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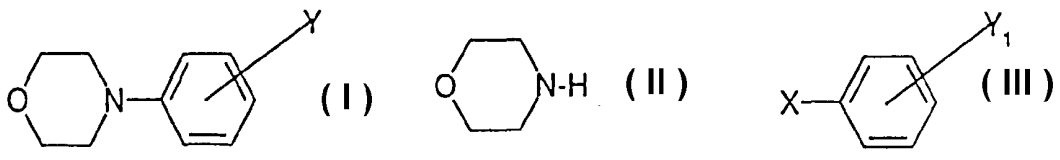
(54) Title: A NEW PROCESS FOR THE SYNTHESIS OF MORPHOLINYLBENZENES



(57) Abstract: A new improved process for synthesizing morpholinylbenzenes of the formula I by reacting morpholine of formula II with a substituted benzene of formula III, wherein morpholine is used as a reactant and as the only one solvent.

A NEW PROCESS FOR THE SYNTHESIS OF MORPHOLINYLBENZENES.

Field of the Invention

The present invention relates to a new improved process for synthesizing morpholinylbenzenes, preferably 4-morpholinylbenzenes. There is a need for a simple and suitable large-scale synthesis possible to achieve high overall yield within an acceptable reaction time.

Prior art

Tetrahedron letters, 1999, 40 (6), 1219-1222 and Tetrahedron, 1999, 55 (46), 13285-13300 disclose a process for synthesizing 4-(4-morpholinyl) benzonitrile and 4-(4-morpholinyl) benzoic acid ethyl ester by reacting morpholine and 4-fluorobenzonitril or ethyl 4-fluorobenzoate in the solvent dimethyl sulfoxide (DMSO).

Synthesis, 1990, 1145-1149 discloses a process for synthesizing 4-(4-morpholinyl) benzonitrile and 1-[4-(4-morpholinyl)phenyl] ethanone in the solvent acetonitrile under 10 kbar pressure. The reacting starting materials in said process are morpholine and 4-fluorobenzonitril or 1-(4-fluorophenyl) ethanone, respectively.

US 5817877 discloses a method of preparing 4-(4-morpholinyl) benzonitrile in the presence of a palladium catalyst comprising a chelating ligand, in sodium t-butoxide (NaO-t-Bu) and toluene. The starting material in the process disclosed in US 5817877 is morpholine and 4-cyanophenyltriflate.

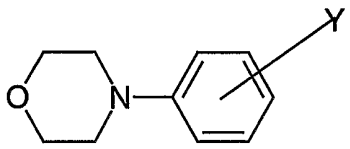
EP 805152-B discloses a method of preparing 1-(4-morpholinophenyl) alkylketone by reaction of morpholine and the corresponding 1-(4-bromophenyl) alkylketone in aqueous solution under 5-6 bar pressure.

JP 04089459 discloses a method of preparing 4-(4-nitrophenyl) morpholine and 2-(4-nitrophenyl) morpholine by reaction of morpholine and 4-(4-nitrophenyltriflate) morpholine or 4-(4-nitrophenyl triflate) morpholine, respectively, in acetonitrile.

Disclosure of the Invention

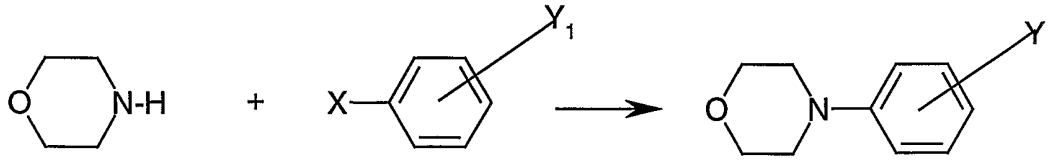
This invention discloses a nucleophile aromatic amination method different from all those previously disclosed methods in the prior art. The process of the present invention does not need any additional solvent, it uses morpholine as the reactant and as the only one solvent, if a solvent is present.

The object of the present invention is to provide a new and improved process to synthesize 4-(4-morpholinyl) benzene and 2-(4-morpholinyl) benzene of the formula I.



