Titanium Tetrachloride Induced Fries Rearrangement: A New Route to Disubstituted 2'-Hydroxypropiophenones

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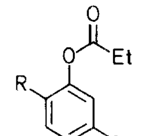
Fries rearrangement of some dialkylphenyl propionates with titanium tetrachloride proves to be a convenient route to hindered dialkyl 2'-hydroxypropiophenones. The sequential use of *soft* titanium tetrachloride to perform the Fries rearrangement followed by *hard* aluminum chloride to achieve the elimination of a protecting *tert*-butyl group allows the synthesis of some previously unknown 3',6'- and 5',6'-dialkyl-2-hydroxypropiophenones.

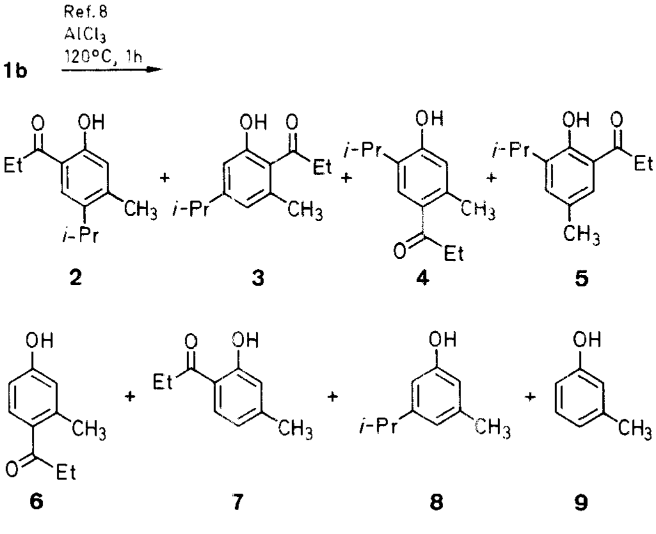
The aluminum chloride induced Fries rearrangement[1-2] of phenyl esters is directed by electronic and steric effects of their substituents.[3-5] When high temperatures are used to induce the *ortho*-rearrangement, migrations or eliminations of alkyl groups may occur. Thus, we had previously observed that ester **1a** gives a quantitative yield of 2'-hydroxy-3',5'-dimethylpropiophenone[6] arising from a methyl migration.[7]



1a R = CH$_3$
b R = *i*-Pr

A new example, observed during the course of the present work, is given by the rearrangement undergone by thymyl propionate (**1b**), when it was reacted with aluminum chloride at 120 °C without solvent. This reaction actually provides a mixture of eight compounds, instead of the sole 2'-hydroxy-3'-isopropyl-6'-methylpropiophenone (**10b**), as previously reported.[8] In fact, this ketone **10b** has never been disclosed in the reaction products. The eight rearranged products of the thymyl ester **1b** are made out of six ketones **2–7** and two phenols **8**, **9** resulting from Fries rearrangement, isopropyl group migration or elimination, respectively (Scheme A).

At a lower temperature (20 °C), 2,5-dimethylphenyl propionate (**1a**) and thymyl propionate (**1b**) give the classical products of



Scheme A

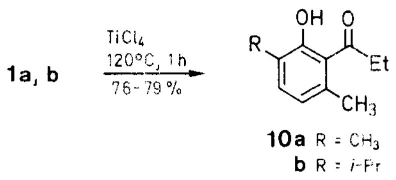
Table 1. Starting Materials **1**, **11**, **13**, **15**, and **16** Prepared

