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(54) Title: PROCESS FOR THE PREPARATION OF 4-FLUORO-3-METHOXYANILINE

(57) Abstract: A method of preparing 4-fluoro-3-methoxyaniline comprising reducing 1-bromo-5-fluoro-4-methoxy-2-nitrobenzene with a catalyst that produces increased yields.

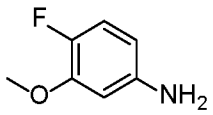
Process for the preparation of 4-fluoro-3-methoxyaniline

TECHNICAL FIELD

The present invention is in the field of organic synthesis, specifically in the area of aniline synthesis and most specifically, in the synthesis of 4-fluoro-3-methoxyaniline.

BACKGROUND

4-fluoro-3-methoxyaniline is an intermediate used in the synthesis of a number of biologically active compounds.



US Patent No. 4,044,049 discloses the synthesis of 4-fluoro-3-methoxyaniline from 2-fluoro-5-nitrophenol via 2-fluoro-5-nitroanisole (See Example 1).

EP 3 438 107 discloses the synthesis of 1-bromo-5-fluoro-4-methoxy-2-nitrobenzene from 4-bromo-2-fluorophenol (See Example 1). However, there is no disclosure of reducing this compound to 4-fluoro-3-methoxyaniline.

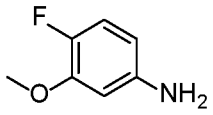
Other syntheses of 4-fluoro-3-methoxyaniline described in the literature rely on the use of alike expensive starting materials such as 4-fluoro-3-methoxybenzoic acid (see US20040204427) or 1-fluoro-2-methoxy-4-nitrobenzene (see WO2017132928).

WO 2019/196619 discloses the synthesis of 4-bromo-2-fluorophenol (see page 45).

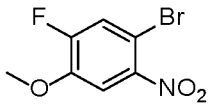
New methods of producing 4-fluoro-3-methoxyaniline with improved yields and with minimal by-products are needed.

SUMMARY OF INVENTION

A method of preparing 4-fluoro-3-methoxyanaline



comprising reducing 1-bromo-5-fluoro-4-methoxy-2-nitrobenzene

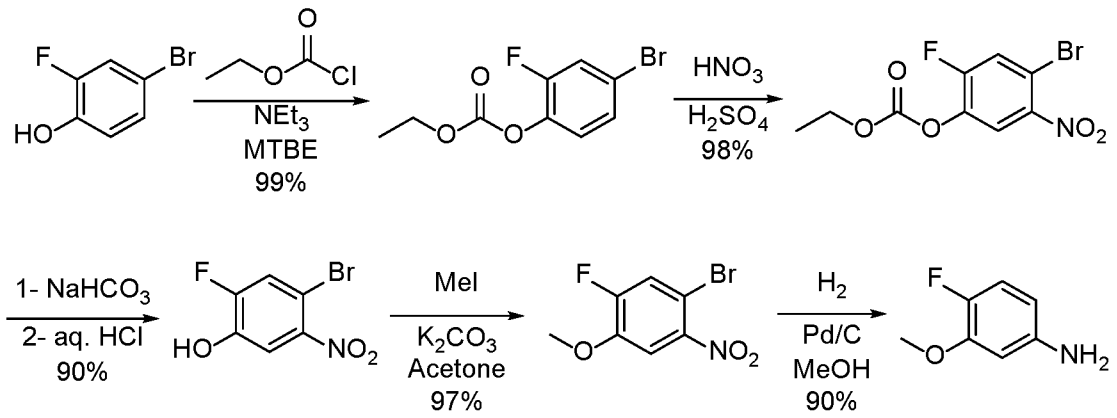


with a catalyst.

Detailed Description

Applicants have invented a novel method of synthesizing 4-fluoro-3-methoxyaniline with improved yields and with minimal by-products. It has been unexpectedly demonstrated that the concerted reduction-dehalogenation step can produce the desired compound in high yield and purity which makes the process economically attractive. Specifically, it has been found that the penultimate substituted nitrobenzene can be reduced to the corresponding substituted aniline with removal of the bromine substituent while retaining the fluoro and methoxy substituents.