I

This invention discloses a simple and improved method to synthesize morpholinylbenzene of the formula I



II III I

by reacting morpholine of formula II with a substituted benzene of formula III, wherein

Y and Y_1 are a substituent in 2- or 4- position and

Y is Y_1 or COOH,

Y_1 is CN, NO_2, CF_3, $COOR^1$, COR^1 and $CONR^2R^3$,

where R^1 is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkylC_{3-6} cycloalkyl, C_6-C_{10} aryl or a heterocyclic ring containing one or two heteroatoms selected from N, O, S, and said heterocyclic ring may optionally be substituted;

where R^2, R^3 is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkylC_{3-6} cycloalkyl and C_6-C_{10} aryl or heterocyclic ring containing one or two heteroatoms selected from N, O, S, and said heterocyclic ring may optionally be substituted, or may together with the nitrogen atom form a heterocyclic ring;

with the provisio that Y_1 is not COOH;

X is a leaving group;

characterized in that the morpholine is used as a reactant and as the only one solvent, if solvent is present;

and, if necessary, hydrolysis to form a compound wherein Y is COOH.

A preferred embodiment of the present invention is an improved process for the synthesizing of morpholinylbenzene of formula I, wherein Y is COOH starting from a morpholinylbenzene of formula I, wherein Y is Y_1, where Y_1 is $COCH_3$ followed by a haloform reaction or Y_1 is CN, $CONH_2$, $COOC_2H_5$ followed by basic hydrolysis but an acid hydrolysis is possible as well. Particularly preferred is, when the whole process is performed using one pot without any isolation of the product before the hydrolysis.

Another preferred embodiment of the present invention is an improved process for the synthesizing of morpholinylbenzene of formula I, wherein Y is CN, $CONH_2$, $COOC_2H_5$, $COCH_3$, COOH and NO_2, by reacting morpholine of formula II with a substituted benzene

of formula III, wherein X is F, Cl, Br or CF_3SO_3, preferably F and Y_1 is CN, $CONH_2$, $COOC_2H_5$, $COCH_3$ and NO_2.

Another preferred embodiment of the present invention is an improved process for the synthesizing of morpholinylbenzene of formula I, wherein Y is NO_2, by reacting morpholine of formula II with a substituted benzene of formula III, wherein X is F and Y_1 is NO_2.

A preferred embodiment of the present invention is an improved process for the synthesizing of morpholinylbenzene of formula I, wherein the electron-withdrawing group Y is in the 4-position.

A preferred embodiment of the present invention is an improved process for the synthesizing of morpholinylbenzene of formula I, wherein the molar ratio of the reactant morpholine to substituted benzene may be up to 10:1, preferably in the ranges from 6,7:1 to 1:1, more preferably from 3.5:1 to 1:1. No excess of morpholine (molar ratio 1:1) is needed when Y_1 is NO_2. After the conversion of morpholinylbenzenes is completed the aqueous mixture is made basic by a base, such as $NaHCO_3$, if the molar ratio of morpholine to substituted benzene in the reaction is 1:1. This is to keep the product from being protonated by HX, which is generated during the reaction.
The crude product may be used without working-up or isolation as a starting material for the next reaction.

In the present context C_1-C_6 alkyl may be straight or branched. C_1-C_6 alkyl may be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl or i-hexyl.

In the present context C_3-C_6 cycloalkyl may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl. C_{1-6} alkylC_{3-6} cycloalkyl may be methylcyclopropyl, ethylcyclopropyl, methylcyclobutyl, ethylcyclobutyl, or methylcyclopentyl.

In the present context C_6-C_{10} aryl may be a phenyl or a naphthyl, which groups may optionally be substituted.

In the present context a heterocyclic ring containing one or two heteroatoms selected from O, S, N, is preferably a 5- or 6- membered ring for example imidiazolidinyl, imidiazolinyl, morpholinyl, piperazinyl, piperidinyl, piperonidyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, thiomorpholinyl, preferably, piperidino, 1-piperazinyl, morpholino, thiomorpholino and 4-piperidon-1-yl.

