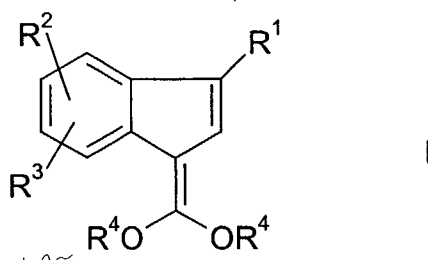


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IMPROVED PROCESS FOR THE PREPARATION OF 1,3-SUBSTITUTED INDENES**Background of the Invention**

The present invention relates to an improved process for the preparation of 1,3-substituted indenenes of the formula



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wherein R^1 , R^2 , R^3 and R^4 are as defined below.

Compounds of formula I are useful intermediates in the preparation of certain aryl fused azapolycyclic compounds which exhibit activity as agents for the treatment of neurological and psychological disorders.

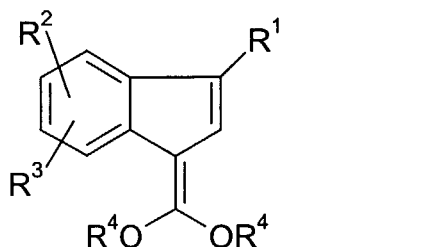
10 United States Patent Application Serial No. 09/514002 filed February 25, 2000 discloses the preparation of 3-aminomethyl-indan-1-carboxylic acid methyl ester and the use of that compound as an intermediate in the synthesis of certain aryl fused azapolycyclic compounds.

15 United States Patent Application Serial No. 10/124,135 filed April 04, 2002 discloses the preparation of aryl-fused azapolycyclic compounds from intermediates having the formula I.

20 The synthesis, composition, and methods of use of certain aryl fused azapolycyclic compounds which exhibit activity as agents for the treatment of neurological and psychological disorders is disclosed in United States Patent No. 6,410,550 B1. The foregoing patent applications and patent are incorporated by reference herein in their entirety.

Summary of the Invention

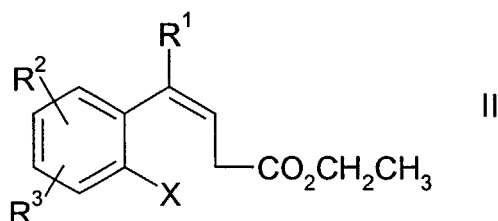
The present invention provides an improved process for preparing a compound of the formula



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by conducting a solvent-free reaction between a compound of the formula

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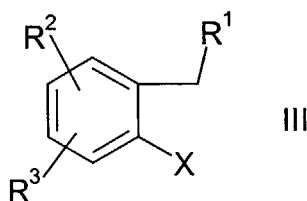


and an alcohol in the presence of sulfuric acid. The alcohol is a monohydric alcohol of the formula R^4OH or a dihydric alcohol selected from the group consisting of ethylene glycol, 1,3 propylene glycol, and 1,2 propylene glycol.

- 5 In a preferred embodiment, the alcohol is a dihydric alcohol. Preferably the dihydric alcohol is ethylene glycol.

As used herein, the term, solvent-free, refers to the complete absence of an inert organic solvent.

Compounds having the formula II are prepared by reacting a compound of formula



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with ethyl 3-ethoxyacrylate in an inert water miscible organic solvent. The reaction is catalyzed by a mixture of palladium II acetate, tricyclohexylphosphine, and a base. Upon completion of the reaction, the inert water miscible organic solvent is completely removed. In a preferred embodiment the solvent is removed by distillation.

