595668

COMMONWEALTH OF AUSTRALIA

Patents Act 1952

Form 1 Regulation 9

Case: 07-21(386)A

APPLICATION FOR A STANDARD PATENT OR A STANDARD PATENT OF ADDITION

~~I~~/We, MONSANTO COMPANY, a Corporation organised and existing under the laws of the State of Delaware, United States of America, having its principal place of business at 800 North Lindbergh Boulevard, St. Louis, State of Missouri, United States of America, hereby apply for the grant of a Standard Patent ~~Standard Patent of Addition~~ for an invention entitled:

"PREPARATION OF SUBSTITUTED AROMATIC AMINES"

which is described in the accompanying ~~provisional~~ complete specification.

This application is a Convention application and is based on an application/s numbered 942,743 for a patent or similar protection made in United States of America on 1/th December 1986.

~~My~~/Our address for service is care of E. F. WELLINGTON & CO., Patent Attorneys, 457 St. Kilda Road, Melbourne, in the State of Victoria, Commonwealth of Australia.

FEE STAMP TO VALUE OF $ 195 ATTACHED
MAIL OFFICER ...

DATED this 16th day of December, A.D. 1987

LODGED AT SUB-OFFICE 16 DEC 1987 Melbourne

For and on behalf of MONSANTO COMPANY,

BRUCE S. WELLINGTON
Patent Attorney for Applicant Company

To: The Commissioner of Patents, Commonwealth of Australia.

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 1.2.90

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

FORM 8 REGULATION 12(2)

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION.

In support of the Convention Application made by MONSANTO COMPANY for a patent for an invention entitled:

PREPARATION OF SUBSTITUTED AROMATIC AMINES

I, William Harry Duffey, General Patent Counsel, Monsanto Company, of 800 North Lindbergh Boulevard, St. Louis, 63167, in the State of Missouri, United States of America, do solemnly and sincerely declare as follows:

1. I am authorized by MONSANTO COMPANY, the applicant for the Patent to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was made at the Patent Office, Washington, District of Columbia, in the United States of America on the 17th of December 19 86, by Ralph Albert Genetti and Arthur John Solodar.

3. RALPH ALBERT GENETTI, 211 Scenic View Drive, Copley, Ohio 44321, U.S.A.; ARTHUR JOHN SOLODAR, 8135 Cornell Court, University City, Missouri 63130, U.S.A.

~~is~~/are the actual inventor(s) of the invention, and the facts upon which the MONSANTO COMPANY is entitled to make the application are as follows:
The Company is the assignee of the actual inventor(s).

4. The basic application referred to in paragraph 2 of this declaration was the first application made in a Convention country in respect of the invention, the subject of the application.

DECLARED at St. Louis, Missouri, aforesaid this 8th day of September, 1987.

William Harry Duffey

WILLIAM HARRY DUFFEY

To Commissioner of Patents
COMMONWEALTH OF AUSTRALIA

(12) PATENT ABRIDGMENT (11) Document No. AU-B-82594/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 595668

(54) Title
PREPARATION OF SUBSTITUTED AROMATIC AMINES

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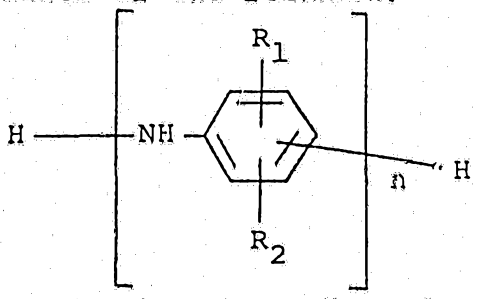
(72) Inventor(s)
RALPH ALBERT GENETTI; ARTHUR JOHN SOLODAR

(74) Attorney or Agent
E.F. WELLINGTON & CO, MELBOURNE.

(56) Prior Art Documents
GB 1440767

(57) Claim

1. A process for the preparation of substituted aromatic amines of the formula:



wherein n equals from 2 to 5, and R_1 and R_2 are either the same or different aliphatic radicals or hydrogen, which comprises (1) contacting one or more primary aromatic amine with a hypohalite oxidizing agent in a mixture containing water, an organic solvent and a base, and (2) reducing the solution with a reducing agent to produce the substituted aromatic amine.