X is a leaving group, preferably halogen such as F, Cl, Br, I or CF_3SO_3, particularly preferred is F.

Both pure enantiomers and racemic mixture of the compounds of formula I is within the scope of the present invention.

In the present context a base may be alkali metal carbonates such as a sodium carbonate and a potassium carbonate, or alkali metal hydrogen carbonates such as a sodium hydrogen carbonate and a potassium hydrogen carbonate, or alkali metal hydroxides such as a sodium hydroxide and a potassium hydroxide, or amines such as an alkylamines, e.g. triethylamine, diethylamine, ethanolamine. Other possible bases known to a person skilled in the art may be used, too. Sodium hydrogen carbonate is one of the preferred bases.

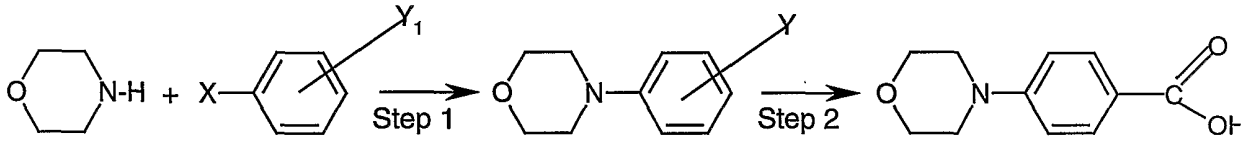
Detailed Description of the invention

A mixture of the two reagents, morpholine and the substituted benzene is gently warmed up. The reaction temperature may vary for example from 20° C to 130° C, preferably from 40° C up to 120° C, depending on the nature of the electron withdrawing group Y_1.

A low reaction temperature of about 40 °C is typically when Y_1 is NO_2, a reaction temperature of about 120°C is typically when Y_1 is CN, $CONH_2$, $COOC_2H_5$ or $COCH_3$.

The reaction times may vary for example between 0.5 hours to 72 hours, preferably 0.5 hours to 36 hours, depending on the nature of the electron withdrawing group Y_1. After the reaction is completed, water is added into the reaction mixture. In most cases, the product 4-morpholinylbenzene of formula I precipitates from the aqueous solution, and is collected by filtration.

The present invention discloses a process to prepare 4-(4-morpholinyl) benzoic acid, directly from the halobenzene derivative by a two step process as shown below. The product from the first step is directly hydrolyzed in the same reactor in the second step to obtain a high yield of the 4-(4-morpholinyl) benzoic acid. This is defined as a one-pot method. A basic hydrolysis is preferred in the second step, preferably with sodium hydroxide, but acid hydrolysis is possible.



II III I IV

This object is achieved by the process of the present invention, which is characteterized in that the morpholine is used as a reactant and as the only one solvent. This advantageously avoids the use of catalyst and base over processes known in the art. Further advantageous is, that the process of the invention produces good yields under mild conditions, such as normal pressure. However, to work under pressure will also function.

Compounds of formula I, wherein Y is an electron-withdrawing group such as a nitrile, cyano, trifluormethyl, carboxylic ester, ketone or amide group, are useful intermediates. They are widely used as building blocks in the synthesis of new drugs. An efficient method for the preparation of these compounds is therefore very desirable and of commercial value.

Examples

This invention is further illustrated by the following examples.

Example 1

Preparation of 4-(4-morpholinyl) benzonitrile:

A mixture of morpholine (50 g, 0.6 mol) and 4-fluorobenzonitrile (24 g, 0.2 mol) is heated at 120°C. The conversion of the 4-fluorobenzonitrile is complete after 5 hours. Water (10 ml) is then added into the reaction mixture. The precipitate is filtered off, washed with water and dried under vacuum (30°C) to give 37 g of the title-compound. Yield: 95%; m.p. 82-83 °C; MS 188 (100, M^+); H^1 NMR ($CDCl_3$): δ 7.46 (dd, 2H), 6.81 (dd, 2H), 3.79 (t, 4H), 3.22 (t, 4H); C^{13} NMR ($CDCl_3$): δ 153.69, 133.71, 120.07, 114.26, 101.16, 66.65, 47.49.

