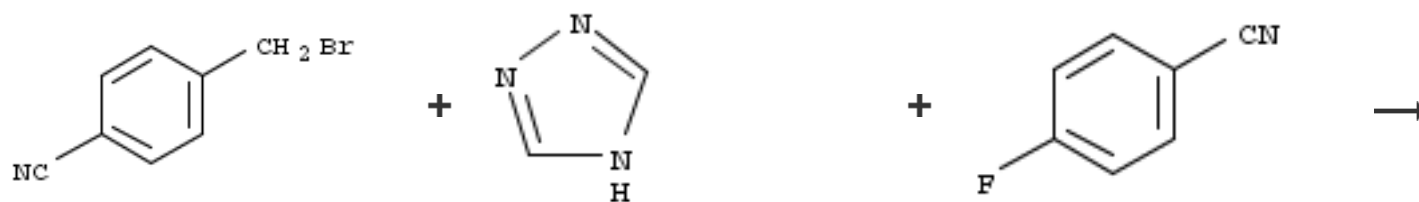
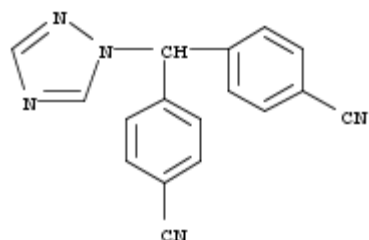


1. 2 Steps



[Step 2.2]

[Overview](#)

Steps/Stages

- 1.1 R:K₂CO₃, C:KI, S:Me₂CO, 12 h, reflux
- 2.1 R:t-BuOK, S:DMF, 1 h, -5°C
- 2.2 30 min, -5°C; 1 h, -5°C
- 2.3 R:HCl, S:H₂O, pH 5

Notes

regioselective, Reactants: 3, Reagents: 3, Catalysts: 1, Solvents: 3, Steps: 2, Stages: 4, Most stages in any one step: 3

References

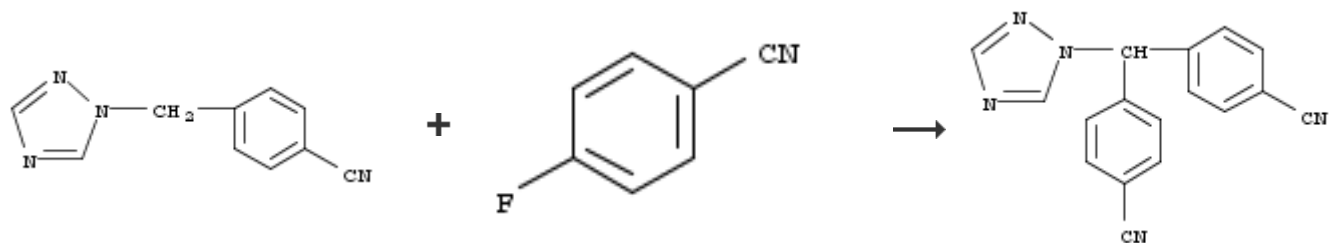
[Synthesis and structure-activity relationship of 1- and 2-substituted-1,2,3-triazole letrozole-based analogues as aromatase inhibitors](#)

By Doiron, Jeremie et al

From European Journal of Medicinal Chemistry, 46(9), 4010-4024; 2011

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2. Single Step

[Overview](#)

Steps/Stages

Notes

- 1.1 R:t-BuOK, S:DMF, 1 h, -5°C
 1.2 30 min, -5°C; 1 h, -5°C
 1.3 R:HCl, S:H₂O, pH 5

Reactants: 2, Reagents: 2, Solvents: 2, Steps: 1, Stages: 3, Most stages in any one step: 3

References

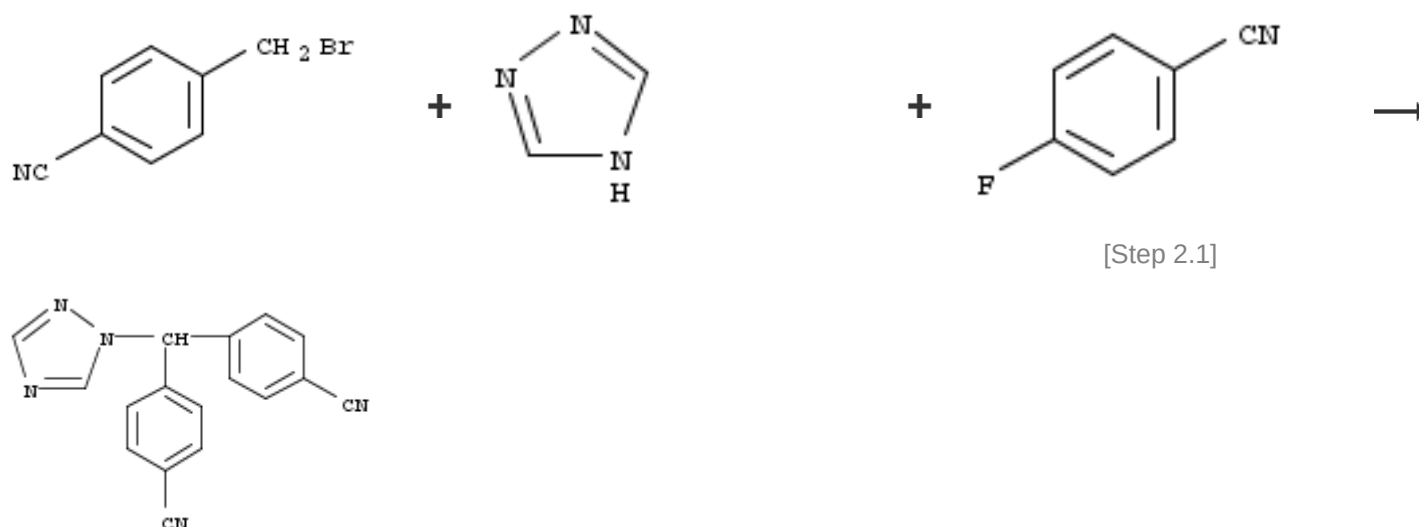
[Synthesis and structure-activity relationship of 1- and 2-substituted-1,2,3-triazole letrozole-based analogues as aromatase inhibitors](#)

By Doiron, Jeremie et al

From European Journal of Medicinal Chemistry, 46(9), 4010-4024; 2011

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3. 2 Steps



Overview

Steps/Stages

- 1.1 R:K₂CO₃, C:KI, S:Me₂CO, 2 h, 25-30°C
 2.1 R:t-BuOK, S:DMF, 1 h, -20 - -15°C
 2.2 R:AcOH, S:H₂O, 10 min

Notes

regioselective, Reactants: 3, Reagents: 3, Catalysts: 1, Solvents: 3, Steps: 2, Stages: 3, Most stages in any one step: 2

References

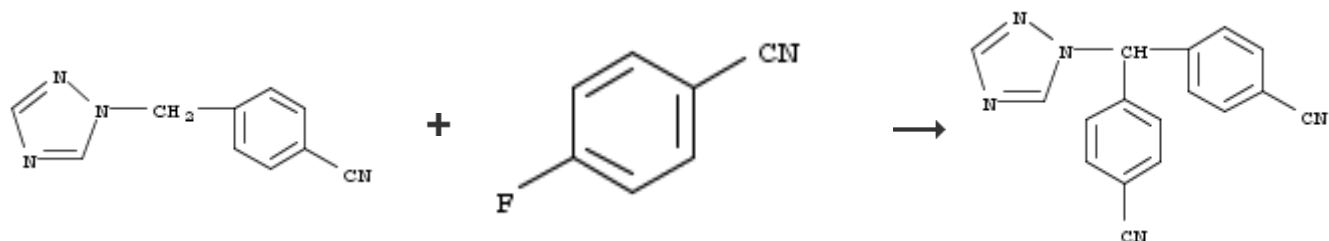
[An improved process for the preparation of letrozole](#)

By Bhaskar, Pallooru Muni et al

From Indian Pat. Appl., 2010DE00389, 26 Aug 2011

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4. Single Step



Overview

Steps/Stages

- 1.1 R:t-BuOK, S:DMF, 1 h, -20 - -15°C
- 1.2 R:AcOH, S:H₂O, 10 min

Notes

Reactants: 2, Reagents: 2, Solvents: 2, Steps: 1, Stages: 2, Most stages in any one step: 2

References

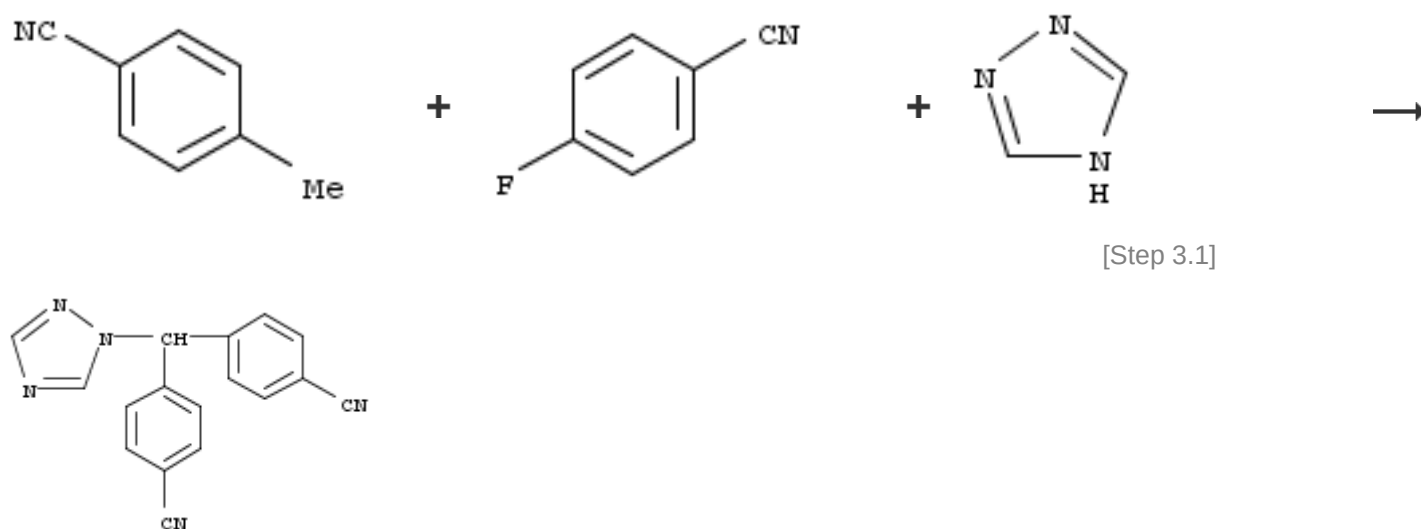
[An improved process for the preparation of letrozole](#)

By Bhaskar, Pallooru Muni et al

From Indian Pat. Appl., 2010DE00389, 26 Aug 2011

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5. 3 Steps



Overview

Steps/Stages

- 1.1 C:NaOMe, S:THF, < 0°C; 2 h, < 0°C
- 2.1 R:Bromosuccinimide, C:AIBN, S:CHCl₃, 9-10 h, rt → reflux
- 3.1 R:K₂CO₃, C:Bu₄N⁺ •Br⁻, S:Me₂CHOH, 8-9 h, rt → reflux

Notes

alternative reaction conditions gave lower yield, Reactants: 3, Reagents: 2, Catalysts: 3, Solvents: 3, Steps: 3, Stages: 3, Most stages in any one step: 1

References

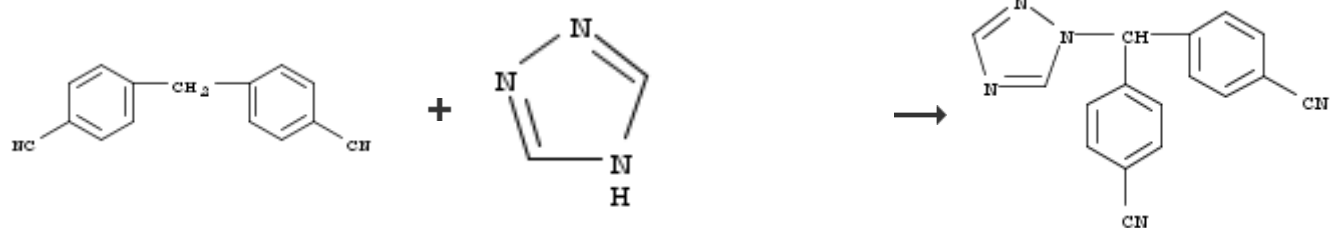
[Method for synthesis of letrozole](#)

By Li, Libiao et al

From Faming Zhuanli Shenqing, 102070542, 25 May 2011

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6. 2 Steps



[Step 2.1]

Overview

Steps/Stages

- 1.1 R:Bromosuccinimide, C:AIBN, S:CHCl₃, 9-10 h, rt → reflux
- 2.1 R:K₂CO₃, C:Bu₄N⁺ •Br⁻, S:Me₂CHOH, 8-9 h, rt → reflux

Notes

alternative reaction conditions gave lower yield, Reactants: 2, Reagents: 2, Catalysts: 2, Solvents: 2, Steps: 2, Stages: 2, Most stages in any one step: 1

References

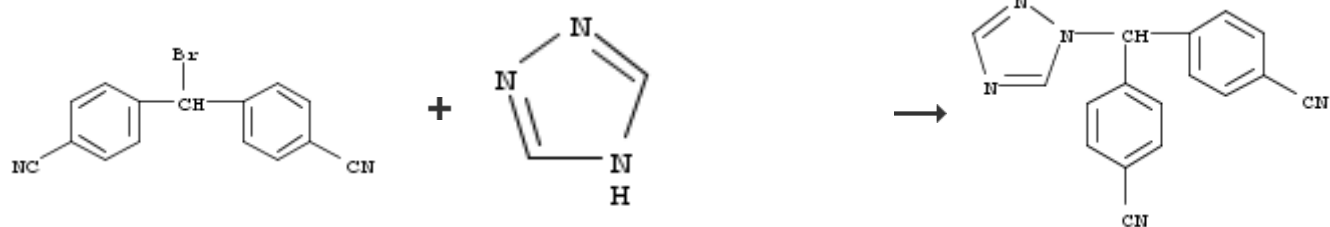
[Method for synthesis of letrozole](#)

By Li, Libiao et al

From Faming Zhuanli Shenqing, 102070542, 25 May 2011

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7. Single Step



26%

Overview

Steps/Stages

- 1.1 R:K₂CO₃, C:Bu₄N⁺ •Br⁻, S:Me₂CHOH, 8-9 h, rt → reflux

Notes

alternative reaction conditions gave lower yield, Reactants: 2, Reagents: 1, Catalysts: 1, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

References

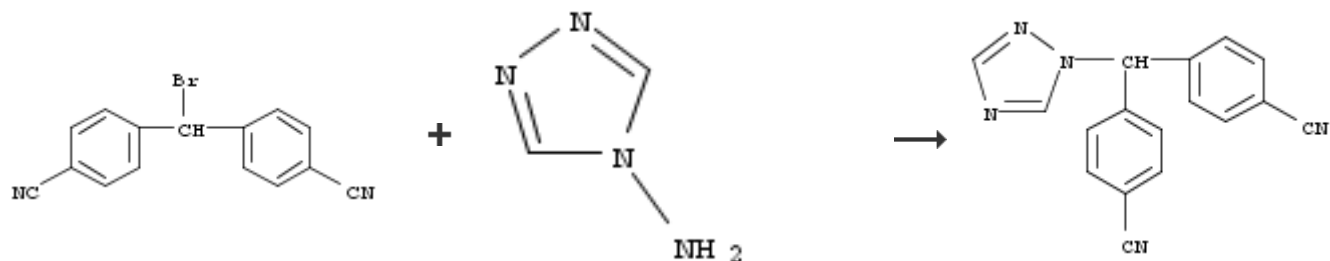
[Method for synthesis of letrozole](#)

By Li, Libiao et al

From Faming Zhuanli Shenqing, 102070542, 25 May 2011

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8. 2 Steps



Overview

Steps/Stages

- 1.1 S:Me₂CHOH, 25 h, reflux; reflux → 0°C
- 2.1 R:NaNO₂, R:HCl, S:H₂O, 0-5°C; 2 h, 0-5°C; 2 h, rt
- 2.2 R:NH₃, rt, pH 8-8.5

Notes

regioselective, Reactants: 2, Reagents: 3, Solvents: 2, Steps: 2, Stages: 3, Most stages in any one step: 2

References

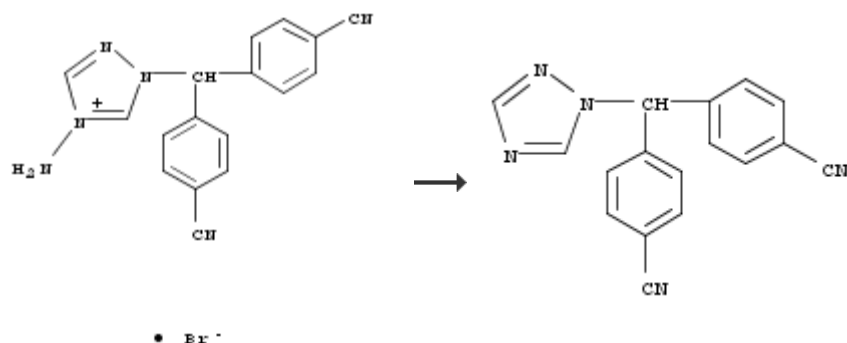
[Method of producing 1-\[di \(4-cyanophenyl\)methyl\]-1,2,4-triazole](#)

By Kazankov, M. V. et al

From Russ., 2425038, 27 Jul 2011

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9. Single Step



97%

Overview

Steps/Stages

- 1.1 R:NaNO₂, R:HCl, S:H₂O, 0-5°C; 2 h, 0-5°C; 2 h, rt
- 1.2 R:NH₃, rt, pH 8-8.5

Notes

Reactants: 1, Reagents: 3, Solvents: 1, Steps: 1, Stages: 2, Most stages in any one step: 2

References

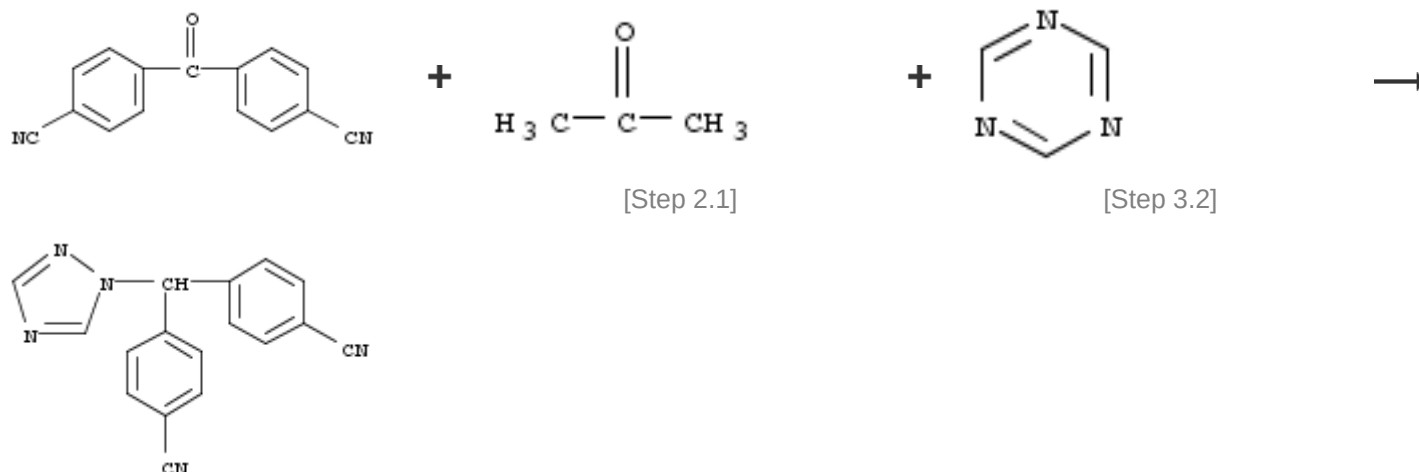
[Method of producing 1-\[di \(4-cyanophenyl\)methyl\]-1,2,4-triazole](#)

By Kazankov, M. V. et al

From Russ., 2425038, 27 Jul 2011

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10. 3 Steps



Overview

Steps/Stages

- 1.1 S:MeOH, 55-65°C
- 1.2 R:AcOH
- 1.3 R:N₂H₄-H₂O, 4-5 h, reflux
- 2.1 S:Me₂CO, S:MeOH, 25-30°C
- 2.2 R:H₂, C: Pd, 25-30°C, 1 atm
- 3.1 R:HCl, S:H₂O, S:MeOH, rt; 3-4 h, rt
- 3.2 S:MeOH, rt; 3-4 h, reflux

Notes

Reactants: 3, Reagents: 4, Catalysts: 1, Solvents: 3, Steps: 3, Stages: 7, Most stages in any one step: 3

References

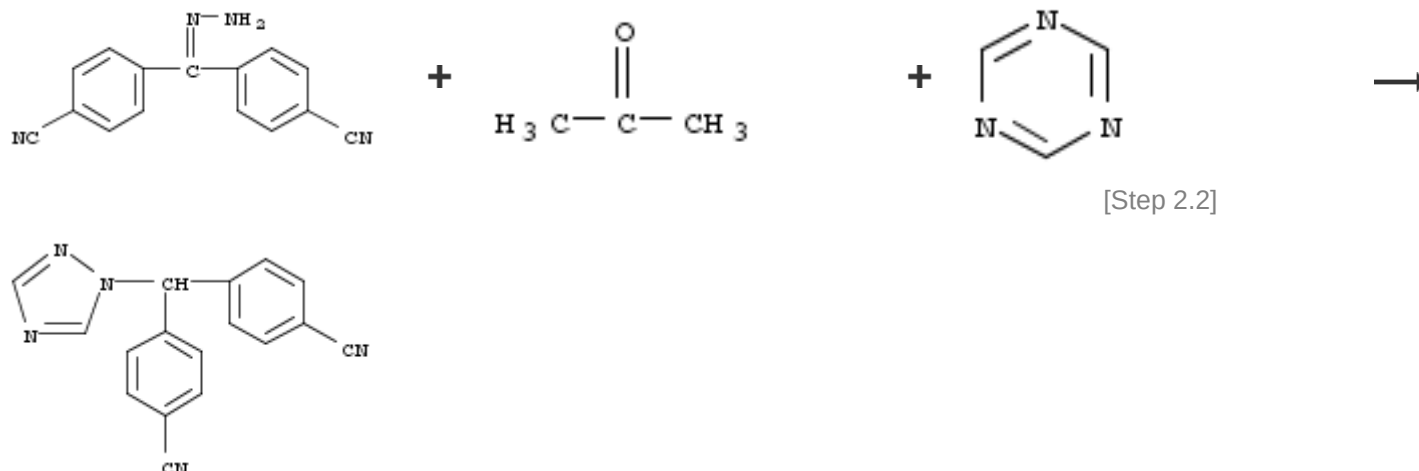
[Regioselective synthesis of letrozole and \(triazolylmethyl\)benzonitrile](#)

By Gore, Vinayak et al

From Indian Pat. Appl., 2009KO00859, 17 Dec 2010

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11. 2 Steps



Overview

Steps/Stages

- 1.1 S:Me₂CO, S:MeOH, 25-30°C
 1.2 R:H₂, C:Pd, 25-30°C, 1 atm
 2.1 R:HCl, S:H₂O, S:MeOH, rt; 3-4 h, rt
 2.2 S:MeOH, rt; 3-4 h, reflux

Notes

Reactants: 3, Reagents: 2, Catalysts: 1,
 Solvents: 3, Steps: 2, Stages: 4, Most stages
 in any one step: 2

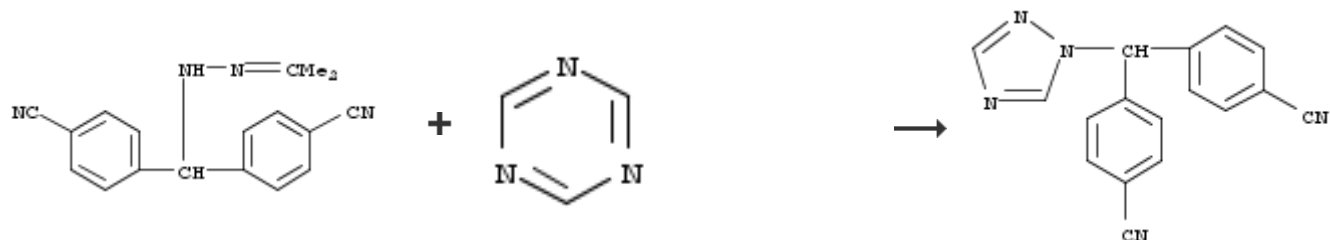
References

[Regioselective synthesis of letrozole and \(triazolylmethyl\)benzonitrile](#)

By Gore, Vinayak et al

From Indian Pat. Appl., 2009KO00859, 17
 Dec 2010

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12. Single Step[Overview](#)**Steps/Stages**

- 1.1 R:HCl, S:H₂O, S:MeOH, rt; 3-4 h, rt
 1.2 S:MeOH, rt; 3-4 h, reflux

Notes

Reactants: 2, Reagents: 1, Solvents: 2, Steps:
 1, Stages: 2, Most stages in any one step: 2

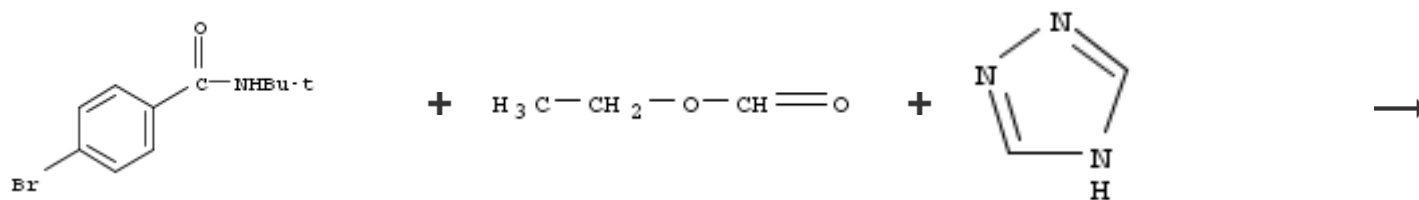
References

[Regioselective synthesis of letrozole and \(triazolylmethyl\)benzonitrile](#)

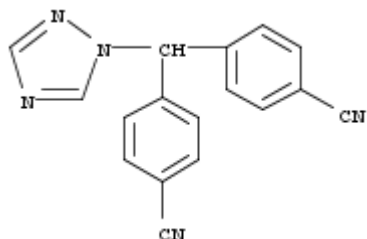
By Gore, Vinayak et al

From Indian Pat. Appl., 2009KO00859, 17
 Dec 2010

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13. 3 Steps

[Step 3.1]



Overview

Steps/Stages

- 1.1 R:BuLi, S:THF
- 2.1 R:SOCl₂
- 3.1 S:DMF, heated

Notes

1) prophetic reaction, 2) prophetic reaction, Reactants: 3, Reagents: 2, Solvents: 2, Steps: 3, Stages: 3, Most stages in any one step: 1

References

[Therapies for treating cancer using combinations of COX-2 inhibitors and aromatase inhibitors or combinations of COX-2 inhibitors and estrogen receptor antagonists](#)

By Estok, Thomas M. et al

From PCT Int. Appl., 2009042612, 02 Apr 2009

Experimental Procedure

Step 1

Starting amide F is treated with n-BuLi in THF at low temperature followed by ethyl formate to give the addition product G.

Step 2

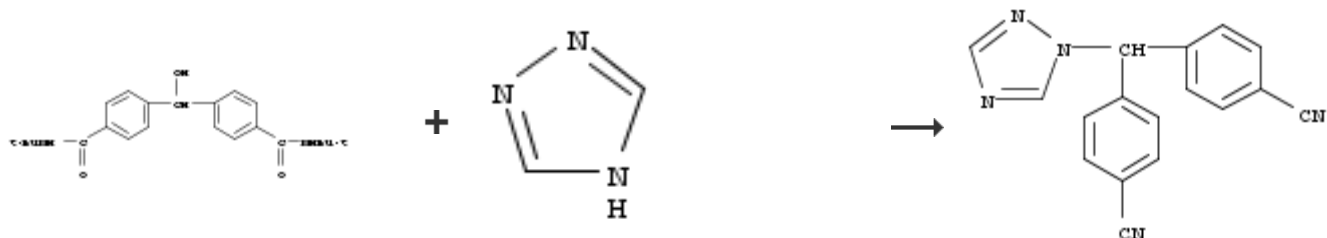
Alcohol G is heated with thionyl chloride to afford the chloro compound H which has also been dehydrated at the amide functional groups.

Step 3

Treatment of bis-nitrile H with the triazole base in hot DMF will provide the desired product letrozole (I).

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14. 2 Steps



[Step 2.1]

Overview

Steps/Stages

Notes

- 1.1 R:SOCl₂
2.1 S:DMF, heated

prophetic reaction, Reactants: 2, Reagents: 1, Solvents: 1, Steps: 2, Stages: 2, Most stages in any one step: 1

References

[Therapies for treating cancer using combinations of COX-2 inhibitors and aromatase inhibitors or combinations of COX-2 inhibitors and estrogen receptor antagonists](#)

By Estok, Thomas M. et al

From PCT Int. Appl., 2009042612, 02 Apr 2009

Experimental Procedure

Step 1

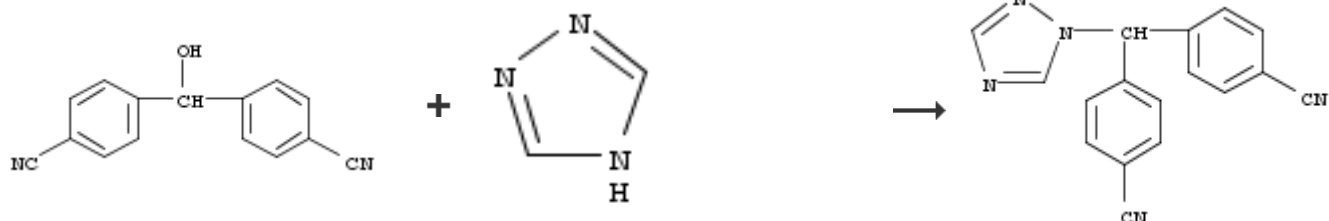
Alcohol G is heated with thionyl chloride to afford the chloro compound H which has also been dehydrated at the amide functional groups.

Step 2

Treatment of bis-nitrile H with the triazole base in hot DMF will provide the desired product letrozole (I).

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15. Single Step



Overview

Steps/Stages

- 1.1 S:DMF, heated

Notes

Reactants: 2, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

References

[Therapies for treating cancer using combinations of COX-2 inhibitors and aromatase inhibitors or combinations of COX-2 inhibitors and estrogen receptor antagonists](#)

By Estok, Thomas M. et al

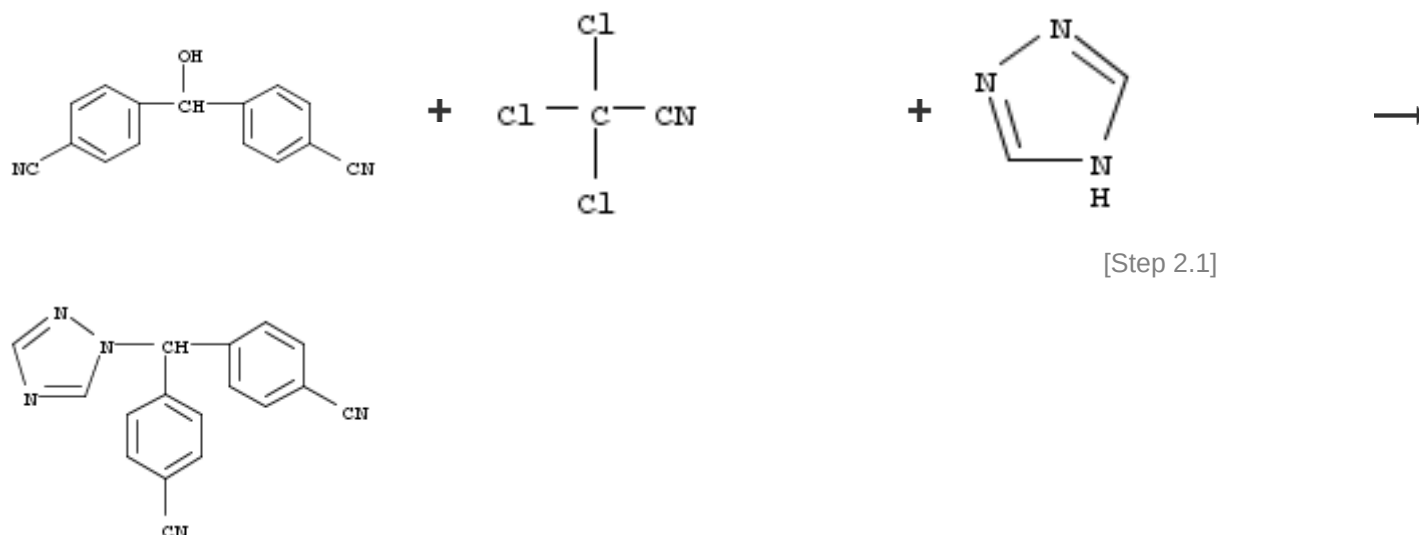
From PCT Int. Appl., 2009042612, 02 Apr 2009

Experimental Procedure

Treatment of bis-nitrile H with the triazole base in hot DMF will provide the desired product letrozole (I).

