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(54) Title: PROCESS FOR THE SYNTHESIS OF HYDROXY AROMATIC ACIDS

(57) Abstract: Hydroxy aromatic acids are produced in high yields and high purity (>95%) from halogenated aromatic acids in a reaction mixture containing a copper source and a ligand that coordinates to copper.

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TITLE

PROCESS FOR THE SYNTHESIS OF HYDROXY AROMATIC ACIDS

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Technical Field

This invention relates to the manufacture of hydroxy aromatic acids, which are valuable for a variety of purposes such as use as intermediates or as monomers to make polymers.

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Background

Hydroxy aromatic acids are useful as intermediates and additives in the manufacture of many valuable materials including pharmaceuticals and compounds active in crop protection, and are also useful as monomers in the production of polymers. Salicylic acid (o-hydroxybenzoic acid), for example, is used in the manufacture of aspirin and has other pharmaceutical applications. Esters of p-hydroxybenzoic acid, known as "parabens", are used as food and cosmetic preservatives. P-hydroxybenzoic acid and 6-hydroxy-2-naphthoic acid are each used as a component of liquid crystalline polymers.

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Various preparations of hydroxybenzoic acids, including 2,5-dihydroxyterephthalic acid ("DHTA"), are known. Marzin, in *Journal fuer Praktische Chemie*, 1933, 138, 103-106, teaches the synthesis of 2,5-dihydroxyterephthalic acid ("DHTA") from 2,5-dibromoterephthalic acid ("DBTA") in the presence of copper powder.

30

Singh et al, in *Jour. Indian Chem. Soc.*, Vol. 34, No. 4, pages 321-323 (1957), report the preparation of a product that includes DHTA by the condensation of DBTA with phenol in the presence of KOH and copper powder.

Rusonik et al, *Dalton Trans.*, 2003, 2024-2028, describe the transformation of 2-bromobenzoic acid into salicylic acid, benzoic acid, and diphenic acid in a reaction catalyzed by Cu(I) in the presence of various ligands. A tertiary tetraamine minimizes the formation of diphenic acid in use with Cu(I).

Comdom et al, *Synthetic Communications*, 32(13), 2055-59 (2002), describe a process for the synthesis of salicylic acids from 2-chlorobenzoic acids. Stoichiometric amounts of pyridine (0.5 to 2.0 moles per mole of 2-chlorobenzoic acid) are used such as at least 1.0 mole pyridine per mole 2-chlorobenzoic acid. Cu powder is used as a catalyst along with the pyridine.

Gelmont et al, *Organic Process Research & Development*, 6(5), 591-596 (2002), and U.S. Patent 5,703,274, describe a process for the preparation of 5-hydroxyisophthalic acid by hydrolyzing 5-bromoisophthalic acid, mixtures of 5-bromoisophthalic acid, dibromoisophthalic acid isomers, and salts thereof in an aqueous alkaline solution in the presence of a copper catalyst at a temperature of 100 to 270°C.

Israeli Patent 112,706 discloses a process for the preparation of 4-hydroxyphthalic acid, and a mixture of 3- and 4-hydroxyphthalic acids, by hydrolyzing the corresponding bromophthalic acids in an aqueous

alkaline solution in the presence of a copper catalyst at a temperature of 100 to 160°C. Examples of copper catalysts disclosed include Cu(0), CuCl, CuCl₂, Cu₂O, CuO, CuBr₂, CuSO₄, Cu(OH)₂, and copper (II) acetate.

5

The various prior art processes for making hydroxybenzoic acids are characterized by long reaction times, limited conversion resulting in significant productivity loss, or the need to run under pressure and/or at higher temperatures (typically 140 to 250°C) to get reasonable rates and productivity. A need therefore remains for a process by which hydroxybenzoic acids can be produced economically; with low inherent operational difficulty; and with high yields and high productivity in small- and large-scale operation, and in batch and continuous operation.

Summary

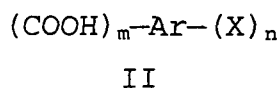
One embodiment of this invention provides a process for preparing a hydroxy aromatic acid that is described generally by the structure of Formula I



25

wherein Ar is a C₆-C₂₀ arylene radical, n and m are each independently a nonzero value, and n + m is less than or equal to 8, by (a) contacting a halogenated aromatic acid that is described generally by the structure of Formula II,

30



35

wherein each X is independently Cl, Br or I, and Ar, n and m are as set forth above, with a base in water to form therefrom the corresponding m-basic salt of the halogenated aromatic acid in water; (b) contacting the m-basic salt of the halogenated aromatic acid with a base in water, and with a copper source in the presence of a ligand that coordinates to copper, to form the m-basic salt of a hydroxy aromatic acid from the m-basic salt of the halogenated aromatic acid at a solution pH of at least about 8,; (c) optionally, separating the m-basic salt of the hydroxy aromatic acid from the reaction mixture in which it is formed; and (d) contacting the m-basic salt of the hydroxy aromatic acid with acid to form therefrom a n-hydroxy aromatic acid.

