BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 46, 2211—2215 (1973)

The Oxidative Coupling of Alkyl Aryl Ketones by Iron(III) Chloride

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(Received February 3, 1973)

The oxidative carbon-carbon coupling of two enolizable ketones, propiophenone and butyrophenone, with iron(III) chloride is investigated. The ketones are converted to γ-diketones (II) and 2,5-diphenylfurans (III) in high yields, while iron(III) chloride is reduced to iron(II) chloride. III is produced by the dehydration of II with iron(III) chloride and/or hydrogen chloride. During the reaction, iron(III) chloride is regenerated partially by the oxidation of iron(II) chloride with oxygen in the presence of hydrogen chloride. However, oxygen enhances the formation of III and the polymeric material. The addition of pyridine, calcium oxide, or zinc oxide to the iron(III) chloride-ketone system brings about the selective formation of α-chloroketones. A combination of iron(III) chloride with copper(II) chloride or oxide is effective for the oxidative coupling. Under irradiation, the reactions result both in oxidative coupling and in chlorination at the α-position of the carbonyl group, accompanied by chlorination at the β-position.

The oxidative coupling with phenols of compounds containing the –CH=C(OH)– group has been well known.[1] As the oxidizing agents, $K_3Fe(CN)_6$,[1] $VOCl_3$,[2] VCl_4,[2] Mn(acetylacetonate)$_3$,[3] [Fe(dimethylformamide)$_3Cl_2$][$FeCl_4$],[4] and the Cu-amine-O_2 system[1] have been investigated. In recent years considerable attention has been given to the mechanistic aspects of the coupling of phenoxy radicals.[5–7] We

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[3] M. J. S. Dewar and T. Nakaya, *ibid.*, **90**, 7134 (1968).

[4] S. Tobinaga and E. Kotani, *ibid.*, **94**, 309 (1972).

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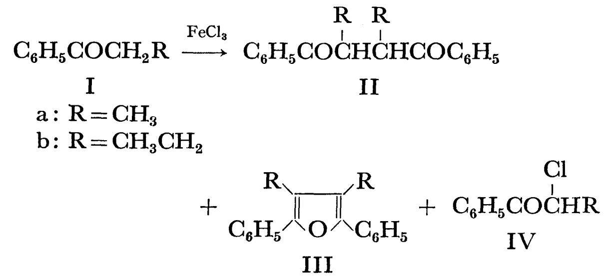
have now examined the oxidative carbon-carbon coupling of enolizable ketones with iron(III) chloride. The carbon-carbon coupling of the compounds containing the activated CH, CH_2, or CH_3 groups has been investigated with a large variety of oxidants.[8] However, no method for the direct coupling of the α-carbon of simple ketones has been reported. We will describe herein a new reaction in which propiophenone (Ia) or butyrophenone (Ib) successfully undergoes carbon-carbon coupling by iron(III) chloride to give the γ-diketones (II) and 2,5-diphenylfurans (III). Furthermore, we will report on the influence of additives, such as pyridine, water, copper(II) chloride, metal oxides, and metal, upon the reactions. Some of the results of this investigation have been reported in a previous communication.[9]



$$C_6H_5COCH_2R \xrightarrow{FeCl_3} C_6H_5CO\overset{R}{C}H\overset{R}{C}HCOC_6H_5 + \text{III} + C_6H_5CO\overset{Cl}{C}HR$$

a: $R=CH_3$
b: $R=CH_3CH_2$

Results and Discussion

Oxidative Coupling. When a solution of anhydrous iron(III) chloride in I was heated without a solvent at 70 °C under an atmosphere of air, γ-diketones (II) were obtained, together with 2,5-diphenylfurans (III) and α-chloroketones (IV). Iron(III) chloride was reduced to iron(II) chloride, which was precipitated as white crystals. The formation curve of the products against the reaction time is shown in Fig. 1. In a separate experiment, it was observed that II was converted to III with the aid of hydrogen chloride and iron(III) chloride. Therefore, III would be produced consecutively by the dehydration of II with hydrogen chloride and/or iron(III) chloride. II was produced parallel with IV without an induction period. In order to investigate whether or not II is produced from IV, a solution of IV in I in the presence of iron(II) or iron(III) chloride was heated at 70 °C. IV was recovered unchanged. This means that II is not produced either by the reductive coupling of IV by iron(II) chloride or by the reaction of IV and the enol of I with iron(III) chloride.

