The Fries Rearrangement.

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Titanium tetrachloride has been found to catalyse the rearrangement of phenyl and *o*-tolyl acetates to hydroxyacetophenones. In the latter case, in particular, almost exclusive migration to the *para*-position occurred. The effectiveness of the solvents used was in the order nitrobenzene >*s*-tetrachloroethane >chlorobenzene >benzene. Enhanced yields resulted when more than 1 equivalent of catalyst was employed. Better yields were also obtained when the starting materials were *o*-cresol and acetyl chloride.

Although aluminium chloride is the catalyst usually employed in the conversion of phenol esters into hydroxy-ketones, *e.g.*, $C_6H_5{\cdot}O{\cdot}COR \longrightarrow HO{\cdot}C_6H_4{\cdot}COR$, yet titanium tetrachloride has been found by Ralston, Segebrecht, and McCorkle (*J. Org. Chem.*, 1942, **7**, 522) to catalyse the rearrangement of phenyl hexanoate, and by d'Ans and Zimmer (*Ber.*, 1952, **85**, 585) that of α-naphthyl acetate.

It is generally claimed that the Fries method gives better results than the Friedel–Crafts reaction between phenols and acid chlorides, but it is now shown that under the same experimental conditions the latter can give increased yields of hydroxy-ketones. The Fries method is, however, a convenient one and when carried out with titanic chloride as catalyst in nitrobenzene, *s*-tetrachloroethane, chlorobenzene, or benzene the reaction can be performed in a homogeneous medium, this being more satisfactory than in the absence of a solvent.

The Fries rearrangement.

(0·1 Mole of ester was taken in all cases. The solvent is nitrobenzene, except where otherwise stated.)

TiCl$_4$, mole	Sol-vent, c.c.	Time (hr.)	Temp.	Yields, % Hydroxy-ketone			TiCl$_4$, mole	Sol-vent, c.c.	Time (hr.)	Temp.	Yields, % Hydroxy-ketone		
				p-	*o*-	*o*-Cresol					*p*-	*o*-	*o*-Cresol
						Phenyl acetate							
0·1	50	6	50°	34	6	—	0·1	50	12	50°	42	8	—
0·1	50	9	50	48	9	—							
						o-Tolyl acetate							
0·1	50	6	50	50	3	37	0·3	150	9	30	75	3	14
0·1	50	9	50	58	4	33	0·05	150	9	30	11	trace	19
0·1	50	12	50	56	1	21	0·1	50	9	40	59	2	13
0·05	100	6	30	10	1	25	0·1	50 *	9	40	22	1	26
0·1	100	6	30	47	2	29	0·1	100 *	9	40	20	1	28
0·2	100	6	30	73	2	17	0·1	100 †	9	40	10	trace	21
0·2	100	14	30	78	2	13	0·1	100 ‡	9	40	12	trace	22
0·1	50	9	30	54	1	22	0·1	100	9	40	60	2	20
0·1	100	9	30	50	2	27	0·1	50	20	30	53	2	15
0·1	150	9	30	50	2	24	0·1	50	6	30	47	1	27
0·2	100	9	30	75	2	15	0·1	50	15	30	57	1	16
0·2	150	9	30	75	3	17							
						o-Cresol (0·1 mole) and acetyl chloride (0·1 mole)							
0·1	50	20	30	66	3	15	0·1	100	6	30	48	2	17
0·1	50	6	30	50	3	20	0·1	50	15	30	65	3	16

* *s*-Tetrachloroethane; † benzene; ‡ chlorobenzene.

It is generally held that the solvent may have a pronounced effect on the course of the transformation; the present work shows that nitrobenzene gives much higher yields than tetrachloroethane when used under the same experimental conditions. It is also seen from the Table that variation in the amount of solvent, without change in the other conditions, has a very slight effect on the reaction. However, variation in the proportion of catalyst to ester up to a molecular ratio of 2 : 1 has a marked effect on yields, although above this ratio the effect is only slight. It should be noted that considerable amounts of the free phenol are always present among the reaction products.

EXPERIMENTAL

Materials.—Precautions were taken to ensure that all the materials used were dry.

Nitrobenzene was dried (P_2O_5) and distilled before use. *s*-Tetrachloroethane was distilled with steam, dried (K_2CO_3), and distilled; the colourless product had b. p. 145·5°. Titanic chloride was boiled under reflux over copper turnings and distilled, yielding a colourless liquid, b. p. 136°. Phenyl and *o*-tolyl acetate, acetyl chloride, and *o*-cresol were distilled before use; the esters gave no colour with ferric chloride solution.

It was found, however, that rigid purification had very little effect on the results obtained.

Action of Titanium Tetrachloride on o-*Tolyl Acetate.*—In a typical experiment the catalyst was added to a solution of the ester in nitrobenzene immersed in a freezing mixture. The reaction vessel, which was fitted with a mercury seal, was then placed in a thermostat at the required temperature for the requisite time, continuous stirring being maintained throughout. The flask was then cooled rapidly in ice-water, and the dark red homogeneous liquid was treated with dilute hydrochloric acid. Extraction of the nitrobenzene layer with 2N-sodium hydroxide gave a solution which contained both 2- and 4-hydroxy-3-methylacetophenones, together with *o*-cresol. After acidification with concentrated hydrochloric acid, distillation with steam removed the *o*-hydroxy-ketone and cresol, the *p*-hydroxy-ketone remaining. This was extracted from the tarry product with boiling water, from which it separated on cooling as prisms, m. p. 104° (Klingel, *Ber.*, 1885, **18**, 2699). Addition of excess of alcoholic 2 : 4-dinitrophenylhydrazine hydrochloride to the steam-distillate precipitated all the *o*-hydroxy-ketone as its dinitrophenylhydrazone, and from the filtrate bromine water precipitated 4 : 6-dibromo-*o*-cresol (OH = 1). The 2 : 4-*dinitrophenylhydrazone* of 2-hydroxy-3-methylacetophenone crystallised from ethyl acetate in red plates, m. p. 252° (decomp.) (Found : N, 17·2. $C_{15}H_{14}O_5N_4$ requires N, 17·0%). The corresponding *hydrazone* from 2-hydroxyacetophenone, orange needles from the same solvent, had m. p. 204° (Found : N, 18·0. $C_{14}H_{12}O_5N_4$ requires N, 17·7%).

When *s*-tetrachloroethane was used as solvent, decomposition was brought about by the action of the alkali, trichloroethylene being formed. The tendency to form tar was less marked with tetrachloroethane, chlorobenzene, or benzene than with nitrobenzene. It was also found that, although under the conditions herein described the reaction medium remained homogeneous, the resinous material being formed only on decomposition of the reaction products, yet when larger amounts of catalyst were employed some tar tended to separate during the actual rearrangement.

When ferric chloride (0·2 mole) was substituted for titanic chloride, *o*-tolyl acetate (0·1 mole) in nitrobenzene (50 c.c.), after being heated for 6 hr. at 50°, gave 60% of *p*- and 5% of *o*-hydroxy-ketones. In the absence of any solvent the corresponding yields were 42 and 3%. In the latter experiment the dark mass formed was treated with hydrochloric acid, and the product extracted with ether. Otherwise the separation of products was carried out in the usual way.

When the catalyst used was aluminium chloride (0·1 mole), the ester (0·1 mole) in nitrobenzene (50 c.c.) gave after 24 hr. at 17° a 44% yield of 4- and a 4% yield of 2-hydroxy-3-methylacetophenone.

The usual method was adopted in the reaction between titanic chloride, acetyl chloride, and *o*-cresol, but considerable evolution of hydrogen chloride occurred during the experiment.

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