

Synthesis of Trans-And Cis-Diphenyl-4-Acrylic Acid

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(Received 24th June 1982)

Summary: trans-Diphenyl-4-acrylic acid has been synthesized from diphenyl-4-carboxaldehyde which has been prepared by a new route starting from diphenyl. Diphenyl was first nitrated. The 4-nitro derivative was separated from its 2-isomer and reduced to the amino compound. The iodo derivative of diphenyl was prepared from the amino compound through its diazonium salt and converted to the aldehyde through its Grignard reagent. The aldehyde was then condensed with malonic acid to get the trans-diphenyl-4-acrylic acid. The dibromide of the ethyl ester of this acid was then prepared and subjected to dehydrobromination to get diphenyl-4-propionic acid which was reduced catalytically to give cis-diphenyl-4-acrylic acid.

Introduction

Apart from their academic importance, diphenyl and its derivatives are extensively used in industry. Hey¹ was the first to prepare diphenyl-4-acrylic acid but only in the trans form. In spite of the emphasis placed on stereochemistry during the last fifty years, its cis isomer has not been reported so far. The synthesis of diphenyl-2-acrylic acid in both the isomeric forms has already been reported². The present study therefore deals with the preparation of trans-diphenyl-4-acrylic acid by a different route, and its conversion to its cis-isomer.

Among the derivatives of diphenyl, nitro derivatives are of special interest as they form the starting materials for a number of reactive diphenyls. Generally, mixed acid reagent, i.e., conc. nitric acid in the presence of conc. sulphuric acid, is used for the nitration of aromatic hydrocarbons. However, in the presence of an activating phenyl group, relatively milder conditions are required for the nitration of one of the benzene rings in diphenyl. Diphenyl was therefore nitrated using a mixture of nitric acid and acetic anhydride³, to provide a mixture of the 4-and 2-isomers.

Primary arylamines are generally prepared by the reduction of nitro compounds by means of a metal-acid reducing system. Iron in the presence of a little hydrochloric acid has been employed to avoid the formation of undesirable by-products⁴. The primary aromatic amines on reaction with nitrous acid in the presence of a mineral acid at about 0°C yield diazonium salts as discrete intermediates. A solution of sodium nitrite in conc. hydrochloric acid, a very effective diazotizing medium, was presently used. Iodo and bromo diphenyls were prepared by Huber et al⁵ by the usual Sandmeyer

reaction. Since the iodo compounds give Grignard derivatives more readily than the other halo compounds, 4-iododiphenyl was prepared by the reaction of the diazonium salt with an equivalent amount of potassium iodide.

The Grignard reagent is usually obtained quite readily by adding an alkyl halide to a suspension of magnesium turnings in anhydrous ether. Initiation of the reaction may require the addition of a few crystals of iodine the purpose of which may be to form a catalytic amount of magnesium iodide or possibly simply to etch the metal surface. Since it is important that the iodine should be concentrated at the metal surface, the mixture should not be stirred at this stage. One of the general methods for the formation of aldehydes from Grignard reagents involves reaction with formamide⁶. Bouveault⁷ prepared benzaldehyde by reacting phenylmagnesium bromide with N-methylformanilide. The same method was found to be satisfactory for the preparation of diphenyl-4-aldehyde.

Aldehydes of the aromatic series are generally converted to cinnamic acids by the Perkin reaction. Lock and Bayer⁸ observed that the introduction of ethyl or phenyl groups in the para position of benzaldehyde reduces the yield of cinnamic acid drastically. In the Knoevenagel synthesis, on the other hand, using malonic acid with pyridine and piperidine as catalysts, the ethyl group in the para position raises the yield to 83%. Hey¹ prepared diphenyl-4-acrylic acid by heating the corresponding aldehyde with sodium acetate and acetic anhydride. Knoevenagel method used in the present case gave a fairly good yield.

