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(54) Title: ETHER SYNTHESIS

(57) Abstract: The present invention relates to processes for preparing novel nano-copper catalyst system. The present invention also relates to manufacturing of 4-fluoro-3- phenoxy-benzaldehyde acetal employing novel nano-copper catalyst system.

ETHER SYNTHESIS

FIELD OF THE INVENTION

The present invention relates to ether synthesis.

Particularly, this invention relates to the use of a novel catalyst in the manufacturing of ethers by the Ullmann reaction.

Still particularly, this invention relates to a manufacturing of catalyst which is used in the manufacturing of ethers by the Ullmann reaction.

BACKGROUND OF THE INVENTION

The expression **Ullmann reaction** or **Ullmann coupling** when used in the specification means a reaction which includes copper-catalyzed nucleophilic aromatic substitution between various nucleophiles (e.g. substituted phenoxides) with aryl halides. The most common example includes the Ullmann Ether Synthesis wherein phenol is reacted with an aryl halide to obtain a diaryl ether in the presence of a copper compound. Eg: p-nitrophenol is coupled with bromobenzene in the presence of copper to obtain p-nitrophenyl phenyl ether.

In general, the Ullmann reaction requires the presence of an activated haloaromatic, such as iodobenzene or bromobenzene. Bromine compounds (aryl bromides) are more reactive than the corresponding chlorine compounds. Only in the case where the aryl nucleus contains further determined activating groups the aryl chlorides are said to be sufficiently reactive.

EXISTING KNOWLEGE

U.S Patent 3472782 and U.S Patent 3371120 disclose processes carried out using ullmann reaction in which 1,4-dichlorobenzene is reacted with 3-chlorophenolate at 165°C under CuCl/KI catalysis to give 3,4'-dichlorodiphenyl ether.

European Patent EP0051235 discloses the preparation of diphenyl ethers by Ullmann reaction in which alkali metal phenolates are coupled with halobenzenes in the presence of basic copper carbonate and/or copper salts of lower aliphatic carboxylic acids as catalysts.

US Patent 4288386 discloses a process for the preparation of a diaryl ether by reacting an unactivated halobenzene with an alkali metal phenolate in the presence of a copper catalyst in the presence of tris-(3,6-dioxaoctyl)-amine (ullmann reaction) .

Published French Application No. 7816746 discloses the Ullmann reaction wherein catalyst used is copper powder or oxide, carbonate, chlorides, bromide or sulfate of copper.

WO/1999/038833 discloses the process for the preparation of 4-fluoro-3-phenoxy benzaldehyde, comprising brominating 4-fluoro-benzaldehyde, acetalizing the crude 3-bromo-4-fluorobenzaldehyde without prior isolation thereof, condensing the 3-bromo-4-fluorophenyldioxolane with potassium phenolate, and hydrolyzing the 4-fluoro-3-phenoxyphenyldioxolane to yield 4-fluoro-3-phenoxybenzaldehyde.

German Patent DE2709264 discloses the process for preparation of 4-fluoro-3-phenoxy-benzaldehyde by reacting 4-fluoro-3-phenoxy-benzyl bromide with hexamethylenetetramine and then heating with acids.

It is clear from the aforementioned processes that they do not provide satisfactory results in respect of yield, reaction control and reaction time. Furthermore, these processes are time consuming and also expensive. The catalysts used in these processes have relatively low selectivity towards the final product.

Thus, there is felt a need for a process for preparing a catalyst which accelerates the rate of the Ullmann reaction and reduces the debromination of the starting material and which is selective towards the product. There is also a need for a process for manufacture of substituted benzaldehyde in high yield and purity in a cost-effective manner.

OBJECTS OF THE INVENTION

It is an object of the present invention to provide a process for preparation of a catalyst.

It is another object of the present invention to provide a process for preparation of a catalyst which accelerates rate of the Ullmann reaction.

It is still another object of the present invention to provide a process for preparation of a catalyst which is tunable.

It is yet another object of the present invention to provide a process for preparation of a catalyst which is used in relatively less quantity.

It is a further object of the present invention to provide a process for preparation of a catalyst which ensures better selectivity towards the product.

According to one aspect of the present invention, there is provided a cost-effective and economically feasible process for the preparation of substituted benzaldehyde by Ullmann reaction.

According to yet another aspect of the present invention there is provided a process for the preparation of substituted benzaldehyde in high yield and high purity.

According to yet another aspect of the present invention there is provided a process for the preparation of substituted benzaldehyde wherein the reaction carried out at low temperature conditions.

Still another object of the present invention is to provide a process for the preparation of substituted benzaldehyde which ensures the easy purification and isolation of the product.