6. A process for the preparation of 4-amino-diphenylamine or 2-aminodiphenylamine or a mixture

thereof, comprising (1) contacting aniline with a hypohalite oxidizing agent in a mixture containing water, an organic solvent consisting of an alcohol selected from the group consisting of methanol, ethanol, 1-propanol and 2-propanol, and a base, and (2) reducing the solution using catalytic reduction to produce the 4-aminodiphenylamine or 2-aminodiphenylamine or the mixture thereof.

13. The process of any one of Claims 1 to 12 wherein the reducing agent is selected from the group consisting of a palladium-on-carbon catalyst and a platinum-on-carbon catalyst.

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-1969

595668 FORM 10

COMPLETE SPECIFICATION

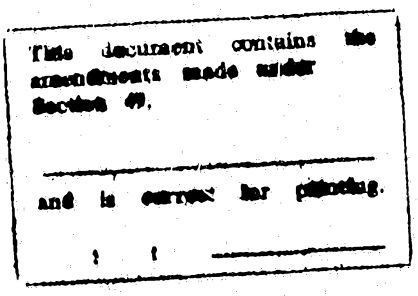
(Original)

Application Number: Class Int. Class
Lodged:

Complete specification Lodged:
Accepted:
Published:

Priority:

Related Art:



Name of Applicant: MONSANTO COMPANY

Address of Applicant: 800 North Lindbergh Boulevard,
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United States of America.

Actual Inventor/s: RALPH ALBERT GENETTI; and
ARTHUR JOHN SOLODAR.

Address for Service: E. F. WELLINGTON & CO.,
Patent and Trade Mark Attorneys,
457 St. Kilda Road,
Melbourne, 3004, Vic.

Complete Specification for the invention entitled:

"PREPARATION OF SUBSTITUTED AROMATIC AMINES"

The following statement is a full description of this invention including the best method of performing it known to me/us:

Field of the Invention

The invention relates to a process for the preparation of substituted aromatic amines. More specifically, the invention relates to the preparation of aminodiphenylamines.

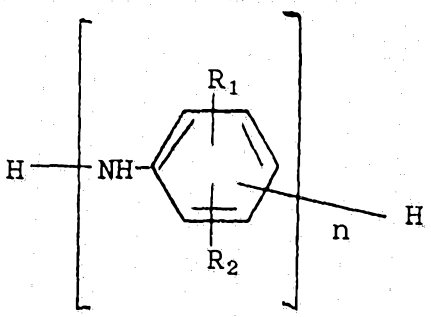
Description of Related Art

British Patent 1,440,767 describes the direct synthesis of 4-aminodiphenylamine (4-ADPA) by the head-to-tail coupling of aniline by oxidation with ferricyanide followed by hydrogenation. This process has numerous disadvantages. Ferricyanide is an expensive catalyst which is relatively difficult to handle. Additionally, the overall selectivities to 4-ADPA are relatively low, in the range of about 9 to 37% based on aniline consumed after the hydrogenation step.

Other references teach the use of hypochlorite as an amine oxidant to prepare compounds other than the present substituted aromatic amines. USSR Patent 712,425 discloses the polycondensation of aniline in the presence of sodium hypochlorite to prepare aniline black. Aust. J. Chem. 1984, 37, 2013-26 discloses a method of synthesizing benzofurans by the oxidation of 2-nitroanilines with alkaline hypochlorite. Neither of the above references, however teach the use of aromatic amines and a hypochlorite oxidizing agent to prepare the substituted aromatic amines described in detail below.

Summary of the Invention

A process for the preparation of substituted aromatic amines of the formula



wherein n equals from 2 to 5,

R_1 and R_2 are either the same or different aliphatic radicals or hydrogen, which comprises (1) contacting one or more primary aromatic amines with a hypohalite oxidizing agent in a mixture containing water and an organic solvent and a base, and (2) reducing the mixture with a reducing agent to form the substituted aromatic amine.

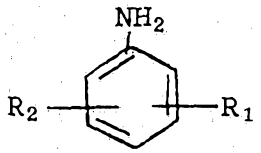
The present process is an improvement over BP 1,440,767, in that the process uses a hypohalite oxidizing agent, rather than ferricyanide, which is less expensive and easier to handle and which provides much higher selectivities to substituted aromatic amines than produced by the methods taught in BP 1,440,767, e.g. in the range of about 16 to 91% based on aniline consumed after the hydrogenation step.