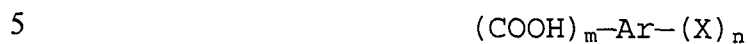
Yet another embodiment of this invention provides a process for preparing an n-alkoxy aromatic acid by preparing an n-hydroxy aromatic acid in the manner described above and then converting the n-hydroxy aromatic acid to an n-alkoxy aromatic acid.

Yet another embodiment of this invention consequently provides a process for preparing an n-alkoxy aromatic acid that is described generally by the structure of Formula VI



wherein Ar is a C₆-C₂₀ arylene radical, each R⁹ is independently a substituted or unsubstituted C₁₋₁₀ alkyl group, n and m are each independently a nonzero value,

and $n + m$ is less than or equal to 8, by (a) contacting a halogenated aromatic acid that is described generally by the structure of Formula II,



II

wherein each X is independently Cl, Br or I, and Ar, n and m are as set forth above, with a base in water to form therefrom the corresponding m-basic salt of the halogenated aromatic acid in water; (b) contacting the m-basic salt of the halogenated aromatic acid with a base in water, and with a copper source in the presence of a ligand that coordinates to copper, to form the m-basic salt of a hydroxy aromatic acid from the m-basic salt of the halogenated aromatic acid at a solution pH of at least about 8; (c) optionally, separating the m-basic salt of the hydroxy aromatic acid from the reaction mixture in which it is formed; (d) contacting the m-basic salt of the hydroxy aromatic acid with acid to form therefrom an n-hydroxy aromatic acid that is described generally by the structure of Formula I,



I

wherein Ar, n and m are as set forth above; and (e) converting the n-hydroxy aromatic acid to an n-alkoxy aromatic acid that is described generally by the structure of Formula VI, wherein Ar, R⁹, n and m are as set forth above.

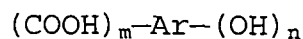
Yet another embodiment of this invention provides a process for preparing a 2,5-dihydroxyterephthalic acid or a 2,5-dialkoxyterephthalic acid as described

above that further includes a step of subjecting the 2,5-dihydroxyterephthalic acid or the 2,5-dialkoxyterephthalic acid to a reaction to prepare therefrom a compound, monomer, oligomer or polymer.

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Yet another embodiment of this invention consequently provides a process for preparing a compound, monomer, oligomer or polymer by preparing a hydroxy aromatic acid that is described generally by the structure of Formula I

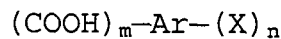
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I

wherein Ar is a C₆-C₂₀ arylene radical, n and m are each independently a nonzero value, and n + m is less than or equal to 8, by (a) contacting a halogenated aromatic acid that is described generally by the structure of Formula II,

20



II

wherein each X is independently Cl, Br or I, and Ar, n and m are as set forth above, with a base in water to form therefrom the corresponding m-basic salt of the halogenated aromatic acid in water; (b) contacting the m-basic salt of the halogenated aromatic acid with a base in water, and with a copper source in the presence of a ligand that coordinates to copper, to form the m-basic salt of a hydroxy aromatic acid from the m-basic salt of the halogenated aromatic acid at a solution pH of at least about 8,; (c) optionally, separating the m-basic salt of the hydroxy aromatic acid from the reaction mixture in which it is formed; (d) contacting

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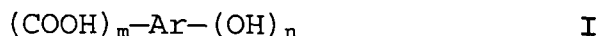
the m-basic salt of the hydroxy aromatic acid with acid to form therefrom an n-hydroxy aromatic acid; (e) optionally, converting the n-hydroxy aromatic acid to a n-alkoxy aromatic acid; and (f) subjecting the n-
5 hydroxy aromatic acid and/or the n-alkoxy aromatic acid to a reaction to prepare therefrom a compound, monomer, oligomer or polymer.

In yet another embodiment, the ligand in one or
10 more of the processes described herein may be an amino acid in which the amine nitrogen and the carboxyl carbon are separated by no more than two carbon atoms.

15 Detailed Description

This invention provides a high yield and high productivity process for preparing a hydroxy aromatic acid as described generally by the structure of Formula
I

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by contacting a halogenated aromatic acid as described generally by the structure of Formula II

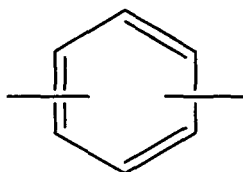
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with base to form the m-basic salt of the halogenated aromatic acid; contacting the m-basic salt of the
30 halogenated aromatic acid with base, and with a copper source in the presence of a ligand that coordinates to copper, to form the m-basic salt of an n-hydroxy aromatic acid; and then contacting the dibasic salt of the n-hydroxy aromatic acid with acid to form the n-
35 hydroxy aromatic acid product.

