

EXTENSION OF THE REFORMATSKY REACTION TO NEW TYPES OF COMPOUNDS

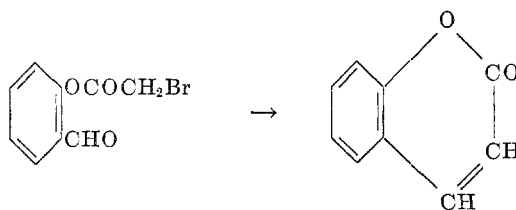
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Although aryl esters have been employed in the Reformatsky reaction as the carbonyl components (1), apparently no use has been made of them as bromoester components. Accordingly, phenyl bromoacetate, *p*-tolyl bromoacetate, and *p*-chlorophenyl bromoacetate were tested in the Reformatsky reaction with benzaldehyde and with mesitaldehyde; they were found to behave normally. The products of condensation with benzaldehyde were dehydrated with phosphorus pentoxide and were isolated as the corresponding α,β -unsaturated esters. The condensation products with mesitaldehyde, after dehydration and hydrolysis, were isolated as 2,4,6-trimethylcinnamic acid. In the condensation of mesitaldehyde with *p*-tolyl bromoacetate and *p*-chlorophenyl bromoacetate some 2,4,6-trimethylcinnamic acid was isolated from the reaction mixture prior to dehydration and hydrolysis.

Since the use of mesitaldehyde in the Reformatsky reaction had not been previously reported, this aldehyde was also condensed with ethyl bromoacetate and with *N*-methyl- α -bromoacetanilide.

Apparently aryl chloroacetates may also serve in the Reformatsky reaction since *p*-chlorophenyl chloroacetate reacts with benzaldehyde in the presence of zinc. One product obtained from the reaction, cinnamic acid, was identified by a mixture melting point determination. When the oily material obtained from the reaction mixture was treated with phosphorus pentoxide, *p*-chlorophenyl cinnamate was also isolated. The total yield of Reformatsky products was 30%.

Examples of intramolecular Reformatsky reactions have been reported (2, 3). Since, however, these did not include aryl bromoacetates, a model compound was chosen for study which possessed this structural feature. 2-(Bromoacetoxy)benzaldehyde (I) was prepared by the reaction of bromoacetyl bromide on the anhydrous sodium salt of salicylaldehyde.



I

Strikingly, this compound did not react with zinc. The resistance to attack by zinc recall a similarly anomalous result with 4-(β -bromoethyl)cyclohexanone and magnesium (4).

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When, however, 2-(bromoacetoxy)benzaldehyde (I) was treated with zinc in the presence of an equimolar amount of anhydrous zinc bromide, the metal was consumed and the reaction mixture was found to contain salicylaldehyde, coumarin, and *o-trans*-coumaric acid. Although the evidence is not conclusive, it is felt that the zinc bromide functions as a coordinating agent with the aldehyde group in this reaction. The use of zinc bromide was suggested by the discovery of Swain and Boyles that magnesium bromide has an important effect on the course of the reaction between diisopropyl ketone and *n*-propylmagnesium bromide (5). The absence of brominated products and the consumption of zinc indicate that the zinc bromide does not serve merely as a condensing agent.

EXPERIMENTAL

Ethyl bromoacetate. With mesitaldehyde. A mixture of 10 g. of mesitaldehyde, 22.5 g. of the ester, 13 g. of zinc, a trace of mercuric chloride, and 75 ml. of dry benzene was warmed until reaction set in. It was then heated under reflux for an additional 2 hours, cooled, and poured into a saturated ammonium chloride solution. After removal of the unchanged zinc (5.7 g.) by filtration, the organic layer was washed several times with small portions of saturated ammonium chloride solution, and the ammonium chloride washings were washed with ether. The organic layers were combined, washed with water, and dried over magnesium sulfate. Evaporation of the solvents left an oil which could not be distilled satisfactorily. It was dissolved in 60 ml. of dry benzene and 4.0 g. of phosphorus pentoxide was added. The mixture was heated under reflux for 8 hours and cooled; the benzene solution was decanted; and the dark residue was washed several times with ether. The organic layers were combined and washed twice with 5% sodium bicarbonate and once with water. The liquid product, isolated by usual procedures, was subjected to distillation. The chief fraction (b.p. 120–140° at 0.5 mm.) crystallized to give 6.0 g. (42%) of a colorless solid; m.p. 35–36°. Ethyl 2,4,6-trimethylcinnamate, made by the Claisen method, was reported to melt at 40° (6).

The ester (0.01 mole) was converted to 2,4,6-trimethylcinnamic acid by heating under reflux for 2 hours with 25 ml. of alcoholic sodium hydroxide. The acid was purified by recrystallization from high-boiling petroleum ether; m.p. 177–178°; yield 1.8 g. (95%).

