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(54) **Title:** PROCESS FOR THE PREPARATION OF 4-SUBSTITUTED- 1-(TRIFLUOROMETHOXY)BENZENE COMPOUNDS

(57) **Abstract:** The present invention provides the process for the preparation of 4-substituted-l- (trifluoromethoxy) benzene compounds..

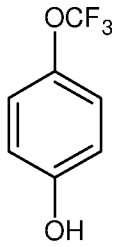
PROCESS FOR THE PREPARATION OF 4- SUSBTITUTED -1-(TRIFLUOROMETHOXY)BENZENE COMPOUNDS

FIELD OF THE INVENTION

The present invention provides the process for the preparation of 4-substituted-l-(trifluoromethoxy)benzene compounds.

BACKGROUND OF THE INVENTION

4-trifluoromethoxyphenol and its intermediates are extremely useful in pharmaceuticals, pesticides, dyes, liquid crystal materials and electronic chemicals.



Formula I

The Chinese Patent Application No. 103553884 provides method for preparing trifluoromethoxybenzene. The method comprises the following steps: (1) introducing chlorine into the raw material of benzaldehyde or a mixture of benzaldehyde and parylene for chlorination; (2) carrying out fluoridation on the chlorination product prepared in the step (1) with anhydrous hydrogen fluoride to obtain trifluoromethoxybenzene and paradibenzenyl.

The Chinese Patent Application No. 1390820A describes the use of carbon tetrachloride as a solvent for introducing chlorine into methoxybenzene, however, the use of carbon tetrachloride is restricted due to its ozone depleting nature. The Chinese Patent Application No. 102557895A alternatively provides

tetrachloroethane, pentachloroethane, hexachloroethane, bis (trichloromethyl) carbonate resin as solvent instead of carbon tetrachloride. However, in these solvents, it is difficult to separate anisole chlorinated products.

The J. Am. Chem. Soc. 1987, 109, 3708-3713 provides a process for nitration of a, a, a-trifluoromethoxybenzene in the presence of nitroniumtetrafluoroborate. The reaction takes place in nitromethane as solvent.

The U.S Patent No. 3,213,124 describes a process for preparation of p-trifluoromethoxyaniline by reduction of p-trifluoromethoxynitrobenzene with 5% palladium-on-charcoal catalyst in the presence of ethanol and hydrogen gas. There are disadvantages, for example, use of special equipment, inconvenient handling and high cost, associated with reduction using palladium-on-charcoal. These disadvantages make such processes non-viable for industrial scale.

While working on present invention, the present inventors, surprisingly, found that p-trifluoromethoxyaniline of Formula VI can be obtained in high yield and purity by using iron and hydrochloric acid for reduction of p-trifluoromethoxynitrobenzene. Such process is simple, easy to handle and industrially viable for larger scale production.

The process of the present invention is simple, uses mild reaction conditions such as non-hazardous and nontoxic reagents and solvents, economical and hence is suitable for industrial production.

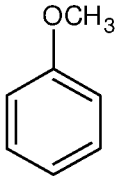
OBJECTIVE OF THE INVENTION

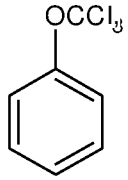
The main objective of the invention is to prepare 4-substituted-l- (trifluoromethoxy) benzene compounds.

SUMMARY OF THE INVENTION

The present invention provides a process for the preparation of l-nitro-4-trifluoromethoxybenzene of Formula V comprising;

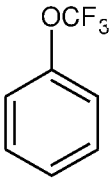
a) reacting compound of Formula II with chlorinating agent and catalyst to obtain compound of Formula III,





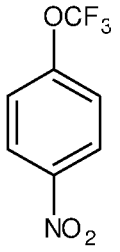
Formula II **Formula III**

b) reacting compound of Formula III with hydrogen fluoride to obtain a compound of Formula IV,



Formula IV

c) reacting a compound of Formula IV with nitric acid and chlorinated solvent to obtain l-nitro-4-trifluoromethoxybenzene, and

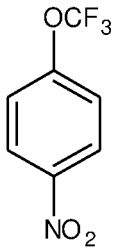


Formula V

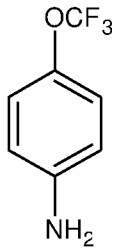
d) isolating l-nitro-4-trifluoromethoxybenzene from step c).

