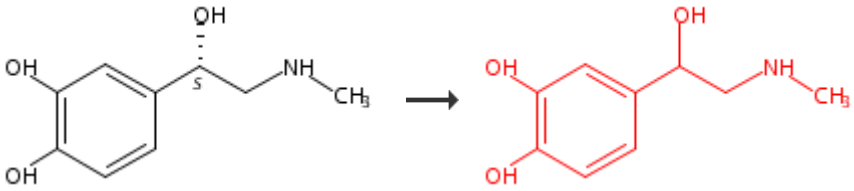
1. Single Step



99%

Overview

Steps/Stages

1.1 R:$NaHSO_3$, R:H_2SO_4, S:H_2O, 7 h, 65°C; 65°C → rt

1.2 R:NH_4OH, S:H_2O, 12 h, rt, pH 8.5

Notes

optimization study, optimized on temperature, time and reagent, Reactants: 1, Reagents: 3, Solvents: 1, Steps: 1, Stages: 2, Most stages in any one step: 2

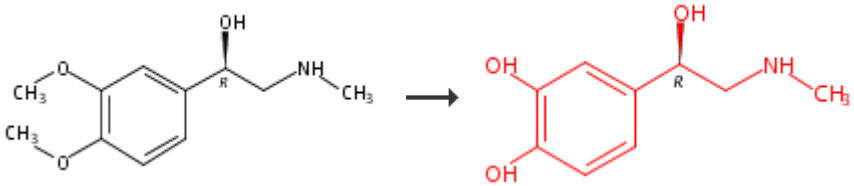
References

A method for preparation of (±)-Adrenaline

By Fang, Yueliang et al

From Faming Zhuanli Shenqing Gongkai Shuomingshu, 101781220, 21 Jul 2010

2. Single Step



97%

Overview

Steps/Stages

1.1 R:BBr_3

Notes

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

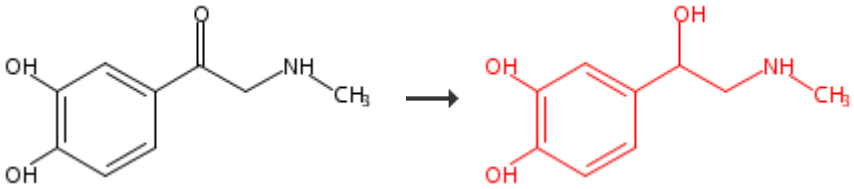
References

An in situ procedure for catalytic, enantioselective acetate aldol addition. Application to the synthesis of (R)-(-)-epinephrine

By Singer, Robert A. and Carreira, Erick M.

From Tetrahedron Letters, 38(6), 927-930; 1997

3. Single Step



80%

Overview

Steps/Stages

1.1

Notes

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

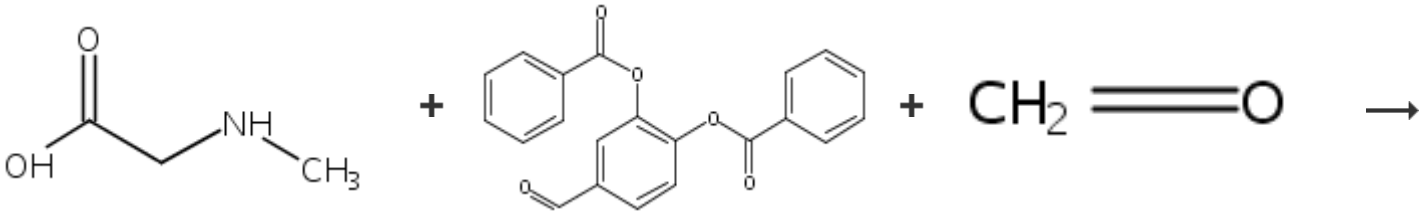
References

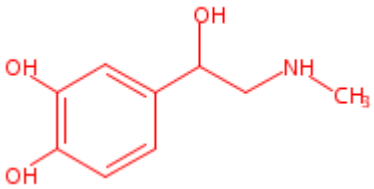
Reduction of some carbonyl groups by ion exchange resin supported borohydride

By Hu, Mougang et al

From Zhongguo Yiyao Gongye Zazhi, 22(10), 461-2; 1991

4. Single Step





67%

Overview

Steps/Stages

Notes

1.1 S:Benzene, 6-8 h, reflux

1.2 R:N_2H_4-H_2O, S:EtOH, 2 d, rt; 3 h, reflux

Dean-Stark trap used (stage 1); azomethine ylide generated in-situ (stage 1); oxazolidine isolated in stage 1 used crude in stage 2, paraformaldehyde used (stage 1), Reactants: 3, Reagents: 1, Solvents: 2, Steps: 1, Stages: 2, Most stages in any one step: 2

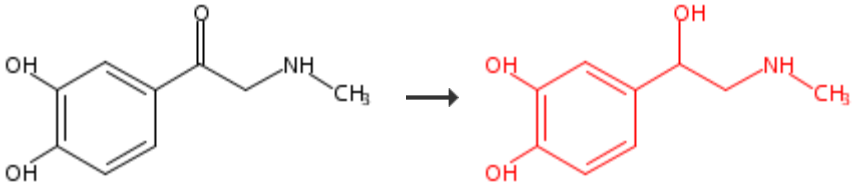
References

A simple two-step synthesis of 2-(alkylamino)-1-arylethanols, including racemic adrenaline, from aromatic aldehydes via 5-aryloxazolidines

By Moshkin, Vladimir S. and Sosnovskikh, Vyacheslav Ya.

From Tetrahedron Letters, 54(44), 5869-5872; 2013

5. Single Step



92%

Overview

Steps/Stages

1.1 R:H_2, C:Ni

Notes

Classification: Reduction; Hydrogenation; # Conditions: Ni /H2; 20 deg 3h-3h 30mn; # Comments: Product DL adrenaline - 80-85% pure, Reactants: 1, Reagents: 1, Catalysts: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

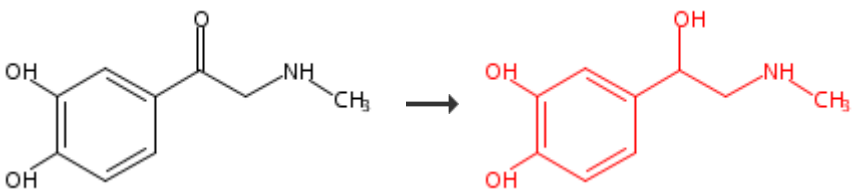
References

Synthesis of some derivatives of adrenaline. I. Synthesis of dl-adrenaline and its analogs

By Remizov, A. L.

From Zhurnal Obshchei Khimii, 28, 2530-8; 1958

6. Single Step



92%

Overview

Steps/Stages

1.1 R:H_2, C:Ni, S:H_2O

Notes

Classification: Reduction; Hydrogenation; # Conditions: /H2 Raney Ni; NaOH H2O; /1.2atm 3h-3h30mn; # Comments: See CA 53, 3127g; Racemic product, Reactants: 1, Reagents: 1, Catalysts: 1, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

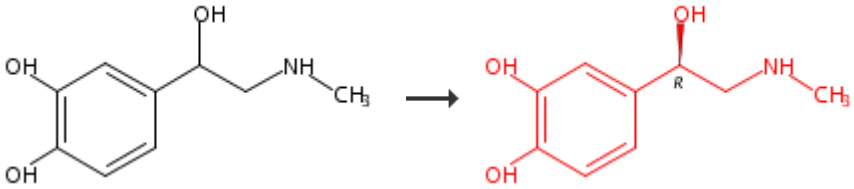
References

Synthesis of some derivatives of adrenaline. I. Synthesis of dl-adrenaline and its analogs

By Remizov, A. L.