Scheme 1: Process for the preparation of 4-fluoro-3-methoxyaniline



An acylating agent is a reagent that supplies an acyl group to an organic substrate. Examples are acyl halides such as acyl chloride or acyl fluoride and acid anhydride such as acetic anhydride.

A nitrating agent is a reagent used to introduce a nitro group to a benzene ring. Examples are nitrogen pentoxide (N_2O_5), nitrogen tetroxide (N_2O_4) and mixtures of nitric acid with sulfuric acid, acetic acid, acetic anhydride, phosphoric acid or chloroform.

Methylating agent is characterized by a leaving group bonded to a methyl carbon. Examples are methyl iodine, methyl methanesulfonate and dimethyl sulfate.

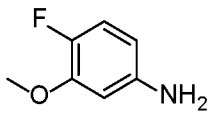
Catalyst is an agent added to a reaction to make the reaction occur more quickly without the catalyst being consumed.

Palladium on carbon (Pd/C) is a common catalyst for hydrogenation and/or hydrogenolysis of various functional groups. It is typically purchased as a black powder which is 5% or 10% palladium (by wt%) adsorbed on carbon. The reagent is normally purchased dry or as a solid which is 50% wet with water.

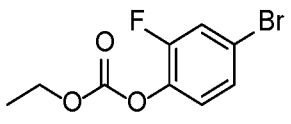
Platinum dioxide, also known as Adams' catalyst, is usually represented as platinum (IV) oxide hydrate, $PtO_2 \cdot H_2O$. It is also a common catalyst for hydrogenation and hydrogenolysis in organic synthesis.

DESCRIPTION OF EMBODIMENTS

An embodiment of the invention is a method of preparing 4-fluoro-3-methoxyanaline comprising

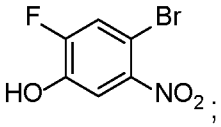


a) acylating 4-bromo-2-fluorophenol with an acylating agent to produce the compound



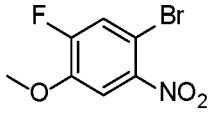
;

b) nitrating the compound of step a with a nitrating agent to produce the compound



;

c) reacting the compound of step b with a methylating agent to produce the compound



; and

d) reducing the compound of step c with a catalyst to produce the 4-fluoro-3-methoxyanaline, wherein the reduction was conducted at greater than or equal to 5 bar pressure of hydrogen and at a temperature of at least 50°C.

In an embodiment of the invention, the acylating agent of step a is an acid chloride or an acid anhydride.

In an embodiment of the invention, the nitrating agent of step b is nitric acid.

In an embodiment of the invention, the methylating agent of step c is methyl iodine.

In an embodiment of the invention, the catalyst of step d is palladium on carbon.

An alternative embodiment of the invention is a method of preparing 4-fluoro-3-methoxyaniline comprising reducing 1-bromo-5-fluoro-4-methoxy-2-nitrobenzene with a catalyst, wherein the reduction was conducted at greater than or equal to 5 bar pressure of hydrogen and at a temperature of at least 50°C.

In an embodiment of the invention, the catalyst is palladium on carbon.

In an alternative embodiment, the pressure is from about 5 to about 50 bar pressure of hydrogen.

In an alternative embodiment, the temperature is from about 50 °C to about 70 °C.

In an alternative embodiment, the temperature is from about 50 °C to less than the decomposition temperature of 4-fluoro-3-methoxyaniline.

In an alternative embodiment, the pressure is greater than or equal to 5 bar pressure of hydrogen and the temperature is at least 50°C.