- 15 With reference to compounds of the formulas I, II, and III above, R^1 is an electron withdrawing group selected from the group consisting of cyano, alkoxy carbonyl, alkylcarbonyl, arylcarbonyl, aryl, trifluoromethyl, and sulfonyl. R^2 and R^3 are selected independently from hydrogen, C_1 to C_5 alkyl, C_1 to C_5 alkoxy, trifluoromethyl, halogen, sulfonyl, alkyl, alkylamino, amide, ester, aryl-alkyl, hetero-alkyl and aryl-alkoxy. Also, R^2 and R^3 together with the carbon atoms to which they are attached can form a monocyclic or bicyclic ring. R^4 is C_1 to C_6 alkyl or two R^4 groups together form a C_2 to C_3 alkylene bridge.
- 20

- In the preparation of compounds having the formula II, the preferred catalyst is comprised of a mixture of palladium II acetate and tricyclohexylphosphine. Suitable bases are alkoxides of Group I metals. Preferably the base is sodium t-butoxide. Suitable inert water miscible organic solvents are tetrahydrofuran, 2-methyltetrahydrofuran, and 1,2-dimethoxyethane.
- 25

Preferably the solvent is tetrahydrofuran.

After complete removal of the organic solvent, the reaction mixture containing the compound of formula II is added to the alcohol. It was surprising and unexpected to find that

prior removal of the organic solvent from the reaction mixture led to a significant improvement in the yield of the compounds of formula I. In a typical example the yield improved from about 55% to about 96%.

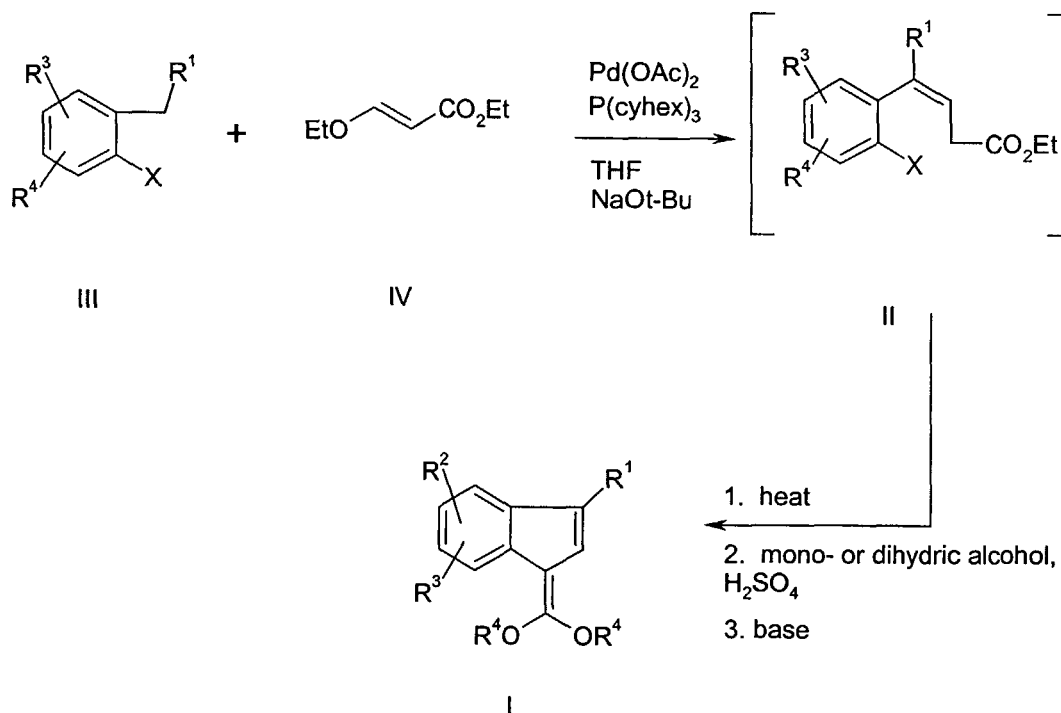
The reaction products having formula I are treated with a suitable base and water to neutralize residual sulfuric acid. Preferably the base is ammonium hydroxide.

In a preferred embodiment, the compound of formula I is 3-[1,3] dioxolan-2-ylidene-3H-indene-1-carbonitrile.

Detailed Description of the Invention

The present invention is an improved process for producing compounds of formula I according to the reaction sequence illustrated in Scheme I.