Phenyl bromoacetate. (a) With benzaldehyde. A mixture of 4.0 g. of the aldehyde, 9.0 g. of the ester (7), 3.3 g. of zinc, a trace of mercuric chloride, and 25 ml. of benzene was warmed to initiate reaction and then heated under reflux for one hour. The product, isolated by the saturated ammonium chloride procedure, was a yellow oil. A solution of the oil in 25 ml. of dry benzene was heated under reflux with 4 g. of phosphorus pentoxide for 8 hours. The product was distilled and the fraction which boiled at 165–200° (0.5 mm.) was collected. It crystallized to give 1.8 g. (20%) of phenyl cinnamate; m.p. 67–68°. After recrystallization from ethanol it melted at 74.5–75.5°. The reported melting point is 76° (8).

The infrared spectrum² of the compound has bands at 1725, 1637, and 975 cm.⁻¹ assignable, respectively, to an α,β -unsaturated ester, a conjugated double bond, and *trans* configuration about the double bond.

(b) With mesitaldehyde. The procedure was similar to that in *a*. The product from 9.5 g. of mesitaldehyde, after dehydration, was an oil believed to be phenyl 2,4,6-trimethylcinnamate. Hydrolysis of the oil gave 1.1 g. (15%) of 2,4,6-trimethylcinnamic acid; m.p. 176–177°, after recrystallization from high-boiling petroleum ether. A mixture melting point with an authentic sample was not depressed.

Phenyl 2,4,6-trimethylcinnamate. A mixture of 1.0 g. of 2,4,6-trimethylcinnamic acid and 2 ml. of thionyl chloride was heated on the steam cone for 2 hours and cooled. To it were added in succession 0.7 g. of phenol in 10 ml. of carbon disulfide and 1 g. of aluminum

² The infrared spectra were determined and interpreted by Miss Helen Miklas.

chloride. The reaction mixture was allowed to stand at room temperature until the evolution of hydrogen chloride ceased and then was decomposed in the usual manner. The ester (0.8 g.), isolated by conventional procedures, crystallized from ethanol as colorless needles; m.p. 68.5–69.5° (uncorr.).

*Anal.*³ Calc'd for $C_{18}H_{18}O_2$: C, 81.19; H, 6.81.

Found: C, 80.80; H, 6.74.

p-Tolyl bromoacetate. (a) *With benzaldehyde.* The viscous, yellow liquid, obtained by condensing 5 g. of benzaldehyde with 12 g. of the ester (9), seemed to undergo partial dehydration when heated. Dehydration with phosphorus pentoxide converted it to *p-tolyl cinnamate*, which crystallized from ethanol as colorless needles; m.p. 98.5–99.5°; yield 6.0 g. (53%). The melting point reported for this compound is 100–101°. The lower-melting sample probably contains a small amount of the *cis* isomer.

(b) *With mesitaldehyde.* The condensation gave an oil along with a small amount of 2,4,6-trimethylcinnamic acid. The oil was subjected to the dehydration procedure and the unsaturated ester was hydrolyzed. From an initial 5.5 g. of mesitaldehyde there was obtained 2.0 g. (29%) of 2,4,6-trimethylcinnamic acid.

p-Tolyl 2,4,6-trimethylcinnamate. A procedure similar to that described for the phenyl ester gave the crude product in 44% yield. The ester after treatment with Darco, crystallized from ethanol as colorless needles; m.p. 78.5–79.5° (uncorr.).

Anal. Calc'd for $C_{19}H_{20}O_2$: C, 81.38; H, 7.19.

Found: C, 81.25; H, 7.09.

p-Chlorophenyl bromoacetate. The procedure of Wittig (9) for the *p*-tolyl bromoacetate was applied to *p*-chlorophenol and bromoacetyl bromide. The product was obtained in 80% yield; b.p. 104.5–105.5° (0.5 mm.); n_D^{20} 1.5570.

Anal. Calc'd for $C_8H_7BrClO_2$: C, 38.51; H, 2.43.

Found: C, 39.12; H, 2.74.

Although an analytically pure sample was not obtained, the identity of this ester is established by the products obtained from it.

(a) *With benzaldehyde.* The procedure was essentially that employed with phenyl bromoacetate. From 2.1 g. of the aldehyde there was obtained 1.0 g. (20%) of the dehydration product, *p*-chlorophenyl cinnamate. It crystallized from ethanol in colorless needles; m.p. 102.5–103.5°.

(b) *With mesitaldehyde.* The usual condensation procedure, involving 5.9 g. of the aldehyde, gave a yellow oil which deposited 1.7 g. of 2,4,6-trimethylcinnamic acid. The oil, subjected to dehydration with phosphorus pentoxide, gave a product which did not crystallize and which could not be distilled satisfactorily. Hydrolysis converted it into 2,4,6-trimethylcinnamic acid; yield 2.7 g. (36%).

p-Chlorophenyl cinnamate. *p*-Chlorophenyl cinnamate was also prepared from cinnamoyl chloride by a procedure analogous to that used to make the 2,4,6-trimethylcinnamates. This product crystallized from ethanol as colorless needles; m.p. 103–104° (uncorr.); yield 76%.