In both Formulae I and II, Ar is a C₆-C₂₀ arylene radical, n and m are each independently a nonzero value, and n + m is less than or equal to 8; and in
5 Formula II, each X is independently Cl, Br or I. The arylene radical denoted by "-Ar-" is a multi-valent aromatic radical formed by the removal of two or more hydrogens from different carbon atoms on the aromatic ring, or on the aromatic rings when the structure is
10 multicyclic. There is consequently, for example, the possibility in the arylene radical that hydrogens may be removed from two up to all six carbon atoms on a benzyl ring, or hydrogens may be removed from any two and up to eight positions on either one or both rings
15 of a naphthyl radical.

The arylene radical, "Ar", may be substituted or unsubstituted. The arylene radical, when
unsubstituted, is a univalent group containing only
20 carbon and hydrogen. In the arylene radical, however, one or more O or S atoms may optionally be substituted for any one or more of the in-chain or in-ring carbon atoms, provided that the resulting structure contains
no -O-O- or -S-S- moieties, and provided that no carbon
25 atom is bonded to more than one heteroatom. One example of a suitable arylene radical is phenylene, as shown below.



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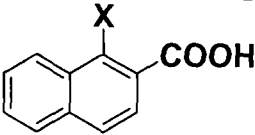
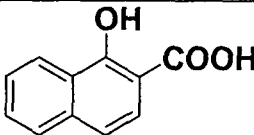
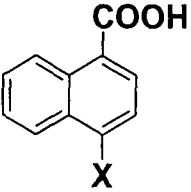
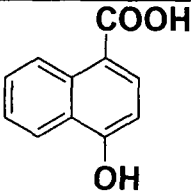
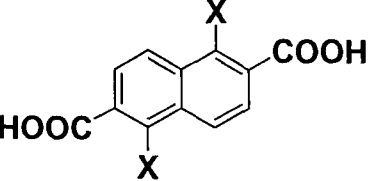
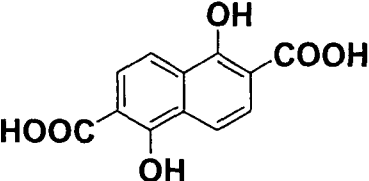
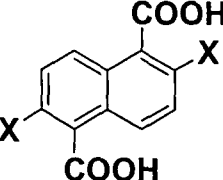
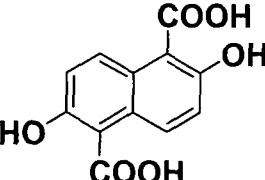
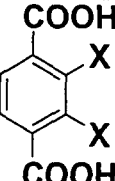
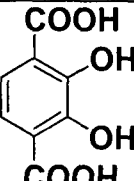
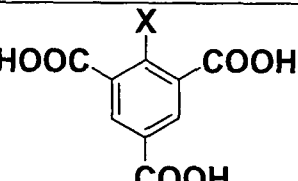
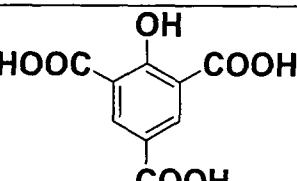
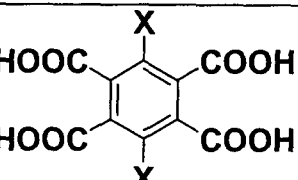
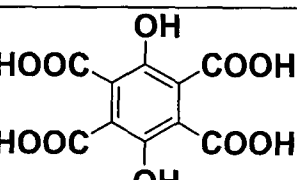
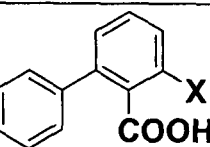
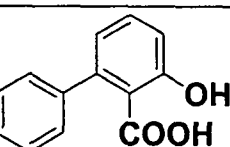
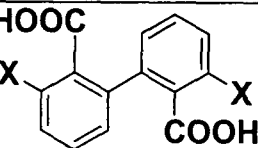
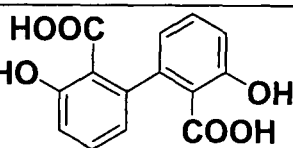
An "m-basic salt", as the term is used herein, is the salt formed from an acid that contains in each molecule m acid groups having a replaceable hydrogen atom.