From Zhurnal Obshchei Khimii, 28, 2530-8; 1958

7. Single Step



Overview

Steps/Stages

1.1 R:L-(+)-Tartaric acid, S:MeOH, 1-3 h, rt

1.2 R:$Na_2S_2O_5$, S:H_2O, rt; rt → 10°C

1.3 R:NH_3, S:H_2O, pH 8.5; 15 min

Notes

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

References

Processes for the preparation of epinephrine

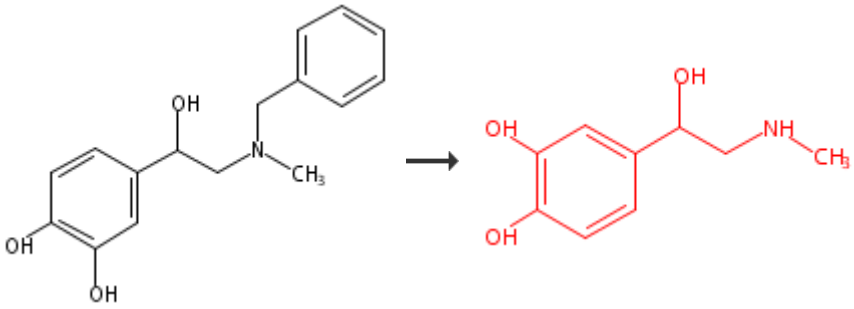
By Yadav, Ramprasad et al

From PCT Int. Appl., 2009004593, 08 Jan 2009

Experimental Procedure

Example -4: (-)-Epinephrine Step A: To a solution of racemic epinephrine (crude) (500 g) in methanol (1.0 L) was added L-tartaric acid (820 g). The reaction was stirred and after 1-3 hours, a thick precipitation was observed. Methanol (1.5 lit) was added and stirred for 24-30 hours at room temperature. The reaction mixture filtered and washed. wet wt. 464 g Step B: Epinephrine tartrate (wet wt.) (464 g) was dissolved in purified water (4.5 L) and sodium meta bisulphite (4 g) was added and the reaction mixture was cooled to 5-10 °C. The pH of the reaction mixture was adjusted with ammonia sol (270 mL) to about 8.5. The reaction stirred for 15 min and filtered. The solid obtained was washed with water (500 mL) followed by methanol (500 mL) and dried to obtain (-)-epinephrine base 232 g as solid. The reaction sequence of Step A and Step B is repeated twice to enrich the optical purity. The crude (-)-epinephrine is used in the next step. To a 5-10 °C cooled suspension of epinephrine base obtained from Example-1 (130 g) in purified water (1.3 L) was added HCl (55 mL) to adjust the pH to ~ 2 to 2.5 to get clear solution. To the clear solution was added carbon (5 g) and sodium meta bisulphite (1 g), the reaction stirred for 30 min. The reaction mass filtered and washed with water (200 mL). The filtrate was cooled to 5-10 °C then added dilute ammonia solution (105 mL) to adjust pH about 8.5. The reaction was stirred for 15 min, the reaction mixture was filtered and washed with water (400 mL) then methanol (400 mL) and dried to get pure epinephrine. Yield: 103 g; Purity: 99.88 %: enantiomeric excess: 95.34 %. (-)-Epinephrine, Yield: 103 g;

8. Single Step



Overview

Steps/Stages

1.1 R:HCl, S:H_2O, S:MeOH, rt, pH 1-2.4

1.2 R:H_2, C:Pd, rt; rt → 40°C; 30-35 h, 40°C

Notes

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

References

Processes for the preparation of epinephrine

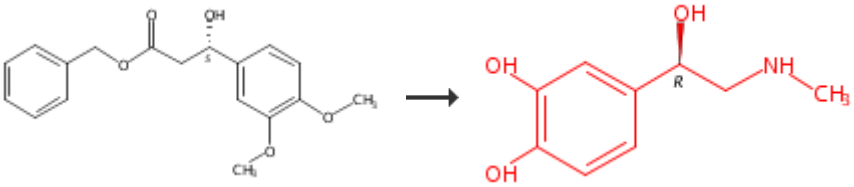
By Yadav, Ramprasad et al

From PCT Int. Appl., 2009004593, 08 Jan 2009

Experimental Procedure

Example-3: Racemic epinephrine N-Benzyl epinephrine (950 g) was dissolved in methanol (9.5 L) and pH was adjusted with dilute HCl (345 mL) to about 1.0-2.4 and stirred. To the reaction mixture, 10% Pd/C (250 g) was added and hydrogen gas was bubbled through the reaction mixture. It was heated to about 40 °C and stirred for about 30-35 hours at 40 °C . After completion of the reaction, the reaction mass was filtered and washed with methanol (1 L). The filtrate was cooled to 10-15 °C and pH was adjusted by ammonia solution (275 ml) to 8.5. The reaction mixture was filtered, washed with methanol (1 L) and dried to get epinephrine. Yield: 523 g Racemic epinephrine, Yield: 523 g

9. Single Step



Overview

Steps/Stages

Notes

1.1

aldol condensation, Several steps, Acetates, Methyl ketones, Unsubstituted dienolates, Enoxysilanes, Stannanes, Acetoacetate, Furans, Domino reactions, Mechanisms, Method comparisons, Catalysts, Aldol tandem reactions, Reactants: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

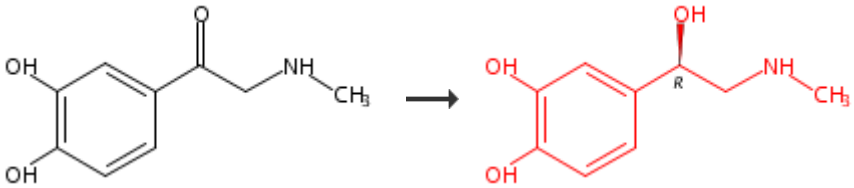
References

Catalytic enantioselective aldol addition reactions

By Carreira, Erick M. et al

From Organic Reactions (Hoboken, NJ, United States), 67, No pp. given; 2006

10. Single Step



Overview

Steps/Stages

1.1 R:Et_3N, R:H_2, C:1044758-45-3, S:MeOH, 50 atm

Notes

Asymmetric Hydrogenation of Functionalized Carbonyl Compounds, high pressure, Reactants: 1, Reagents: 2, Catalysts: 1, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

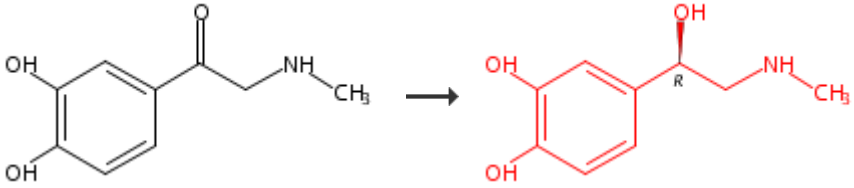
References

Bis(bicyclo[2.2.1]hepta-2,5-diene)rhodium Perchlorate-(R)-1-(S)-1',2-Bis(diphenylphosphino)ferrocenylethanol

By Ito, Yoshihiko and Suginome, Michinori

From e-EROS Encyclopedia of Reagents for Organic Synthesis, , No pp. given; 2001

11. Single Step



Overview

Steps/Stages

1.1 R:H_2, C:Et_3N, S:MeOH, 50 atm

Notes

Hydrogenation Catalysts, Stage 1: [Rh{(R)-(S)-BPPFOH}(nbd))+ClO4-, Reactants: 1, Reagents: 1, Catalysts: 1, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

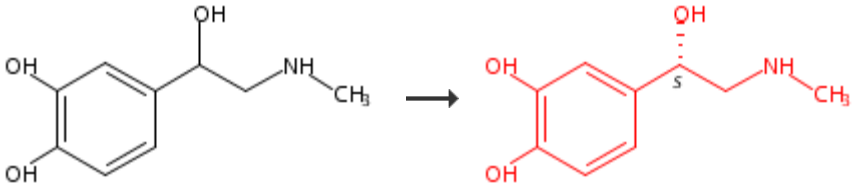
References

Bis(bicyclo[2.2.1]hepta-2,5-diene)rhodium Perchlorate

By Ito, Yoshihiko and Suginome, Michinori

From e-EROS Encyclopedia of Reagents for Organic Synthesis, , No pp. given; 2001

12. Single Step



Overview

Steps/Stages

1.1 C:$BrCH_2CO_2H$

Notes

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

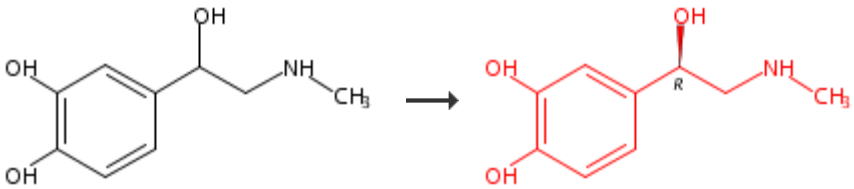
References

Resolution of the enantiomers of drugs containing amino alcohol structure after derivatization with bromoacetic acid

By Guebitz, G. et al

From Chirality, 4(5), 333-7; 1992

13. Single Step



Overview

Steps/Stages

Notes

1.1 C:$BrCH_2CO_2H$

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

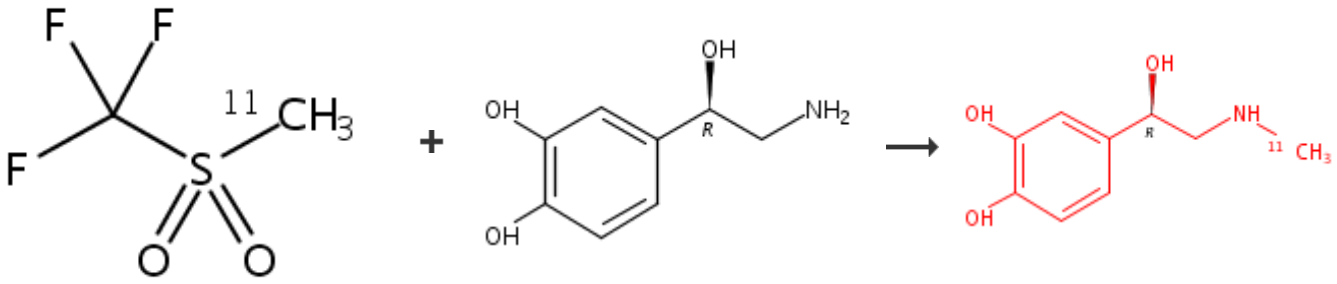
References

Resolution of the enantiomers of drugs containing amino alcohol structure after derivatization with bromoacetic acid

By Guebitz, G. et al

From Chirality, 4(5), 333-7; 1992

14. Single Step



25%

Overview

Steps/Stages

1.1 S:DMF, 4 min, rt

Notes

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

References

Radiolabeled Phenethylguanidines: Novel Imaging Agents for Cardiac Sympathetic Neurons and Adrenergic Tumors