Detailed Description of the Invention

The process involves two steps: the oxidation of a primary aromatic amine and its reduction to form substituted aromatic amines. The substituted amines are oligomers of the primary aromatic amines where n equals from 2 to 5 and R_1 and/or R_2 are hydrogen or the same or different aliphatic radicals.

In the first step, a primary aromatic amine is oxidized to form a mixture of oxidation products which includes some products where benzene rings are bound by azo linkages. The oxidation step is carried out by mixing the amine or a solution of the amine in a mixture containing water, an organic solvent, an oxidizing agent and a base.

Suitable primary aromatic amines are of the structure



where R_1 and R_2 are either the same or different aliphatic radicals or hydrogen. Examples of such primary aromatic amines include 2-methyl aniline, 2-ethyl aniline and 2,6-dimethyl aniline or mixtures of such amines. The preferred amine is aniline, a readily available commodity chemical.

The oxidation step is carried out with an oxidizing agent and a base in a mixture containing water and an organic solvent. The organic solvent can be any of a number of organic solvents such as alcohols, e.g. methanol, ethanol, propanol, isopropanol, butanol, 2-butanol; nitriles such as acetonitrile; ethers such as polyethylene glycols; ketones such as methylethyl ketone and acetone; alkanes such as hexane, cyclohexane, heptane, octane and isooctane and other solvents such as tetrahydrofuran and dimethyl formamide.

The ratio of solvent to water in the oxidation step can be varied widely, in the range of about 5:95 to 95:5 volume ratio, with the preferred volume ratios being in the range of 40:60 to 60:40. The amount of primary aromatic amine reactant present

in the solvent-water solution is very dilute to discourage side reactions, such as polymerization of the substituted amine where n is greater than 5. Typically, the weight ratio of amine to solvent mixture is in the range of about 0.001 to about 1.20, and the preferred range is about 0.01 to about 0.1, to provide a dilute enough solution to discourage excessive polymerization but high enough concentration to produce an appreciable amount of substituted amine.

The oxidizing agent is a hypohalite and is typically added as the hypohalite salt such as sodium hypochlorite, sodium hypobromite, potassium hypochlorite, calcium hypochlorite, and magnesium hypochlorite. The preferred hypochlorite salt is sodium hypochlorite since it is readily available as commercial bleach. The amount of oxidizing agent used can vary widely. The smaller the amount used, the greater the selectivity to the substituted aromatic amines and the lower the conversion. The greater the amount used, the higher the conversion of the primary aromatic amine but the lower the selectivity to substituted aromatic amine. Typically, the mole ratio of oxidizing agent to primary amine is in the range of about 4:1 to about 1:4, with the preferred ratio being about 1:1 to achieve the desired balance of selectivity and conversion.

The reaction mass can be a single homogeneous system or a two-phase system depending on the amount of salt present in the system. If a higher concentration of salt formed from the oxidant and base is present, a two-phase system may occur, requiring more vigorous mixing. However, separation and recovery of the product may be easier in the two-phase system.

The base which is used in the oxidation step can be any of a number of bases, such as sodium

hydroxide, potassium hydroxide, ammonium hydroxide, tetramethyl ammonium hydroxide, ammonium sodium carbonate and lithium hydroxide, or a mixture of such bases. The base may be added with the oxidizing agent as a hypochlorite salt, e.g. sodium hydroxide mixed with hypochlorite to form sodium hypochlorite. Sufficient base is added to raise the pH in the range of about 10 to about 14. The preferred pH is in the range of about 11 to about 13.

The oxidation step reaction occurs quickly and the reaction time, therefore, can be very short. If the reaction is allowed to continue for a long period of time, a slow reaction of the substituted amine continues, resulting in polymers where n is greater than 5 and a subsequent loss of selectivity. The reaction time is typically in the range of about 1 second to about 60 minutes, with the preferred range being about 12 seconds to about 5 minutes.

The oxidation step reaction can be run at relatively low temperatures, with the best results occurring below about 35°C. At higher temperatures the substituted amines can react further to form polymers with n greater than 5 and tars, resulting in a loss of selectivity. The preferred reaction temperature range is about 20°C to 30°C. The most preferred reaction temperature, because of ease of operation, is room temperature, around 23°C although the reaction temperature may temporarily be hotter than 23°C, due to the exothermic oxidation reaction.

