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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



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,



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,



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
10 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-
15 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
20 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,



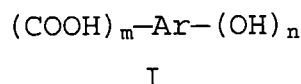
wherein Ar, n and m are as set forth above; and (e) converting the n-hydroxy aromatic acid to an n-alkoxy aromatic acid that is described generally by the structure of Formula VI, wherein Ar, R^9 , n and m are as
30 set forth above.

Yet another embodiment of this invention provides a process for preparing a 2,5-dihydroxyterephthalic acid or a 2,5-dialkoxyterephthalic acid as described
35 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.

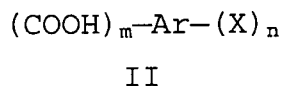
5 Yet another embodiment of this invention consequently provides a process for preparing a compound, monomer, oligomer or polymer by preparing a hydroxy aromatic acid that is described generally by the structure of Formula I

10



wherein Ar is a C₆-C₂₀ arylene radical, n and m are each
15 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



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
25 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-
30 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
35 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-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 more of the processes described herein may be a diketone.

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



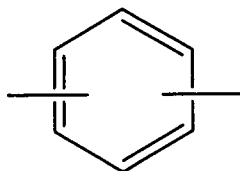
by contacting a halogenated aromatic acid as described generally by the structure of Formula II



with base to form the m-basic salt of the halogenated aromatic acid; contacting the m-basic salt of the 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-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.

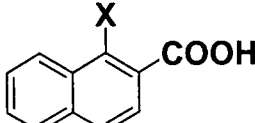
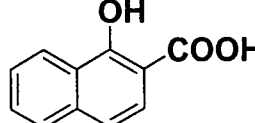


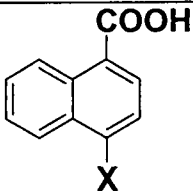
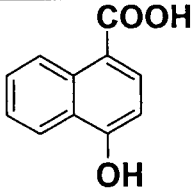
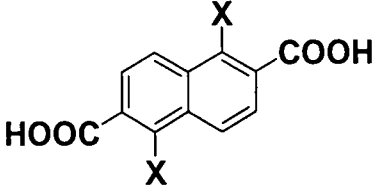
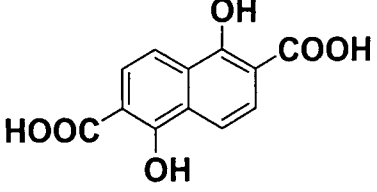
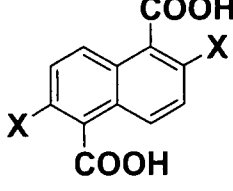
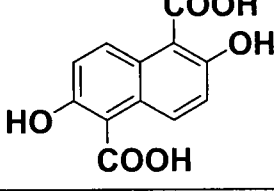
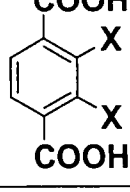
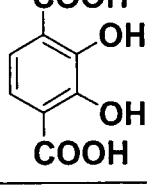
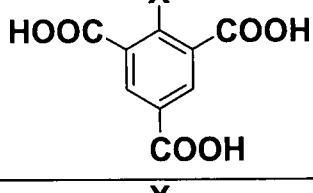
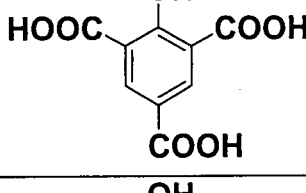
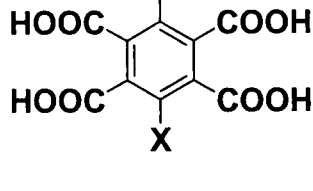
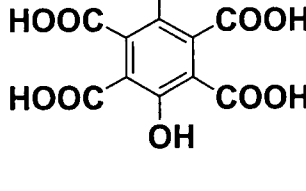
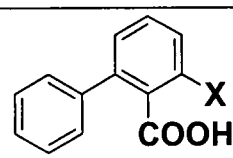
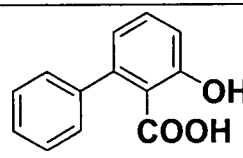
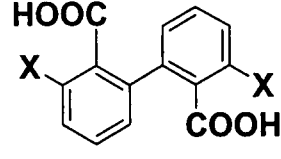
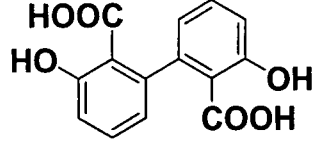
An "m-basic salt", as the term is used herein, is the salt formed from an acid that contains in each molecule m acid groups having a replaceable hydrogen atom.