Example 2

Preparation of 4-(4-morpholinyl) benzonitrile:

A mixture of morpholine (3 g, 34 mmol) and 4-chlorobenzonitrile (1.55 g, 11.2 mmol) is heated at 120°C. The conversion of the 4-chlorobenzonitrile is complete after 12 hours. Water (10 ml) is then added into the reaction mixture. The precipitate is filtered off, washed with water and dried under vacuum (30°C). Recrystallisation (50% aqueous ethanol) of the dried crude product gives 1.1 g of the title-compound. Yield: 52%, m.p. 82-83 °C; MS 188 (100, M^+); H^1 NMR ($CDCl_3$): δ 7.46 (dd, 2H), 6.81 (dd, 2H), 3.79 (t, 4H), 3.22 (t, 4H); C^{13} NMR ($CDCl_3$): δ 153.69, 133.71, 120.07, 114.26, 101.16, 66.65, 47.49.

Example 3

Preparation of 4-(4-morpholinyl) benzonitrile:

A mixture of morpholine (3 g, 34 mmol) and 4-bromobenzonitrile (1.95 g, 10.7 mmol) is heated at 120°C. The conversion of the 4-bromobenzonitrile is complete after 24 hours. Water (10 ml) is then added into the reaction mixture. The precipitate is filtered off, washed with water and dried under vacuum (30°C). Recrystallisation (50% aqueous ethanol) of the dried crude product gives 1.2 g of the title-compound. Yield: 65%, m.p. 82-83 °C; MS 188 (100, M^+); H^1 NMR ($CDCl_3$): δ 7.46 (dd, 2H), 6.81 (dd, 2H), 3.79 (t,

4H), 3.22 (t, 4H); C^{13} NMR ($CDCl_3$): δ 153.69, 133.71, 120.07, 114.26, 101.16, 66.65, 47.49.

Example 4

Preparation of 4-(4-morpholinyl) benzonitrile:

A mixture of morpholine (3 g, 34 mmol) and the freshly prepared 4-[(trifluoromethyl)sulfonyl] benzonitrile (1.2 g, 5.1 mmol, Ref.: A.M.Echavarren and J.K.Stille, J.Am.Chem. Soc. 1987, 109, 5478-5486.), is heated at 120°C. The conversion of the 4-[(trifluoromethyl)sulfonyl]benzonitrile is complete after 20 hours. Water (10 ml) is than added into the reaction mixture. The precipitate is filtered off, washed with water and dried under vacuum (30°C). Recrystallisation (50% aqueous ethanol) of the dried crude product gives 0.5 g of the title-compound. Yield: 52%, m.p. 82-83 °C; MS 188 (100, M^+); H^1 NMR ($CDCl_3$): δ 7.46 (dd, 2H), 6.81 (dd, 2H), 3.79 (t, 4H), 3.22 (t, 4H); C^{13} NMR ($CDCl_3$): δ 153.69, 133.71, 120.07, 114.26, 101.16, 66.65, 47.49.

Example 5

Preparation of 4-(4-morpholinyl) benzamide:

A mixture of morpholine (2.0 g, 23 mmol) and 4-fluorobenzamide (1.2 g, 8.6 mmol) is heated at 120°C. The conversion of the 4-fluorobenzoamide is complete after 10 hours. Water (10 ml) is than added into the reaction mixture. The precipitate is filtered off, washed with water and dried under vacuum (30°C) to give 1.6 g of the title-compound. Yield: 94%; m.p. 220-221 °C; MS 206 (100, M^+); H^1 NMR (DMSO): δ 7.76 (d, 2H), 7.75 (b, 1H), 7.05 (b, 1H), 6.94 (d, 2H), 3.73 (t, 4H), 3.20 (t, 4H); C^{13} NMR ($CDCl_3$): δ 167.61, 152.90, 128.79, 123.93, 113.31, 65.92, 47.36.