There are many methods of performing the oxidation step. One method is to mix the reactants in a single vessel. Another method is to pump separate streams of the reagents through two legs of a Y-shaped tube such that the streams meet in the center and exit out the third leg of the tube. The

reaction time in the Y-shaped reactor is controlled by the rate of pumping in the reactants and the length of the exit tube. Another method is the use of a liquid-liquid extractive reactor, which is used when the salt concentration in the hypohalite phase is such that the final reaction mixture forms two immiscible phases. In this extractive reactor, the heavier, aqueous phase flows into the reactor from the top and the lighter organic phase flows into the reactor from the bottom, effecting good mixing.

The second step of the process to make substituted aromatic amines is to reduce the oxidation product. This results in two reactions. One produces the substituted amines from an unidentified intermediate. The second reduces the azobenzene compounds to the primary aromatic amine, which can be recovered and recycled. The reduction can be carried out by any of many known reductive processes, such as using a hydride such as sodium borohydride or sodium borohydride in conjunction with palladium- or platinum-on-carbon calatyst. The preferred process is catalytic reduction wherein hydrogenation can be effected under pressure in the presence of platinum- or palladium-on-carbon as catalyst. This process is described in detail in "Catalytic Hydrogenation in Organic Synthesis", P. N. Rylander, Academic Press, N.Y. 1979, p 299, which is hereby incorporated by reference.

Examples

The following examples are for illustration purposes only and in no way limit the scope of this invention.

In the following examples, oxidation is effected as follows:

At room temperature, the base, as a solid, the oxidizing agent and about one-half of the water is added to a round bottomed flask with stirring. After the solids dissolve, about one-half of the solvent, a solution of the aniline and the other one-half of the solvent, and the remaining water are added. The mixture is stirred for the designated reaction time.

Hydrogenation is effected as follows:

The reaction mixture is placed in an autoclave reactor with 80 ml ethanol and 0.2 g of 5% palladium-on-charcoal catalyst. Hydrogen is added to the reactor and the solution is hydrogenated at 50°C and 100 psig (689 kPa) for about 30 minutes.

The resulting mixture is analyzed for aniline by gas chromatographic separation on a 30 meter fused silica column of DB wax-30W using either 1-octanol or dodecane as an internal standard. The separation is temperature programmed from 70° to 220°C at 10°/minute.

The reduction product is analyzed by high pressure liquid chromatography (HPLC) to determine azobenzene, 4-ADPA and 2-ADPA. The analysis is performed on a C_{18} reverse phase (ODS) column using acetonitrile-water as the solvent programmed from 35:65 to 75:25 (volume:volume) acetonitrile:water over 15 minutes at 1.0 ml/minute. Fluoranthene or p-nitrochlorobenzene is used as the internal standard. A Hewlett-Packard Diode Array detector set at 282 ± 15 nanometer was employed for peak detection and integration.

Table 1

Examples 1 through 13, given in Table 1, show the effect of varying the type of organic solvent. In Example 1, 2-propanol gave the highest yield, while ethanol (Example 4) gave the highest selectivity.

Table 2

Examples 14 through 21, given in Table 2, show the effect of varying the commercial source of the hypohalite (e.g. Purex® bleach, Clorox® bleach, Aldrich, Fisher Scientific and Perma Tech) or the type of hypohalite e.g. sodium hypochlorite (Examples 14 through 20) or calcium hypochlorite (Example 21). In Examples 19 through 21, the base is present with the hypohalite as the salt of the hypohalite. Higher selectivities are achieved (Examples 14 through 18) when additional base is present.

"Purex" and "Clorox" are registered trade marks in Australia.

Table 1

Varying Solvent

Example	Solvent	Selectivity* (%)	Conversion* (%)	Yield* (%)
1	2-propanol	63	47	29.6
2	Acetonitrile	37	32	11.8
3	Tetrahydrofuran	43	25	10.8
4	Ethanol	70	37	25.9
5	1-Butanol	18	38	6.8
6	2-Butanol	16	18	2.9
7	t-Butanol	43	45	19.4
8	i-Butanol	25	22	5.5
9	Propylene glycol	63	29	15.4
10	1,3-Propanediol	49	38	18.6
11	1,4-butanediol	45	39	17.6
12	1,3-butanediol	54	38	20.5
13	1-Propanol	39	42	16.4

Table 1 (continued)

A single phase system where the hypohalite is 6.0 mmoles of 5.25 weight % sodium hypochlorite in water (Clorox® bleach), with the exception of example 6 which used 11.5 mmoles, 20 ml water, 6.0 mmoles of aniline, 7.2 mmoles of NaOH base, 20 ml of the indicated solvent. The reaction time is 5 minutes at room temperature. All of the examples, except example 7 produced only 4-ADPA isomer and no 2-ADPA. The ratio of 4-ADPA to 2-ADPA is 95/5 for example 7.

