



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C07C 231/06, 209/62, 233/66, 233/80,  211/51, 211/52</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 95/04029</b>  <b>(43) International Publication Date:</b> 9 February 1995 (09.02.95)
<b>(21) International Application Number:</b> PCT/US94/07614  <b>(22) International Filing Date:</b> 12 July 1994 (12.07.94)  <b>(30) Priority Data:</b> 099,973                      30 July 1993 (30.07.93)              US  <b>(71) Applicant:</b> MONSANTO COMPANY [US/US]; 800 North Lindbergh Boulevard, St. Louis, MO 63167 (US).  <b>(72) Inventors:</b> STERN, Michael, Keith; 1075 Wilson Avenue, St. Louis, MO 63130 (US). CHENG, Brian, Kai-Ming; 212 Brayhill Court, Chesterfield, MO 63017 (US).  <b>(74) Agent:</b> BOLDING, James, Clifton; Monsanto Company, 800 North Lindbergh Boulevard, St. Louis, MO 63167 (US).	<b>(81) Designated States:</b> AM, AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KG, KR, KZ, LK, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD).  <b>Published</b> <i>With international search report.</i>	
<b>(54) Title:</b> PROCESS FOR PREPARING P-NITROAROMATIC AMIDES AND PRODUCTS THEREOF		
<b>(57) Abstract</b>  A process for preparing p-nitroaromatic amides is provided which comprises contacting a nitrile, nitrobenzene, a suitable base and water in the presence of a suitable solvent system to form a mixture, and reacting the mixture at a suitable temperature in a confined reaction zone in the presence of a controlled amount of protic material. The p-nitroaromatic amides of the invention can be reduced to p-aminoaromatic amides. In one embodiment, the p-aminoaromatic amide is further reacted with ammonia under conditions which produce the corresponding p-aminoaromatic amine and the amide corresponding to the nitrile starting material or with water in the presence of a suitable basic or acidic catalyst under conditions which produce the corresponding p-aminoaromatic amine and the acid or salt thereof corresponding to the nitrile starting material. In another embodiment, the p-aminoaromatic amine is reductively alkylated to produce alkylated p-aminoaromatic amine. The p-nitroaromatic amide can be reacted with ammonia under conditions which produce the corresponding p-nitroaromatic amine and the amide corresponding to the nitrile starting material or with water in the presence of a suitable basic or acidic catalyst under conditions which produce the corresponding p-nitroaromatic amine and the acid or salt thereof corresponding to the nitrile starting material. In one embodiment, the p-nitroaromatic amine is reduced to produce p-aminoaromatic amine. In another embodiment, the p-aminoaromatic amine is reductively alkylated to produce alkylated p-aminoaromatic amine. In another embodiment, the p-nitroaromatic amine is reductively alkylated to produce p-aminoaromatic amine.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

-1-

PROCESS FOR PREPARING P-NITROAROMATIC AMIDES  
AND PRODUCTS THEREOF

BACKGROUND OF THE INVENTION

This invention relates to the production of  
5 p-nitroaromatic amides. In one aspect, this invention  
relates to the production of p-aminoaromatic amides. In  
another aspect, this invention relates to the production  
of p-nitroaromatic amines. In a further aspect, this  
invention relates to the production of p-aminoaromatic  
10 amines. In a still further aspect, this invention  
relates to the production of alkylated p-aminoaromatic  
amines.

Aromatic amide bonds are currently formed by  
the reaction of an amine with an acid chloride.  
15 Specifically, it is known to prepare p-nitroaromatic  
amides by the reaction of a nitroaromatic amine with an  
acid chloride. This process is disadvantageous in that  
the halide that is displaced is corrosive to the  
reactors and appears in the waste stream and must  
20 therefore be disposed of at considerable expense.  
Furthermore, the nitroaromatic amine is prepared by the  
reaction of halonitroaromatic, e.g., chloronitrobenzene,  
and ammonia and results in the same displacement of  
halide causing additional corrosion and waste disposal  
25 problems. Therefore, a nonhalide route to substituted  
aromatic amides and specifically nitroaromatic amides  
and products thereof would provide significant  
advantages over current technology and result in a more  
efficient and economic commercial process.

30 The process of the invention is such a non-  
halide route to nitroaromatic amides and products  
thereof and therefore eliminates the expensive halide  
removal from the waste stream as well as corrosion  
problems caused by the halide.

-2-

SUMMARY OF THE INVENTION

It is an object of the invention to provide a process for producing p-nitroaromatic amides for use in the preparation of p-nitroaromatic amines,  
5 p-aminoaromatic amines, p-aminoaromatic amides and alkylated p-aminoaromatic amines. It is a further object of the invention to provide an efficient and economic process to produce p-nitroaromatic amides and products thereof that is commercially viable. It is a  
10 further object of the invention to provide a process for producing p-aminoaromatic amines for use as monomers in the production of polyamides or other polymer applications. It is a still further object of the invention to provide a process for producing alkylated  
15 p-aminoaromatic amines for use as antioxidants or antiozonants. It is a still further object of the invention to provide a process for producing p-nitroaromatic amines for use as intermediates to anti-oxidants.