SUMMARY OF THE INVENTION

In accordance with the present invention there is provided a process for manufacturing of 4-fluoro-3-phenoxy-benzaldehyde acetal; said process comprises the following steps:

a. adding drop-wise 3-bromo-4-fluoro benzaldehyde acetal to a predetermined quantity of dehydrated potassium phenoxide under continuous stirring at a temperature of about 80°C to obtain a resultant mass;
b. heating the resultant mass in an environment having a temperature in the range of about 120 to 140°C to obtain a resultant mixture;
c. adding nano-copper catalyst system as herein described to the resultant mixture under continuous stirring for a period of about 5 to 6 hours to obtain a reaction product containing 4-fluoro-3-phenoxy-benzaldehyde acetal;

d. washing the reaction product containing 4-fluoro-3-phenoxy-benzaldehyde with water followed by extracting the product with at least one organic solvent selected from a group consisting of toluene and ethyl acetate and filtering to obtain a filtrate; and
e. evaporating the filtrate to yield a 4-fluoro-3-phenoxy-benzaldehyde acetal.

Typically, the step a optionally comprises addition of at least one solvent selected from a group consisting of dimethoxy ethane, toluene and mixture thereof.

Typically, the step a optionally comprises addition of at least one additive selected from a group consisting of cyclodextrine, crown ether, cryptands containing –OH group and cryptands containing -SH group.

Typically, the nano-copper catalyst system is at least one selected from a group consisting of copper (0) particles, copper (I) oxide particles, copper (II) oxide particles and copper (I) halide particles.

Typically, the nano-copper catalyst system is copper (I) halide particles selected from a group consisting of copper (I)chloride , copper (I) bromide particles and copper (I) iodide particles.

Typically, the amount of nano-copper catalyst system used is in the range of about 0.1 to 1% of the mass of the to 3-bromo-4-fluoro benzaldehyde acetal.

Typically, the ratio of potassium phenoxide to 3-bromo-4-fluoro benzaldehyde acetal is in the range of about 1 to 2 moles.

Typically, the ratio of dimethoxy ethane to 3-bromo-4-fluoro benzaldehyde acetal is in the range of about 0 to 20 moles.

Typically, the ratio of toluene to 3-bromo-4-fluoro benzaldehyde acetal is in the range of about 0 to 20 moles.

Typically, the yield of 4-fluoro-3-phenoxy-benzaldehyde acetal having purity greater than 80 % is greater than 90 %.

In accordance with one of the embodiments of the present invention the nano-copper catalyst system is copper (I) oxide particles prepared by:

a. dissolving a copper salt in deionised water by heating at a temperature of about 50 °C to obtain a solution followed by purging the solution with nitrogen gas to remove dissolved oxygen and adding sodium hydroxide solution drop wise to obtain a mixture;
b. adding drop-wise at least one solvent selected from a group consisting of water, methanol and ethanol to the mixture containing copper salt under constant stirring for a period of about 1 hour to obtain a resultant mass;
c. heating the resultant mass at a temperature of about 80°C for a period of about 2 to 6 hours to obtain copper(I) oxide nano-particles ;
d. adsorbing the copper nanoparticles on the surface of the adsorbing material followed by recovering the adsorbed nano copper by filtration ;
e. washing the recovered nano copper with deionised water to obtain a residual nano copper catalyst; and
f. drying the residual catalyst at a temperature of about 250°C to 260°C for a period of about 2 to 3 hours to obtain an activated copper (I) oxide particles based nano- copper catalyst system.

Typically, the adsorbing material is selected from a group consisting of silica, TiO_2, Al_2O_3, MgO, SnO_2, titania and zirconia.

Typically, the ratio of copper salt to adsorbing material is in the range of about 0.1 to 30 % by weight.

In accordance with another embodiment of the present invention the nano-copper catalyst system is copper (I) oxide particles prepared by:

a. dissolving a copper salt in at least one solvent selected from a group consisting of methylene glycol, diethyelene glycol, triethylene glycol and higher homologues thereof, ethoxylated triol based on glycerol and triethylol propane to obtain a mixture;
b. heating the mixture to reflux at a temperature of about 195°C for a period of about one and half hour to obtain reaction mass; and
c. cooling the reaction mass to obtain copper (I) oxide nano particles based nano- copper catalyst system.

In accordance with still another embodiment of the present invention the nano-copper catalyst system is copper (I) halide particles prepared by:

a. dissolving a copper salt in at least one solvent selected from a group consisting of methylene glycol, diethyelene glycol, triethylene glycol and higher homologues therof, ethoxylated triol based on glycerol and triethylol propane to obtain a mixture;
b. heating the mixture to reflux at a temperature of about 195°C for a period of about one and half hour to obtain reaction mass;
c. cooling the reaction mass to obtain copper (I) oxide nano particles and
d. reacting the copper (I) oxide nano particles with hydrogen halide to form a copper (I) halide particles based nano- copper catalyst system.

