Reformatsky reactions with o- and p-substituted benzophenones

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Nine new $\beta_i\beta_i$ -diarylhydracrylic acids are reported from the condensation of monosubstituted benzophenones with ethyl bromoacetate in Reformatsky reactions. The reaction of 4-nitrobenzophenone which fails to go into classical Reformatsky reactions can be accomplished in excellent yield by the two-step process; however, 2-nitrobenzophenone fails to react under any conditions.

In the case of 2-chlorobenzophenone in benzene-toluene, the hydracrylic acid is not isolated, but rather the unsaturated β -chlorophenyl- β -phenyacrylic acid. Diethyl ether appeared in general to be superior to benzene-toluene as a solvent for the reactions. Anisole under reduced pressure has also been used successfully in two cases.

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This research was undertaken largely on the basis of a comment by Klemm and Bower (1) in 1958 that "there has been very little investigation of the Reformatsky reaction employing diaryl ketones".

The four major objectives of the investigation have been: a study of the influence of substituents in the 2- and 4-positions of the benzophenone nucleus on the yield of products; the comparison of the relative effectiveness of two dissimilar reaction solvents namely diethyl ether and benzene-toluene; experiments to see if nitrobenzophenones which previously have failed to go into the classical (one-step) Reformatsky method might react in the two-stage process introduced in 1953 by Siegel and Keckeis (2); the isolation and characterization of the β_{β} diarylhydracrylic acids resulting when a variety of 2- and 4-substituted benzophenones are condensed with ethyl bromoacetate under appropriate conditions.



The classical Reformatsky reaction is well reviewed up to 1942 by Shriner (3). The following brief review of the literature since this time may be worth while. Natelson and Gottfried (4) reported that best yields were obtained with a solvent giving a reaction temperature of 95– 105 °C and this is best achieved by a benzene– toluene (1:1) solution. Dreiding and Pratt (5) reported a case where different solvents benzene and ether gave different end products. Cason and Fessenden (6) and Evans (7) found that benzeneether gave better yields than benzene itself. The two-stage process was introduced by Siegel and Keckeis (2) and also used by Vinograd and Vul'fson (8), Grob and Brenneisen (9), and Vaughan *et al.* (10). In general this method has permitted reactions between substances that fail in the one-step process and in other cases has given increased yields.

Fifteen β , β -diarylhydracrylic acids have been synthesized in this investigation, nine of which are new compounds namely: β -(2-aminophenyl)-, β -(4-aminophenyl)-, β -(2-hydroxyphenyl)-, β -(4-hydroxyphenyl)-, β -(2-bromophenyl)-, β -(4bromophenyl)-, β -(2-chlorophenyl)-, β -(4-fluorophenyl)-, and β -(4-nitrophenyl)- β -phenylhydracrylic acids (see Table II). Twelve of these acids have been characterized by means of their *p*-nitrobenzyl esters as shown in Table III.

TABLE I Yields with variation of solvent*

x	Solvent	% yield of crude acid	
2-CH ₃ 2-CH ₃ 2-CH ₃ 2-CH ₃ 2-CH ₃ 4-CH ₃ 4-CH ₃ 4-CH ₃ 4-CH ₃	Benzene-toluene† Benzene Benzene-ether‡ Ether Benzene-toluene Benzene Benzene-ether Ether	32 41 53 52 76 62 81 84	
*Compoun †40:35 v/v. ‡1:1 v/v.	ds of structure $X + O + C + C$	<u>)</u> .	