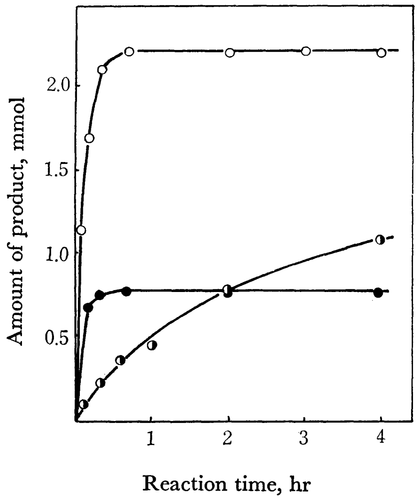
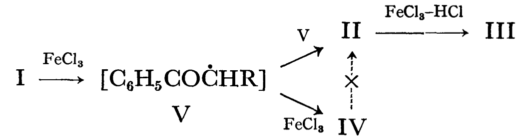


Fig. 1. The formation curves in the reaction of Ia (15 ml) with iron (III) chloride (4.5 mmol) at 70°C.
○: IIa, ◑: IIIa, ●: IVa.

The formation of II and IV together with iron(II) chloride indicates that the initial step involves the oxidation of the ketone by iron(III) chloride, thus leading to the α-keto radical (V). Such a process has also been found in the oxidation of ketones by either manganic or ceric ions.[10–12] The α-keto radicals couple with each other to form II, or are oxidized by the iron(III) chloride to give α-chloroketone (IV).[13]



When the yields of II, III, and IV were calculated by this equation: 200×(the number of moles of the products/the number of moles of iron(III) chloride), the sum of the yields was higher than 100%, as Table 1 shows.

Effect of Oxygen. The oxidation of iron(II) salts by oxygen in an aqueous or nonaqueous solvent has already been studied.[14–16] We carried out the reaction of Ia with iron(III) chloride under an oxygen atmosphere. As Table 1 shows, the reaction resulted in a decreased yield of IIa and an increased yield of IIIa. In addition, a polymeric material, the IR spectrum of which exhibited bands at 3050, 2900, 1700, 1600, 1495, 1440, 1370, 1000, 750, and 695 cm^{-1}, was isolated. Furthermore, we carried out the experiment of heating a dispersed solution of iron(II) chloride in Ia at 70 °C under a slow flow of oxygen and hydrogen chloride for 30 min. In this case, IIa was obtained in a 54% yield, based on the iron(II) chloride. In the absence of hydrogen chloride and oxygen, IIa and IIIa were not obtained at all. Thus, the presence of oxygen

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TABLE 1. THE THERMAL REACTION OF Ia OR Ib WITH IRON(III) CHLORIDE[a)]

Ketone	$FeCl_3$, mmol	Atmosphere	Reaction time, hr	Products, mmol × 10			
				γ-Diketone	Furan	α-Chloroketone	$FeCl_2$
Ia	1.5	Air	24	7.2	4.7	1.9	10.2
Ia	0.3[b)]	Air	24	1.8	1.1	1.3	—
Ia	1.5	O_2	5	3.6	5.1	3.0	—
Ia	1.5	O_2	24	3.5	6.5	2.3	9.6
Ia	1.5	N_2-flowed[c)]	2	7.7	0.0	2.8	—
Ia	1.5	N_2-flowed[c)]	24	19.8	3.5	2.4	8.3
Ib	1.4	Air	48	3.4	—	3.8	9.4
Ib	1.4	N_2	48	4.6	—	3.2	—

a) Experiments were carried out without solvent at 70—75°C, using 5 ml of I.
b) The reaction was carried out in 3 ml of Ia.
c) Nitrogen gas was flowed at 30 ml/min.

and hydrogen chloride brought about the regeneration of iron(III) chloride from iron(II) chloride, but the yield of II decreased due to the consecutive formation of III and the polymeric material. The rate of the formation of the products was not accelerated by oxygen.

In order to remove the excess of oxygen and hydrogen chloride, the reaction was carried out with a slow flow of gaseous nitrogen. As Table 1 shows, II was obtained in a high yield, along with III and IV in low yields. The fact that the yield of II was over 100% indicates that oxygen present in the reaction system contributes to the regeneration of iron(III) chloride. Thus, for preventing the consecutive reaction of II it was effective to remove the excess of oxygen and hydrogen chloride.