5

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
	

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 Na₂CO₃ 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.

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
5 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.

10 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
15 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).

20 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 coordinates to copper. The copper source and the
25 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 ligand in the presence of oxygen in water, or be
30 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 solution of the m -basic salt of the halogenated
35 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 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.

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 hydrochloric acid, sulfuric acid and phosphoric acid.

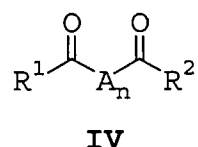
The reaction temperature for steps (a) and (b) is preferably between about 60 and about 120°C, more preferably between about 75 and about 95°C; and the process thus in various embodiments involves a step of heating the reaction mixture. The solution is typically allowed to cool before the acidification in step (d) is carried out. In various embodiments, oxygen may be excluded during the reaction.

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

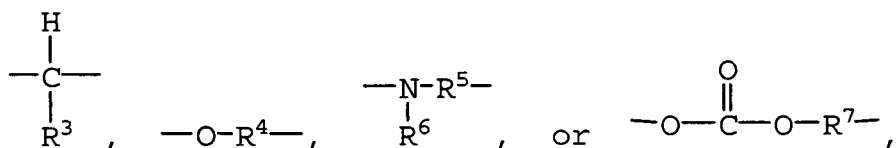
Cu(NO₃)₂ will be included among the useful choices. If the starting halogenated aromatic acid is a chlorobenzoic acid, CuBr, CuI, CuBr₂ and CuI₂ will be included among the useful choices. CuBr and CuBr₂ are in general preferred choices for most systems. The amount of copper used is typically about 0.1 to about 5 mol% based on moles of halogenated aromatic acid.

When the copper source is Cu(0), Cu(I), 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 a diketone described generally by Formula IV



wherein A is



R¹ and R² are each independently selected from substituted and unsubstituted C₁-C₁₆ n-alkyl, iso-alkyl

and tertiary alkyl groups; and substituted and unsubstituted C₆ - C₃₀ aryl and heteroaryl groups;

R³ is selected from H; substituted and
 5 unsubstituted C₁-C₁₆ n-alkyl, iso-alkyl and tertiary alkyl groups; substituted and unsubstituted C₆ - C₃₀ aryl and heteroaryl groups; and a halogen;

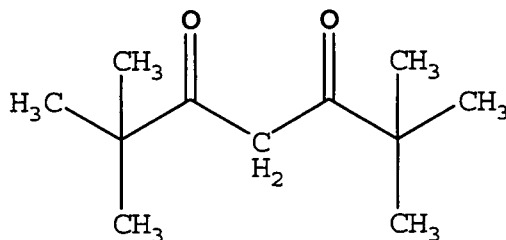
R⁴, R⁵, R⁶ and R⁷ are each independently H or a
 10 substituted or unsubstituted C₁-C₁₆ n-alkyl, iso-alkyl or tertiary alkyl group; and

n = 0 or 1.

15 The term "unsubstituted", as used with reference to an alkyl or aryl group in a diketone as described above, means that the alkyl or aryl group contains no atoms other than carbon and hydrogen. In a substituted alkyl or aryl group, however, one or more O or S atoms
 20 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 atom is bonded to more than one heteroatom. In a preferred embodiment, R³
 25 is H.

In one embodiment, a diketone suitable for use herein as the ligand is 2,2',6,6'-
 tetramethylheptanedione-3,5 (Formula V):

30



V

Other diketones suitable for use herein as the ligand
5 include, without limitation, 2,4-pentanedione and 2,3-pentanedione.