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	% yield	of crude acid	Melting				
	Ĭn	In Benzene-	· point†		Analyses		
х	Et ₂ O	(40:35 v/v)	acid (°C)	Formula	Calculated (%)	Found (%)
2-NH₂ I-NH₂	20	4 23	186–189 ca.171	C ₁₅ H ₁₅ NO ₃	C, 70.0; H, 5.9; N, 5.4	C, 70.1; H, 5.2;	N, 5.6
2-OH	16	29	109-111	$C_{15}H_{14}O_{4}$	C, 69.8; H, 5.4	C, 71.3; H, 5.0	
-ŎĤ	6	42	154-156	$C_{15}H_{14}O_{4}$	C, 69.8; H, 5.4	C, 69.7; H, 4.9	
2-OCH	72	64	139-140.5t		. , .		
-OCH	84	68	154–155§				
2-CH₃ ¯	52	32	147–148				
$-CH_3$	84	76	180–182¶				
H	88	84	210-211**		_		
l-F	95	77	174-175.5	$C_{15}H_{13}FO_3$	C, 69.2; H, 5.0; F, 7.3	C, 69.4; H, 5.2;	F, 8.3
2-Cl	44	40	153–157	$C_{15}H_{13}ClO_3$	C, 65.1; H, 4.7; Cl, 12.8	C, 65.4; H, 4.7;	Cl, 12.8
4-Cl	64	76	187-190††				
2-Br	60	32	154-155	$C_{15}H_{13}BrO_3$	C, 56.1; H, 4.1; Br, 24.9	C, 56.7; H, 4.3;	Br, 24.8
-Br	88	80	186-188	$C_{15}H_{13}BrO_3$	C, 56.1; H, 4.1; Br, 24.9	C, 55.8; H, 4.2;	Br, 25.0
$-NO_2$	0	0	142-143	$C_{15}H_{13}NO_{5}$	N, 4.9		N, 4.9
2-NO₂	0	0					•
			соон	\$1 81	iterature m.p. 139° (21).		
*Comp	ounds of	structure X	-c + c - c - c - c - c - c - c - c - c -	((L ¶]1 **	iterature m.p. 152° (25). Literature m.p. 187° (25). Literature m.p. 212° (26).		

TABLE II β,β-Diarylhydracrylic acids*

†All melted with decomposition (frothing).

In general, diethyl ether proved to be superior to benzene-toluene as a reaction solvent (see Tables I and II). The reaction of 2-chlorobenzophenone in benzene-toluene has resulted in the formation of the unsaturated acid, β -(2-chlorophenyl)- β -phenylacrylic acid rather than the corresponding hydroxyacid isolated from ether.

Resonance and steric effects associated with the substituent groups attached to the benzophenone nucleus, were found to have predictable influences on the yields of the hydroxyacids (Table II). The 4-derivative produces greater yields than the 2-derivative. 4-Nitrobenzophenone which does not react in the classical Reformatsky reaction gives an excellent yield in the two-step process (see Table IV). On the other hand with 2-nitrobenzophenone no yield of acid was obtained by either process. In other cases, the two-step process has given increased yields. (Compare similar substances in Table V and Table II (benzene-toluene).)

Lewis and Wright (11) in their investigation on solvent effects in the Grignard reaction reported that anisole was superior to ether in the reaction of ethyl magnesium bromide with benzophenone. By a reduced pressure technique anisole was successfully used in the present investigation as a Reformatsky solvent (Table V). Due to the relatively high reflux temperature (170°) considerable decomposition occurred at atmospheric pressure and a pressure of 26 mm was employed.

Experimental

Activated Zinc

The zinc used in this investigation was in the form of 20 mesh granules, Fisher Scientific Co. (Z-15) activated by the procedure of Palmer and Reid (12).

Monosubstituted Benzophenones

The sixteen substituted benzophenones employed in this study were all prepared as described in the literature. Syntheses of five of these were sufficiently modified to merit comment.

2-Hydroxybenzophenone

In the past, this appears to have been made by a Friedel-Crafts reaction between 2-methoxybenzoyl chloride and benzene, excess aluminium chloride being used to ensure demethylation as well as aroylation (13). A direct synthesis employing 2-hydroxybenzoyl chloride in the Friedel-Crafts reaction does not appear to have been previously employed.

