in TFE (15 mL) was added Co(salpr)(OH) (0.207 g, 0.5 mmol). The resulting solution was warmed at 60 °C for 2 h. The mixture was evaporated and dissolved in CH_2Cl_2 and chromatographed through a short silica gel column to remove the metal complex. Evaporation of the eluent gave **8**; yield: 0.0873 g (quant.).

7; oil; bp 130 °C/7 Torr.

^{1}H NMR ($CDCl_3$), **K**-form: δ = 1.48 (d, 3 H, *J* = 7.3 Hz), 2.22 (s, 3 H), 2.6–3.1 (m, 1 H), 6.6–8.3 (m, 4 H), 12.18 (s, 1 H).

E-form: δ = 1.22 (t, 3 H, *J* = 7.3 Hz), 1.56 (s, 3 H), 2.6–3.1 (s, 1 H), 3.60 (br s, 1 H), 6.6–8.3 (m, 4 H).

C-form: δ = 1.33 (d, 3 H, *J* = 7.3 Hz), 1.76 (s, 3 H), 2.6–3.1 (m, 1 H), 6.6–8.3 (m, 4 H).

MS: *m/z* = 192. **8**; mp 93–95 °C (Lit.[8] 91–93 °C).

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