EXAMPLES

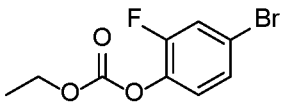
The invention will now be further described by the following, non-limiting, examples. Description of the UPLC-MS method to be added. Analytical Method A

Analytical method

UPLC-MS method

Instrument:	Agilent Technologies UHPLC/MS Series 1290
Column:	Waters Column XP, 2.1 x 50mm Xbridge BEH C18 2.5 µ
Oven temperature:	40 °C
Eluents:	A: acetonitrile with 0.05 % (vol./vol.) formic acid.
	B: water with 0.05 % (vol./vol.) formic acid
Flow:	0.8 mL/min
Gradient:	From 2 to 100 % eluent A in 1.2 min, 0.5 min 100 % eluent A
Run time:	2.2 min
Detection:	ESI/MS, positive and negative ions scan: 100-650 m/z
	UV at 254, 210 and 280 nm

Example 1 – Preparation of 4-bromo-2-fluorophenyl ethyl carbonate



4-Bromo-2-fluorophenol (173 g, 879 mmol) was dissolved in methylenchloride (1385 mL), triethylamine (147 mL, 1054 mmol) was added, and the temperature of the resulting mixture was adjusted to 0 °C. Ethyl chloroformate (95 mL, 966 mmol) was added while maintaining the temperature between 0 to 7 °C. The reaction mixture was then allowed to reach room temperature and was stirred for 30 min. The mixture was washed with water (2 × 1 L), aqueous 0.5N hydrochloric acid (500 mL) and aqueous saturated sodium chloride (500 mL) to afford the desired product (236 g, 879 mmol) as a solution which was directly engaged in step 2.

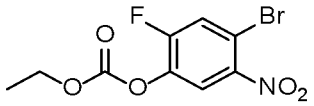
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.35 (dd, *J* = 9.5, 2.2 Hz, 1H), 7.28 (ddd, *J* = 8.7, 2.2, 1.5 Hz, 1H), 7.17 – 7.05 (m, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (76 MHz, $CDCl_3$) δ (ppm): 155.8, 152.5, 138.1, 127.8, 124.71, 120.8 119.3, 65.80, 14.3.

^{19}F NMR (565 MHz, d_6-DMSO) δ (ppm): -57.2.

UPLC/MS (Method A): Rt = 1.17 min.

Example 2 - Preparation of 4-brom-2-fluoro-5-nitrophenyl ethyl carbonate



The 4-bromo-2-fluorophenyl ethyl carbonate solution (236 g, 879 mmol) in methylene chloride (~1700 mL) from Example 1 was concentrated and the remaining residue was taken up in sulfuric acid (390 mL, 7032 mmol). Nitric acid (91 mL, 1319 mmol) was added while keeping the temperature below 20 °C. After completion of the addition, the reaction mixture was stirred for another 20 min. The temperature was then adjusted to 12 °C and cold water (2.3 L) was added. The reaction mixture was then allowed to reach room temperature was extracted with methylene chloride (500 mL). The organic phase was collected, dried and concentrated under reduced pressure to afford the desired product as a light brown oil (270 g, 859 mmol).

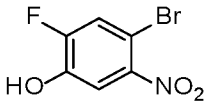
^{1}H NMR (600 MHz, MeOD) δ (ppm): 8.12 (d, *J* = 7.2 Hz, 1H), 7.89 (d, *J* = 9.5 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, MeOD) δ (ppm): 157.8, 156.1, 153.2, 139.4, 124.3, 122.9, 113.1, 67.34, 14.3.

^{19}F NMR (283 MHz, MeOD) δ (ppm): -121.5.

UPLC/MS (Method A): Rt = 1.14 min.

Example 3 - Preparation of 4-bromo-2-fluoro-5-nitrophenol



4-bromo-2-fluoro-5-nitrophenyl ethyl carbonate (270 g, 859 mmol), obtained as a crude product from Example 2, was dissolved in methanol (1.6 L). Sodium hydrogen carbonate (144 g, 1718 mmol) was added, and the resulting mixture was stirred under reflux for 2.5 h. The reaction mixture was concentrated under reduced pressure to a volume of about 400 mL. Water (2.7 L) was added, and the mixture was adjusted to pH of 3 by the addition of aqueous 4N hydrochloric acid (about 400 mL). The formed precipitate was filtered off, the wet cake was rinsed with water (750 mL slurry wash, 250 mL displacement wash) and the obtained solid was dried under reduced pressure at 40 °C to afford the desired product as a beige solid (187 g, 777 mmol).