A suspension of anhydrous aluminium chloride (77 g, 0.58 mole) in benzene (450 ml) was heated under reflux. A solution of 2-hydroxybenzoyl chloride (0.36 mole) prepared by Kirpal's method (14) in benzene (200 ml) was added with stirring to the refluxing solution. The reaction

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			Analyses		
х	Melting point (°C)	Formula	Calculated (%)	Found (%)	
2-OH -OH 2-OCH ₃ 2-CH ₃ -CH ₃ -CH ₃ -F 2-Cl -F 2-Cl -F 2-Br -Br -Br NO ₂	$\begin{array}{r} 86-89\\ 106-108\\ 106.5-108\\ 130-132\\ 101-102.5\\ 105-106\\ 108-110\\ 111.5-112.5\\ 122-123\\ 126.5-128\\ 139-140.5\\ \end{array}$	$\begin{array}{c} C_{22}H_{19}NO_6\\ C_{22}H_{19}NO_6\\ C_{23}H_{21}NO_6\\ C_{23}H_{21}NO_5\\ C_{23}H_{21}NO_5\\ C_{22}H_{18}NFO_5\\ C_{22}H_{18}NFO_5\\ C_{22}H_{18}NCIO_5\\ C_{22}H_{18}NBrO_5\\ C_{22}H_{18$	N, 3.6 N, 3.6 N, 3.4 N, 3.6 N, 3.6 N, 4.8; F, 3.5 N, 3.4; Cl, 8.6 N, 3.4; Cl, 8.6 N, 3.1; Br, 17.5 N, 3.1; Br, 17.5 N, 6.6	N, 3.9 N, 3.3 N, 3.9 N, 3.8 N, 3.7 N, 4.2; F, 3.3 N, 4.2; F, 3.3 N, 3.6; Cl, 8.7 N, 3.6; Cl, 8.7 N, 2.8; Br, 18.2 N, 2.9; Br, 18.4 N, 6.4	
*Compou	ands of structure X	$COOCH_2 - O - NO_2$ CH_2 $C - O - NO_2$ $C - O - NO_2$ $C - O - NO_2$			

TABLE IV

Two-stage reactions*



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TABLE V

Reactions under reduced pressure*

x	Reaction conditions	% yield of crude acid
4-CH₃	Anisole	76
2-CH₃	b.p. 64° at 26 mm Anisole	58
2-CH ₃	b.p. 62° at 26 mm Benzene-toluene†	16
2-CH ₃	b.p. 37° at 82 mm Benzene-toluene	32
2-OCH ₃	B.p. 92° at atm Benzene-toluene	52
2-OCH ₃	Benzene-toluene	64
2-Br	B.p. 91° at atm Benzene–toluene	24
2-Br	Benzene-toluene	32

*Reactions involved compounds of structure X †40:35 v/v. was allowed to continue until the evolution of hydrogen chloride ceased. On cooling, the mixture was poured cautiously onto a mixture of ice and dilute acid. The aqueous layer was separated and extracted with benzene. The benzene extract was washed successively with dilute hydrochloric acid, water, sodium carbonate solution (5%), and water. After drying over magnesium sulfate and removal of the benzene by distillation, the residue was subjected to vacuum distillation. The crude product was collected at 119–138° at 1 mm, as a yellow oil (46.5 g). Recrystallization from aqueous acetone gave a solid (37.2 g) which melted at 39–41 °C. DeTar and Relyea (15) have reported 38.5-39 °C.

2-Aminobenzophenone

This ketone was prepared by the method of Scheifele and DeTar (16) with the following modification.

The benzene reaction mixture after the completion of the Friedel-Crafts reaction was cooled to room temperature and poured onto a mixture of ice and con-centrated hydrochloric acid. This hydrolyzed mixture was filtered free of a considerable quantity of light olivegreen solid. This solid which was apparently impure 2-toluenesulfonylamidobenzophenone was readily hydrolyzed by hot hydrochloric acid (10%) to 2-aminobenzophenone. The benzene layer from the filtrate was separated from the aqueous phase, washed with water, and dried. Removal of the benzene in vacuo afforded a considerable quantity of a brown solid. This solid was heated with concentrated sulfuric acid (200 ml) on a steam bath for 15 min. The resultant solution was cooled, poured into water (500 ml), and filtered free of a solid which was apparently phenyl p-tolyl sulfone. The filtrate was neutralized with 6 N sodium hydroxide solution. The precipitate of impure 2-aminobenzophenone was collected, combined with the main portion isolated above by hydrochloric acid hydrolysis and recrystallized from aqueous ethanol. The yield of 2-aminobenzophenone was 40.8. g (41% on basis of p-toluenesulfonylanthranilic acid). It melted at 105-107 °C.