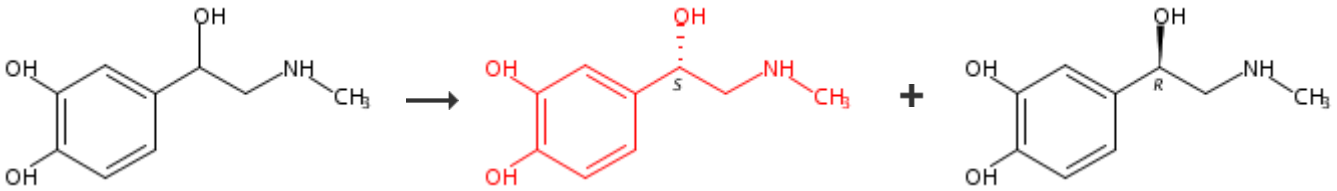
By Raffel, David M. et al

From Journal of Medicinal Chemistry, 50(9), 2078-2088; 2007

Experimental Procedure

General/Typical Procedure: **Radiosynthesis of [^{11}C]HED and [^{11}C]EPI.** [^{11}C]HED was synthesized by N-methylation of (-)-metaraminol as the free base, by use of previously described methods14 with a few modifications. Briefly, [^{11}C]methyl triflate[50] in a N_2 carrier gas stream was bubbled at room temperature through 0.25 mL of dimethylformamide (DMF) containing 1.0 mg of (-)-metaraminol until the radioactivity trapped in the reaction vial reached a maximum (4 min). Because of the high reactivity of [^{11}C]methyl triflate, the reaction to form HED is extremely rapid and no heating of the reaction vial is necessary. HED was purified by HPLC (Phenomenex Partisil 10 µm SCX 4.6 x 250 mm column; mobile phase 60 mM NaH_2PO_4 monohydrate; flow rate 2.0 mL/min; *Rt* 6 min). Total synthesis time, including HPLC purification and product formulation, was 35 min. Corrected radiochemical yields were 20-25%, with radiochemical purity >98% and specific activity >500 Ci/mmol. [^{11}C]- EPI was synthesized under comparable conditions, except the [^{11}C]methyl triflate was passed through 0.25 mL of dimethyl sulfoxide (DMSO) containing 1.0 mg of (-)-norepinephrine as the free base. HPLC purification conditions were the same as used for [^{11}C]HED except the mobile phase was 25 mM NaH_2PO_4 monohydrate; flow rate 3.0 mL/min; *Rt* 6 min. Corrected radiochemical yields, radiochemical purities, and specific activities were comparable to those achieved with [^{11}C]HED.

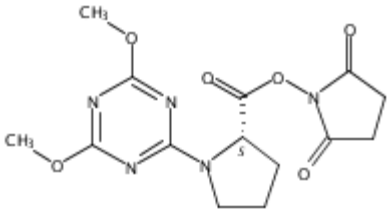
15. Single Step



Overview

Steps/Stages

1.1 R:



R:Et_3N, S:H_2O, S:MeCN, 40 min, 20°C

1.2

Notes

separation by reversed-phase chromatography on ODS column in stage 2, Reactants: 1, Reagents: 2, Solvents: 2, Steps: 1, Stages: 2, Most stages in any one step: 2

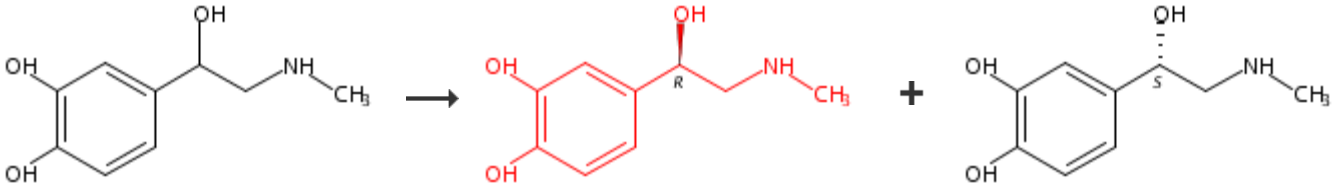
References

Towards the chiral metabolomics: Liquid chromatography-mass spectrometry based DL-amino acid analysis after labeling with a new chiral reagent, (S)-2,5-dioxopyrrolidin-1-yl-1-(4,6-dimethoxy-1,3,5-triazin-2-yl)pyrrolidine-2-carboxylate, and the application to saliva of healthy volunteers

By Mochizuki, Toshiki et al

From Analytica Chimica Acta, 875, 73-82; 2015

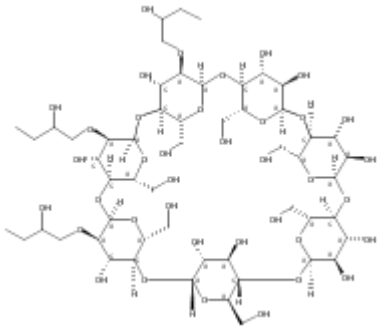
16. Single Step



Overview

Steps/Stages

1.1 R:



S:H_2O, rt, pH 2.5

Notes

Electrochem., buffered soln., during chromatog. (capillary electrophoresis), resoln. step, Reactants: 1, Reagents: 1, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

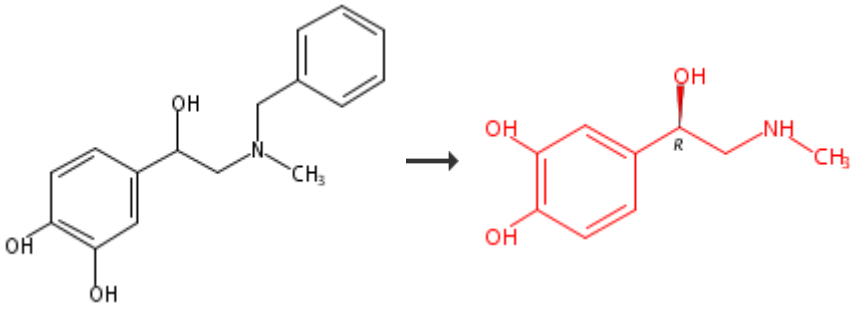
References

New cyclomaltoheptaose (β-cyclodextrin) derivative 2-O-(2-hydroxybutyl)cyclomaltoheptaose: preparation and its application for the separation of enantiomers of drugs by capillary electrophoresis

By Zhao, Ming-gang et al

From Carbohydrate Research, 340(8), 1563-1565; 2005

17. 2 Steps



Overview

Steps/Stages

1.1 R:HCl, S:H_2O, S:MeOH, rt, pH 1-2.4

1.2 R:H_2, C:Pd, rt; rt → 40°C; 30-35 h, 40°C

2.1 R:L-(+)-Tartaric acid, S:MeOH, 1-3 h, rt

2.2 R:$Na_2S_2O_5$, S:H_2O, rt; rt → 10°C

2.3 R:NH_3, S:H_2O, pH 8.5; 15 min

Notes

2) stereoselective, Reactants: 1, Reagents: 5, Catalysts: 1, Solvents: 2, Steps: 2, Stages: 5, Most stages in any one step: 3

References

Processes for the preparation of epinephrine

By Yadav, Ramprasad et al

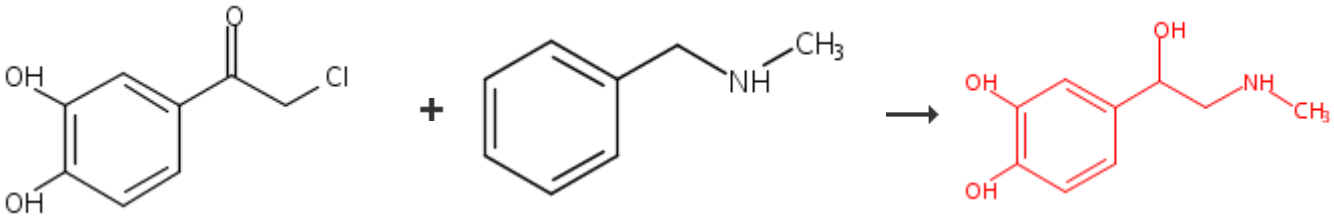
From PCT Int. Appl., 2009004593, 08 Jan 2009

Experimental Procedure

Step 1
Example-3: Racemic epinephrine N-Benzyl epinephrine (950 g) was dissolved in methanol (9.5 L) and pH was adjusted with dilute HCl (345 mL) to about 1.0-2.4 and stirred. To the reaction mixture, 10% Pd/C (250 g) was added and hydrogen gas was bubbled through the reaction mixture. It was heated to about 40 °C and stirred for about 30-35 hours at 40 °C . After completion of the reaction, the reaction mass was filtered and washed with methanol (1 L). The filtrate was cooled to 10-15 °C and pH was adjusted by ammonia solution (275 ml) to 8.5. The reaction mixture was filtered, washed with methanol (1 L) and dried to get epinephrine. Yield: 523 g Racemic epinephrine, Yield: 523 g