A ligand suitable for use herein may be selected
as any one or more or all of the members of the whole
10 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 (1, 2, 6, 10 or 20, for example), and
15 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 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
20 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 from
the whole population to form the subgroup.

25 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
copper. As used herein, the term "molar equivalent"
indicates the number of moles of ligand that will
30 interact with one mole of copper.

When the halogenated aromatic acid is a 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
35 the presence of oxygen in water, or a

solvent mixture containing water. Alternatively, when the Cu(I) salt is CuBr, and the ligand is one of the diketones named specifically above (such as 2,2',6,6'-tetramethylheptanedione-3,5), the ligand may be
5 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.

The ligand is believed to facilitate the action of
10 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.

15 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:



wherein Ar, m and n are described as set forth above, and each R⁹ is independently a substituted or
25 unsubstituted C₁₋₁₀ alkyl group. An R⁹ 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
30 the resulting structure contains no -O-O- or -S-S- moieties, and provided that no carbon atom is bonded to more than one heteroatom.

An n-hydroxy aromatic acid, as prepared by the
35 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 $(R^9)_nSO_4$. 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 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 functionality, ether functionality, amide functionality, imide functionality, imidazole functionality, carbonate functionality, acrylate functionality, epoxide functionality, urethane functionality, acetal functionality, and anhydride 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 from a 2,5-dihydroxyterephthalic acid and either diethylene glycol or triethylene glycol in the presence of 0.1% of $Zn_3(BO_3)_2$ in 1-methylnaphthalene under

nitrogen, as disclosed in US 3,047,536 (which is incorporated in its entirety as a part hereof for all purposes). Similarly, a 2,5-dihydroxyterephthalic acid is disclosed as suitable for copolymerization with a
5 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 representative conditions involve forming a prepolymer in the presence of titanium tetraisopropoxide in
10 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
15 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
20 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
25 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-
30 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,
35 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.

10

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.

20

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

25

The 2-bromobenzoic acid (97% purity), 2,2',6,6'-tetramethylheptanedione-3,5 (>98% purity), 2,4-pentanedione (99+% purity) and 2,3-pentanedione (97% purity) were obtained from Aldrich Chemical Company (Milwaukee, Wisconsin, USA).

30

Copper(II) sulfate ("CuSO₄") (98% purity) was obtained from Strem Chemicals, Inc. (Newburyport, Massachusetts, USA). Copper(I) bromide ("CuBr") (98%) and copper (II) bromide ("CuBr₂") were obtained from

35

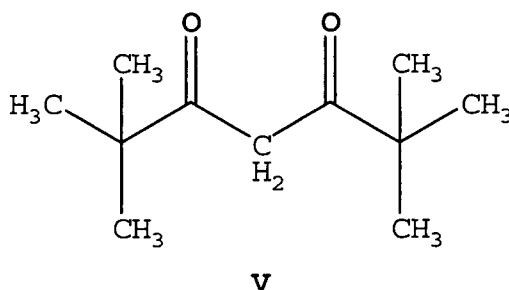
Acros Organics (Geel, Belgium). Na_2CO_3 (99.5%) was obtained from EM Science (Gibbstown, New Jersey).

As used herein, the term "conversion" refers to
5 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
10 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,
15 isolated sample is actually the specified substance.

The term "35% HCl" as used in the Examples denotes
aqueous hydrochloric acid whose concentration is 35
20 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
25 (percent), "T" means temperature, and "t" means time.