Typically, the hydrogen halide is at least one selected from a group consisting of hydrogen bromide, hydrogen chloride and hydrogen iodide.

Typically, the copper salt is at least one selected from a group consisting of copper acetate, copper sulphate, copper hydroxide, copper hydroxyl carbonate and copper oxide.

Typically, the particle size of nano copper catalyst is in the range of about 5 nm to 300 nm.

DETAILED DESCRIPTION OF THE INVENTION

4-fluoro-3-phenoxy-benzaldehyde acetal is used as an intermediate product for pesticidally active pyrethroids. The conventional methods for manufacturing of 4-fluoro-3-phenoxy-benzaldehyde suffer from disadvantages which includes use of expensive catalysts, comparatively low yield, purity, high temperature reaction conditions and thus economically not feasible methods.

In accordance with the present invention there is provided a process for manufacturing of 4-fluoro-3-phenoxy-benzaldehyde acetal; said process comprises the following steps:

The first step is drop-wise addition of 3-bromo-4-fluoro benzaldehyde acetal to a predetermined quantity of dehydrated potassium phenoxide under continuous stirring at a temperature of about 80°C to obtain a resultant mass.

The resultant mass is then heated in an environment having a temperature in the range of about 120 to 140°C to obtain a resultant mixture.

The next step is addition of nano-copper catalyst system as herein described to the resultant mixture under continuous stirring for a period of about 5 to 6 hours to obtain a reaction product containing 4-fluoro-3-phenoxy-benzaldehyde acetal.

The obtained reaction product containing 4-fluoro-3-phenoxy-benzaldehyde acetal is then washed with water followed by extracting the product with at least one organic solvent selected from a group consisting of toluene and ethyl acetate and filtering to obtain a filtrate.

The final step after filtration is evaporation of the filtrate to yield a 4-fluoro-3-phenoxy-benzaldehyde acetal.

In accordance with another embodiment of the present invention, the first step comprises drop-wise addition of 3-bromo-4-fluoro benzaldehyde acetal to a mixture containing predetermined quantities of dehydrated potassium phenoxide and at least one solvent selected from a group consisting of dimethoxy ethane, toluene and mixture thereof under continuous stirring at a temperature of about 80°C to obtain a resultant mass.

In accordance with still another embodiment of the present invention, the first step optionally comprises addition of at least one additive selected from a group consisting of cyclodextrine, crown ether, cryptands containing –OH group and cryptands containing -SH group.

The nano-copper catalyst system used for the synthesis of 4-fluoro-3-phenoxy-benzaldehyde acetal in accordance with the present invention is at least one selected from a group consisting of copper (0) particles, copper (I) oxide particles, copper (II) oxide particles and copper (I) halide particles.

In accordance with one of the embodiments the nano-copper catalyst system is copper (I) halide particles selected from a group consisting of copper (I) chloride, copper (I) bromide particles and copper (I) iodide particles.

The amount of nano-copper catalyst system used for the preparation of 4-fluoro-3-phenoxy-benzaldehyde acetal in accordance with the present invention is in the range of about 0.1 to 1% of the mass of the to 3-bromo-4-fluoro benzaldehyde acetal.

The ratio of potassium phenoxide to 3-bromo-4-fluoro benzaldehyde acetal used to prepare 4-fluoro-3-phenoxy-benzaldehyde acetal in accordance with the present invention is in the range of about 1 to 2 moles.

The ratio of dimethoxy ethane to 3-bromo-4-fluoro benzaldehyde acetal used to prepare 4-fluoro-3-phenoxy-benzaldehyde acetal in accordance with the present invention is in the range of about 0 to 20 moles.

The ratio of toluene to 3-bromo-4-fluoro benzaldehyde acetal used to prepare 4-fluoro-3-phenoxy-benzaldehyde acetal in accordance with the present invention is in the range of about 0 to 20 moles.

In accordance with the present invention the yield of 4-fluoro-3-phenoxy-benzaldehyde acetal having purity greater than 80 % is greater than 90 %.

In accordance with one of the embodiments of the present invention the nano-copper catalyst system is copper (I) oxide particles prepared by:

a. dissolving a copper salt in deionised water by heating at a temperature of about 50 °C to obtain a solution followed by purging the solution with nitrogen gas to remove dissolved oxygen and adding sodium hydroxide solution drop wise to obtain a mixture;
b. adding drop-wise at least one solvent selected from a group consisting of water, methanol and ethanol to the mixture containing copper salt under constant stirring for a period of about 1 hour to obtain a resultant mass;

c. heating the resultant mass at a temperature of about 80°C for a period of about 2 to 6 hrs to obtain copper(I) oxide nano-particles ;
d. adsorbing the copper nanoparticles on the surface of the adsorbing material followed by recovering the adsorbed nano copper by filtration ;
e. washing the recovered nano copper with deionised water to obtain a residual nano copper catalyst; and
f. drying the residual catalyst at a temperature of about 250°C to 260°C for a period of about 2 to 3 hours to obtain an activated copper (I) oxide particles based nano- copper catalyst system.