Step 2
Example -4: (-)-Epinephrine Step A: To a solution of racemic epinephrine (crude) (500 g) in methanol (1.0 L) was added L-tartaric acid (820 g). The reaction was stirred and after 1-3 hours, a thick precipitation was observed. Methanol (1.5 lit) was added and stirred for 24-30 hours at room temperature. The reaction mixture filtered and washed. wet wt. 464 g Step B: Epinephrine tartrate (wet wt.) (464 g) was dissolved in purified water (4.5 L) and sodium meta bisulphite (4 g) was added and the reaction mixture was cooled to 5-10 °C. The pH of the reaction mixture was adjusted with ammonia sol (270 mL) to about 8.5. The reaction stirred for 15 min and filtered. The solid obtained was washed with water (500 mL) followed by methanol (500 mL) and dried to obtain (-)-epinephrine base 232 g as solid. The reaction sequence of Step A and Step B is repeated twice to enrich the optical purity. The crude (-)-epinephrine is used in the next step. To a 5-10 °C cooled suspension of epinephrine base obtained from Example-1 (130 g) in purified water (1.3 L) was added HCl (55 mL) to adjust the pH to ~ 2 to 2.5 to get clear solution. To the clear solution was added carbon (5 g) and sodium meta bisulphite (1 g), the reaction stirred for 30 min. The reaction mass filtered and washed with water (200 mL). The filtrate was cooled to 5-10 °C then added dilute ammonia solution (105 mL) to adjust pH about 8.5. The reaction was stirred for 15 min, the reaction mixture was filtered and washed with water (400 mL) then methanol (400 mL) and dried to get pure epinephrine. Yield: 103 g; Purity: 99.88 %: enantiomeric excess: 95.34 %. (-)-Epinephrine, Yield: 103 g;

18. 2 Steps



Overview

Steps/Stages

1.1 S:AcNMe$_2$, 10-15°C; 15°C → 35°C; 2-4 h

1.2 R:HCl, S:H$_2$O, 20°C, pH 5.5

2.1 R:HCl, S:H$_2$O, S:MeOH, rt, pH 1-2.4

2.2 R:H$_2$, C:Pd, rt; rt → 40°C; 30-35 h, 40°C

Notes

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

References

Processes for the preparation of epinephrine

By Yadav, Ramprasad et al

From PCT Int. Appl., 2009004593, 08 Jan 2009

Experimental Procedure

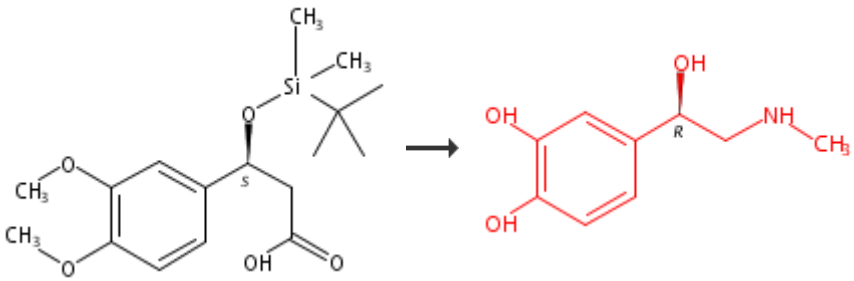
Step 1

Example -2: N-benzyl epinephrine To a cooled solution of 3,4-dihydroxyphenyl acetyl chloride (750 g) in N,N-dimethyl acetamide (2.1 L), N-methyl benzyl amine (912 g) was added drop wise at about 10-15 °C. After the addition, temperature of the reaction mixture was raised to 30-35 °C and stirred for another 2-4 hours. After completion of the reaction, the reaction mixture was filtered and washed with isopropyl alcohol (1.0 L). The filtrate was cooled to about 20 °C and the pH was adjusted to about 5.5 with dilute HCl (150 mL). Water (8 L) was added and further stirred for 15 minutes. pH of the reaction mixture was adjusted to 8.5 with dilute ammonia (240 mL). Solid so obtained was filtered and wet solid was washed with water (4 L). The wet solid was suspended in water (10 L) and pH was adjusted to 5.5. The suspension was stirred for 1 hour and the solid obtained was filtered and dried. Yield: 1027 g N-benzyl epinephrine, Yield: 1027 g

Step 2

Example-3: Racemic epinephrine N-Benzyl epinephrine (950 g) was dissolved in methanol (9.5 L) and pH was adjusted with dilute HCl (345 mL) to about 1.0-2.4 and stirred. To the reaction mixture, 10% Pd/C (250 g) was added and hydrogen gas was bubbled through the reaction mixture. It was heated to about 40 °C and stirred for about 30-35 hours at 40 °C . After completion of the reaction, the reaction mass was filtered and washed with methanol (1 L). The filtrate was cooled to 10-15 °C and pH was adjusted by ammonia solution (275 ml) to 8.5. The reaction mixture was filtered, washed with methanol (1 L) and dried to get epinephrine. Yield: 523 g Racemic epinephrine, Yield: 523 g

19. 2 Steps



Overview

Steps/Stages

Notes

1.1 R:$SOCl_2$

1.2 R:NH_4OH

1.3 R:$PhI(OAc)_2$, R:KOH

1.4 R:$LiAlH_4$, S:THF, reflux

2.1 R:BBr_3

Reactants: 1, Reagents: 6, Solvents: 1, Steps: 2, Stages: 5, Most stages in any one step: 4

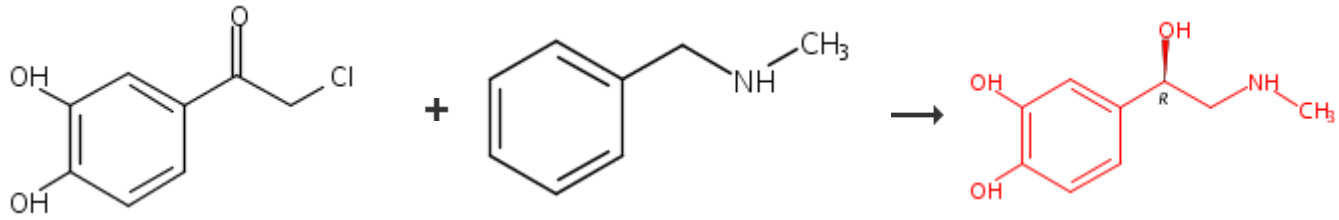
References

An in situ procedure for catalytic, enantioselective acetate aldol addition. Application to the synthesis of (R)-(-)-epinephrine

By Singer, Robert A. and Carreira, Erick M.

From Tetrahedron Letters, 38(6), 927-930; 1997

20. 3 Steps



Overview

Steps/Stages

1.1 S:$AcNMe_2$, 10-15°C; 15°C → 35°C; 2-4 h

1.2 R:HCl, S:H_2O, 20°C, pH 5.5

2.1 R:HCl, S:H_2O, S:MeOH, rt, pH 1-2.4

2.2 R:H_2, C:Pd, rt; rt → 40°C; 30-35 h, 40°C

3.1 R:L-(+)-Tartaric acid, S:MeOH, 1-3 h, rt

3.2 R:$Na_2S_2O_5$, S:H_2O, rt; rt → 10°C

3.3 R:NH_3, S:H_2O, pH 8.5; 15 min

Notes

3) stereoselective, Reactants: 2, Reagents: 5, Catalysts: 1, Solvents: 3, Steps: 3, Stages: 7, Most stages in any one step: 3

References

Processes for the preparation of epinephrine

By Yadav, Ramprasad et al

From PCT Int. Appl., 2009004593, 08 Jan 2009

Experimental Procedure

Step 1

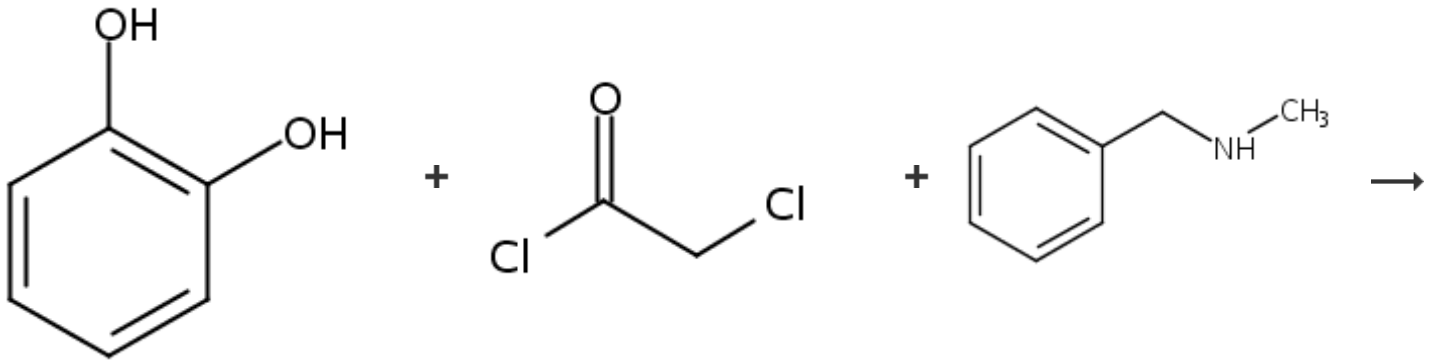
Example -2: N-benzyl epinephrine To a cooled solution of 3,4-dihydroxyphenyl acetyl chloride (750 g) in N,N-dimethyl acetamide (2.1 L), N-methyl benzyl amine (912 g) was added drop wise at about 10-15 °C. After the addition, temperature of the reaction mixture was raised to 30-35 °C and stirred for another 2-4 hours. After completion of the reaction, the reaction mixture was filtered and washed with isopropyl alcohol (1.0 L). The filtrate was cooled to about 20 °C and the pH was adjusted to about 5.5 with dilute HCl (150 mL). Water (8 L) was added and further stirred for 15 minutes. pH of the reaction mixture was adjusted to 8.5 with dilute ammonia (240 mL). Solid so obtained was filtered and wet solid was washed with water (4 L). The wet solid was suspended in water (10 L) and pH was adjusted to 5.5. The suspension was stirred for 1 hour and the solid obtained was filtered and dried. Yield: 1027 g N-benzyl epinephrine, Yield: 1027 g

