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SYNTHESIS OF DIETHYL ARYLMALONATES FROM DIETHYL MESOXALATE

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Diethyl arylmalonates are commonly prepared from ethyl arylacetates, either by condensation with diethyl oxalate followed by decarbonylation of the resulting oxaloesters (1, 2), or by condensation with diethyl carbonate (3, 4, 5). Some ethyl arylacetates can be obtained only by rather long routes, and in such cases a more direct synthesis of diethyl arylmalonates would be advantageous. This paper reports a synthesis of diethyl arylmalonates from diethyl aryltartronates, $ArC(OH)(COOC_2H_5)_2$, by treatment with thionyl chloride to form diethyl arylchloromalonates, followed by catalytic hydrogenation to replace the chlorine by hydrogen. This method should be useful in cases in which the diethyl aryltartaronates are more readily available than ethyl arylacetates.

A number of diethyl aryltartronates have been prepared by condensation of aromatic hydrocarbons or their derivatives with diethyl mesoxalate in the presence of acidic catalysts, such as sulfuric acid or stannic chloride (6, 7, 8, 9, 10, 11, 12).[1] This synthesis has proved to be very useful in a number of instances in which the aromatic compounds are reactive enough to condense with diethyl mesoxalate, and where the directive influence of substituents produces the desired orientation of the entering $-C(OH)(COOC_2H_5)_2$ group. This paper describes a new synthesis of diethyl aryltartronates, in which Grignard reagents are added selectively to the very reactive carbonyl group of diethyl mesoxalate at $-70°$.[2] It should be possible to extend this synthetic method to many of the aryl halides from which Grignard reagents can be prepared, and the method should be useful in some of the cases in which diethyl aryltartronates cannot be prepared by the condensation of aromatic compounds with diethyl mesoxalate.

In the synthesis of diethyl 9-phenanthrylmalonate (IV), 9-phenanthrylmagnesium bromide was added to diethyl mesoxalate at a reaction temperature of $-70°$ to $-65°$. Hydrolysis of the adduct gave diethyl 9-phenanthryltartronate (I) in 46% yield.

$$9\text{-}C_{14}H_9MgBr + CO(COOC_2H_5)_2 \xrightarrow{\text{(after hydrolysis)}}$$

$$9\text{-}C_{14}H_9C(OH)(COOC_2H_5)_2 \xrightarrow{\text{KOH, then HCl}} 9\text{-}C_{14}H_9CH(OH)COOH$$

I II

[1] Diethyl diarylmalonates are formed from the same reactants in some cases under more strenuous conditions (13, 14).

[2] A reaction temperature of $-70°$ was used because of the greater selectivity observed for the reaction of Grignard reagents with other polyfunctional compounds at low temperatures in certain instances, such as the preparation of ketones from Grignard reagents and acid anhydrides reported by Newman and Booth (15) and Newman and Smith (16).

The crystalline ester I was characterized by saponification and decarboxylation, which yielded 9-phenanthrylglycolic acid (II). Treatment of diethyl 9-phenanthryltartronate (I) with thionyl chloride and a small amount of pyridine gave diethyl 9-phenanthrylchloromalonate (III) in 84–95% yield. The chloroester III decomposed with evolution of hydrogen chloride at the melting point, which was somewhat erratic although the ester was analytically pure. Catalytic hydrogenation of III in the presence of palladium on Norit gave diethyl 9-phenanthrylmalonate (IV) in yields of 94–98%. IV was characterized by saponification and decarboxylation to 9-phenanthrylacetic acid (V), which was identified by m.p. and mixture m.p. with a known sample (17).[3]

$$\text{I} \xrightarrow{SOCl_2} \underset{\text{III}}{9\text{-}C_{14}H_9C(Cl)(COOC_2H_5)_2} \xrightarrow{H_2,\ Pd} \underset{\text{IV}}{9\text{-}C_{14}H_9CH(COOC_2H_5)_2} \xrightarrow{KOH,\ \text{then HCl}} \underset{\text{V}}{9\text{-}C_{14}H_9CH_2COOH}$$

Diethyl α-naphthylmalonate was prepared by a sequence of reactions similar to the one outlined above, beginning with the addition of α-naphthylmagnesium bromide to diethyl mesoxalate. Diethyl α-naphthyltartronate was obtained as a sirup which failed to crystallize, but was characterized as a crystalline ester (prepared by reaction with benzoyl chloride), diethyl O-benzoyl-α-naphthyltartronate. The reaction of diethyl α-naphthyltartronate with thionyl chloride yielded diethyl α-naphthylchloromalonate as a sirup which was 86% pure (according to chlorine analysis) after short-path distillation at low pressure. Hydrogenation of the impure diethyl α-naphthylchloromalonate gave diethyl α-naphthylmalonate in 40% yield.