Scheme I



Compound II is produced by the addition reaction of the compound of formula III to the unsaturated ethyl 3-ethoxy acrylate (IV) in the presence of tricyclohexylphosphine, palladium II acetate and a base in an inert water miscible organic solvent, preferably tetrahydrofuran (THF). The reaction proceeds at a temperature between about 58°C to about 62°C, preferably at 60°C. The reaction is carried out for a period of time of about 3 to about 4 hours; preferably about 3.5 hours.

Compounds of formula II are cyclized and converted into the acetal (I) by reaction with an alcohol and sulfuric acid. Generally a compound of formula II is not isolated prior to conversion into compound I. In a preferred embodiment, compound II is added, without prior

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isolation, to the alcohol followed by the addition of sulfuric acid. The reaction is conducted at about 35°C to about 45°C; preferably at about 40°C, for a period of time of about 6 hours to about 8 hours, preferably about 7 hours.

5 The process improvement disclosed herein relates to the inert water miscible solvent employed in the reaction leading to compounds having formula II; and, specifically, to removal of the solvent upon completion of the reaction.

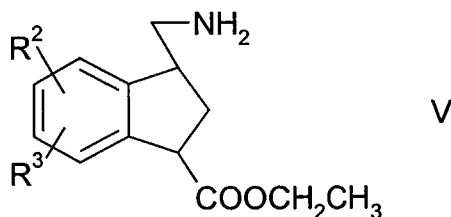
When the reaction of compounds of formula II with a monohydric or dihydric alcohol was carried out in the presence of the water miscible organic solvent, the physical state of the reaction mixture became extremely difficult to handle and a substantial quantity of product
10 was lost. Specifically, a large amount of foam was generated due possibly to in situ formation of a surfactant. Furthermore, the product was in a gelatinous state making separation by filtration impractical.

Removal of the inert water miscible solvent prior to the reaction of compounds of formula II with the alcohol eliminated these problems. Solvent removal was a critical step in
15 obtaining product yields of compounds of formula I of at least 90%.

In a preferred embodiment the THF solvent was removed by distillation prior to the addition of compound II to the alcohol. In a preferred embodiment, the alcohol is a dihydric alcohol; and, most preferably the dihydric alcohol is ethylene glycol.

In a preferred embodiment of the present invention, R¹ is a nitrile group.

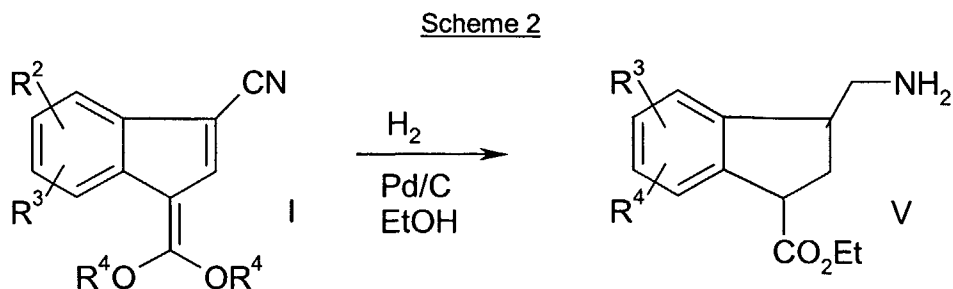
20 Compounds of formula I wherein R¹ is nitrile are useful in the preparation of compounds having the formula



As disclosed in United States Patent Application Serial No. 09/514,002, filed February 25, 2000, compounds of formula V are useful intermediates in the synthesis of certain aryl fused
25 azapolycyclic compounds exhibiting activities in the treatment of neurological and psychological disorders.