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16. 2 Steps



Overview

Steps/Stages

- 1.1 S:Me₂CO, 10-15 min, 10-20°C
- 1.2 R:NaOH, S:H₂O, pH 7; 2-3 h
- 2.1 R:Me₃SiCl, R:(Me₃Si)₂NH, S:ClCH₂CH₂Cl, 20-22 h, 90°C
- 2.2 R:BF₃-Et₂O, S:ClCH₂CH₂Cl, 24-30 h, rt

Notes

First stage reactant made in situ, Reactants: 3, Reagents: 4, Solvents: 3, Steps: 2, Stages: 4, Most stages in any one step: 2

References

[Process and intermediate of letrozole](#)

By Vishnukant, B.

From PCT Int. Appl., 2009078036, 25 Jun 2009

Experimental Procedure

Step 1

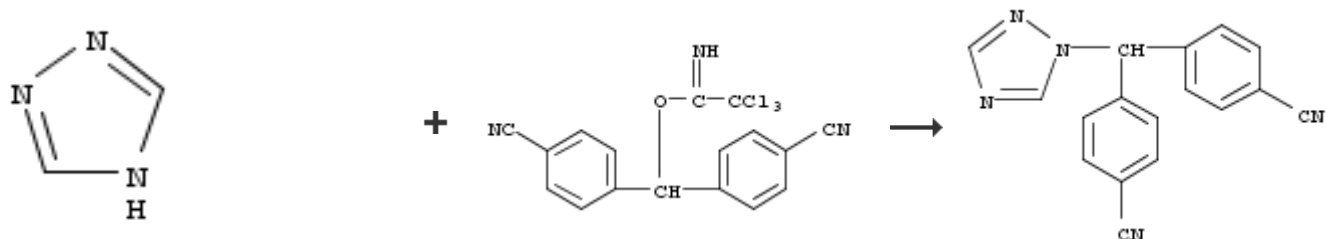
EXAMPLES: Example 1: Preparation of Trichloroacetimidate-bis-(4-cyanophenyl) methyl ester of formula (I.) To a cooled solution of 4,4'-hydroxymethylene bis benzonitrile (40g) in acetone (200ml) added Trichloroacetonitrile (36 ml) in the portions and stirred at temperature between 10°C- 20°C for a period of 10- 15 min. To this solution added 10% aqueous sodium hydroxide(60ml) to adjust the pH to around 7.00, continued stirring for further 2 to 3 hrs. HPLC monitoring of the reaction mixture showed traces of starting material .Worked up the reaction mixture by adding water (800 ml), stirred for 30 mints and filtered the precipitated solid. Washed the solid thoroughly with water till the water washing is neutral, dried the solid between 40 to 45°C under high vacuum for an overnight. Yield = 6.0.0 gms.

Step 2

Example 2: Preparation of N-trimethylsilyl 1,2,4-triazole. To a suspension of 1,2,4- triazole (30 g) in ethylene dichloride (300 ml) added trimethyl silyl chloride (39.0 ml) and hexamethyl disilazone (96.0 ml) and the mixture heated around 90° for 20 h to 22 h. The solution become clear cooled the reaction mixture to room temperature to obtain silyl derivative in situ. Example 3: Preparation of Letrozole: To a solution of silylated derivative of example 2 added trimethylsilyl trifluoromethane sulphpnate (21.0ml) followed by product of example 1(60g) in ethylene dichloride(150ml). The mixture was stirred at room temperature for 24 to 30 hrs Worked up by adding water (75 ml), stirring, separating aqueous layer and organic layer. Adjusted the pH of aqueous layer between 7.00 to 8.00 below a temperature of 20°C. Extracted with methylene chloride, separated methylene chloride layer concentrated Methylene chloride layer to a small volume and added n-hexane to obtain Letrozole(3.6g).

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17. Single Step



Overview

Steps/Stages

- 1.1 R:Me₃SiCl, R:(Me₃Si)₂NH, S:ClCH₂CH₂Cl, 20-22 h, 90°C
- 1.2 R:BF₃-Et₂O, S:ClCH₂CH₂Cl, 24-30 h, rt

Notes

First stage reactant made in situ, Reactants: 2, Reagents: 3, Solvents: 1, Steps: 1, Stages: 2, Most stages in any one step: 2

References

Process and intermediate of letrozole

By Vishnukant, B.

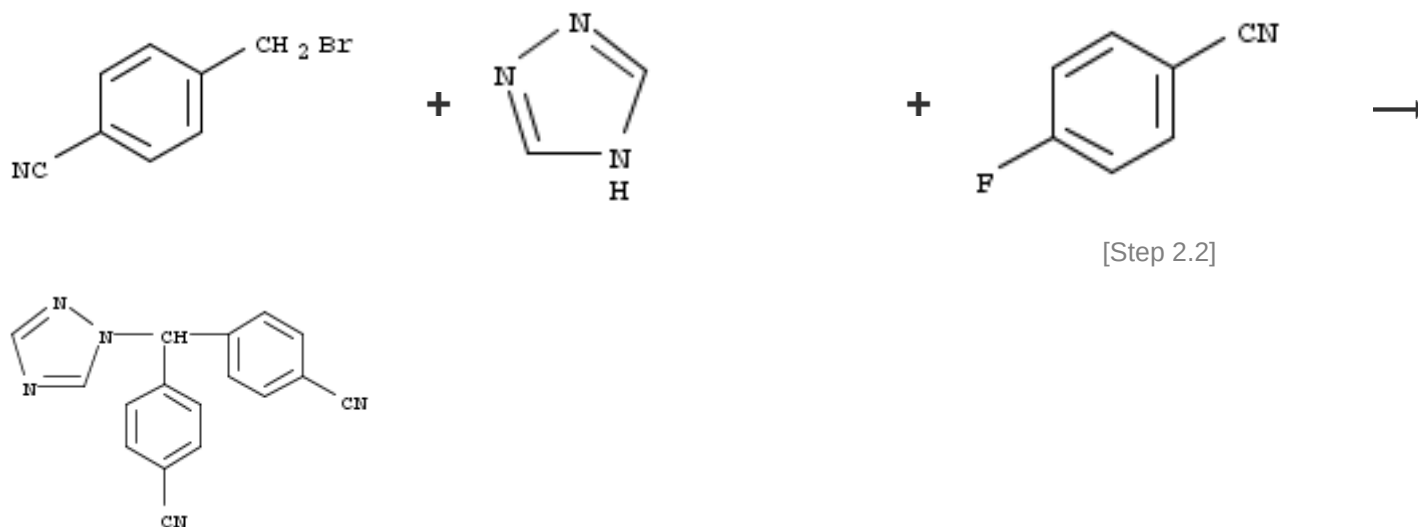
From PCT Int. Appl., 2009078036, 25 Jun 2009

Experimental Procedure

Example 2: Preparation of N-trimethylsilyl 1,2,4-triazole. To a suspension of 1,2,4-triazole (30 g) in ethylene dichloride (300 ml) added trimethyl silyl chloride (39.0 ml) and hexamethyl disilazone (96.0 ml) and the mixture heated around 90° for 20 h to 22 h. The solution become clear cooled the reaction mixture to room temperature to obtain silyl derivative in situ. Example 3: Preparation of Letrozole: To a solution of silylated derivative of example 2 added trimethylsilyl trifluoromethane sulphpnate (21.0ml) followed by product of example 1(60g) in ethylene dichloride(150ml). The mixture was stirred at room temperature for 24 to 30 hrs Worked up by adding water (75 ml), stirring, separating aqueous layer and organic layer. Adjusted the pH of aqueous layer between 7.00 to 8.00 below a temperature of 20°C. Extracted with methylene chloride, separated methylene chloride layer concentrated Methylene chloride layer to a small volume and added n-hexane to obtain Letrozole(3.6g).

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18. 2 Steps



Overview

Steps/Stages

Notes

- 1.1 R:K₂CO₃, S:PhMe, 30 min, 25-30°C
 1.2 3 h; 105-110°C; 3 h, 105-110°C
 2.1 R:t-BuOK, S:DMF, rt → -25°C; 5 min, -25 - -20°C; 60 min, -25 - -20°C
 2.2 5 min, -25 - -20°C; 1 h, -25 - -20°C
 2.3 R:HCl, S:H₂O, -20 - 0°C, pH 6-6.5

1) optimization study, 2) alternative preparation shown, Reactants: 3, Reagents: 3, Solvents: 3, Steps: 2, Stages: 5, Most stages in any one step: 3

References

[An improved process for preparation of letrozole and its intermediates](#)

By Shrawat, Vimal Kumar et al

From PCT Int. Appl., 2009069140, 04 Jun 2009

Experimental Procedure

Step 1

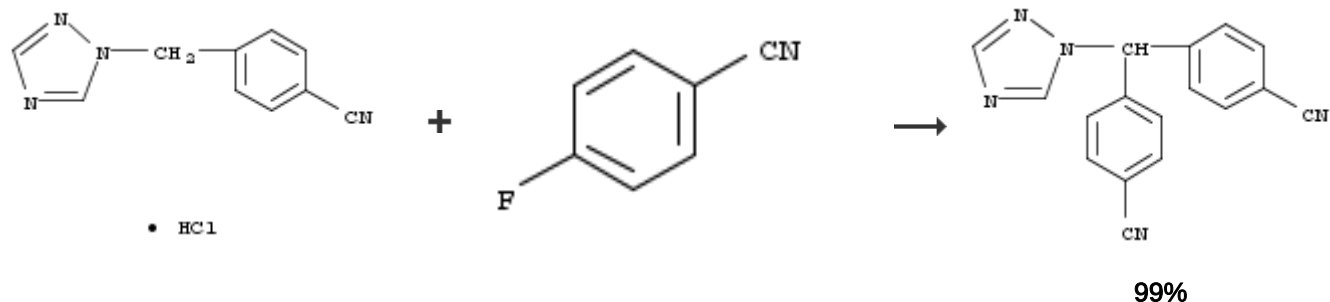
Example-2. Preparation of 4-(1H-1,2,4-triazol-1-ylmethyl)bemomitrile hydrochloride (VII) through addition of 1H-1,2,4-triazole in 1 to 4 hours. To a solution of 4-bromomethyl benzonitrile (II, 500 gm; 2.5 mol) in toluene (2.5 Lt) was added potassium carbonate (528 gm; 3.82 mol) and the mixture was maintained at a temperature of 25° to 30°C for 30 minutes under agitation. To the mixture was added 1H-1,2,4-triazole (III, 176 gm; 2.55 mol), slowly in lots over 3 hours. After the complete addition, the temperature was raised to 105° to 110° C, and the reaction mixture was thereafter heated under agitation at a temperature of 105° to 110° C, for 3 hours, when the reaction was found to be complete. The reaction mixture was cooled to room temperature and filtered to remove the insoluble potassium carbonate. The filter bed was washed with toluene (250 ml) and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (3 Lt) and washed successively three times with water (4 Lt each). The ethyl acetate layer was dried over anhydrous sodium sulfate and the solution cooled to 0° to 5°C. To the cooled solution was added a solution of isopropanol hydrochloride (18% w/w) at the same temperature till the pH of the solution is adjusted between 0 and 2. The mass was agitated at 0° to 5°C for further 6 hours and the solid was filtered, washed with cold ethyl acetate (100 ml) and dried to give the title compound (VII, 452 gm; 80.8%), with a purity of 99.2%.

Step 2

Example-3. Preparation of 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl) methyl]benzonitrile (Letrozole, I). To a mixture of potassium tertiarybutoxide (635.92 gm; 5.66 mol) and N,N-dimethylformamide (3.75 Lt). under an atmosphere of nitrogen and cooled to a temperature of -20° to -25°C, was added 4-(1 H-1,2,4-triazol-1-ylmethyl)benzonitrile hydrochloride (VII, as obtained in Examples 1 or 2; 250 gm; 1.13 mol) within 5 minutes and was stirred for 60 minutes at -20 °C to -25°C. To the mixture was added 4-fluoro benzonitrile (VI, 150.9 gm; 1.24 mol) within 5 minutes and the mass agitated for an hour at -20 °C to -25 °C. After completion of the reaction, pH of the mixture, was adjusted to between 6.0 to 6.5 by addition of 50% aqueous hydrochloric acid, maintaining the temperature between -20 °C to 0 °C. After the addition of the hydrochloric acid solution, the reaction mass was stirred for additional 30 minutes and filtered. To the filtrate was added ethyl acetate and water and the ethyl acetate layer was separated and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum to give a residual solid amounting to 244 gm (75%) of Letrozole (I), having a purity of 99%. The material (244 gm) was further dissolved in ethyl acetate (500 ml) at 70 °C to 75 °C, and the solution was filtered hot. The filtrate was cooled to 0° to SOC for 4 hours, and the solid filtered, washed with cold ethyl acetate and dried to give Letrozole (I, 221 gm; 98.6%), having a purity of 99.7%.

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19. Single Step



[Overview](#)

[Steps/Stages](#)

[Notes](#)

- 1.1 R:t-BuOK, S:DMF, rt → -25°C; 5 min, -25 - -20°C; 60 min, -25 - -20°C
 1.2 5 min, -25 - -20°C; 1 h, -25 - -20°C
 1.3 R:HCl, S:H₂O, -20 - 0°C, pH 6-6.5

alternative preparation shown, Reactants: 2, Reagents: 2, Solvents: 2, Steps: 1, Stages: 3, Most stages in any one step: 3

References

[An improved process for preparation of letrozole and its intermediates](#)

By Shrawat, Vimal Kumar et al

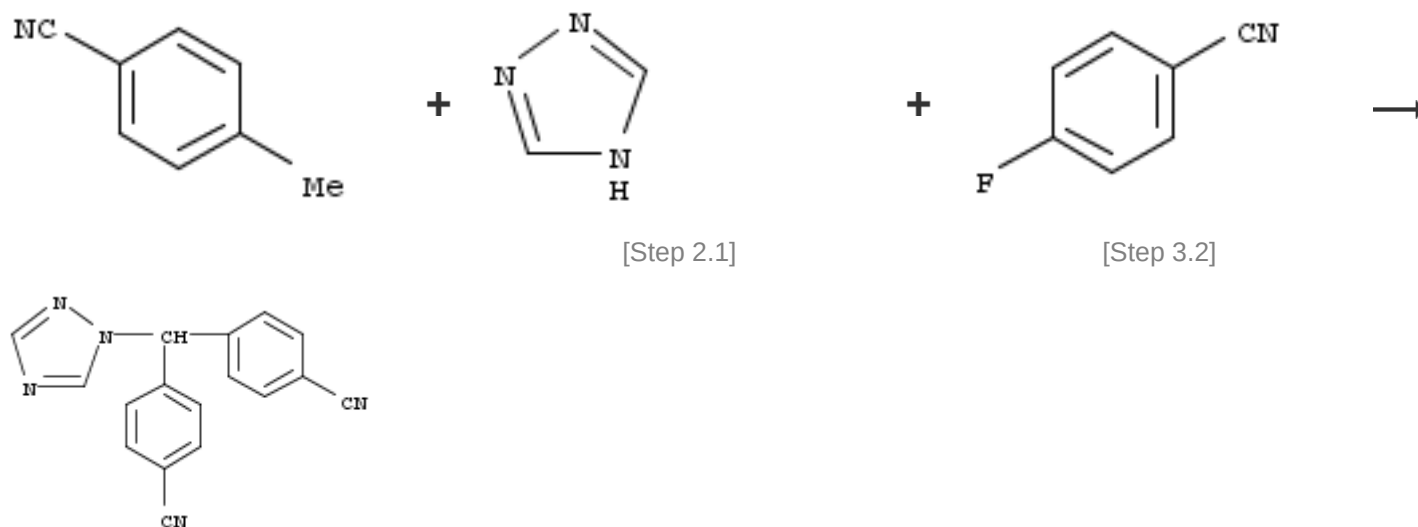
From PCT Int. Appl., 2009069140, 04 Jun 2009

Experimental Procedure

Example-3. Preparation of 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl) methyl]benzonitrile (Letrozole, I). To a mixture of potassium tertiarybutoxide (635.92 gm; 5.66 mol) and N,N-dimethylformamide (3.75 Lt). under an atmosphere of nitrogen and cooled to a temperature of -20° to -25°C, was added 4-(1 H-1,2,4-triazol-1-ylmethyl)benzonitrile hydrochloride (VII, as obtained in Examples 1 or 2; 250 gm; 1.13 mol) within 5 minutes and was stirred for 60 minutes at -20 °C to -25°C. To the mixture was added 4-fluoro benzonitrile (VI, 150.9 gm; 1.24 mol) within 5 minutes and the mass agitated for an hour at -20 °C to -25 °C. After completion of the reaction, pH of the mixture, was adjusted to between 6.0 to 6.5 by addition of 50% aqueous hydrochloric acid, maintaining the temperature between -20 °C to 0 °C. After the addition of the hydrochloric acid solution, the reaction mass was stirred for additional 30 minutes and filtered. To the filtrate was added ethyl acetate and water and the ethyl acetate layer was separated and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum to give a residual solid amounting to 244 gm (75%) of Letrozole (I), having a purity of 99%. The material (244 gm) was further dissolved in ethyl acetate (500 ml) at 70 °C to 75 °C, and the solution was filtered hot. The filtrate was cooled to 0° to SOC for 4 hours, and the solid filtered, washed with cold ethyl acetate and dried to give Letrozole (I, 221 gm; 98.6%), having a purity of 99.7%.

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20. 3 Steps



Overview

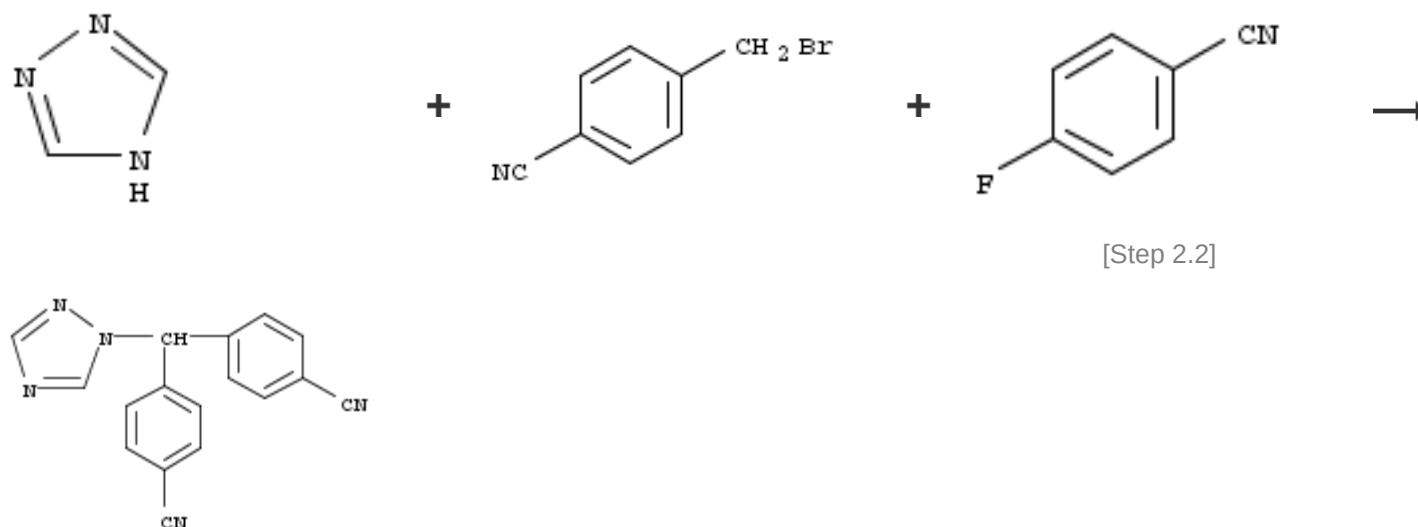
Steps/Stages

Notes

- 1.1 R:Bromosuccinimide, C:AIBN, S:CCl₄, rt → reflux; 20 min, reflux
- 2.1 R:NaOH, S:H₂O, S:PhMe, heated; 3 h, reflux
- 2.2 S:MeCN, 1 h, reflux
- 2.3 R:HCl, S:EtOH, 0.5 h, 0°C, pH 2-3
- 2.4 R:NaHCO₃, S:H₂O, pH 9
- 3.1 R:t-BuOK, S:DMF, rt → -5°C; 0.5 h, -5 - 0°C; 0.5 h, 0°C
- 3.2 S:DMF, 0.5 h, 5-10°C
- 3.3 R:HCl, S:H₂O, 1 h, 5-10°C, pH 7

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21. 2 Steps



Overview

Steps/Stages

- 1.1 R:NaOH, S:H₂O, S:PhMe, heated; 3 h, reflux
- 1.2 S:MeCN, 1 h, reflux
- 1.3 R:HCl, S:EtOH, 0.5 h, 0°C, pH 2-3
- 1.4 R:NaHCO₃, S:H₂O, pH 9
- 2.1 R:t-BuOK, S:DMF, rt → -5°C; 0.5 h, -5 - 0°C; 0.5 h, 0°C
- 2.2 S:DMF, 0.5 h, 5-10°C
- 2.3 R:HCl, S:H₂O, 1 h, 5-10°C, pH 7

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22. Single Step

45.7% yield over 3 steps from 4-methylbenzonitrile, Reactants: 3, Reagents: 5, Catalysts: 1, Solvents: 6, Steps: 3, Stages: 8, Most stages in any one step: 4

References

[Synthesis of 4,4'-\(1H-1,2,4-triazol-1-ylmethylene\)bis\[benzonitrile\] \(letrozole\)](#)

By He, Guodong and Zhou, Zhiming

From Guangdong Huagong, 34(1), 38-40; 2007

Notes

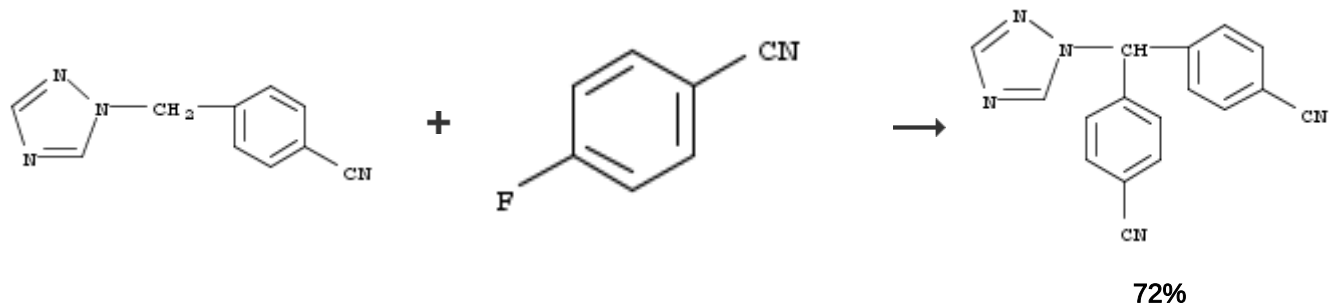
45.7% yield over 3 steps from 4-methylbenzonitrile, Reactants: 4, Solvents: 5, Steps: 2, Stages: 7, Most stages in any one step: 4

References

[Synthesis of 4,4'-\(1H-1,2,4-triazol-1-ylmethylene\)bis\[benzonitrile\] \(letrozole\)](#)

By He, Guodong and Zhou, Zhiming

From Guangdong Huagong, 34(1), 38-40; 2007



Overview

Steps/Stages

- 1.1 R:t-BuOK, S:DMF, rt → -5°C; 0.5 h, -5 - 0°C; 0.5 h, 0°C
- 1.2 S:DMF, 0.5 h, 5-10°C
- 1.3 R:HCl, S:H₂O, 1 h, 5-10°C, pH 7

Notes

45.7% yield over 3 steps from 4-methyl-Benzonitrile, Reactants: 2, Reagents: 2, Solvents: 2, Steps: 1, Stages: 3, Most stages in any one step: 3

References

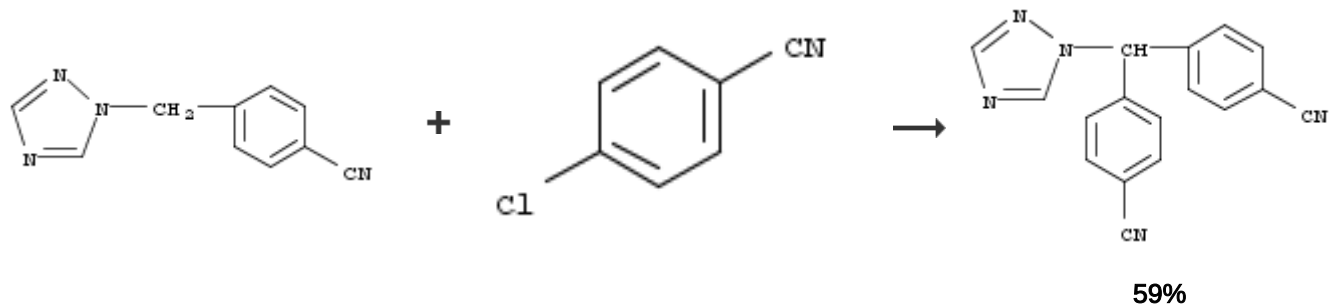
[Synthesis of 4,4'-\(1H-1,2,4-triazol-1-ylmethylene\)bis\[benzonitrile\] \(letrozole\)](#)

By He, Guodong and Zhou, Zhiming

From Guangdong Huagong, 34(1), 38-40; 2007

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23. Single Step



Overview

Steps/Stages

- 1.1 R:t-BuOK, S:DMF, 40 min, rt
- 1.2 rt; 50 min, rt
- 1.3 R:NH₄Cl, S:H₂O, rt

Notes

Reactants: 2, Reagents: 2, Solvents: 2, Steps: 1, Stages: 3, Most stages in any one step: 3

References

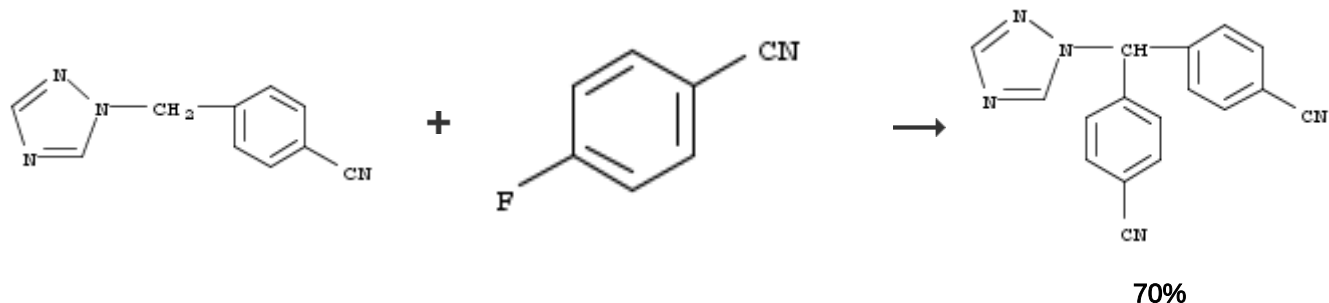
[Study on the synthesis of letrozole](#)

By Tang, Li-juan et al

From Huaihai Gongxueyuan Xuebao, Ziran Kexueban, 15(4), 38-40; 2006

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24. Single Step



Overview

Steps/Stages

- 1.1 R:t-BuOK, S:DMF, 40 min, rt
- 1.2 rt; 50 min, rt
- 1.3 R:NH₄Cl, S:H₂O, rt

Notes

Reactants: 2, Reagents: 2, Solvents: 2, Steps: 1, Stages: 3, Most stages in any one step: 3

References

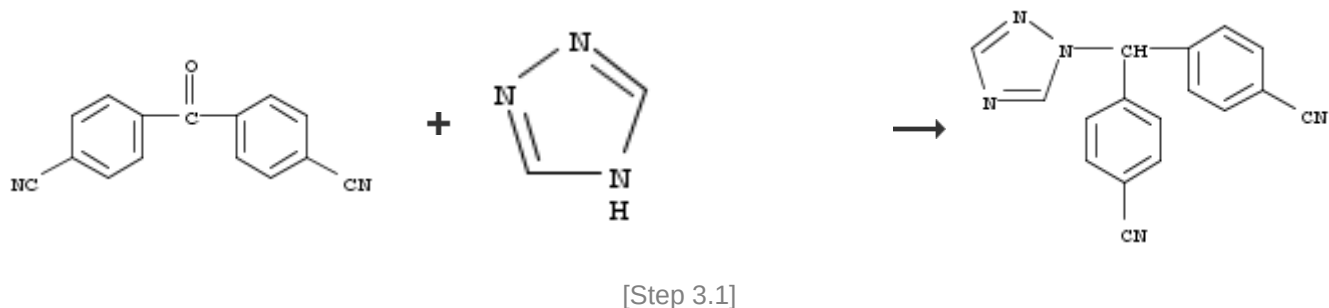
[Study on the synthesis of letrozole](#)

By Tang, Li-juan et al

From Huaihai Gongxueyuan Xuebao, Ziran Kexueban, 15(4), 38-40; 2006

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25. 3 Steps



Overview

Steps/Stages

- 1.1 R:NaBH₄, S:MeOH, rt → -5°C; < -5°C; 1 h, 5°C
- 2.1 R:C₅H₅N, S:CHCl₃, heated
- 2.2 R:SOCl₂, 50 min, reflux; 4.5 h, reflux
- 3.1 R:K₂CO₃, S:CHCl₃, 30 min, reflux
- 3.2 S:CHCl₃, 30-40 min, reflux; 31 h, reflux

Notes

Reactants: 2, Reagents: 4, Solvents: 2, Steps: 3, Stages: 5, Most stages in any one step: 2

References

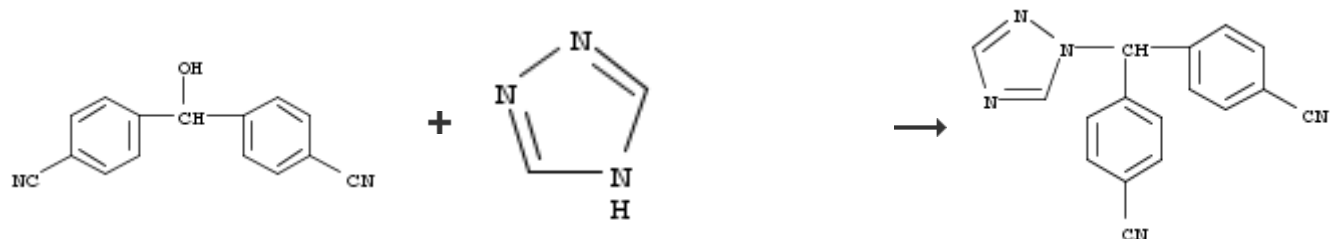
[Process for preparation of Letrozole](#)

By Du, Huanda et al

From Faming Zhuanli Shenqing Gongkai Shuomingshu, 101066953, 07 Nov 2007

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26. 2 Steps



[Step 2.1]

[Overview](#)**Steps/Stages**

- 1.1 R:C₅H₅N, S:CHCl₃, heated
- 1.2 R:SOCl₂, 50 min, reflux; 4.5 h, reflux
- 2.1 R:K₂CO₃, S:CHCl₃, 30 min, reflux
- 2.2 S:CHCl₃, 30-40 min, reflux; 31 h, reflux

Notes

Reactants: 2, Reagents: 3, Solvents: 1, Steps: 2, Stages: 4, Most stages in any one step: 2

