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An Improved Method for the Preparation of Diazoacetophenone

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In connection with proposed studies in this Laboratory on the metabolism of amino acids by the isotope tracer technique it is necessary to prepare carboxylic acids labelled in the alpha position with isotopic carbon. The Arndt–Eistert synthesis[2] using labelled diazomethane would provide such a method but would only utilize one-half of the isotope as shown by equations (1) and (2).

$$RCOCl + CH_2N_2 \longrightarrow RCOCHN_2 + HCl \qquad (1)$$

$$CH_2N_2 + HCl \longrightarrow CH_3Cl + N_2 \qquad (2)$$

The present investigation was undertaken (A) to improve this procedure so that the diazomethane would be utilized more fully and (B) to improve the methods of preparation of diazomethane.

The most efficient methods[3] of preparing diazomethane involve the formation of nitroso-β-methylaminoisobutyl methyl ketone (I) which is decomposed into diazomethane in the presence of a suitable base. In the present investigation (I) was prepared so as to give the maximum yield on the basis of methylamine used. The procedure for the decomposition of (I) to diazomethane was essentially that used previously.[3] It was found that the amount of base and rate of distillation of product had a marked influence on the yield of diazomethane.

For the experiments on the diazoketone synthesis benzoyl chloride was used as a model. To improve the yield of diazoketone various bases were employed in an attempt to neutralize the hydrochloric acid as it is formed and thus prevent reaction (2). It was found that if a solution of triethylamine and diazomethane in ether were added to benzoyl chloride in ether the yield of diazoketone based on diazomethane was increased from 50 to 90–95%. A slight excess of benzoyl chloride was used to ensure more complete reaction with diazomethane. Excess benzoyl chloride was removed by precipitation with triethylamine. The diazoketone was not isolated in the pure form but was determined by measuring the nitrogen evolved when hydrochloric acid was added.

Having used benzoyl chloride as a model an attempt was made to extend this procedure to phenacetyl chloride. Various relative concentrations of ingredients, temperatures and types of bases were used without success.

Experimental

Nitroso-β-methylaminoisobutyl Methyl Ketone (I).—In a 300-ml. three-necked flask provided with a stirrer and a dropping funnel were placed 29.4 g. (0.3 mole) of mesityl oxide, 13.5 g. (0.2 mole) of methylamine hydrochloride and 20 ml. of water. The flask was cooled in ice and 22 ml. of 40% aqueous sodium hydroxide was added, dropwise, with constant stirring, over a period of one hour. Stirring was continued for thirty minutes after the addition of the sodium hydroxide and then the mixture was neutralized with glacial acetic acid in such a way that the temperature of the reaction was kept below 10°. Thirty-six grams of sodium nitrite, 40 ml. of water and 20 ml. of glacial acetic acid was added consecutiviely and the mixture was stirred for two and a half hours. During this time the reaction vessel was kept in ice for thirty minutes and then in a water-bath which was gradually warmed to 35° within one hour after the removal of the ice-bath. The reaction mixture was extracted twice with ether; the aqueous layer was saturated with sodium chloride and extracted two more times with ether. The extracts were dried over sodium sulfate and the ether and other low boiling substances were removed under reduced pressure at 50–100°. The nitroso compound was distilled under reduced pressure (b. p. 117–119° at 5 mm.). The yield was 27–29 g. (85–90%).

Diazomethane.—A solution of 0.3 g. of sodium in 10 ml. of boiling cyclohexanol was cooled to room temperature, broken into a mash, and added to 200 ml. of anhydrous ether in a 500-ml. three-necked flask provided with a stirrer and water condenser. To this was added 7.9 g. (0.05 mole) of (I); the mixture was stirred and the diazomethane in ether was distilled by heating the reaction slowly in a water-bath. The diazomethane–ether was condensed into a 250-ml. volumetric flask containing 50 ml. of anhydrous ether and cooled in a salt–ice-bath. The time for the distillation was twenty to thirty minutes during which time the water-bath was heated from room temperature to 55°. The yield was 1.7–1.8 g. (80–85%). Amounts of sodium from 0.03 to 1.0 g. per 0.05 mole of nitroso compound were used, with best results being obtained when 0.3 g. were used.

Diazoacetophenone.—In a 500-ml. three-necked flask provided with a condenser, stirrer and dropping funnel were placed 7.4 g. (0.053 mole) of benzoyl chloride and 50 ml. of anhydrous ether. The flask was kept in a salt–ice-bath and through the funnel was added dropwise, over a period of two hours a solution of 2.1 g. (0.05 mole) of diazomethane and 5.1 g. (0.05 mole) of triethylamine in 300 ml. of cold, anhydrous ether. This was followed by the addition of 1.0 g. of triethylamine and stirring was continued for fifteen minutes. The mixture was filtered and the ether and triethylamine were removed under reduced pressure at room temperature. The diazoketone was not isolated in the pure state but was determined in the following manner.

The crude diazoketone was dissolved in alcohol; hydrochloric acid (6 *N*) was added dropwise and the volume of nitrogen evolved was measured. The yield was 90–95%.

Summary

An improved method has been described for the preparation of diazoacetophenone. The method of preparation of diazomethane from methylamine and mesityl oxide has been modified to give maximum yields on the basis of methylamine used.

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[2] W. E. Bachmann and W. Struve, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. I, 1942, p. 38.

[3] Adamson and Kenner, *J. Chem. Soc.*, 286 (1935); 1551 (1937); 181 (1939); Redemann, Rice, Roberts and Ward, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Vol. XXV, 1945, p. 28.