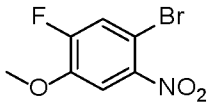
^{1}H NMR (300 MHz, MeOD) δ (ppm): 7.57 (d, *J* = 10.2 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR (151 MHz, MeOD) δ (ppm): 155.4, 153.7, 146.8, 123.1, 116.0, 103.4.

^{19}F NMR (283 MHz, MeOD) δ (ppm): -128.9 (dd, *J* = 10.2, 8.1 Hz).

UPLC/MS (Method A): Rt = 0.96 min.

Example 4 - Preparation of 1-bromo-5-fluoro-4-methoxy-2-nitrobenzene



To a solution of 4-bromo-2-fluoro-5-nitrophenol (187 g, 777 mmol) in acetone (1.5 L) was added potassium carbonate (131 g, 951 mmol) and iodomethane (52.3 mL, 832 mmol). The resulting mixture was heated at 60°C for 2 h. After the temperature of the reaction mixture was lowered to ambient temperature, salts were filtered off. The filtrate was taken up in ethyl acetate, acetone was distilled off, and the organic layer was sequentially washed with aqueous 1N hydrochloric acid (500 mL), 10% aqueous sodium thiosulfate (300 mL) and aqueous saturated sodium chloride (500 mL). The organic phase collected and concentrated under reduce pressure to deliver the desired product as a yellow crystalline solid (194.6 g, 771 mmol).

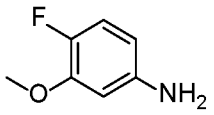
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.58 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 9.9 Hz, 1H), 3.96 (s, 3H).

^{13}C NMR (76 MHz, $CDCl_3$) δ (ppm): 155.8, 152.3, 147.6, 122.3, 111.1, 105.9, 57.0.

^{19}F NMR (283 MHz, $CDCl_3$) δ (ppm): -123.9 (dd, *J* = 9.9, 7.8 Hz).

UPLC/MS (Method A): Rt = 1.09 min.

Example 5 - Preparation of 4-fluoro-3-methoxyaniline



A hydrogenation pressure reactor was charged under inert atmosphere with 1-bromo-5-fluoro-4-methoxy-2-nitrobenzene (194.6 g, 771 mmol), methanol (1654 mL), sodium carbonate (49.5 g, 467 mmol) and 10 wt.% Pd on activated carbon (84.14 g, 3.89 mmol). A pressure of 5 bar hydrogen was applied to the resulting mixture which was reacted under stirring at 50°C. After 8 h, reaction went to completion, the solids were removed by filtration through a pad of celite and were rinsed with methanol (100 mL). The combined filtrates were concentrated under reduced pressure and the residue taken up in ethyl acetate (500 mL). The organic layer was washed with water (500 mL), dried and concentrated under reduced pressure to obtain the desired product as a black crystalline solid (107.4 g, 698 mmol, 90.5% yield).

^{1}H NMR (300 MHz, MeOD) δ (ppm): 6.79 (dd, *J* = 11.4, 8.6 Hz, 1H), 6.47 (dd, *J* = 7.4, 2.6 Hz, 1H), 6.22 (ddd, *J* = 8.6, 3.5, 2.6 Hz, 1H), 3.80 (s, 3H).

^{13}C NMR (76 MHz, MeOD) δ (ppm): 149.2, 148.8, 145.4, 116.6, 107.9, 102.9, 56.5.

^{19}F NMR (283 MHz, MeOD) δ (ppm): -151.4 (ddd, *J* = 11.2, 7.5, 3.5 Hz).

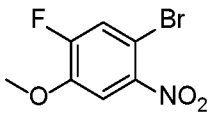
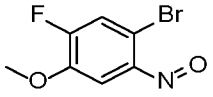
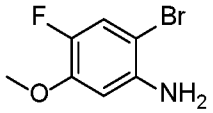
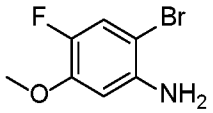
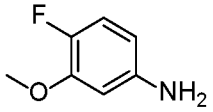
UPLC/MS (Method A): Rt = 0.51 min.