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4-Nitrobenzophenone

This ketone was prepared in a Friedel–Crafts reaction by dropwise addition of a solution of 4-nitrobenzoyl chloride in benzene to a well stirred suspension of anhydrous aluminium chloride in benzene at room temperature and then allowing the mixture to stand overnight. A 95% yield of ketone was obtained which melted at 135–137 °C. If the Friedel–Crafts reaction is carried out at the more usual temperature of 50 °C the yield falls to 60%. Schroeter (17) has reported a melting point of 138 °C.

Reduction of this nitroketone with iron and acetic acid according to the directions of Simpson *et al.* (18) for the corresponding 2-nitroketone gave an excellent yield (88%) of 4-aminobenzophenone.

4-Methylbenzophenone

This ketone was prepared in 57% yield by treating 4methylbenzoyl chloride with diphenyl cadmium according to the directions of Cason and Prout (19) for the preparation of methyl 4-keto-7-methyloctanoate. Purification was accomplished by vacuum distillation, b.p. 127-130° at 1 mm, and recrystallization from alcohol, m.p. 56-59 °C. Blakely and Scarborough (20) have reported a melting point of 56 °C.

2-Nitrobenzophenone

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This proved the most difficult of the starting ketones to obtain. A number of syntheses are reported in the literature, but none of these presented a simple method giving a pure product in good yield. Even the diphenyl cadmium method used above for 4-methylbenzophenone gave only an impure product which contained a considerable quantity of biphenyl. The method which was eventually successful was the oxidation of 2-nitrobenzhydrol according to the directions of Stoermer and Fridericji (21) and also used by us in the preparation of 2-methoxybenzophenone.

A solution of potassium dichromate (55.6 g) concentrated sulfuric acid (46 ml) and water (256 ml) was added in one portion, with stirring, to 2-nitrobenzhydrol (30.9 g). The temperature of the mixture was observed to rise quickly to 45° and then slowly dropped back to room temperature. The dark colored liquid was poured into water (500 ml), the crude product isolated by filtration, washed with water and air-dried. Recrystallization of the crude ketone (30.8 g) from methanol afforded a product which melted at 104–106 °C. Hay and Mulley (22) have reported a figure of 103–104 °C.

General Procedures for Synthesis of β , β -Diarylhydracrylic Acids

(a) Classical (One-stage) Reaction

Activated zinc granules (3.8 g, 0.058 g-atom) were added to a solution of diarylketone (0.025 mole) and ethyl bromoacetate (4.5 g, 0.027 mole) in anhydrous solvent (30 ml). The reaction mixture was contained in a 100 ml three-necked flask, equipped with a magnetic stirrer, electric heating mantle, thermometer, and an efficient reflux condenser with the outlet protected by a calcium chloride tube.

The mixture was stirred and cautiously heated to the reflux temperature. If, after several minutes of refluxing, the reaction showed no signs of having initiated (a distinct change in clarity and/or color of the solution), one or two small crystals of iodine and/or mercuric chloride were added to reactivate the zinc *in situ*. In the event that the initial exothermic reaction threatened to "froth over", the heating mantle was removed and the flask was cooled as long as it was necessary to keep the reaction under control, but not enough to stop the reaction. Once under control, the reaction was refluxed and stirred for an additional 2 h.

At the end of this period, the reaction mixture was decanted from the unreacted zinc, and both the zinc and the flask were rinsed with additional solvent. The zinc was dried and its weight recorded. The decanted mixture was combined with the solvent and hydrolyzed with 10% sulfuric acid (20 ml). The resultant two-phase system was separated; the aqueous layer was extracted with ether (2 × 25 ml), and then discarded. The combined organic layers were evaporated under reduced pressure and the residue was saponified according to the directions of Palmer and Reid (12) by refluxing with potassium hydroxide solution (13 ml, 2.5 N) in ethanol (25 ml) for 4 h. The saponification mixture was diluted with water (25 ml) and most of the alcohol was removed at 60° under reduced pressure.