Product	Yield (%)	bp (°C)/mbar and/or mp (°C) (solvent)	Molecular Formula[a] or Lit. bp (°C)/mbar and/or mp (°C)	IR (CH$_2$Cl$_2$) $\nu_{C=O}$ (cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS) δ, *J* (Hz)	MS *m/z* (%)
1a	94	126–127/21	124.5–125.5/17[9]	1757	–	–
1b	94	132–134/15	180/19[8] 133.5–134.5/13[9]	1762	–	–
11a	95	119/11	140/25[19]	1752	–	–
11b	94	149/19	150/15[20]	1752	–	–
13a	88	116/11	142/25[21]	1757	–	–
13b	95	139/15	$C_{13}H_{18}O_2$ (206.3)	1757	1.27 [m, 9H, C$\underline{H}_3$CH$_2$ + (C$\underline{H}_3$)$_2$CH]; 2.33 (s, 3H, CH$_3$); 2.57 (q, 2H, CH$_3$C$\underline{H}_2$); 2.87 (m, 1H, CH); 6.73 (s, 2H$_{arom}$, H-2, 6); 6.9 (s, 1H$_{arom}$, H-4)	206 (M$^+$, 23); 150 (100)
15a	90	125–126/10 46–47 (pentane)	127/10[13] 46[14]	3585 (OH)	1.37 (s, 9H, *t*-C$_4$H$_9$); 2.17 (s, 6H, 2CH$_3$); 4.50 (s, 1H, OH); 6.43 (s, 1H$_{arom}$, H-6); 7.0 (s, 1H, H-3)	178 (M$^+$, 34); 163 (100)
15b	90	134–135/10	113–114[15,b]	3584 (OH)	1.17 [m, 6H, (C$\underline{H}_3$)$_2$CH]; 1.37 (s, 9H, *t*-C$_4$H$_9$); 2.20 (s, 3H, CH$_3$); 3.0 (q, 1H, CH); 4.50 (s, 1H, OH); 6.37 (s, 1H, H-6); 7.07 (s, 1H$_{arom}$, H-3)	206 (M$^+$, 23); 191 (100)
16a	97	147/11	$C_{15}H_{22}O_2$ (234.3)	1752	1.30 (t, 3H, C$\underline{H}_3$CH$_2$); 1.38 (s, 9H, *t*-C$_4$H$_9$); 2.25, 2.28 (2s, 6H, 2CH$_3$); 2.63 (q, 2H, CH$_3$C$\underline{H}_2$); 6.80 (s, 1H$_{arom}$, H-6); 7.17 (s, 1H$_{arom}$, H-3)	234 (M$^+$, 19); 163 (100)
16b	98	157/10	$C_{17}H_{26}O_2$ (262.4)	1752	1.27 [m, 9H, C$\underline{H}_3$CH$_2$ + (C$\underline{H}_3$)$_2$CH]; 1.37 (s, 9H, *t*-C$_4$H$_9$); 2.3 (s, 3H, CH$_3$); 2.62 (q, 2H, CH$_3$C$\underline{H}_2$); 3.13 (m, 1H, CH); 6.77 (s, 1H$_{arom}$, H-6); 7.27 (s, 1H$_{arom}$, H-3)	262 (M$^+$, 16); 191 (100)

[a] Satisfactory microanalyses obtained: C ±0.37, H ±0.12.
[b] Evidently erroneous, *p*-thymol, the starting material, melts at 112–113 °C,[16] 114 °C.[17-18]

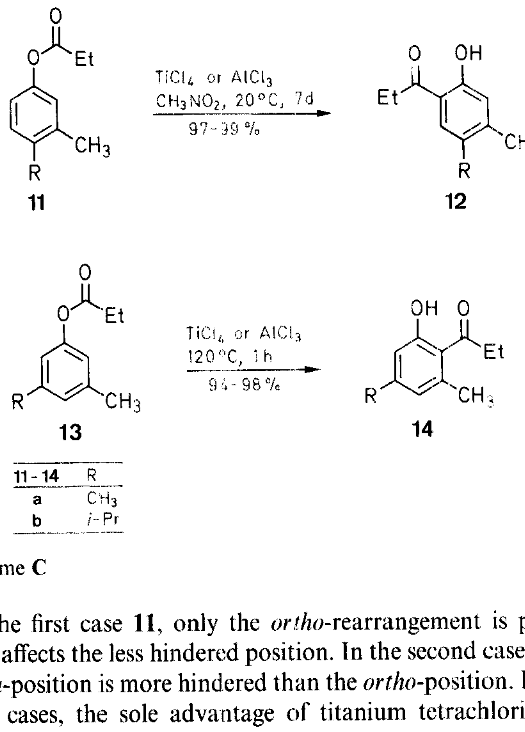
para-rearrangement[9-10] accompanied in the first case by only 11 % of the 2'-hydroxy-3',6'-dimethylpropiophenone (**10a**).[7]

Using titanium tetrachloride as catalyst, we wish to report herein a high yield synthesis of the 3',6'-disubstituted-2'-hydroxypropiophenone **10a** and of its unknown analogue **10b**, which we need as intermediates for pharmaceutical purposes (Scheme **B**).



Scheme **B**

On the contrary, in the cases of 3,4-dialkylphenyl propionates **11** and 3,5-dialkylphenyl propionates **13**, both aluminum chloride and titanium tetrachloride lead to the formation of the *ortho*-rearrangement products, **12** and **14**, respectively (Scheme **C**).