Example 1

This example demonstrates the formation of 2,5-
30 dihydroxyterephthalic acid from 2,5-dibromoterephthalic
acid using CuBr and the diketone ligand 2,2',6,6'-
tetramethylheptanedione-3,5 (as shown in Formula V):



Under nitrogen, 2.00 g (6.2 mmol) of 2,5-
 5 dibromoterephthalic acid was combined with 15 g of H₂O;
 0.679 g (6.4 mmol) of Na₂CO₃ was then added. The
 mixture was heated to reflux with stirring for 30 min,
 remaining under a nitrogen atmosphere. Another 0.940 g
 (9.0 mmol) of Na₂CO₃ was added to the reaction mixture
 10 and reflux was continued for 30 min. Separately, 9 mg
 (0.06 mmol) (0.01 mol equiv) of CuBr and 25 mg (0.14
 mmol) (0.02 mol equiv) of 2,2',6,6'-
 tetramethylheptanedione-3,5 were combined with 2 mL H₂O
 under nitrogen. The resulting mixture was stirred
 15 under an air atmosphere until the CuBr was dissolved.
 This solution was added to the stirred reaction mixture
 via syringe at 80°C under nitrogen and stirred for 30 h
 at 80°C. After cooling to 25°C, the reaction mixture
 was acidified with HCl (conc.), producing a dark yellow
 20 precipitate. The yellow precipitate was filtered and
 washed with water. After drying, a total of 1.26 g of
 crude 2,5-dihydroxyterephthalic acid and 2-
 hydroxyterephthalic acid was collected. The purity of
 2,5-dihydroxyterephthalic acid was determined by ¹H NMR
 25 to be about 89%. The net yield of 2,5-
 dihydroxyterephthalic acid was determined to be 92%.

Example 2

Under nitrogen, 2.01 g (10 mmol) of 2-bromobenzoic
 30 acid was combined with 10 g of H₂O; 1.32 g (12.5 mmol)
 of Na₂CO₃ was then added. The mixture was heated to

reflux with stirring for 60 min, remaining under a nitrogen atmosphere. Separately, 67 mg (0.3 mmol) (0.03 mol equiv) of CuBr₂ and 63 mg (0.0.6 mmol) (0.6 mol equiv) of 2,4-pentanedione were combined with 2 mL H₂O under nitrogen. This solution was added to the stirred reaction mixture via syringe at 80°C under nitrogen and stirred for 27 h at 80°C. After cooling to 25°C, the reaction mixture was acidified with HCl (conc.), producing an off-white precipitate. The precipitate was filtered, washed with water and dried. Both the conversion and selectivity of salicylic acid were determined to be 98% by ¹H NMR. The net yield was determined to be 96%.

15 Example 3

Under nitrogen, 2.01 g (10 mmol) of 2-bromobenzoic acid was combined with 10 g of H₂O; 1.32 g (12.5 mmol) of Na₂CO₃ was then added. The mixture was heated to reflux with stirring for 60 min, remaining under a nitrogen atmosphere. Separately, 67 mg (0.3 mmol) (0.03 mol equiv) of CuBr₂ and 66 mg (0.0.6 mmol) (0.6 mol equiv) of 2,3-pentanedione were combined with 2 mL H₂O under nitrogen. This solution was added to the stirred reaction mixture via syringe at 80°C under nitrogen and stirred for 16 h at 80°C. After cooling to 25°C, the reaction mixture was acidified with HCl (conc.), producing an off-white precipitate. The precipitate was filtered, washed with water and dried. The conversion and selectivity of salicylic acid were determined to be 100% and 94%, respectively, by ¹H NMR. The net yield was determined to be 94%.

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
5 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
10 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
15 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
20 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.

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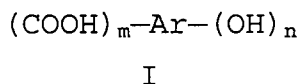
Where a range of numerical values is recited herein, unless otherwise stated, the range is intended to include the endpoints thereof, and all integers and fractions within the range. It is not intended that
30 the scope of the invention be limited to the specific values recited when defining a range.