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Various halogenated aromatic acids, to be used as a starting material in the process of this invention, are commercially available. For example, 2-bromobenzoic acid is available from Aldrich Chemical Company (Milwaukee, Wisconsin). It can be synthesized, however, by oxidation of bromomethylbenzene as described in Sasson et al, *Journal of Organic Chemistry* (1986), 51(15), 2880-2883. Other halogenated aromatic acids that can be used include without limitation 2,5-dibromobenzoic acid, 2-bromo-5-nitrobenzoic acid, 2-bromo-5-methylbenzoic acid, 2-chlorobenzoic acid, 2,5-dichlorobenzoic acid, 2-chloro-3,5-dinitrobenzoic acid, 2-chloro-5-methylbenzoic acid, 2-bromo-5-methoxybenzoic acid, 5-bromo-2-chlorobenzoic acid, 2,3-dichlorobenzoic acid, 2-chloro-4-nitrobenzoic acid, 2,5-dichloroterephthalic acid, and 2-chloro-5-nitrobenzoic acid, all of which are commercially available.

Other halogenated aromatic acids useful as a starting material in the process of this invention include those shown in the left column of the table below, wherein X = Cl, Br or I, and wherein the corresponding hydroxy aromatic acid produced therefrom by the process of this invention is shown in the right column:

$(\text{COOH})_m\text{-Ar-(X)}_n$	I	$(\text{COOH})_m\text{-Ar-(OH)}_n$	II
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In step (a), a halogenated aromatic acid is contacted with base in water to form therefrom the corresponding m-basic salt of the halogenated aromatic acid. In step (b), the m-basic salt of the halogenated aromatic acid is contacted with base in water, and with a copper source in the presence of a ligand that coordinates to copper, to form the m-basic salt of a hydroxy aromatic acid from the m-basic salt of the halogenated aromatic acid.

The base used in step (a) and/or step (b) may be an ionic base, and may in particular be one or more of a hydroxide, carbonate, bicarbonate, phosphate or hydrogen phosphate of one or more of Li, Na, K, Mg or Ca. The base used may be water-soluble, partially water-soluble, or the solubility of the base may increase as the reaction progresses and/or as the base is consumed. NaOH and Na_2CO_3 are preferred, but other suitable organic bases may be selected, for example, from the group consisting of trialkylamines (such as tributylamine); N,N,N',N'-tetramethylethylenediamine; and N-alkyl imidazoles (for example, N-methylimidazole). In principle any base capable of maintaining a pH above 8 and/or binding the acid produced during the reaction of the halogenated aromatic acid is suitable.

The specific amounts of base to be used in steps (a) and/or (b) depend on the strength of the base. In step (a), a halogenated aromatic acid is preferably contacted with at least about m equivalents of water-soluble base per equivalent of halogenated aromatic acid. One "equivalent" as used for a base in this

context is the number of moles of base that will react with one mole of hydrogen ions; for an acid, one equivalent is the number of moles of acid that will supply one mole of hydrogen ions.

5

In step (b), enough base should be used to maintain a solution pH of at least about 8, or at least about 9, or at least about 10, and preferably between about 9 and about 11. Thus, typically in step (b), the
10 dibasic salt of the halogenated aromatic acid is contacted with at least about n equivalents of base, such as a water-soluble base, per equivalent of the m -basic salt of the halogenated aromatic acid.

15 In alternative embodiments, however, it may be desirable in steps (a) and (b) to use a total of at least about $n+m+1$ equivalents of base, such as a water-soluble base, in the reaction mixture per equivalent of the halogenated aromatic acid originally used at the
20 start of the reaction. A base used in an amount as described above is typically a strong base, and is typically added at ambient temperature. The base used in step (b) may be the same as, or different than, the base used in step (a).

As mentioned above, in step (b), the m-basic salt of the halogenated aromatic acid is also contacted with a copper source in the presence of a ligand that
5 coordinates to copper. The copper source and the ligand may be added sequentially to the reaction mixture, or may be combined separately (for example, in a solution of water or acetonitrile) and added together. The copper source may be combined with the
10 ligand in the presence of oxygen in water, or be combined with a solvent mixture containing water.

From the presence together in the reaction mixture of the copper source and the ligand, in a basic
15 solution of the m-basic salt of the halogenated aromatic acid, there is obtained an aqueous mixture containing the m-basic salt of a hydroxy aromatic acid, copper specie(s), the ligand, and a halide salt. If desired, the m-basic salt of the hydroxy aromatic acid
20 may, at this stage and before the acidification in step (d), be separated from the mixture [as optional step (c)], and may be used as an m-basic salt in another reaction or for other purposes.

25 The m-basic salt of the hydroxy aromatic acid is then contacted in step (d) with acid to convert it to the hydroxy aromatic acid product. Any acid of sufficient strength to protonate the m-basic salt is suitable. Examples include without limitation
30 hydrochloric acid, sulfuric acid and phosphoric acid.

The reaction temperature for steps (a) and (b) is preferably between about 60 and about 120°C, more preferably between about 75 and about 95°C; and the
35 process thus in various embodiments involves a step of

heating the reaction mixture. The solution is typically allowed to cool before the acidification in step (d) is carried out. In various embodiments, oxygen may be excluded during the reaction.