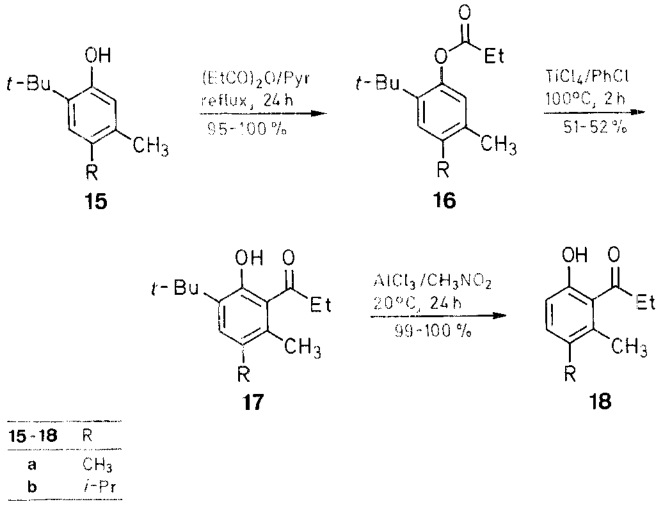
Scheme C

In the first case **11**, only the *ortho*-rearrangement is possible and affects the less hindered position. In the second case **13**, the *para*-position is more hindered than the *ortho*-position. In these two cases, the sole advantage of titanium tetrachloride is a slightly better yield in the formation of **14b**.

As yet, a complete vicinal rearrangement has never been observed starting from esters **11**, although the all vicinally substituted 2'-hydroxypropiophenones **18** are rather attractive synthetic intermediates for many purposes.

We describe here a two-step preparation of the ketones **18** based on the *soft* catalytic properties of titanium tetrachloride to carry out the Fries rearrangement of the 6-*tert*-butylated aryl esters **16**, followed by the use of the well-known properties of aluminum chloride to induce the cleavage of the *tert*-butyl protecting group[12] (Scheme **D**).

In the same solvent and at the same temperature, but using aluminum chloride as catalyst, the ester **16a** gives the de-*tert*-butylated non-vicinal ketone **12a** (58 %) as major product and 3,4-dimethylphenol (42 %). The ester **16b** leads to *meta*-cresol (61 %) as major product and the non-vicinal ketone **12b** (26 %).



Scheme D

Melting points (uncorrected) were determined on a Kofler apparatus (> 60°C) or with a capillary tube. IR spectra were recorded on a Perkin Elmer 1710 and the UV spectra on a Varian Techtron 635 spectrometers. ^{1}H-NMR spectra were recorded at 90 MHz on a Varian EM 390 using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were obtained on a Ribermag R-10-10-C apparatus. The purity of all the compounds was checked by TLC and GC (OV-17, - 15%, 4 m, 260°C, carrier gas: Helium). The yields were estimated by GC. Elementary analyses were performed by the Central Service of Microanalyses, CNRS, Solaise.

Starting Materials: The xylenols and isopropylcresols are commercially available. The preparation of *tert*-butyl substituted phenols **15a**, **b** and the general procedure for the esterification of phenols are given below.

2-tert-Butyl-4,5-dimethylphenol (**15a**) *and 2-tert-Butyl-4-isopropyl-5-methylphenol* (**15b**): A mixture of the appropriate phenol (200 mmol) and *tert*-butyl chloride (38 mL, 350 mmol) are heated together with stirring at 80–85°C for 24 h. The mixture is allowed to cool to room temperature and ether (300 mL) is added. The ether layer is separated and washed with 8 % aq. NaOH solution (3 × 300 mL), 10 % aq. $NaHCO_3$ solution (150 mL), and finally with water (4 × 100 mL). The ether layer is dried (Na_2SO_4), the solvent removed, and the residue is distilled (Table 1).

Aryl Propionates 1, 11, 13, 16; General Procedure:
A solution of the appropriate phenol (250 mmol), propionic anhydride (40 mL, 310 mmol) and pyridine (50 mL, 620 mmol) is refluxed for 24 h, and then allowed to cool to about 80°C. Water (50 mL) is added, and the mixture is refluxed for 30 min. The mixture is cooled, ether (300 mL) is added, the organic layer washed successively with water (4 × 100 mL), 2 N H_2SO_4 (4 × 100 mL), water (2 × 100 mL), 2 N aq. NaOH solution (2 × 100 mL), and finally again with water (5 × 100 mL). The ether layer is dried (Na_2SO_4) and evaporated. The residue is distilled to provide the pure ester (Table 1).