In accordance with the present invention the adsorbing material used to adsorb the copper nano particles is selected from a group consisting of silica, TiO_2, Al_2O_3, MgO, SnO_2, titania and zirconia.

In accordance with the present invention the ratio of copper salt to adsorbing material is in the range of about 0.1 to 30 % by weight.

In accordance with another embodiment of the present invention the nano-copper catalyst system is copper (I) oxide particles prepared by:

a. dissolving a copper salt in at least one solvent selected from a group consisting of methylene glycol, diethyelene glycol, triethylene glycol and higher homologues thereof, ethoxylated triol based on glycerol and triethylol propane to obtain a mixture;
b. heating the mixture to reflux at a temperature of about 195°C for a period of about one and half hour to obtain reaction mass; and
c. cooling the reaction mass to obtain copper (I) oxide nano particles based nano- copper catalyst system.

In accordance with still another embodiment of the present invention the nano-copper catalyst system is copper (I) halide particles prepared by:

a. dissolving a copper salt in at least one solvent selected from a group consisting of methylene glycol, diethyelene glycol, triethylene glycol and higher homologues therof, ethoxylated triol based on glycerol and triethylol propane to obtain a mixture;
b. heating the mixture to reflux at a temperature of about 195°C for a period of about one and half hour to obtain reaction mass;
c. cooling the reaction mass to obtain copper (I) oxide nano particles and
d. reacting the copper (I) oxide nano particles with hydrogen halide to form a copper (I) halide particles based nano- copper catalyst system.

In accordance with the present invention, the hydrogen halide used to prepare copper (I) halide particles based nano- copper catalyst system is at least one selected from a group consisting of hydrogen bromide, hydrogen chloride and hydrogen iodide.

In accordance with the present invention the copper salt used to prepare nano- copper catalyst system of the present invention is at least one selected from a group consisting of copper acetate, copper sulphate, copper hydroxide, copper hydroxyl carbonate and copper oxide.

The particle size of nano copper catalyst prepared in accordance with the present invention is in the range of about 5 nm to 300 nm.

The invention will now be described with respect to the following examples which do not limit the invention in any way and only exemplify the invention.

Example 1:

Preparation of nano copper (I) oxide catalyst:

Methylene glycol (1.0 mol) was taken into a round bottom flask at a room temperature and nitrogen was purged to remove the dissolved oxygen. To this 0.038 mol of copper

acetate was added and the mixture was heated to reflux at 195°C for one and half hour. Then the mixture was allowed to cool to room temperature. The copper (I) oxide nano particle thus obtained was used as master batch for phenoxylation reactions. The particle size of the nano particles was in the range 5 nm-300 nm with a mean size of 70-80 nm.

Example 2:

Preparation of nano copper(II) oxide coated on Silica

Copper (II) acetate (0.3147g, 0.0015 moles) was taken into 100 ml round bottom flask at a room temperature. To this water (10g) was added at a room temperature. Then the temperature of the solution was raised to 50°C in order to dissolve copper acetate. To this solution sodium hydroxide solution (prepared by dissolving 0.1371g 0.00342 moles of NaOH in 2.9g of water) was added drop wise over a period of one hour during which the colour of the solution began to change to dark brown. Then the solution was heated to 80°C and maintained for 3 hrs. Then silica (based on 1 wt%, 2wt%, 5wt% and 10wt% of CuO) was added and stirred for 2 hrs at 80°C. These copper nano particles were then got adsorbed on the surface of Slica gel. The nano copper coated on Silica was recovered by filtration followed by the washing with deionised water (3 x100 ml) which resulted into residue of catalyst. The residue was activated by drying at 250 °C for 2-3 h. The activated catalyst was used for phenoxylation reaction. Particle size of the CuO obtained were in the range 5 nm - 40 nm with a mean diameter at 15 nm (measured by TEM.)

Example 3:

Preparation of nano copper (II) oxide coated on Titanium oxide

Copper acetate (0.3147g 0.0015 moles) was taken into 100 ml round bottom flask at a room temperature. To this 10 gm of water was added to obtain a mixture. Then this mixture was heated to attain 50°C and the temperature was maintained for 30 min. in

order to dissolve copper acetate. To this solution, sodium hydroxide solution prepared in water (0.1371g 0.00342 moles NaOH in 2.9g H_2O) was added drop wise over a period of an hour during which colour of the solution started changing to black. After complete addition of sodium hydroxide, the mixture was heated at 80°C under continuous stirring and kept for 3 hours. Then TiO_2 (based on 5 wt% or 10 wt% CuO) was added and the mixture was stirred for 2 hrs. These copper nano particles were adsorbed on the surface of TiO_2. The nano copper coated on TiO_2 was recovered by filtration followed by washing with de-ionised water (3x100 ml) to obtain residue of catalyst. The residue was then activated by drying at 250-260°C for 2-3 hours for. The activated catalyst was used for the further phenoxylation reaction.