Effect of Concentration of Iron(III) Chloride. The amounts of II and III produced after a certain reaction time increased with an increase in the concentration of iron(III) chloride up to nearly the saturation point of iron(III) chloride. When iron(III) chloride came to be dispersed in I, however, the amount of IV increased, while the amounts of II and III decreased.

Effects of Solvents. The use of such solvents as benzene and diglyme was not preferred for the oxidative coupling reaction: the reaction of Ia with iron(III) chloride in diglyme gave mainly IVa in an 80% yield (concentration of iron(III) chloride and Ia, 0.33 mol/l; reaction time, 48 hr; reaction temperature, 70—80 °C).

Effects of Additives. Pyridine or Water: When pyridine was added to a solution of iron(III) chloride in I, an iron(III) chloride–pyridine complex was precipitated. The complex was dispersed in I and was then heated at 70—75 °C for 24 or 48 hr. As Table 2 shows, the yield of IV increased with an increase of the pyridine/iron(III) chloride ratio up to the molar ratio of 1—2: 1, accompanied by a decrease in the yields of II and III. At the molar ratio of 5: 1, however, no product was obtained. These facts indicate that II, III, and IV are produced through the coordination of I to iron(III) chloride and that the addition of pyridine to the iron(III) chloride–I system alters the reaction pathway to the course of the formation of IV:

$$\mathrm{I} \xrightarrow{FeCl_3\text{-}C_5H_5N} \mathrm{IV}$$

The reaction pathway was also influenced by the addition of water instead of pyridine. The increase in the water/iron(III) chloride molar ratio brought about a decrease in the yields of II and III, along with a slight increase in that of IV.

TABLE 2. EFFECTS OF PYRIDINE AND WATER ON THE THERMAL REACTION OF I WITH IRON(III) CHLORIDE[a)]

Ketone	Additive	Molar ratio Additive /$FeCl_3$	Yields of products, %[b)]		
			γ-Diketone	Furan	α-Chloroketone
Ia	C_5H_5N	0	96	63	25
Ia	C_5H_5N	0.5	5	0	69
Ia	C_5H_5N	0.9	0	0	65
Ia	C_5H_5N	2.0	0	0	43
Ia	C_5H_5N	5.0	0	0	0
Ia	H_2O	2.0	42	40	36
Ia	H_2O	6.0	27	23	52
Ib	C_5H_5N	0.5	23	—	18
Ib	C_5H_5N	1.0	0	0	63

a) The starting amount of iron(III) chloride was 1.5 mmol in 5 ml of I. The reactions were carried out under atmosphere at 70—75 °C for 24 hr (Ia) and 48 hr (Ib).
b) The yield was calculated by 200 × (the number of moles of the products that of iron(III) chloride).

Copper(II) Chloride, Metal Oxide, and Metal. The reaction of Ia with iron(III) chloride in the presence of copper(II) chloride was carried out under conditions similar to those in the absence of copper(II) chloride. Since copper(II) chloride was insoluble in Ia, it was dispersed under stirring in a solution of iron(III) chloride in Ia. As is shown in Table 3, the maximum yield of IIa, along with low yields of IIIa and IVa, was observed in the iron(III) chloride/copper(II) chloride plus iron(III) chloride ratio of 0.2: 1. The yield, being over 100%, was higher than in the absence of copper(II) chloride. The amount of IIIa produced increased with an increase in the ratio. On the other hand, the reaction of Ia with copper(II) chloride gave only IVa. The amount of IVa produced decreased with the addition of iron(III) chloride to the copper(II) chloride–I system. Thus, the binary iron(III) chloride–copper(II) chloride system was effective for the oxidative coupling reaction, although the mechanism of the action of the binary metal salts is not as yet clear.

TABLE 3. EFFECTS OF COPPER(II) CHLORIDE ON THE THERMAL REACTION OF Ia WITH IRON(III) CHLORIDE[a)]

$FeCl_3/(FeCl_3+CuCl_2)$[b)] ratio	Products, mmol × 10		
	γ-Diketone	Furan	α-Chloroketone
0	0	0	4.0
0.1	1.4	0	1.8
0.2	7.8	1.8	1.5
0.3	7.0	4.2	1.5
0.5	6.1	4.2	1.5
1.0	4.3	3.0	1.1

a) Experiments were carried out under air atmosphere at 70—75 °C for 24 hr, using 3 ml of Ia.

b) The starting amount of iron(III) chloride plus copper(II) chloride was 0.9 mmol.