Example 6

Preparation of 4-(4-morpholinyl) benzoic acid ethyl ester:

A mixture of morpholine (12 g, 0.14 mol) and ethyl 4-fluorobenzoate (8 g, 0.04 mol) is heated at 120°C. The conversion of the 4-fluorobenzoate is complete after 24 hours. Water (10 ml) is than added into the reaction mixture. The precipitate is filtered off, washed with

water and dried under vacuum (30°C) to give 9.2 g of pure 4-(4-morpholinyl) benzoic acid ethyl ester after recrystallisation from aqueous ethanol (50%, v/v). Yield: 89%.

m.p. 82-83 °C; MS 235 (100, M^+); H^1 NMR ($CDCl_3$): δ 7.93 (d, 2H), 6.86 (dd, 2H), 4.33 (q, 2H), 3.85 (t, 4H), 3.28 (t, 4H), 1.37 (t, 3H); C^{13} NMR ($CDCl_3$): δ 166.57, 154.14, 131.14, 120.70, 113.46 66.60, 60.39, 47.75, 14.40.

Example 7

Preparation of 1-[4-(4-morpholinyl) phenyl] ethanone:

A mixture of morpholine (3.2 g, 37 mmol) and 1-(4-fluorophenyl) ethanone (1.5 g, 11 mmol) is heated at 120°C. The conversion of the 1-(4-fluorophenyl) ethanone is complete after 10 hours. Water (10 ml) is than added into the reaction mixture. The precipitate is filtered off, washed with water and dried under vacuum (30°C) to give 2.1 g of the title-compound. Yield: 93%; m.p. 95-96 °C; MS 205 (100, M^+); H^1 NMR ($CDCl_3$): δ 7.99 (d, 2H), 6.86 (d, 2H), 3.86 (t, 4H), 3.30 (t, 4H), 2.53 (s, 3H); C^{13} NMR ($CDCl_3$): δ 196.76, 154.43, 130.55, 128.36, 113.48, 101.16, 66.7, 47.73, 26.37.

Example 8

Preparation of 4-(4-nitrophenyl) morpholine:

A mixture of morpholine (1.0 g, 11 mmol) and 1-fluoro-4-nitrobenzene (1.48 g, 10.5 mmol) is heated at 40 °C. The conversion of 4-(4-nitrophenyl)morpholine is complete after 30 min. Cold water (10 ml) is added into the reaction mixture and the aqueous mixture is made pH 8 by the addition of saturated $NaHCO_3$. The yellow precipitate is filtered off, washed with water and dried under vacuum (30 °C) to give 2.0 g of the title-compound after recrystallisation from 70% ethanol. Yield: 95%; m.p. 152-153 °C; MS 208 (100, M^+); H^1 NMR ($CDCl_3$): δ 8.13 (d, 2H), 6.82 (d, 2H), 3.86 (t, 4H), 3.36 (t, 4H); C^3 NMR ($CDCl_3$): δ 154.95, 138.94, 125.84, 112.58, 66.32, 47.08.

Example 9

Preparation of 4-(2-nitrophenyl) morpholine:

A mixture of morpholine (0.9 g, 10.03 mmol) and 1-fluoro-2-nitrobenzene (1.41 g, 10 mmol) is heated at 40°C. The conversion of 4-(2-nitrophenyl)morpholine is complete after

1h. Cold water (10 ml) and diethylether (10 ml) are added into the reaction mixture and the aqueous mixture is made pH 8 by the addition of saturated $NaHCO_3$. The organic phase is separated from the water phase. The product is obtained as a syrup after the removal of the diethylether and gives 2.0 g of the title-compound. Yield: 96%; MS 208 (100, M^+); H^1 NMR ($CDCl_3$): δ 7.77 (dd, 1H), 7.52 (dt, 1H), 7.13 (dd, 1H), 7.07 (dt, 1H), 3.83 (dt, 4H), 3.05 (t, 4H); C^3 NMR ($CDCl_3$): δ 145.77, 143.67, 133.54, 125.86, 122.26, 120.87, 66.82, 52.05.