Example 4:

Preparation of nano copper (0) coated on Slica

0.1 M solution of CuSO4 was prepared by dissolving (2.49g) in 100 ml of deionised water and nitrogen was purged to remove the dissolved oxygen. 100 ml 0.5 M sodium citrate was added to it and allowed to stir for 30 minutes under the nitrogen atmosphere. To this 10 ml of 0.1 M aqueous solution of sodium borohydride was added drop wise under constant stirring in N_2 atmosphere. The colour of the solution change to dark brown on complete addition of reducing agent indicated the formation of citrate protected copper nanoparticles. These copper nano particles were adsorbed on the surface by adding Silica gel. The suspension was stirred at 80 °C 2 hours. The nano copper coated Silica was recovered by filtration followed by the washing with deionised water (3×100 ml) to obtain residual catalyst. The residual solid catalyst was activated by dried at 250-260 °C for 2-3 hours. The activated catalyst was used for the further phenoxylation reaction.

Example 5:

Preparation of nano copper(II) oxide particles

Copper acetate (0.3147g 0.0015 moles) was taken into the 100 ml round bottom flask at a room temperature. To this water (10g) was added at a room temperature. The mixture was then heated to 50 °C with stirring and kept for 30 min. in order to dissolve the copper acetate. To this mixture sodium hydroxide solution (0.1371g 0.00342 moles NaOH in 2.9g H2O) was added drop wise over a period of an hour. After addition of NaOH solution, the mixture was heated at 80°C for 5 hours during which black CuO nano particles are formed. Then water was removed from reaction mass on evaporator to get black solids.

Example 6:

Preparation of nano Copper (I)oxide particles

Step-1: Preparation of Cupric Hydroxide [Cu (OH) $_2$]

5 gm of Copper (II) Chloride (37.1 mmol) was dissolved in 10.0mL of water to get clear blue solution. To this 14.0mL of 4M NaOH solution was added to give thick viscous blue colour precipitate. The reaction mass was then filtered and vacuum dried till constant weight is obtained. Solid Cupric hydroxide formed was further used for preparation of copper oxide.

Step 2: Preparation of nano copper oxide catalyst from cupric hydroxide

Cupric hydroxide (3.8g, 38.9mmol, 1.0 Mol Eq) was added to mono ethylene glycol (64.22g, 1.03 mol, 36.6 Mol Eq.) in 250 mL round bottom flask under N_2 atmosphere and heated to reflux at 195°C for 1.5 hours. During the reaction the colour began to change from bluish green to yellowish green in suspension form. The heating was then stopped and the mixture was allowed to cool to room temperature. The copper (I) oxide nano particle formed was used directly for further phenoxylation reaction.

Example 7:

Preparation of nano Copper (I) chloride from Cu_2O

Copper Oxide (I) in mono ethylene glycol (63.78 g) was transferred to the three necked 250 ml round bottom flask having one end connected with glass inlet for purging dry HCl gas at a room temperature.

Sodium chloride powder (20.0g, 1.0 mol eq) was transferred to 100 mL three necked flask to which H_2SO_4 98% (34.2g, 1.0 Mol Eq.) was added drop wise to generate HCl gas.

The gas generated was passed through the mixture containg Cu_2O and methylene glycol for 30 min. After completion of reaction (which is indicated by formation of white material), N_2 gas was purged through the reaction mass to remove trapped HCl. The suspension as such was used for the phenoxylation reaction.

Example 8:

Preparation of nano Copper (I) bromide:

Copper Oxide (I) in mono ethylene glycol (63.78g) was taken into the three necked 250 ml round bottom flask having one end connected with glass inlet for purging Dry HBr gas at a room temperature.

Potassium bromide powder (25.0g, 1.0 mol eq) was taken in 100 mL three necked flask to which H_2SO_4 (20.58g, 1.0 Mol Eq.) was added drop wise to generate HBr gas. The gas generated was passed through methylene glycol containing Cu2O suspension for 30 min. Change in colour from yellowish green to whitish green (in suspension form) was observed. After completion of the reaction, N_2 gas was purged through reaction mass to remove trapped HBr.

Example 9:

Preparation of nano Copper (I) iodide

Copper Oxide (I) in mono ethylene glycol (50.0 g) was taken into the three necked

100 ml round bottom flask at a room temperature and under N_2 atmosphere. To this 57% HI (2.65g) was added drop wise till the colour changes from yellow to pale bluish green (in suspension form) was observed. After completion of the reaction, N_2 gas was purged through reaction mass to remove trapped HI.