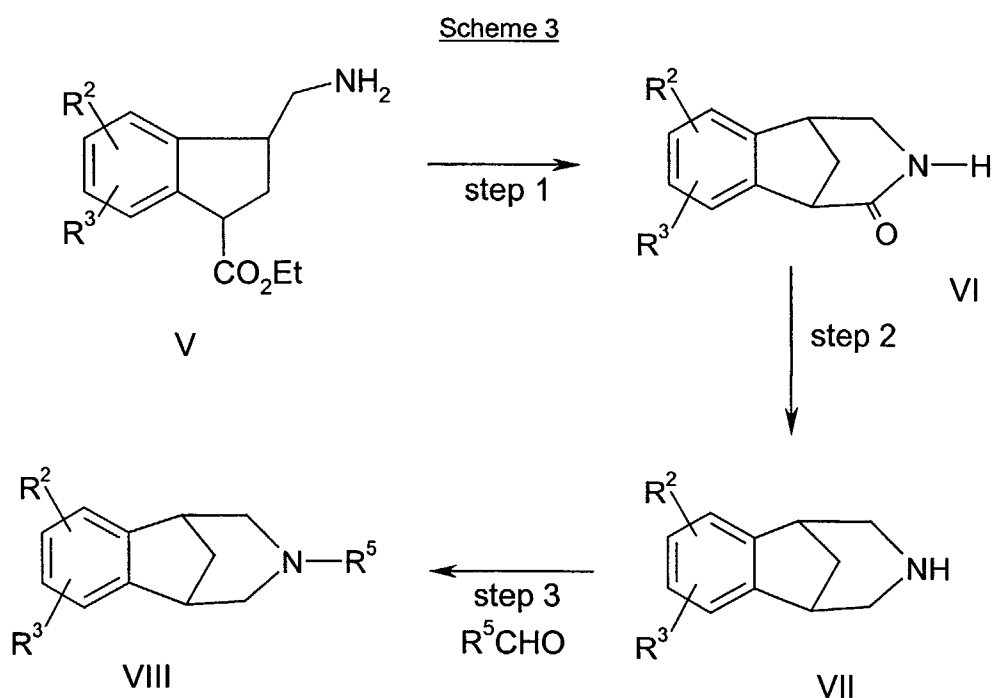
Scheme 2 illustrates the conversion of selected nitrile compounds of formula I into compounds of formula V

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The conversion of compounds of formula V into the aryl fused azapolycyclic compounds of formula is illustrated in Scheme 3.

5



R^5 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, unconjugated $\text{C}_3\text{-C}_6$ alkenyl, benzyl or alkoxy $\text{C}_1\text{-C}_6$.

In step 1 the amine-ester compound of formula V is cyclized with sodium t-butoxide in ethanol to form the nitrogen ring compound of formula VI. The carbonyl function is reduced with sodium borohydride-borontrifluoride giving the aryl fused azapolycyclic compound of formula VII.

15

Examples of specific compounds of the formula VII are the following compounds:

4-ethynyl-5-chloro-10-aza-tricyclo[6.3.0^{2,7}]dodeca-2(7),3,5-triene;

3-trifluoromethyl-10-aza-tricyclo[6.3.0^{2,7}]dodeca-2(7),3,5-triene;

4,5-bistrifluoromethyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene;

4-choro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene;

4-amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene;

4-nitro-10-aza-tricyclo[6.3.0^{2,7}]dodeca-2(7),3,5-triene;

4-methyl-10-aza-tricyclo[6.3.0^{2,7}]dodeca-2(7),3,5-triene;

4-fluoro-10-aza-tricyclo[6.3.0^{2.7}]dodeca-2(7),3,5-triene;

4-trifluoromethyl-10-aza-tricyclo[6.3.0^{2.7}]dodeca-2(7),3,5-triene;

4,5-difluoro-10-aza-tricyclo[6.3.0^{2.7}]dodeca-2(7),3,5-triene;

Compounds of formula VIII bind to neuronal nicotinic acetylcholine specific receptor sites
5 and are useful in modulating cholinergic function. Such compounds are useful in the treatment of
inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma
gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain,
acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar
disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive
10 dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid
hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical
dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco
products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, migraine,
stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis,
15 Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct
dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, senile
dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity
disorder (ADHD) and Tourette's Syndrome.

