ORGANIC SYNTHESES

AN ANNUAL PUBLICATION OF SATISFACTORY METHODS FOR THE PREPARATION OF ORGANIC CHEMICALS

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INTRODUCTION TO THE SERIES

THE publication of this series of pamphlets has been undertaken to make available in a permanent form complete detailed directions for the preparation of various organic chemical reagents. In announcing this purpose it may be well to mention at the outset some of the difficulties in the way of the research chemist, which it is hoped this series will be able to overcome. The cost of chemicals is prohibitive to the majority of chemists; this was true before the war when Kahlbaum's complete supply was available, and to-day with our dependence on domestic stocks, this cost has increased. The delay in obtaining chemicals, especially from abroad, even if the expense need not be considered, is an important factor. These difficulties have therefore thrown the research chemist on his own resources. The preparation of materials for research, always time consuming and annoying, is made increasingly so by the inexactness of the published information which so often omits essential details. Because of this, much needless experimentation is necessary in order to obtain the results given in the published reports. As the additional information thus acquired is seldom published, duplication of such experiments occurs again and again,—a waste of time and material. It is hoped these difficulties may be remedied by the publication of this series of pamphlets. In other words, the authors hope to make this a clearing house for the exchange of information as to methods of preparation of some of the most needed organic chemical reagents.

On account of the impossibility of obtaining the less common organic chemicals in the United States during the past few years,

university laboratories have had no option but to prepare their own supplies. At the University of Illinois, for instance, a special study has been made of this field, and methods for the production of various substances have been investigated. As a result, reliable methods and directions have been developed for producing the materials in one-half to five pound lots. Such work as Illinois has done is now being given an even more extensive scope at the Research Laboratory of the Eastman Kodak Company. It is felt that the results from these various laboratories should be available to all chemists and it is hoped that they eventually will be completely incorporated in these pamphlets.

The organic chemicals herein discussed have been quite arbitrarily chosen, being those which have been needed in various research laboratories in the last years and for which the directions happen now to be ready for publication. The methods are in only a few cases new ones; they are in general the most satisfactory to be found in the literature. Only such details have been added as will enable a man with a reasonable amount of experience in organic chemistry to duplicate the results without difficulty. To be absolutely sure that each set of directions can be repeated, every experiment has been carried out in at least two laboratories. Only after exact duplication of the results in both laboratories are the directions considered ready for publication. The names of the chemists who have studied the various experiments are given so that further information concerning any obscure point can be obtained if any question arises in using these directions. And finally, in describing the experiments, special attention has been given to the explanation of why it is necessary to follow the directions carefully, and what will happen if these directions are not followed.

Although the main object in this series is to give the most convenient laboratory methods for preparing various substances in one-half to five pound lots, an attempt has also been made to have these processes as far as possible adaptable to large scale development. For example, extractions have been avoided wherever possible, cheap solvents have been sub-

stituted for expensive ones, and mechanical agitation, a procedure extremely important in the success of many commercial processes, has usually been specified. The apparatus used is always carefully described and wherever necessary an illustration is given. Accompanying each preparation there will be found a bibliography containing references to all the methods for the production of the substance described in the literature. This is given in order to aid any future investigator who may wish to study or improve the methods of preparation. It is not claimed that the methods are, in every case, completely perfect, but only that the yields are very satisfactory and allow the production of the substances at a reasonable cost. It is hoped therefore that the pamphlets will benefit not only the scientific research man of the university, but also the technical chemist who desires to develop the preparation of one of these substances to a large scale process of manufacture. The editors trust also that this work may be used to advantage as a preparation manual in intermediate or advanced courses in organic chemistry in university laboratories, and that it will aid small colleges in the production of necessary reagents which they are often financially unable to purchase.

The pamphlets are to be edited by the following committee: Roger Adams, University of Illinois, Urbana, Illinois; J. B. Conant, Harvard University, Cambridge, Massachusetts; H. T. Clarke, Eastman Kodak Company, Rochester, New York; Oliver Kamm, Parke, Davis Company, Detroit, Michigan; each to act for one year as editor-in-chief and the other three to assist him as associate editors. A new number of the series will appear annually, and every five years the data will be rearranged, revised, corrected, and then published in book form. The number of preparations to be completed yearly is not fixed. There will be, it is certain, about twenty; and it is hoped, as the interest is stimulated in this work, that this number may increase considerably. The editors especially desire to solicit contributions from other chemists, not only in this country but abroad. Whenever a compound is thoroughly and extensively studied in connection with some research, it is hoped that

complete directions for its preparation will be assembled and sent to the editor. He will then have them checked and published in a subsequent number. Directions for the preparation of substances already on the market are needed to make this work complete and will be gladly accepted.