Example 10:

Preparation of 3-phenoxy 4-fluoro benzaldehyde Acetal from 3-bromo-4-fluorobenzaldehyde acetal

To the mixture containing dehydrated potassium phenoxide (20g, 0.1515 mol) and dimethoxy ethane (5g ,0.055mol), 3-bromo 4-fluoro benzaldehyde acetal(30g, 0.1209 moles) was added drop wise at 80^0C. Then the mixture was heated to 125 to 140 °C. To this heated mixture 0.9g of nano CuO coated SiO_2 was added and the mixture was stirred for 5-6 hours to complete the conversion of starting material. The progress of the reaction was monitored by GC at every hour. The GC sample was prepared by extracting the sample with a toluene/ ethyl acetate mixture. The inorganics were separated by water wash and the isolated organic phase was evaporated to get syrupy liquid showing 90% conversion with >80% selectivity.

Example 11:

Preparation of 3-phenoxy 4-fluoro benzaldehyde Acetal

To the mixture containing dehydrated potassium phenoxide (20g, 0.1515 mol) and toluene (5g ,0.0543mol), 3-bromo 4-fluoro benzaldehyde acetal (30g, 0.1209 moles) was added drop wise. Then the mixture was heated to 80°C. The mixture was further heated to attain 125 to 140°C. To this heated mixture 0.9 g of nano CuO coated SiO_2 was added. The resulting mixture was heated with continuous stirring for 5-6 hours to complete the conversion of starting material. The reaction was monitored by GC at every hour by taking a sample. After completion of the reaction, the product was washed with water and extracted by a toluene/ ethyl acetate mixture. The filtrate was

then evaporated to yield the product as syrupy liquid containing 90% product with the selectivity of 78%

Example 12:

To the mixture containing dehydrated potassium phenoxide (20g, 0.1515 mol) and toluene (5g ,0.0543mol), 3-bromo 4-fluoro benzaldehyde acetal (30g, 0.1209 moles) was added drop wise at 80°C. The resulting mixture was heated to 125 to 140 °C. To this 0.9g of nano copper coated TiO_2 was added with stirring. After completion of addition, the mixture was stirred for 5-6 hours by maintaining the same temperature. The reaction was monitored by GC at time intervals of one hour. After completion of the reaction the mixture was cooled to room temperature and washed with water. The organic layer was extracted with toluene/ethyl acetate mixture and evaporated to get syrupy liquid showing 80% product in the crude by GC area %.

Example 13:

To the mixture containing dehydrated potassium phenoxide (20g, 0.1515 mol) and toluene (5g ,0.0543mol), 3-bromo 4-fluoro benzaldehyde acetal (30g, 0.1209 moles) was added drop wise at 80°C. The resulting mixture was heated to 125 to 140 °C. To this 0.3 mole % of nano Cu_2O with respect to acetal was added. The resulting mixture was stirred for 5-6 hr to complete the conversion of starting material. The reaction was monitored by GC analysis of the sample at every hour. After completion of the reaction, the product was washed with water and extracted with a mixture of toluene/ ethyl acetate (50 ml). The isolated organic phase was evaporated to get syrupy liquid showing 99% conversion of the starting material and >82% selectivity.

Example 14:

To the mixture containing dehydrated potassium phenoxide (20g, 0.1515 mol) and dimethoxy ethane (5g ,0.055mol), 3-bromo 4-fluoro benzaldehyde acetal (30g, 0.1209 moles) was added drop wise at 80°C. The resulting mixture was heated to 125

to 140 °C Then 0.3 mole% of nano Cu_2O was added and the suspension was stirred for 5-6 hours to complete the conversion of starting material. Reaction was monitored by GC at time intervals of one hour. The reaction mixture was then cooled to room temperature and washed with water. The organic layer was extracted with a toluene/ ethyl acetate mixture (50 ml). The organic layer containing the product was evaporated to get syrupy liquid showing complete conversion of starting material. The GC area% shows >85% selectivity of the product.

Example 15:

To the mixture containing dehydrated potassium phenoxide (20g, 0.1515 mol) and toluene (5g ,0.0543mol), 3-bromo 4-fluoro benzaldehyde acetal (30g, 0.1209 moles) was added drop wise at 80°C. The resulting mixture was heated to 125 to 140 °C. To this 0.9 g of nano Cu_2O was added and the heating was continued for 5-6 hours to complete the conversion of startingmaterial. The reaction was monitored by GC at time intervals of one hour. After completion of the reaction the product was cooled to room temperature and washed with water. The organic layer was extracted with toluene/ ethyl acetate(50 ml) and then evaporated to get brown liquid. The GC area % of the crude shows >98% conversion and 81% selectivity.