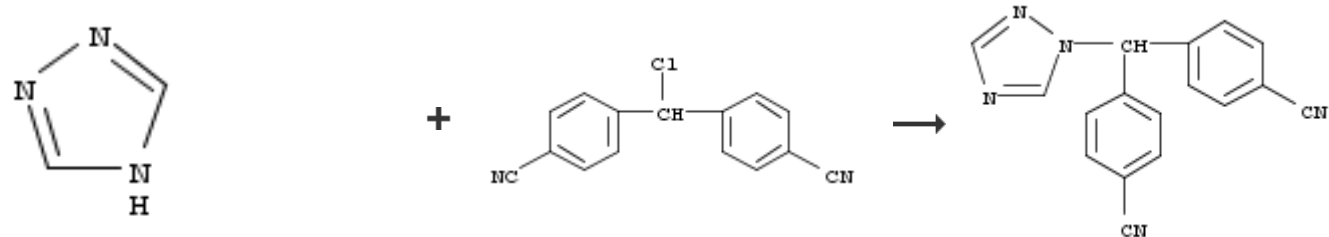
References

[Process for preparation of Letrozole](#)

By Du, Huanda et al

From Faming Zhuanli Shenqing Gongkai
Shuomingshu, 101066953, 07 Nov 2007

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27. Single Step

67%

[Overview](#)**Steps/Stages**

- 1.1 R:K₂CO₃, S:CHCl₃, 30 min, reflux
- 1.2 S:CHCl₃, 30-40 min, reflux; 31 h, reflux

Notes

Reactants: 2, Reagents: 1, Solvents: 1, Steps: 1, Stages: 2, Most stages in any one step: 2

References

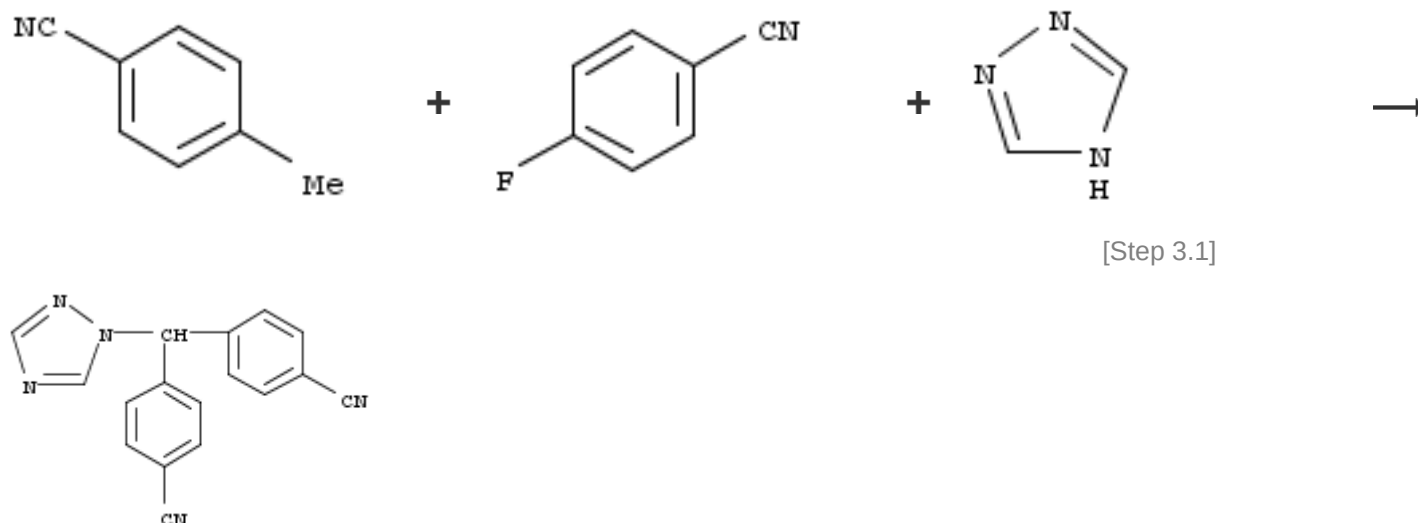
[Process for preparation of Letrozole](#)

By Du, Huanda et al

From Faming Zhuanli Shenqing Gongkai
Shuomingshu, 101066953, 07 Nov 2007

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28. 3 Steps



Overview

Steps/Stages

- 1.1 R:t-BuOK, S:DMF, 2-3 h, -10°C; 2 h, -10°C
- 1.2 R:NH₄Cl, S:H₂O
- 2.1 R:Bromosuccinimide, R:(PhCO₂)₂, S:CHCl₃, rt → reflux; 9-10 h, reflux
- 3.1 R:K₂CO₃, R:Bu₄N⁺ •Br⁻, S:Me₂CHOH, rt → reflux; 8-9 h, reflux

Notes

Reactants: 3, Reagents: 6, Solvents: 4, Steps: 3, Stages: 4, Most stages in any one step: 2

References

[A method of manufacture of letrozole](#)

By Kompella, Amala Kishan et al

From PCT Int. Appl., 2007144896, 21 Dec 2007

Experimental Procedure

Step 1

Examples (a) Preparation of the 4,4'-Dicyanodiphenyl methane of the formula (VI): To a solution of 1.8 Kg of potassium-(t)-butoxide in 5.4 Lts of DMF at -10°C, is added a mixture of 1.0 of p-tolunitrile and 1.14 kg of p-Fluorobenzonitrile during 2-3 hours. The mixture is maintained at the same temperature for 2 hrs and quenched into saturated ammonium chloride solution. The reaction mixture is extracted with chloroform; the organic phase is separated, washed with brine, dried over sodium sulphate and evaporated. The resulting crystalline product is filtered after trituration with Isopropyl ether (yield: 0.65 Kgs). melting point: 168.3°C, purity by HPLC: 99.9%

Step 2

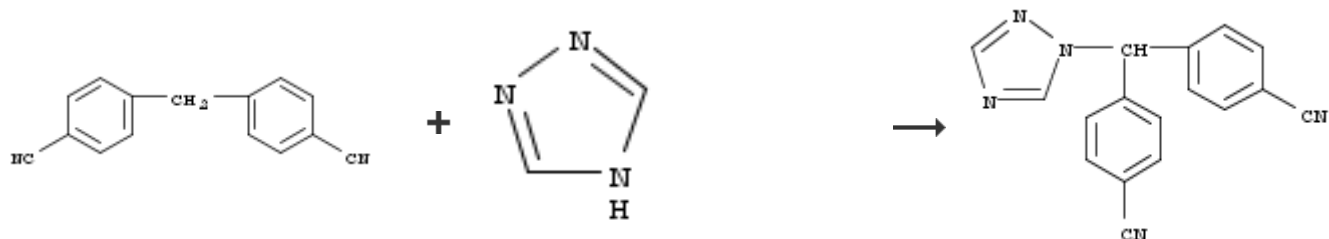
(b) Preparation of 4-(α-Bromo-4-cyanobenzyl) benzonitrile of the formula (VII): To a solution of 0.65 kgs of 4,4'-Dicyanodiphenyl methane of formula (VI) in 10L of chloroform are added 0.53 kgs of N-bromo succinimide and 8 gms of benzoyl peroxide sequentially. The reaction mixture is heated to reflux temperature and maintained at the same temperature for 9-10 hrs. The reaction mixture is poured into 3.5 L of water and extracted with chloroform. The chloroform extract is water washed, dried over sodium sulphate and evaporated. To the residue a mixture of 2L of ethyl acetate and 1.3 L of hexane is added and stirred for 1 hr at room temperature. The resulting solid is filtered to yield 0.54 kgs of compound of formula (VII). melting point: 120.8°C, purity by HPLC: 96%

Step 3

(c) Preparation of letrozole of the formula (I): To a solution of 0.54 kg of 4-(α-Bromo-4-cyanobenzyl) benzonitrile of the formula (VII) in 10L of Isopropanol are charged 0.502 kgs of 1,2,4-Triazole, 0.250 kgs of potassium carbonate and 58 gms of tetra butyl ammonium bromide. The reaction mixture is heated to reflux temperature and maintained at the same temperature for 8-9 hrs. The reaction mass is distilled to a residual volume of 2.5 L, cooled to room temperature, filtered and washed with water. Thus obtained crude letrozole is recrystallized twice with methanol to yield 252 gms of pure letrozole. Melting point: 186.3°C; purity by HPLC: 99.94%

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29. 2 Steps



[Step 2.1]

[Overview](#)**Steps/Stages**

- 1.1 R:Bromosuccinimide, R:(PhCO₂)₂, S:CHCl₃, rt → reflux; 9-10 h, reflux
- 2.1 R:K₂CO₃, R:Bu₄N⁺•Br⁻, S:Me₂CHOH, rt → reflux; 8-9 h, reflux

Notes

Reactants: 2, Reagents: 4, Solvents: 2, Steps: 2, Stages: 2, Most stages in any one step: 1

References[A method of manufacture of letrozole](#)

By Kompella, Amala Kishan et al

From PCT Int. Appl., 2007144896, 21 Dec 2007

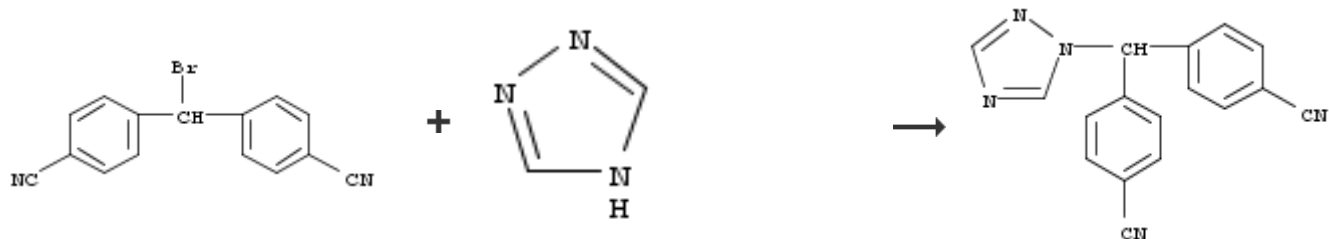
[Experimental Procedure](#)**Step 1**

(b) Preparation of 4-(α-Bromo-4-cyanobenzyl) benzonitrile of the formula (VII): To a solution of 0.65 kgs of 4,4'-Dicyanodiphenyl methane of formula (VI) in 10L of chloroform are added 0.53 kgs of N-bromo succinimide and 8 gms of benzoyl peroxide sequentially. The reaction mixture is heated to reflux temperature and maintained at the same temperature for 9-10 hrs. The reaction mixture is poured into 3.5 L of water and extracted with chloroform. The chloroform extract is water washed, dried over sodium sulphate and evaporated. To the residue a mixture of 2L of ethyl acetate and 1.3 L of hexane is added and stirred for 1 hr at room temperature. The resulting solid is filtered to yield 0.54 kgs of compound of formula (VII). melting point: 120.8°C, purity by HPLC: 96%

Step 2

(c) Preparation of letrozole of the formula (I): To a solution of 0.54 kg of 4-(α-Bromo-4-cyanobenzyl) benzonitrile of the formula (VII) in 10L of Isopropanol are charged 0.502 kgs of 1,2,4-Triazole, 0.250 kgs of potassium carbonate and 58 gms of tetra butyl ammonium bromide. The reaction mixture is heated to reflux temperature and maintained at the same temperature for 8-9 hrs. The reaction mass is distilled to a residual volume of 2.5 L, cooled to room temperature, filtered and washed with water. Thus obtained crude letrozole is recrystallized twice with methanol to yield 252 gms of pure letrozole. Melting point: 186.3°C; purity by HPLC: 99.94%

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30. Single Step[Overview](#)**Steps/Stages****Notes**

1.1 R:K₂CO₃, R:Bu₄N⁺•Br⁻, S:Me₂CHOH, rt → reflux; 8-9 h, reflux

Reactants: 2, Reagents: 2, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

References

[A method of manufacture of letrozole](#)

By Kompella, Amala Kishan et al

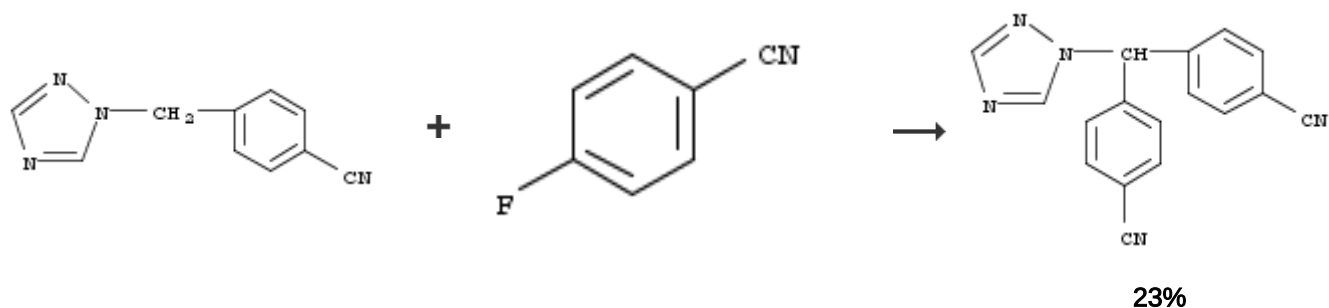
From PCT Int. Appl., 2007144896, 21 Dec 2007

Experimental Procedure

(c) Preparation of letrozole of the formula (I): To a solution of 0.54 kg of 4-(α -Bromo-4-cyanobenzyl) benzonitrile of the formula (VII) in 10L of Isopropanol are charged 0.502 kgs of 1,2,4-Triazole, 0.250 kgs of potassium carbonate and 58 gms of tetra butyl ammonium bromide. The reaction mixture is heated to reflux temperature and maintained at the same temperature for 8-9 hrs. The reaction mass is distilled to a residual volume of 2.5 L, cooled to room temperature, filtered and washed with water. Thus obtained crude letrozole is recrystallized twice with methanol to yield 252 gms of pure letrozole. Melting point: 186.3°C; purity by HPLC: 99.94%

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31. Single Step



Overview

Steps/Stages

- 1.1 C:t-BuOK, S:DMF, 28°C; 1 h, rt
- 1.2 S:DMF, rt; 0.5 h, rt
- 1.3 R:HCl, S:H₂O, rt, pH 7

Notes

Reactants: 2, Reagents: 1, Catalysts: 1, Solvents: 2, Steps: 1, Stages: 3, Most stages in any one step: 3

References

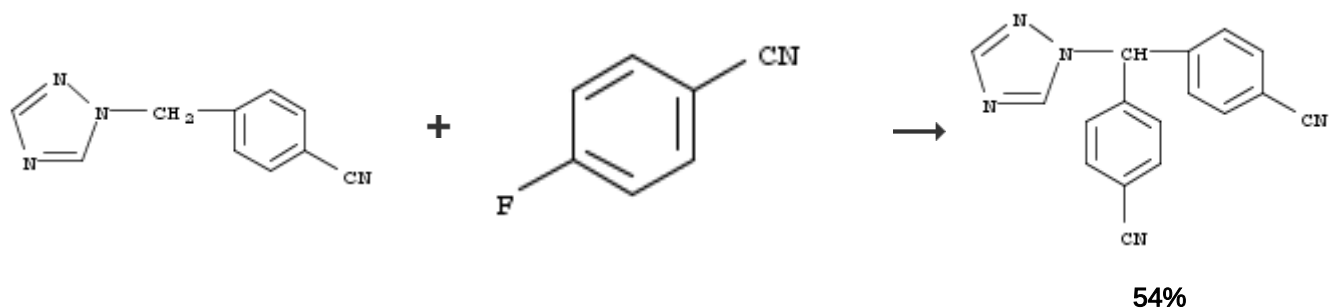
[Method for preparation of Letrozole](#)

By Chen, Tuyao

From Faming Zhuanli Shenqing Gongkai Shuomingshu, 101033214, 12 Sep 2007

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32. Single Step



[Overview](#)**Steps/Stages**

- 1.1 C:NaOEt, S:DMF, 28°C; 1 h, rt
- 1.2 S:DMF, rt; 0.5 h, rt
- 1.3 R:HCl, S:H₂O, rt, pH 7

Notes

Reactants: 2, Reagents: 1, Catalysts: 1,
Solvents: 2, Steps: 1, Stages: 3, Most stages
in any one step: 3

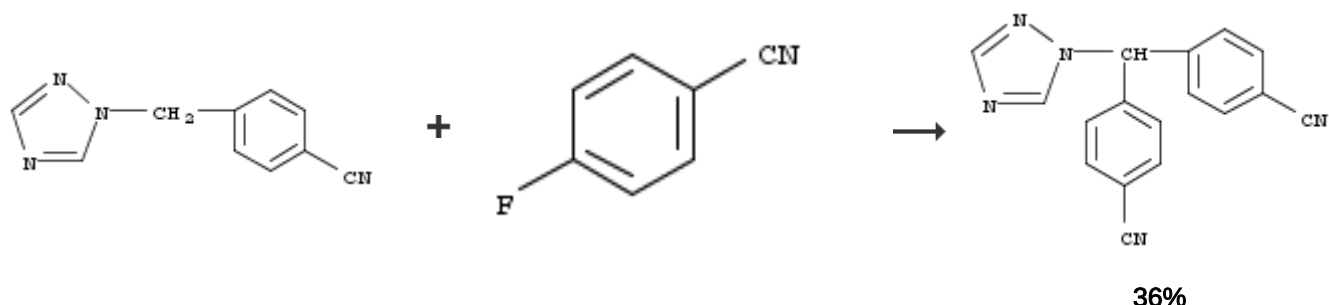
References

[Method for preparation of Letrozole](#)

By Chen, Tuyao

From Faming Zhuanli Shenqing Gongkai
Shuomingshu, 101033214, 12 Sep 2007

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33. Single Step[Overview](#)**Steps/Stages**

- 1.1 C:t-BuOK, S:DMF, 20°C; 1 h, rt
- 1.2 S:DMF, rt; 0.5 h, rt
- 1.3 R:HCl, S:H₂O, rt, pH 7

Notes

Reactants: 2, Reagents: 1, Catalysts: 1,
Solvents: 2, Steps: 1, Stages: 3, Most stages
in any one step: 3

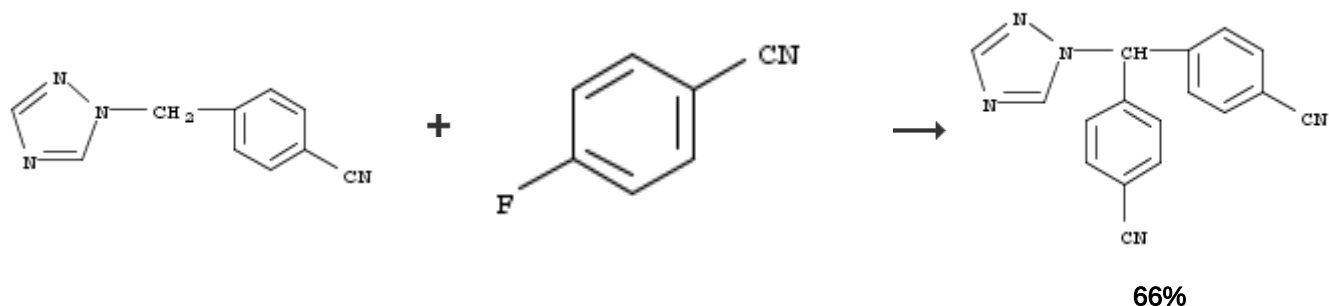
References

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34. Single Step[Overview](#)**Steps/Stages****Notes**

- 1.1 C:NaOEt, S:DMF, 20°C; 1 h, rt
 1.2 S:DMF, rt; 0.5 h, rt
 1.3 R:HCl, S:H₂O, rt, pH 7

Reactants: 2, Reagents: 1, Catalysts: 1,
 Solvents: 2, Steps: 1, Stages: 3, Most stages
 in any one step: 3

References

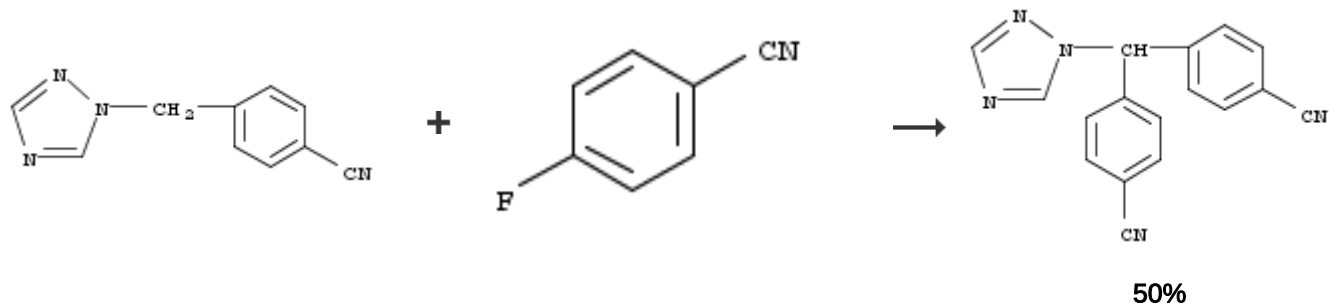
[Method for preparation of Letrozole](#)

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 Shuomingshu, 101033214, 12 Sep 2007

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35. Single Step



[Overview](#)

Steps/Stages

- 1.1 C:t-BuOK, S:DMF, 10°C; 1 h, rt
 1.2 S:DMF, rt; 0.5 h, rt
 1.3 R:HCl, S:H₂O, rt, pH 7

Notes

Reactants: 2, Reagents: 1, Catalysts: 1,
 Solvents: 2, Steps: 1, Stages: 3, Most stages
 in any one step: 3

References

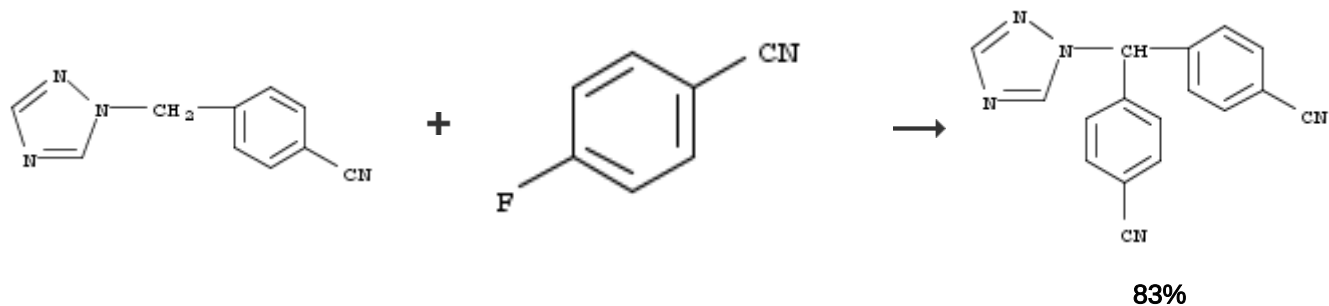
[Method for preparation of Letrozole](#)

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36. Single Step



[Overview](#)

Steps/Stages

Notes

- 1.1 C:NaOEt, S:DMF, 10°C; 1 h, rt
 1.2 S:DMF, rt; 0.5 h, rt
 1.3 R:HCl, S:H₂O, rt, pH 7

Reactants: 2, Reagents: 1, Catalysts: 1,
 Solvents: 2, Steps: 1, Stages: 3, Most stages
 in any one step: 3

References

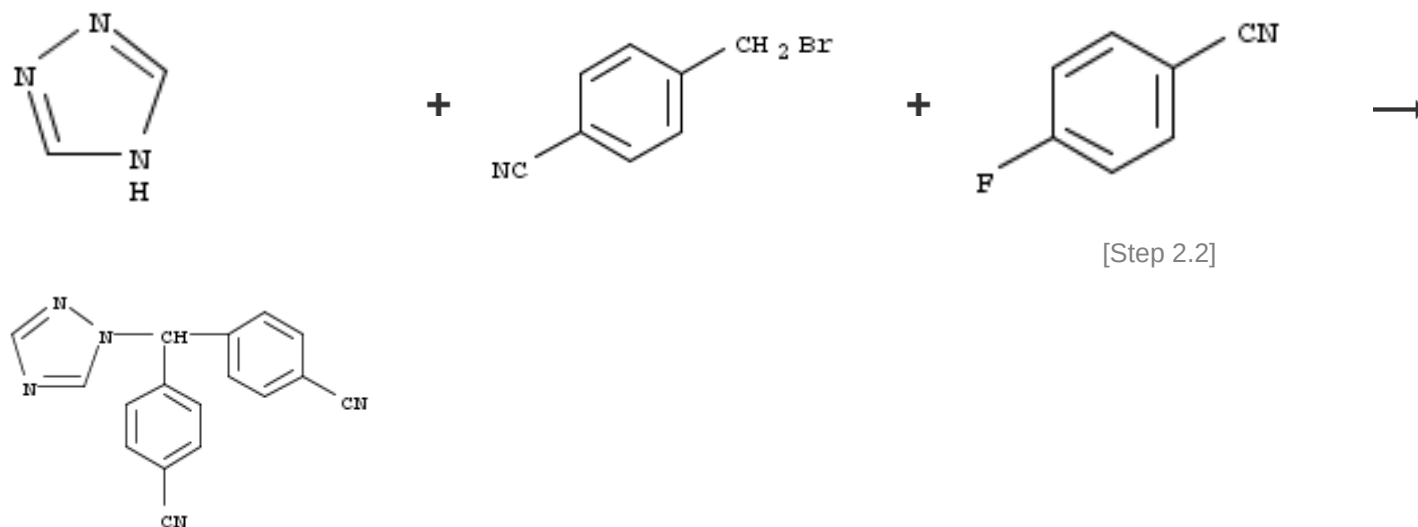
[Method for preparation of Letrozole](#)

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From Faming Zhuanli Shenqing Gongkai
 Shuomingshu, 101033214, 12 Sep 2007

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37. 2 Steps



Overview

Steps/Stages

- 1.1 R:Cs₂CO₃, C:KI, S:Me₂CO, 4 h, rt → 55°C; 55°C → rt
 1.2 S:CH₂Cl₂, 2 h, rt; 3 h, reflux
 1.3 R:HCl, S:CH₂Cl₂, S:H₂O, rt, pH 1
 2.1 R:t-BuOK, S:DMF, 90 min, -5 - 0°C; 30 min, -5 - 0°C
 2.2 S:DMF, 15 min, 0-5°C

Notes

alternative preparation shown, Reactants: 3,
 Reagents: 3, Catalysts: 1, Solvents: 4, Steps:
 2, Stages: 5, Most stages in any one step: 3

References

[Synthesis of 4-\[1-\(4-cyanophenyl\)-\(1H-1,2,4-triazol-1-yl\)methyl\]benzonitrile and 4-\[1-\(1H-1,2,4-triazol-1-yl\)methyl\]benzonitrile intermediate](#)

By Srinivas, Pathi Laxminarayan et al

From PCT Int. Appl., 2007107733, 27 Sep 2007

Experimental Procedure

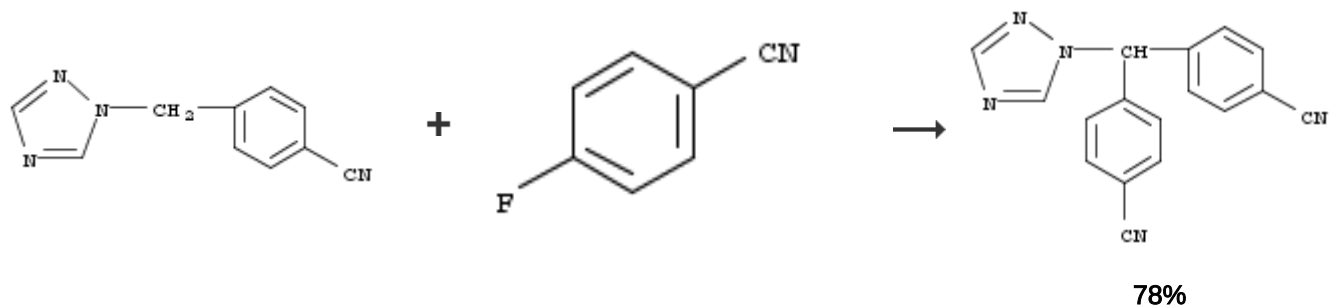
Step 1

Example 1 Preparation of 4-[1-(1,2,4-triazole-1-yl)methyl]benzonitrile, Compound of Formula II Acetone (1500 ml), 1,2,4-triazole (200 gm; 2.895 mol. eq), cesium carbonate (142 gm; 0.436 mol. eq) and potassium iodide (9 gm) was heated to reflux (55° C.) for 4 hours. The reaction mixture was cooled to room temperature. To this, a solution of 4-bromomethyl benzonitrile (100 gm; 0.510 mol. eq) in dichloromethane (450 ml) was added over a period of 2 hours. The reaction mixture was refluxed for 3 hours. After the completion of reaction, the mass was cooled to 25° C. and the insolubles filtered. The filtrate was concentrated to residue under vacuum. The residue was dissolved in dichloromethane (500 ml), washed with saturated solution of sodium chloride, acidified to a pH 1.0 with concentrated hydrochloric acid and concentrated under vacuum. To the residue, a mixture of diisopropyl ether (160 ml) and n-Heptane (160 ml) was added, stirred at 10° C. for 30 minutes, filtered, washed with n-Heptane and dried under vacuum at 40-45° C. to give 4-[1-(1,2,4-triazole-1-yl)methyl]benzonitrile (76 gm, 81% yield, 99.0% HPLC purity).

Step 2

Example 2 Preparation of 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile, Compound of Formula I A solution of 4-[1-(1,2,4-triazolyl)methyl]benzonitrile (100 gm; 0.543 mol. eq) in dimethyl formamide (480 ml) was added at a temperature of 5 to 0° C under nitrogen atmosphere to a solution of potassium tertiary butoxide (192 gm; 1.711 mol. eq) in dimethyl formamide (800 ml) over a period of 90 minutes and further stirred for 30 minutes. To this solution, a solution of 4-fluorobenzonitrile (92 gm; 0.760 mol. eq) in dimethyl formamide (480 ml) was added at temperature of 0-5° C and stirred at 5-10° C for 15 minutes. After the completion of reaction, water was added at 5-10° C and the product was extracted with ethyl acetate. The organic layer was washed with water and concentrated under vacuum below 40° C to give a syrupy liquid, to which n-Heptane (160 ml) was added, stirred at 25-30° C. for 15 minutes, filtered and washed with n-Heptane to give the crude product. The crude product was dissolved in methanol (15 volumes) at reflux temperature, treated with activated charcoal (20 gm), filtered at hot and the filtrate was concentrated to a minimum volume. The contents were then cooled to 0-5°C. for 30 minutes, filtered, washed with methanol. The product so filtered was slurried in methanol-acetone mixture at 40-45° C for 30 minutes, cooled to 20-25° C, filtered, washed with methanol and dried under vacuum at 40-45° C to give 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile (113-120 gm, 73-77.5% yield, >99.7% HPLC purity).