20 According to the invention, a process for preparing p-nitroaromatic amides is provided which comprises contacting a nitrile, nitrobenzene, a suitable base and water in the presence of a suitable solvent system to form a mixture, and reacting the mixture at a  
25 suitable temperature in a confined reaction zone in the presence of a controlled amount of protic material.

Further, according to the invention, a process for preparing p-aminoaromatic amides is provided which comprises reducing the p-nitroaromatic amides prepared  
30 according to the invention. In one embodiment, the p-aminoaromatic amide is further reacted with ammonia under conditions which produce the corresponding p-aminoaromatic amine and the amide corresponding to the nitrile starting material. In another embodiment, the  
35 p-aminoaromatic amide is further reacted with water in the presence of a suitable basic or acidic catalyst

-3-

under conditions which produce the corresponding p-aminoaromatic amine and the acid or salt thereof corresponding to the nitrile starting material. In a further embodiment, the p-aminoaromatic amine is  
5 reductively alkylated to produce alkylated p-aminoaromatic amine.

Further, according to the invention, the process for preparing p-nitroaromatic amines is provided which comprises reacting the p-nitroaromatic amide  
10 prepared according to the invention with ammonia under conditions which produce the corresponding p-nitroaromatic amine and the amide corresponding to the nitrile starting material or with water in the presence of a suitable basic or acidic catalyst under conditions  
15 which produce the corresponding p-nitroaromatic amine and the acid or salt thereof corresponding to the nitrile starting material. In one embodiment, the p-nitroaromatic amine is reduced to produce p-aminoaromatic amine. In another embodiment, the p-  
20 nitroaromatic amine is reductively alkylated to produce alkylated p-aminoaromatic amine. In another embodiment, the p-aminoaromatic amine is reductively alkylated to produce alkylated p-aminoaromatic amine.

#### DETAILED DESCRIPTION OF THE INVENTION

25 The invention relates to a process for preparing p-nitroaromatic amides comprising:

(a) contacting a nitrile, nitrobenzene, a suitable base and water in the presence of a suitable solvent system to form a mixture, and

30 (b) reacting the mixture at a suitable temperature in a confined reaction zone in the presence of a controlled amount of protic material.

For producing p-aminoaromatic amides, the process of the invention further comprises:

35 (c) reducing the reaction product of (b) under conditions which produce p-aminoaromatic amides.

For producing p-aminoaromatic amines from p-aminoaromatic amides, the process of the invention further comprises:

(d) reacting the p-aminoaromatic amide with ammonia under conditions which produce the corresponding p-aminoaromatic amine and amide corresponding to the nitrile of (a).

Alternatively, for producing p-aminoaromatic amines from p-aminoaromatic amides, the process of the invention further comprises:

(d) reacting the p-aminoaromatic amide with water in the presence of a suitable basic or acidic catalyst under conditions which produce the corresponding p-aminoaromatic amine and the acid or salt thereof corresponding to the nitrile of (a).

For producing the alkylated p-aminoaromatic amine, the process of the invention further comprises:

(e) reductively alkylating the p-aminoaromatic amine.

For producing p-nitroaromatic amine, the process of the invention further comprises:

(c') reacting the reaction product of (b) with (i) ammonia or (ii) water in the presence of a suitable basic or acidic catalyst under conditions which produce the corresponding p-nitroaromatic amine and the amide corresponding to the nitrile of (a) or the acid or salt thereof corresponding to the nitrile of (a).

For producing alkylated p-aminoaromatic amine, the process of the invention further comprises:

(d') reductively alkylating the p-nitroaromatic amine.

For producing p-aminoaromatic amine, the process of the invention further comprises:

(d'') reducing the p-nitroaromatic amine under conditions which produce the corresponding p-aminoaromatic amine.

-5-

For producing alkylated p-aminoaromatic amine, the process of the invention further comprises:

(e") reductively alkylating the p-aminoaromatic amine.

5           The p-nitroaromatic amide produced by the process of the invention can be in the form of the neutral compound, i.e., not in the form of a salt, and/or in the form of the salt of such p-nitroaromatic amide. The salt is produced in the reaction mixture  
10 from reaction of the p-nitroaromatic amide with the base. Thus, the reaction mixture produced in the process of the invention can include the p-nitroaromatic amide compound, or salts or mixtures thereof depending on the specific reaction conditions  
15 selected.

The molar ratio of nitrile to nitrobenzene can vary from a large excess of nitrile to a large excess of nitrobenzene. When nitrobenzene is used as the suitable solvent for the reaction, nitrobenzene is preferably  
20 present in a large excess relative to the nitrile. When the nitrile is used as the suitable solvent for the reaction, nitrile is preferably present in a large excess relative to the nitrobenzene. When nitrobenzene or nitrile is not used as the solvent for the reaction,  
25 the molar ratio of nitrile to nitrobenzene can vary over a wide range, but is preferably about 1:1.