Fries Rearrangement of Aryl Propionates; General Procedure:
The Fries rearrangements are carried out according to the experimental conditions indicated in Table 2. After the reaction is over, the mixture is cooled, and quenched with 4 N HCl (20 mL). The product is dissolved in ether (50 mL) and the ether layer is washed successively with 4 N HCl (2 × 5 mL), water (2 × 20 mL), 10 % aq. $NaHCO_3$ solution (5 mL), and finally with water (3 × 20 mL). The ether layer is dried (Na_2SO_4), and evaporated. The modes of purification of the products are given in Table 2.

2'-Hydroxy-5',6'-dimethylpropiophenone (18a) and 2'-Hydroxy-5'-isopropyl-6'-methylpropiophenone (18b):
To a cooled (0°C) and well stirred solution of the ketone **17** (10 mmol) in dry CH_3NO_2 (10 mL), $AlCl_3$ (2 g, 15 mmol) is added in one portion. Stirring is continued for 24 h at 20°C, then the mixture is quenched with 4 N HCl (20 mL) and worked up as given in the procedure under Fries rearrangement. The purification of the dealkylated ketones is carried out by column chromatography on silica gel (70 g, eluent: CH_2Cl_2). The ketones **18a** and **18b** obtained are recrystallized from pentane (Table 3).

Table 2. Reaction Conditions of Fries Rearrangement

Method (Ester)	Reactants		Solvent (mL)	Reaction Conditions	Purification of Ketones[a]
	Ester (mmol)	$TiCl_4$ (mL/mmol)		Temp. (°C)/Time (h)	
A (**1a, b**: **13a, b**)	12	2/18	none	120/1	**10a:** C, then R (70% EtOH) **10b:** D, then C **14a:** R (*n*-hexane) **14b:** D
B (**11a, b**)	10	1.65/15	CH_3NO_2/6	20/100	**12a, b:** R (EtOH)
C (**16a, b**)	8	1/9	PhCl/6	100/2	**17a, b:** C, then R (EtOH)

[a] C = column chromatography on silica gel [70 g, eluent: benzene/petroleum ether (bp 40–65°C), 3 : 7]; R = recrystallization; D = distillation.