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38. Single Step**Overview****Steps/Stages**

- 1.1 R:t-BuOK, S:DMF, 90 min, -5 - 0°C; 30 min, -5 - 0°C
- 1.2 S:DMF, 15 min, 0-5°C

Notes

alternative preparation shown, Reactants: 2, Reagents: 1, Solvents: 1, Steps: 1, Stages: 2, Most stages in any one step: 2

References

[Synthesis of 4-\[1-\(4-cyanophenyl\)-\(1H-1,2,4-triazol-1-yl\)methyl\]benzonitrile and 4-\[1-\(1H-1,2,4-triazol-1-yl\)methyl\]benzonitrile intermediate](#)

By Srinivas, Pathi Laxminarayan et al

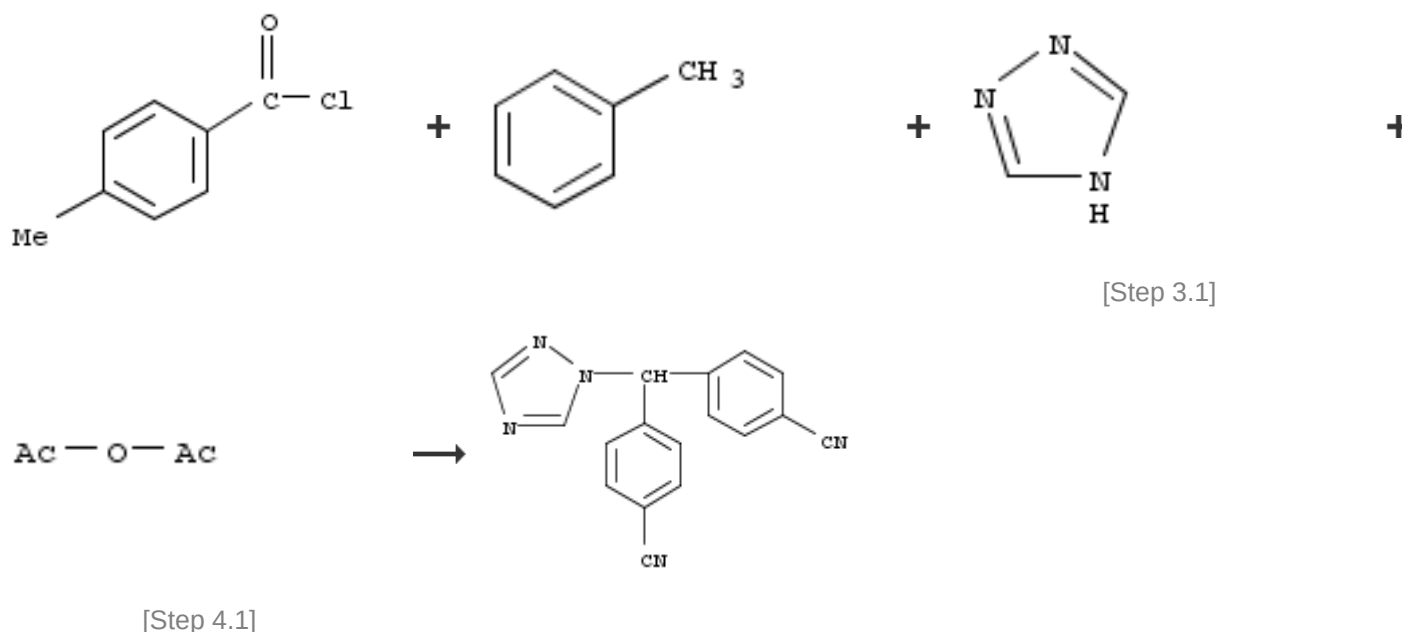
From PCT Int. Appl., 2007107733, 27 Sep 2007

Experimental Procedure

Example 2 Preparation of 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile, Compound of Formula I A solution of 4-[1-(1,2,4-triazolyl)methyl]benzonitrile (100 gm; 0.543 mol. eq) in dimethyl formamide (480 ml) was added at a temperature of 5 to 0° C under nitrogen atmosphere to a solution of potassium tertiary butoxide (192 gm; 1.711 mol. eq) in dimethyl formamide (800 ml) over a period of 90 minutes and further stirred for 30 minutes. To this solution, a solution of 4-fluorobenzonitrile (92 gm; 0.760 mol. eq) in dimethyl formamide (480 ml) was added at temperature of 0-5° C and stirred at 5-10° C for 15 minutes. After the completion of reaction, water was added at 5-10° C and the product was extracted with ethyl acetate. The organic layer was washed with water and concentrated under vacuum below 40° C to give a syrupy liquid, to which n-Heptane (160 ml) was added, stirred at 25-30° C. for 15 minutes, filtered and washed with n-Heptane to give the crude product. The crude product was dissolved in methanol (15 volumes) at reflux temperature, treated with activated charcoal (20 gm), filtered at hot and the filtrate was concentrated to a minimum volume. The contents were then cooled to 0-5°C. for 30 minutes, filtered, washed with methanol. The product so filtered was slurried in methanol-acetone mixture at 40-45° C for 30 minutes, cooled to 20-25° C, filtered, washed with methanol and dried under vacuum at 40-45° C to give 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile (113-120 gm, 73-77.5% yield, >99.7% HPLC purity).

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39. 7 Steps



Overview

Steps/Stages

- 1.1 R:AlCl₃, 1 h, -5 - 0°C; 5-6 h, 0°C
- 2.1 R:NaBH₄, S:MeOH, 30-35°C; 30 min, 3-35°C
- 3.1 R:H₂SO₄, S:ClCH₂CH₂Cl, 30 min, -10°C; 3-4 h, -10°C
- 4.1 R:H₂SO₄, 30 min, -15°C; 30 h, -15°C
- 4.2 R:CrO₃, 1 h, -15 - -10°C; 4 h, -15 - -10°C
- 5.1 R:KOH, S:MeOH, 30 min, rt
- 5.2 R:HCl, S:MeOH, S:H₂O, neutralized
- 6.1 R:KOH, R:H₂NOH-HCl, S:Me₂CHOH, S:H₂O, 4 h, reflux
- 7.1 R:Ac₂O, 8-10 h, reflux

Experimental Procedure

Notes

Reactants: 4, Reagents: 8, Solvents: 4, Steps: 7, Stages: 9, Most stages in any one step: 2

References

[Intermediates for preparation of letrozole](#)

By Agarwal, Shiv Kumar et al

From PCT Int. Appl., 2007074474, 05 Jul 2007

Step 1

Preparation of 4,4'- Dimethyl benzophenone (8) To a solution of p-Toluoyl chloride (50g, 0.32 mol) in toluene (250ml) cooled to -5 °C. was added Aluminium chloride (75.5g, 0.56 mol) in lots over a period of 1h maintaining temperature between -5 to 0°C. after complete addition of Aluminium chloride, the reaction was further stirred for 5 - 6h to ensure complete consumption of p-toluoyl chloride (by HPLC). The reaction mixture was then slowly poured in to a mixture of crashed ice (1.5 Kg) and cone. HCl (750ml) maintaining temperature between 0 to 10°C. The products were extracted into ethyl acetate (1000 ml). The ethyl acetate layer was separated and washed with water to neutral PH (6 - 7). Finally ethyl acetate was concentrated on a rota evaporator to give 4,4'-dimethyl benzophenone as a solid (50g). (M.Pt. 90- 93°C) ¹H NMR (CDCl₃): δ 7.74 - 7.70 (m, 4H), 7.31 - 7.28 (m, 4H), 2.46 (s, 6H). Mass Spectrum: [M+1], 211

Step 2

Preparation of 4,4'- Dimethyl benzhydrol (9) To a solution of 4,4'-dimethyl benzophenone obtained from experiment 1 (50g, 0.23 mol) in methanol (1500 ml) at ambient temperature was added Sodium borohydride (15g, 0.39 mol) in lots maintaining temperature at 30 - 35°C. After complete addition of sodium borohydride, the reaction mixture was stirred for further 30 min. The reaction mixture was adjusted to PH ~7 and methanol was recovered on a rota- evaporator under reduced pressure to give an oily mass which was diluted with water (500ml) and cooled to 10 - 15°C to give a solid. The solid was filtered and washed with water and dried (50g). (M.Pt. 70 - 72°C.) ¹H NMR (CDCl₃): δ 7.26 - 7.23 (m, 4H), 7.14 - 7.11 (m, 4H), 5.77 (s, 1H), 2.3 (s, 6H) Mass Spectrum: [M+ Na], 235

Step 3

Preparation of α - (1H-1, 2,4-Triazolyl) - 4,4'-dimethyldiphenylmethane (IIa) A solution of 4,4'-dimethyl benzhydrol (25g, 0.11mol) in 1,2-dichloroethane (1000 ml) was cooled to -10 °C. and to it was added cone. Sulphuric acid (25 ml) drop-wise over a period of 30 minutes. The solution was stirred at this temperature for 30 min. more and added 1.2,4-triazole (250g, 3.61 mol) in one lot. The reaction mixture was stirred for 3- 4h. Unconsumed triazole was filtered out and the filtrate washed with (2x200ml) of water. The organic layer was dried over Anh. Sodium Sulphate and then concentrated on a rota- evaporator to give alpha (1H-1, 2,4-Triazolyl) - 4,4'-dimethyldiphenylmethane (28g). This was further purified by column chromatography (SiO₂ 60-120, Ethyl acetate: hexane). M.P. - 101°C. ¹H NMR (CDCl₃): δ 8.0 (s, 1H), 7.9 (s, 1H), 7.25 - 7.15 (m, 4H), 7.02 - 7.00 (m, 4H) 6.68 (s, 1H), 2.34 (s, 12H). IR (KBr) (ν Cm⁻¹): 1513.5, 1431.6 Mass Spectrum: [M+Na], 286

Step 4

Preparation of α - (1H-1, 2,4-Triazolyl) - 4,4'-dimethylidinetetraacetoxy diphenylmethane (IIb) To a solution of alpha (1H-1, 2,4-Triazolyl) - 4,4'-dimethyldiphenylmethane (25g, 0.09 mol) in acetic anhydride (250ml) cooled to -15 °C, was added cone. Sulphuric acid (40 ml) over a period of 30 min. and stirred for another 30 min. at the same temperature. A solution of chromium trioxide (37.5g, 0.37 mol) in acetic anhydride (250 ml) was added to the reaction slowly at -15 -to -10°C in 1H. The reaction mixture was further stirred for 4h The reaction mixture was poured into 2L of water and extracted with ethyl acetate (1L). The ethyl acetate layer was dried and evaporated to give crude α - (1H-1, 2,4-Triazolyl) - 4,4'-dimethylidinetetraacetoxy diphenylmethane (40g). This is on purification by column chromatography (SiO₂, Ethyl acetate: Hexane) followed by recrystallisation from IPA produced the titled compound (12 g). (M.Pt.103°C) . IR (KBr) (ν Cm⁻¹): 1753, 1515, 1424.5 ¹H NMR (CDCl₃): δ 8.03 (s, 1H), 7.97 (s, 1H), 7.66 (s, 2H), 7.55 - 7.52 (m, 4H), 7.26 - 7.17 (m, 4H), 6.76 (s, 1H), 2.12 (s, 12H). Mass Spectrum: [M+H]⁺ 496, [M+ Na]⁺ 518.1

Step 5

Preparation of α - (1H-1, 2,4-Triazolyl) - 4,4'-diformyl diphenylmethane (IIc) To a solution of alpha (1H-1, 2,4-Triazolyl) - 4,4'-dimethylidinetetraacetoxy diphenylmethane (5g, 0.01 mol) in methanol (200 ml) was added a solution of potassium hydroxide (2.25g, 0.04 mol) dissolved in methanol (25 ml) at room temperature. The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was neutralized with 6 N Hydrochloric acid. Methanol was removed under reduced pressure. Water (100 ml) was added to the residue and the products were extracted into ethyl acetate (100ml). Removal of ethyl acetate under reduced pressure gives crude alpha (1H- 1 , 2,4-Triazolyl) - 4,4'-diformyl diphenylmethane (2.8g). This was further purified by column chromatography to give the pure product (Ig). IR (KBr) (ν Cm⁻¹): 1703.8, 1605.8, 1503.5 ¹H NMR (CDCl₃): δ 10.04 (s,2H), 8.08 (m, 2H,Tz), 7.93 - 7.91 (m, Ar, 4H), 7.36 - 7.27 (m,4H,Ar), 6.88 (s, 1H) Mass Spectrum: [M-1], 290.2

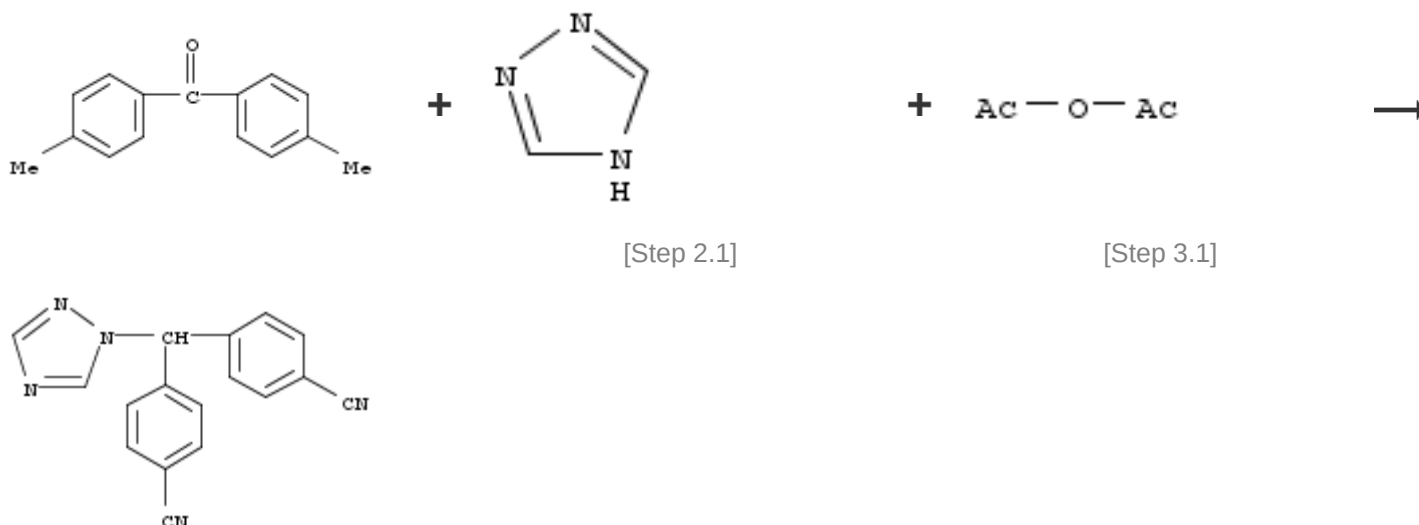
Step 6

Preparation of α - (1H-1, 2,4-Triazolyl) - 4,4'-diformaldoxime diphenylmethane (IId) To a solution of α - (1H-1, 2,4-Triazolyl) - 4,4'-diformyl diphenylmethane (5g, 0.017 mol) in isopropyl alcohol (150 ml) was added a solution of hydroxy lamine hydrochloride (4.77g, 0.068 mol) in water (30ml) previously neutralized with potassium hydroxide (3.84g, 0.068 mol) at room temperature. The reaction mixture was refluxed for 4hrs. Isopropyl alcohol was removed on a rota-evaporator under reduced pressure to leave a gummy mass. Water (50ml) was added to the residue and stirred for 2-3h at 10 °C. The solid mass separated was filtered and dried (4.13g). M.Pt. 222 - 224 °C. A sample of the product was further recrystallised from methanol to give the pure compound. m. p. 234.6° C. IR (KBr) (ν Cm⁻¹): 3270, 2970, 1510, and 1450 ¹H NMR (DMSO-d₆): δ ppm 11.3 (s,2H), 8.12 (s, 1H), 8.08 (s, 1H), 7.61 - 7.58 (m, 4H), 7.26 - 7.24 (m,4H), 7.13 (s, 1H), Mass Spectrum: [M+H]⁺, 322.1 , [M+ Na]⁺, 344.1 , [M-Triazole+ H]⁺, 254.2

Step 7

Preparation of 4,4'-(1H-1, 2,4-triazol-1-yl-methylene)-bisbenzonitrile / Letrozole (I) A solution of alpha (1H-1, 2,4-Triazolyl) - 4,4'-diformaldoxime diphenylmethane (5g, 0.015 mol) in acetic anhydride (12.5ml) was refluxed for 8-10h. The reaction mixture was cooled to room temperature and poured into water (200ml) and stirred for 1h. The solid mass precipitated was filtered. The residue was washed several times with water to remove acetic anhydride. The solid was dried to get Letrozole (4.3g). ¹H NMR (CDCl₃): δ ppm 8.09 (s, 1H), 8.07 (s, 1H), 7.72 - 7.69 (m, 4H), 7.36 - 7.27 (m, 4H), 6.84 (s, 1H), Mass Spectrum: [M-1], 284.3

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40. 6 Steps**Overview****Steps/Stages**

- 1.1 R:NaBH₄, S:MeOH, 30-35°C; 30 min, 3-35°C
- 2.1 R:H₂SO₄, S:ClCH₂CH₂Cl, 30 min, -10°C; 3-4 h, -10°C
- 3.1 R:H₂SO₄, 30 min, -15°C; 30 h, -15°C
- 3.2 R:CrO₃, 1 h, -15 - -10°C; 4 h, -15 - -10°C
- 4.1 R:KOH, S:MeOH, 30 min, rt
- 4.2 R:HCl, S:MeOH, S:H₂O, neutralized
- 5.1 R:KOH, R:H₂NOH-HCl, S:Me₂CHOH, S:H₂O, 4 h, reflux
- 6.1 R:Ac₂O, 8-10 h, reflux

Experimental Procedure**Step 1**

Preparation of 4,4'- Dimethyl benzhydrol (9) To a solution of 4,4 '-dimethyl benzophenone obtained from experiment 1 (50g, 0.23 mol) in methanol (1500 ml) at ambient temperature was added Sodium borohydride (15g, 0.39 mol) in lots maintaining temperature at 30 - 35°C. After complete addition of sodium borohydride, the reaction mixture was stirred for further 30 min. The reaction mixture was adjusted to PH ~7 and methanol was recovered on a rota- evaporator under reduced pressure to give an oily mass which was diluted with water (500ml) and cooled to 10 - 15°C to give a solid. The solid was filtered and washed with water and dried (50g). (M.Pt. 70 - 72°C.) ¹H NMR (CDCl₃): δ 7.26 - 7.23 (m, 4H), 7.14 - 7.11 (m, 4H), 5.77 (s, 1H), 2.3 (s, 6H) Mass Spectrum: [M+ Na], 235

Notes

Reactants: 3, Reagents: 7, Solvents: 4, Steps: 6, Stages: 8, Most stages in any one step: 2

References

[Intermediates for preparation of letrozole](#)

By Agarwal, Shiv Kumar et al

From PCT Int. Appl., 2007074474, 05 Jul 2007

Step 2

Preparation of α - (1H-1, 2,4-Triazolyl) - 4,4'-dimethyldiphenylmethane (IIa) A solution of 4,4'-dimethyl benzhydrol (25g, 0.11mol) in 1,2-dichloroethane (1000 ml) was cooled to -10 °C. and to it was added cone. Sulphuric acid (25 ml) drop-wise over a period of 30 minutes. The solution was stirred at this temperature for 30 min. more and added 1.2,4-triazole (250g, 3.61 mol) in one lot. The reaction mixture was stirred for 3- 4h. Unconsumed triazole was filtered out and the filtrate washed with (2x200ml) of water. The organic layer was dried over Anhydrous Sodium Sulphate and then concentrated on a rota- evaporator to give α (1H-1, 2,4-Triazolyl) - 4,4'-dimethyldiphenylmethane (28g). This was further purified by column chromatography (SiO₂ 60-120, Ethyl acetate: hexane). M.P. - 101°C. ¹H NMR (CDCl₃): δ 8.0 (s, 1H), 7.9 (s, 1H), 7.25 - 7.15 (m, 4H), 7.02 - 7.00 (m, 4H) 6.68 (s, 1H), 2.34 (s, 12H). IR (KBr) (ν Cm⁻¹): 1513.5, 1431.6 Mass Spectrum: [M+Na], 286

Step 3

Preparation of α - (1H-1, 2,4-Triazolyl) - 4,4'-dimethylidinetetraacetoxy diphenylmethane (IIb) To a solution of α (1H-1, 2,4-Triazolyl) - 4,4'-dimethyldiphenylmethane (25g, 0.09 mol) in acetic anhydride (250ml) cooled to -15 °C, was added cone. Sulphuric acid (40 ml) over a period of 30 min. and stirred for another 30 min. at the same temperature. A solution of chromium trioxide (37.5g, 0.37 mol) in acetic anhydride (250 ml) was added to the reaction slowly at -15 to -10°C in 1H. The reaction mixture was further stirred for 4h The reaction mixture was poured into 2L of water and extracted with ethyl acetate (1L). The ethyl acetate layer was dried and evaporated to give crude α - (1H-1, 2,4-Triazolyl) - 4,4'-dimethylidinetetraacetoxy diphenylmethane (40g). This is on purification by column chromatography (SiO₂, Ethyl acetate: Hexane) followed by recrystallisation from IPA produced the titled compound (12 g). (M.Pt.103°C) . IR (KBr) (ν Cm⁻¹): 1753, 1515, 1424.5 ¹H NMR (CDCl₃): δ 8.03 (s, 1H), 7.97 (s, 1H), 7.66 (s, 2H), 7.55 - 7.52 (m, 4H), 7.26 - 7.17 (m, 4H), 6.76 (s, 1H), 2.12 (s, 12H). Mass Spectrum: [M+H]⁺ 496, [M+ Na]⁺ 518.1

Step 4

Preparation of α - (1H-1, 2,4-Triazolyl) - 4,4'-diformyl diphenylmethane (IIc) To a solution of α (1H-1, 2,4-Triazolyl) - 4,4'-dimethylidinetetraacetoxy diphenylmethane (5g, 0.01 mol) in methanol (200 ml) was added a solution of potassium hydroxide (2.25g, 0.04 mol) dissolved in methanol (25 ml) at room temperature. The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was neutralized with 6 N Hydrochloric acid. Methanol was removed under reduced pressure. Water (100 ml) was added to the residue and the products were extracted into ethyl acetate (100ml). Removal of ethyl acetate under reduced pressure gives crude α (1H- 1 , 2,4-Triazolyl) - 4,4'-diformyl diphenylmethane (2.8g). This was further purified by column chromatography to give the pure product (1g). IR (KBr) (ν Cm⁻¹): 1703.8, 1605.8, 1503.5 ¹H NMR (CDCl₃): δ 10.04 (s,2H), 8.08 (m, 2H,Tz), 7.93 - 7.91 (m, Ar, 4H), 7.36 - 7.27 (m,4H,Ar), 6.88 (s, 1H) Mass Spectrum: [M-1], 290.2

Step 5

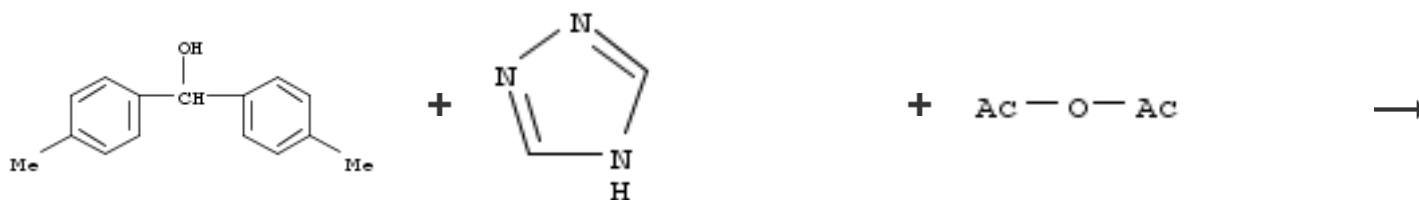
Preparation of α - (1H-1, 2,4-Triazolyl) - 4,4'-diformaldoxime diphenylmethane (IId) To a solution of α - (1H-1, 2,4-Triazolyl) - 4,4'-diformyl diphenylmethane (5g, 0.017 mol) in isopropyl alcohol (150 ml) was added a solution of hydroxy lamine hydrochloride (4.77g, 0.068 mol) in water (30ml) previously neutralized with potassium hydroxide (3.84g, 0.068 mol) at room temperature. The reaction mixture was refluxed for 4hrs. Isopropyl alcohol was removed on a rota-evaporator under reduced pressure to leave a gummy mass. Water (50ml) was added to the residue and stirred for 2-3h at 10 °C. The solid mass separated was filtered and dried (4.13g). M.Pt. 222 - 224 °C. A sample of the product was further recrystallised from methanol to give the pure compound. m. p. 234.6° C. IR (KBr) (ν Cm⁻¹): 3270, 2970, 1510, and 1450 ¹H NMR (DMSO-d₆): δ ppm 11.3 (s,2H), 8.12 (s, 1H), 8.08 (s, 1H), 7.61 - 7.58 (m, 4H), 7.26 - 7.24 (m,4H), 7.13 (s, 1H), Mass Spectrum: [M+H]⁺, 322.1 , [M+ Na]⁺, 344.1 , [M-Triazole+ H]⁺, 254.2

Step 6

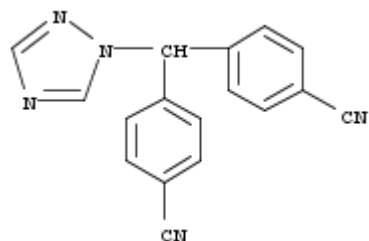
Preparation of 4,4'-(1H-1, 2,4-triazol-1yl-methylene)-bisbenzonitrile / Letrozole (I) A solution of α (1H-1, 2,4-Triazolyl) - 4,4'-diformaldoxime diphenylmethane (5g, 0.015 mol) in acetic anhydride (12.5ml) was refluxed for 8-10h. The reaction mixture was cooled to room temperature and poured into water (200ml) and stirred for 1H. The solid mass precipitated was filtered. The residue was washed several times with water to remove acetic anhydride. The solid was dried to get Letrozole (4.3g). ¹H NMR (CDCl₃): δ ppm 8.09 (s, 1H), 8.07 (s, 1H), 7.72 - 7.69 (m, 4H), 7.36 - 7.27 (m, 4H), 6.84 (s, 1H), Mass Spectrum: [M-1], 284.3

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41. 5 Steps



[Step 2.1]



Overview

Steps/Stages

- 1.1 R:H₂SO₄, S:ClCH₂CH₂Cl, 30 min, -10°C; 3-4 h, -10°C
- 2.1 R:H₂SO₄, 30 min, -15°C; 30 h, -15°C
- 2.2 R:CrO₃, 1 h, -15 - -10°C; 4 h, -15 - -10°C
- 3.1 R:KOH, S:MeOH, 30 min, rt
- 3.2 R:HCl, S:MeOH, S:H₂O, neutralized
- 4.1 R:KOH, R:H₂NOH-HCl, S:Me₂CHOH, S:H₂O, 4 h, reflux
- 5.1 R:Ac₂O, 8-10 h, reflux

Notes

Reactants: 3, Reagents: 6, Solvents: 4, Steps: 5, Stages: 7, Most stages in any one step: 2

References

[Intermediates for preparation of letrozole](#)

By Agarwal, Shiv Kumar et al

From PCT Int. Appl., 2007074474, 05 Jul 2007

Experimental Procedure

Step 1

Preparation of α - (1H-1, 2,4-Triazolyl) - 4,4'-dimethyldiphenylmethane (IIa) A solution of 4,4'-dimethyl benzhydrol (25g, 0.11mol) in 1,2-dichloroethane (1000 ml) was cooled to -10 °C. and to it was added cone. Sulphuric acid (25 ml) drop-wise over a period of 30 minutes. The solution was stirred at this temperature for 30 min. more and added 1.2,4-triazole (250g, 3.61 mol) in one lot. The reaction mixture was stirred for 3- 4h. Unconsumed triazole was filtered out and the filtrate washed with (2x200ml) of water. The organic layer was dried over Anh. Sodium Sulphate and then concentrated on a rota- evaporator to give α (1H-1, 2,4-Triazolyl) - 4,4'-dimethyldiphenylmethane (28g). This was further purified by column chromatography (SiO₂ 60-120, Ethyl acetate: hexane). M.P. - 101°C. ¹H NMR (CDCl₃): δ 8.0 (s, 1H), 7.9 (s, 1H), 7.25 - 7.15 (m, 4H), 7.02 - 7.00 (m, 4H) 6.68 (s, 1H), 2.34 (s, 12H). IR (KBr) (ν Cm⁻¹): 1513.5, 1431.6 Mass Spectrum: [M+Na], 286

Step 2

Preparation of α - (1H-1, 2,4-Triazolyl) - 4,4'-dimethylidinetetraacetoxy diphenylmethane (IIb) To a solution of α (1H-1, 2,4-Triazolyl) - 4,4'-dimethyldiphenylmethane (25g, 0.09 mol) in acetic anhydride (250ml) cooled to -15 °C, was added cone. Sulphuric acid (40 ml) over a period of 30 min. and stirred for another 30 min. at the same temperature. A solution of chromium trioxide (37.5g, 0.37 mol) in acetic anhydride (250 ml) was added to the reaction slowly at -15 -to -10°C in 1h. The reaction mixture was further stirred for 4h The reaction mixture was poured into 2L of water and extracted with ethyl acetate (1L). The ethyl acetate layer was dried and evaporated to give crude α - (1H-1, 2,4-Triazolyl) - 4,4'-dimethylidinetetraacetoxy diphenylmethane (40g). This is on purification by column chromatography (SiO₂, Ethyl acetate: Hexane) followed by recrystallisation from IPA produced the titled compound (12 g). (M.Pt.103°C) . IR (KBr) (ν Cm⁻¹): 1753, 1515, 1424.5 ¹H NMR (CDCl₃): δ 8.03 (s, 1H), 7.97 (s, 1H), 7.66 (s, 2H), 7.55 - 7.52 (m, 4H), 7.26 - 7.17 (m, 4H), 6.76 (s, 1H), 2.12 (s, 12H). Mass Spectrum: [M+H]⁺ 496, [M+ Na]⁺ 518.1

Step 3

Preparation of α - (1H-1, 2,4-Triazolyl) - 4,4'-diformyl diphenylmethane (IIc) To a solution of α - (1H-1, 2,4-Triazolyl) - 4,4'-dimethylidinetetraacetoxy diphenylmethane (5g, 0.01 mol) in methanol (200 ml) was added a solution of potassium hydroxide (2.25g, 0.04 mol) dissolved in methanol (25 ml) at room temperature. The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was neutralized with 6 N Hydrochloric acid. Methanol was removed under reduced pressure. Water (100 ml) was added to the residue and the products were extracted into ethyl acetate (100ml). Removal of ethyl acetate under reduced pressure gives crude α - (1H-1, 2,4-Triazolyl) - 4,4'-diformyl diphenylmethane (2.8g). This was further purified by column chromatography to give the pure product (Ig). IR (KBr) (ν cm^{-1}): 1703.8, 1605.8, 1503.5 ^1H NMR (CDCl_3): δ 10.04 (s, 2H), 8.08 (m, 2H, Tz), 7.93 - 7.91 (m, Ar, 4H), 7.36 - 7.27 (m, 4H, Ar), 6.88 (s, 1H) Mass Spectrum: [M-1], 290.2

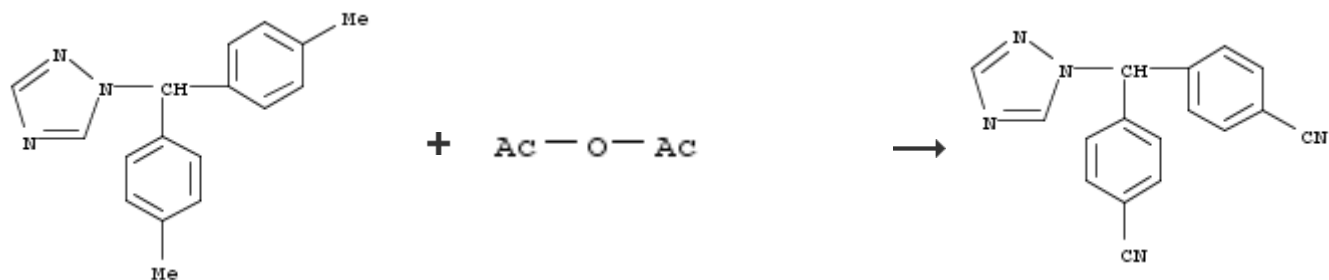
Step 4

Preparation of α - (1H-1, 2,4-Triazolyl) - 4,4'-diformaldoxime diphenylmethane (IIId) To a solution of α - (1H-1, 2,4-Triazolyl) - 4,4'-diformyl diphenylmethane (5g, 0.017 mol) in isopropyl alcohol (150 ml) was added a solution of hydroxy lamine hydrochloride (4.77g, 0.068 mol) in water (30ml) previously neutralized with potassium hydroxide (3.84g, 0.068 mol) at room temperature. The reaction mixture was refluxed for 4hrs. Isopropyl alcohol was removed on a rota-evaporator under reduced pressure to leave a gummy mass. Water (50ml) was added to the residue and stirred for 2-3h at 10 °C. The solid mass separated was filtered and dried (4.13g). M.Pt. 222 - 224 °C. A sample of the product was further recrystallised from methanol to give the pure compound. m. p. 234.6° C. IR (KBr) (ν cm^{-1}): 3270, 2970, 1510, and 1450 ^1H NMR ($\text{DMSO}-d_6$): δ ppm 11.3 (s, 2H), 8.12 (s, 1H), 8.08 (s, 1H), 7.61 - 7.58 (m, 4H), 7.26 - 7.24 (m, 4H), 7.13 (s, 1H), Mass Spectrum: [M+H]⁺, 322.1, [M+ Na]⁺, 344.1, [M-Triazole+ H]⁺, 254.2