Step 2

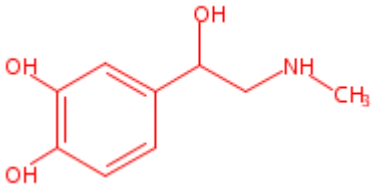
Example-3: Racemic epinephrine N-Benzyl epinephrine (950 g) was dissolved in methanol (9.5 L) and pH was adjusted with dilute HCl (345 mL) to about 1.0-2.4 and stirred. To the reaction mixture, 10% Pd/C (250 g) was added and hydrogen gas was bubbled through the reaction mixture. It was heated to about 40 °C and stirred for about 30-35 hours at 40 °C . After completion of the reaction, the reaction mass was filtered and washed with methanol (1 L). The filtrate was cooled to 10-15 °C and pH was adjusted by ammonia solution (275 ml) to 8.5. The reaction mixture was filtered, washed with methanol (1 L) and dried to get epinephrine. Yield: 523 g Racemic epinephrine, Yield: 523 g

Step 3
Example -4: (-)-Epinephrine Step A: To a solution of racemic epinephrine (crude) (500 g) in methanol (1.0 L) was added L-tartaric acid (820 g). The reaction was stirred and after 1-3 hours, a thick precipitation was observed. Methanol (1.5 lit) was added and stirred for 24-30 hours at room temperature. The reaction mixture filtered and washed. wet wt. 464 g Step B: Epinephrine tartrate (wet wt.) (464 g) was dissolved in purified water (4.5 L) and sodium meta bisulphite (4 g) was added and the reaction mixture was cooled to 5-10 °C. The pH of the reaction mixture was adjusted with ammonia sol (270 mL) to about 8.5. The reaction stirred for 15 min and filtered. The solid obtained was washed with water (500 mL) followed by methanol (500 mL) and dried to obtain (-)-epinephrine base 232 g as solid. The reaction sequence of Step A and Step B is repeated twice to enrich the optical purity. The crude (-)-epinephrine is used in the next step. To a 5-10 °C cooled suspension of epinephrine base obtained from Example-1 (130 g) in purified water (1.3 L) was added HCl (55 mL) to adjust the pH to ~ 2 to 2.5 to get clear solution. To the clear solution was added carbon (5 g) and sodium meta bisulphite (1 g), the reaction stirred for 30 min. The reaction mass filtered and washed with water (200 mL). The filtrate was cooled to 5-10 °C then added dilute ammonia solution (105 mL) to adjust pH about 8.5. The reaction was stirred for 15 min, the reaction mixture was filtered and washed with water (400 mL) then methanol (400 mL) and dried to get pure epinephrine. Yield: 103 g; Purity: 99.88 %: enantiomeric excess: 95.34 %. (-)-Epinephrine, Yield: 103 g;

21. 3 Steps



[Step 2.1]



Overview

Steps/Stages

1.1 R:$AlCl_3$, S:$ClCH_2CH_2Cl$, 15-30 min, 10-15°C; 5-10 min; 20-30 min
1.2 10-15°C; 15°C → rt; 16-20 h

1.3 R:HCl, S:H_2O, 5-10°C
2.1 S:$AcNMe_2$, 10-15°C; 15°C → 35°C; 2-4 h

2.2 R:HCl, S:H_2O, 20°C, pH 5.5

3.1 R:HCl, S:H_2O, S:MeOH, rt, pH 1-2.4

3.2 R:H_2, C:Pd, rt; rt → 40°C; 30-35 h, 40°C

Experimental Procedure

Notes

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

References

Processes for the preparation of epinephrine

By Yadav, Ramprasad et al

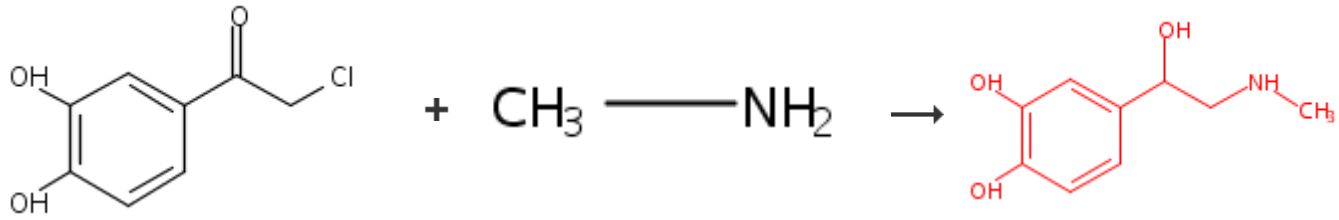
From PCT Int. Appl., 2009004593, 08 Jan 2009

Step 1
Example -1: 3,4-Dihydroxyphenyl acetyl chloride To a cooled solution of 1,2-dichloroethane (5 L) at about 10-15 °C, aluminum chloride (1.5 Kg) was added and the reaction mixture was stirred at 10-15 °C for about 15-30 minutes. To the stirred reaction mixture, catechol (500 g) was added portion wise within about 5-10 minutes and the reaction mixture was further stirred for about 20-30 minutes. To the above solution, chloroacetyl chloride (546 g) was added at 10-15 °C. The temperature of the reaction mixture was raised to room temperature and further stirred for about 16-20 hours. After completion of the reaction, the reaction was quenched with dilute hydrochloric acid solution (10 L) at 5-10 °C and stirred for 2-3 hours at room temperature. The solid so obtained was filtered and the wet solid was washed with water (4 L). The w et solid was suspended in dilute acetic acid (mixture of acetic acid 600 mL and water 4 L) and heated to about 85-90 °C to get a clear solution. To the clear solution, carbon (15 g) was added and stirred for 30 minutes. The reaction mixture was filtered hot. The filtrate was cooled and the solid so obtained was filtered and washed with water (4 L). It was dried to obtain 3,4-dihydroxyphenacyl chloride. Yield: 725 g; 3,4-Dihydroxyphenyl acetyl chloride, yield 725 g; HPLC Purity: 99.83%; M.P.: 175.1-176.7 0C.

Step 2
Example -2: N-benzyl epinephrine To a cooled solution of 3,4-dihydroxyphenyl acetyl chloride (750 g) in N,N-dimethyl acetamide (2.1 L), N-methyl benzyl amine (912 g) was added drop wise at about 10-15 °C. After the addition, temperature of the reaction mixture was raised to 30-35 °C and stirred for another 2-4 hours. After completion of the reaction, the reaction mixture was filtered and washed with isopropyl alcohol (1.0 L). The filtrate was cooled to about 20 °C and the pH was adjusted to about 5.5 with dilute HCl (150 mL). Water (8 L) was added and further stirred for 15 minutes. pH of the reaction mixture was adjusted to 8.5 with dilute ammonia (240 mL). Solid so obtained was filtered and wet solid was washed with water (4 L). The wet solid was suspended in water (10 L) and pH was adjusted to 5.5. The suspension was stirred for 1 hour and the solid obtained was filtered and dried. Yield: 1027 g N-benzyl epinephrine, Yield: 1027 g

Step 3
Example-3: Racemic epinephrine N-Benzyl epinephrine (950 g) was dissolved in methanol (9.5 L) and pH was adjusted with dilute HCl (345 mL) to about 1.0-2.4 and stirred. To the reaction mixture, 10% Pd/C (250 g) was added and hydrogen gas was bubbled through the reaction mixture. It was heated to about 40 °C and stirred for about 30-35 hours at 40 °C . After completion of the reaction, the reaction mass was filtered and washed with methanol (1 L). The filtrate was cooled to 10-15 °C and pH was adjusted by ammonia solution (275 ml) to 8.5. The reaction mixture was filtered, washed with methanol (1 L) and dried to get epinephrine. Yield: 523 g Racemic epinephrine, Yield: 523 g

22. 2 Steps



Overview

Steps/Stages **Notes**

1.1 R:H_2O

2.1 R:H_2, C:Ni, S:H_2O

1) Classification: C-Amination; # Conditions: MeNH2(40%) H2O; cool 30mn ice bath; # Comments: crude product, 65% yield when purified as HCl salt, 2) Classification: Reduction; Hydrogenation; # Conditions: /H2 Raney Ni; NaOH H2O; /1.2atm 3h-3h30mn; # Comments: See CA 53, 3127g; Racemic product, Reactants: 2, Reagents: 2, Catalysts: 1, Solvents: 1, Steps: 2, Stages: 2, Most stages in any one step: 1

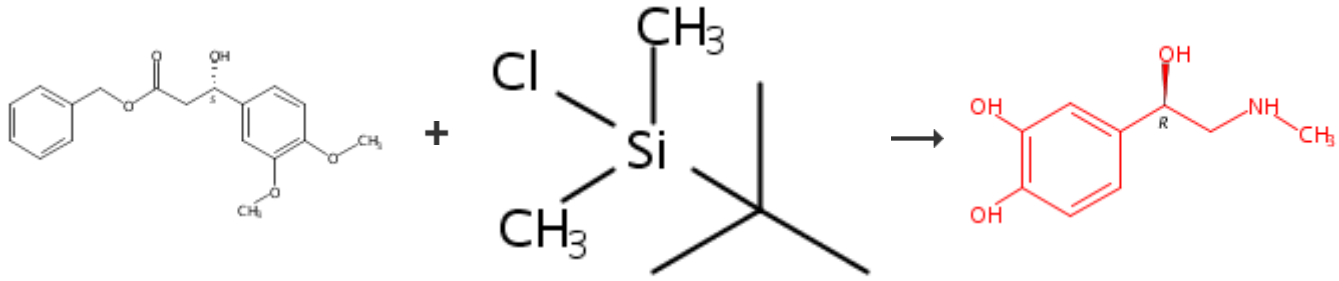
References

Synthesis of some derivatives of adrenaline. I. Synthesis of dl-adrenaline and its analogs

By Remizov, A. L.