It will, of course, be recognized that an occasional mistake or omission will inevitably be found in such a pamphlet as this which contains so many references and formulæ. The committee on publication will therefore deem it a favor if they are notified when any such error is discovered. It is hoped also that if any chemist knows a better method for the preparation of any of the compounds considered, or if anyone discovers any improvements in the methods, he will furnish the authors with such information. Any points which may arise in regard to the various preparations will be gladly discussed. In conclusion, the editors are ready to do all they can to make this work successful, and welcome suggestions of any kind. They feel that the success of the series will undoubtedly depend upon the cooperation of others, and as its success promises to be important to research chemists, the editors urge all interested to assist.

THE EDITORS

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ORGANIC SYNTHESES

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BENZALACETOPHENONE

$$C_6H_5CHO + C_6H_5COCH_3 + (NaOH) \rightarrow C_6H_5CH=CHCOC_6H_5 + H_2O$$

Prepared by E. P. KOHLER and H. M. CHADWELL.
Checked by H. T. CLARKE and R. P. LEAVITT.

1. Procedure

A SOLUTION of 218 g. of sodium hydroxide in 1960 g. of water and 1000 g. of 95 per cent alcohol are introduced into a 5500-cc. bottle which is loosely covered with a perforated disk of cardboard, supplied with an effective stirrer, and supported in a larger vessel so as to permit cooling with cracked ice. Into the alkaline solution, 520 g. of pure acetophenone is poured, the bottle is rapidly surrounded with cracked ice, and the stirrer started; 460 g. of benzaldehyde (U. S. P.) are then added at once. The temperature of the mixture should not be below 15° and it should not be allowed to rise above 30° during the reaction. If it tends to do so, the stirring is not sufficiently vigorous.

It is advantageous, though not essential, to inoculate the mixture with a little powdered benzalacetophenone after stirring for half an hour. After two to three hours, the mixture becomes so thick that the stirring is no longer effective. The stirrer is then removed and the mixture left to itself in an ice-box for about ten hours. The mixture now is a thick paste composed of

small shot-like grains suspended in an almost colorless liquid. It is cooled in a freezing mixture and then either centrifuged or filtered on a large Buchner funnel, washed with water until the washings are neutral to litmus, and finally washed with 200 cc. of alcohol, which has previously been cooled to 0°. After thorough drying in the air, the crude product weighs about 880 g. (yield 97 per cent of the theoretical amount) and melts at 50–54°. It is sufficiently pure for most purposes but tenaciously holds traces of water. It is most readily purified by recrystallization from four to four and a half times its weight of 95 per cent alcohol. Eight hundred and eighty grams of crude product give 770 g. (85 per cent of the theoretical amount) of light-yellow material (m. p. 55–57°) and 40–50 g. that require recrystallization.

2. Notes

The acetophenone should be as pure as possible (m. p. 20°). Commercial acetophenone contains variable quantities of impurities which reduce the yield. By distilling commercial acetophenone with the help of a good still-head (preferably under diminished pressure) and using only the fraction which boils at 201–202° (76–77°/10 mm.) greater quantities of benzalacetophenone can be obtained than by using the entire sample.

Commercial benzaldehyde can be used in place of the purer product, but the amount used must be increased to make up for the impurities which are present.

If the temperature is too low, or the stirring too slow, the product separates as an oil, which later solidifies in large lumps.

If the temperature is allowed to rise above 30°, secondary reactions diminish both the yield and the purity of the product. The most favorable temperature is 25°.

In recrystallizing benzalacetophenone, the alcohol should be saturated at 50°. If the solution is saturated above this temperature, the benzalacetophenone tends to separate as an oil. The solution should be allowed to cool gradually, and should finally be chilled in a freezing mixture.

3. Other Methods of Preparation

The methods for producing benzalacetophenone are: the action of acids on a mixture of benzaldehyde and acetophenone or on a solution of these substances in glacial acetic acid;[1] the condensation of benzaldehyde and acetophenone with a 30 per cent solution of sodium methylate at low temperatures;[2] the action of sodium hydroxide on an alcoholic solution of benzaldehyde and acetophenone.[3]

The methods based on the use of acids as condensing agents were not considered, because Claisen, who devised them, abandoned them after he found that alkaline condensing agents gave better results. The preliminary experiments showed that condensation with sodium methylate takes a long time and gives a product which it is difficult to handle in large quantities. The method devised by Kostanecki and Rossbach[3] has therefore been developed.

[1] Ber. **14**, 2463 (1881).
[2] Ber. **20**, 657 (1887).
[3] Ber. **29**, 1492 (1896).