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

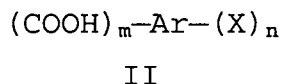


wherein Ar is a C₆-C₂₀ arylene radical, n and m are each independently a nonzero value, and n + m is less than or equal to 8, comprising the steps of

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

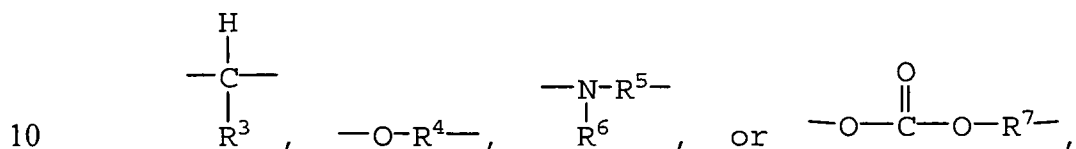
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solution pH of at least about 8, wherein the ligand comprises a diketone described generally by Formula IV



wherein A is



15 R^1 and R^2 are each independently selected from substituted and unsubstituted C_1 - C_{16} n-alkyl, iso-alkyl and tertiary alkyl groups; and substituted and unsubstituted C_6 - C_{30} aryl and heteroaryl groups;

20 R^3 is selected from H; substituted and unsubstituted C_1 - C_{16} n-alkyl, iso-alkyl and tertiary alkyl groups; substituted and unsubstituted C_6 - C_{30} aryl and heteroaryl groups; and a halogen;

25 R^4 , R^5 , R^6 and R^7 are each independently H or a substituted or unsubstituted C_1 - C_{16} n-alkyl, iso-alkyl or tertiary alkyl group; and

$n = 0$ or 1 ;

30

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

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

2. A process according to Claim 1 wherein, in
10 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.

15 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.

20

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
25 aromatic acid.

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.

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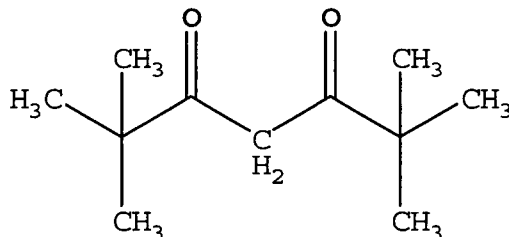
6. A process according to Claim 1 wherein the copper source is selected from the group consisting of CuCl, CuBr, CuI, Cu₂SO₄, CuNO₃, CuCl₂, CuBr₂, CuI₂, CuSO₄, Cu(NO₃)₂, and mixtures thereof.

35

7. A process according to Claim 1 wherein R³ is H.

8. A process according to Claim 1 wherein the ligand is 2,4-pentanedione, 2,3-pentanedione or

5 2,2',6,6'-tetramethylheptanedione-3,5 (as shown below):



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

10. A process according to Claim 8 wherein the copper source comprises CuBr.

15

11. A process according to Claim 1 wherein the copper source comprises CuBr; the ligand is 2,2',6,6'-tetramethylheptanedione-3,5; the ligand is provided in an amount of two molar equivalents per mole of copper;
20 and the CuBr is combined with the ligand in 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,
25 phosphate, carbonate, or bicarbonate of one or more of Li, Na, K, Mg, or Ca.

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

30

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/US2007/024469

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C51/02 C07C51/41 C07C51/367 C07C65/03 C07C65/05
C07C65/11 C07C65/105

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	<p>RUSONIK IRENA ET AL: "Cu(I)(2,5,8,11-tetramethyl-2,5,8,11-tetra- azadodecane)+ as a catalyst for Ullmann's reaction" JOURNAL OF THE CHEMICAL SOCIETY, DALTON TRANSACTIONS, CHEMICAL SOCIETY. LETCWORTH, GB, 2003, pages 2024-2028, XP002472757 ISSN: 1472-7773 the whole document</p> <p style="text-align: center;">----- -/--</p>	1

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

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- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
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- *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
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- * & * document member of the same patent family

Date of the actual completion of the international search

17 April 2008

Date of mailing of the international search report

25/04/2008

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Delanghe, Patrick

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/024469

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>COMDOM ROLANDO F PELLON ET AL: "Synthesis of salicylic acid derivatives from the corresponding 2- chlorobenzoic acid using water as solvent"</p> <p>SYNTHETIC COMMUNICATIONS, TAYLOR & FRANCIS, PHILADELPHIA, PA, US, vol. 32, no. 13, 2002, pages 2055-2059, XP002472756</p> <p>ISSN: 0039-7911</p> <p>page 2056 - page 2057</p> <p>-----</p>	1