Table 3. Ketones **10**, **12**, **14**, **17**, and **18** Prepared

Product	Yield (%)	bp (°C)/mbar and/or mp (°C)[a] (solvent)	Molecular Formula[b] or Lit. bp (°C)/mbar and/or mp (°C)	UV (EtOH) λ_{max} (nm) (log ε)	IR (CH_2Cl_2) $\nu_{C=O}$ (cm^{-1})	^1H-NMR ($CDCl_3$/TMS) δ, J(Hz)	MS *m/z* (%)
10a	76	43 (70% EtOH)	43[7]	203 (4.20), 216 (4.12), 260 (3.52)	1620	1.2 (t, 3H, $C\underline{H}_3CH_2$); 2.2 (s, 3H, 3'-CH_3); 2.53 (s, 3H, 6'-CH_3); 2.79 (q, 2H, $CH_3C\underline{H}_2$); 6.6 (d, 1H, H-4', J = 7.5); 7.13 (d, 1H, H-5', J = 7.5); 12.1 (s, 1H, OH)	178 (M^+, 28); 149 (100)
10b	79	156–157/14 39 (70% EtOH)	$C_{13}H_{18}O_2$[c] (206.3)	202 (4.23), 216 (4.15), 267 (3.63)	1622	1.2 [m, 9H, $(C\underline{H}_3)_2CH + C\underline{H}_3CH_2$]; 2.55 (s, 3H, CH_3); 2.93 (q, 2H, $CH_3C\underline{H}_2$); 3.3 (m, 1H, CH); 6.66 (d, 1H, H-5', J = 8); 7.2 (d, 1H, H-4', J = 8); 12.26 (s, 1H, OH)	206 (M^+, 20); 177 (100)
12a	99	140/10 61 (EtOH)	101/7[19] 60[11]	215 (4.32), 261 (4.13), 333 (3.67)	1639	1.2 (m, 3H, $C\underline{H}_3CH_2$); 2.2 + 2.26 (2s, 6H, 2CH_3); 3.0 (m, 2H, $CH_3C\underline{H}_2$); 6.73 (s, 1H, H-3'); 7.43 (s, 1H, H-6'); 12.16 (s, 1H, OH)	178 (M^+, 35); 149 (100)
12b	97	161–162/17 35 (EtOH)	$C_{13}H_{18}O_2$ (206.3)	217 (4.31), 261 (4.10), 333 (3.60)	1644	1.2 [m, 9H, $(C\underline{H}_3)_2CH + C\underline{H}_3CH_2$]; 2.3 (s, 3H, CH_3); 3.0 (m, 3H, $CH_3C\underline{H}_2$ + CH); 6.63 (s, 1H, H-3'); 7.53 (s, 1H, H-6'); 12.1 (s, 1H, OH)	206 (M^+, 36); 177 (100)
14a	98	78 (*n*-hexane)	78[22]	203 (4.23), 219 (4.12), 257 (3.57)	1626	1.2 (m, 3H, $C\underline{H}_3CH_2$); 2.26 (s, 3H, 4'-CH_3); 2.53 (s, 3H, 6'-CH_3); 2.93 (q, 2H, $CH_3C\underline{H}_2$); 6.5 (br s, 1H, H-3'); 6.63 (br s, 1H, H-5'); 12.3 (s, 1H, OH)	178 (M^+, 24); 149 (100)
14b	94	164/14 23	$C_{13}H_{18}O_2$ (206.3)	202 (4.25), 217 (4.13), 257 (3.60)	1626	1.2 [m, 9H, $(C\underline{H}_3)_2CH + C\underline{H}_3CH_2$]; 2.57 (s, 3H, CH_3); 2.9 (m, 3H, $CH_3C\underline{H}_2$ + CH); 6.57 (d, 1H, H-3', $J_{3',5'}$ = 2.5); 6.7 (d, 1H, H-5', $J_{5',3}$ = 2.5); 12.3 (s, 1H, OH)	206 (M^+, 22); 177 (100)
17a	52	56 (EtOH)	$C_{15}H_{22}O_2$ (234.3)	203 (4.30), 217 (4.13), 270 (3.57)	1630	1.3 (m, 12H, t-$C_4H_9 + C\underline{H}_3CH_2$); 2.2 + 2.3 (2s, 6H, 2$CH_3$); 2.86 (q, 2H, $CH_3C\underline{H}_2$); 7.13 (s, 1H, H-4'); 10.2 (s, 1H, OH)	234 (M^+, 24); 205 (100)
17b	51	73 (EtOH)	$C_{17}H_{26}O_2$ (262.4)	203 (4.31), 218 (4.12), 271 (3.48)	1631	1.2 [m, 9H, $(C\underline{H}_3)_2CH + C\underline{H}_3CH_2$]; 1.4 (s, 9H, t-C_4H_9); 2.36 (s, 3H, CH_3); 2.86 (q, 2H, $CH_3C\underline{H}_2$); 3.1 (q, 1H, J = 8, CH); 7.26 (s, 1H, H-4'); 9.76 (s, 1H, OH)	262 (M^+, 18); 233 (100)
18a	100	70 (pentane)	$C_{11}H_{14}O_2$ (178.2)	202 (4.11), 216 (4.08), 288 (3.31)	1701, 1636	1.2 (t, 3H, $C\underline{H}_3CH_2$); 2.2 (s, 3H, 3'-CH_3); 2.33 (s, 3H, 2'-CH_3); 2.86 (q, 2H, $CH_3C\underline{H}_2$); 6.7 (d, 1H, H-5', J = 8.3); 7.1 (d, 1H, H-4', J = 8.3); 9.26 (s, 1H, OH)	178 (M^+, 25); 149 (100)
18b	99	70 (pentane)	$C_{13}H_{18}O_2$[d] (206.3)	203 (4.12), 217 (4.05), 287 (3.24)	1699, 1636	1.2 [m, 9H, $(C\underline{H}_3)_2CH + C\underline{H}_3CH_2$]; 2.33 (s, 3H, CH_3); 2.87 (q, 2H, $CH_3C\underline{H}_2$); 3.1 (m, 1H, CH); 6.7 (d, 1H, H-5', J = 8.5); 7.2 (d, 1H, H-4', J = 8.5); 8.7 (s, 1H, OH)	206 (M^+, 20); 177 (100)

[a] Melting points are uncorrected.

[b] Satisfactory microanalyses obtained: C ±0.32, H ±0.14.

[c] The reported boiling points (161°C/6 mbar[8] and 117–118°C/11 mbar[23]) are obviously erroneous, since they correspond to a mixture of products, where the expected compound **10b** is not included.

[d] The structures previously reported in the literature[20] (boiling point 150°C/15 mbar) is wrong. We have ascertained here that the procedure described by these authors leads to **12b** instead of **18b**.

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