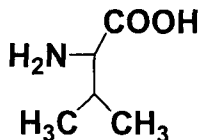
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The copper source is copper metal ["Cu(0)"], one or more copper compounds, or a mixture of copper metal and one or more copper compounds. The copper compound may be a Cu(I) salt, a Cu(II) salt, or mixtures thereof. Examples include without limitation CuCl, CuBr, CuI, Cu₂SO₄, CuNO₃, CuCl₂, CuBr₂, CuI₂, CuSO₄, and Cu(NO₃)₂. The selection of the copper source may be made in relation to the identity of the halogenated aromatic acid used. For example, if the starting halogenated aromatic acid is a bromobenzoic acid, CuCl, CuBr, CuI, Cu₂SO₄, CuNO₃, CuCl₂, CuBr₂, CuI₂, CuSO₄, and Cu(NO₃)₂ will be included among the useful choices. If the starting halogenated aromatic acid is a chlorobenzoic acid, CuBr, CuI, CuBr₂ and CuI₂ will be included among the useful choices. CuBr and CuBr₂ are in general preferred choices for most systems. The amount of copper used is typically about 0.1 to about 5 mol% based on moles of halogenated aromatic acid.

When the copper source is Cu(0), Cu(0), copper bromide and a ligand may be combined in the presence of air. In the case of Cu(0) or Cu(I), a predetermined amount of metal and ligand may be combined in water, and the resulting mixture may be reacted with air or dilute oxygen until a colored solution is formed. The resulting metal/ligand solution is added to the reaction mixture containing the m-basic salt of the halogenated aromatic acid and base in water.

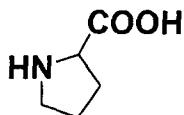
The ligand may be an amino acid in which the amine nitrogen and the carboxyl carbon are separated by no more than two carbon atoms, for example, α -amino acids, in which the amine N is attached to a carbon atom that
5 is next to the carboxyl group. Examples of suitable amino acid ligands include without limitation:

Valine



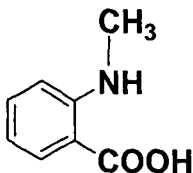
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Proline



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N-methylantranilic acid



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25 A ligand suitable for use herein may be selected as any one or more or all of the members of the whole population of ligands described by name or structure above. A suitable ligand may, however, also be selected as any one or more or all of the members of a

subgroup of the whole population, where the subgroup may be any size, and where the subgroup is formed by omitting any one or more of the members of the whole population as described above. As a result, the ligand
5 may in such instance not only be selected as one or more or all of the members of any subgroup of any size that may be formed from the whole population of ligands as described above, but the ligand may also be selected in the absence of the members that have been omitted
10 from the whole population to form the subgroup.

In various embodiments, the ligand may be provided in an amount of about 1 to about 10, preferably about 1 to about 2, molar equivalents of ligand per mole of
15 copper. As used herein, the term "molar equivalent" indicates the number of moles of ligand that will interact with one mole of copper.

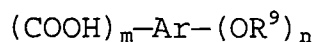
When the halogenated aromatic acid is a
20 brominated aromatic acid, the copper source may be Cu(0) and/or a Cu(I) salt, and it may be combined with the ligand in the presence of oxygen in water, or a solvent mixture containing water. Alternatively, when the Cu(I) salt is CuBr, and the ligand is valine,
25 proline, or anthranilic acid, the ligand may be provided in an amount of two molar equivalents per mole of copper, and the CuBr may be combined with the ligand in the presence of water and air.

30 The ligand is believed to facilitate the action of the copper source as a catalyst, and/or the copper source and the ligand are believed to function together to act as a catalyst, to improve one or more attributes of the reaction.

35

The process described above also allows for effective and efficient synthesis of related compounds, such as n-alkoxy aromatic acids, which may be described generally by the structure of Formula VI:

5



VI

wherein Ar, m and n are described as set forth above, and each R^9 is independently a substituted or unsubstituted C_{1-10} alkyl group. An R^9 is, when unsubstituted, a univalent group containing only carbon and hydrogen. In any such alkyl group, however, one or more O or S atoms may optionally be substituted for any one or more of the in-chain carbon atoms, provided that the resulting structure contains no -O-O- or -S-S- moieties, and provided that no carbon atom is bonded to more than one heteroatom.

20 An n-hydroxy aromatic acid, as prepared by the process of this invention, may be converted to an n-alkoxy aromatic acid, and such conversion may be accomplished, for example, by contacting the hydroxy aromatic acid under basic conditions with an n-alkyl sulfate of the formula $(\text{R}^9)_n\text{SO}_4$. One suitable method of running such a conversion reaction is as described in Austrian Patent No. 265,244. Suitable basic conditions for such conversion are a solution pH of at least about 8, or at least about 9, or at least about 10, and preferably about 9 to about 11, using one or more bases such as described above.

