[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

THE USE OF ORGANOCADMIUM REAGENTS FOR THE PREPARATION OF SUBSTITUTED β-AROYLPROPIONIC ACIDS

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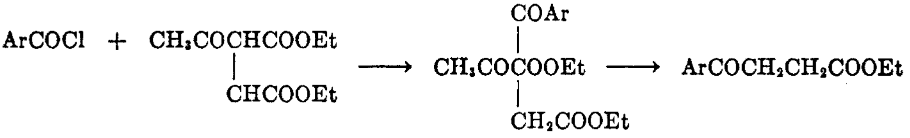
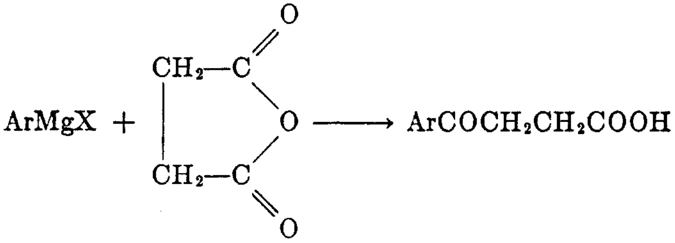
The preparation of *para*-substituted β-aroylaliphatic acids in which the *para*-substituent is an *ortho-para*-directing substituent is easily accomplished by means of the Friedel and Crafts reaction involving an anhydride or an ω-carbalkoxylacid chloride (1). Such a method is not generally applicable for the preparation of *ortho*- and *meta*-substituted acids of this series.

These latter types of acids usually have been prepared in one of three general ways. One method has been the acylation of diethyl acetosuccinate and subsequent hydrolysis but this method has not found wide application and the yields have generally been low (2, 3). A second method has been the stepwise lengthening of the side-chain of a methyl aryl ketone by a laborious procedure involving bromination of the ketone, alkylation of malonic ester, and hydrolysis of the substituted malonic ester. This scheme usually has been used only in those cases where acetylation and succinoylation in the Friedel and Crafts reaction do not occur at the same position (1). A third method has made use of the reaction of a Grignard reagent with succinic anhydride.



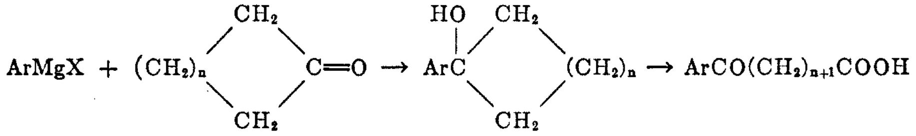
$$\mathrm{ArCOCl} + \mathrm{CH_3CO}\underset{\mathrm{CHCOOEt}}{\mathrm{C}}\mathrm{HCOOEt} \longrightarrow \mathrm{CH_3CO}\overset{\mathrm{COAr}}{\underset{\mathrm{CH_2COOEt}}{\mathrm{C}}}\mathrm{OOEt} \longrightarrow \mathrm{ArCOCH_2CH_2COOEt}$$

$$\mathrm{ArCOCH_3} \rightarrow \mathrm{ArCOCH_2Br} \rightarrow \mathrm{ArCOCH_2CH(COOEt)_2} \rightarrow \mathrm{ArCOCH_2CH_2COOH}$$



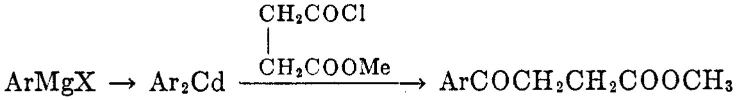
The yields generally have been poor (4, 5, 6, 7, 8) except in cases of hindered anhydrides such as dimethylsuccinic anhydride (9) or bulky bromides such as 1-bromonaphthalene (10). Newman has recently reported that better yields of keto acids can be obtained from the unhindered reagents when the reaction is conducted at −70° (11, 12). For example, phenylmagnesium bromide and succinic anhydride give a 50–70% of β-benzoylpropionic acid. The only other aromatic halide studied by these workers was *o*-bromotoluene which gave only 35% yield. Although this modification has greatly increased the utility of such a reaction, the new manipulations involved make it somewhat troublesome to execute.

An extremely novel approach has been developed by Fieser and Szmuszkovicz (13), who have found that good yields of keto acids may be obtained by the oxidation of the tertiary alcohol, resulting from the reaction of a Grignard reaction and a cyclic ketone.