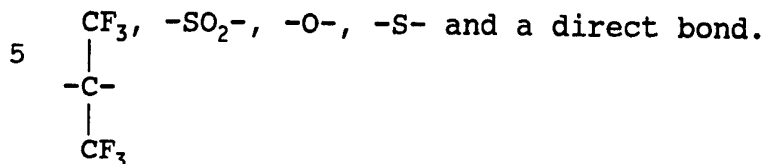
Nitriles that can be employed according to the invention include aromatic nitriles, aliphatic nitriles, substituted aromatic nitrile derivatives, substituted  
30 aliphatic nitrile derivatives and dinitriles having the formula:



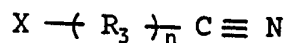
wherein  $\text{R}_1$  and  $\text{R}_2$  are independently selected from the  
35 group consisting of aromatic groups, aliphatic groups

-6-

and a direct bond, and A is selected from the group consisting of



The aliphatic nitriles and substituted  
10 aliphatic nitrile derivatives that can be employed according to the invention are represented by the formula:



15 wherein n is 0 or 1, R<sub>3</sub> is selected from the group consisting of alkyl, arylalkyl, alkenyl, arylalkenyl, cycloalkyl and cycloalkenyl groups and X is selected from the group consisting of hydrogen, -NO<sub>2</sub>, -NH<sub>2</sub>, aryl  
20 groups, alkoxy groups, sulfonate groups, -SO<sub>3</sub>H, -OH, -COH, -COOH, and alkyl, aryl, arylalkyl or alkylaryl groups containing at least one -NH<sub>2</sub> group. Sulfonate groups, as used herein, are the esters of sulfonic acids. Examples of sulfonates include, but are not  
25 limited to, alkyl sulfonates, aralkyl sulfonates, aryl sulfonates and the like. The preferred alkyl and alkoxy groups contain from 1 to about 6 carbon atoms. The preferred aryl, arylalkyl and alkylaryl groups contain from about 6 to about 18 carbon atoms.

30 Examples of aliphatic nitriles and substituted aliphatic nitrile derivatives include, but are not limited to, acetonitrile, n-valeronitrile, butyronitrile, isobutyronitrile, cyanamide, and mixtures thereof.

35 As used herein, the term "substituted aromatic nitrile derivatives" means aromatic nitriles containing one or more electron withdrawing or electron releasing substituents on the aromatic ring. Applicable substituents include, but are not limited to, halides,



-7-

-NO<sub>2</sub>, -NH<sub>2</sub>, alkyl groups, alkoxy groups, sulfonate groups, -SO<sub>3</sub>H, -OH, -COH, -COOH, and alkyl, aryl, arylalkyl or alkylaryl groups containing at least one -NH<sub>2</sub> group. Halides are selected from the group consisting of chloride, bromide and fluoride. The preferred alkyl and alkoxy groups contain from 1 to about 6 carbon atoms. The preferred aryl, arylalkyl and alkylaryl groups contain from about 6 to about 18 carbon atoms.

10           Examples of aromatic nitriles and substituted aromatic nitrile derivatives include, but are not limited to, benzonitrile, 4-methoxybenzonitrile, 4-chlorobenzonitrile, 4-nitrobenzonitrile, 4-aminobenzonitrile, o-tolunitrile, p-tolunitrile and  
15 mixtures thereof.

Dinitriles that can be employed according to the process of the invention include, but are not limited to, 1,4-dicyanobenzene, 1,4-dicyanobutane, 1,6-dicyanohexane, 2,6-dicyanotoluene, 1,2-dicyanocyclobutane, 1,2-dicyano-3,4,5,6-tetrafluorobenzene, 4,4'-dicyanobiphenyl and mixtures thereof.

The reaction for forming the p-nitroaromatic amide is carried out in a suitable solvent system. As used herein, the phase "suitable solvent system" means a polar aprotic solvent.

Suitable solvent systems include, but are not limited to, solvents such as, for example, nitrobenzene, dimethylsulfoxide, dimethylformamide, N-methyl-2-pyrrolidone, pyridine, N-methylaniline, chlorobenzene, tetrahydrofuran, 1,4-dioxane, tetraalkyl ammonium hydroxides or nitriles having a melting point below the reaction temperature, e.g., molten tetramethyl ammonium hydroxide and benzonitrile, and mixtures thereof. The currently preferred suitable solvents are nitrobenzene, dimethylsulfoxide, dimethylformamide and N-methyl-2-

-8-

pyrrolidone. Most preferably, nitrobenzene is used in excess in the reaction as stated above, and the nitrobenzene in excess of the molar amount of nitrile serves as the solvent. As described in more detail

5 below, solvent mixtures can be utilized wherein one or more of the suitable solvents and another solvent, such as a controlled amount of a protic solvent, are combined. Examples of protic solvent include, but are not limited to, methanol, water and mixtures thereof.

