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PREPARATION OF ISONICOTINIC ACID ESTERS

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This invention relates to an improved process for preparing lower alkyl esters of isonicotinic acid, and more particularly, to an improved process for converting the lower alkyl esters of 2,6-dihalopyridine-4-carboxylic acid to the corresponding isonicotinic acid esters by hydrogenolysis in the presence of a palladium catalyst.

It is known that a 2,6-dihalopyridine-4-carboxylic acid, such as 2,6-dichloropyridine-4-carboxylic acid, can be reduced to isonicotinic acid by hydrogenolysis in the presence of a hydrogenation catalyst. The isonicotinic acid thus prepared is readily converted to its alkyl esters which find application in the preparation of isonicotinic acid hydrazide, a compound useful in the treatment of tuberculosis. However, the reduction of the dichloro-acid and its subsequent conversion to an ester involves certain disadvantages, among which is a costly distillation step to remove water from the reaction mixture prior to esterification.

It has now been found that the lower alkyl esters, such as the methyl, ethyl, propyl and butyl esters, of isonicotinic acid can be prepared in excellent yields and with a minimum of catalyst by hydrogenolysis of the corresponding esters of 2,6-dihalopyridine-4-carboxylic acid under superatmospheric pressure and at an elevated temperature with the aid of a palladium catalyst, provided that the reaction is conducted under non-hydrolytic conditions in the presence of a base. In general, the invention is applicable to the reduction of normal and branched chain esters wherein the alkyl group of the ester may vary from 1 to 6 carbon atoms in length and higher.

The alkyl esters of 2,6-dihalopyridine-4-carboxylic acid may be obtained by first halogenating citrazinic acid, and then esterifying the resulting product with a lower alkanol by methods well known in the art. The methyl ester of 2,6-dichloropyridine-4-carboxylic acid is preferred for reasons of economy.

The hydrogenolysis is carried out in an organic solvent, such as a hydrocarbon or alcohol solvent, illustrative of which are aliphatic hydrocarbons such as hexane; aromatic hydrocarbons, such as benzene, xylene, toluene; aliphatic alcohols, such as methyl, ethyl, propyl, butyl alcohols and the like; and aromatic alcohols, such as benzyl alcohol. When an aliphatic alcohol is employed, it is preferred to select an alcohol corresponding to the ester undergoing reduction in order to obviate the danger of ester interchange during reduction if a substantially pure product is desired.

The reaction mixture is maintained substantially free from water which complicates separation of the resulting products and causes saponification of the ester. The reaction is conducted in the presence of a base which is preferably employed in an amount sufficient to maintain the reaction mixture under alkaline conditions throughout the hydrogenolysis, thereby taking up the hydrogen halide which is split off and preventing the development of acid conditions which tend to cause over-reduction of the pyridine ring. About two equivalents of such base per equivalent of the 2,6-dihalopyridine-4-carboxylic acid ester are generally adequate to accomplish this purpose, a moderate excess of the base having no harmful effects. Non-hydroxylic bases are employed in order to maintain the desired non-hydrolytic condition of the reaction mixture.

A wide variety of non-hydroxylic bases are successfully employed in accordance with the process of this invention. Thus, the bases which are useful include primary, secondary and tertiary aliphatic amines, such as n-amyl amine, n-heptyl amine, diethylamine and triethylamine; heterocyclic amines, such as morpholine and pyridine; mixed aliphatic-aromatic amines, such as dimethylaniline; anhydrous ammonia, fused sodium acetate, and sodium methoxide. The preferred combination of solvent and base is that of benzene and triethylamine, since the hydrochloride of the base separates completely during the reaction, thus facilitating purification of the product and recovery of the base.

After the 2,6-dihalopyridine-4-carboxylic acid ester has been dissolved, the palladium catalyst is added to the solution in preparation for the hydrogenolysis. The catalyst which has been found to be particularly effective for the reaction is a reduced palladium supported on charcoal, which is commercially available from a number of sources. Alternatively, palladium hydroxide on charcoal may be employed and reduced in situ during hydrogenolysis. Although relatively large ratios of catalyst to the 2,6-dihalopyridine-4-carboxylic acid can be employed successfully, it has been found that excellent yields can be obtained with as little palladium catalyst as 1.5 percent by weight of the 2,6-dihalopyridine-4-carboxylic acid ester, when using approximately 2 equivalents of alkaline material per equivalent of ester. Use of more than 5 percent of palladium is usually impractical, since no proportionate improvement in reaction efficiency is thereby achieved.

The hydrogenolysis is preferably carried out within the temperature range of 50 to 60° C. and at a pressure from 15 to 40 pounds of hydrogen per square inch, although both temperature and pressure may be varied considerably above and below these ranges. The time of reaction may also vary considerably, depending upon the reaction conditions, etc., but in general, from about 1 to 3 hours is sufficient to complete the desired conversion under the conditions specified. The reaction is terminated when approximately 2 mols of hydrogen have been reacted per mol of the 2,6-dihalopyridine-4-carboxylic acid ester. Care should be taken to avoid extreme conditions, since saturation of the ring might occur.