In certain embodiments, it may be desired to separate the n-hydroxy aromatic acid from the reaction

mixture in which it was formed before converting it to an n-alkoxy aromatic acid.

The process described above also allows for
5 effective and efficient synthesis of products made from
the resulting 2,5-dihydroxyterephthalic acid or 2,5-
dialkoxyterephthalic acid such as a compound, a
monomer, or an oligomer or polymer thereof. These
produced materials may have one or more of ester
10 functionality, ether functionality, amide
functionality, imide functionality, imidazole
functionality, carbonate functionality, acrylate
functionality, epoxide functionality, urethane
functionality, acetal functionality, and anhydride
15 functionality.

Representative reactions involving a material made
by the process of this invention, or a derivative of
such material, include, for example, making a polyester
20 from a 2,5-dihydroxyterephthalic acid and either
diethylene glycol or triethylene glycol in the presence
of 0.1% of $\text{ZN}_3(\text{BO}_3)_2$ in 1-methylnaphthalene under
nitrogen, as disclosed in US 3,047,536 (which is
incorporated in its entirety as a part hereof for all
25 purposes). Similarly, a 2,5-dihydroxyterephthalic acid
is disclosed as suitable for copolymerization with a
dibasic acid and a glycol to prepare a heat-stabilized
polyester in US 3,227,680 (which is incorporated in its
entirety as a part hereof for all purposes), wherein
30 representative conditions involve forming a prepolymer
in the presence of titanium tetraisopropoxide in
butanol at 200~250°C, followed by solid-phase
polymerization at 280°C at a pressure of 0.08 mm Hg.

A 2,5-dihydroxyterephthalic acid has also been polymerized with the trihydrochloride-monohydrate of tetraaminopyridine in strong polyphosphoric acid under slow heating above 100°C up to about 180°C under reduced pressure, followed by precipitation in water, as disclosed in US 5,674,969 (which is incorporated in its entirety as a part hereof for all purposes); or by mixing the monomers at a temperature from about 50°C to about 110°C, and then 145°C to form an oligomer, and then reacting the oligomer at a temperature of about 160°C to about 250°C as disclosed in U.S. Provisional Application No. 60/665,737, filed March 28, 2005 (which is incorporated in its entirety as a part hereof for all purposes), published as WO 2006/104974. The polymer that may be so produced may be a pyridobisimidazole-2,6-diyl(2,5-dihydroxy-p-phenylene) polymer such as a poly(1,4-(2,5-dihydroxy) phenylene-2,6-pyrido[2, 3-d: 5,6-d']bisimidazole) polymer, or a poly[(1,4-dihydrodiimidazo[4,5-b:4',5'-e]pyridine-2,6-diyl) (2,5-dihydroxy-1,4-phenylene)] polymer. The pyridobisimidazole portion thereof may, however, be replaced by any or more of a benzobisimidazole, benzobisthiazole, benzobisoxazole, pyridobisthiazole and a pyridobisoxazole; and the 2,5-dihydroxy-p-phenylene portion thereof may be replaced by the derivative of one or more of isophthalic acid, terephthalic acid, 2,5-pyridine dicarboxylic acid, 2,6-naphthalene dicarboxylic acid, 4,4'-diphenyl dicarboxylic acid, 2,6-quinoline dicarboxylic acid, and 2,6-bis(4-carboxyphenyl)pyridobisimidazole.

EXAMPLES

The present invention is further defined in the following examples. It should be understood that these

examples, while indicating preferred embodiments of the invention, are given by way of illustration only. From the above discussion and these examples, one skilled in the art can ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various uses and conditions.

10 Materials: The following materials were used in the examples. All reagents were used as received. Product purity was determined by ^1H NMR.

15 The 2-bromobenzoic acid (97% purity), proline (99% purity) and N-methylantranilic acid (95% purity) were obtained from Aldrich Chemical Company (Milwaukee, Wisconsin, USA). Valine (98+% purity) was obtained from TCI America (Portland, Oregon, USA). Copper(II) sulfate (" CuSO_4 ") (98% purity) was obtained from Strem
20 Chemicals, Inc. (Newburyport, Massachusetts, USA). Na_2CO_3 (99.5%) was obtained from EM Science (Gibbstown, New Jersey).

25 As used herein, the term "conversion" refers to how much reactant was used up as a fraction or percentage of the theoretical amount. The term "selectivity" for a product P refers to the molar fraction or molar percentage of P in the final product mix. The conversion multiplied by the selectivity thus
30 equals the maximum "yield" of P; the actual or "net" yield will normally be somewhat less than this because of sample losses incurred in the course of activities such as isolating, handling, drying, and the like. The term "purity" denotes what percentage of the in-hand,
35 isolated sample is actually the specified substance.