From Zhurnal Obshchei Khimii, 28, 2530-8; 1958

23. 3 Steps



Overview

Steps/Stages

1.1 R:NaOH, S:H_2O, S:MeOH

2.1 R:$SOCl_2$

2.2 R:NH_4OH

2.3 R:$PhI(OAc)_2$, R:KOH

2.4 R:$LiAlH_4$, S:THF, reflux

3.1 R:BBr_3

Notes

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

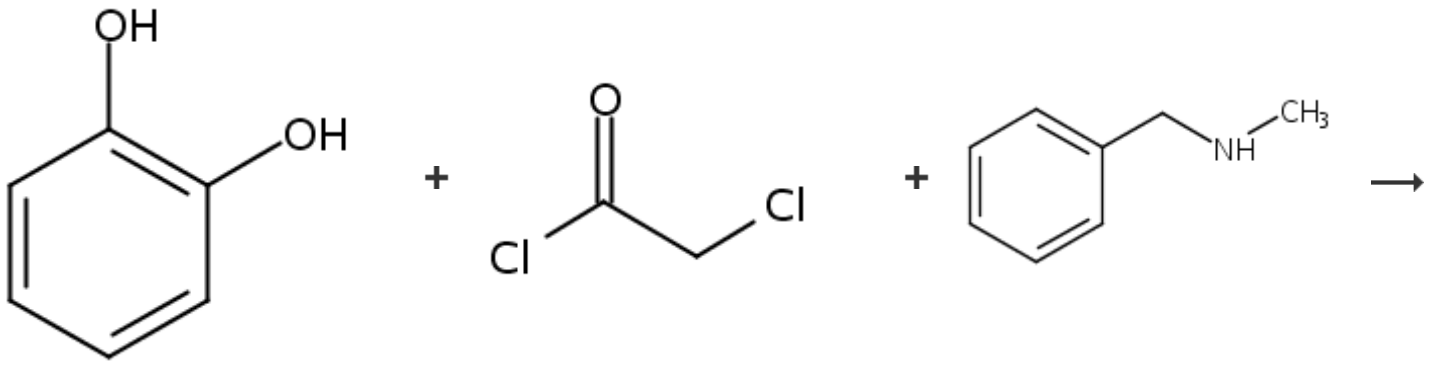
References

An in situ procedure for catalytic, enantioselective acetate aldol addition. Application to the synthesis of (R)-(-)-epinephrine

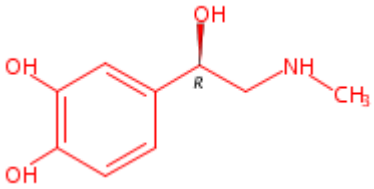
By Singer, Robert A. and Carreira, Erick M.

From Tetrahedron Letters, 38(6), 927-930; 1997

24. 4 Steps



[Step 2.1]



Overview

Steps/Stages

1.1 R:$AlCl_3$, S:$ClCH_2CH_2Cl$, 15-30 min, 10-15°C; 5-10 min; 20-30 min
1.2 10-15°C; 15°C → rt; 16-20 h

1.3 R:HCl, S:H_2O, 5-10°C
2.1 S:$AcNMe_2$, 10-15°C; 15°C → 35°C; 2-4 h

2.2 R:HCl, S:H_2O, 20°C, pH 5.5

3.1 R:HCl, S:H_2O, S:MeOH, rt, pH 1-2.4

3.2 R:H_2, C:Pd, rt; rt → 40°C; 30-35 h, 40°C

4.1 R:L-(+)-Tartaric acid, S:MeOH, 1-3 h, rt

4.2 R:$Na_2S_2O_5$, S:H_2O, rt; rt → 10°C

4.3 R:NH_3, S:H_2O, pH 8.5; 15 min

Notes

4) stereoselective, Reactants: 3, Reagents: 6, Catalysts: 1, Solvents: 4, Steps: 4, Stages: 10, Most stages in any one step: 3

References

Processes for the preparation of epinephrine

By Yadav, Ramprasad et al

From PCT Int. Appl., 2009004593, 08 Jan 2009

Experimental Procedure

Step 1

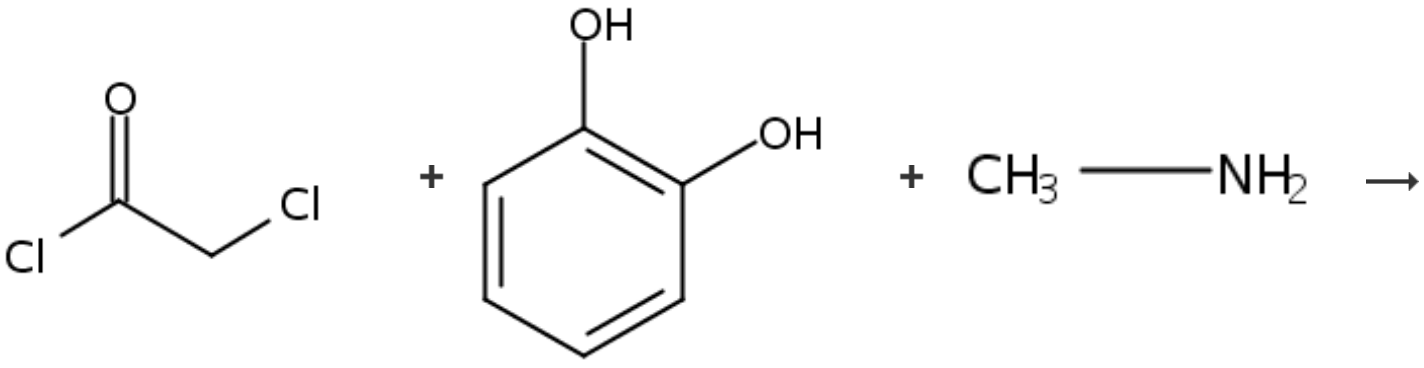
Example -1: 3,4-Dihydroxyphenyl acetyl chloride To a cooled solution of 1,2-dichloroethane (5 L) at about 10-15 °C, aluminum chloride (1.5 Kg) was added and the reaction mixture was stirred at 10-15 °C for about 15-30 minutes. To the stirred reaction mixture, catechol (500 g) was added portion wise within about 5-10 minutes and the reaction mixture was further stirred for about 20-30 minutes. To the above solution, chloroacetyl chloride (546 g) was added at 10-15 °C. The temperature of the reaction mixture was raised to room temperature and further stirred for about 16-20 hours. After completion of the reaction, the reaction was quenched with dilute hydrochloric acid solution (10 L) at 5-10 °C and stirred for 2-3 hours at room temperature. The solid so obtained was filtered and the wet solid was washed with water (4 L). The w et solid was suspended in dilute acetic acid (mixture of acetic acid 600 mL and water 4 L) and heated to about 85-90 °C to get a clear solution. To the clear solution, carbon (15 g) was added and stirred for 30 minutes. The reaction mixture was filtered hot. The filtrate was cooled and the solid so obtained was filtered and washed with water (4 L). It was dried to obtain 3,4-dihydroxyphenacyl chloride. Yield: 725 g; 3,4-Dihydroxyphenyl acetyl chloride, yield 725 g; HPLC Purity: 99.83%; M.P.: 175.1-176.7 0C.

Step 2
Example -2: N-benzyl epinephrine To a cooled solution of 3,4-dihydroxyphenyl acetyl chloride (750 g) in N,N-dimethyl acetamide (2.1 L), N-methyl benzyl amine (912 g) was added drop wise at about 10-15 °C. After the addition, temperature of the reaction mixture was raised to 30-35 °C and stirred for another 2-4 hours. After completion of the reaction, the reaction mixture was filtered and washed with isopropyl alcohol (1.0 L). The filtrate was cooled to about 20 °C and the pH was adjusted to about 5.5 with dilute HCl (150 mL). Water (8 L) was added and further stirred for 15 minutes. pH of the reaction mixture was adjusted to 8.5 with dilute ammonia (240 mL). Solid so obtained was filtered and wet solid was washed with water (4 L). The wet solid was suspended in water (10 L) and pH was adjusted to 5.5. The suspension was stirred for 1 hour and the solid obtained was filtered and dried. Yield: 1027 g N-benzyl epinephrine, Yield: 1027 g

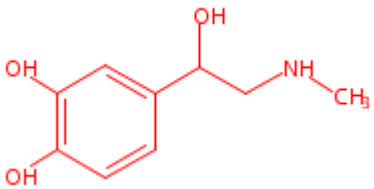
Step 3
Example-3: Racemic epinephrine N-Benzyl epinephrine (950 g) was dissolved in methanol (9.5 L) and pH was adjusted with dilute HCl (345 mL) to about 1.0-2.4 and stirred. To the reaction mixture, 10% Pd/C (250 g) was added and hydrogen gas was bubbled through the reaction mixture. It was heated to about 40 °C and stirred for about 30-35 hours at 40 °C . After completion of the reaction, the reaction mass was filtered and washed with methanol (1 L). The filtrate was cooled to 10-15 °C and pH was adjusted by ammonia solution (275 ml) to 8.5. The reaction mixture was filtered, washed with methanol (1 L) and dried to get epinephrine. Yield: 523 g Racemic epinephrine, Yield: 523 g