The present invention further provides a process for the preparation of p-trifluoromethoxyaniline of Formula VI comprising;

a) reacting compound of Formula V with iron and hydrochloric acid to obtain compound of Formula VI, and



Formula V



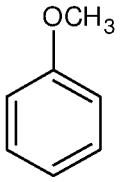
Formula VI

b) isolating compound of Formula VI.

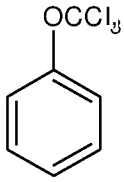
DETAILED DESCRIPTION OF THE INVENTION

The main objective of the invention is to prepare 4-substituted-l- (trifluoromethoxy) benzene compounds. In an aspect, the present invention provides a process for the preparation of l-nitro-4-trifluoromethoxybenzene of Formula V comprising;

a) reacting compound of Formula II with chlorinating agent and catalyst to obtain compound of Formula III,

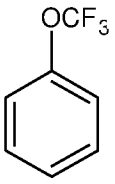


Formula II



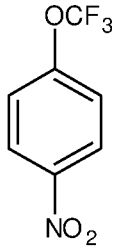
Formula III

b) reacting compound of Formula III with hydrogen fluoride to obtain a compound of Formula IV,



Formula IV

c) reacting a compound of Formula IV with nitric acid and chlorinated solvent to obtain l-nitro-4-trifluoromethoxybenzene, and



Formula V

d) isolating l-nitro-4-trifluoromethoxybenzene from step c).

The compound of Formula II is commercially obtained. The chlorinating agent in step a) is selected from chlorine, sulfuryl chloride and N-chlorosuccinimide. The catalyst in step a) is selected from phosphorus trichloride, azobisisobutyronitrile, derivatives of azobisisobutyronitrile and benzoyl peroxide or mixture thereof. The step a) may take place in the presence of solvent. The solvent may be selected from benzotrifluoride, 4-chlorobenzotrifluoride, chlorobenzene and dichlorobenzenes or mixture thereof. The step b) may take place at a temperature of about 50°C to about 120°C, for example, about 60°C to about 100°C for about 1 hour to about 12 hours, for example, for about 5 hours to about 9 hours.

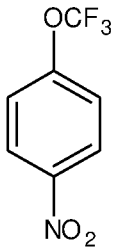
The step c) may take place in the presence of sulphuric acid. The step c) may take place in the presence of solvent. The solvent may be selected from chlorinated solvents, for example, dichloromethane, chloroform and carbon tetrachloride or mixture thereof. The step c) may take place at a temperature of about 2°C to about 35°C, for about 2hour to about 5 hours. The l-nitro-4-trifluoromethoxybenzene may be isolated by any of the methods in the art, for example, evaporation, distillation, filtration and layer separation or mixture thereof.

In yet another aspect, use of l-nitro-4-trifluoromethoxybenzene, as prepared by present invention, for the preparation of compound of 4-trifluoromethoxyphenol of Formula I.

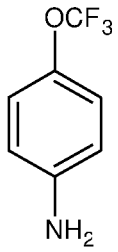
The 4-trifluoromethoxyphenol of Formula I may be prepared from l-nitro-4-trifluoromethoxybenzene by any method known in the art.

In another aspect, the present invention provides a process for the preparation of p-trifluoromethoxyaniline of Formula VI comprising;

a) reacting compound of Formula V with iron and hydrochloric acid to obtain compound of Formula VI, and



Formula V



Formula VI

b) isolating compound of Formula VI.