The term "35% HCl" as used in the Examples denotes aqueous hydrochloric acid whose concentration is 35 grams of HCl per 100 mL of solution. The meaning of abbreviations is as follows "h" means hour(s), "mL" means milliliter(s), "mmol" means millimole(s), "NMR" means nuclear magnetic resonance spectroscopy, "CONV" means conversion (percent), "SEL" means selectivity (percent), "T" means temperature, and "t" means time.

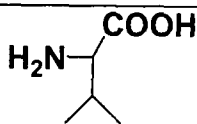
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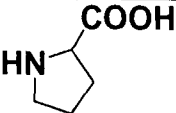
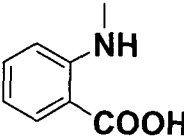
Examples 1-3

Under nitrogen, 10 mmol of 2-bromobenzoic acid was stirred with a solution of 12.5 mmol Na₂CO₃ in 10 mL H₂O at 50-75°C until all of the 2-bromobenzoic acid was dissolved. Subsequently, 0.01 mmol CuSO₄ and 0.04 mmol of ligand (valine, proline or N-methylanthranilic acid as indicated in Table 1), dissolved under stirring with air in 1 mL deionized water, were added; and the reaction mixture was heated at the temperature and for the different times as noted in Table 1. After cooling to ambient temperature, the reaction mixtures were acidified with 35% aqueous HCl. The products were isolated by filtration, washed with water and dried under vacuum. The crude reaction product was analyzed by ¹H NMR (d6-dmsO). The results are summarized in Table 1.

30

Table 1.

Example	Ligand	CONV (%)	SEL (%)	T (°C)	t (h)	Ligand Structure
1	Valine	70	>98	80	3	

1 (a)	same	>99	>98	80	9	
2	Proline	84	>98	80	3	
2 (a)	same	>99	>98	80	9	
3	N-methyl-anthranilic acid	7	>95	80	3	
3 (a)	same	17	>95	80	9	
3 (b)	same	38	>95	80	12	

Where an embodiment of this invention is stated or described as comprising, including, containing, having, being composed of or being constituted by certain features, it is to be understood, unless the statement or description explicitly provides to the contrary, that one or more features in addition to those explicitly stated or described may be present in the embodiment. An alternative embodiment of this invention, however, may be stated or described as consisting essentially of certain features, in which embodiment features that would materially alter the principle of operation or the distinguishing characteristics of the embodiment are not present therein. A further alternative embodiment of this invention may be stated or described as consisting of certain features, in which embodiment, or in insubstantial variations thereof, only the features specifically stated or described are present.

Where the indefinite article "a" or "an" is used with respect to a statement or description of the presence of a step in a process of this invention, it is to be understood, unless the statement or

description explicitly provides to the contrary, that the use of such indefinite article does not limit the presence of the step in the process to one in number.

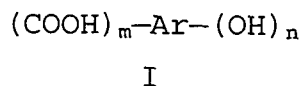
5 Where a range of numerical values is recited herein, unless otherwise stated, the range is intended to include the endpoints thereof, and all integers and fractions within the range. It is not intended that the scope of the invention be limited to the specific
10 values recited when defining a range.

CLAIMS

5 What is claimed is:

1. A process for preparing a hydroxy aromatic acid that is described generally by the structure of Formula I

10

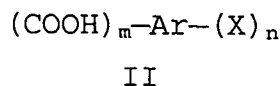


wherein Ar is a C₆-C₂₀ arylene radical, n and m are each independently a nonzero value, and n + m is less than or equal to 8, comprising the steps of

15

(a) contacting a halogenated aromatic acid that is described generally by the structure of Formula II,

20



wherein each X is independently Cl, Br or I, and Ar, n and m are as set forth above, with a base in water to form therefrom the corresponding m-basic salt of the halogenated aromatic acid in water;

25

(b) contacting the m-basic salt of the halogenated aromatic acid with a base in water, and with a copper source in the presence of a ligand that coordinates to copper, to form the m-basic salt of a hydroxy aromatic acid from the m-basic salt of the halogenated aromatic acid at a

30
35

solution pH of at least about 8, wherein the ligand comprises an amino acid in which the amine nitrogen and the carboxyl carbon are separated by no more than two carbon atoms;

5

(c) optionally, separating the m-basic salt of the hydroxy aromatic acid from the reaction mixture in which it is formed; and

10

(d) contacting the m-basic salt of the hydroxy aromatic acid with acid to form therefrom an n-hydroxy aromatic acid.

15

2. A process according to Claim 1 wherein, in step (a), the halogenated aromatic acid is contacted with at least about two normal equivalents of water-soluble base per equivalent of halogenated aromatic acid.