10 Suitable bases include, but are not limited to, organic and inorganic bases such as alkali metals, such as sodium metal, alkali metal hydrides, hydroxides and alkoxides, such as sodium hydride, lithium hydroxide, sodium hydroxide, cesium hydroxide, potassium

15 hydroxide, potassium t-butoxide, and the like, including mixtures thereof. Other acceptable base materials include, but are not limited to, phase transfer catalysts in conjunction with a suitable base source such as tetrasubstituted ammonium hydroxides or halides

20 wherein each substituent is independently selected from alkyl, aryl or arylalkyl groups wherein the alkyl, aryl and arylalkyl groups preferably have 1 to about 18 carbon atoms, including tetraalkyl ammonium hydroxides, e.g., tetramethyl ammonium hydroxide, tetraalkyl

25 ammonium halides, e.g., tetrabutyl ammonium chloride, aryl, trialkyl ammonium hydroxides, e.g., phenyltrimethylammonium hydroxide, arylalkyl, trialkyl ammonium hydroxides, e.g., benzyltrimethyl ammonium hydroxide, alkyl substituted diammonium hydroxides,

30 e.g., bis-dibutylethylhexamethylene diammonium hydroxide, and other combinations of phase transfer catalysts and suitable bases such as suitable bases in conjunction with aryl ammonium salts, crown ethers and the like, and amine bases such as lithium,

35 bis(trimethylsilyl) amide, and the like, including mixtures thereof. Preferred materials for use as bases

-9-

are tetraalkylammonium hydroxides such as tetramethylammonium hydroxide or tetrabutylammonium hydroxide.

5 Preferably, the base and water are added to the nitrile to produce a mixture which is then combined with the nitrobenzene. Alternatively, the base and water can be added after the nitrile and nitrobenzene have been combined. Addition of materials can be above or below surface addition.

10 The amount of base employed according to the invention can be conveniently expressed in terms of the ratio of equivalents of suitable base to equivalents of nitrile. Broadly, the ratio of equivalents of base to equivalents of nitrile will be about 1:1 to about 10:1, 15 preferably about 1:1 to about 4:1, and most preferably about 1:1 to about 2:1.

The reaction is conducted at a suitable temperature which can vary over a wide range. For example, the temperature can fall within a range of from 20 about 5°C to about 150°C, such as from about 15°C to about 100°C, preferably from about 25°C to about 90°C. A most preferred temperature for conducting the reaction of the invention is from about 60°C to about 80°C.

Control of the amount of protic material 25 present in the reaction is important. The amount of protic material employed according to the invention can be conveniently expressed in terms of a molar ratio based on the amount of base present at the beginning of the reaction which results in the formation of the p- 30 nitroaromatic amide. Broadly, the molar ratio of protic material to base will be less than about 5:1, preferably less than about 3:1, more preferably less than about 2:1, and most preferably less than about 1:1. Thus, the present reaction could be conducted under anhydrous 35 conditions. As used herein, the term "controlled amount" of protic material is an amount up to that which

-10-

inhibits the formation of p-nitroaromatic amide. The upper limit for the amount of protic material present in the reaction varies with the solvent. In addition, the amount of protic material tolerated will vary with the  
5 type of base, amount of base, and base cation, used in the various solvent systems. However, it is within the skill of one in the art, utilizing the teachings of the present invention, to determine the specific upper limit of the amount of protic material for a specific solvent,  
10 type and amount of base, base cation and the like. The minimum amount of protic material necessary to maintain selectivity of the desired products will also depend upon the solvent, type and amount of base, base cation and the like, that is utilized and can also be  
15 determined by one skilled in the art.

Since the amount of protic material present in the reaction is important, it is possible to reduce the amount of protic material present as much as possible and then add back to the reaction the desired amount.  
20 Protic materials that can be utilized to add back to the reaction are known to those skilled in the art and include, but are not limited to, water, methanol and the like, and mixtures thereof. Methods for measuring the amount of protic material and for reducing the amount of  
25 protic material as much as possible are well known in the art. For example, the amount of water present in certain reagents can be determined by utilizing a Karl-Fischer apparatus, and the amount of water can be reduced through distillation and/or drying under reduced  
30 pressure, drying in the presence of  $P_2O_5$  and other agents, azeotropic distillation utilizing, for example, xylene, and the like, including combinations thereof.

In one embodiment for controlling the amount of protic material during the reaction to form the p-  
35 nitroaromatic amide, a desiccant is added so as to be present during the reaction. For example, when the

-11-

protic material is water, the desiccant removes water present during the reaction and results in higher conversion of nitrobenzene and yields of p-nitroaromatic amide. As used herein, desiccant is a compound present  
5 during the reaction in addition to the suitable base used. Examples of suitable desiccants include, but are not limited to, anhydrous sodium sulfate, molecular sieves, such as types 4A, 5A, and 13X available from the Union Carbide Corporation, calcium chloride,  
10 tetramethylammonium hydroxide dihydrate, anhydrous bases such as KOH and NaOH, and activated alumina. When the nitrile is used in excess in relation to the nitrobenzene, such as when the nitrile serves as the suitable solvent, the nitrile can serve as the  
15 desiccant.

In another embodiment for controlling the amount of protic material during the reaction to form the p-nitroaromatic amide, protic material is continuously removed from the reaction mixture by  
20 distillation. If the protic material present forms an azeotrope with one of the compounds in the reaction mixture, the protic material can be removed by continuous azeotropic distillation of protic material utilizing the azeotrope.