The presence of CaO and ZnO in the iron(III) chloride–Ia system resulted in the selective formation of IVa in a high yield, although Ia did not react with CaO and ZnO, as is shown in Table 4. In the cases of TiO_2, Fe_2O_3, and Cr_2O_3, IIa, IIIa, and IVa were obtained. The $FeCl_3$–CuO system gave IIa in a high yield, plus IIIa and IVa in low yields. These results also support the idea of the effectiveness of the Fe(III)–Cu(II) combination system for the oxidative coupling reaction. The reaction of Ia with iron(III) chloride in the presence of Fe^0 or Cu^0 resulted in the formation of IVa without IIa and IIIa, as Table 4 shows.

TABLE 4. EFFECTS OF METAL OXIDE AND METAL ON THE THERMAL REACTION OF Ia WITH IRON(III) CHLORIDE[a)]

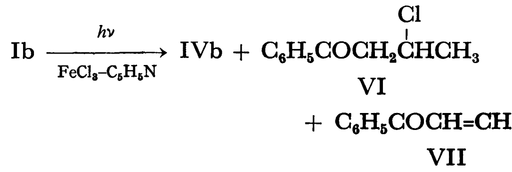
Additive	Product, mmol × 10		
	γ-Diketone	Furan	α-Chloroketone
CaO	0.4	0	8.4
ZnO	0.4	0	7.0
Cr_2O_3	10.9	6.5	2.4
TiO_2	4.9	4.2	2.5
Fe_2O_3	4.8	5.0	5.2
CuO	11.6	0.7	2.2
Fe	0	0	4.6
Cu	0.6	0	4.4

a) The amount of iron(III) chloride used was 1.5 mmol in 5 ml of Ia. The metal oxide or metal /iron(III) chloride molar ratio was 1. The reactions were carried out under air atmosphere at 70—75 °C for 24 hr.

As has been described above, the effects of the concentrations, the additives, and the solvents on the reaction pathway suggest that the course of either coupling or chlorination is governed by the state of an aggregate of iron(III) chloride in the solution—for example, a dimer form of iron(III) chloride, although the details are uncertain. Furthermore, it is interesting to note that a combination of iron(III) chloride and an oxidizing agent is effective for the coupling reaction.

Under Irradiation. A solution of iron(III) chloride in I, which had been placed in a quartz tube, was irradiated with a 100 W high-pressure mercury lamp at a distance of 4 cm under an atmosphere of air at room temperature for 24 hr. During the reaction, white crystals of iron(II) chloride were precipitated. As is shown in Table 5, Ia was converted to IIa, IIIa, and IVa in lower yields than in the case of the thermal reaction. In the case of Ib, however, 3-chlorobutyrophenone (VI), acetophenone, and ethylene were obtained in addition to IIb and IVb. Acetophenone and ethylene were produced after the complete conversion of the iron(III) chloride to iron(II) chloride. The reaction probably proceeded by means of a Norrish Type II process.[17)] When pyridine was added to the reaction system in the pyridine/iron(III) chloride molar ratio of 1: 1, the reaction resulted in chlorination at the α- and/or β-position of the carbonyl group. In the case of Ib, however, crotophenone (VII) was produced by the dehydrochlorination of VI.

$$\text{Ib} \xrightarrow{h\nu} C_6H_5COCH_3 + CH_2{=}CH_2$$



$$\text{Ib} \xrightarrow[FeCl_3\text{–}C_5H_5N]{h\nu} \text{IVb} + \underset{\text{VI}}{C_6H_5COCH_2\overset{\overset{\displaystyle Cl}{|}}{C}HCH_3} + \underset{\text{VII}}{C_6H_5COCH{=}CHCH_3}$$

Other Ketones. The reactions of acetophenone and aliphatic ketones, such as acetone, 2-heptanone, and cyclohexanone, with anhydrous iron(III) chloride at 70 °C resulted in aldol condensation, giving the corresponding α,β-unsaturated ketones. That is, the oxidative coupling by iron(III) chloride was specific for the α-methylene group of alkyl aryl ketones.

$$C_6H_5COCH_3 \xrightarrow{FeCl_3} C_6H_5COCH{=}\overset{\overset{\displaystyle CH_3}{|}}{C}\text{–}C_6H_5$$