II

BENZYL BENZOATE

$$2\,C_6H_5CHO + C_6H_5CH_2ONa \rightarrow C_6H_5CO_2CH_2C_6H_5 + C_6H_5CH_2ONa$$

Prepared by O. KAMM and W. F. KAMM.
Checked by ROGER ADAMS and R. L. JENKINS.

1. Procedure

THREE grams of metallic sodium are dissolved by warming for half an hour in 70 g. of pure benzyl alcohol (see notes), and after the mixture has cooled to room temperature the solution is added gradually, with thorough mixing, to 454 g. of c. p. benzaldehyde (which must contain *less* than 1 per cent of benzoic acid). The reaction mixture has a tendency to become warm, but the temperature should be kept slightly below 50–60° by cooling, if necessary. A pasty gelatinous mass results. After about half an hour the temperature of the mixture no longer rises; it is then warmed on the water bath for about one or two hours, with occasional shaking.

The cooled reaction product is treated with 200 cc. of water, the layer of oil separated, washed once with a second portion of water, and subjected to distillation *in vacuo*. The first fraction of the distillate contains benzyl alcohol together with unchanged aldehyde, as well as a small quantity of water. The temperature then rises rapidly to the boiling-point of benzyl benzoate, when the receivers are changed. The product boils at 184–185°/15 mm., and analysis by saponification shows it to consist of 99 per cent ester. A yield of 410–420 g. is obtained, which corresponds to 90–93 per cent of the theoretical amount. This benzyl benzoate supercools readily, but after solidifying

melts within one degree of the highest recorded value (19.4°) and therefore need not be refractionated, unless material of exceptional grade is required.

2. Notes

In the presence of sodium benzylate two molecules of benzaldehyde react with the alcoholate to form an addition product. When the reaction mixture is overheated an important side reaction may occur, as follows:

$$C_6H_5C\begin{matrix}OCH_2C_6H_5\\OCH_2C_6H_5\\ONa\end{matrix} \rightarrow C_6H_5CO_2Na + C_6H_5CH_2OCH_2C_6H_5$$

Dibenzyl ether no doubt forms the chief impurity in benzyl benzoate. Since the boiling-point of the former lies near that of the ester, it is not removed during the process of purification by distillation.

The causes of variations in yield by the use of the older methods can now be explained. When benzaldehyde is added *to the alcoholate*, and especially when the latter is still warm, local overheating results; in fact, the temperature may rise far above 100° with the result that benzyl ether is formed. Simultaneously, the sodium benzylate is converted into sodium benzoate, which is of no value for inducing the desired reaction, and consequently very little benzyl benzoate is obtained. The same side reactions explain the failure of this experiment when the benzyl alcohol used in preparing the catalyst (sodium benzylate) is contaminated with benzaldehyde.

The benzyl alcohol used in this preparation must be free from impurities, especially aldehyde. One cc. dissolved in 50 cc. of water and treated with a freshly prepared clear solution of phenylhydrazine acetate should give no appreciable precipitate. If it is not pure, it must first be treated with alkali as described below.

The benzaldehyde should be titrated in order to determine its acidity. If it is found to contain sufficient benzoic acid to react with a considerable proportion of the sodium alcoholate,

a poor yield of ester will be obtained. Less than 1 per cent of benzoic acid will not interfere seriously with the yields obtained, but the presence of larger quantities of acid will be found to be detrimental and must be removed by washing the benzaldehyde with a sodium carbonate solution and redistilling with the precautions necessary to prevent too free an access of air to the distillate.

The order of mixing the reagents and the temperature of the ingredients at the time of mixing are the most important factors in the experiment. The temperature at which the reaction mixture is maintained after mixing, provided that it is held below 100°, is less important from the standpoint of purity.

The reaction mixture is not treated with acetic acid, as usually recommended, for the reason that such a procedure yields a final product contaminated with benzoic acid, unless an alkaline wash is applied subsequently.

The recovered benzyl alcohol can be used for the preparation of a second lot of benzyl benzoate only after it has been boiled with strong sodium hydroxide to remove all traces of benzaldehyde.

3. Other Methods of Preparation

Benzyl benzoate has been identified in certain natural plant products.[1] In the laboratory it has been prepared by the action of (*a*) benzoyl chloride upon benzyl alcohol,[2] (*b*) benzyl chloride upon sodium benzoate, and (*c*) alcoholates upon benzaldehyde.[3] Recently, Gomberg and Buchler[4] have shown that reaction (*b*) may be conducted even with aqueous solutions of sodium benzoate.