25 The reaction can be conducted under aerobic or anaerobic conditions. Under aerobic conditions, the reaction is conducted essentially as described above in the reaction zone which is exposed to oxygen, usually by exposure to air. Under aerobic conditions, the pressure  
30 at which the reaction is conducted can vary and the optimal pressure, as well as the optimal combination of pressure and temperature, are easily determined by one skilled in the art. For example, the reaction can be conducted at room temperature and at a pressure ranging  
35 from about 0 psig (0 kg/cm<sup>2</sup>) to about 250 psig (17.6 kg/cm<sup>2</sup>), such as from about 14 psig (1 kg/cm<sup>2</sup>) to about

-12-

150 psig (10.5 kg/cm<sup>2</sup>). Under anaerobic conditions, the reaction can be conducted at atmospheric pressure or reduced or elevated pressures, in the presence of an inert gas such as, for example, nitrogen or argon.

5 Optimal conditions for a particular set of reaction parameters, such as temperature, base, solvent and the like, are easily determined by one skilled in the art utilizing the teaching of the present invention. It is currently preferred to conduct the reaction under  
10 aerobic conditions because formation of by-product azoxybenzene can be eliminated.

The p-nitroaromatic amides and/or their salts can be reduced to p-aminoaromatic amides. The neutral compounds can be generated from the salts utilizing  
15 water and/or an acid. Alternatively, the salts can be reduced. In another embodiment of the invention, p-nitroaromatic amine can be reduced to p-aminoaromatic amine. These reductions can be carried out by any of many known reductive processes, such as using a hydride  
20 source, e.g., sodium borohydride in conjunction with palladium- or platinum-on-carbon catalysts. Preferably, this reduction is conducted by a catalytic reduction wherein hydrogenation is effected under hydrogen pressure in the presence of platinum- or palladium-on-  
25 carbon, nickel, and the like. This hydrogenation process is described in detail in "Catalytic Hydrogenation in Organic Synthesis", P. N. Rylander, Academic Press, N.Y., page 299 (1979), which is incorporated by reference herein. The hydrogenation can  
30 be conducted in a variety of solvents including, but not limited to, toluene, xylene, aniline, ethanol, dimethylsulfoxide, water and mixtures thereof. Preferably, the hydrogenation is conducted utilizing a  
35 suitable solvent such as, for example, either ethanol, aniline, or dimethylsulfoxide, mixtures thereof, or

mixtures which include water as the solvent and a hydrogen pressure of from 100 psig (7 kg/cm<sup>2</sup>) H<sub>2</sub> to about 340 psig (23.9 kg/cm<sup>2</sup>) H<sub>2</sub> at a temperature of about 80°C.

Aminolysis of p-nitroaromatic amide and

- 5 p-aminoaromatic amide can be conducted by reacting p-nitroaromatic amide or p-aminoaromatic amide with ammonia to produce the corresponding p-nitroaromatic amine or p-aminoaromatic amine, respectively, and the amide corresponding to the nitrile starting material.
- 10 See for example, Jencks, W.P., *J. Am. Chem. Soc.*, Vol. 92, pp. 3201-3202 (1970). The ammonia can be utilized in the aminolysis reaction as either ammonia or a mixture of ammonia and ammonium hydroxide. If ammonium hydroxide is present, the reaction will produce the acid
- 15 corresponding to the nitrile starting material in addition to the amide corresponding to the nitrile starting material. Preferably, p-nitroaromatic amide or p-aminoaromatic amide is reacted with ammonia in the presence of a solvent, e.g., methanol.

- 20 Hydrolysis of p-nitroaromatic amide and p-aminoaromatic amide can be conducted by reacting p-nitroaromatic amide or p-aminoaromatic amide with water in the presence of a suitable basic or acidic catalyst to produce the corresponding p-nitroaromatic
- 25 amine or p-aminoaromatic amine, respectively, and the acid or salt thereof corresponding to the nitrile starting material. Examples of suitable basic catalysts include, but are not limited to, alkali metal hydroxides, alkaline earth metal hydroxides, alkali
- 30 metal alkoxides, tetraalkylammonium hydroxides, ammonium hydroxide, and the like, and mixtures thereof. Examples of suitable acidic catalysts include, but are not limited to, sulfuric acid, hydrochloric acid, nitric acid, phosphoric acid, and the like, and mixtures
- 35 thereof. It is currently preferred to use a basic catalyst since selected suitable bases used in the

-14-

preparation of p-nitroaromatic amides may also be utilized as the basic catalyst in the hydrolysis reaction. The temperature of the hydrolysis reaction will generally be in the range of about 60°C to about  
5 120°C.

Reductive alkylation of p-aminoaromatic amine to produce anti-oxidants or antiozonants can be conducted by any one of several well-known methods. See, for example, US 4,900,868. Preferably, p-  
10 aminoaromatic amine and a suitable ketone or aldehyde are reacted in the presence of hydrogen and platinum-on-carbon as catalysts. Suitable ketones include, but are not limited to, methylisobutyl ketone (MIBK), acetone, methylisoamyl ketone and 2-octanone. It should  
15 be noted that reduction of p-nitroaromatic amines and alkylation of the reduced material can be conducted in the same reaction vessel utilizing the ketone as a solvent. See, for example, US 3,414,616, US 4,463,191, and Bannerjee et al, *J. Chem. Soc. Chem. Comm.*, 18, pp  
20 1275-76 (1988).