Example 10

Preparation of 4-(4-morpholinyl) benzoic acid staring from 4-fluorobenzonitrile by the one-pot method using basic hydrolysis:

A mixture of 4-fluorobenzonitrile (5.04 g, 41.6 mmol) and morpholine (9.12 g, 104.6 mmol) is heated at 120°C to achieve a complete conversion of 4-fluorobenzonitrile after 5 hours. Water (100 ml) and NaOH (4.1 g, 10 mmol) are added to the reaction mixture. The whole mixture is kept refluxing for another 5 h, cooled down to room temperature and made acidic by the addition of HCl (5%) with efficient stirring. The precipitate is filtered off, washed with water and dried under vacuum (60°C) to give 8.34 g of the title-compound. Yield: 99%; m.p. 275-277 °C; MS 207 (100, M^+); H^1 NMR (DMSO): 12.33 (b, 1H), 7.78 (d, 2H), 6.95 (d, 2H), 3.72 (t, 2H), 3.23 (t, 2H); δ C^3 NMR ($CDCl_3$): δ 167.25, 153.90, 130.81, 119.91, 113.22, 65.87, 46.97.

Example 11

Preparation of 4-(4-morpholinyl) benzoic acid staring from ethyl 4-fluorobenzoate by the one-pot method using basic hydrolysis:

A mixture of ethyl 4-fluorobenzoate (3.5 g, 21 mmol) and morpholine (6.2 g, 70 mmol) is heated at 130°C to achieve complete conversion of ethyl 4-fluorobenzoate after 12 hours. Water (15 ml) and NaOH (20%, 10 ml) are added to the reaction mixture. The whole mixture is then kept refluxing for another 3.5 hours, cooled down to room temperature and made acidic by the addition of HCl (5%) with efficient stirring. The precipitate is filtered off, washed with water and dried under vacuum (60°C) to give 3.9 g of the title-compound. Yield: 90%, m.p. 275-277 °C; MS 207 (100, M^+); H^1 NMR (DMSO): 12.33 (b, 1H), 7.78

(d, 2H), 6.95 (d, 2H), 3.72 (t, 2H), 3.23 (t, 2H); δ C^3 NMR ($CDCl_3$): δ 167.25, 153.90, 130.81, 119.91, 113.22, 65.87, 46.97.

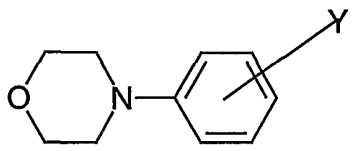
Example 12

Preparation of 4-(4-morpholinyl) benzoic acid staring from 4-fluorobenzonitrile by the one-pot method using acidic hydrolysis:

A mixture of 4-fluorobenzonitrile (1.11 g, 9.17 mmol) and morpholine (0.8 g, 9.19 mmol) is heated at 120°C to achieve a complete conversion of ethyl 4-fluorobenzonitrile after 5 hours. Hydrochloric acid (10 ml, 20 %) is then added into the reaction mixture. The whole mixture is then kept refluxing for another 15 hours, cooled down to room temperature and made pH 2 by the additon of NaOH (10%). The precipitate is filtered off, washed with water and dried under vacuum (60°C) to give 1.5 g of the title-compound. Yield: 80 %, m.p. 275-277 °C; MS 207 (100, M^+); H^1 NMR (DMSO): 12.33 (b, 1H), 7.78 (d, 2H), 6.95 (d, 2H), 3.72 (t, 2H), 3.23 (t, 2H); δ C^3 NMR ($CDCl_3$): δ 167.25, 153.90, 130.81, 119.91, 113.22, 65.87, 46.97.

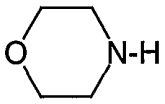
Claims

1. An improved process for synthesizing 4-morpholinylbenzene of the formula I

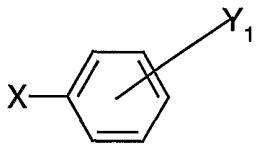


I

by reacting morpholine of formula II with a substituted benzene of formula III,



II



III

wherein

Y and Y_1 are a substituent in 2- or 4- position and

Y is Y_1 or COOH,

Y_1 is CN, NO_2, CF_3, $COOR^1$, COR^1, $CONR^2R^3$

where R^1 is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-3} alkylC_{3-6} cycloalkyl, C_6-C_{10} aryl or a heterocyclic ring containing one or two heteroatoms selected from N, O, S, and said heterocyclic ring may optionally be substituted;

