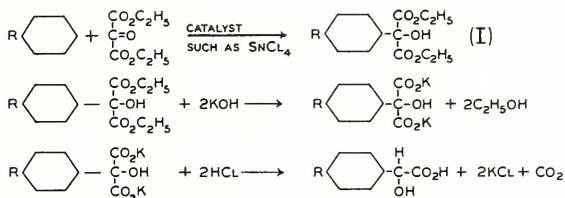


# A Detailed Study of a Reaction Used for the Preparation of Alkyl Mandelic Acids

J. L. RIEBSOMER, JAMES IRVINE, and ROBERT ANDREWS  
DePauw University

We have been interested in the preparation of substituted mandelic acids. Up to the present most of our work has been confined to the alkyl substituted type.

The most common methods for the preparation of mandelic acids has been to treat an aldehyde such as benzaldehyde with hydrogen cyanide, and then to hydrolyze the nitrile thus formed to the acid. This method would be reasonably satisfactory if all the desired aldehydes were readily available. Since the synthesis of these aldehydes requires much time and is often accompanied by poor yields, another method suggested by Ando<sup>1</sup> has been used. The essential features of the method may be represented by the following equations:



Since the process proved to be rather general in its application, it was considered worth while to make a careful study of the conditions of time, temperature, and concentrations of reagents to produce the best yields. In addition, we have tried the effects of various catalysts and have tried a variety of solvents as reaction media.

For the purpose of this study, toluene was chosen as a representative hydrocarbon, thus producing p-methyl mandelic acid as the final product.

## Experimental

**Reagents.**—The toluene was purified by distilling the stock reagent from sodium through a suitable column. Ethyl oxomalonate was prepared using the directions in Organic Syntheses.<sup>2</sup>

The general procedure for the reaction was as follows. The toluene and ethyl oxomalonate were mixed in a 3-necked round-bottomed flask fitted with a stirrer, a condenser, and a burette carrying the stannic chloride. Suitable precautions were taken to exclude moisture. The stannic chloride was added dropwise with stirring, and stirring continued for the desired length of time. In most cases during the addi-

<sup>1</sup> Ando, 1935. Jour. Chem. Soc. Japan 56:745-756; Chem. Abstr. 29:7960.

<sup>2</sup> Gilman, 1932. Organic Syntheses (Collective Vol. I). John Wiley and Sons, New York. p. 261.

tion of stannic chloride, a solid separated, and the supernatant liquid became pink to deep red in color. The mixture was poured into water acidified with hydrochloric acid. This liquid mixture was extracted with ether, and the ethereal solution washed with water until the washings were chloride free and then dried with calcium chloride and distilled. The excess of toluene was recovered and the intermediate compound (I) collected at 150-155° at 5 mm. The intermediate was weighed to determine the yields since it was found that this product could be saponified to give almost a quantitative yield of p-methyl mandelic acid. All yields throughout this discussion were calculated on the basis of the ethyl oxomalonate used.

The first series of experiments was designed to learn the optimum concentration of the hydrocarbon to use. Five one-hundredths of a mole (8.7 g.) of ethyl oxomalonate, 0.05 mole (13.0 g.) stannic chloride, and varying amounts of toluene were reacted. About thirty minutes were required to add stannic chloride, and stirring was continued for fifteen minutes longer. The temperature was held at 20° during the reaction and the mixture allowed to stand at the same temperature for forty-eight hours. The product was then treated by the general procedure and the intermediate compound collected and weighed.

TABLE I.—Yields of intermediate using varying amounts of toluene

Moles toluene used	Yield %
0.05	44.9
0.10	47.7
0.20	52.8
0.30	53.8
0.40	55.3
0.60	57.7

In the second series of reactions, 0.25 moles of toluene, 0.05 moles ethyl oxomalonate and varying amounts of stannic chloride were reacted at 20°. The stannic chloride was added dropwise, and stirring was continued for fifteen minutes after the last was added. The mixtures then stood at 20° for 48 hours. Table II shows the data.

TABLE II.—Yield of intermediate using varying amounts of Stannic Chloride

Moles Stannic Chloride used	Yield %
.031	46.2
.042	51.5
.057	57.9
.077	59.7
.100	58.6

In the third series of reactions 0.05 moles of ethyl oxomalonate, 0.077 moles stannic chloride and 0.25 moles toluene were reacted at 20°. The addition of stannic chloride and stirring was carried out over a period of two hours, and the reaction mixture allowed to stand for varying periods of time. Table III summarizes the data.