*Selectivity and conversion are calculated based on aniline ranges recovered after hydrogenation. Yield is selectivity multiplied by conversion.

Table 2

Varying Base

Example	Aniline (mmoles)	Base (mmoles)	Hypohalite (mmoles)		Selectivity (%)	Conversion (%)	Yield (%)
14	6.0	7.2	6.0	A	89	35	31
15	6.0	7.2	6.0	B	79	42	33
16	6.0	7.2	6.0	C	63	43	27
17	6.0	7.2	6.0	D	90	36	32
18	24.0	28.8	24.0	E	70	34	24
19	12.0	0	12.0	B	39	39	15
20	12.0	0	12.0	A	30	11	3
21	12.5	0	12.0	F	33	45	15

The reaction mass included 20 ml of water, 20 ml of 1-propanol solvent, and NaOH as base. The reaction time is 5 minutes at room temperature. All examples except, example 21 produced only 4-ADPA isomer and no 2-ADPA. The ratio of 4-ADPA to 2-ADPA is 78/22 for example 21. Examples 14-17 were single phase and Examples 18-21 were two-phase reactions.

Table 2 (continued)

A 5.25 weight % of NaOCl in water (Purex® bleach)
B 5.25 weight % of NaOCl in water (Clorox® bleach)
C 5.25 weight % of NaOCl in water (from Aldrich)
D 5.25 weight % of NaOCl in water (from Fisher Scientific)
E 10.5 weight % of NaOCl in water (from Perma Tech)
F Solid calcium hypochlorite from Fisher Scientific.

Table 3

Varying Reaction Temperature

Example	Temperature Range* (°C)	Selectivity (%)	Conversion (%)	Yield (%)
22	5-27	61	54	33
23	8-37	71	52	36
24	22-45	77	50	38
25	35-47	24	74	18

The reaction run time was 5 min. 85 ml of water, 100 ml of 1-propanol and 60.4 mmole of aniline were charged to the reactor. 58.5 mmoles of 5.25 wt. % of HClO in water (Clorox® Bleach) and 72.0 mmoles of NaOH were then added. All of the examples were two phase and produced only the 4-ADPA isomer.

*The temperature range is determined by a thermometer immersed in the liquid in the reaction flask.

Table 4
Changing other Variables

Example	Addition Time(min)	Reaction Time(min)	H_2O (ml)	Solvent (ml)	Aniline (mmoles)	Base (mmole)	Hypohalite (mmoles)	Select. (%)	Conv. (%)	Yield (%)
26	0	5	17	20	12	14.4	12	80	38	30
27	1	5	17	20	12	14.4	12	78	34	27
28	10	5	17	20	12	14.4	12	91	35	32
29	10	5	17	20	24	15.2	12	84	18	15
30	18	5	34	40	24	28.8	24.4	74	42	31
31	0	5	20	20	6	7.2	6	79	42	33
32	10	5	20	20	6	7.2	6	68	41	28
33	20	10	24	16	6	6.0	12	62	62	38
34	1	10	24	16	24	24.0	12	38	19	7
35	20	10	24	16	6	6.0	6	70	45	32
36	1	10	26	102	6	6.0	18	60	67	40
37	1	1	26	17	6	24.0	18	24	100	24
38	1	10	24	16	24	24.0	6	45	14	6
39	1	1	8.5	34	24	6.0	6	37	16	6
40	20	1	8.5	34	6	24.0	6	60	47	28
41	20	1	26	17	24	6.0	18	53	33	17
42	20	10	26	102	24	24.0	18	65	36	23
43	26	13	8.5	38.5	24	6.0	6	66	12	8
44	26	13	26	17	6	6.0	18	56	62	35
45	10	5	17	20	12	14.4	12	54	44	24
46	10	5	17	20	12	14.4	12.3	53	39	21
47	10	5	17	20	12	14.4	12.3	75	39	29

The water, 1-propanol solvent and aniline were charged to the vessel. The base (NaOH) and oxidant (5.25 wt. % HClO in water, sold as Clorox® Bleach) were pumped in during the indicated time period. All of the examples were two phase and produced only the 4-ADPA isomer and no 2-ADPA.