Upon completion of the hydrogenolysis, the catalyst and insoluble by-products of the reaction are filtered off, and the filtrate can be treated by known methods to obtain the isonicotinic acid alkyl ester. For example, the filtrate may then be stripped of solvent, leaving a crude ester which may be purified by distillation directly or after further treatment, depending upon the particular solvent and base employed during the reaction. Alternatively, the crude ester remaining after solvent removal may be treated with water, and then subjected to solvent extraction with suitable solvents, such as chloroform and carbon tetrachloride, prior to distillation.

The invention is further illustrated by the following examples:

Example I

A mixture of 20.6 grams of the methyl ester of 2,6-dichloropyridine-4-carboxylic acid, 20.2 grams triethylamine, 5 grams of 5% palladium-on-charcoal and 200 ml. of methyl alcohol was charged to a hydrogenation vessel. Hydrogen was then introduced at a pressure of 40 pounds per square inch gauge, and the bomb was shaken for a period of one hour, while maintaining a temperature between 50 and 60° C. During this period the pressure dropped to 22 pounds per square inch gauge, indicating

a hydrogen uptake of about 2 mols of hydrogen per mol of ester. After removal of the catalyst by filtration, the filtrate was stripped of methyl alcohol under vacuum. Water was then added, and thereafter, the product was extracted with chloroform, which was subsequently removed under vacuum. The extract was distilled to obtain 11.5 grams of methyl isonicotinate in a yield of 83.7 percent.

Example II

The hydrogenolysis outlined in Example I was repeated for a period of ¾ of an hour, using 1 gram of the palladium catalyst in lieu of the 5 grams employed in accordance with Example I. After extraction with chloroform and distillation of the ester as indicated in Example I, 11.1 grams of methyl ester were recovered. The yield was 81 percent.

Example III

Another hydrogenolysis under the same conditions with 2 grams of catalyst resulted in an identical yield of 11.1 grams of ester, equivalent to the 81 percent yield above indicated.

Example IV

A mixture of 20.6 grams of methyl ester of 2,6-dichloropyridine-4-carboxylic acid, 30.3 grams of triethylamine, 1 gram of 5% palladium-on-charcoal and 100 ml. of benzene was charged to a hydrogenation vessel and shaken under a hydrogen pressure of 40 pounds per square inch gauge. The temperature was maintained at about 60° C. for a period of 3 hours. The reaction mixture was then filtered to remove the catalyst and triethylamine hydrochloride formed during the reaction. After the filtrate was stripped of benzene, the crude methyl ester of isonicotinic acid was distilled for purposes of purification. The amount of ester thus obtained was 12.2 grams, amounting to an overall yield of 89 percent.

Example V

A mixture of 20.6 grams of methyl ester of 2,6-dichloropyridine-4-carboxylic acid, 4 grams of anhydrous ammonia, 5 grams of 5% palladium-on-charcoal, and 200 ml. of methanol was subjected to hydrogenolysis and further treatment as in Example I. The distilled ester was recovered in an amount of 8.9 grams or a 65 percent yield.

Example VI

A mixture of 20.6 grams of methyl ester of 2,6-dichloropyridine-4-carboxylic acid, 15.8 grams of pyridine, 5 grams of 5% palladium-on-charcoal and 200 ml. of methanol was charged to a hydrogen vessel and subjected to an initial hydrogen pressure of 40 pounds per square inch gauge. The temperature was maintained at 60° C. for a period of ½ hour, during which the pressure dropped to 24 pounds per square inch gauge. Thereafter, the catalyst was removed by filtration and the mixture neutralized to a pH of 7.2 with a saturated solution of sodium bicarbonate. After stripping off the methanol and removing the solids which had formed as a result thereof, water was added to the filtrate and the solution was acidified to a pH of 6.7 with dilute hydrochloric acid. The resulting ester was then extracted with chloroform and distilled to obtain 4.6 grams of ester in a yield of 33.8 percent.

Example VII

A mixture of 20.6 grams of methyl ester of 2,6-dichloropyridine-4-carboxylic acid, 2.5 grams of fused sodium acetate, 5 grams of 5% palladium-on-charcoal and 200 ml. of methanol was subjected to hydrogenolysis for a period of 3 hours in accordance with the procedure outlined in Example I. After further treating the product as in Example I, 4.9 grams of ester were obtained in a yield of 40 percent.

Example VIII

A mixture of 20.6 grams of methyl ester of 2,6-dichloropyridine-4-carboxylic acid, 17.4 grams of morpholine, 1 gram of 5% palladium-on-charcoal and 200 ml. of methanol was subjected to hydrogenolysis as in Example I, and the purified ester thus produced was recovered in an amount of 11.5 grams or a yield of 83.9 percent.