where R^2, R^3 is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-3} alkylC_{3-6} cycloalkyl and C_6-C_{10} aryl or a heterocyclic ring containing one or two heteroatoms selected from N, O, S, and said heterocyclic ring may optionally be substituted, or may together with the nitrogen atom form a heterocyclic ring;

with the provisio that Y_1 is not COOH,

X is a leaving group,

characterized in that the morpholine is used as reactant and the only one solvent, if solvent is present,

and, if necessary, hydrolysis to form a compound wherein Y is COOH.

2. A process according to claim 1, wherein

X is F, Cl, Br, I, or CF_3SO_3.

3. A process according to claim 1, wherein

X is F, and

Y_1 is CN, $CONH_2$, $COOC_2H_5$, or $COCH_3$.

4. A process according to claim 1, wherein

X is F, and

Y_1 is NO_2.

5. A process according to any one of the proceeding claims, wherein the substituent Y and Y_1 is in the 4-position .

6. A process according to any one of the proceeding claims, wherein the molar ratio of the reactant morpholine to substituted benzene ranges preferably in the ranges from 6,7:1 to 1:1, more preferably from 3.5:1 to 1:1.

7. A process according to claims 4 or 6, wherein the molar ratio of the reactant morpholine to substituted benzene is 1: 1.

8. A process according to any one of the proceeding claims performed in absence of an additional base.

9. A process according to any one of the proceeding claims performed in the absence of a catalyst.

10. A process according to any one of the proceeding claims, wherein the process is performed under normal pressure and at a temperature range from 20° C to 130° C.

11. A process according to claim 10 wherein the temperature is about 120° C, when Y_1 is CN, $CONH_2$, $COOC_2H_5$ and $COCH_3$.

12. A process according to any one of claims 4 and 7, wherein the temperature is about 40° C, when Y_1 is NO_2.

13. A process according to claim 1, wherein the said desired 4-morpholinyl benzenes is 4-morpholinyl benzoic acid.

14. A process according to claim 13 using a one-pot method.

15. Use of the process according to any one of claims 1 to 14, for synthesizing morpholinylbenzene of formula I, wherein Y, R^1, R^2 and R^3 are defined as in claim 1.

16. Use of the process according to claim 15 for synthesizing 4-morpholinylbenzene of formula I, wherein Y is COOH.

17. A compound of formula I of claim 1 prepared by the process according to anyone of claim 1-14.

INTERNATIONAL SEARCH REPORT

Inte_____nal application No.
PCT/SE 01/01064

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 295/04
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)

IPC7: C07D

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, WPI-DATA, PAJ, CHEM.ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0805152 A2 (CIBA SPECIALTY CHEMICALS HOLDING INC.), 5 November 1997 (05.11.97)	1-16
X	--	17
A	TETRAHEDRON, Volume 55, No 38, Sept 1999, Andrew J Belfield et al, "Recent Synthetic Advances in the Nucleophilic Amination of Benzenes", page 11399 - page 11428	1-16
X	--	17

[X] Further documents are listed in the continuation of Box C. [X] 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
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 August 2001	28 -08- 2001
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

Inte...ial application No.
PCT/SE 01/01064

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	TETRAHEDRON LETTERS, Volume 40, No 6, February 1999, George R Brownet et al, "High Yields of meta-Substituted Amination Products in the SNAr Substitution of Benzenes", page 1219 - page 1222	1-16
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A	JP 4089459 A (CENTRAL GLASS CO LTD) 1992-03-23 (abstract) World Patent Index (online). London, U.K.: Derwent Publications, Ltd. (retrieved on 2000-12-15). Retrieved from EPO WPI Database. DW199218, Accession no. 1992-147570; & JP 4089459 A (CENTRAL GLASS CO LTD) 1992-03-23 (abstract). (online) (retrieved on 2000-12-15). Retrieved from EPO PAJ Database	1-16
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INTERNATIONAL SEARCH REPORT

Information on patent family members

02/08/01

International application No.
PCT/SE 01/01064

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