Table 3

Examples 22 through 25 given in Table 3, show the effect of varying reaction temperature. As seen when comparing Example 25 to Examples 22 through 24, temperatures above 35°C tend to result in higher conversion but lower selectivity.

Table 4

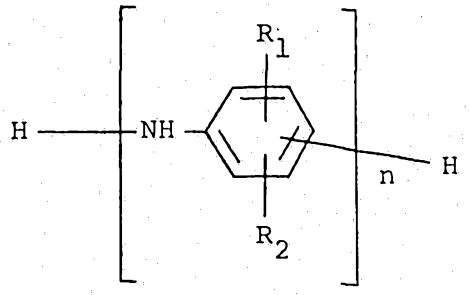
Examples 26 through 47 given in Table 4, show the effect of varying addition time, reaction time, solvent to water ratio, aniline, base and hypohalite concentrations.

Example 48 involves the use of sodium hypobromite as the oxidation catalyst. The sodium hypobromite was formed by mixing 0.79 g NaOH, 20 ml water and 0.31 ml liquid bromine, then added to 20 ml of 1-propanol and 0.55 ml aniline and mixed for 8 minutes. The oxidation mixture was reduced as described above. The conversion to 4-ADPA was 50%, the selectivity to 4-ADPA was 56% and the yield was 28%.

The matter contained in each of the following claims is to be read as part of the general description of the present invention.

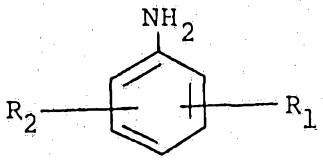
The claims defining the invention are as follows:

1. A process for the preparation of substituted aromatic amines of the formula:



wherein n equals from 2 to 5, and R_1 and R_2 are either the same or different aliphatic radicals or hydrogen, which comprises (1) contacting one or more primary aromatic amine with a hypohalite oxidizing agent in a mixture containing water, an organic solvent and a base, and (2) reducing the solution with a reducing agent to produce the substituted aromatic amine.

2. The process of Claim 1 wherein the primary aromatic amines are of the structure:



where R_1 and R_2 are either the same or different aliphatic radicals or hydrogen.

3. The process of Claim 1 wherein the primary aromatic amine is aniline.

4. The process of Claim 1 wherein n equals 2 and the substituted aromatic amine comprises 4-aminodiphenylamine or 2-aminodiphenylamine or a mixture thereof.

5. The process of any one of Claims 1 to 4 wherein the organic solvent is selected from the group consisting of methanol, ethanol, 1-propanol, 1-butanol, 2-propanol, 2-butanol, acetonitrile and tetrahydrofuran.

6. A process for the preparation of 4-aminodiphenylamine or 2-aminodiphenylamine or a mixture thereof, comprising (1) contacting aniline with a hypohalite oxidizing agent in a mixture containing water, an organic solvent consisting of an alcohol selected from the group consisting of methanol, ethanol, 1-propanol and 2-propanol, and a base, and (2) reducing the solution using catalytic reduction to produce the 4-aminodiphenylamine or 2-aminodiphenylamine or the mixture thereof.

7. The process of any one of Claims 1 to 6 wherein the volume ratio of the organic solvent to water is in the range of 5:95 to 95:5.

8. The process of any one of Claims 1 to 7 wherein the weight ratio of primary amine or aniline to the mixture containing water and the organic solvent is in the range of 0.001 to 1.20.

9. The process of any one of Claims 1 to 8 wherein the mole ratio of the hypohalite oxidizing agent to primary amine or aniline is in the range of 4:1 to 1:4.

10. The process of any one of Claims 1 to 9 wherein the mole ratio of base to the hypohalite oxidizing agent is in the range of 1:1 to 4:1.

11. The process of any one of Claims 1 to 10 wherein the hypohalite oxidizing agent is a hypohalite salt.

12. The process of any one of Claims 1 to 11 wherein the oxidation step is run at a temperature of less than 35°C.

13. The process of any one of Claims 1 to 12 wherein the reducing agent is selected from the group consisting of a palladium-on-carbon catalyst and a platinum-on-carbon catalyst.

14. Substituted aromatic amines obtained by the process of any one of claims 1 to 13.

DATED this 16th day of December, A.D. 1987

MONSANTO COMPANY
By its Patent Attorneys,
E. F. WELLINGTON & CO.,
By:

Bruce Wellington

B. S. WELLINGTON