The compound of Formula V may be prepared as per the prior art, for example, U.S Patent No. 3,213,124. The step a) may take place in the presence of organic solvent. The organic solvent may be selected from alcoholic solvent. The alcoholic solvent may be selected from methanol, ethanol, n-propanol, n-butanol, iso-butanol and n-pentanol or mixture thereof. The hydrochloric acid may be in the form of liquid or gas. The step a) may take place at a temperature of about 0°C to about 100°C, for example, about 30°C to about 80°C for about 0.5 hour to about 12 hours, for example, for about 2 hours to about 5 hours.

The compound of Formula VI may be isolated by any of the methods in the art, for example, evaporation, distillation, filtration, decantation, crystallization and layer separation or mixture thereof.

In another aspect, use of compound of Formula VI, as prepared by present invention, for the preparation of 4-trifluoromethoxyphenol of Formula I.

The 4-trifluoromethoxyphenol of Formula I may be isolated by any of the methods in the art, for example, evaporation, distillation, filtration and layer separation or mixture thereof.

The 4-trifluoromethoxyphenol of Formula I, as obtained by present invention, has purity of about 90% to about 99.5%, preferably about 99% to about 99.5%.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLES

Step 1: Anisole (150g) and radical initiator (7.5g) and 4-Chlorobenzotrifluoride (750g) added together for 4-5 hrs at 90-100°C which is illuminated with polychromatic UV. Then 15 to 20 LPH of chlorine flow rate is maintained simultaneously with the addition at 90 to 100°C. After addition, the mixture is further maintained the chlorine flow of about 20LPH for 2 h for reaction completion and total about 345g chlorine is used. Reaction mass is purged with nitrogen gas to expel the dissolved chlorine and HC1 followed by solvent removal to get the step 1 crude (296g). Crude as such used in step 2.

Step 2: Trifluoromethoxy benzene is prepared from Trichloromethoxy benzene with anhydrous HF at 80°C for 4-6 hrs, by product from this reaction is hydrochloric acid. Observed 30-35kg/cm2 Maximum as pressure in this reaction. The crude material is distilled at atm pressure for isolating the pure Trifluoromethoxy benzene.

Procedure: Trichloromethoxy benzene (265g) and AHF (252g) are charged in an SS 316 autoclave and heated to 80°. Maintained for 4 to 6 Hrs at the temp. under pressure conditions. After completion of the reaction - HC1 & AHF are vented and expelled the dissolved HC1 & AHF by heating and purging with Nitrogen gas. Crude (190g) trifluoromethoxy benzene is then boiled off to get the pure product in the initial cuts (About 120g).

Step 3: Triflоromethoxybenzene is nitrated with concentrated Sulphuric acid + concentrated nitric acid at 00c (Nitration mixture) to 35°C.The reaction produces mixture of isomers having close boiling points. Between ortho and para isomer, para isomer was formed as major and is about 90%. And the by-product formed during

the reaction is Sulphuric acid and water. The crude product isolated by using DCM layer separation followed by the evaporation of DCM solvent.

Trifluoromethoxy benzene(118g) and dichloromethane(590g) are charged in glass round bottomed flask and cooled to about 0°C. The nitration mixture (HN03 (58.24 g) +H_2S0_4(174.24g)) was added from top at temperature in the range of 5° to 10°C for about 1 hour. The temperature of the mixture was raised slowly to 30°C and maintained for additional 1 hour. After the completion of the reaction, the reaction mass was quenched into ice cold water and solvent layers were separated. The aqueous layers so extracted with the solvent were combined with the solvent layers, dried and evaporated to obtain l-Nitro-4-trifluoromethoxy-benzene (135g)

Selectivity: 90%

Yield: 85%

Preparation of p-Trifluoromethoxy aniline

Nitro triflоromethoxybenzene (204 g) was added together with iron (185 g), concentrated HC1 (44 ml) in methanol (800 ml) at 60°C to 65°C. The reaction was stirred and monitored for completion. The iron sludge was filtered off from the reaction mass using celite bed and the filtrate was boiled off. The pH was adjusted to 9-10 to get the desired crude product. The crude product was taken in water and dichloromethane for inorganics removal. The organic layer was extracted and evaporated to obtain the crude title product.