The compounds of formula VII and their nitrogen substituted derivatives of formula
20 VIII, and their pharmaceutically acceptable salts (hereafter "the active compounds") can be
administered via either the oral, transdermal (e.g., through the use of a patch), intranasal,
sublingual, rectal, parenteral or topical routes. Transdermal and oral administration are
preferred. These compounds are, most desirably, administered in dosages ranging from about
0.01 mg up to about 1500 mg per day, preferably from about 0.1 to about 300 mg per day in
25 single or divided doses, although variations will necessarily occur depending upon the weight
and condition of the subject being treated and the particular route of administration chosen.
However, a dosage level that is in the range of about 0.001 mg to about 10 mg per kg of body
weight per day is most desirably employed. Variations may nevertheless occur depending upon
the weight and condition of the persons being treated and their individual responses to said
30 medicament, as well as on the type of pharmaceutical formulation chosen and the time period
and interval during which such administration is carried out. In some instances, dosage levels
below the lower limit of the aforesaid range may be more than adequate, while in other cases still
larger doses may be employed without causing any harmful side effects, provided that such
larger doses are first divided into several small doses for administration throughout the day.

35 The active compounds can be administered alone or in combination with
pharmaceutically acceptable carriers or diluents by any of the several routes previously indicated.
More particularly, the active compounds can be administered in a wide variety of different dosage

forms, e.g., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, transdermal patches, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents. In addition, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compounds are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets may contain a variety of excipients, disintegrants, lubricating agents, and fillers.

Aqueous suspensions for oral administration may be embodied with flavor, coloring matter, and diluent.

For parenteral administration, a solution of the active compound may be suitably buffered and may be diluted with a vegetable oil or propylene glycol.

The following example is provided for the purpose of further illustration and is not intended to limit the scope of the claimed invention.

Example

3-[1,3]Dioxolan-2-ylidene-3H-indene-1-carbonitrile

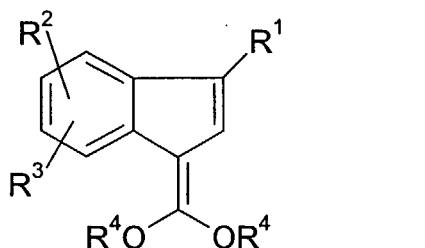
Ethyl 3-ethoxyacrylate (36.9 kg, 255.0 moles), 2-bromophenyl acetonitrile (50 kg, 255.1 moles), and tetrahydrofuran (57 L) were combined in reactor 1 and the resultant solution was stirred at 25°C until needed (4 hours.). Palladium II acetate (1.3 kg, 5.7 moles), tricyclohexylphosphine (1.9 kg, 6.7 moles), and tetrahydrofuran (148 L) were combined in reactor 2 and the resultant mixture was stirred for 30 minutes at 25°C. The mixture was then cooled to 5°C and sodium t-butoxide (61.3 kg, 637.7 moles) was added to reactor 2 at 5°C. The resulting mixture was warmed to 15°C and stirred for 15 minutes and then cooled back to 5°C. The contents in reactor 1 were then slowly charged to reactor 2 over 2 hours. at 10°C and then the contents in reactor 2 were stirred for 15 minutes at 10°C. Reactor 2 was then slowly heated to 60°C at a rate of 8 to 2°C per hour (5 hours.) and then held at 60°C for 4 hours. The reaction was then cooled to 5°C and ethylene glycol was added at 5°C. The Tetrahydrofuran in the reaction was then distilled off. The reaction was again cooled to 10°C and sulfuric acid (88.4 kg) added over 1.5 hours at 10°C. The reaction was heated to 40°C at a rate of 8 to 12°C per hour (3 hours) and held at 40°C for 8 hours. The reaction was cooled to 10°C and ammonium hydroxide (44.8 kg) and water (201 L) were added. The slurry was warmed to 20°C and granulated for 2 hours. The solid was filtered and washed with water (61 L). The crude solid was recharged to the reactor and water (220 L) added. The slurry

was granulated at 20°C for 4.5 hours and then filtered. The filter cake was washed with water (61 L) and the product dried at 55°C.