Cinnamic acid was brominated for the first time by Sudborough and Thompson⁹. Abbott and Althomson¹⁰ reported that the addition of bromine to cinnamic acid by the usual method, i.e. using ice-cold solvents, is discouragingly slow. However, the reaction can be carried out satisfactorily with a solution of bromine in carbon tetrachloride at room temperature, and a positive test is indicated by the decolorization of the solution. The acid was esterified before the addition of bromine to protect the acid group. The interaction between an acid and alcohol is a reversible process and proceeds very slowly. The equilibrium is obtained after refluxing the mixture for several days. However, if 3% of the weight of the alcohol, conc. sulphuric acid or hydrochloric acid is added, the equilibrium is attained in 6-7 hours. The equilibrium is displaced in favour of the ester by the use of an excess of alcohol and spontaneous removal of water. The dibromide of the ester was subjected to dehydrobromination with alcoholic potash according to the method of Perkin¹¹, which was also accompanied by the simultaneous hydrolysis of the ester group to get diphenyl-4-propionic acid which was hydrogenated catalytically to yield exclusively the cis form of diphenyl-4-acrylic acid.

Experimental

Materials: Inorganic salts were of reagent grade and were used without further purification, but the organic compounds were purified before use either by recrystallization or by distillation.

Iron turnings were washed first with water and then with acetone and dried at 100-110°C. These were moistened with conc. hydrochloric acid, dried at room temperature and used immediately. Commercial magnesium turnings were washed with dry ether to remove any surface grease, dried at 100°C and allowed to cool in a desiccator. Pyridine was refluxed with sodium hydroxide for four hours and then distilled and collected at 114-116°C and kept over anhydrous magnesium sulphate. N-Methylformanilide was prepared by refluxing 107 g (1 mole) of N-methylaniline and 46 g (1 mole) of pure formic acid, both freshly distilled, for six hours. The mixture was then distilled and N-methylformanilide was obtained at 240-245°C as a colourless oil. Palladium sol (0.5%) was prepared by dissolving palladium chloride in water on heating. It was filtered and 1.0 g of gum arabica was dissolved in it as a stabiliser. The solution was cooled

and neutralized with hydrazine hydrate giving thereby a black palladium sol.

4-Nitrodiphenyl: Added 20 ml of fuming nitric acid to 100 ml of acetic anhydride in a 500 ml round bottomed flask. A solution of 31.0 g (0.2 mole) of diphenyl in 100 ml of acetic anhydride was then added in portions of 2-3 ml with shaking to ensure thorough mixing. The temperature was kept below 55°C by immersing the flask in cold water when necessary. When the addition was complete, the flask was fitted with a reflux condenser and heated on a water bath maintained at 60°C for about an hour with occasional shaking. The contents of the flask were allowed to cool to room temperature and poured into 500 ml of cold water in a beaker and stirred well to ensure the complete hydrolysis of acetic anhydride. The mixture was extracted with chloroform thrice using 100 ml of chloroform each time. The chloroform solution was washed with sodium bicarbonate, dried over sodium sulphate and evaporated. An oily liquid (28 g) consisting of a mixture of 4- and 2-nitrodiphenyl was left behind which was separated by fractional crystallization from ethanol.

The oily mixture was dissolved in 200 ml of hot ethanol and allowed to cool. Pale yellow needles (18 g) of 4-nitrodiphenyl separated out first which were recrystallised from ethanol; m. pt. 114-5°C. The mother liquor of the first crystallization on evaporation yielded 9 g of 2-nitrodiphenyl, a pale yellow solid, which was recrystallized from ethanol and had m.pt. 35-6°C. For 4-nitrodiphenyl, found: C, 72.5; H, 4.4; N, 6.8; C₁₂H₉O₂N requires: C, 72.36; H, 4.52; N, 7.04.

4-Aminodiphenyl: In a one-litre three-necked flask equipped with a mechanical stirrer, a reflux condenser and a dropping funnel, placed 40 g (0.7 mole) of pre-treated iron turnings and 30 ml of water. A solution of 20 g (0.1 mole) of 4-nitrodiphenyl in 50 ml of benzene was added to it slowly. The mixture was heated on a boiling water bath till it became clear. 5.0 ml of conc. hydrochloric acid was added in portions of 1.0 ml each at intervals of five minutes; heating being continued with constant stirring. Heating was continued for one hour more to complete the reaction. A solution of 2.0 g of sodium hydroxide in 10 ml of water was then added to decompose any amine hydrochloride that might have been formed. The reaction mixture was then extracted with benzene and the benzene solution was vigorously agitated with 10 ml of conc.

hydrochloric acid. A white precipitate of hydrochloride of 4-aminodiphenyl separated out. It was filtered and the precipitate treated with 10 ml of 4N-sodium hydroxide solution to liberate the free amine. It was then extracted with ether. The ethereal solution was dried over magnesium sulphate and evaporated to obtain 15.0 g of 4-aminodiphenyl; m.pt. 48-9°C. Found: C, 85.3; H, 6.6; N, 8.4; $C_{12}H_{11}N$ requires: C, 85.2; H, 6.5; N, 8.28.