Example 16:

To the mixture containing dehydrated potassium phenoxide (20g, 0.1515 mol) and toluene (5g ,0.0543mol), 3-bromo 4-fluoro benzaldehyde acetal (30g, 0.1209 moles) was added drop wise. The resulting mixture was heated to 125 to 140 °C. To the resulting mixture 0.3 wt % of nano Cu_2O with respect to starting material was added with stirring and the mixture was kept for 5-6 hr to complete the conversion of starting material. The reaction was monitored by GC at time interval of one hour. After

completion of the reaction, the crude was cooled to room temperature and washed with water. The product was extracted by adding a mixture of toluene/ ethyl acetate (50 ml) and evaporated to get brown liquid. The GC area% showed >99% conversion and >84% product selectivity.

Example 17:

To the mixture containing dehydrated potassium phenoxide 33.33g (0.2525mol) and toluene 16.3g (0.1771mol), 3-bromo 4-fluoro benzaldehyde acetal (50g, 0.2016 mol.) was added drop wise. The resulting mixture was heated to 125 to 140 °C. To the resulting mixture 0.3wt% of nano CuCl with respect to starting material was added and the suspension was stirred for 5-6 hr to complete the conversion of starting material. The reaction was monitored by GC at time intervals of one hour. After completion of the reaction, the reaction mass was cooled to room temperature. The mixture was then washed with water and the product was extracted with a mixture of toluene/ ethyl acetate (50 ml). The organic layer was evaporated to get brown liquid showing 98% conversion and 77% selectivity.

Example 18:

To the mixture containing dehydrated potassium phenoxide 33.33g (0.2525mol) and toluene 16.3g (0.1771mol), 3-bromo 4-fluoro benzaldehyde acetal (50g, 0.2016 mol.) was added drop wise. The resulting mixture was heated to 125 to 140 °C. Under this condition 0.3 wt% of nano CuI was added and the suspension was stirred for 5-6 hr to complete the conversion of starting molecule. The reaction was monitored by GC at time intervals of one hour. After completion of the reaction the reaction mixture was cooled to room temperature. The product was then washed with water and extracted with a mixture of toluene/ ethyl acetate, 50 ml. The organic layer thus obtained was evaporated to get brown liquid. The GC result shows 99% conversion and 82% selectivity.

Example 19:

To the mixture containing dehydrated potassium phenoxide 33.33g (0.2525mol) and dimethoxy ethane 16.3g (0.1881mol), 3-bromo 4-fluoro benzaldehyde acetal (50g, 0.2016 mol.) was added drop wise. The resulting mixture was heated to 125 to 140 °C. To this 0.3% of nano CuCI was added with continuous stirring. The suspension was then heated for 5-6 hr to complete the conversion of starting molecule. The reaction was monitored by GC at time intervals of one hour. After completion of the reaction the reaction mixture was cooled to room temperature. The crude thus obtained was washed with water and extracted with a mixture of toluene/ ethyl acetate (50 ml). The final organic layer was separated and evaporated to get brown liquid. GC results show the conversion of 99% and the selectivity of the product > 84% based on area %.

Technical Advancement:

The uniqueness of the present invention lies in the use of novel nano copper coated Cu (I/II) oxide in Ullmann reactions. Furthermore, the process in accordance with the invention provides synthesis of 4-fluoro-3-phenoxy-benzaldehyde using novel nano copper coated Cu (I/II) oxide in high yield, purity and better selectivity.

While considerable emphasis has been placed herein on the specific steps of the preferred process, it will be appreciated that many steps can be made and that many changes can be made in the preferred steps without departing from the principles of the invention. These and other changes in the preferred steps of the invention will be apparent to those skilled in the art from the disclosure herein, whereby it is to be distinctly understood that the foregoing descriptive matter is to be interpreted merely as illustrative of the invention and not as a limitation.

Claims:

1. A process for manufacturing of 4-fluoro-3-phenoxy-benzaldehyde acetal; said process comprises the following steps:
    a. adding drop-wise 3-bromo-4-fluoro benzaldehyde acetal to a predetermined quantity of dehydrated potassium phenoxide under continuous stirring at a temperature of about 80°C to obtain a resultant mass;
    b. heating the resultant mass in an environment having a temperature in the range of about 120 to 140°C to obtain a resultant mixture;
    c. adding nano-copper catalyst system as herein described to the resultant mixture under continuous stirring for a period of about 5 to 6 hours to obtain a reaction product containing 4-fluoro-3-phenoxy-benzaldehyde acetal;
    d. washing the reaction product containing 4-fluoro-3-phenoxy-benzaldehyde with water followed by extracting the product with at least one organic solvent selected from a group consisting of toluene and ethyl acetate and filtering to obtain a filtrate; and
    e. evaporating the filtrate to yield a 4-fluoro-3-phenoxy-benzaldehyde acetal.