Step 5

Preparation of 4,4'-(1H-1, 2,4-triazol-1yl-methylene)-bisbenzonitrile / Letrozole (I) A solution of α - (1H-1, 2,4-Triazolyl) - 4,4'-diformaldoxime diphenylmethane (5g, 0.015 mol) in acetic anhydride (12.5ml) was refluxed for 8-10h. The reaction mixture was cooled to room temperature and poured into water (200ml) and stirred for 1h. The solid mass precipitated was filtered. The residue was washed several times with water to remove acetic anhydride. The solid was dried to get Letrozole (4.3g). ^1H NMR (CDCl_3): δ ppm 8.09 (s, 1H), 8.07 (s, 1H), 7.72 - 7.69 (m, 4H), 7.36 - 7.27 (m, 4H), 6.84 (s, 1H), Mass Spectrum: [M-1], 284.3

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42. 4 Steps[Overview](#)**Steps/Stages**

- 1.1 R:H₂SO₄, 30 min, -15°C; 30 h, -15°C
- 1.2 R:CrO₃, 1 h, -15 - -10°C; 4 h, -15 - -10°C
- 2.1 R:KOH, S:MeOH, 30 min, rt
- 2.2 R:HCl, S:MeOH, S:H₂O, neutralized
- 3.1 R:KOH, R:H₂NOH-HCl, S:Me₂CHOH, S:H₂O, 4 h, reflux
- 4.1 R:Ac₂O, 8-10 h, reflux

[Experimental Procedure](#)**Notes**

Reactants: 2, Reagents: 6, Solvents: 3, Steps: 4, Stages: 6, Most stages in any one step: 2

References

[Intermediates for preparation of letrozole](#)

By Agarwal, Shiv Kumar et al

From PCT Int. Appl., 2007074474, 05 Jul 2007

Step 1

Preparation of α - (1H-1, 2,4-Triazolyl) - 4,4'-dimethylidinetetraacetoxy diphenylmethane (IIb) To a solution of α (1H-1, 2,4-Triazolyl) - 4,4'-dimethyldiphenylmethane (25g, 0.09 mol) in acetic anhydride (250ml) cooled to -15 °C, was added cone. Sulphuric acid (40 ml) over a period of 30 min. and stirred for another 30 min. at the same temperature. A solution of chromium trioxide (37.5g, 0.37 mol) in acetic anhydride (250 ml) was added to the reaction slowly at -15 -to -10°C in 1H. The reaction mixture was further stirred for 4h The reaction mixture was poured into 2L of water and extracted with ethyl acetate (1L). The ethyl acetate layer was dried and evaporated to give crude α - (1H-1, 2,4-Triazolyl) - 4,4'-dimethylidinetetraacetoxy diphenylmethane (40g). This is on purification by column chromatography (SiO₂, Ethyl acetate: Hexane) followed by recrystallisation from IPA produced the titled compound (12 g). (M.Pt.103°C) . IR (KBr) (ν Cm⁻¹): 1753, 1515, 1424.5 ¹H NMR (CDCl₃): δ 8.03 (s, 1H), 7.97 (s, 1H), 7.66 (s, 2H), 7.55 - 7.52 (m, 4H), 7.26 - 7.17 (m, 4H), 6.76 (s, 1H), 2.12 (s, 12H). Mass Spectrum: [M+H]⁺ 496, [M+ Na]⁺ 518.1

Step 2

Preparation of α - (1H-1, 2,4-Triazolyl) - 4,4'-diformyl diphenylmethane (IIc) To a solution of α (1H-1, 2,4-Triazolyl) - 4,4'-dimethylidinetetraacetoxy diphenylmethane (5g, 0.01 mol) in methanol (200 ml) was added a solution of potassium hydroxide (2.25g, 0.04 mol) dissolved in methanol (25 ml) at room temperature. The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was neutralized with 6 N Hydrochloric acid. Methanol was removed under reduced pressure. Water (100 ml) was added to the residue and the products were extracted into ethyl acetate (100ml). Removal of ethyl acetate under reduced pressure gives crude α (1H- 1 , 2,4-Triazolyl) - 4,4'-diformyl diphenylmethane (2.8g). This was further purified by column chromatography to give the pure product (Ic). IR (KBr) (ν Cm⁻¹): 1703.8, 1605.8, 1503.5 ¹H NMR (CDCl₃): δ 10.04 (s,2H), 8.08 (m, 2H,Tz), 7.93 - 7.91 (m, Ar, 4H), 7.36 - 7.27 (m,4H,Ar), 6.88 (s, 1H) Mass Spectrum: [M-1], 290.2

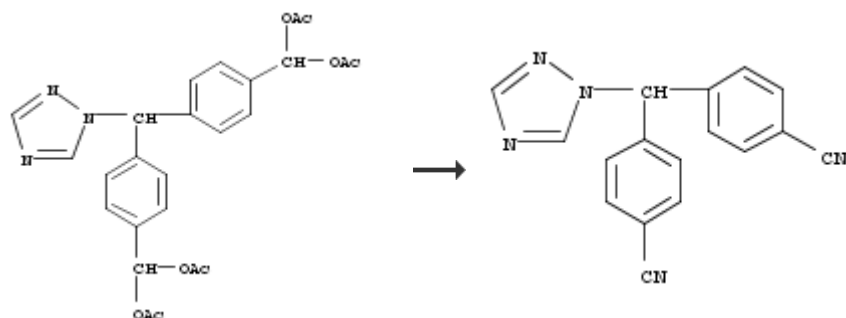
Step 3

Preparation of α - (1H-1, 2,4-Triazolyl) - 4,4'-diformaldoxime diphenylmethane (IId) To a solution of α - (1H-1, 2,4-Triazolyl) - 4,4'-diformyl diphenylmethane (5g, 0.017 mol) in isopropyl alcohol (150 ml) was added a solution of hydroxy lamine hydrochloride (4.77g, 0.068 mol) in water (30ml) previously neutralized with potassium hydroxide (3.84g, 0.068 mol) at room temperature. The reaction mixture was refluxed for 4hrs. Isopropyl alcohol was removed on a rota-evaporator under reduced pressure to leave a gummy mass. Water (50ml) was added to the residue and stirred for 2-3h at 10 °C. The solid mass separated was filtered and dried (4.13g). M.Pt. 222 - 224 °C. A sample of the product was further recrystallised from methanol to give the pure compound. m. p. 234.6° C. IR (KBr) (ν Cm⁻¹): 3270, 2970, 1510, and 1450 ¹H NMR (DMSO-d₆): δ ppm 11.3 (s,2H), 8.12 (s, 1H), 8.08 (s, 1H), 7.61 - 7.58 (m, 4H), 7.26 - 7.24 (m,4H), 7.13 (s, 1H), Mass Spectrum: [M+H]⁺, 322.1 , [M+ Na]⁺, 344.1 , [M-Triazole+ H]⁺, 254.2

Step 4

Preparation of 4,4'-(1H-1, 2,4-triazol-1yl-methylene)-bisbenzonitrile / Letrozole (I) A solution of α (1H-1, 2,4-Triazolyl) - 4,4'-diformaldoxime diphenylmethane (5g, 0.015 mol) in acetic anhydride (12.5ml) was refluxed for 8-10h. The reaction mixture was cooled to room temperature and poured into water (200ml) and stirred for 1H. The solid mass precipitated was filtered. The residue was washed several times with water to remove acetic anhydride. The solid was dried to get Letrozole (4.3g). ¹H NMR (CDCl₃): δ ppm 8.09 (s, 1H), 8.07 (s, 1H), 7.72 - 7.69 (m, 4H), 7.36 - 7.27 (m, 4H), 6.84 (s, 1H), Mass Spectrum: [M-1], 284.3

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43. 3 Steps
[Overview](#)
[Steps/Stages](#)
[Notes](#)

- 1.1 R:KOH, S:MeOH, 30 min, rt
 1.2 R:HCl, S:MeOH, S:H₂O, neutralized
 2.1 R:KOH, R:H₂NOH-HCl, S:Me₂CHOH, S:H₂O, 4 h, reflux
 3.1 R:Ac₂O, 8-10 h, reflux

Reactants: 1, Reagents: 4, Solvents: 3, Steps: 3, Stages: 4, Most stages in any one step: 2

References

[Intermediates for preparation of letrozole](#)

By Agarwal, Shiv Kumar et al

From PCT Int. Appl., 2007074474, 05 Jul 2007

Experimental Procedure

Step 1

Preparation of α - (1H-1, 2,4-Triazolyl) - 4,4'-diformyl diphenylmethane (IIc) To a solution of α (1H-1, 2,4-Triazolyl) - 4,4'-dimethylidinetetraacetoxypiphenylmethane (5g, 0.01 mol) in methanol (200 ml) was added a solution of potassium hydroxide (2.25g, 0.04 mol) dissolved in methanol (25 ml) at room temperature. The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was neutralized with 6 N Hydrochloric acid. Methanol was removed under reduced pressure. Water (100 ml) was added to the residue and the products were extracted into ethyl acetate (100ml). Removal of ethyl acetate under reduced pressure gives crude α (1H-1, 2,4-Triazolyl) - 4,4'-diformyl diphenylmethane (2.8g). This was further purified by column chromatography to give the pure product (Ig). IR (KBr) (ν cm^{-1}): 1703.8, 1605.8, 1503.5 ¹H NMR (CDCl₃): δ 10.04 (s, 2H), 8.08 (m, 2H, Tz), 7.93 - 7.91 (m, Ar, 4H), 7.36 - 7.27 (m, 4H, Ar), 6.88 (s, 1H) Mass Spectrum: [M-1], 290.2

Step 2

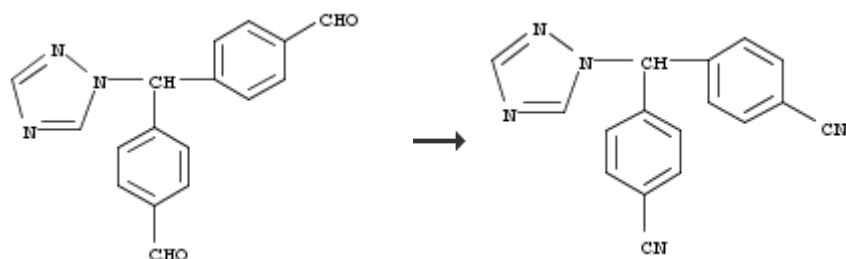
Preparation of α - (1H-1, 2,4-Triazolyl) - 4,4'-diformaldoxime diphenylmethane (IIId) To a solution of α - (1H-1, 2,4-Triazolyl) - 4,4'-diformyl diphenylmethane (5g, 0.017 mol) in isopropyl alcohol (150 ml) was added a solution of hydroxy lamine hydrochloride (4.77g, 0.068 mol) in water (30ml) previously neutralized with potassium hydroxide (3.84g, 0.068 mol) at room temperature. The reaction mixture was refluxed for 4hrs. Isopropyl alcohol was removed on a rota-evaporator under reduced pressure to leave a gummy mass. Water (50ml) was added to the residue and stirred for 2-3h at 10 °C. The solid mass separated was filtered and dried (4.13g). M.Pt. 222 - 224 °C. A sample of the product was further recrystallised from methanol to give the pure compound. m. p. 234.6° C. IR (KBr) (ν cm^{-1}): 3270, 2970, 1510, and 1450 ¹H NMR (DMSO-d₆): δ ppm 11.3 (s, 2H), 8.12 (s, 1H), 8.08 (s, 1H), 7.61 - 7.58 (m, 4H), 7.26 - 7.24 (m, 4H), 7.13 (s, 1H), Mass Spectrum: [M+H]⁺, 322.1, [M+ Na]⁺, 344.1, [M-Triazole+ H]⁺, 254.2

Step 3

Preparation of 4,4'-(1H-1, 2,4-triazol-1yl-methylene)-bisbenzonitrile / Letrozole (I) A solution of α (1H-1, 2,4-Triazolyl) - 4,4'-diformaldoxime diphenylmethane (5g, 0.015 mol) in acetic anhydride (12.5ml) was refluxed for 8-10h. The reaction mixture was cooled to room temperature and poured into water (200ml) and stirred for 1H. The solid mass precipitated was filtered. The residue was washed several times with water to remove acetic anhydride. The solid was dried to get Letrozole (4.3g). ¹H NMR (CDCl₃): δ ppm 8.09 (s, 1H), 8.07 (s, 1H), 7.72 - 7.69 (m, 4H), 7.36 - 7.27 (m, 4H), 6.84 (s, 1H), Mass Spectrum: [M-1], 284.3

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44. 2 Steps



Overview

Steps/Stages

Notes

1.1 R:KOH, R:H₂NOH-HCl, S:Me₂CHOH, S:H₂O, 4 h, reflux

2.1 R:Ac₂O, 8-10 h, reflux

Reactants: 1, Reagents: 3, Solvents: 2, Steps: 2, Stages: 2, Most stages in any one step: 1

References

[Intermediates for preparation of letrozole](#)

By Agarwal, Shiv Kumar et al

From PCT Int. Appl., 2007074474, 05 Jul 2007

Experimental Procedure

Step 1

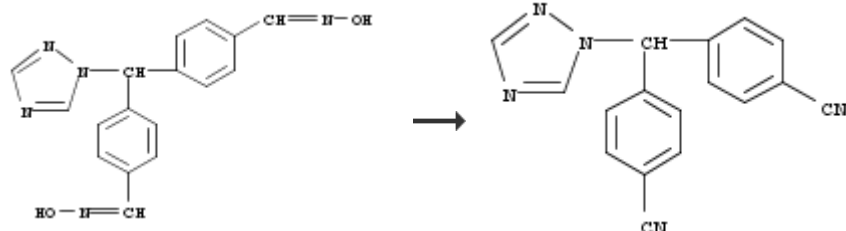
Preparation of α - (1H-1, 2,4-Triazolyl) - 4,4'-diformaldoxime diphenylmethane (IId) To a solution of α - (1H-1, 2,4-Triazolyl) - 4,4'-diformyl diphenylmethane (5g, 0.017 mol) in isopropyl alcohol (150 ml) was added a solution of hydroxy lamine hydrochloride (4.77g, 0.068 mol) in water (30ml) previously neutralized with potassium hydroxide (3.84g, 0.068 mol) at room temperature. The reaction mixture was refluxed for 4hrs. Isopropyl alcohol was removed on a rota-evaporator under reduced pressure to leave a gummy mass. Water (50ml) was added to the residue and stirred for 2-3h at 10 °C. The solid mass separated was filtered and dried (4.13g). M.Pt. 222 - 224 °C. A sample of the product was further recrystallised from methanol to give the pure compound. m. p. 234.6° C. IR (KBr) (ν Cm⁻¹): 3270, 2970, 1510, and 1450 ¹H NMR (DMSO-d₆): δ ppm 11.3 (s, 2H), 8.12 (s, 1H), 8.08 (s, 1H), 7.61 - 7.58 (m, 4H), 7.26 - 7.24 (m, 4H), 7.13 (s, 1H), Mass Spectrum: [M+H]⁺, 322.1 , [M+ Na]⁺, 344.1 , [M-Triazole+ H]⁺, 254.2

Step 2

Preparation of 4,4'-(1H-1, 2,4-triazol-1yl-methylene)-bisbenzonitrile / Letrozole (I) A solution of alpha (1H-1, 2,4-Triazolyl) - 4,4'-diformaldoxime diphenylmethane (5g, 0.015 mol) in acetic anhydride (12.5ml) was refluxed for 8-10h. The reaction mixture was cooled to room temperature and poured into water (200ml) and stirred for 1H. The solid mass precipitated was filtered. The residue was washed several times with water to remove acetic anhydride. The solid was dried to get Letrozole (4.3g). ¹H NMR (CDCl₃): δ ppm 8.09 (s, 1H), 8.07 (s, 1H), 7.72 - 7.69 (m, 4H), 7.36 - 7.27 (m, 4H), 6.84 (s, 1H), Mass Spectrum: [M-1], 284.3

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45. Single Step



Overview

Steps/Stages

1.1 R:AcONa, R:AcOH, S:Ac₂O, rt; 3-4 h, reflux

Notes

Reactants: 1, Reagents: 2, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

References

[Intermediates for preparation of letrozole](#)

By Agarwal, Shiv Kumar et al

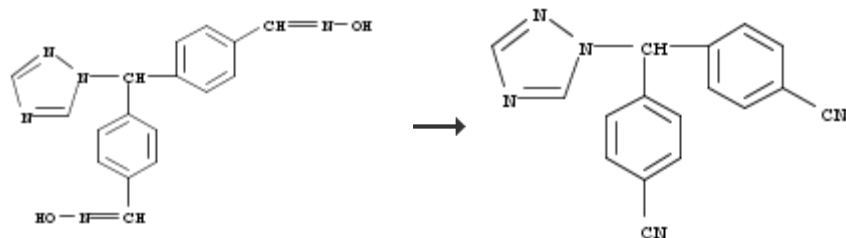
From PCT Int. Appl., 2007074474, 05 Jul 2007

Experimental Procedure

Preparation of 4,4'-(1H-1, 2,4-triazol-1-yl-methylene)-bisbenzonitrile / Letrozole (I) To a suspension of α -(1H-1, 2,4-Triazolyl) - 4,4'-diformaldoxime diphenylmethane (5g, 0.015 mol) in acetic acid (75 ml) was added acetic anhydride (7.35 ml) and sodium acetate (6.38 g, 0.77 mol) at room temperature. The mixture was then refluxed for 3-4h. The reaction mixture was cooled to room temperature and poured into water (400ml) at room temperature and stirred for 1H. The solid mass precipitated was filtered. The residue was washed several times with water to remove acetic anhydride. The solid was dried to give Letrozole (4.6g).

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46. Single Step



Overview

Steps/Stages

1.1 R:Ac₂O, 8-10 h, reflux

Notes

Reactants: 1, Reagents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

References

[Intermediates for preparation of letrozole](#)

By Agarwal, Shiv Kumar et al

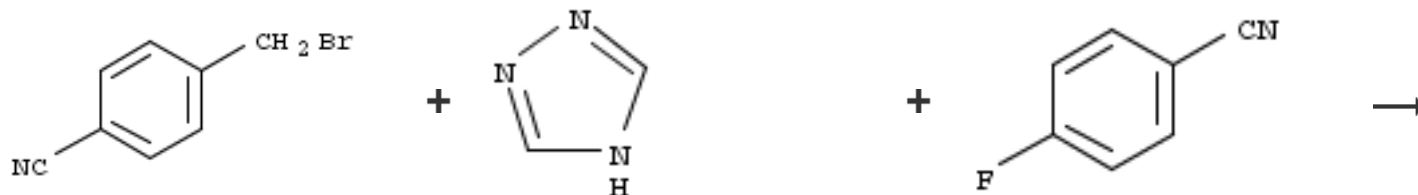
From PCT Int. Appl., 2007074474, 05 Jul 2007

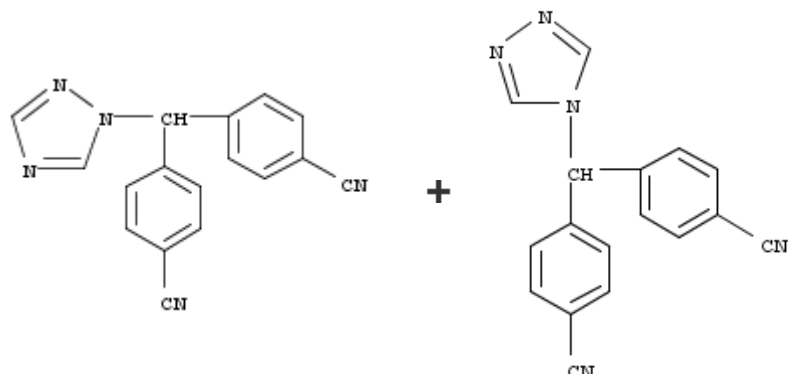
Experimental Procedure

Preparation of 4,4'-(1H-1, 2,4-triazol-1-yl-methylene)-bisbenzonitrile / Letrozole (I) A solution of alpha (1H-1, 2,4-Triazolyl) - 4,4'-diformaldoxime diphenylmethane (5g, 0.015 mol) in acetic anhydride (12.5ml) was refluxed for 8-10h. The reaction mixture was cooled to room temperature and poured into water (200ml) and stirred for 1H. The solid mass precipitated was filtered. The residue was washed several times with water to remove acetic anhydride. The solid was dried to get Letrozole (4.3g). ¹H NMR (CDCl₃): δ ppm 8.09 (s, 1H), 8.07 (s, 1H), 7.72 - 7.69 (m, 4H), 7.36 - 7.27 (m, 4H), 6.84 (s, 1H), Mass Spectrum: [M-1], 284.3

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47. 3 Steps (Converging)





Overview

Steps/Stages

- 1.1 R: K₂CO₃, S: Me₂CHOH, rt; 1 h, rt → 65°C
- 1.1 R: K₂CO₃, S: Me₂CHOH, rt; 1 h, rt → 65°C
- 2.1 R: t-BuOK, S: THF, 30 min, rt; rt → -15°C
- 2.2 S: THF, 4-5 h, -15°C; 3 h, -15°C

Notes

alternative preparation shown, regioselective, alternative preparation shown, regioselective (1,2,4-triazol-1-yl regioisomer is the major product), alternative preparation shown, Reactants: 3, Reagents: 2, Solvents: 2, Steps: 3, Stages: 4, Most stages in any one step: 2

References

Method for preparing letrozole free from regioisomeric and process impurities by utilizing selective extraction and/or selective crystallization techniques

By Haider, Hussain et al

From PCT Int. Appl., 2007054964, 18 May 2007

Experimental Procedure

Sequence 1

Step 1

Preparation of 4-[(1,2,4-triazol-1-yl)methyl]benzonitrile (3) In a 1.0 lit R. B. Flask fitted with a reflux condenser and a thermometer pocket, isopropanol (225 mL), p-cyanobenzyl bromide (150 g), 1,2,4-triazole (160 g) and potassium carbonate (315 g) were charged to the reaction mixture at RT with stirring. The reaction mixture was heated to 60-65 °C for 1.0 hr. The progress of reaction was monitored over TLC for the completion of reaction. The reaction mixture was cooled down to RT and water (500 mL) was added to the reaction mixture and reaction mass was transferred to a three lit R. B. Flask containing water (1750 mL). Cone. HCl (420 mL) was added very slowly to the reaction mass to adjust pH 2 - 3. The reaction mixture was extracted from toluene (600 mL x 3). Aqueous layer was basified to pH 8 using 20 % sodium hydroxide solution (60 mL). The aqueous layer was saturated with sodium chloride (660 g) and again extracted from fresh toluene (600 mL x 3). All the six toluene extracts were combined and washed with water (720 mL x 2). Both the aqueous washings were combined and extracted with toluene (290 mL x 2). Both the toluene extracts were combined and washed with water (110 mL x 2). The entire toluene layers were collected and distilled completely under vacuum at 60 °C. To the residue cyclohexane (100 mL) was added and distilled completely to get solid product, which was recrystallised from a mixture of isopropanol and cyclohexane to give 90 gm of pure 4-[(1,2,4-triazol-1-yl)methyl]benzonitrile (3) free from regioisomer . HPLC Purity >99%. Regioisomer ~ Not Detected. Melting Point: 78 - 80 °C.

Sequence 2

Step 1

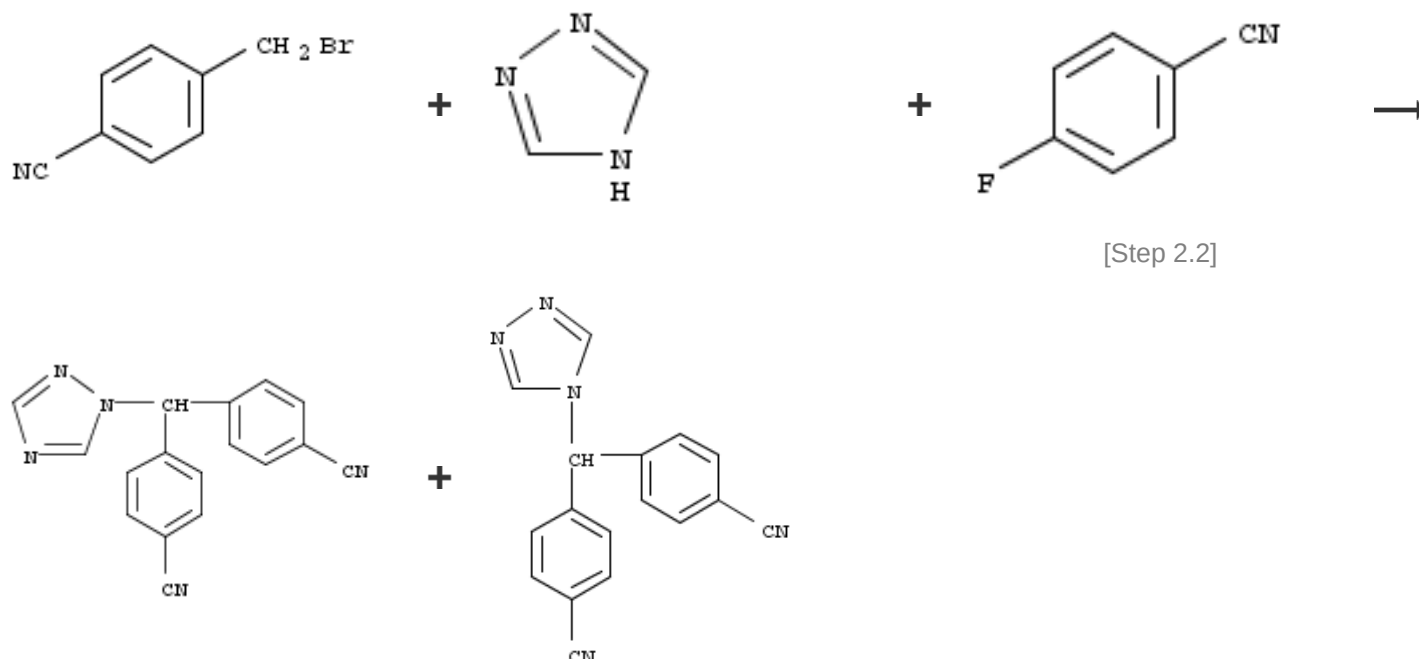
4-[(1,2,4-triazol-1-yl)methyl]benzonitrile (3) with a mixture of 4-[(1,3,4-triazol-1-yl)methyl]benzonitrile (4) To a 250 mL three neck R. B. Flask fitted with a reflux condenser and a thermometer pocket, isopropanol (37.5 mL), p-cyanobenzylbromide (25 g), 1,2,4-triazole (26.4 g) and potassium carbonate (52.8 g) were charged to the reaction mixture at RT with stirring. The reaction mixture was heated to 60-65 °C for 1.0 hr. The progress of reaction was monitored over TLC for the absence of p-cyanobenzylbromide. After completion, the reaction mixture was cooled down to RT and water (100 mL) was added to the reaction mixture and reaction mass was transferred to a one lit R. B. Flask containing water (275 mL). Cone. HCl (50 mL) was added very slowly to the reaction mass to adjust pH 7 - 8. The reaction mixture was extracted from dichloromethane (250 mL). Dichloromethane layer was distilled out at 50 °C giving 21.0 gm viscous oily residue. The residue is crystallized from a mixture of IPA: Cyclohexane (1:10) to give 18 g of 4-[(1,2,4-triazol-1-yl)methyl]benzonitrile (3) with a mixture of its regioisomer (4). HPLC Purity ~ 85%; Regioisomer ~ 13%.

Step 2

4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile (6) & 4-[1-(4-cyanophenyl)-1-(1,3,4-triazol-1-yl)methyl]benzonitrile (7) In a 250 mL three neck flask, equipped with thermometer pocket, mechanical stirrer and a guard tube, THF (50 mL) was charged at room temperature. Potassium tert-butoxide (12.3 gm) is added in small portions in 30 minutes. The solution was cooled to -15 °C and a solution of product from example-3 (10 g) and p-fluorobenzonitrile (8.5 g) in THF (50 mL) is added very slowly to the reaction mixture in 4-5 hrs. Stir the reaction mixture at same temperature for 3 hrs. Progress of the reaction is monitored on TLC. Dichloromethane (200 mL) is added to the reaction mixture followed by the addition of acetic acid (7 g). Reaction mixture is added to another flask containing water (220 mL). pH of the reaction mixture is adjusted to 7-8 by addition of 5% sodium bicarbonate solution (180 mL). Dichloromethane layer is washed with water (200 mL), separated, filtered through hyfiow bed and distilled at a temperature below 50 °C. The residue obtained was crystallized from Isopropanol (20 mL) to get the solid product (4.9 g). HPLC Purity: 89.6%. Regioisomer: 7.41%.

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48. 2 Steps


[Overview](#)
[Steps/Stages](#)
[Notes](#)

- 1.1 R:K₂CO₃, S:Me₂CHOH, rt; 1 h, rt → 65°C
 2.1 R:t-BuOK, S:THF, 30 min, rt; rt → -15°C
 2.2 S:THF, 4-5 h, -15°C; 3 h, -15°C

1) alternative preparation shown, regioselective (1,2,4-triazol-1-yl regioisomer is the major product), 2) alternative preparation shown, Reactants: 3, Reagents: 2, Solvents: 2, Steps: 2, Stages: 3, Most stages in any one step: 2

References

Method for preparing letrozole free from regioisomeric and process impurities by utilizing selective extraction and/or selective crystallization techniques

By Haider, Hussain et al

From PCT Int. Appl., 2007054964, 18 May 2007

Experimental Procedure

Step 1

4-[(1,2,4-triazol-1-yl)methyl]benzonitrile (3) with a mixture of 4-[(1,3,4-triazol-1-yl)methyl]benzonitrile (4)

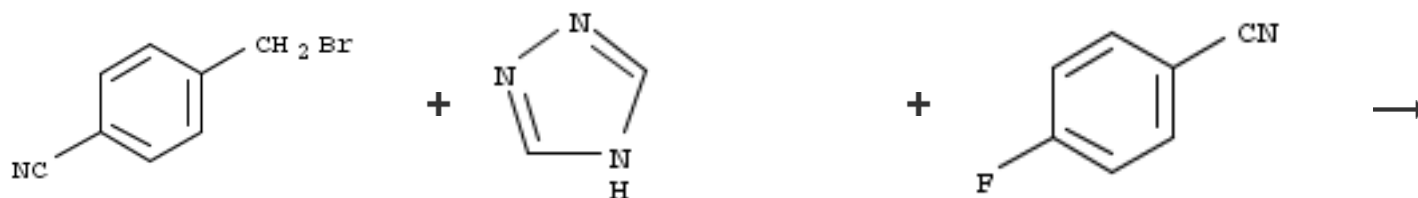
To a 250 mL three neck R. B. Flask fitted with a reflux condenser and a thermometer pocket, isopropanol (37.5 mL), p-cyanobenzylbromide (25 g), 1,2,4-triazole (26.4 g) and potassium carbonate (52.8 g) were charged to the reaction mixture at RT with stirring. The reaction mixture was heated to 60-65 °C for 1.0 hr. The progress of reaction was monitored over TLC for the absence of p-cyanobenzylbromide. After completion, the reaction mixture was cooled down to RT and water (100 mL) was added to the reaction mixture and reaction mass was transferred to a one lit R. B. Flask containing water (275 mL). Cone. HCl (50 mL) was added very slowly to the reaction mass to adjust pH 7 - 8. The reaction mixture was extracted from dichloromethane (250 mL). Dichloromethane layer was distilled out at 50 °C giving 21.0 gm viscous oily residue. The residue is crystallized from a mixture of IPA: Cyclohexane (1:10) to give 18 g of 4-[(1,2,4-triazol-1-yl)methyl]benzonitrile (3) with a mixture of its regioisomer (4). HPLC Purity ~ 85%; Regioisomer ~ 13%.

Step 2

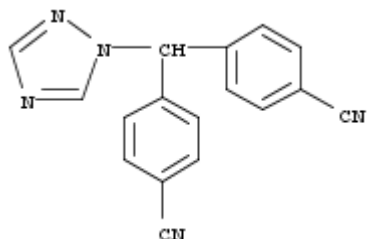
4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile (6) & 4-[1-(4-cyanophenyl)-1-(1,3,4-triazol-1-yl)methyl]benzonitrile (7) In a 250 mL three neck flask, equipped with thermometer pocket, mechanical stirrer and a guard tube, THF (50 mL) was charged at room temperature. Potassium tert-butoxide (12.3 gm) is added in small portions in 30 minutes. The solution was cooled to -15 °C and a solution of product from example-3 (10 g) and p-fluorobenzonitrile (8.5 g) in THF (50 mL) is added very slowly to the reaction mixture in 4-5 hrs. Stir the reaction mixture at same temperature for 3 hrs. Progress of the reaction is monitored on TLC. Dichloromethane (200 mL) is added to the reaction mixture followed by the addition of acetic acid (7 g). Reaction mixture is added to another flask containing water (220 mL). pH of the reaction mixture is adjusted to 7-8 by addition of 5% sodium bicarbonate solution (180 mL). Dichloromethane layer is washed with water (200 mL), separated, filtered through hyfiow bed and distilled at a temperature below 50 °C. The residue obtained was crystallized from Isopropanol (20 mL) to get the solid product (4.9 g). HPLC Purity: 89.6%. Regioisomer: 7.41%.