Anal. Calc'd for $C_{15}H_{11}ClO_2$: C, 69.66; H, 4.29.

Found: C, 69.46; H, 4.55.

A mixture of this product and that made by the Reformatsky method showed no lowering of the melting point.

The infrared spectra of the samples were identical. They showed bands at 1736, 1634, and 972 cm^{-1} , indicative of a conjugate, vinyl ester, a conjugated carbon-carbon double bond, and a *trans* bond, respectively.

p-Chlorophenyl 2,4,6-trimethylcinnamate. This ester was made from 0.9 g. of 2,4,6-trimethylcinnamic acid by a procedure similar to that outlined for the phenyl analog. It crystallized from ethanol as colorless needles; (0.8 g.) m.p. 77–78° (uncorr.).

³ Microanalyses were by Mrs. Katherine Pih, Mrs. Esther Fett, Mrs. Jean Fortney, and Mr. Joseph Nemeth of the University of Illinois Microanalytical Laboratory.

Anal. Calc'd for $C_{13}H_{17}ClO_2$: C, 71.87; H, 5.70.

Found: C, 71.70; H, 5.83.

p-Chlorophenyl chloroacetate with benzaldehyde. This ester was prepared in the manner of Fries (10). The condensation procedure was essentially that employed for the bromoacetates except that the period of heating was 19 hours. Two products were isolated; cinnamic acid (11%) and *p*-chlorophenyl cinnamate (19%).

N-Methyl- α -bromoacetanilide. With benzaldehyde. The anilide, prepared by the method of Bischoff (11), was condensed with benzaldehyde in the usual way, a trace of ethyl bromoacetate being added to the reaction mixture. A solid product was isolated (m.p. 107-108°) which appeared to be isomorphic with the starting material. This compound was identified as β -hydroxy- β -phenyl-*N*-methylpropionanilide. Recrystallization from high-boiling petroleum ether gave colorless platelets; m.p. 110-110.5°; yield 5.8 g. (57%).

Anal. Calc'd for $C_{15}H_{17}NO_3$: C, 75.25; H, 6.71; N, 5.49.

Found: C, 75.39; H, 6.75; N, 5.63.

(b) With mesitaldehyde. The product obtained from 9.5 g. of the anilide and 5.2 g. of the aldehyde was a mixture from which it was possible to isolate 2.7 g. of β -hydroxy- β -mesityl-*N*-methylpropionanilide. It separated from high-boiling petroleum ether in colorless needles; m.p. 114.5-115.5° (uncorr.).

Anal. Calc'd for $C_{18}H_{22}O_2$: C, 76.73; H, 7.79; N, 4.71.

Found: C, 76.96; H, 7.95; N, 4.75.

2-(Bromoacetoxy)benzaldehyde (I). The sodium salt of salicylaldehyde (12) was treated with bromoacetyl bromide by a method similar to that employed for I. The ester distilled at 125° (0.5 mm.) as a colorless liquid; n_D^{25} 1.5680; yield 76%.

Anal. Calc'd for $C_9H_7BrO_3$: C, 44.47; H, 2.90.

Found: C, 44.89; H, 3.11.

The 2,4-dinitrophenylhydrazone was prepared by the general method of Shriner and Fuson (13) m.p. 186-186.5° (uncorr.).

Anal. Calc'd for $C_{15}H_{11}BrN_4O_8$: C, 42.58; H, 2.62; N, 13.24.

Found: C, 43.22; H, 2.60; N, 13.22.

Cyclization of I. Anhydrous zinc bromide was prepared by dropping 2 ml. (0.04 mole) of bromine into a flask in which there was 6.5 g. (0.1 g.-atom) of zinc and 15 ml. of dry ether. To this solution was then added 9.8 g. (0.04 mole) of I in 15 ml. of benzene. This reaction mixture was heated under reflux for 2 hours, cooled, and worked up in a conventional manner. From the reaction mixture were obtained salicylaldehyde (65%), coumarin (26%), and *o*-*trans*-coumaric acid (9%).

SUMMARY

Phenyl, *p*-tolyl, and *p*-chlorophenyl bromoacetates as well as *N*-methyl- α -bromoacetanilide have been condensed with benzaldehyde and mesitaldehyde by the Reformatsky method. *p*-Chlorophenyl chloroacetate was found to behave normally with benzaldehyde under Reformatsky conditions.

The cyclization of 2-(bromoacetoxy)benzaldehyde by the Reformatsky method was found to occur in the presence of an equimolar amount of anhydrous zinc bromide. Without the zinc bromide the reaction failed to take place.

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