Contemplated equivalents of the reactants and reagents set forth above are reactants and reagents otherwise corresponding thereto and having the same general properties wherein one or more of the various  
25 groups, e.g., -NO<sub>2</sub> are simple variations. In addition, where a substituent is designated as, or can be, a hydrogen, the exact chemical nature of a substituent which is other than hydrogen at that position is not critical so long as it does not adversely affect the  
30 overall activity and/or synthesis procedure.

The chemical reactions described above are generally disclosed in terms of their broadest application to the process of this invention. Occasionally, the reaction conditions may not be  
35 applicable as specifically described to each reactant and reagent within the disclosed scope. For example,



-15-

certain suitable bases may not be as soluble in one solvent as they are in other solvents. The reactants and reagents for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate adjustments in temperature, pressure and the like, by changing to alternative conventional reagents such as other solvents or other bases, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the process of this invention. In all preparative methods, all starting materials are known or are readily preparable from known starting materials.

#### Examples

Materials and Methods. Nitriles and nitrobenzene were reagent grade and were used without further purification. Solvents were purchased from Aldrich Chemical and were anhydrous grade. The tetramethylammonium hydroxide was purchased as the pentahydrate and dried in a desiccator over  $P_2O_5$  under vacuum for several days before use. Titration of the resulting solid showed the dried material to be the dihydrate. Unless indicated otherwise, all yields were determined by HPLC according to the following method.

HPLC Analysis Method:

A Waters 600 series HPLC equipped with a Vydac 201HS54 (4.6 X 250 mm) column and UV detection at 254 nm was used to monitor all reactions. The external standard method was utilized in all the analyses. Authentic samples of products to be used as standards were prepared by known literature methods.

-16-

Elution Gradient

<u>Time (Min.)</u>	<u>% Solvent A (Water)</u>	<u>% Solvent B (40% Methanol in ACN)</u>
0	75	25
35	20	80
5 40	0	100
45	0	100
46	75	25
55	75	25

10 Example 1

This example illustrates the preparation of N-(4-nitrophenyl)-benzamide by the reaction of benzonitrile and nitrobenzene in the presence of air.

A solution containing 10 g of nitrobenzene,  
15 1.27 g of tetramethylammonium hydroxide dihydrate and 1 g of benzonitrile was stirred at 60°C with air bubbled into the solution via a syringe needle for 1 hour. Analysis of a sample of the reaction product by HPLC revealed N-(4-nitrophenyl)-benzamide was produced in 45%  
20 yield based on the tetramethylammonium hydroxide. No azoxybenzene was detected in the reaction product.

Example 2

This example illustrates the preparation of N-(4-nitrophenyl)-benzamide by the reaction of  
25 benzonitrile and nitrobenzene under anaerobic conditions.

A solution containing 10 g of nitrobenzene, 1.27 g of tetramethylammonium hydroxide dihydrate and 1 g of benzonitrile was stirred at 60°C with nitrogen  
30 bubbled into the solution via a syringe needle for 1 hour. Analysis of a sample of the reaction product by HPLC revealed N-(4-nitrophenyl)-benzamide was produced in 45% yield and azoxybenzene was generated in 22% yield based on tetramethylammonium hydroxide.

35

Example 3

This example illustrates the effect of water on the production of N-(4-nitrophenyl)-benzamide in the reaction of benzonitrile and nitrobenzene.

5           A) A solution of 1.27 g of tetramethylammonium hydroxide dihydrate, 156 mg of biphenyl (as internal standard) and 10 ml of nitrobenzene was stirred in a 100 ml 3-neck round bottom flask equipped with a drying tube. Benzonitrile (1 mL) was added and stirred at 60°C  
10 in air. After the solution was stirred for 3 hours, an aliquot was sampled for RP-HPLC analysis. The yield of N-(4-nitrophenyl)-benzamide was 17% based on tetramethylammonium hydroxide charged.

          B) A solution of 1.8 g of tetramethylammonium  
15 hydroxide pentahydrate, 160 mg of biphenyl (as internal standard) and 10 ml of nitrobenzene was stirred in a 100 ml 3-neck round bottom flask equipped with a drying tube. Benzonitrile (1 mL) was added and stirred at 60°C in air. After the solution was stirred for 3 hours, an  
20 aliquot was sampled for RP-HPLC analysis. The yield of N-(4-nitrophenyl)-benzamide was calculated to be 0.91% based on tetramethylammonium hydroxide charged.

WHAT IS CLAIMED IS:

1. A process for preparing p-nitroaromatic amides comprising:

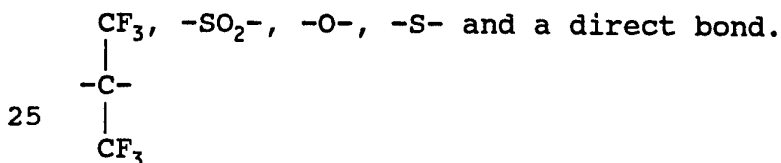
(a) contacting a nitrile, nitrobenzene, a  
5 suitable base and water in the presence of a suitable solvent system to form a mixture, and

(b) reacting said mixture at a suitable temperature in a confined reaction zone in the presence of a controlled amount of protic material.