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49. 2 Steps



[Step 2.2]



Overview

Steps/Stages

- 1.1 R:K₂CO₃, S:Me₂CHOH, rt; 1 h, rt → 65°C
- 2.1 R:t-BuOK, S:THF, 30 min, rt; rt → -15°C
- 2.2 S:THF, 4-5 h, -15°C; 3 h, -15°C

Notes

alternative preparation shown, regioselective (1,2,4-triazol-1-yl regioisomer is the major product), Reactants: 3, Reagents: 2, Solvents: 2, Steps: 2, Stages: 3, Most stages in any one step: 2

References

Method for preparing letrozole free from regioisomeric and process impurities by utilizing selective extraction and/or selective crystallization techniques

By Haider, Hussain et al

From PCT Int. Appl., 2007054964, 18 May 2007

Experimental Procedure

Step 1

4-[(1,2,4-triazol-1-yl)methyl]benzonitrile (3) with a mixture of 4-[(1,3,4-triazol-1-yl)methyl]benzonitrile (4)

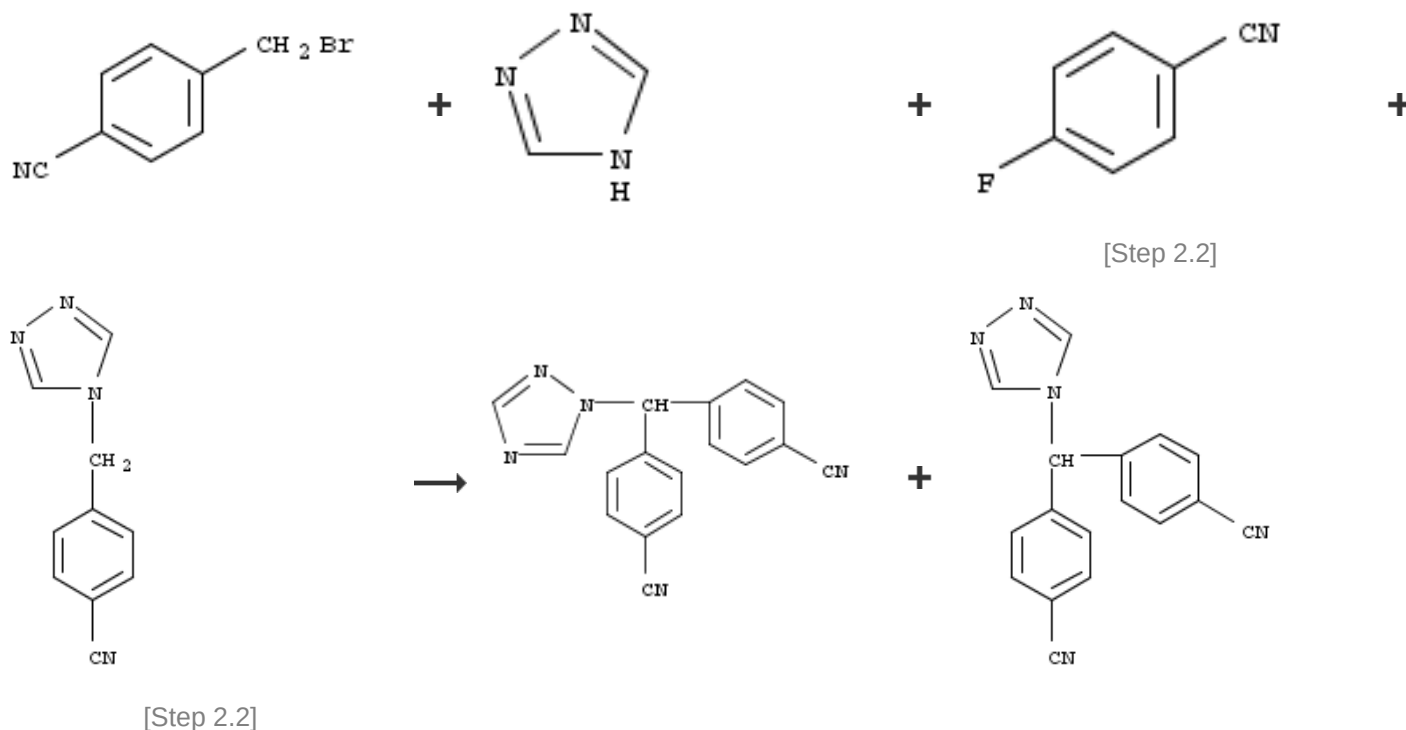
To a 250 mL three neck R. B. Flask fitted with a reflux condenser and a thermometer pocket, isopropanol (37.5 mL), p-cyanobenzylbromide (25 g), 1,2,4-triazole (26.4 g) and potassium carbonate (52.8 g) were charged to the reaction mixture at RT with stirring. The reaction mixture was heated to 60-65 °C for 1.0 hr. The progress of reaction was monitored over TLC for the absence of p-cyanobenzylbromide. After completion, the reaction mixture was cooled down to RT and water (100 mL) was added to the reaction mixture and reaction mass was transferred to a one lit R. B. Flask containing water (275 mL). Cone. HCl (50 mL) was added very slowly to the reaction mass to adjust pH 7 - 8. The reaction mixture was extracted from dichloromethane (250 mL). Dichloromethane layer was distilled out at 50 °C giving 21.0 gm viscous oily residue. The residue is crystallized from a mixture of IPA: Cyclohexane (1:10) to give 18 g of 4-[(1,2,4-triazol-1-yl)methyl]benzonitrile (3) with a mixture of its regioisomer (4). HPLC Purity ~ 85%; Regioisomer ~ 13%.

Step 2

Preparation of 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile (6) In a one liter three neck flask, equipped with thermometer pocket, mechanical stirrer and a guard tube, THF (500 mL) was charged at room temperature. Potassium tert-butoxide (122 gm) was added in small portions in 30 minutes. The solution was cooled to -15 °C and a solution of 4-[(1,2,4-triazol-1-yl)methyl]benzonitrile (100 g) and p-fluorobenzonitrile (86 g) in THF (500 mL) was added very slowly to the reaction mixture in 4-5 hrs. The reaction mixture was stirred at same temperature for 3 hrs. Progress of the reaction was monitored on TLC. Dichloromethane (1000 mL) was added to the reaction mixture followed by the addition of acetic acid (65 g). Reaction mixture was added to another flask containing water (1100 mL). pH of the reaction mixture was adjusted to 7-8 by addition of 5% sodium bicarbonate solution (900 mL). Dichloromethane layer was separated out and again washed with water (1000 mL). Dichloromethane layer separated, filtered through hyflow bed and distilled at a temperature below 50 °C. The residue obtained was crystallized by the addition of Isopropanol. (100 mL) to get the crude product (82 g), which was recrystallised from methanol (160 mL) to get pure Letrozole (74 gm). HPLC Purity >99.8%. Regioisomer : Not Detected.

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50. 2 Steps



Overview

Steps/Stages

- 1.1 R:K₂CO₃, S:Me₂CHOH, rt; 1 h, rt → 65°C
- 2.1 R:t-BuOK, S:THF, 30 min, rt; rt → -15°C
- 2.2 S:THF, 4-5 h, -15°C; 3 h, -15°C

Notes

1) alternative preparation shown, regioselective, 2) alternative preparation shown, Reactants: 4, Reagents: 2, Solvents: 2, Steps: 2, Stages: 3, Most stages in any one step: 2

References

[Method for preparing letrozole free from regioisomeric and process impurities by utilizing selective extraction and/or selective crystallization techniques](#)

By Haider, Hussain et al

From PCT Int. Appl., 2007054964, 18 May 2007

Experimental Procedure

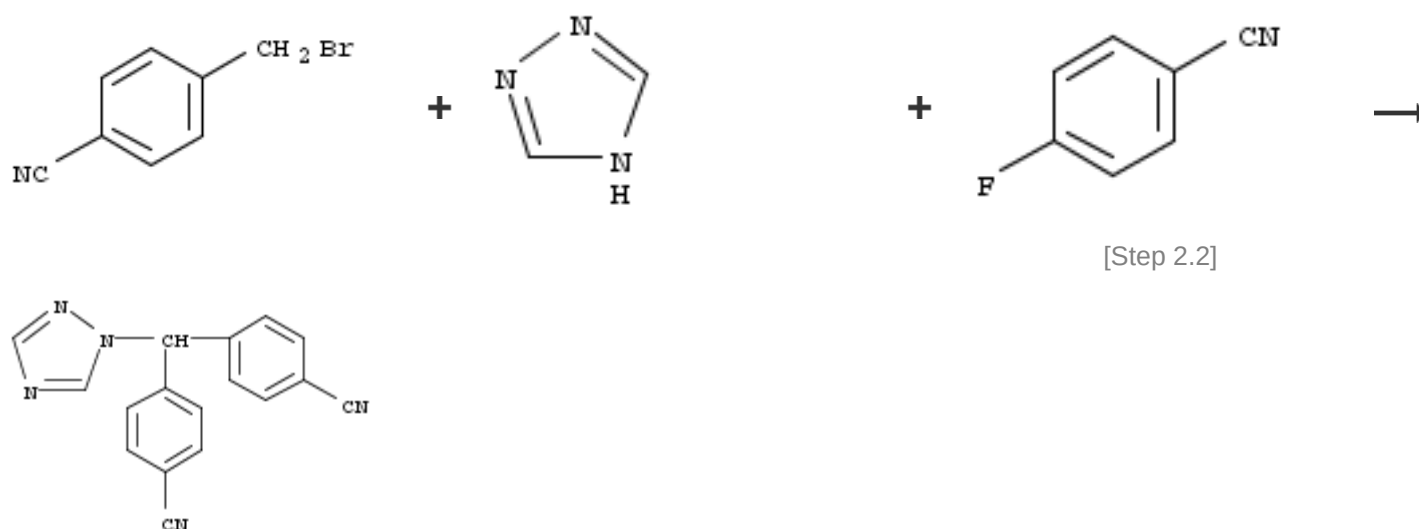
Step 1

Preparation of 4-[(1,2,4-triazol-1-yl)methyl]benzonitrile (3) In a 1.0 lit R. B. Flask fitted with a reflux condenser and a thermometer pocket, isopropanol (225 mL), p-cyanobenzylbromide (150 g), 1,2,4-triazole (160 g) and potassium carbonate (315 g) were charged to the reaction mixture at RT with stirring. The reaction mixture was heated to 60-65 °C for 1.0 hr. The progress of reaction was monitored over TLC for the completion of reaction. The reaction mixture was cooled down to RT and water (500 mL) was added to the reaction mixture and reaction mass was transferred to a three lit R. B. Flask containing water (1750 mL). Cone. HCl (420 mL) was added very slowly to the reaction mass to adjust pH 2 - 3. The reaction mixture was extracted from toluene (600 mL x 3). Aqueous layer was basified to pH 8 using 20 % sodium hydroxide solution (60 mL). The aqueous layer was saturated with sodium chloride (660 g) and again extracted from fresh toluene (600 mL x 3). All the six toluene extracts were combined and washed with water (720 mL x 2). Both the aqueous washings were combined and extracted with toluene (290 mL x 2). Both the toluene extracts were combined and washed with water (110 mL x 2). The entire toluene layers were collected and distilled completely under vacuum at 60 °C. To the residue cyclohexane (100 mL) was added and distilled completely to get solid product, which was recrystallised from a mixture of isopropanol and cyclohexane to give 90 gm of pure 4-[(1,2,4-triazol-1-yl)methyl]benzonitrile (3) free from regioisomer . HPLC Purity >99%. Regioisomer ~ Not Detected. Melting Point: 78 - 80 °C.

Step 2

4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile (6) & 4-[1-(4-cyanophenyl)-1-(1,3,4-triazol-1-yl)methyl]benzonitrile (7) In a 250 mL three neck flask, equipped with thermometer pocket, mechanical stirrer and a guard tube, THF (50 mL) was charged at room temperature. Potassium tert-butoxide (12.3 gm) is added in small portions in 30 minutes. The solution was cooled to -15 °C and a solution of product from example-3 (10 g) and p-fluorobenzonitrile (8.5 g) in THF (50 mL) is added very slowly to the reaction mixture in 4-5 hrs. Stir the reaction mixture at same temperature for 3 hrs. Progress of the reaction is monitored on TLC. Dichloromethane (200 mL) is added to the reaction mixture followed by the addition of acetic acid (7 g). Reaction mixture is added to another flask containing water (220 mL). pH of the reaction mixture is adjusted to 7-8 by addition of 5% sodium bicarbonate solution (180 mL). Dichloromethane layer is washed with water (200 mL), separated, filtered through hyfiow bed and distilled at a temperature below 50 °C. The residue obtained was crystallized from Isopropanol (20 mL) to get the solid product (4.9 g). HPLC Purity: 89.6%. Regioisomer: 7.41%.

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51. 2 Steps[Overview](#)**Steps/Stages**

- 1.1 R:K₂CO₃, S:Me₂CHOH, rt; 1 h, rt → 65°C
- 2.1 R:t-BuOK, S:THF, 30 min, rt; rt → -15°C
- 2.2 S:THF, 4-5 h, -15°C; 3 h, -15°C

Notes

alternative preparation shown, regioselective, Reactants: 3, Reagents: 2, Solvents: 2, Steps: 2, Stages: 3, Most stages in any one step: 2

References

[Method for preparing letrozole free from regioisomeric and process impurities by utilizing selective extraction and/or selective crystallization techniques](#)

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[Experimental Procedure](#)

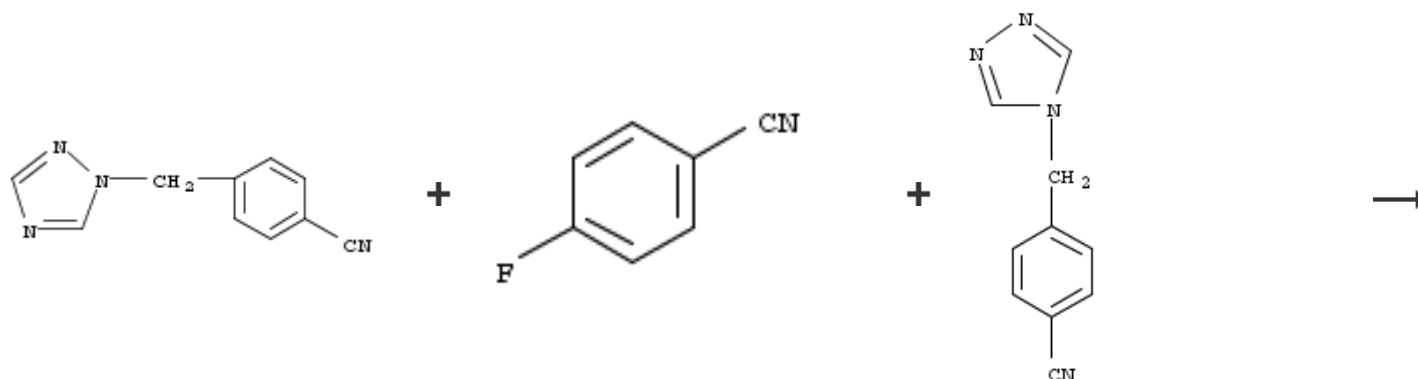
Step 1

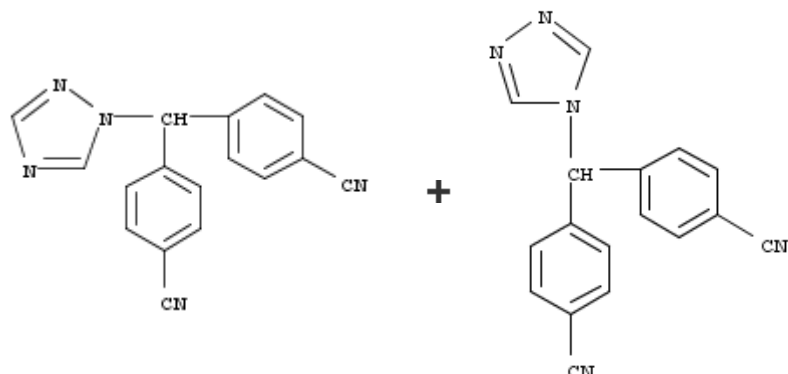
Preparation of 4-[(1,2,4-triazol-1-yl)methyl]benzonitrile (3) In a 1.0 lit R. B. Flask fitted with a reflux condenser and a thermometer pocket, isopropanol (225 mL), p-cyanobenzylbromide (150 g), 1,2,4-triazole (160 g) and potassium carbonate (315 g) were charged to the reaction mixture at RT with stirring. The reaction mixture was heated to 60-65 °C for 1.0 hr. The progress of reaction was monitored over TLC for the completion of reaction. The reaction mixture was cooled down to RT and water (500 mL) was added to the reaction mixture and reaction mass was transferred to a three lit R. B. Flask containing water (1750 mL). Cone. HCl (420 mL) was added very slowly to the reaction mass to adjust pH 2 - 3. The reaction mixture was extracted from toluene (600 mL x 3). Aqueous layer was basified to pH 8 using 20 % sodium hydroxide solution (60 mL). The aqueous layer was saturated with sodium chloride (660 g) and again extracted from fresh toluene (600 mL x 3). All the six toluene extracts were combined and washed with water (720 mL x 2). Both the aqueous washings were combined and extracted with toluene (290 mL x 2). Both the toluene extracts were combined and washed with water (110 mL x 2). The entire toluene layers were collected and distilled completely under vacuum at 60 °C. To the residue cyclohexane (100 mL) was added and distilled completely to get solid product, which was recrystallised from a mixture of isopropanol and cyclohexane to give 90 gm of pure 4-[(1,2,4-triazol-1-yl)methyl]benzonitrile (3) free from regioisomer. HPLC Purity >99%. Regioisomer ~ Not Detected. Melting Point: 78 - 80 °C.

Step 2

Preparation of 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile (6) In a one liter three neck flask, equipped with thermometer pocket, mechanical stirrer and a guard tube, THF (500 mL) was charged at room temperature. Potassium tert-butoxide (122 gm) was added in small portions in 30 minutes. The solution was cooled to -15 °C and a solution of 4-[(1,2,4-triazol-1-yl)methyl]benzonitrile (100 g) and p-fluorobenzonitrile (86 g) in THF (500 mL) was added very slowly to the reaction mixture in 4-5 hrs. The reaction mixture was stirred at same temperature for 3 hrs. Progress of the reaction was monitored on TLC. Dichloromethane (1000 mL) was added to the reaction mixture followed by the addition of acetic acid (65 g). Reaction mixture was added to another flask containing water (1100 mL). pH of the reaction mixture was adjusted to 7-8 by addition of 5% sodium bicarbonate solution (900 mL). Dichloromethane layer was separated out and again washed with water (1000 mL). Dichloromethane layer separated, filtered through hyflow bed and distilled at a temperature below 50 °C. The residue obtained was crystallized by the addition of Isopropanol. (100 mL) to get the crude product (82 g), which was recrystallised from methanol (160 mL) to get pure Letrozole (74 gm). HPLC Purity >99.8%. Regioisomer : Not Detected.

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52. Single Step



Overview

Steps/Stages

- 1.1 R:t-BuOK, S:THF, 30 min, rt; rt → -15°C
- 1.2 S:THF, 4-5 h, -15°C; 3 h, -15°C

Notes

alternative preparation shown, Reactants: 3, Reagents: 1, Solvents: 1, Steps: 1, Stages: 2, Most stages in any one step: 2

References

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By Haider, Hussain et al

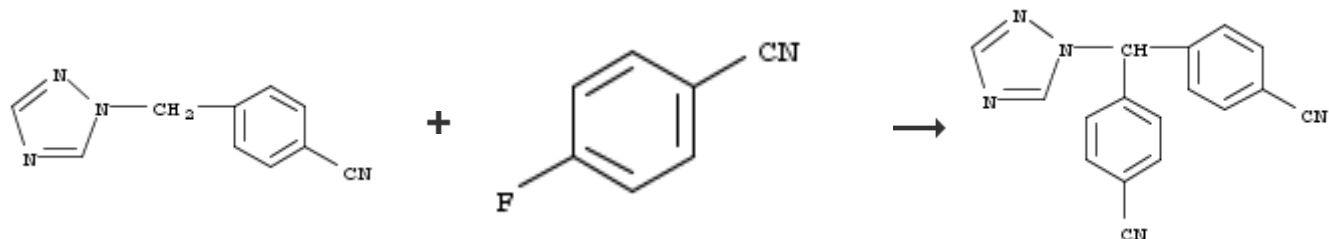
From PCT Int. Appl., 2007054964, 18 May 2007

Experimental Procedure

4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile (6) & 4-[1-(4-cyanophenyl)-1-(1,3,4-triazol-1-yl)methyl]benzonitrile (7) In a 250 mL three neck flask, equipped with thermometer pocket, mechanical stirrer and a guard tube, THF (50 mL) was charged at room temperature. Potassium tert-butoxide (12.3 gm) is added in small portions in 30 minutes. The solution was cooled to -15 °C and a solution of product from example-3 (10 g) and p-fluorobenzonitrile (8.5 g) in THF (50 mL) is added very slowly to the reaction mixture in 4-5 hrs. Stir the reaction mixture at same temperature for 3 hrs. Progress of the reaction is monitored on TLC. Dichloromethane (200 mL) is added to the reaction mixture followed by the addition of acetic acid (7 g). Reaction mixture is added to another flask containing water (220 mL). pH of the reaction mixture is adjusted to 7-8 by addition of 5% sodium bicarbonate solution (180 mL). Dichloromethane layer is washed with water (200 mL), separated, filtered through hyfiow bed and distilled at a temperature below 50 °C. The residue obtained was crystallized from Isopropanol (20 mL) to get the solid product (4.9 g). HPLC Purity: 89.6%. Regioisomer: 7.41%.

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53. Single Step



Overview

Steps/Stages

Notes

1.1 R:t-BuOK, S:THF, 30 min, rt; rt → -15°C

1.2 S:THF, 4-5 h, -15°C; 3 h, -15°C

Reactants: 2, Reagents: 1, Solvents: 1, Steps: 1, Stages: 2, Most stages in any one step: 2

References

[Method for preparing letrozole free from regioisomeric and process impurities by utilizing selective extraction and/or selective crystallization techniques](#)

By Haider, Hussain et al

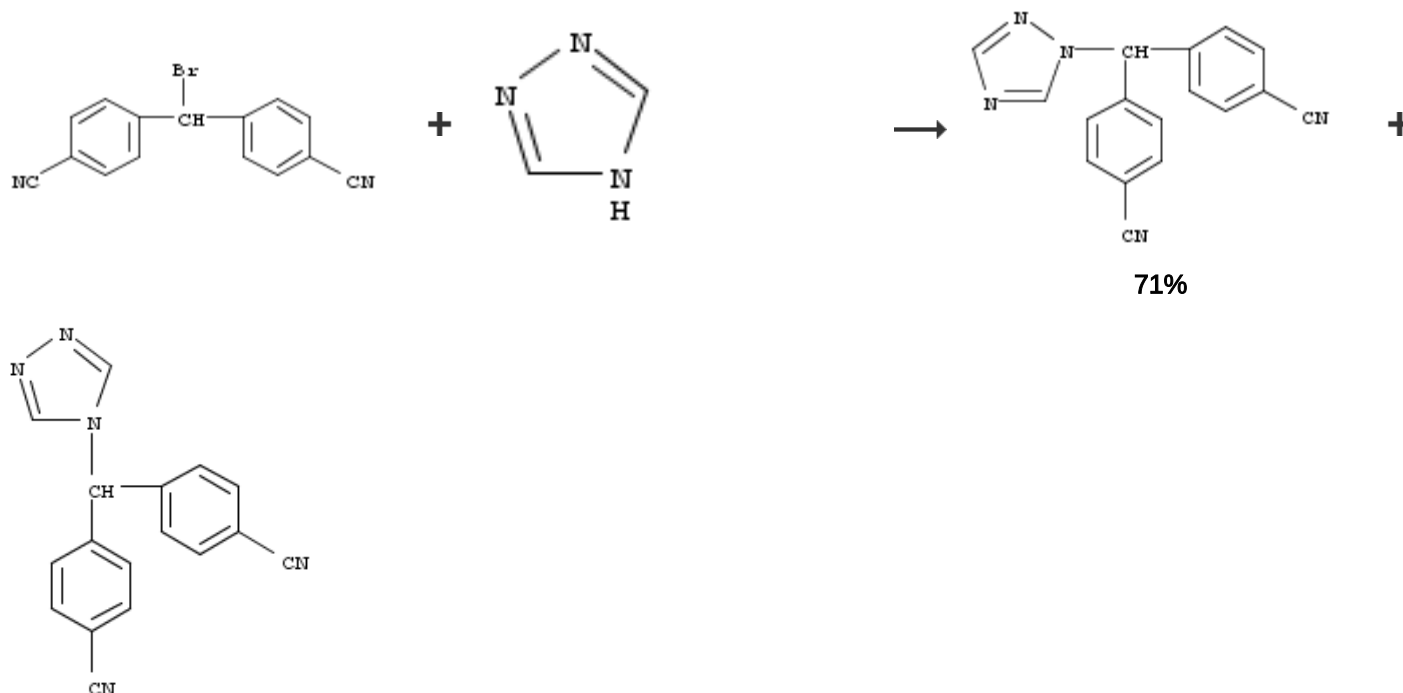
From PCT Int. Appl., 2007054964, 18 May 2007

Experimental Procedure

Preparation of 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile (6) In a one liter three neck flask, equipped with thermometer pocket, mechanical stirrer and a guard tube, THF (500 mL) was charged at room temperature. Potassium tert-butoxide (122 gm) was added in small portions in 30 minutes. The solution was cooled to -15 °C and a solution of 4-[(1,2,4-triazol-1-yl)methyl]benzonitrile (100 g) and p-fluorobenzonitrile (86 g) in THF (500 mL) was added very slowly to the reaction mixture in 4-5 hrs. The reaction mixture was stirred at same temperature for 3 hrs. Progress of the reaction was monitored on TLC. Dichloromethane (1000 mL) was added to the reaction mixture followed by the addition of acetic acid (65 g). Reaction mixture was added to another flask containing water (1100 mL). pH of the reaction mixture was adjusted to 7-8 by addition of 5% sodium bicarbonate solution (900 mL). Dichloromethane layer was separated out and again washed with water (1000 mL). Dichloromethane layer separated, filtered through hyflow bed and distilled at a temperature below 50 °C. The residue obtained was crystallized by the addition of Isopropanol. (100 mL) to get the crude product (82 g), which was recrystallised from methanol (160 mL) to get pure Letrozole (74 gm). HPLC Purity >99.8%. Regioisomer : Not Detected.

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54. Single Step



[Overview](#)

Steps/Stages

Notes

1.1 S:DMF, S:PhMe, rt → 60°C; 80°C; 1.5 h, 80°C

workup, Reactants: 2, Solvents: 2, Steps: 1,
Stages: 1, Most stages in any one step: 1

References

[Letrozole preparation and purification process for the removal of isoletrozole by air oxidation into 4,4'-dicyanobenzophenone](#)

By Hasson, Michal et al

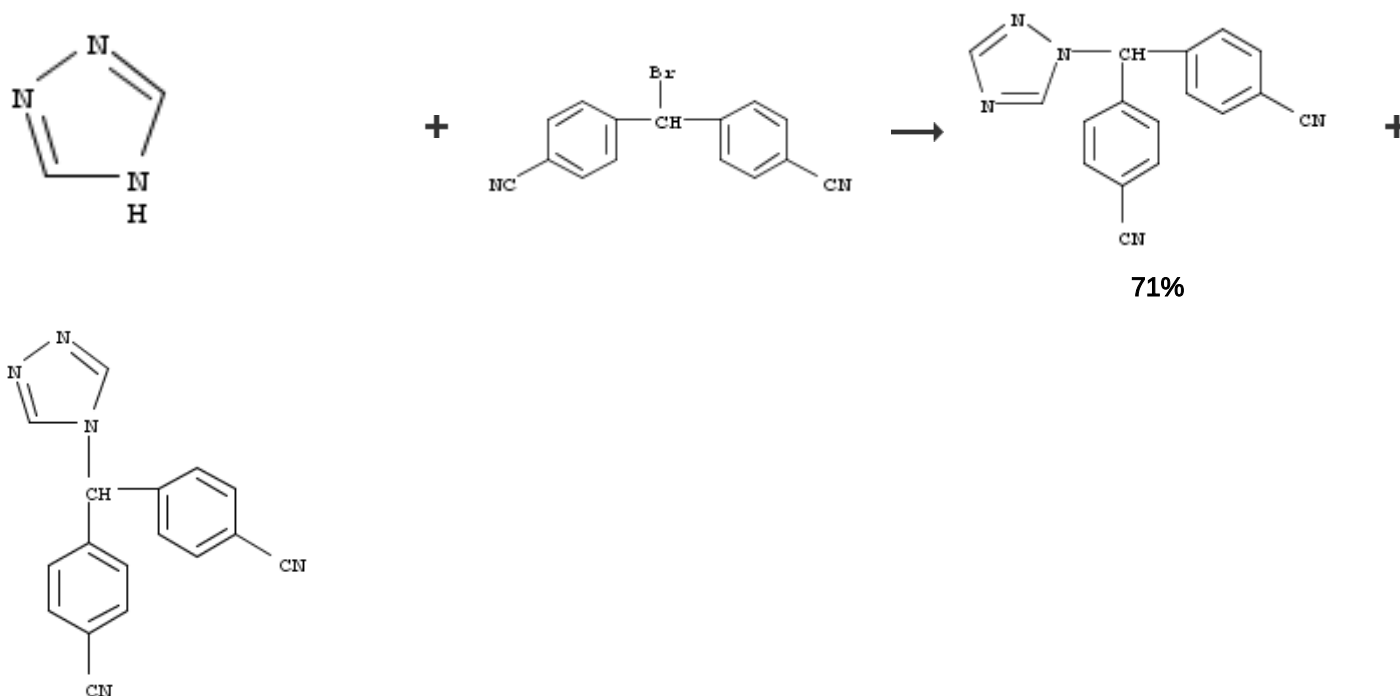
From U.S. Pat. Appl. Publ., 20070112203, 17 May 2007

Experimental Procedure

REFERENCE EXAMPLE 1 [0047] A reactor was charged with triazole (104 g, 1.5 moles) and bromobis(4-cyanophenyl)methane (108 g, 0.6 mole) followed by addition of DMF (720 ml) and toluene (1080 ml), and the impeller speed was set at 800 RPM. The temperature was raised to 60° C. and potassium carbonate was added (83.5 g, 0.6 mole). Then, the temperature was raised to 80° C. and mixing was maintained at this temperature during about 1.5 hours. An aliquot was withdrawn from the reaction mixture, diluted with a mixture of water and acetonitrile and analyzed by HPLC. The letrozole content was 83%, the isoletrozole content was 11.4%, while the content of 4,4'-dicyanobenzophenone was 1.6%. After cooling to a temperature of 25° C., acetic acid (57.6 ml) was added. DMF (414 ml) and water (1760 ml) were added to the reaction mixture to form a suspension (two liquid phases and a solid inter-phase in between). After heating the suspension to 60° C. the resulting mixture was allowed to cool to 25° C. for one hour and then the mixture was cooled to 20° C. and mixed at that temperature for 2 hours. The precipitated crystals were washed with water (80 ml) and dried to obtain 120.5 g of crude letrozole in 70.5% yield, having a purity of 96% by HPLC, (containing 3.5% isoletrozole).