The Claisen method (*c*) furnishes the most convenient and practical procedure for the preparation of this ester. The materials are cheap, the experimental procedure simple, and the product obtained is free from objectionable traces of benzyl

[1] Ann. **152**, 131 (1869).
[2] Gmelin's Handbuch der Organ. Chem. **3**, 40.
[3] Ber. **20**, 649 (1887). Cf. also J. Chem. Soc. **75**, 1155 (1899).
[4] J. Am. Chem. Soc. **42**, 2059 (1920).

chloride. Unfortunately, the method has been found to be extremely erratic in regard to yield (10-95 per cent), as well as in regard to purity of the product (87-97 per cent ester).[1] As a result of the present study,[2] causes for variations are fully accounted for and the procedure has been converted into a satisfactory method of preparation.

[1] C. A. **14**, 3500 (1920).
[2] J. Am. Pharm. Assoc. **11**, 599 (1922).

III

BENZYL CYANIDE

$$C_6H_5CH_2Cl + NaCN \rightarrow C_6H_5CH_2CN + NaCl$$

Prepared by ROGER ADAMS and A. F. THAL.
Checked by O. KAMM and A. O. MATTHEWS.

1. Procedure

IN a 5-l. round-bottom flask, fitted with a stopper holding a reflux condenser and separatory funnel, are placed 500 g. of powdered sodium cyanide (96–98 per cent pure) and 450 cc. of water. The mixture is warmed on a water bath in order to dissolve most of the sodium cyanide, and then 1 kg. of benzyl chloride (b. p. 170–180°) mixed with 1 kg. of alcohol is run in through the separatory funnel in the course of one-half to three-quarters of an hour. The mixture is then heated with a reflux condenser on the steam bath for four hours, cooled and filtered with suction to remove most of the sodium chloride. It is well to wash the filtered salt with a small portion of alcohol in order to remove any benzyl cyanide which may have been mechanically held. The flask is now fitted with a condenser, and as much alcohol as possible is distilled off on the steam bath. The residual liquid is cooled, filtered if necessary, and the layer of benzyl cyanide separated. This crude benzyl cyanide is now placed in a Claisen distilling flask and distilled *in vacuo*, the water and alcohol coming over first, and finally the cyanide. It is advantageous to use a fractionating column or, better still, a Claisen flask with a modified side-arm [1] (Vol. 1, p. 40, Fig. 3) which gives the same effect as a fractionating column. The material is collected from 135–140°/38 mm. (115–120°/10 mm.). The yield is 740–830 g. (80–90 per cent of the theoretical amount).

[1] J. Am. Chem. Soc. **39**, 2718 (1917).

2. Notes

The quality of the benzyl chloride markedly affects the yield of pure benzyl cyanide. If a poor technical grade is used, the yields will not be more than 60–75 per cent of the theoretical, whereas consistent results of about 85 per cent or more were always obtained when a product was used that boiled over 10°. The technical benzyl chloride at hand yielded on distillation about 8 per cent of high-boiling material; a technical grade from another source was of unusual purity and boiled over a 2° range for the most part.

It is advisable to distil off the last portion of alcohol and water *in vacuo* and also to distil the benzyl cyanide *in vacuo*, since under ordinary pressures a white solid invariably separates during the distillation.

One method of purifying the benzyl cyanide is to steam distil it after the alcohol has been first distilled from the reaction mixture. At ordinary pressures, this steam distillation is very slow and, with an ordinary condenser, requires eighteen to twenty hours in order to remove all of the volatile product from a run of 500 g. of benzyl chloride. The distillate separates into two layers; the benzyl cyanide layer is removed and distilled. The product obtained in this way is very pure and contains no tarry material, and, after the excess of benzyl chloride has been removed, boils practically constant. This steam distillation is hardly advisable in the laboratory.

The benzyl cyanide, prepared according to the procedure as outlined, is collected over a 5° range. It varies in appearance from a colorless to a straw-colored liquid and often develops appreciable color upon standing. For a product of special purity, it should be redistilled under diminished pressure and collected over a 1–2° range. For most purposes, such as the preparation of phenylacetic acid or ester, the fraction boiling 135–140°/38 mm. is perfectly satisfactory.

3. Other Methods of Preparation

Benzyl cyanide occurs naturally in certain oils.[1] The only feasible method of preparing it that has been described in the literature is the one in which alcoholic potassium cyanide and benzyl chloride [2] are employed. The cheaper sodium cyanide is just as satisfactory as the potassium cyanide and therefore is the best material to use. Gomberg has recently prepared benzyl cyanide from benzyl chloride and an aqueous solution of sodium cyanide.[3]

[1] Ber. **7**, 519, 1293 (1874); **32**, 2337 (1899).
[2] Ann. **96**, 247 (1855); Ber. **3**, 198 (1870); **14**, 1645 (1881); **19**, 1950 (1886).
[3] J. Am. Chem. Soc. **42**, 2059 (1920).