10 2. The process of Claim 1 wherein said nitrile is selected from the group consisting of aromatic nitriles, aliphatic nitriles, substituted aromatic nitrile derivatives, substituted aliphatic nitrile derivatives and dinitriles having the formula:



wherein  $\text{R}_1$  and  $\text{R}_2$  are independently selected from the group consisting of aromatic groups, aliphatic groups and a direct bond, and A is selected from the group  
20 consisting of



3. The process of Claim 2 wherein said aliphatic nitriles and said substituted aliphatic nitrile derivatives are represented by the formula:



wherein n is 0 or 1,  $\text{R}_3$  is selected from the group consisting of alkyl, arylalkyl, alkenyl, arylalkenyl, cycloalkyl and cycloalkenyl groups and X is selected from the group consisting of hydrogen,  $-\text{NO}_2$ ,  $-\text{NH}_2$ , aryl  
35 groups, alkoxy groups, sulfonate groups,  $-\text{SO}_3\text{H}$ ,  $-\text{OH}$ ,  $-\text{COH}$ ,  $-\text{COOH}$ , and alkyl, aryl, arylalkyl or alkylaryl groups containing at least one  $-\text{NH}_2$  group.

-19-

4. The process of Claim 2 wherein the substituent of said substituted aromatic nitrile derivatives is selected from the group consisting of halides,  $-\text{NO}_2$ ,  $-\text{NH}_2$ , alkyl groups, alkoxy groups, 5 sulfonate groups,  $-\text{SO}_3\text{H}$ ,  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-\text{COH}$  and alkyl, aryl, arylalkyl or alkylaryl groups containing at least one  $-\text{NH}_2$  group, wherein halides are selected from the group consisting of chloride, bromide and fluoride.

5. The process of Claim 1 wherein said suitable 10 solvent system includes a solvent selected from the group consisting of nitrobenzene, dimethylsulfoxide, dimethylformamide, N-methyl-2-pyrrolidone, pyridine, N-methylaniline, chlorobenzene, tetrahydrofuran, 1,4-dioxane, tetraalkyl ammonium hydroxide or nitriles 15 having a melting point below the reaction temperature and mixtures thereof.

6. The process of Claim 5 wherein said suitable solvent system includes a protic solvent.

7. The process of Claim 1 wherein the molar 20 ratio of said protic material to said suitable base is less than about 5:1 and the ratio of equivalents of said suitable base to equivalents of said nitrile is about 1:1 to about 10:1.

8. The process of Claim 1 wherein said suitable 25 temperature is from about  $5^\circ\text{C}$  to about  $150^\circ\text{C}$ .

9. The process of Claim 1 wherein said suitable base is selected from the group consisting of organic and inorganic bases.

10. The process of Claim 9 wherein said organic 30 and inorganic bases are selected from the group consisting of alkali metals, alkali metal hydrides, alkali metal hydroxides, alkali metal alkoxides, phase transfer catalyst in conjunction with a base source, amines, crown ethers in conjunction with a base source, 35 alkyl magnesium halides, and mixtures thereof.

-20-

11. The process of Claim 1 wherein said base is selected from the group consisting of an aryl ammonium, alkyl ammonium, aryl/alkyl ammonium and alkyl diammonium salt in conjunction with a base source.

5 12. The process of Claim 1 wherein the reaction of step (b) is conducted under aerobic conditions.

13. The process of Claim 1 wherein the reaction of step (b) is conducted under anaerobic conditions.

10 14. The process of Claim 1 wherein a desiccant is present during Step (b) to control the amount of protic material present during the reaction.

15 15. The process of Claim 1 wherein the amount of protic material of Step (b) is controlled by the continuous distillation of said protic material.

16 16. The process of Claim 1 further comprising:  
(c) reducing the reaction produce of (b) under conditions which produce p-aminoaromatic amides.

17 17. The process of Claim 16 further comprising:  
(d) reacting the p-aminoaromatic amide with  
20 ammonia under conditions which produce the corresponding p-aminoaromatic amine and amide corresponding to said nitrile of (a).

18 18. The process of Claim 17 further comprising:  
(e) reductively alkylating the p-aminoaromatic  
25 amine to produce alkylated p-aminoaromatic amine.

19. The process of Claim 18 wherein said p-aminoaromatic amine is reductively alkylated utilizing a compound selected from the group consisting of ketones and aldehydes.

30 20. The process of Claim 16 further comprising:  
(d) reacting the p-aminoaromatic amide with water in the presence of a suitable basic or acidic catalyst under conditions which produce the corresponding p-aminoaromatic amine and the acid or salt thereof  
35 corresponding to the nitrile of (a).