Step 4
Example -4: (-)-Epinephrine Step A: To a solution of racemic epinephrine (crude) (500 g) in methanol (1.0 L) was added L-tartaric acid (820 g). The reaction was stirred and after 1-3 hours, a thick precipitation was observed. Methanol (1.5 lit) was added and stirred for 24-30 hours at room temperature. The reaction mixture filtered and washed. wet wt. 464 g Step B: Epinephrine tartrate (wet wt.) (464 g) was dissolved in purified water (4.5 L) and sodium meta bisulphite (4 g) was added and the reaction mixture was cooled to 5-10 °C. The pH of the reaction mixture was adjusted with ammonia sol (270 mL) to about 8.5. The reaction stirred for 15 min and filtered. The solid obtained was washed with water (500 mL) followed by methanol (500 mL) and dried to obtain (-)-epinephrine base 232 g as solid. The reaction sequence of Step A and Step B is repeated twice to enrich the optical purity. The crude (-)-epinephrine is used in the next step. To a 5-10 °C cooled suspension of epinephrine base obtained from Example-1 (130 g) in purified water (1.3 L) was added HCl (55 mL) to adjust the pH to ~ 2 to 2.5 to get clear solution. To the clear solution was added carbon (5 g) and sodium meta bisulphite (1 g), the reaction stirred for 30 min. The reaction mass filtered and washed with water (200 mL). The filtrate was cooled to 5-10 °C then added dilute ammonia solution (105 mL) to adjust pH about 8.5. The reaction was stirred for 15 min, the reaction mixture was filtered and washed with water (400 mL) then methanol (400 mL) and dried to get pure epinephrine. Yield: 103 g; Purity: 99.88 %: enantiomeric excess: 95.34 %. (-)-Epinephrine, Yield: 103 g;

25. 3 Steps



[Step 2.1]



Overview

Steps/Stages

1.1 R:$POCl_3$, S:Benzene

2.1 R:H_2O

3.1 R:H_2, C:Ni, S:H_2O

Notes

1) Classification: Regioselective; C-Acylation; Condensation; # Conditions: POCl3 benzene; Rf water bath 50h, 2) Classification: C-Amination; # Conditions: MeNH2(40%) H2O; cool 30mn ice bath; # Comments: crude product, 65% yield when purified as HCl salt, 3) Classification: Reduction; Hydrogenation; # Conditions: /H2 Raney Ni; NaOH H2O; /1.2atm 3h-3h30mn; # Comments: See CA 53, 3127g; Racemic product, Reactants: 3, Reagents: 3, Catalysts: 1, Solvents: 2, Steps: 3, Stages: 3, Most stages in any one step: 1

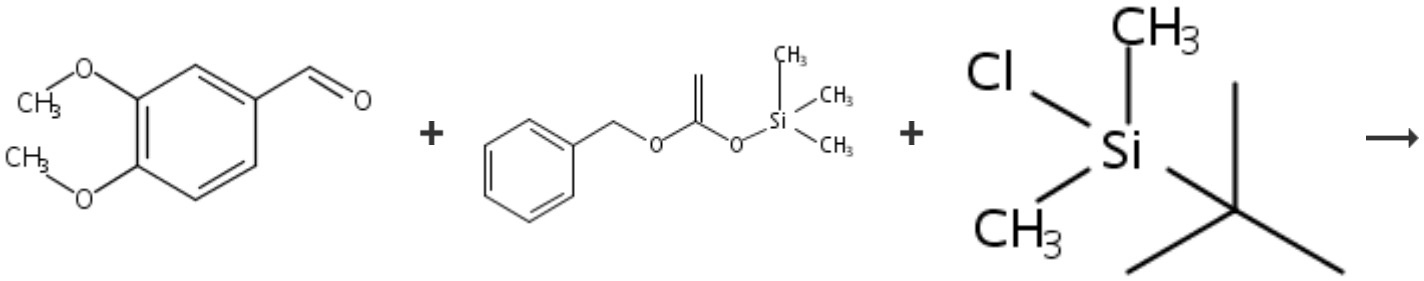
References

Synthesis of some derivatives of adrenaline. I. Synthesis of dl-adrenaline and its analogs

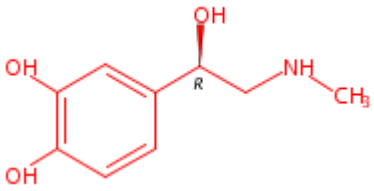
By Remizov, A. L.

From Zhurnal Obshchei Khimii, 28, 2530-8; 1958

26. 4 Steps



[Step 2.1]



Overview

Steps/Stages

Notes

1.1 C:187939-47-5, S:Et_2O

1.2

1.3 R:H_2O

1.4 R:F_3CCO_2H, S:THF

2.1 R:NaOH, S:H_2O, S:MeOH

3.1 R:$SOCl_2$

3.2 R:NH_4OH

3.3 R:$PhI(OAc)_2$, R:KOH

3.4 R:$LiAlH_4$, S:THF, reflux

4.1 R:BBr_3

1) catalyst prepd. in-situ before addn. of reactants, stereoselective, Reactants: 3, Reagents: 9, Catalysts: 1, Solvents: 4, Steps: 4, Stages: 10, Most stages in any one step: 4

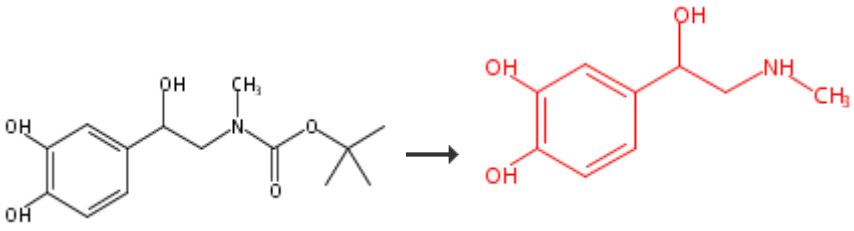
References

An in situ procedure for catalytic, enantioselective acetate aldol addition. Application to the synthesis of (R)-(-)-epinephrine

By Singer, Robert A. and Carreira, Erick M.

From Tetrahedron Letters, 38(6), 927-930; 1997

27. Single Step



- HCl

100%

Overview

Steps/Stages

1.1 R:Me_3SiCl, S:MeOH, 3 h, reflux

Notes

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

References

A new and efficient route for the synthesis of naturally occurring catecholamines

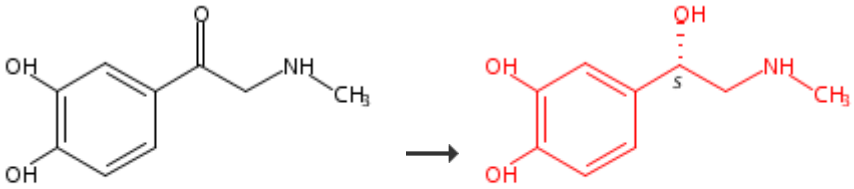
By Bernini, Roberta et al

From Synthesis, (22), 3838-3842; 2009

Experimental Procedure

Deprotection of *N*-Boc-Amines; General Procedure[19] The substrate (1.0 mmol) was dissolved in MeOH (20 mL) and TMSCl (217 mg, 2.0 mmol) was added. The mixture was kept at reflux temperature for 3 h. After the evaporation of the solvent under reduced pressure, the amine hydrochloride derivative was isolated in quantitative yields. Spectroscopic and analytical data of **1b**, **2b**, and **3b** were accord with authentic samples. Compound **3b**, quantitative yield.

28. Single Step



• HCl

• HCl

97%

Overview

Steps/Stages

1.1 R:Et_3N, S:Benzene

1.2 R:Ph_2SiH_2, C:$[RhCl(COD)]_2$, C:196930-37-7

1.3 R:HCl, S:H_2O

Notes

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

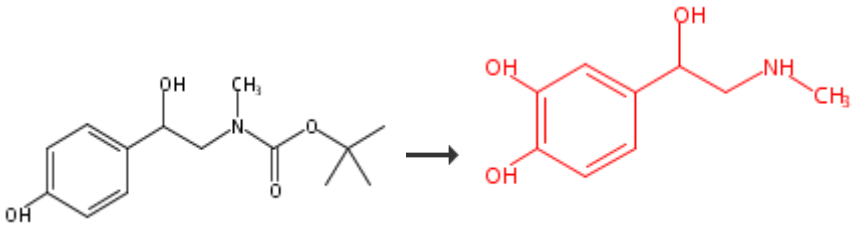
References

Synthesis of α-amino alcohols via Rh(I)-catalytic asymmetric hydrosilylation of amino ketones