In a search for alternate routes for the synthesis of diethyl arylmalonates, ethyl arylcyanoacetates or arylmalononitriles, a number of reactions were investigated with negative results. These included the reaction of metal cyanides or liquid hydrogen cyanide with the benzoate and the benzenesulfonate of mandelonitrile, the reaction of diethyl bromomalonate with benzene in the presence of aluminum chloride, the reaction of diethyl tartronate with naphthalene in the presence of stannic chloride or hydrogen fluoride, and the reaction of mandelonitrile with liquid hydrogen cyanide.

EXPERIMENTAL[4]

Diethyl 9-phenanthryltartronate (I). Commercial (90%) phenanthrene was purified and brominated (18). The 9-bromophenanthrene was redistilled and recrystallized from 95% ethanol; m.p. 63.5–65°. Diethyl mesoxalate (12) was purified by conversion to its hydrate (diethyl dihydroxymalonate), which was washed with carbon disulfide (19), reconverted to diethyl mesoxalate by treatment with phosphorus pentoxide, extracted with ether and distilled from a small amount of phosphorus pentoxide (20); b.p. 98–100° (14 mm.).

[3] Kindly supplied by Dr. Erich Mosettig, National Institutes of Health.

[4] Melting points are corrected and boiling points are uncorrected. We are indebted to Mr. S. M. Nagy and Mrs. Louise W. Spencer for analyses.

9-Phenanthrylmagnesium bromide was prepared by a procedure similar to one described by Bachmann (21) from 4.3 g. of magnesium turnings, 0.23 g. of iodine, 30 g. of 9-bromophenanthrene, and 70 ml. each of anhydrous ether and toluene. The mixture was stirred and heated under reflux for seven and one-half hours, at which time acidimetric titration indicated a 96–97% yield of the Grignard reagent. The suspension of 9-phenanthrylmagnesium bromide was diluted with 200 ml. of dry toluene, cooled to room temperature, and filtered to remove magnesium (through a stopcock sealed to the bottom of the flask in which the Grignard reagent was prepared). The Grignard reagent was added dropwise with vigorous stirring to a solution of 24.4 g. of purified diethyl mesoxalate in 300 ml. of dry toluene, cooled to −70° to −65° in a Dry Ice-bath, during one and three-quarters hours. The resulting orange suspension was stirred at −70° for forty-five minutes, warmed to 0°, and acidified by the dropwise addition of 18.5 ml. of 25% sulfuric acid at 0°, followed by 30 ml. of water (hydrolysis by saturated aqueous ammonium chloride solution in other preparations appeared to offer no advantage). The aqueous layer was extracted with ether and the combined organic layers were washed with 5% sodium bicarbonate solution and then with water until neutral. The solution was dried over magnesium sulfate and concentrated under reduced pressure. The residual red oil was dissolved in 250 ml. of dry cyclohexane containing 15% of ether and the product was allowed to crystallize at room temperature overnight and then at 5° until crystallization was complete. The product was separated by filtration and washed with 50 ml. of cold cyclohexane containing 15% of ether; yield 23.7 g. (58%) of a tan solid, m.p. 76.5–85°. No additional product crystallized from the mother liquors. The product was dissolved in 200 ml. of cyclohexane containing 15% of ether, heated with 2 g. of Darco, filtered, and cooled nearly to room temperature. The solution was decanted from a small amount of a dark oil which separated and allowed to stand first at room temperature and then at 5° until crystallization was complete. The yield of cream colored clusters of fine needles of diethyl 9-phenanthryltartronate (I), m.p. 87–87.5°, was 18.8 g. (46%). A sample from another preparation was obtained as a colorless solid with a constant melting point by crystallization from cyclohexane-ether, cyclohexane-benzene, and carbon tetrachloride; m.p. 88–88.5°. I gave a yellow solution in concentrated sulfuric acid which quickly darkened to an olive color.

Anal. Calc'd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72.

Found: C, 71.65; H, 5.90.

The use of diethyl mesoxalate as ordinarily prepared by the oxidation of diethyl malonate with nitrogen oxides and purified only by distillation in the preparation of I gave yields of 34–36%. An amount of phenanthrene equivalent to 16% of the original Grignard reagent was isolated from the mother liquors of one such preparaton. The phenanthrene was presumed to be formed by reaction of active hydrogen compounds in the diethyl mesoxalate with 9-phenanthrylmagnesium bromide, and purification of the ester by the procedure described resulted in an increase in the yield of I to 46%.