TABLE 5. THE PHOTO-REACTIONS OF I WITH IRON(III) CHLORIDE

Ketone	Molar ratio[a)] $C_5H_5N/FeCl_3$	Yields of products, %[b)]				
		γ-Diketone	Furan	α-Chloro-ketone	β-Chloro-ketone	$FeCl_2$
Ia	0	40	29	25	—	94
Ia	1	0	0	20	—	—
Ib	0	26	—	26	14	83
Ib[c)]	1	0	0	48	14	—

a) The amount of iron(III) chloride used was 1.5 mmol in 5 ml of I. The reactions were carried out under air atmosphere at room temperature for 24 hr.

b) The yield was calculated by 200 × (the number of moles of the products/that of iron(III) chloride).

c) Crotophenone was obtained in 6% yield.

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17) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley & Sons, Inc., New York, N. Y. (1967), p. 382.

Experimental

Materials. The aliphatic ketones, acetophenone, metal salts, metal oxides, and metal were purchased from commercial sources. The aliphatic ketones and acetophenone were distilled twice before use. The propiophenone and butyrophenone were prepared by the methods described in the literature.[18] The anhydrous iron(III) chloride was prepared by the sublimation of the commercial iron(III) chloride under the reduced pressure of 1 mmHg at 300 °C. The purity of the iron(III) chloride used was 99—99.8%; it was measured from the content percentage of Fe(III) and chloride ions. Furthermore, the UV absorption spectrum of the iron(III) chloride in dry dioxane coincided with that described in the literature.[19]

Reactions. Similar procedures were used for all the reactions. A solution of 1.3—1.5 mmol of iron(III) chloride in 5 ml of ketones was heated at 70—75 °C or was irradiated with a 100 W high pressure mercury lamp at room temperature for the desired time. II, III, and IV were isolated by gas chromatography after a work-up. The isolation of II and III was carried out by the following method. After a reaction period, dry ether was added to the reaction mixture, the resulting solution was filtered off, and the filtrate was washed repeatedly with water and dried over calcium chloride. After the ether and then the starting ketone and IV had been removed, the residue was distilled under the reduced pressure of 3×10^{-3} mmHg at 100—110 °C. The high-boiling components containing II and III were submitted to chromatography on silica gel (elution with dry carbon tetrachloride), and then to gas chromatography, thus leading to the isolation of II and III.

The NMR spectrum (CCl_4) of IIa showed signals of δ 1.35 and 1.50 (d, 6H, CH_3), 4.25 and 5.60 (q, 2H, CH), and 7.1—8.0 (m, 10H, aromatic protons). The IR spectrum of IIa exhibited strong bands at 1680 cm^{-1} (CO). Mass *m/e*; 266 (parent peak).

Found: C, 81.33; H, 6.80%. Calcd for $C_{18}H_{18}O_2$: C, 81.20; H, 6.76%.

IIb exhibited NMR (CCl_4) signals at δ 0.7—1.3 (m, 6H, CH_3), 1.6—2.1 (m, 4H, CH_2), 4.05 and 5.55 (q and t, 2H, CH), and 6.9—8.0 (m, 10H, aromatic protons), and an IR (liquid film) peak at 1680 cm^{-1} (CO). Mass *m/e*; 294 (parent peak).

Found: C, 81.56; H, 7.55%. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53%.

IIIa, mp 52—54 °C, exhibited NMR (CCl_4) signals at δ 2.16 and 2.33 (s, 6H, CH_3), and 7.2—7.8 (m, 10H, aromatic protons). Mass *m/e*; 248 (parent peak).

Found: C, 86.92; H, 6.50%. Calcd for $C_{18}H_{16}O$: C, 87.09; H, 6.45%.

The other products were identified by a comparison of their IR and NMR spectra, the results of elementary analyses of their 2,4-dinitrophenylhydrazones, their retention times in gas chromatography, and their molecular weights with those of authentic specimens.

Analyses. After a reaction period, the iron(II) chloride produced was filtered off, washed by *n*-hexane, dried over calcium chloride, and then weighed. The determination of the iron(III) chloride and iron(II) chloride was carried out by the methods described in the literature.[20] The amounts of the products were determined by means of gas chromatography using a 3 mm×2 m column of 30% high-vacuum Silicone grease on Celite 545 (80—100 mesh).

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