This method suffers from the limitation in that to introduce four carbon atoms, cyclobutanone would be required.

In view of the limitations of the above-mentioned schemes for the preparation of aroylpropionic acids by methods other than the Friedel and Crafts reaction, an easily executed process which will proceed in good yield is still desired. The development by Cason (14) of the cadmium reaction for the synthesis of aliphatic keto acids has prompted us to investigate the use of the diaryl cadmium reagent for the preparation of aromatic keto acids of the above type.



$$ArMgX \rightarrow Ar_2Cd \xrightarrow{\substack{CH_2COCl \\ | \\ CH_2COOMe}} ArCOCH_2CH_2COOCH_3$$

Riegel and his associates (15) have previously reported the preparation of β-(α-naphthoyl)propionic acid in a yield of 45% from the reaction of di-α-naphthyl cadmium and β-carbomethoxypropionyl chloride. The preparation of methyl β-(*o*-methoxybenzoyl)propionate in a 45% yield by the same general procedure has also been reported by Dauben and Tanabe (16). Soffer and co-workers (17) have prepared methyl 10-keto-10-phenyldecanoate in a yield of 40% from diphenyl cadmium and 9-carbomethoxynonanoyl chloride. The present study has extended the application of the cadmium reaction and the results are summarized in Table I.

It was found that with most of the compounds studied the yield of aroylpropionic ester was relatively good (40–60%) and that those aryl bromides which were substituted so that they possessed a +I inductive effect appeared to proceed in the highest yield. It is interesting to note that in the bromotoluene series the yields obtained from all three isomers were about the same (56–62%). In the bromoanisole group, however, the *o*- and *p*-isomers gave good results (50–54%) whereas the *m*-isomer yielded only 27% of the desired keto ester. This latter low yield may be due to the extreme insolubility of the reaction complex; a factor which has been shown to be definitive in the success of the cadmium reaction with ester acid chlorides (14). From these reactions, it would appear that there is no "*ortho* effect" (18) in the reaction of a diaryl cadmium reagent with an acid chloride. This result is consistent with evidence (19, 20) that such a reaction may possibly proceed by direct displacement, either intra- or inter-molecularly, rather than by primary addition to the carbonyl linkage.

α-Naphthyl bromide was reinvestigated and was found to yield the desired ester in 64% yield as compared to the previously reported 45%. The much lower yield (34%) obtained with β-bromonaphthalene is consistent with other work reported on the relative usefulness of these two isomers in the Grignard reaction (21).

Various workers (14, 22, 23) have reported that the preparation of a cadmium derivative from an alkylmagnesium iodide proceeds in poor yield. It has been found in the present work that this generality is apparently also true in the aromatic series. When phenylmagnesium iodide was employed as the source of diphenyl cadmium, the yield of methyl β-benzoylpropionate was only 17% as compared to 51% from the corresponding bromide.

TABLE I

YIELDS AND PROPERTIES OF METHYL β-AROYLPROPIONATES

AROYL GROUP	YIELD, %	B.P. °C.	MM.	n_D°C	ANALYSES			
					Calc'd		Found	
					C	H	C	H
Benzoyl	51	119–120[a]	0.4	1.5260^{19}				
o-Toluyl	58	110–111	.3	1.5203^{25}	69.88	6.84	70.06	7.04
m-Toluyl	62	118–119	.5	1.5258^{27}	69.88	6.84	69.95	6.68
p-Toluyl	56	119–120[b]	.5					
o-Methoxybenzoyl	50	135–136[c]	.6	1.5296^{25}				
m-Methoxybenzoyl	27	150–151	.5	1.5432^{29}	64.85	6.35	65.08	6.31
p-Methoxybenzoyl	54	149–150[d]	.5					
o-Chlorobenzoyl	32	149–150[e]	1.0	1.5274^{28}	58.29	4.89	58.43	4.88
p-Chlorobenzoyl	40	134–135[f]	0.8					
α-Naphthoyl	64	173–174[g]	.8	1.5921^{26}				
β-Naphthoyl	34	178–179[h]	.7					

[a] Kugel (28) reports b.p. 187–187.5° (30 mm.). [b] The solid ester was recrystallized from ether, m.p. 49–51°; Limpricht (29) reports 43°. [c] Dauben and Tanabe (16) report b.p. 161–162° (1.5 mm.), n_D^{27} 1.5311. [d] The solid ester was recrystallized from ether, m.p. 48–49°; Soffer and Hunt (30) report 47.5–49.5°. [e] *Anal.* Calc'd for $C_{11}H_{11}ClO_3$: Cl, 15.64. Found: Cl, 15.65. [f] The solid ester was recrystallized three times from ether, m.p. 51.6–52.8°. The reported melting point is 63° (31). [g] Riegel and co-workers (15) report 184–185° (1 mm.). [h] The solid ester was recrystallized from ether, m.p. 74–75°; Giua (32) reports 74°.