9-Phenanthrylglycolic acid (II). I was converted to II by a procedure similar to one used by Riebsomer and Irvine (12). A mixture of 1 g. of I and 0.8 g. of potassium hydroxide in 3 ml. of water containing a few drops of alcohol was heated on a steam-bath for six and one-half hours. After extraction with ether to remove any neutral material, 1.7 ml. of concentrated hydrochloric acid was added to the aqueous solution, which was heated on a steam-bath with stirring for an additional two hours. The product was extracted with ether, which was dried over magnesium sulfate and then concentrated. The residual oil was dissolved in dilute potassium hydroxide solution, which was extracted with ether and chloroform to remove any neutral material and then acidified with hydrochloric acid. The solid which separated was reprecipitated twice from alkaline solution by acidification, after treatment with Darco. The yield of 9-phenanthrylglycolic acid (II), m.p. 158–160° (dec.) was 0.49 g. (68%). Recrystallization from aqueous ethanol, ethyl acetate, and methanol gave colorless needles with a constant m.p. of 163–164° (dec.). II gave an olive color with concentrated sulfuric acid and a rather faint orange color with ferric chloride solution.

Anal. Calc'd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80.

Found: C, 75.86; H, 4.84.

Diethyl 9-phenanthrylchloromalonate (III). The method used for converting I to III was adapted from a procedure described for a similar transformation by Gerrard and French (22). A solution of 37 g. of I and 0.3 ml. of pyridine in 60 ml. of dry benzene was placed in a three-necked flask protected from the air with drying tubes and cooled to 5°. A solution of 13.8 g. of thionyl chloride in 50 ml. of dry benzene was added dropwise with stirring during ten minutes, with cooling to maintain a reaction temperature of 0–5°. After stirring for an additional thirty minutes the mixture was heated under reflux for one and one-half hours, at which time the initially vigorous evolution of gas had practically stopped. The solution was concentrated under reduced pressure and the residual oil was dissolved in benzene. After again concentrating and seeding, the oil which separated crystallized. The solid was triturated with 50 ml. of dry hexane containing 15% of ether, separated by filtration and washed with cold hexane containing 15% of ether. After drying briefly in a vacuum desiccator the solid was dissolved in 50 ml. of of hot carbon tetrachloride, filtered to remove pyridine hydrochloride, and cooled. The crystalline product was collected on a filter, washed with 10 ml. of cold carbon tetrachloride, and dried in a vacuum desiccator. III was obtained as fine pale yellow crystals, m.p. 91–110° (dec.); yield 32.9 g. (84%). A sample of III was recrystallized three times from dry carbon tetrachloride and three times from dry ethyl acetate; after five crystallizations the m.p. was 116–118.5° (dec.). Another crystallization from ethyl acetate lowered the m.p. to 97–100° (dec., immersed at 90° and heated at 1° per minute), but the material with m.p. 97–100° gave satisfactory analyses.

Anal. Calc'd for $C_{21}H_{19}ClO_4$: C, 68.01; H, 5.16; Cl, 9.56.

Found: C, 67.87; H, 5.22; Cl, 9.46.

Diethyl 9-phenanthrylmalonate (IV). A solution of 29 g. of III (m.p. 91–110°) in 230 ml. of purified, anhydrous dioxane was hydrogenated at room temperature and atmospheric pressure in the presence of 5 g. of palladium-on-Norit catalyst (23). The reduction required two hours and 1802 ml. (103%) of hydrogen was absorbed. The catalyst was separated by filtration, washed with dioxane, and the filtrate concentrated under reduced pressure to a volume of about 60 ml. The solution was poured into 300 ml. of water, which was then extracted with ether. The extract was washed with water, dried over magnesium sulfate and concentrated under reduced pressure to an oil which quickly solidified. After recrystallization from 50 ml. of 95% ethanol, 24.6 g. (94%) of IV was obtained as nearly colorless prisms, m.p. 106–108.5°. Concentration of the mother liquors yielded an additional 0.4 g. (2%), m.p. 83–96°. Recrystallization of the first crop from 200 ml. of cyclohexane gave 23.5 g. (89%) of IV as colorless crystals, m.p. 108–109°. An analytical sample crystallized to constant melting point from 95% ethanol, cyclohexane, and hexane had m.p. 110–110.5°.

Anal. Calc'd for $C_{21}H_{20}O_4$: C, 74.98; H, 5.99.