Comparative example 6 – Reaction conditions for the preparation of 4-fluoro-3-methoxyaniline

Comparative examples of the preparation of 4-fluoro-3-methoxyanaline from_1-bromo-5-fluoro-4-methoxy-2-nitrobenzene that demonstrate the significance of pressure and temperature on this reaction.

Reactions conducted at lower hydrogen pressure (<5bar) leads to only partial reduction of the nitro group. Reactions conducted at lower temperature (<50°C) does not produce successful hydrodehalogenation (see Table 1 below).

Table 1

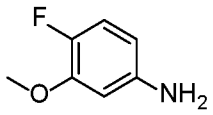
Comparative Reaction No.	Reaction temperature (°C)	Hydrogen pressure (bar)	Structure of the obtained product	Comment
1	50	1		No conversion
2	30	20		Partial reduction of the nitro group to a nitroso group
3	40	5		Full reduction of the nitro group into the aniline. No hydrodehalogenation
4	40	50		Full reduction of the nitro group into the aniline. No hydrodehalogenation
5	50	5		Full reduction of the nitro group into the aniline and full hydrodehalogenation

High pressure and temperature are typically avoided in industrial scale chemical production. Such reactions are more expensive to run and usually require specialized equipment. The same can be said for lower pressure and temperature reaction conditions. Ideally, reactions should be run as close to ambient temperature and atmospheric pressure as possible. It was unexpected that to achieve both the reduction of the nitro group and the elimination of the bromine required to produce 4-fluoro-3-methoxyaniline

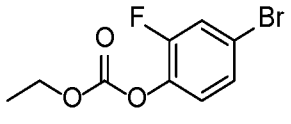
from 1-bromo-5-fluoro-4-methoxy-2-nitrobenzene, it was necessary to run the reaction under the elevated pressure and temperature disclosed in Example 5 above.

CLAIMS

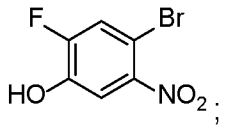
1. A method of preparing 4-fluoro-3-methoxyanaline comprising



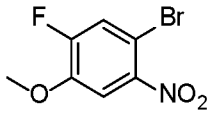
a) acylating 4-bromo-2-fluorophenol with an acylating agent to produce the compound


;

b) nitrating the compound of step a with a nitrating agent to produce the compound


;

c) reacting the compound of step b with a methylating agent to produce the compound


; and

d) reducing the compound of step c with a catalyst to produce the 4-fluoro-3-methoxyaniline, wherein the reduction was conducted at greater than or equal to 5 bar pressure of hydrogen and at a temperature of at least 50°C.

2. The method of claim 1, wherein the acylating agent of step a is an acid chloride or an acid anhydride.

3. The method of claim 1, wherein the nitrating agent of step b is nitric acid.

4. The method of claim 1, wherein the methylating agent of step c is methyl iodine.

5. The method of claim 1, wherein the catalyst of step d is palladium on carbon.

6. A method of preparing 4-fluoro-3-methoxyaniline comprising reducing 1-bromo-5-fluoro-4-methoxy-2-nitrobenzene with a catalyst, wherein the reduction was conducted at greater than or equal to 5 bar pressure of hydrogen and at a temperature of at least 50°C.

7. The method of claim 6, wherein the catalyst is palladium on carbon.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/083032

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C68/02 C07C201/08 C07C201/14 C07C213/02
ADD.

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/015972 A1 (RIGEL PHARMACEUTICALS INC [US]; LI HUI [US] ET AL.) 2 February 2012 (2012-02-02) page 141, Scheme VII; page 143, lines. 5-10.; page 140 - page 143	1-7
A	US 4 044 049 A (RUYLE WILLIAM V ET AL) 23 August 1977 (1977-08-23) cited in the application paragraph 8, lines: 15-33	1-7

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent 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	Date of mailing of the international search report
30 January 2025	13/02/2025

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Savic, Aleksandar

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2024/083032

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