4-Iododiphenyl: Added 34 g (0.2 mole) of 4-aminodiphenyl to a mixture of 55 ml of conc. hydrochloric acid and 55 ml of water in a 500 ml round bottomed flask. Boiled the mixture to ensure the conversion of amine to its hydrochloride. Cooled the mixture with vigorous stirring to 0°C by immersing it in a freezing mixture of ice and salt. A solution of 15 g (0.22 mole) of sodium nitrite in 75 ml of water chilled by immersing in the ice bath, was added in small portions (2-3 ml at a time) to the cold amine hydrochloride solution with constant stirring. The temperature was kept below 5°C to avoid any decomposition of the diazonium compound and of nitrous acid. Ice was added to the reaction mixture when necessary. The addition of sodium nitrite solution was slowed down towards the end (about 1 ml at a time) and was continued until a slight excess of nitrous acid was present which was detected by a blue colour given by a drop of the reaction mixture on potassium iodide-starch paper.

To the reaction mixture now containing diphenyl-4-diazonium chloride added a solution of 33.2 g (0.2 mole) of potassium iodide in 40 ml of water slowly with stirring. A violet black solid started floating on the surface. The mixture was allowed to stand for three hours and then filtered. The precipitate of 4-iododiphenyl was washed with sodium thiosulphate to remove the free iodine, dissolved in ethanol and refluxed for fifteen minutes in the presence of 5 g of animal charcoal. The mixture was filtered while hot. The filtrate on cooling yielded pale yellow crystals of 4-iododiphenyl, m. pt. 113-14°C, yield was 55% on the basis of 4-aminodiphenyl. Found: C, 51.2; H, 3.1; $C_{12}H_9I$ requires: C, 51.4; H, 3.2

Diphenyl-4-carboxaldehyde: Equipped a two litre round-bottomed flask with a mercury sealed stirrer, a dropping funnel and an efficient double surface condenser, both containing guard tubes on the top. All the apparatus was completely dry and was so arranged that

the flask could be heated with a 200 watt electric bulb. Placed 26.7 g (1.12 mole) of pre-treated magnesium turnings and a crystal of iodine in the flask. In the dropping funnel placed 280 g (1.0 mole) of 4-iododiphenyl dissolved in 800 ml of dry ether. Dropped 250 ml of this solution into the flask and the flask was heated gently with the bulb to start the reaction. When the reaction started, heating was stopped and stirring started. The remainder of the ethereal solution of 4-iododiphenyl was added to the flask slowly over a period of one hour. When the reaction became vigorous, it was controlled by cooling the flask with iced-water. After the addition was complete, the mixture was refluxed with constant stirring for another 30 minutes to complete the formation of the Grignard reagent, indicated by the disintegration of magnesium and the appearance of a brownish turbidity in the solution.

N-Methylformanilide (135 g, 1.0 mole) was mixed with 200 ml of dry ether and dropped slowly with the help of the dropping funnel into the flask containing diphenyl-4-magnesium iodide with constant heating and stirring. A copious white precipitate appeared immediately. After the addition was complete, heating and stirring was continued for half an hour more. The mixture was then allowed to cool and 200 ml of dilute hydrochloric acid added to decompose the complex. The ethereal layer containing diphenyl-4-carboxaldehyde was separated. Any aldehyde in the aqueous layer was also extracted twice with 50 ml of ether. The total ethereal layer was dried over anhydrous sodium carbonate and evaporated to get diphenyl-4-carboxaldehyde which was purified by distillation under reduced pressure (b.pt. 176-8°C/43 mm). The viscous light yellow liquid solidified on standing which was recrystallised from light petroleum to yield yellow crystals with m. pt. 60°C (lit¹ m.pt. 60-61°C). Yield was 57% on the basis of 4-iododiphenyl. 2,4-Dinitrophenyl hydrazone of the aldehyde, recrystallized from xylene to scarlet plates, had m. pt. 236-9°C (lit¹ m.pt. 239°C).