20

3. A process according to Claim 1 wherein, in step (b), the m-basic salt of the halogenated aromatic acid is contacted with at least about two normal equivalents of water-soluble base per equivalent of the m-basic salt of the halogenated aromatic acid.

25

4. A process according to Claim 1 wherein, in steps (a) and (b), a total of about $n+m+1$ normal equivalents of water-soluble base are added to the reaction mixture per equivalent of the halogenated aromatic acid.

30

5. A process according to Claim 1 wherein the copper source comprises Cu(0), a Cu(I) salt, a Cu(II) salt, or a mixture thereof.

35

6. A process according to Claim 1 wherein the copper source is selected from the group consisting of CuCl, CuBr, CuI, Cu₂SO₄, CuNO₃, CuCl₂, CuBr₂, CuI₂,
5 CuSO₄, Cu(NO₃)₂, and mixtures thereof.

7. A process according to Claim 1 wherein the ligand is an α -amino acid.

10 8. A process according to Claim 1 wherein the ligand is valine, proline, or N-methylantranilic acid.

9. A process according to Claim 1 further comprising a step of combining the copper source with
15 the ligand before adding them to the reaction mixture.

10. A process according to Claim 1 wherein the copper source comprises CuBr.

20 11. A process according to Claim 1 wherein the copper source comprises CuBr; the ligand comprises valine, proline, or anthranilic acid; the ligand is provided in an amount of two molar equivalents per mole of copper; and the CuBr is combined with the ligand in
25 the presence of water and air.

12. A process according to Claim 1 wherein a base comprises one or more of a water-soluble hydroxide, phosphate, carbonate, or bicarbonate of one or more of
30 Li, Na, K, Mg, or Ca.

13. A process according to Claim 1 wherein a base comprises NaOH or Na₂CO₃.

14. A process according to Claim 1 wherein copper is provided in an amount of between about 0.1 and about 5 mol% based on moles of halogenated aromatic acid.

5 15. A process according to Claim 1 wherein the ligand is provided in an amount of between about one and about two molar equivalents per mole of copper.

16. A process according to Claim 1 further
10 comprising a step of converting the n-hydroxy aromatic acid to an n-alkoxy aromatic acid.

17. A process according to Claim 16 wherein the n-hydroxy aromatic acid is contacted under basic
15 conditions with a dialkyl sulfate of the formula $R^9 R^{10} SO_4$ wherein R^9 and R^{10} are each independently a substituted or unsubstituted C_{1-10} alkyl group.

18. A process according to Claim 1 further
20 comprising a step of subjecting the n-hydroxy aromatic acid to a reaction to prepare therefrom a compound, monomer, oligomer or polymer.

19. A process according to Claim 18 wherein a
25 polymer prepared comprises a pyridobisimidazole-2,6-diyl(2,5-dihydroxy-p-phenylene) polymer.

20. A process according to Claim 16 further
comprising a step of subjecting the n-alkoxy aromatic
30 acid to a reaction to prepare therefrom a compound, monomer, oligomer or polymer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/024470

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C51/02 C07C51/367 C07C51/41 C07C65/03 C07C65/05
C07C65/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	RUSONIK, IRENA ET AL: "Cu(I)(2,5,8,11-tetramethyl-2,5,8,11-tetra azadodecane)+ as a catalyst for Ullmann's reaction" DALTON TRANSACTIONS , (10), 2024-2028 CODEN: DTARAF; ISSN: 1477-9226, 2003, XP002472757 cited in the application the whole document ----- -/--	1

☒ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
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Date of the actual completion of the international search

2 April 2008

Date of mailing of the international search report

08/04/2008

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Delanghe, Patrick

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/024470

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	COMDOM, ROLANDO F. PELLON ET AL: "Synthesis of salicylic acid derivatives from the corresponding 2- chlorobenzoic acid using water as solvent" SYNTHETIC COMMUNICATIONS , 32(13), 2055-2059 CODEN: SYNCAV; ISSN: 0039-7911, 2002, XP002472756 cited in the application page 2056 - page 2057 -----	1
A	ZHANG, HUI ET AL: "Amino Acid Promoted CuI-Catalyzed C-N Bond Formation between Aryl Halides and Amines or N-Containing Heterocycles" JOURNAL OF ORGANIC CHEMISTRY , 70(13), 5164-5173 CODEN: JOCEAH; ISSN: 0022-3263, 2005, XP002472753 page 5164, column 2, paragraph 2 - page 5165, column 1, paragraph 1 table 1, entry 1 -----	1
A	MA, DAWEI ET AL: "Mild Method for Ullmann Coupling Reaction of Amines and Aryl Halides" ORGANIC LETTERS , 5(14), 2453-2455 CODEN: ORLEF7; ISSN: 1523-7060, 2003, XP002472755 abstract table 2 -----	1