Example IX

A mixture of 20.6 grams of methyl ester of 2,6-dichloropyridine-4-carboxylic acid, 24.2 grams of dimethylaniline, 1 gram of 5% palladium on carbon, and 150 ml. of methanol was charged to a hydrogenation vessel and shaken under a hydrogen pressure of 40 pounds per square inch. The temperature was maintained at about 60° for three hours. The reaction mixture was then filtered to remove the catalyst and methanol was stripped from the filtrate. After addition of water and extraction with chloroform, the crude ester was distilled, giving 7.4 grams of the methyl ester in a yield of 54%.

Example X

A mixture of 20.6 grams of methyl ester of 2,6-dichloropyridine-4-carboxylic acid, 17.4 grams of n-amyl amine, 1 gram of 5% palladium on carbon and 150 ml. of methanol was charged to a hydrogenation vessel and shaken under a hydrogen pressure of 40 pounds per square inch gauge. The temperature was maintained at about 60° for one hour. After removing the catalyst by filtration and stripping off the methanol, 100 cc. of water were added and the water mixture was extracted with chloroform. The chloroform was stripped and the ester distilled, giving 5.4 grams of ester which amounted to a yield of 39.4 percent.

It is readily apparent from the above examples that this invention provides an economical and efficient process for preparing the lower alkyl esters of isonicotinic acid without the disadvantages which attend prior art methods. The esters so obtained are useful as intermediates in organic syntheses, and, as indicated herein, they are particularly useful in the preparation of isonicotinic acid hydrazide, which has shown utility in the treatment of tuberculosis.

Resort may be had to such modifications and equivalents as fall within the spirit of the invention and the scope of the appended claims.

We claim:

1. A process for preparing a lower alkyl ester of isonicotinic acid which comprises hydrogenating a solution of a lower alkyl ester of 2,6-dihalopyridine-4-carboxylic acid under non-hydrolytic conditions and under superatmospheric pressure and at an elevated temperature, in the presence of a palladium catalyst and a non-hydrolytic base, and terminating the reaction when approximately two mols of hydrogen have been reacted per mol of said 2,6-dihalopyridine-4-carboxylic acid ester.

2. A process for preparing a lower alkyl ester of isonicotinic acid which comprises hydrogenating a lower alkyl ester of 2,6-dihalopyridine-4-carboxylic acid in an organic solvent under non-hydrolytic conditions and superatmospheric pressure and at an elevated temperature, in the presence of a palladium catalyst and about two equivalents of a non-hydroxylic base per equivalent of 2,6-dihalopyridine-4-carboxylic acid ester, and terminating the reaction when approximately two mols of hydrogen have been reacted per mol of said 2,6-dihalopyridine-4-carboxylic acid ester.

3. A process for preparing a lower alkyl ester of isonicotinic acid which comprises hydrogenating a hydrocarbon solution of a lower alkyl ester of 2,6-dihalopyridine-4-carboxylic acid and triethylamine non-hydrolytic and non-hydroxylic conditions and under superatmospheric pressure and at a temperature from about 50 to 60° C. in the presence of a palladium catalyst, and terminating the reaction when approximately two mols of hydrogen have been reacted per mol of said 2,6-dihalopyridine-4-carboxylic acid ester.

4. A process for preparing a lower alkyl ester of iso-

nicotinic acid which comprises hydrogenating an alcohol solution of a lower alkyl ester of 2,6-dichloropyridine-4-carboxylic acid and anhydrous ammonia non-hydrolytic and non-hydroxylic conditions and under superatmospheric pressure and at a temperature from about 50 to 60° C. in the presence of a palladium catalyst, and terminating the reaction when approximately two mols of hydrogen have been reacted per mol of said 2,6-dichloropyridine-4-carboxylic acid ester.

5. A process for preparing a lower alkyl ester of isonicotinic acid which comprises hydrogenating an alcohol solution of a lower alkyl ester of 2,6-dichloropyridine-4-carboxylic acid and morpholine non-hydrolytic and non-hydroxylic conditions and under superatmospheric pressure and at a temperature from about 50 to 60° C. in the presence of a palladium catalyst, and terminating the reaction when approximately two mols of hydrogen have been reacted per mol of said 2,6-dichloropyridine-4-carboxylic acid ester.

6. A process for preparing the methyl ester of isonicotinic acid which comprises hydrogenating a solution of 2,6-dichloropyridine-4-carboxylic acid methyl ester and triethylamine in benzene non-hydrolytic and non-hydroxylic conditions and at a pressure from about 15 to 40 pounds per square inch and at a temperature from about 50 to 60° C. in the presence of a palladium catalyst on charcoal, and terminating the reaction when approximately two mols of hydrogen have been reacted per mol of said 2,6-dichloropyridine-4-carboxylic acid methyl ester.

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