2. The process as claimed in claim 1, wherein the step a optionally comprises addition of at least one solvent selected from a group consisting of dimethoxy ethane, toluene and mixture thereof.

3. The process as claimed in claim 1, wherein the step a optionally comprises addition of at least one additive selected from a group consisting of cyclodextrine, crown ether, cryptands containing –OH group and cryptands containing -SH group.

4. The process as claimed in claim 1, wherein the nano-copper catalyst system is at least one selected from a group consisting of copper (0) particles, copper (I) oxide particles, copper (II) oxide particles and copper (I) halide particles.

5. The process as claimed in claim 4, wherein the nano-copper catalyst system is copper (I) halide particles selected from a group consisting of copper (I)chloride , copper (I) bromide particles and copper (I) iodide particles.

6. The process as claimed in claim 1, wherein the amount of nano-copper catalyst system used is in the range of about 0.1 to 1% of the mass of the to 3-bromo-4-fluoro benzaldehyde acetal.

7. The process as claimed in claim 1, wherein the ratio of potassium phenoxide to 3-bromo-4-fluoro benzaldehyde acetal is in the range of about 1 to 2 moles.

8. The process as claimed in any of the preceding claims, wherein the ratio of dimethoxy ethane to 3-bromo-4-fluoro benzaldehyde acetal is in the range of about 0 to 20 moles.

9. The process as claimed in any of the preceding claims, wherein the ratio of toluene to 3-bromo-4-fluoro benzaldehyde acetal is in the range of about 0 to 20 moles.

10. The process as claimed in claim 1, wherein the yield of 4-fluoro-3-phenoxy-benzaldehyde acetal having purity greater than 80 % is greater than 90 %.

11. The process as claimed in claim 1 and 4, wherein the nano-copper catalyst system is copper (I) oxide particles prepared by:

a. dissolving a copper salt in deionised water by heating at a temperature of about 50 °C to obtain a solution followed by purging the solution with nitrogen gas to remove dissolved oxygen and adding sodium hydroxide solution drop wise to obtain a mixture;
b. adding drop-wise at least one solvent selected from a group consisting of water, methanol and ethanol to the mixture containing copper salt under constant stirring for a period of about 1 hour to obtain a resultant mass;
c. heating the resultant mass at a temperature of about 80°C for a period of about 2 to 6 hours to obtain copper(I) oxide nano-particles ;
d. adsorbing the copper nanoparticles on the surface of the adsorbing material followed by recovering the adsorbed nano copper by filtration ;
e. washing the recovered nano copper with deionised water to obtain a residual nano copper catalyst; and
f. drying the residual catalyst at a temperature of about 250°C to 260°C for a period of about 2 to 3 hours to obtain an activated copper (I) oxide particles based nano- copper catalyst system.

12. The process as claimed in claim 1 and 4, wherein the nano-copper catalyst system is copper (I) oxide particles prepared by:
a. dissolving a copper salt in at least one solvent selected from a group consisting of methylene glycol, diethyelene glycol, triethylene glycol and higher homologues thereof, ethoxylated triol based on glycerol and triethylol propane to obtain a mixture;
b. heating the mixture to reflux at a temperature of about 195°C for a period of about one and half hour to obtain reaction mass; and
c. cooling the reaction mass to obtain copper (I) oxide nano particles based nano- copper catalyst system.

13. The process as claimed in claim 1 and 4, wherein the nano-copper catalyst system is copper (I) halide particles prepared by:
    a. dissolving a copper salt in at least one solvent selected from a group consisting of methylene glycol, diethyelene glycol, triethylene glycol and higher homologues therof, ethoxylated triol based on glycerol and triethylol propane to obtain a mixture;
    b. heating the mixture to reflux at a temperature of about 195°C for a period of about one and half hour to obtain a reaction mass;
    c. cooling the reaction mass to obtain copper (I) oxide nano particles; and
    d. reacting the copper (I) oxide nano particles with hydrogen halide to form a copper (I) halide particles based nano- copper catalyst system.

14. The process as claimed in claim 13, wherein the hydrogen halide is at least one selected from a group consisting of hydrogen bromide, hydrogen chloride, and hydrogen iodide.

15. The process as claimed in claim 11, 12 and 13, wherein the copper salt is at least one selected from a group consisting of copper acetate, copper sulphate, copper hydroxide, copper hydroxyl carbonate and copper oxide.

16. The process as claimed in claim 11, wherein the adsorbing material is selected from a group consisting of silica, TiO_2, Al_2O_3, MgO, SnO_2, titania and zirconia.

17. The process as claimed in claim 11, wherein the ratio of copper salt to adsorbing material is in the range of about 0.1 to 30 % by weight.

18. The process as claimed in any of the preceding claims, wherein the particle size of nano copper catalyst is in the range of about 5 nm to 300 nm.