The residue was extracted with ether $(2 \times 25 \text{ ml}, 2 \times 10 \text{ ml})$ and the combined ethereal extracts were washed with 5% sodium carbonate solution (these washings were combined with the main aqueous layer). Then the ether layer was dried over magnesium sulfate and filtered into a tared distillation flask. Removal of the ether under reduced pressure left a neutral residue (mainly unreacted ketone) whose weight was recorded.

The combined aqueous layers (above), containing the potassium salt of the hydroxy acid and excess base, were heated on a steam bath to drive off traces of ether, cooled, and acidified with dilute hydrochloric acid. In most instances the precipitated acid was isolated by suction filtration, washed, and dried. In a few cases, it was necessary to extract the acid with ether, with subsequent washing, drying, and removal of the ether. The weight of the crude acid was recorded and the percentage yield calculated on this figure, in general, agreed well with that calculated on the basis of the recovered ketone.

(b) Reaction under Reduced Pressure

This procedure was exactly the same as the above except that the apparatus was connected (via the top of the condenser) to a vacuum pump, manometer, and bleeder valve for adjusting and maintaining a constant low pressure. This setup permitted the reaction mixture to be refluxed at a temperature considerably lower than at atmospheric pressure. The low pressure was maintained throughout the initiation, and the 2 h reflux period.

(c) Two-stage Reaction

As the heading implies, this reaction was carried out in two steps. First, a reaction of activated zinc granules (3.8 g, 0.058 g-atom) with ethyl bromoacetate (4.5 g, 0.027 mole) in anhydrous ether (30 ml) was initiated as in the one-stage procedure and refluxed for 1 h beyond initiation. At the end of this period the ethereal solution was cooled and quickly decanted into another dry reaction flask. Second, a solution of the diarylketone (0.0063 mole¹) in 30 ml of benzene-toluene (40:35 v/v) was added in one portion to the above ether solution.

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The total reaction mixture was refluxed for 2 h, and worked up as in the one-stage procedure.

Purification and Characterization of the β , β -Diarylhydracrylic Acids

The crude acids (Table II) from the Reformatsky reactions and hydrolysis of the esters were crystallized for analysis or for comparison with literature melting points from aqueous alcohol. The 2-hydroxy and the 4-nitro acids were crystallized from benzene. All were colorless except the 2-amino acid which was in the form of yellow needles. The 4-amino compound was not obtained in pure enough condition for analysis. The melting points of the purified acids and the analytical results are reported in Table II.

The *p*-nitrobenzyl esters of these acids were prepared according to the directions of Shriner, Fuson, and Curtin (23). Melting points and analytical results are recorded in Table III.

In the case of the reaction with 2-chlorobenzophenone in benzene-toluene the hydroxy acid was not formed, but rather the corresponding unsaturated β -2-chlorophenyl- β -phenyl acrylic acid. On crystallization from aqueous alcohol this melted at 140-141.5 °C.

Anal. Calcd. for C15H11O2Cl (neutralization equivalent, 258.5): Cl, 70.0; H, 4.25; Cl, 13.7. Found (neutralization equivalent, 260 ± 3): C, 69.7; H, 4.28; Cl, 13.9.

When a hot alkaline solution of β-4-methoxyphenyl-βphenylhydracrylic acid, (m.p. 154°) was acidified with dilute hydrochloric acid, carbon dioxide and water were lost and a-methoxyphenyl-a-phenylethylene was produced. After crystallization from aqueous alcohol it melted at 74-76 °C. Hurd and Webb (24) reported 75 °C as the melting point.

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Anal. Calcd. for C15H14O: C, 85.7; H, 6.7. Found: C, 85.5; H, 6.5.

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¹The mole fraction of ketone is reduced from that of the one-step procedure to ensure that it remains the limiting factor in the second stage in spite of self condensation of the Reformatsky reagent during stage one.