-21-

21. The process of Claim 20 further comprising:  
(e) reductively alkylating the p-aminoaromatic amine to produce alkylated p-aminoaromatic amine.
22. The process of Claim 21 wherein said p-  
5 aminoaromatic amine is reductively alkylated utilizing a compound selected from the group consisting of ketones and aldehydes.
23. The process of Claim 1 further comprising:  
(c) reacting the reaction product of (b) with (i)  
10 ammonia or (ii) water in the presence of a suitable basic or acidic catalyst under conditions which produce the corresponding p-nitroaromatic amine and the amide corresponding to the nitrile of (a) or the acid or salt thereof corresponding to the nitrile of (a).
- 15 24. The process of Claim 23 further comprising:  
(d) reducing the p-nitroaromatic amine under conditions which produce the corresponding p-aminoaromatic amine.
25. The process of Claim 24 further comprising:  
20 (e) reductively alkylating the p-aminoaromatic amine to produce alkylated p-aminoaromatic amine.
26. The process of Claim 25 wherein said p-aminoaromatic amine is reductively alkylated utilizing a compound selected from the group consisting of ketones  
25 and aldehydes.
27. The process of Claim 23 further comprising:  
(d) reductively alkylating the p-nitroaromatic amine to produce alkylated p-aminoaromatic amine.
28. The process of Claim 27 wherein said  
30 p-nitroaromatic amine is reductively alkylated utilizing a compound selected from the group consisting of ketones and aldehydes.
29. p-Nitroaromatic amides prepared by the process of Claim 1.
- 35 30. p-Aminoaromatic amides prepared by the process of Claim 16.

31. p-Aminoaromatic amines prepared by the process of Claim 17.

32. p-Aminoaromatic amines prepared by the process of Claim 20.

5 33. Alkylated p-aminoaromatic amines prepared by the process of Claim 18.

34. Alkylated p-aminoaromatic amines prepared by the process of Claim 21.

10 35. p-Nitroaromatic amines prepared by the process of Claim 23.

36. p-Aminoaromatic amines prepared by the process of Claim 24.

37. Alkylated p-aminoaromatic amines prepared by the process of Claim 25.

15 38. Alkylated p-aminoaromatic amines prepared by the process of Claim 27.



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 94/07614

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07C231/06 C07C209/62 C07C233/66 C07C233/80 C07C211/51 C07C211/52		
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) IPC 6 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)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 117 063 (M. K. STERN, J. K. BASHKIN) 26 May 1992 see the whole document ---	1-38
A	TETRAHEDRON LETTERS, vol.31, no.22, 1990, OXFORD GB pages 3217 - 3220 N. R. AYYANGAR ET AL. 'A novel reaction of acetanilide with nitrobenzene in DMSO - an unusual solvent assisted regioselective aromatic nucleophilic substitution' see page 3220, reference 2 --- -/--	1,5
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
° Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "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 "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. "&" document member of the same patent family		
Date of the actual completion of the international search  20 October 1994		Date of mailing of the international search report  11. 11. 94
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016		Authorized officer  Seufert, G

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 94/07614

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 109, no. 23, 5 December 1988, Columbus, Ohio, US; abstract no. 210729q, I. V. A. HALVIK, D. GAGEONEA page 632 ; see abstract	1
X	& RO,A,93 051 (INTREPRINDEREA DE COLORANTI) ----	29
X	CHEMICAL ABSTRACTS, vol. 101, no. 13, 24 September 1984, Columbus, Ohio, US; abstract no. 110472s, M. KAKIMOTO ET AL page 614 ; see abstract & CHEM. LETT., no.5, 1984 pages 821 - 824 ----	29
X	CHEMICAL ABSTRACTS, vol. 92, no. 23, 9 June 1980, Columbus, Ohio, US; abstract no. 198069v, M. YAMASHITA ET AL. page 651 ; see abstract & SCI. ENG.REV. DOSHISHA UNIV., vol.20, no.3, 1979 pages 147 - 152 ----	30
X	Chemical Abstracts 11th Collective Index, vol. 96-105, 1982-1986, Columbus, Ohio, US see page 8008CS, RN 106-50-3 ----	31,32,36
X	Chemical Abstracts 11th Collective Index vol. 96-105, 1982-1986, Columbus, Ohio, US see page 5886CS, RN 100-01-6 ----	35
X	US,A,3 968 080 (H. L. MERTEN, G. R. WILDER) 6 July 1976 see column 1, line 49 - line 68; column 2, line 30 1- line 68 -----	33,34, 37,38

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 94/ 07614

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 29-38  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
- See annex -
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

(Claims searched completely: 1-28. Claims searched incompletely 29-38.)

Compounds of claims 29-38 (compounds made by the claimed process) were regarded as pure compound claims (see Guidelines, part C, III, 4.7b).

As these claims encompass a huge variety of compounds a complete search was not possible for economic reasons.

Even a limitation to compounds obtained by aromatic, optionally substituted nitriles as starting material (see examples) revealed too many answers which could not all be cited in the search report.

Therefore neither the search nor the search report should be considered complete for claims 29-38.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US 94/07614

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5117063	26-05-92	AU-B- 653249	22-09-94
		AU-A- 2224592	25-01-93
		CA-A- 2065056	22-12-92
		CZ-A- 9302484	16-03-94
		EP-A- 0590053	06-04-94
		WO-A- 9300324	07-01-93
-----			
RO-A-93051		NONE	
-----			
US-A-3968080	06-07-76	NONE	
-----			