EXPERIMENTAL

Microanalyses are by the Microanalytical Division of the Department of Chemistry of the University of California. All melting points are corrected; all boiling points are uncorrected. The halides used as starting materials were purified commercial products except *m*-bromoanisole and *o*-chlorobromobenzene. These latter two compounds were prepared in the usual manner (24, 25). The cadmium reactions were conducted in an atmosphere of nitrogen and with 0.3 mole of halide, 0.3 mole of magnesium, 0.18 mole of anhydrous cadmium chloride, and 0.3 mole of β-carbomethoxypropionyl chloride (26). All reactions were carried out in a manner similar to that described for methyl β-benzoylpropionate. The yields and properties of the keto esters are reported in Table I. The esters were saponified and the acids purified by recrystallization from aqueous methanol. The properties of the acids are reported in Table II.

Methyl β-benzoylpropionate. A solution consisting of 47.1 g. (0.3 mole) of bromobenzene dissolved in 150 cc. of dry ether and 50 cc. of anhydrous benzene was added dropwise over the course of one hour to 7.25 g. (0.3 mole) of magnesium turnings. The Grignard solution was cooled in an ice-bath and 33 g. (0.18 mole) of anhydrous cadmium chloride was added in one portion. The resulting mixture was heated under reflux with stirring until a negative Gilman test (27) was obtained. This required about 30 minutes. The ether was distilled until the mixture in the flask became a thin slurry and the distillation became slow. Anhydrous benzene (200 cc.) was then added and 25 cc. of benzene was distilled.

A solution containing 45.2 g. (0.3 mole) of β-carbomethoxypropionyl chloride dissolved in 50 cc. of dry benzene was added with vigorous stirring to the hot mixture as rapidly as possible. A very exothermic reaction ensued and during the addition the cadmium complex precipitated as small grey granules. The mixture was then heated under reflux with stirring for one hour and processed in the usual manner. There was obtained 29.5 g. (51%) of *methyl β-benzoylpropionate*, b.p. 119–120° (0.4 mm.), $n_{\mathrm{D}}^{18.5}$ 1.5260.

TABLE II

PROPERTIES OF β-AROYLPROPIONIC ACIDS

AROYL GROUP	M.P., °C.		REF.
	Found	Reported	
Benzoyl	115–117	116	2
o-Toluyl	104.3–104.7	98–102	12
m-Toluyl	114–115	115–117	3
p-Toluyl	127–128	129	29, 33, 34, 35
o-Methoxybenzoyl	93.5–95	94–95	16
m-Methoxybenzoyl	146–148[a]	107–108, 111	36, 37
o-Chlorobenzoyl	71.5–73.5[b]		
p-Chlorobenzoyl	130–131.5	131	31
α-Naphthoyl	130–131	132–133	38, 39

[a] *Anal.* Calc'd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81; Neut. Equiv., 208.2.
Found: C, 63.75; H, 5.69; Neut. equiv., 209.7.

The acid was converted into a *semicarbazone* which was recrystallized twice from ethanol, m.p. 177.5–178°; reported (36, 37) 177–178°.

Anal. Calc'd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84.
Found: C, 54.65; H, 5.74; N, 15.16.

[b] *Anal.* Calc'd for $C_{10}H_9ClO_3$: C, 56.48; H, 4.27; Cl, 16.63.
Found: C, 56.34; H, 4.40; Cl, 16.54.

The ester was saponified and the *β-benzoylpropionic acid* recrystallized from aqueous methanol, m.p. 115–117°. DeBenneville (23) reports a 30% yield of this acid directly by the reaction of diphenylcadmium and succinic anhydride.

SUMMARY

The preparation of substituted β-aroylpropionic acids by means of the reaction of a diaryl cadmium reagent with β-carbomethoxypropionyl chloride has been studied. In most cases, the reaction proceeds in relatively good yield. Such a method is quite useful for the preparation of *ortho-* and *meta*-substituted acids of this series. It appears that there is no steric effect in this reaction.

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