TABLE III.—Yield of intermediate varying the reaction time

Time	Yield %
2 hours	55.6
6 hours	59.9
1 day	59.1
2 days	58.4
4 days	59.3
6 days	59.1

In the fourth series, the same concentrations of reagents were used as in the third, the reaction was continued two hours with stirring, and the temperature was varied. The reaction product was immediately poured into ice water at the end of two hours. Table IV shows the results.

TABLE IV.—Yield of intermediate varying the temperature of the reaction

Temperature (°C)	Yield %
-10	55.3
5	56.0
20	55.6
70	29.7

To determine the effect of adding the reagents in a different order, 0.25 mole of toluene, and 0.077 mole of stannic chloride were mixed, and ethyl oxomalonate was added drop by drop, and stirring was continued for two hours at  $-10^{\circ}$  C. The yield of the intermediate was 41.4%.

*The effect of various catalysts.*—These reactions were carried out using 0.25 mole of toluene, 0.05 mole of ethyl oxomalonate and 0.10 mole of each of the catalysts. The procedure was the same as for the stannic chloride except the solid anhydrous catalysts and toluene were mixed and the ethyl oxomalonate was added. The temperature was  $0^{\circ}$ C., and the reaction time three hours. The data are summarized in Table V.

TABLE V.—Yield of intermediate using various catalysts

Catalyst	Yield %
Stannic Chloride	60.2
Ferric Chloride	56.3
Aluminum Chloride	negligible
Zinc Chloride	negligible
Cuprous Chloride	negligible

Finally, 0.25 mole toluene, 0.05 mole of ethyl oxomalonate, and 0.077 mole of stannic chloride were reacted at  $0^{\circ}$ C. and for three hours in 25 grams of various solvents. Table VI shows the results.

TABLE VI.—Yield of intermediate using various solvents for reaction media

Solvent	Yield %
Petroleum ether (b.p. $30-40^{\circ}$ )	41.2
Chloroform	53.3
Carbon Tetrachloride	60.7
Carbon Disulphide	60.4
Methyl Alcohol	20.6
Acetone	negligible
Ether	negligible

**Discussion of Results.**—From the tables it can be seen that the best yields are obtained by using five moles of toluene to one mole of ethyl oxomalonate. Fortunately, the excess of hydrocarbon can be recovered with almost no loss. The optimum quantity of stannic chloride is about one to one and five-tenths moles of the chloride to one mole of the ester. Increased amounts of the chloride make little difference.

The yield changes slightly whether the reaction mixture stands for three hours or for six days, and little difference is noted in the yields from minus ten degrees up to room temperature. At higher temperatures a different product forms, which is much higher boiling than the product desired. We hope to obtain more of this material and examine it in the future.

This reaction seems to be a special case of the Friedel-Craft type. Four reasons for this suggestion may be cited.

1. In appearance it is quite similar to the reaction of benzene with acetyl chloride to give acetophenone. In this reaction we might consider the first step to be an addition of phenyl and hydrogen to a carbonyl oxygen followed by the loss of a molecule of hydrogen chloride. In the case under consideration, however, the intermediate may be considered as an addition of the hydrocarbon to a carbonyl oxygen, but there is no group present which splits out easily.

2. The condensing agents, stannic chloride, and ferric chloride favor the Friedel-Craft reaction just as this one. The fact that aluminum chloride, which is highly desirable in most Friedel-Craft reactions, did not produce the results desired here, is not necessarily an argument against the above suggestion. Aluminum chloride did cause a reaction, but the product formed had a very high boiling point. This probably means that two or three moles of the ester reacted with one mole of the hydrocarbon to produce a complex derivative or a complex mixture. It is possible that if the temperature had been much lower and if a solvent had been present, the desired product would have been produced. This experiment has not been tried.

3. The fact that carbon disulfide, when used as a solvent, gave a good yield, as it does in most Friedel-Craft reactions, points in the same direction.

4. Finally, when nitrobenzene and ethyl oxomalonate are mixed in the presence of stannic chloride, no reaction takes place. This has its parallel in the Friedel-Craft reaction, in which nitrobenzene is often used as a solvent.

### Summary

1. A method for the preparation of alkyl mandelic acids has been studied in detail using the preparation of p-methyl mandelic acid as an example.
2. The optimum reaction conditions have been discovered.
3. The reaction is believed to be of the Friedel-Craft type.