Diphenyl-4-acrylic acid: Placed 91 g (0.5 mole) of diphenyl-4-carboxaldehyde, 75 g (0.72 mole) of malonic acid and 80 ml of pyridine in a 500 ml round-bottomed flask fitted with a reflux condenser. Heated the flask on a boiling water bath for 8 hours. Then cooled the reaction mixture and poured into 300 ml of dilute hydrochloric acid (1:1) with stirring, to combine with

pyridine. Filtered off diphenyl-4-acrylic acid, washed with water and dried. The yield was 70%. It was recrystallized from toluene to get dirty coloured fine needles with m. pt. 222-3°C, (lit¹. m.pt. 223-24°C). Found: C, 80.8; H, 5.6; C₁₅H₁₂O₂ requires: C, 80.36, H, 5.36.

Ethyl diphenyl-4-acrylate: Diphenyl-4-acrylic acid (44.8 g, 0.2 mole) was added to 200 ml of absolute alcohol saturated with hydrogen chloride at 0°C in a 500 ml round-bottomed flask and refluxed for six hours on a water bath. The solution was then concentrated by evaporating some alcohol and allowed to cool. Very fine yellow crystals of ethyl diphenyl-4-acrylate separated out which were obtained by filtration and recrystallized from absolute alcohol to m. pt. 86-87°C. The yield was 70%. Found: C, 81.2; H, 6.5; C₁₇H₁₆O₂ requires: C, 80.95; H, 6.35.

Ethyl -α, β-dibromo-β-4-diphenyl propionate: Dissolved 25.2 g (0.1 mole) of ethyl diphenyl-4-acrylate in 100 ml of dry carbon tetrachloride by shaking in a 500 ml round-bottomed flask fitted with a dropping funnel. A solution of 17.6 g (0.11 mole) of bromine in 50 ml of carbon tetrachloride was added gradually with shaking with the help of the dropping funnel. The mixture was left overnight. It was then transferred to a china dish which was heated at 60°C on a water bath to allow carbon tetrachloride and unreacted bromine to escape leaving behind 37 g (90%) of dirty white solid. It was recrystallized from absolute alcohol to white needles with m. pt. 121-22°C. Found: C, 49.4; H, 3.9; Br, 39.0; C₁₇H₁₆O₂ Br₂ requires: C, 49.5; H, 3.88, Br. 38.83.

Diphenyl-4-propionic acid: A solution of 11.2 g (0.2 mole) of potassium hydroxide in 200 ml of alcohol was placed in a 500 ml round-bottomed flask fitted with a reflux condenser and to it was added a solution of 8.25 g (0.02 mole) of ethyl-α,β-dibromo-β-4-diphenyl propionate in 100 ml of alcohol. The mixture was refluxed on a water bath for 12 hours and then alcohol was removed by distillation leaving behind a viscous mass which was dissolved in 200 ml of water and acidified with hydrochloric acid. A white precipitate of diphenyl-4-propionic acid separated which was filtered, dried and recrystallized from light petroleum (40-60°C) -chloroform to obtain colourless needles with m. pt.

177-78°C (yield, 75%). It was free from bromine. Found: C, 80.9; H, 4.8; C₁₅H₁₀O₂ requires: C, 81.08; H, 4.5.

cis-Diphenyl-4-acrylic acid: G.P. Hydrogenation apparatus was used for the catalytic hydrogenation of diphenyl-4-propionic acid. 2.2 g (0.01 mole) of diphenyl-4-propionic acid were dissolved in 20 ml of 5% solution of sodium bicarbonate and placed alongwith 10 ml of 0.5% palladium sol in the reaction flask. Calculated volume of hydrogen gas was passed through it with constant shaking. The reaction flask was then removed from the apparatus and 20 ml of 1.0 N hydrochloric acid added to it. *cis-Diphenyl-4-acrylic acid* thus produced was extracted with ether and treated with 10 ml of 10% ammoniacal solution of barium chloride for one hour. The solution was then filtered and acidified with hydrochloric acid to get the purified *cis-diphenyl-4-acrylic acid* in 75% yield. It was recrystallized from alcohol to m. pt. 181-82°C. Found: C, 80.4; H, 5.3; C₁₅H₁₂O₂ requires: C, 80.36; H, 5.36.

Acknowledgement:

We wish to thank the University Chemical Laboratory, Cambridge, England for doing the elemental analysis.

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