Yield: 155 g

Purity: 88.3%

Preparation of p-Trifluoromethoxyphenol

The 4-(triflоromethoxy) aniline (75 g) was diazotized in 9N H_2S0_4 (750 niL) and aqueous $NaN0_2$ (31 g in 62 niL water) solution at temperature below 5°C.

The formed diazonium saltwas decomposed in boiling 9N H_2S0_4 solution (750 mL) at 110°C for 2hrs. The reaction mixture was cooled to 25°C. The bottom layer of reaction mixture was separated. The remaining reaction mixture was extracted with dichloromethane. All organic layers were combined, dried over Na_2S0_4, filtered and evaporated to obtain the title compound.

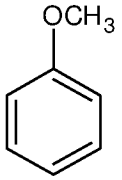
Yield: 50 g

Purity: 99.5%

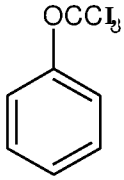
We claim:

1. A process for preparation of l-nitro-4-trifluoromethoxybenzene of Formula V comprising;

a) reacting compound of Formula II with chlorinating agent and catalyst to obtain compound of Formula III,

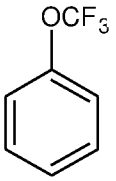


Formula II



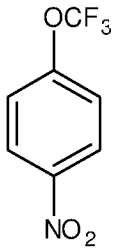
Formula III

b) reacting compound of Formula III with hydrogen fluoride to obtain compound of Formula IV,



Formula IV

c) reacting compound of Formula IV with nitric acid and chlorinated solvent to obtain l-nitro-4-trifluoromethoxybenzene, and



Formula V

d) isolating l-nitro-4-trifluoromethoxybenzene obtained from step c).

2. The process as claimed in claim 1, wherein the chlorinating agent in step a) is selected from the group consisting of chlorine, sulfuryl chloride and N-chlorosuccinimide.

3. The process as claimed in claim 1, wherein the catalyst in step a) is selected from the group consisting of phosphorus trichloride, azobisisobutyronitrile, derivatives of azobisisobutyronitrile and benzoyl peroxide or mixture thereof.

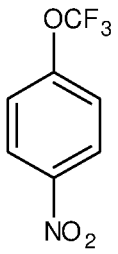
4. The process as claimed in claim 1, wherein the step a) takes place in the presence of solvent selected from the group consisting of benzotrifluoride, 4-chlorobenzotrifluoride, chlorobenzene and dichlorobenzenes or mixture thereof.

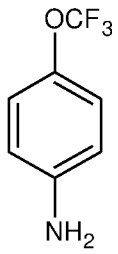
5. The process as claimed in claim 1, wherein the step c) takes place in the presence of solvent selected from the group consisting of dichloromethane, chloroform and carbon tetrachloride or mixture thereof.

6. The process as claimed in claim 1, wherein the l-nitro-4-trifluoromethoxybenzene is isolated by any of the method selected from evaporation, distillation, filtration and layer separation or mixture thereof.

7. A process for the preparation of p-trifluoromethoxyaniline of Formula VI comprising;

a) reacting compound of Formula V with iron and hydrochloric acid to obtain compound of Formula VI, and





Formula V **Formula VI**

b) isolating compound of Formula VI.

8. The process as claimed in claim 7, wherein step a) takes place in the presence of the alcoholic solvent selected from the group consisting of methanol, ethanol, n-propanol, n-butanol, iso-butanol and n-pentanol or mixture thereof.

9. The method of preparing 4-trifluoromethoxyphenol of Formula I by using compound of Formula VI, wherein compound of Formula VI is prepared as in claim 7.

10. The process as claimed in claim 9, wherein 4-trifluoromethoxyphenol of Formula I obtained has purity of about 99 % to about 99.5%.