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55. Single Step



[Overview](#)

Steps/Stages

Notes

1.1 R:K₂CO₃, S:PhMe, S:DMF, rt → 60°C; 80°C; 1.5 h, 80°C

workup, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

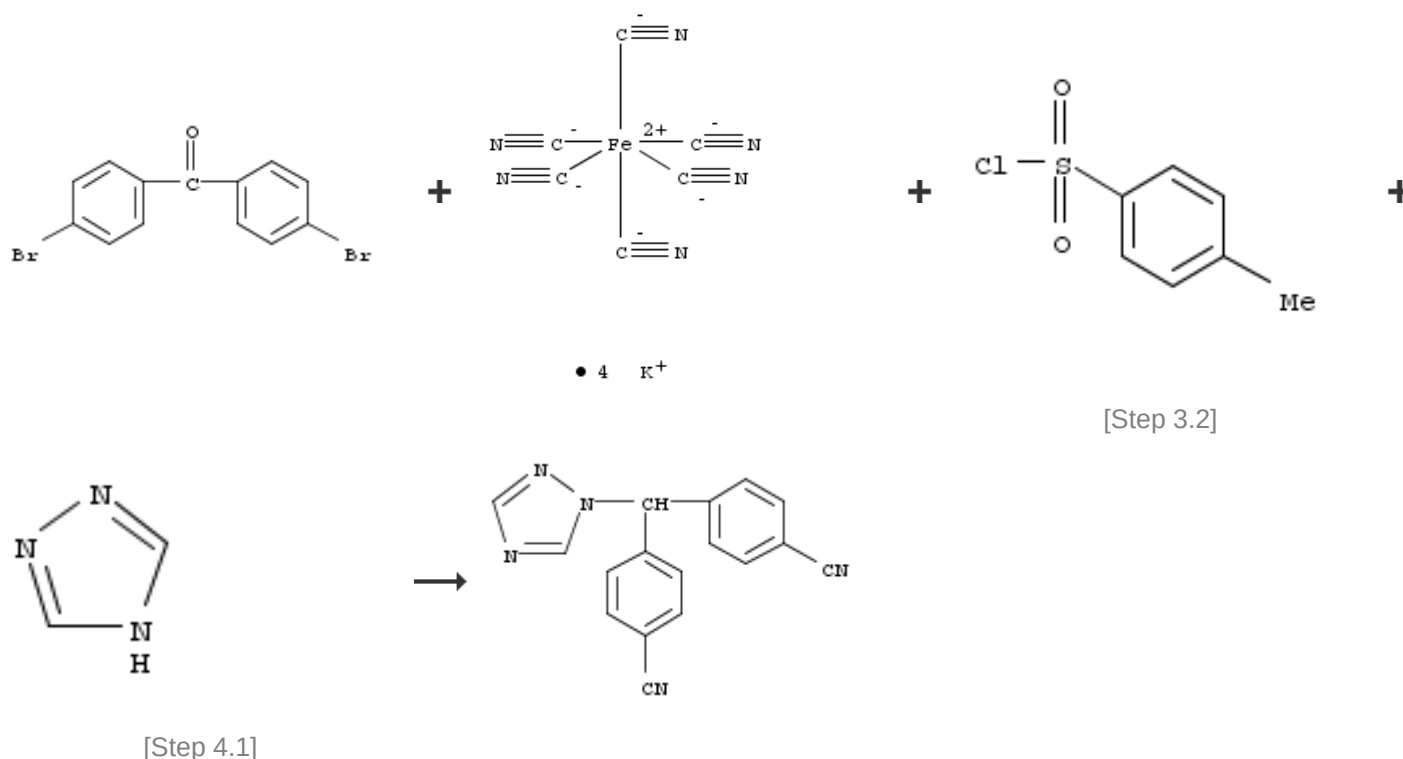
[Process for the preparation and purification of letrozole](#)

By Isenberg, Hila et al

From Brit. UK Pat. Appl., 2432157, 16 May 2007

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56. 4 Steps



Overview

Steps/Stages

- 1.1 S:AcNMe₂, 10 min, 25-35°C
- 1.2 R:Disodium carbonate, C:PdCl₂, 95-100°C; 6 h, 95-100°C
- 2.1 S:MeOH, 10 min, rt
- 2.2 R:NaBH₄, 0-5°C; 30 min, 25-30°C
- 2.3 R:AcOH, pH 6.33
- 3.1 S:Me₂CO, 10 min, rt; rt → 5°C; 5 min
- 3.2 S:Me₂CO, 5 min
- 3.3 R:NaOH, S:H₂O, 45 min, 0-5°C
- 4.1 R:K₂CO₃, S:H₂O, 5 min, rt; 10 min, rt
- 4.2 R:Bu₄N⁺ • Br⁻, S:i-BuC(=O)Me, rt; 2 h, rt
- 4.3 20-30°C; 48 h

Experimental Procedure

Notes

workup, Reactants: 4, Reagents: 6, Catalysts: 1, Solvents: 5, Steps: 4, Stages: 11, Most stages in any one step: 3

References

[Process for preparation of letrozole](#)

By Palle, Venkata Raghavendra Acharyulu et al

From U.S. Pat. Appl. Publ., 20070100149, 03 May 2007

Step 1

PREPARATION OF 4,4'-DICYANOBENZOPHENONE OF FORMULA III 100 g of 4,4-dibromobenzophenone were suspended in 1000 ml of N,N-dimethylacetamide (DMA) and stirred for 10 minutes at 25-35° C. 93.2 g of potassium ferrocyanide, 62.5 g of sodium carbonate and 512 mg of palladium chloride were charged to the suspension. The suspension was heated to 95-100° C. and stirred for 6 hours at 95-100° C. Then the reaction mass was cooled to 27° C. and filtered through a celite bed followed by washing the celite bed with 100 ml of N,N-dimethylacetamide (DMA). 2 L of methanol were charged to the filtrate and stirred for 2 hours at 25° C., followed by filtering at 25° C. Methanol was distilled from the filtrate and 1.1 L of water was charged at 25° C. The resultant suspension was filtered followed by washing the solid with 100 ml of water and drying the solid at 58° C. under vacuum for 4 hours, to afford 54 g of title compound with a purity by HPLC of 98.99% and a water content by the Karl Fischer method of 0.08%.

Step 2

PREPARATION OF 4,4'-(HYDROXY METHYLENE)BISBENZONITRILE OF FORMULA IV 200 ml of methanol was taken into a round bottom flask followed by charging 40 g of 4,4-dicyanobenzophenone and stirring for about 10 minutes. 3.28 g of sodium borohydride was added slowly to the above suspension at 0-5° C. followed by stirring at 25-30° C. for 30 minutes, and the formed solution was neutralized with 25 ml of glacial acetic acid to a pH of 6.33. 800 ml of water was charged to the above-neutralized suspension and stirred for 30 minutes, and the precipitate was filtered, washed with 400 ml of water and finally subjected to drying at 55-60° C. under vacuum for 4 hours to afford 40 g of title compound having a purity by HPLC of 99.36% and a water content by the Karl Fischer method of 0.27%.

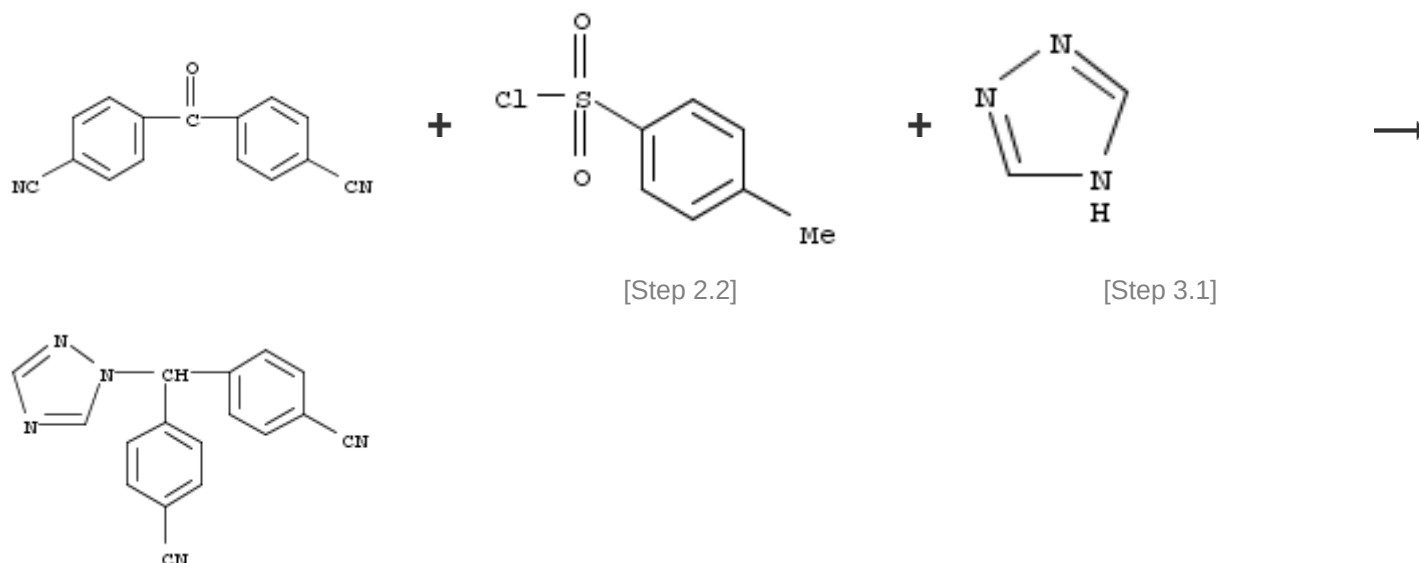
Step 3

PREPARATION OF TOLUENE SULPHONIC ACID BIS-(4-CYANOPHENYL)METHYL ESTER OF FORMULA V 250 ml of acetone was taken into a round bottom flask to which was then added 50 g of 4,4-(hydroxymethylene)bis benzonitrile and the mixture was stirred for 10 minutes. The obtained solution was cooled to 0-5° C. and stirred for 5 minutes. 53.5 g of p-toluenesulphonyl chloride dissolved in 100 ml of acetone was slowly added to the above solution and stirred for 5 minutes followed by the dropwise addition of 200 ml of 2N aqueous sodium hydroxide at 0-5° C. over 45 minutes. The reaction mass was subjected to stirring for 30 minutes at 0 to 5° C. The obtained solid mass was filtered, washed with 100 ml of water and suction dried for 1 hour to afford 78 g of title compound having purity by HPLC of 97.36% and a water content by the Karl Fischer method of 1.07% w/w.

Step 4

PREPARATION OF LETROZOLE OF FORMULA I 700 ml of water was taken into a round bottom flask to which was then added 49.8 g of 1,2,4-triazole with stirring for about 5 minutes, and then 99.6 g of potassium carbonate was added with stirring for 10 minutes. 350 ml of methyl isobutyl ketone (MIBK) and 58.1 g of tetrabutylammonium bromide were charged and stirred for 2 hours. 70 g of toluene sulphonic acid bis-(4-cyano phenyl)methyl ester was charged to the obtained reaction mixture at 20-30° C. and stirred for 48 hours. The formed aqueous and organic layers were separated and the aqueous layer extracted with 140 ml of methyl isobutyl ketone (MIBK) followed by washing the obtained organic layer with 700 ml of water. 1050 ml of 5N hydrochloric acid was charged to the organic layer, and stirred for 60 minutes. The formed aqueous and organic layers were separated and the organic layer extracted with 140 ml of aqueous 5N hydrochloric acid followed by washing the aqueous layer with 2×40 ml of n-hexane. The aqueous layer was basified with 350 g of sodium carbonate to get a pH of about 8.5 at a temperature below 25° C. followed by extraction with 2×350 ml of dichloromethane and the organic layer was washed with 700 ml of water. The resultant organic layer was distilled completely at below 40° C. and 350 ml of methanol and 1050 ml of water were charged, and stirred for 1 hour at 10-15° C. The formed precipitate was filtered followed by washing the solid with 350 ml of water, and suction drying of the solid for 30 minutes to afford 97.42% pure title compound. Dissolved the above-obtained letrozole compound in 140 ml of dichloromethane. A silica gel bed was prepared, using 140 g of silica gel (230-400 mesh) on a fritted glass filter funnel (10 cm height and 10 cm diameter), and the silica bed was washed with 1.4 L of dichloromethane. The dichloromethane solution was passed through the silica gel bed and the bed washed with 28 L of dichloromethane. The obtained filtrate was concentrated below 40° C. to a volume of about 140 ml of dichloromethane then 500 ml of methanol was charged and stirred for 10 minutes. The obtained solution was concentrated below 40° C. to a volume of 105-120 ml and 350 ml of water was charged and stirred for 1 hour. The formed solid was filtered followed by washing the solid with 140 ml of water and drying the solid at 55-60° C. for 4 hours under reduced pressure to afford 11.4 g of title compound having purity by HPLC of 99.8% and all other impurities 0.15%.

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Overview

Steps/Stages

- 1.1 S:MeOH, 10 min, rt
- 1.2 R:NaBH₄, 0-5°C; 30 min, 25-30°C
- 1.3 R:AcOH, pH 6.33
- 2.1 S:Me₂CO, 10 min, rt; rt → 5°C; 5 min
- 2.2 S:Me₂CO, 5 min
- 2.3 R:NaOH, S:H₂O, 45 min, 0-5°C
- 3.1 R:K₂CO₃, S:H₂O, 5 min, rt; 10 min, rt
- 3.2 R:Bu₄N⁺ • Br⁻, S:i-BuC(=O)Me, rt; 2 h, rt
- 3.3 20-30°C; 48 h

Experimental Procedure

Step 1

PREPARATION OF 4,4'-(HYDROXY METHYLENE)BISBENZONITRILE OF FORMULA IV 200 ml of methanol was taken into a round bottom flask followed by charging 40 g of 4,4-dicyanobenzophenone and stirring for about 10 minutes. 3.28 g of sodium borohydride was added slowly to the above suspension at 0-5° C. followed by stirring at 25-30° C. for 30 minutes, and the formed solution was neutralized with 25 ml of glacial acetic acid to a pH of 6.33. 800 ml of water was charged to the above-neutralized suspension and stirred for 30 minutes, and the precipitate was filtered, washed with 400 ml of water and finally subjected to drying at 55-60° C. under vacuum for 4 hours to afford 40 g of title compound having a purity by HPLC of 99.36% and a water content by the Karl Fischer method of 0.27%.

Step 2

PREPARATION OF TOLUENE SULPHONIC ACID BIS-(4-CYANOPHENYL)METHYL ESTER OF FORMULA V 250 ml of acetone was taken into a round bottom flask to which was then added 50 g of 4,4-(hydroxymethylene)bis benzonitrile and the mixture was stirred for 10 minutes. The obtained solution was cooled to 0-5° C. and stirred for 5 minutes. 53.5 g of p-toluenesulphonyl chloride dissolved in 100 ml of acetone was slowly added to the above solution and stirred for 5 minutes followed by the dropwise addition of 200 ml of 2N aqueous sodium hydroxide at 0-5° C. over 45 minutes. The reaction mass was subjected to stirring for 30 minutes at 0 to 5° C. The obtained solid mass was filtered, washed with 100 ml of water and suction dried for 1 hour to afford 78 g of title compound having purity by HPLC of 97.36% and a water content by the Karl Fischer method of 1.07% w/w.

Notes

workup, Reactants: 3, Reagents: 5, Solvents: 4, Steps: 3, Stages: 9, Most stages in any one step: 3

References

Process for preparation of letrozole

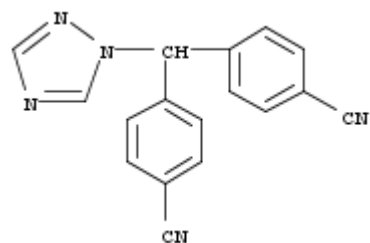
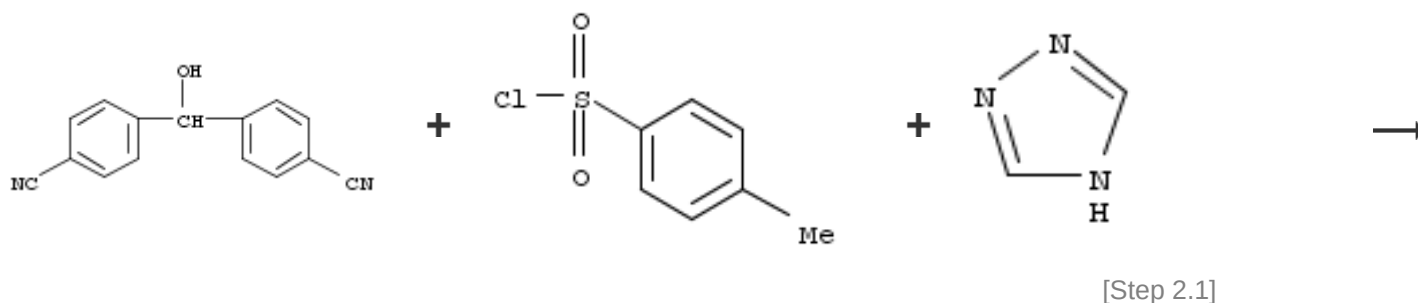
By Palle, Venkata Raghavendra Acharyulu et al

From U.S. Pat. Appl. Publ., 20070100149, 03 May 2007

Step 3

PREPARATION OF LETROZOLE OF FORMULA I 700 ml of water was taken into a round bottom flask to which was then added 49.8 g of 1,2,4-triazole with stirring for about 5 minutes, and then 99.6 g of potassium carbonate was added with stirring for 10 minutes. 350 ml of methyl isobutyl ketone (MIBK) and 58.1 g of tetrabutylammonium bromide were charged and stirred for 2 hours. 70 g of toluene sulphonic acid bis-(4-cyano phenyl)methyl ester was charged to the obtained reaction mixture at 20-30° C. and stirred for 48 hours. The formed aqueous and organic layers were separated and the aqueous layer extracted with 140 ml of methyl isobutyl ketone (MIBK) followed by washing the obtained organic layer with 700 ml of water. 1050 ml of 5N hydrochloric acid was charged to the organic layer, and stirred for 60 minutes. The formed aqueous and organic layers were separated and the organic layer extracted with 140 ml of aqueous 5N hydrochloric acid followed by washing the aqueous layer with 2×40 ml of n-hexane. The aqueous layer was basified with 350 g of sodium carbonate to get a pH of about 8.5 at a temperature below 25° C. followed by extraction with 2×350 ml of dichloromethane and the organic layer was washed with 700 ml of water. The resultant organic layer was distilled completely at below 40° C. and 350 ml of methanol and 1050 ml of water were charged, and stirred for 1 hour at 10-15° C. The formed precipitate was filtered followed by washing the solid with 350 ml of water, and suction drying of the solid for 30 minutes to afford 97.42% pure title compound. Dissolved the above-obtained letrozole compound in 140 ml of dichloromethane. A silica gel bed was prepared, using 140 g of silica gel (230-400 mesh) on a fritted glass filter funnel (10 cm height and 10 cm diameter), and the silica bed was washed with 1.4 L of dichloromethane. The dichloromethane solution was passed through the silica gel bed and the bed washed with 28 L of dichloromethane. The obtained filtrate was concentrated below 40° C. to a volume of about 140 ml of dichloromethane then 500 ml of methanol was charged and stirred for 10 minutes. The obtained solution was concentrated below 40° C. to a volume of 105-120 ml and 350 ml of water was charged and stirred for 1 hour. The formed solid was filtered followed by washing the solid with 140 ml of water and drying the solid at 55-60° C. for 4 hours under reduced pressure to afford 11.4 g of title compound having purity by HPLC of 99.8% and all other impurities 0.15%.

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58. 2 Steps
[Overview](#)
[Steps/Stages](#)
[Notes](#)

- 1.1 S:Me₂CO, 10 min, rt; rt → 5°C; 5 min
 1.2 S:Me₂CO, 5 min
 1.3 R:NaOH, S:H₂O, 45 min, 0-5°C
 2.1 R:K₂CO₃, S:H₂O, 5 min, rt; 10 min, rt
 2.2 R:Bu₄N⁺ • Br⁻, S:i-BuC(=O)Me, rt; 2 h, rt
 2.3 20-30°C; 48 h

workup, Reactants: 3, Reagents: 3, Solvents: 3, Steps: 2, Stages: 6, Most stages in any one step: 3

References

[Process for preparation of letrozole](#)

By Palle, Venkata Raghavendra Acharyulu et al

From U.S. Pat. Appl. Publ., 20070100149, 03 May 2007

Experimental Procedure

Step 1

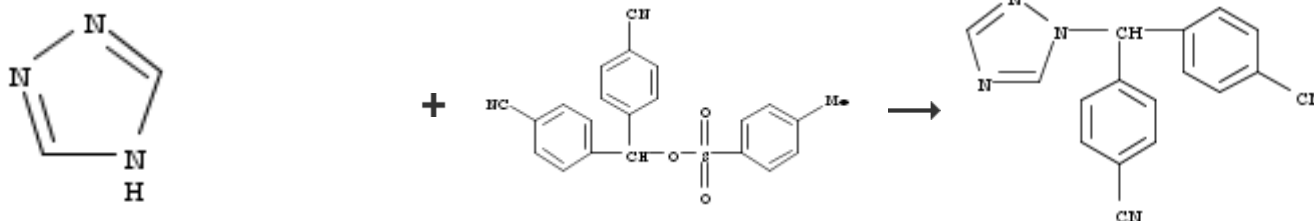
PRÉPARATION OF TOLUENE SULPHONIC ACID BIS-(4-CYANOPHENYL)METHYL ESTER OF FORMULA V 250 ml of acetone was taken into a round bottom flask to which was then added 50 g of 4,4-(hydroxymethylene)bis benzonitrile and the mixture was stirred for 10 minutes. The obtained solution was cooled to 0-5° C. and stirred for 5 minutes. 53.5 g of p-toluenesulphonyl chloride dissolved in 100 ml of acetone was slowly added to the above solution and stirred for 5 minutes followed by the dropwise addition of 200 ml of 2N aqueous sodium hydroxide at 0-5° C. over 45 minutes. The reaction mass was subjected to stirring for 30 minutes at 0 to 5° C. The obtained solid mass was filtered, washed with 100 ml of water and suction dried for 1 hour to afford 78 g of title compound having purity by HPLC of 97.36% and a water content by the Karl Fischer method of 1.07% w/w.

Step 2

PRÉPARATION OF LETROZOLE OF FORMULA I 700 ml of water was taken into a round bottom flask to which was then added 49.8 g of 1,2,4-triazole with stirring for about 5 minutes, and then 99.6 g of potassium carbonate was added with stirring for 10 minutes. 350 ml of methyl isobutyl ketone (MIBK) and 58.1 g of tetrabutylammonium bromide were charged and stirred for 2 hours. 70 g of toluene sulphonic acid bis-(4-cyano phenyl)methyl ester was charged to the obtained reaction mixture at 20-30° C. and stirred for 48 hours. The formed aqueous and organic layers were separated and the aqueous layer extracted with 140 ml of methyl isobutyl ketone (MIBK) followed by washing the obtained organic layer with 700 ml of water. 1050 ml of 5N hydrochloric acid was charged to the organic layer, and stirred for 60 minutes. The formed aqueous and organic layers were separated and the organic layer extracted with 140 ml of aqueous 5N hydrochloric acid followed by washing the aqueous layer with 2×40 ml of n-hexane. The aqueous layer was basified with 350 g of sodium carbonate to get a pH of about 8.5 at a temperature below 25° C. followed by extraction with 2×350 ml of dichloromethane and the organic layer was washed with 700 ml of water. The resultant organic layer was distilled completely at below 40° C. and 350 ml of methanol and 1050 ml of water were charged, and stirred for 1 hour at 10-15° C. The formed precipitate was filtered followed by washing the solid with 350 ml of water, and suction drying of the solid for 30 minutes to afford 97.42% pure title compound. Dissolved the above-obtained letrozole compound in 140 ml of dichloromethane. A silica gel bed was prepared, using 140 g of silica gel (230-400 mesh) on a fritted glass filter funnel (10 cm height and 10 cm diameter), and the silica bed was washed with 1.4 L of dichloromethane. The dichloromethane solution was passed through the silica gel bed and the bed washed with 28 L of dichloromethane. The obtained filtrate was concentrated below 40° C. to a volume of about 140 ml of dichloromethane then 500 ml of methanol was charged and stirred for 10 minutes. The obtained solution was concentrated below 40° C. to a volume of 105-120 ml and 350 ml of water was charged and stirred for 1 hour. The formed solid was filtered followed by washing the solid with 140 ml of water and drying the solid at 55-60° C. for 4 hours under reduced pressure to afford 11.4 g of title compound having purity by HPLC of 99.8% and all other impurities 0.15%.

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59. Single Step



Overview

Steps/Stages

- 1.1 R:K₂CO₃, S:H₂O, 5 min, rt; 10 min, rt
 1.2 R:Bu₄N⁺ •Br⁻, S:i-BuC(=O)Me, rt; 2 h, rt
 1.3 20-30°C; 48 h

Notes

workup, Reactants: 2, Reagents: 2, Solvents: 2, Steps: 1, Stages: 3, Most stages in any one step: 3

References

Process for preparation of letrozole

By Palle, Venkata Raghavendra Acharyulu et al

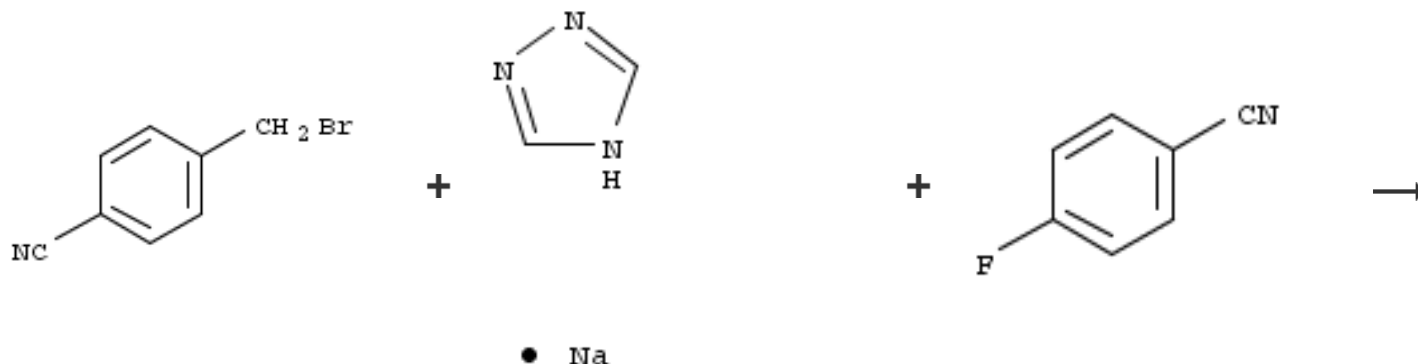
From U.S. Pat. Appl. Publ., 20070100149, 03 May 2007

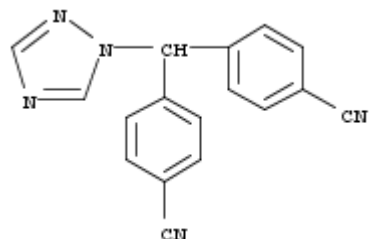
Experimental Procedure

PREPARATION OF LETROZOLE OF FORMULA I 700 ml of water was taken into a round bottom flask to which was then added 49.8 g of 1,2,4-triazole with stirring for about 5 minutes, and then 99.6 g of potassium carbonate was added with stirring for 10 minutes. 350 ml of methyl isobutyl ketone (MIBK) and 58.1 g of tetrabutylammonium bromide were charged and stirred for 2 hours. 70 g of toluene sulphonic acid bis-(4-cyano phenyl)methyl ester was charged to the obtained reaction mixture at 20-30° C. and stirred for 48 hours. The formed aqueous and organic layers were separated and the aqueous layer extracted with 140 ml of methyl isobutyl ketone (MIBK) followed by washing the obtained organic layer with 700 ml of water. 1050 ml of 5N hydrochloric acid was charged to the organic layer, and stirred for 60 minutes. The formed aqueous and organic layers were separated and the organic layer extracted with 140 ml of aqueous 5N hydrochloric acid followed by washing the aqueous layer with 2×40 ml of n-hexane. The aqueous layer was basified with 350 g of sodium carbonate to get a pH of about 8.5 at a temperature below 25° C. followed by extraction with 2×350 ml of dichloromethane and the organic layer was washed with 700 ml of water. The resultant organic layer was distilled completely at below 40° C. and 350 ml of methanol and 1050 ml of water were charged, and stirred for 1 hour at 10-15° C. The formed precipitate was filtered followed by washing the solid with 350 ml of water, and suction drying of the solid for 30 minutes to afford 97.42% pure title compound. Dissolved the above-obtained letrozole compound in 140 ml of dichloromethane. A silica gel bed was prepared, using 140 g of silica gel (230-400 mesh) on a fritted glass filter funnel (10 cm height and 10 cm diameter), and the silica bed was washed with 1.4 L of dichloromethane. The dichloromethane solution was passed through the silica gel bed and the bed washed with 28 L of dichloromethane. The obtained filtrate was concentrated below 40° C. to a volume of about 140 ml of dichloromethane then 500 ml of methanol was charged and stirred for 10 minutes. The obtained solution was concentrated below 40° C. to a volume of 105-120 ml and 350 ml of water was charged and stirred for 1 hour. The formed solid was filtered followed by washing the solid with 140 ml of water and drying the solid at 55-60° C. for 4 hours under reduced pressure to afford 11.4 g of title compound having purity by HPLC of 99.8% and all other impurities 0.15%.

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60. Single Step





85%

Overview

Steps/Stages

- 1.1 S:DMF, 2 h, 40°C; 40°C → -5°C
- 1.2 R:t-BuOK, 30 min; 2 h, 0-5°C
- 1.3 30 min, -5 - 0°C; 2 h, 0-5°C

Notes

Reactants: 3, Reagents: 1, Solvents: 1, Steps: 1, Stages: 3, Most stages in any one step: 3

References

[A one-pot process for the preparation of 4-\[1-\(cyanophenyl\)-1-\(1,2,4-triazol-1-yl\)methyl\]benzonitrile \(letrozole\)](#)

By Tarur, Venkatasubramanian
Radhakrishnan et al

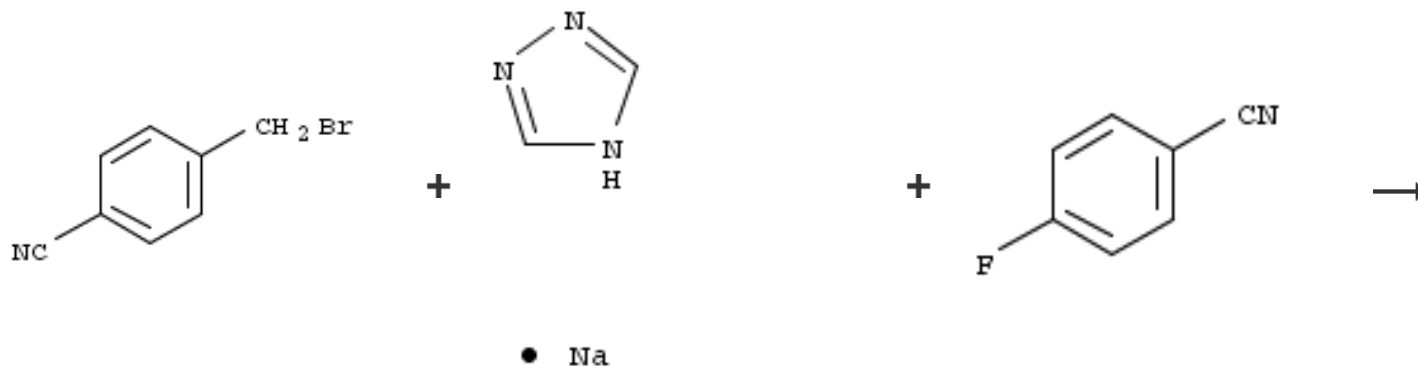
From PCT Int. Appl., 2007039912, 12 Apr 2007

Experimental Procedure

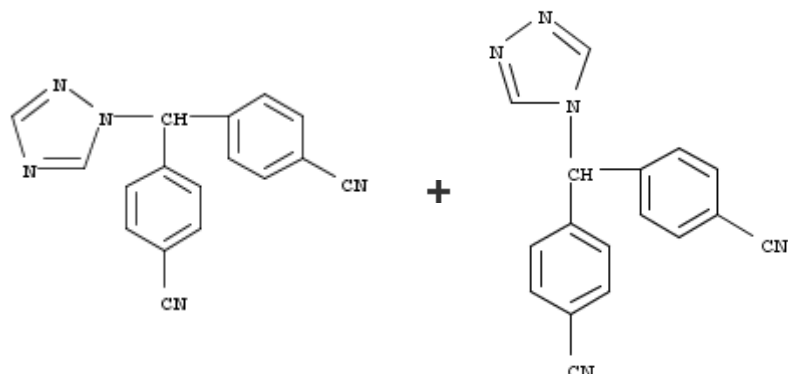
Example 1 .eqvsim.-Bromotolunitrile (10 g, 0.051 moles) was heated with a sodium salt of 1,2,4-triazole (6.3 g, 0.068 moles) in N,N-dimethylformamide (50 ml) for 2 hour at 40°C. The reaction mixture was cooled at -5°C and potassium tertiary butoxide (14.3 g, 0.127 moles) was added in small portions for 30 min. The reaction mixture was stirred at 0 to 5°C for 2 hour. To this reaction mixture, 4-fluorobenzonitrile (6.5 g, 0.053 moles) was added in 30 min at -5 to 0°C and stirred at 0 to 5°C for 2 hour. The reaction mixture was poured into cooled 2N hydrochloric acid and extracted with ethyl acetate. An organic layer was washed with water and concentrated under vacuum to yellow solid. [Yield of crude Letrozole: 12.30 g (85%); Purity: 90% (HPLC)].