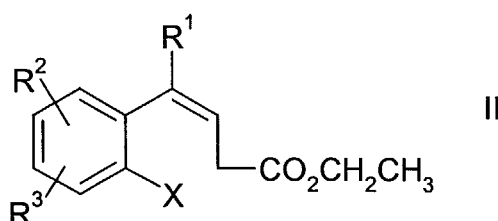
The melting point was 227-229°C

We claim

1. A improved process for preparing a compound of the formula



which comprises (a) conducting a solvent-free reaction between a compound of formula



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and a monohydric or dihydric alcohol in the presence of sulfuric acid; and

(b) treating the reaction product with a base and water to neutralize residual sulfuric acid;

wherein R¹ is an electron withdrawing group selected from the group consisting of cyano, alkoxycarbonyl, alkylcarbonyl, aryl, nitro, trifluoromethyl, and sulfonyl;

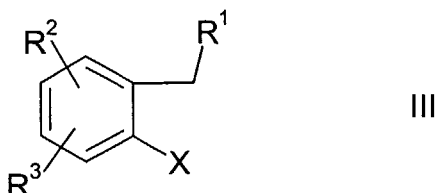
R² and R³ are selected independently from hydrogen, C₁-C₅ alkyl, C₁-C₅alkoxy, trifluoromethyl, halogen, sulfonyl alkyl, alkyamino, amide, ester, aryl-alkyl, hetero-alkyl and arly-alkoxy;

or R² and R³ together with the carbon atoms to which they are attached form a monocyclic or bicyclic ring;

and each R⁴ is independently C₁ to C₆ alkyl or two R⁴ groups together form a C₂ to C₃ alkylene bridge; and X is selected from the group consisting of chlorine, bromine, and iodine.

2. The process according to claim 1 wherein said alcohol is a monohydric alcohol of formula R⁴ OH wherein R⁴ is C₁ to C₆ alkyl or a dihydric alcohol wherein said dihydric alcohol is selected from the group consisting of ethylene glycol, 1,3, propylene glycol, and 1,2 propylene glycol.

3. The process according to claim 1 wherein said compound of formula II is prepared by (a) reacting a compound of formula III



with ethyl 3-ethoxyacrylate in the presence of a catalyst and an inert water miscible solvent and (b) completely removing said solvent upon completion of said reaction; wherein

R^1 is an electron withdrawing group selected from the group consisting of cyano, alkoxycarboxyl, alkylcarbonyl, arylcarbonyl, aryl, nitro, trifluoromethyl, and sulfonyl; and X is
5 selected from the group consisting of chlorine, bromine, and iodine; and

R^2 and R^3 are selected independently from hydrogen, C_1 to C_5 alkyl, C_1 to C_5 alkoxy, trifluoromethyl, halogen, sulfonyl alkyl, alkyamino, amide, ester, aryl-alkyl, hetero-alkyl and aryl-alkoxy;

or R^2 and R^3 together with carbon atoms to which they are attached form a
10 monocyclic or bicyclic ring.

4. The process according to claim 3 wherein said catalyst is a mixture of palladium II acetate, tricyclohexylphosphine, and a base.

5. The process according to claim 3 wherein said solvent is removed by distillation.

15 6. The process according to claim 2 wherein said alcohol is a dihydric alcohol.

7. The process according to claim 6 wherein said dihydric alcohol is ethylene glycol.

8. The process of claim 3 wherein said inert water miscible solvent is selected from the group consisting of tetrahydrofuran, 2-methyltetrahydrofuran, and 1,2- dimethoxy ethane.
20

9. The process according to claim 8 wherein said inert water miscible organic solvent is tetrahydrofuran.

10. The process according to claim 1 wherein said base is ammonium hydroxide.

11. The process according to claim 1 wherein the compound of the formula I is 3-
25 [1,3] dioxolan-2-yliden-3H-indene-1-carbonitrile.

12. The process according to claim 4 wherein said base is an alkoxide of a Group I metal.

13. The process according to claim 12, wherein said base is sodium t-butoxide.