Found: C, 74.78; H, 5.85.

IV was converted to *9-phenanthrylacetic acid* (V) for identification, by a procedure similar to the one used for converting I to II. IV (0.801 g.) was heated on a steam-bath with 1.06 g. of potassium hydroxide in 4 ml. of water for five hours. After extraction with ether, the aqueous solution was acidified with an excess of hydrochloric acid and heated for an additional two hours. Extraction with ether and recrystallization of the acid from absolute ethanol gave 0.387 g. (69%) of V, m.p. 221.5–224°. Reprecipitation of the acid from alkaline solution by acidification and two recrystallizations from methanol raised the m.p. of V to 224–225°. V did not depress the m.p. of an authentic sample (17).

Diethyl α-naphthylmalonate. α-Naphthylmagnesium bromide was prepared from 5.3 g. of magnesium, 45 g. of redistilled α-bromonaphthalene, and 110 ml. of dry ether by the procedure of Gilman, St. John, and Schulze (24), except that the Grignard reagent was dissolved by addition of 135 ml. of dry toluene (rather than benzene). The Grignard reagent was added dropwise with stirring during one and one-quarter hours to a solution of 38 g. of diethyl mesoxalate (purified only by redistillation) in 100 ml. of dry toluene at a reaction temperature of −70 to −60°. The resulting suspension was stirred for one-half hour at −70° and then acidified with dilute sulfuric acid at about −10°. The organic layer and a benzene extract of the aqueous layer were combined, washed with water, dried over magnesium sulfate and treated with Darco. After filtration and concentration 58 g. of a viscous

red sirup was obtained which failed to crystallize. After a short-path distillation at a bath temperature of 130–165° and 0.01 mm. the product remained a sirup.

Diethyl O-benzoyl-α-naphthyltartronate was prepared as a crystalline derivative of the impure diethyl α-naphthyltartronate by a procedure based on one used in a similar case by Jackson and Phinney (25). The sirup (3 g.) was heated with 15 ml. of benzoyl chloride at 110° for seven hours, after which the excess benzoyl chloride was removed under reduced pressure. The residue was dissolved in toluene, which was removed under reduced pressure. After repetition of this process a benzene solution of the residue was treated with Darco, again concentrated, and the red glassy residue was heated at 110° and 0.1 mm. for several hours. On standing, partial crystallization occurred, and the crystalline solid was separated by trituration with 15 ml. of cold absolute ethanol and filtration; yield 0.8 g. (20%), m.p. 109.5–110.5°. Recrystallization from aqueous ethanol and from methylcyclohexane gave diethyl O-benzoyl-α-naphthyltartronate with a constant m.p. of 111–111.5°.

Anal. Calc'd for $C_{24}H_{22}O_6$ C, 70.92; H, 5.46.

Found: C, 70.89; H, 5.63.

Preparation of the benzoate by reaction of diethyl α-naphthyltartronate with benzoyl chloride in pyridine or by treating the bromomagnesium compound formed by addition of α-naphthylmagnesium bromide to diethyl mesoxalate with benzoyl chloride failed to give a higher yield.

The crude diethyl α-naphthyltartronate was converted to diethyl α-naphthylchloromalonate by reaction with thionyl chloride in the presence of a small amount of pyridine in the same manner that I was converted to III. The *diethyl α-naphthylchloromalonate* was obtained as a sirup which after two short-path distillations at a bath temperature of 110–125° and 0.02–0.04 mm. was 86% pure (Calc'd Cl, 11.05; Found, 9.46); n_D^{25} 1.5550; yield 52%. Hydrogenation of 2.09 g. of this crude product in a manner similar to that used for preparation of IV from III gave 0.75 g. (40%) of *diethyl α-naphthylmalonate* after crystallization from hexane; m.p. 57–60.5°. Recrystallization from cyclohexane and from a hexane-pentane-ether mixture raised the m.p. to 62–63°, in agreement with the reported value of 62° (26).

Anal. Calc'd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34.

Found: C, 71.18; H, 6.42.

Diethyl α-naphthylmalonate was prepared by this route as a model case, and undoubtedly is better prepared from ethyl α-naphthylacetate (26).

SUMMARY

Diethyl 9-phenanthrylmalonate has been prepared by the addition of 9-phenanthrylmagnesium bromide to diethyl mesoxalate at −70°, conversion of the resulting diethyl 9-phenanthryltartronate to diethyl 9-phenanthrylchloromalonate by reaction with thionyl chloride, and removal of the chlorine by catalytic hydrogenation.

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