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61. 2 Steps



[Step 2.1]



Overview

Steps/Stages

- 1.1 S:AcNMe₂, 1.5 h, -5°C
- 2.1 R:(Me₃Si)₂NH •Na, S:THF, 2 h, 0-5°C
- 2.2 R:AcOH, S:H₂O, 15 min

Notes

1) optimization study (optimized on reactant, reagent, solvent, temperature), regioselective, 2) alternate reagents and solvents used, alternate one-pot preparation also described, Reactants: 3, Reagents: 2, Solvents: 3, Steps: 2, Stages: 3, Most stages in any one step: 2

References

[Process for the preparation of letrozole from 4-halomethylbenzonitriles, 4-halobenzonitriles, and 1H-1,2,4-triazole salts.](#)

By Macdonald, Peter Lindsay et al

From U.S. Pat. Appl. Publ., 20070066831, 22 Mar 2007

Experimental Procedure

Step 1

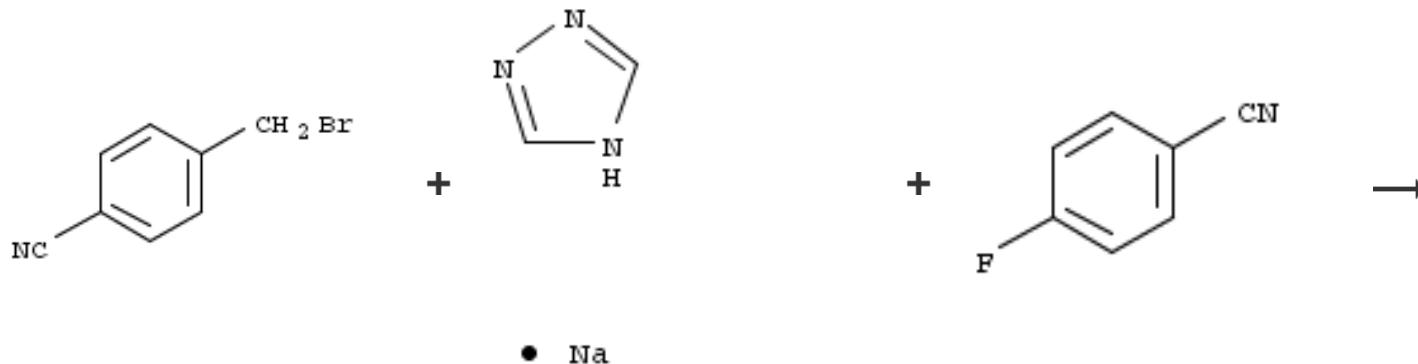
Run 32.

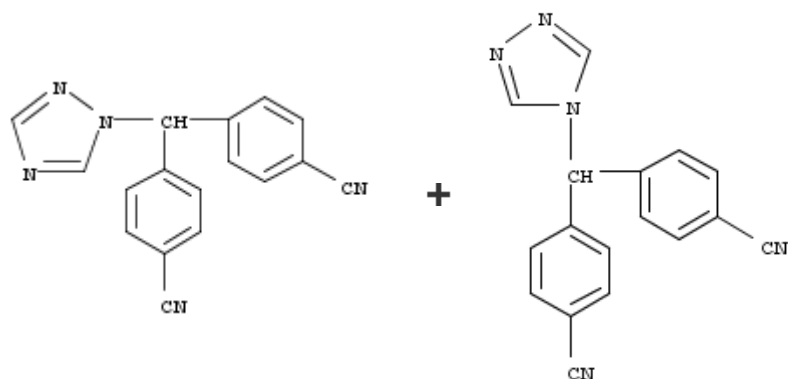
Step 2

Example 5 Preparation of Letrozole from Intermediate III Using the New Base [0059] To the oily residue of intermediate III, from example 2, 63 grams of 4-fluorobenzonitrile and 2064 grams of tetrahydrofuran were added. At 0 to 5° C. under a nitrogen atmosphere, 480 grams of a 40 percent sodium bis(trimethylsilyl)amide in THF solution were added dropwise over a period of 2 hours. After the addition was complete, the reaction mixture was quenched by the addition of 206 grams of acetic acid, followed by 1030 grams of water. After 15 minutes under agitation, the two-phase reaction mixture was allowed to stratify, and the organic phase was separated, and concentrated under vacuum to a volume of about 500 mL.

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62. Single Step





Overview

Steps/Stages

- 1.1 S:DMF, -10 - 0°C; 1 h, 0°C
- 1.2 R:(Me₃Si)₂NH •Na, S:THF, -10 - -5°C
- 1.3 R:AcOH, S:H₂O

Notes

alternative preparation shown, regioselective (1h-1,2,4-triazole compound is the major isomer), Reactants: 3, Reagents: 2, Solvents: 3, Steps: 1, Stages: 3, Most stages in any one step: 3

References

[Process for the preparation of letrozole from 4-halomethylbenzonitriles, 4-halobenzonitriles, and 1H-1,2,4-triazole salts.](#)

By Macdonald, Peter Lindsay et al

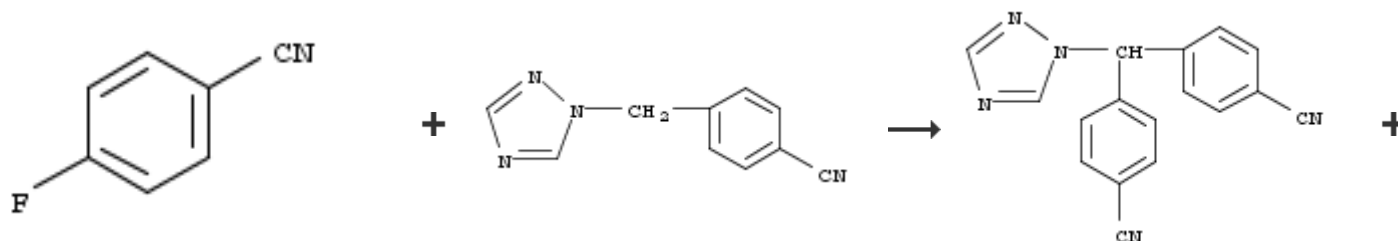
From U.S. Pat. Appl. Publ., 20070066831, 22 Mar 2007

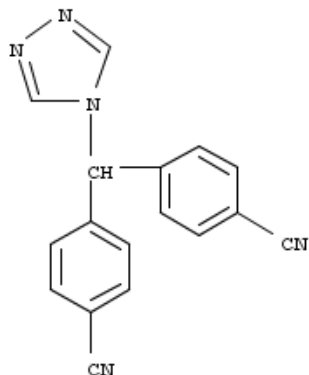
Experimental Procedure

Example 9 One-Pot Preparation of Letrozole [0063] A glass reactor was charged with 24.3 grams of 1,2,4-triazolylsodium and 500 grams of dimethylformamide. At a temperature between -10° C. and 0° C, 50 grams of 4-(bromomethyl)benzonitrile (53.2 grams with a purity of about 94 percent by weight, containing about 6 percent by weight of 4-tolunitrile) were added in portions. After stirring at 0° C. for 1 hour, 30.9 grams of 4-fluorobenzonitrile were added, and, while maintaining a temperature of -5° C. to -10° C, 245 grams of a 40 percent solution of sodium bis(trimethylsilyl)amide in THF were added dropwise. After the addition was completed, the reaction was quenched by the addition of 200 grams of 50 percent acetic acid, followed by precipitation of the product by the addition of 1500 grams of water. The resulting suspension was stirred and cooled to about 15° C, and the precipitate was collected and rinsed with water.

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63. Single Step





Overview

Steps/Stages

- 1.1 R:(Me₃Si)₂NH •Na, S:THF, 2 h, 0-5°C
- 1.2 R:AcOH, S:H₂O, 15 min

Notes

alternate reagents and solvents used, alternate one-pot preparation also described, Reactants: 2, Reagents: 2, Solvents: 2, Steps: 1, Stages: 2, Most stages in any one step: 2

References

[Process for the preparation of letrozole from 4-halomethylbenzonitriles, 4-halobenzonitriles, and 1H-1,2,4-triazole salts.](#)

By Macdonald, Peter Lindsay et al

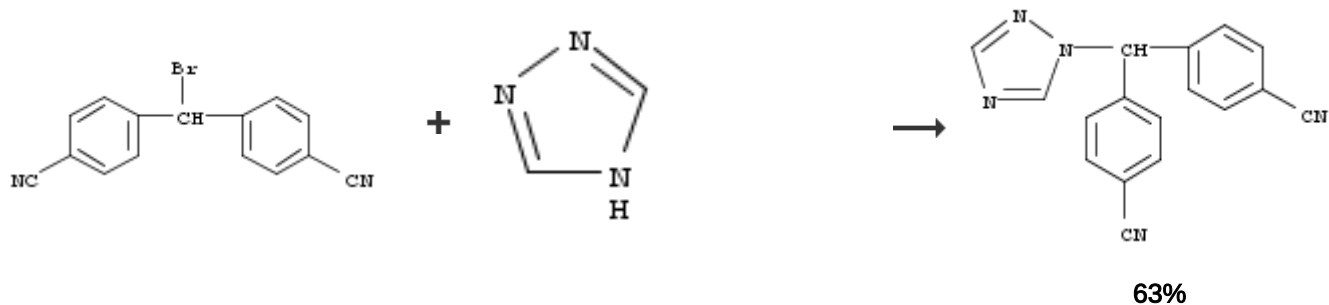
From U.S. Pat. Appl. Publ., 20070066831, 22 Mar 2007

Experimental Procedure

Example 5 Preparation of Letrozole from Intermediate III Using the New Base [0059] To the oily residue of intermediate III, from example 2, 63 grams of 4-fluorobenzonitrile and 2064 grams of tetrahydrofuran were added. At 0 to 5° C. under a nitrogen atmosphere, 480 grams of a 40 percent sodium bis(trimethylsilyl)amide in THF solution were added dropwise over a period of 2 hours. After the addition was complete, the reaction mixture was quenched by the addition of 206 grams of acetic acid, followed by 1030 grams of water. After 15 minutes under agitation, the two-phase reaction mixture was allowed to stratify, and the organic phase was separated, and concentrated under vacuum to a volume of about 500 mL.

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64. Single Step



Overview

Steps/Stages

Notes

1.1 R:K₂CO₃, C:KI, S:Me₂CO, 10 h, 55°C

Reactants: 2, Reagents: 1, Catalysts: 1,
Solvents: 1, Steps: 1, Stages: 1, Most stages
in any one step: 1

References

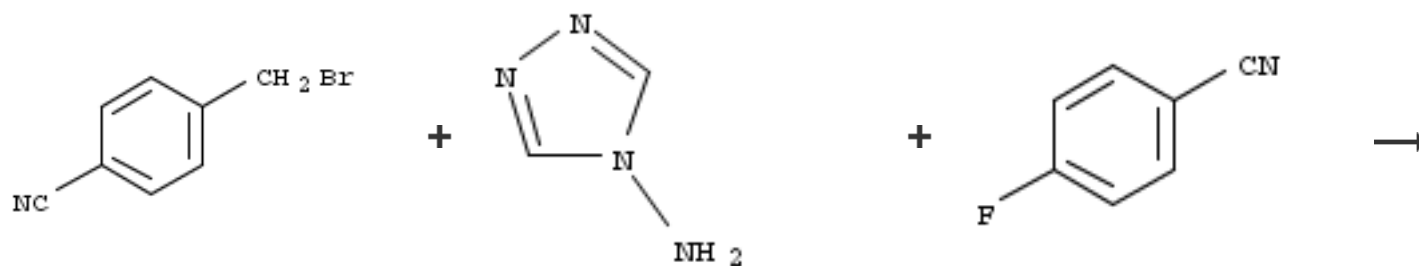
[Synthesis, characterization and single crystal structure of 4,4'-\(1H-1,2,4 triazol- 1-methylene\)bisbenzonitrile](#)

By Wang, Jun et al

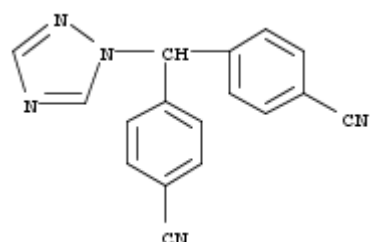
From Youji Huaxue, 24(5), 550-553; 2004

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65. 3 Steps



[Step 3.2]



Overview

Steps/Stages

- 1.1 S:Me₂CHOH, 5 h, 80-85°C; 85°C → rt; rt → 5°C; 2 h
- 2.1 S:H₂O, rt → 5°C
- 2.2 R:HCl, R:NaNO₂, S:H₂O, 0-5°C; 6 h, 0-5°C; 2-3 h, 30-35°C
- 2.3 R:O=C(NH₂)₂
- 3.1 R:t-BuOK, S:DMF, 1 h
- 3.2 S:DMF, 3 h
- 3.3 R:HCl, S:H₂O, pH 7.5-8.0

Notes

Reactants: 3, Reagents: 4, Solvents: 3, Steps: 3, Stages: 7, Most stages in any one step: 3

References

[Improved regiospecific process for preparation of 4,4'-\(1H-1,2,4-triazol-1-ylmethylene\)bisbenzonitrile \(Letrazole\) free of isomeric impurities and 4,4',4''-methylidynetris\(benzonitrile\)](#)

By Patel, Hetalkumar Virendrabhai et al

From PCT Int. Appl., 2004076409, 10 Sep 2004

Experimental Procedure

Step 1

(a) Preparation of 4-[(4-amino-1,2,4-triazolium-1-yl)methyl]benzonitrile bromide, compound of formula 2: 4-bromomethylbenzonitrile (300.0 gm, 1.530 moles) was heated with 4-amino-1,2,4-triazole (141.5 gm, 1.683 moles) in isopropanol (3.0 L) as a solvent for 5.0 hours at 80-85°C temperature. Reaction mixture was cooled gradually to room temperature and further to 0°-5°C temperature and stirred for 2.0 hrs and filtered. **(b) Purification of 4-[(4-amino-1,2,4-triazolium-1-yl)methyl]benzonitrile bromide, compound of formula 2:** The filtered solid was washed with isopropanol (300.0 ml) followed by hexane (300.0 ml), gave 4-[(4-amino-1,2,4-triazolium-1-yl)methyl]benzonitrile bromide, compound of formula 2. (310.0 gm, 72.2% yield). **4-[(4-amino-1,2,4-triazolium-1-yl)methyl]benzonitrile bromide**, yield (310.0 gm, 72.2% yield).

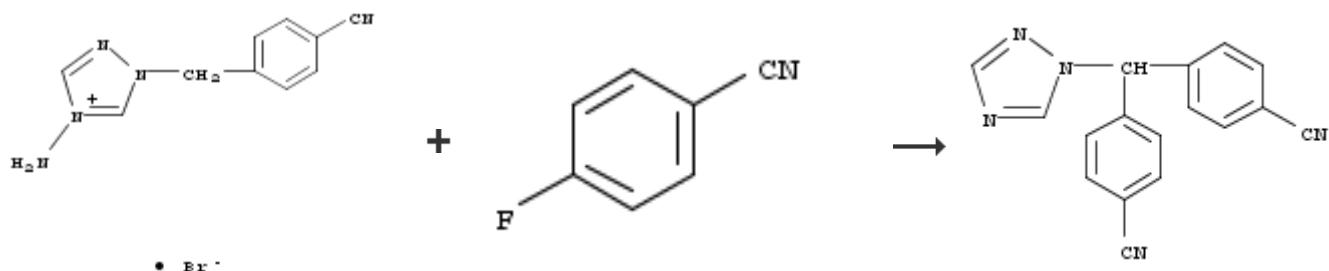
Step 2

(c) Preparation of 4-[1-(1,2,4-triazol-1-yl)methyl]benzonitrile, compound of formula 3: 4-[(4-amino-1,2,4-triazolium-1-yl)methyl]benzonitrile bromide (275.0 gm, 0.982 moles) was dissolved in water (1.1L) and cooled to 0°-5°C temperature. To this solution, was added hydrochloric acid (196.5 ml, 1.963 moles) at 0°-5°C temperature followed by solution of sodium nitrite (74.5 gm, 1.080 moles) in water (275.0 ml) at 0°-5°C temperature within 6.0 hrs, followed by stirring at 30°-35°C temperature for 2.0-3.0 hrs. After reaction was over, unreacted nitrous acid was decomposed with urea, extracted with dichloromethane to remove impurities. Finally, aqueous layer was basified to pH 8.0-8.5 by adding 25% ammonia solution and product was extracted with dichloromethane. An organic layer containing product was washed with water and concentrated to give syrupy liquid, to which was added isopropanol:hexane (20:80), slurry so obtained was cooled to 8-10°C temperature, stirred for 2.0 hrs, filtered and washed with hexane (75.0ml) to give 4-[1-(1,2,4-triazol-1-yl)methyl]benzonitrile, compound of formula 3 free of compound of formula 4. (150.0 gm, 82.9% yield) **4-[1-(1,2,4-triazol-1-yl)methyl]benzonitrile**, yield (150.0 gm, 82.9% yield)

Step 3

(d) Preparation of 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile, compound of formula 1: The solution of 4-[1-(1,2,4-triazol-1-yl)methyl]benzonitrile (100 gm, 0.543 moles) in N,N-dimethylformamide (500 ml) was added at -10° to -5°C temperature to the solution of potassium tertiary butoxide (122 gm, 1.085 moles) in N,N-dimethylformamide (750 ml) and stirred for 1.0 hour. To this solution, was added a solution of 4-fluorobenzonitrile (77 gm, 0.592 moles) in N,N-dimethylformamide (500 ml) at -10° to -5°C temperature and stirred for 3.0 hours. Reaction mixture was then neutralized to pH 7.5-8.0 by adding 1.0 N hydrochloric acid (700 ml) and concentrated to remove N,N-dimethylformamide under vacuum. To the residue was added water and product was extracted with ethyl acetate. An organic layer was washed with water and concentrated under vacuum. To the residue was added, isopropyl alcohol, stirred for 1.0 hour and filtered the crude product (125.0 gm). Crude product was recrystallized from hot ethyl acetate (1.37 L) to give 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile, compound of formula 1. (90 g, 58 % yield, 99.90 % HPLC purity). **4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile**, yield (90 g, 58 %)

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66. 2 Steps

[Step 2.2]

[Overview](#)[Steps/Stages](#)[Notes](#)

- 1.1 S:H₂O, rt → 5°C
 1.2 R:HCl, R:NaNO₂, S:H₂O, 0-5°C; 6 h, 0-5°C; 2-3 h, 30-35°C
 1.3 R:O=C(NH₂)₂
 2.1 R:t-BuOK, S:DMF, 1 h
 2.2 S:DMF, 3 h
 2.3 R:HCl, S:H₂O, pH 7.5-8.0

Reactants: 2, Reagents: 4, Solvents: 2, Steps: 2, Stages: 6, Most stages in any one step: 3

References

Improved regiospecific process for preparation of 4,4'-(1H-1,2,4-triazol-1-ylmethylene)bisbenzonitrile (Letrazole) free of isomeric impurities and 4,4',4"-methylidynetris(benzonitrile)

By Patel, Hetalkumar Virendrabhai et al

From PCT Int. Appl., 2004076409, 10 Sep 2004

Experimental Procedure

Step 1

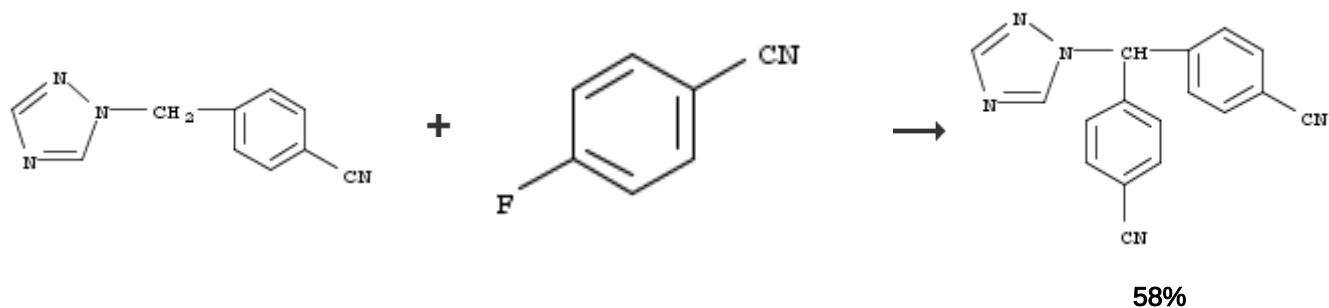
(c) Preparation of 4-[1-(1,2,4-triazol-1-yl)methyl]benzonitrile, compound of formula 3: 4-[(4-amino-1,2,4-triazolium-1-yl)methyl]benzonitrile bromide (275.0 gm, 0.982 moles) was dissolved in water (1.1L) and cooled to 0°-5°C temperature. To this solution, was added hydrochloric acid (196.5 ml, 1.963 moles) at 0°-5°C temperature followed by solution of sodium nitrite (74.5 gm, 1.080 moles) in water (275.0 ml) at 0°-5°C temperature within 6.0 hrs, followed by stirring at 30°-35°C temperature for 2.0-3.0 hrs. After reaction was over, unreacted nitrous acid was decomposed with urea, extracted with dichloromethane to remove impurities. Finally, aqueous layer was basified to pH 8.0-8.5 by adding 25% ammonia solution and product was extracted with dichloromethane. An organic layer containing product was washed with water and concentrated to give syrupy liquid, to which was added isopropanol:hexane (20:80), slurry so obtained was cooled to 8-10°C temperature, stirred for 2.0 hrs, filtered and washed with hexane (75.0ml) to give 4-[1-(1,2,4-triazolyl)methyl]benzonitrile, compound of formula 3 free of compound of formula 4. (150.0 gm, 82.9% yield) **4-[1-(1,2,4-triazol-1-yl)methyl]benzonitrile**, yield (150.0 gm, 82.9% yield)

Step 2

(d) Preparation of 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile, compound of formula 1: The solution of 4-[1-(1,2,4-triazolyl)-methyl]benzonitrile (100 gm, 0.543 moles) in N,N-dimethylformamide (500 ml) was added at -10° to -5°C temperature to the solution of potassium tertiary butoxide (122 gm, 1.085 moles) in N,N-dimethylformamide (750 ml) and stirred for 1.0 hour. To this solution, was added a solution of 4-fluorobenzonitrile (77 gm, 0.592 moles) in N,N-dimethylformamide (500 ml) at -10° to -5°C temperature and stirred for 3.0 hours. Reaction mixture was then neutralized to pH 7.5-8.0 by adding 1.0 N hydrochloric acid (700 ml) and concentrated to remove N,N-dimethylformamide under vacuum. To the residue was added water and product was extracted with ethyl acetate. An organic layer was washed with water and concentrated under vacuum. To the residue was added, isopropyl alcohol, stirred for 1.0 hour and filtered the crude product (125.0 gm). Crude product was recrystallized from hot ethyl acetate (1.37 L) to give 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile, compound of formula 1. (90 g, 58 % yield, 99.90 % HPLC purity). **4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile**, yield (90 g, 58 %)

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67. Single Step



Overview

Steps/Stages

Notes

- 1.1 R:t-BuOK, S:DMF, 1 h
 1.2 S:DMF, 3 h
 1.3 R:HCl, S:H₂O, pH 7.5-8.0

Reactants: 2, Reagents: 2, Solvents: 2, Steps: 1, Stages: 3, Most stages in any one step: 3

References

[Improved regiospecific process for preparation of 4,4'-\(1H-1,2,4-triazol-1-ylmethylene\)bisbenzonitrile \(Letrazole\) free of isomeric impurities and 4,4',4"-methylidynetris\(benzonitrile\)](#)

By Patel, Hetalkumar Virendrabhai et al

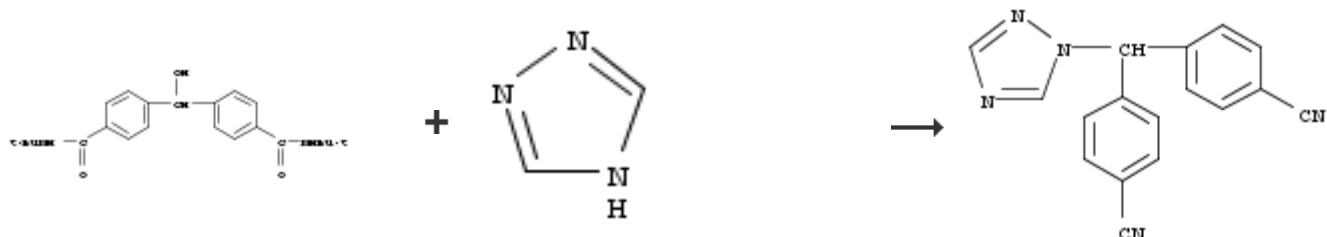
From PCT Int. Appl., 2004076409, 10 Sep 2004

Experimental Procedure

(d) Preparation of 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile, compound of formula 1: The solution of 4-[1-(1,2,4-triazolyl)-methyl]benzonitrile (100 gm, 0.543 moles) in N,N-dimethylformamide (500 ml) was added at -10° to -5°C temperature to the solution of potassium tertiary butoxide (122 gm, 1.085 moles) in N,N-dimethylformamide (750 ml) and stirred for 1.0 hour. To this solution, was added a solution of 4-fluorobenzonitrile (77 gm, 0.592 moles) in N,N-dimethylformamide (500 ml) at -10° to -5°C temperature and stirred for 3.0 hours. Reaction mixture was then neutralized to pH 7.5-8.0 by adding 1.0 N hydrochloric acid (700 ml) and concentrated to remove N,N-dimethylformamide under vacuum. To the residue was added water and product was extracted with ethyl acetate. An organic layer was washed with water and concentrated under vacuum. To the residue was added, isopropyl alcohol, stirred for 1.0 hour and filtered the crude product (125.0 gm). Crude product was recrystallized from hot ethyl acetate (1.37 L) to give 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile, compound of formula 1. (90 g, 58 % yield, 99.90 % HPLC purity). 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile, yield (90 g, 58 %)

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68. 2 Steps



[Step 2.1]

Overview

Steps/Stages

- 1.1
 2.1

Notes

Reactants: 2, Steps: 2, Stages: 2, Most stages in any one step: 1

References

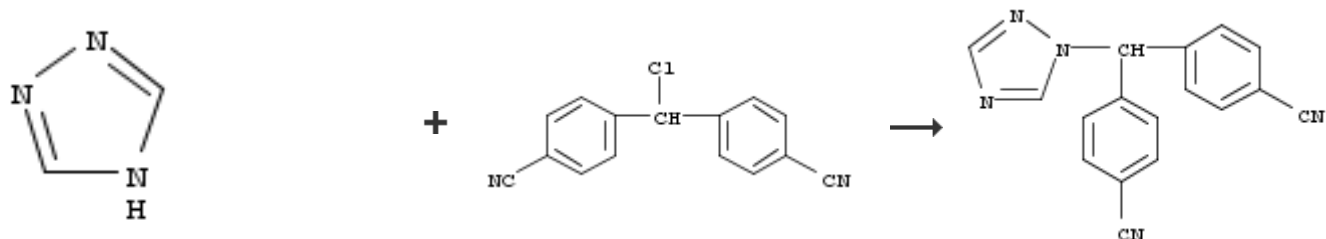
[Preparation and formulation of triazolymethylbenzonitriles and analogs as aromatase inhibitors](#)

By Bowman, Robert M. et al

From U.S., 4978672, 18 Dec 1990

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69. Single Step



Overview

Steps/Stages

1.1

Notes

Reactants: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

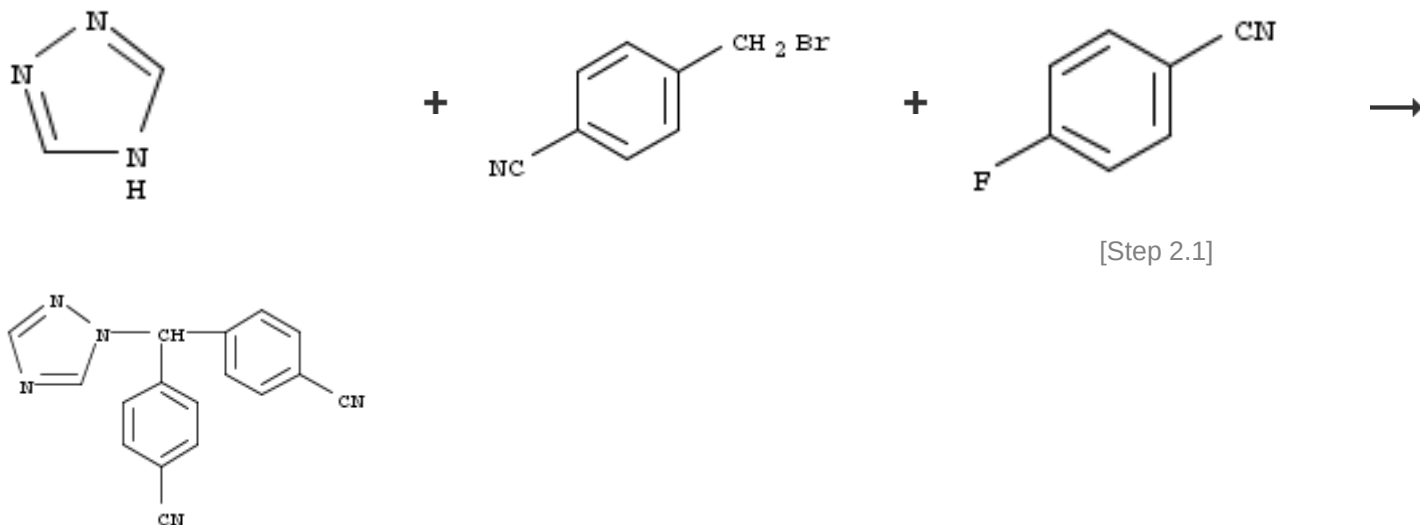
[Preparation and formulation of triazolymethylbenzonitriles and analogs as aromatase inhibitors](#)

By Bowman, Robert M. et al

From U.S., 4978672, 18 Dec 1990

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70. 2 Steps



Overview

Steps/Stages

1.1 S:CHCl₃, S:MeCN

2.1

Notes

Reactants: 3, Solvents: 2, Steps: 2, Stages: 2, Most stages in any one step: 1

References

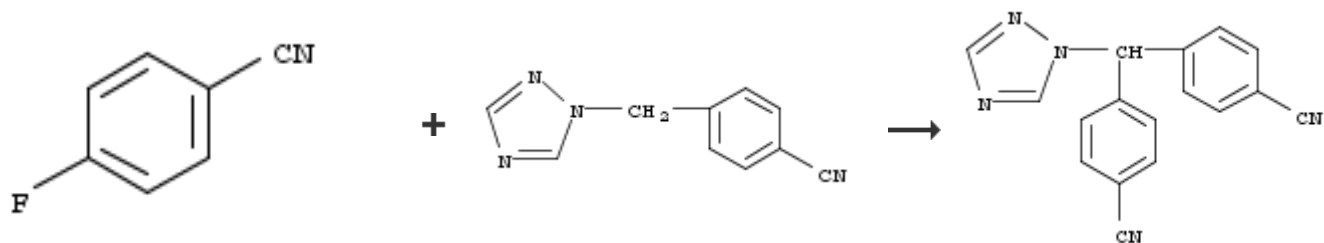
[Preparation of \(imidazolymethyl\)benzonitriles as aromatase inhibitors](#)

By Bowman, Robert M. et al

From U.S., 4937250, 26 Jun 1990

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71. Single Step



Overview

Steps/Stages

1.1

Notes

Reactants: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

[Preparation of \(imidazolylmethyl\)benzonitriles as aromatase inhibitors](#)

By Bowman, Robert M. et al

From U.S., 4937250, 26 Jun 1990

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