By Yao, Jin-shui and Wu, You-shi

From Gaodeng Xuexiao Huaxue Xuebao, 23(1), 68-70; 2002

29. 2 Steps



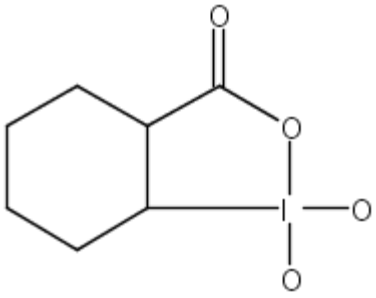
• HCl

Overview

Steps/Stages

Notes

1.1 R:



<AMD>(polymer-supported)</AMD>, S:THF, 0.5 h, rt

1.2 R:$Na_2S_2O_3$, S:H_2O, 5 min, rt

2.1 R:Me_3SiCl, S:MeOH, 3 h, reflux

1) alternative preparation shown, reusable reagent, key step, green chemistry-reagent, regioselective, solid-supported reaction, solid-supported reagent, Reactants: 1, Reagents: 3, Solvents: 3, Steps: 2, Stages: 3, Most stages in any one step: 2

References

A new and efficient route for the synthesis of naturally occurring catecholamines

By Bernini, Roberta et al

From Synthesis, (22), 3838-3842; 2009

Experimental Procedure

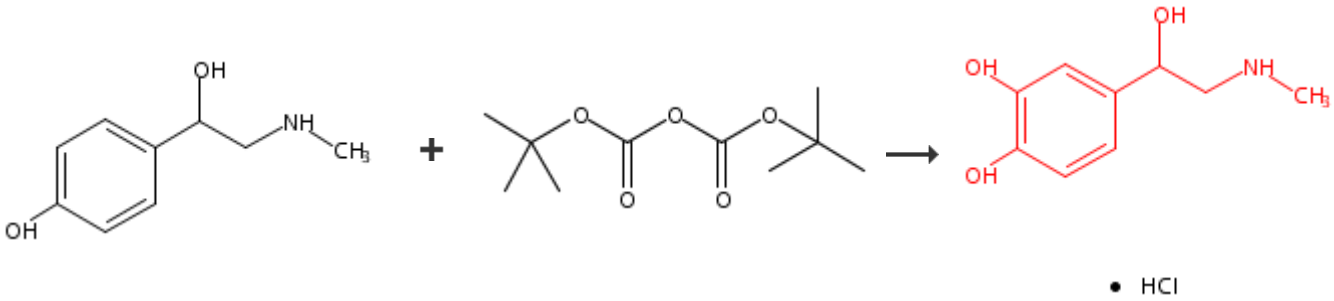
Step 1

General/Typical Procedure: *(b) Heterogeneous conditions:* The substrate (1.0 mmol) was solubilized in the appropriate solvent (8.0 mL) at r.t. under magnetic stirring and then commercial polymer-supported IBX (954 mg, 2.1 mmol) was added. When the substrate had been completely consumed, the polymer was recovered by simple filtration and the remaining soln was treated with H_2O (8.0 mL) and $Na_2S_2O_4$ (348 mg, 2.0 mmol). After the evaporation of the solvent under reduced pressure, the final products were extracted with EtOAc from the aqueous residue. The combined organic phases were washed with sat. NaCl soln and dried (Na_2SO_4). After evaporation of the solvent, hydroxylated compounds were isolated. Polymer-supported IBX was regenerated by treating the filtered resin with a soln of tetrabutylammonium oxone and MsOH according to the procedure reported by us in a previous paper.[11] ***tert*-Butyl [2-(3,4-Dihydroxyphenyl)-2-hydroxyethyl](methyl) carbamate [*N*-(*tert*-Butoxycarbonyl)epinephrine, 16]** White solid; yield: 98%. mp 159-160 °C IR (KBr): 3523, 3288, 2979, 2933, 2877, 1650, 1230 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$-CD_3OD): δ = 6.71 (s, 1 H), 6.61 (d, *J*= 8.1 Hz, 1 H), 6.53-6.49 (m, 1 H), 4.59-4.57 (m, 1 H), 3.21-3.11 (m, 2 H), 2.62 (s, 3 H), 1.24 (s, 9 H). ^{13}C NMR (50 MHz, $CDCl_3$-CD_3OD): δ = 156.2, 144.3, 143.8, 134.5, 117.6, 114.7, 112.8, 79.7, 72.7, 56.9, 35.6, 28.7. MS (EI, 70 eV): *m*/*z* (%) = 269 (25), 251 (100). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94; O, 28.24. Found: C, 59.40; H, 7.52; N, 4.90; O, 28.18.

Step 2

Deprotection of *N*-Boc-Amines; General Procedure[19] The substrate (1.0 mmol) was dissolved in MeOH (20 mL) and TMSCl (217 mg, 2.0 mmol) was added. The mixture was kept at reflux temperature for 3 h. After the evaporation of the solvent under reduced pressure, the amine hydrochloride derivative was isolated in quantitative yields. Spectroscopic and analytical data of **1b**, **2b**, and **3b** were accord with authentic samples. Compound **3b**, quantitative yield.

30. 3 Steps

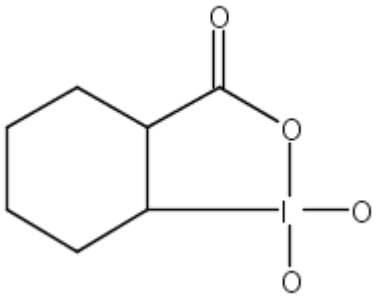


Overview

Steps/Stages **Notes**

1.1 R:$NaHCO_3$, S:H_2O, S:MeOH, rt; 2-24 h, rt

2.1 R:



<AMD>(polymer-supported)</AMD>, S:THF, 0.5 h, rt

2.2 R:$Na_2S_2O_3$, S:H_2O, 5 min, rt

3.1 R:Me_3SiCl, S:MeOH, 3 h, reflux

Experimental Procedure

Step 1
General/Typical Procedure: **Protection of the Amino Group with Di-*tert*-butyl Dicarbonate; General Procedure[18]** The amine (1.0 mmol) was solubilized in MeOH-H_2O (2:1, 6 mL). Then $NaHCO_3$ (252 mg, 3.0 mmol) and $(Boc)_2O$ (327 mg, 1.5 mmol) were slowly added. The mixture was kept under magnetic stirring for 2-24 h depending on the substrate. When the substrate had been consumed, MeOH was evaporated under vacuum and the residue was solubilized in EtOAc and washed with 1 M HCl. The organic extracts were treated with sat. NaCl soln and dried (Na_2SO_4), filtered, and concentrated under vacuum. Purification of crude mixture by chromatography (silica gel, hexane-EtOAc, 1:1) gave **9**, **12**, and **15**, which were characterized by analytical and spectroscopic analysis. ***tert*-Butyl [2-Hydroxy-2-(4-hydroxyphenyl)ethyl](methyl)carbamate [*N*-(*tert*-Butoxycarbonyl)synephrine, 15]** White solid; yield: >98%. mp 45-46 °C IR (KBr): 3444, 1670, 1367, 1230 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$-CD_3OD): δ = 7.04 (d, *J*= 8.0 Hz, 2 H), 6.62 (d, *J*= 8.0 Hz, 2 H), 4.69-4.65 (m, 1 H), 3.79-3.70 (m, 1 H), 3.38-3.19 (m, 1 H), 2.66 (s, 3 H), 1.21 (s, 9 H). ^{13}C NMR (50 MHz, $CDCl_3$-CD_3OD): δ = 157.4, 156.2, 133.2, 127.1, 115.1, 80.1, 72.4, 56.8, 35.7, 28.2. MS (EI, 70 eV): *m*/*z* (%) = 267 (0.5), 194 (2.9), 145 (11.0), 136 (15.2), 123 (100).

Step 2
General/Typical Procedure: *(b) Heterogeneous conditions:* The substrate (1.0 mmol) was solubilized in the appropriate solvent (8.0 mL) at r.t. under magnetic stirring and then commercial polymer-supported IBX (954 mg, 2.1 mmol) was added. When the substrate had been completely consumed, the polymer was recovered by simple filtration and the remaining soln was treated with H_2O (8.0 mL) and $Na_2S_2O_4$ (348 mg, 2.0 mmol). After the evaporation of the solvent under reduced pressure, the final products were extracted with EtOAc from the aqueous residue. The combined organic phases were washed with sat. NaCl soln and dried (Na_2SO_4). After evaporation of the solvent, hydroxylated compounds were isolated. Polymer-supported IBX was regenerated by treating the filtered resin with a soln of tetrabutylammonium oxone and MsOH according to the procedure reported by us in a previous paper.[11] ***tert*-Butyl [2-(3,4-Dihydroxyphenyl)-2-hydroxyethyl](methyl) carbamate [*N*-(*tert*-Butoxycarbonyl)epinephrine, 16]** White solid; yield: 98%. mp 159-160 °C IR (KBr): 3523, 3288, 2979, 2933, 2877, 1650, 1230 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$-CD_3OD): δ = 6.71 (s, 1 H), 6.61 (d, *J*= 8.1 Hz, 1 H), 6.53-6.49 (m, 1 H), 4.59-4.57 (m, 1 H), 3.21-3.11 (m, 2 H), 2.62 (s, 3 H), 1.24 (s, 9 H). ^{13}C NMR (50 MHz, $CDCl_3$-CD_3OD): δ = 156.2, 144.3, 143.8, 134.5, 117.6, 114.7, 112.8, 79.7, 72.7, 56.9, 35.6, 28.7. MS (EI, 70 eV): *m*/*z* (%) = 269 (25), 251 (100). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94; O, 28.24. Found: C, 59.40; H, 7.52; N, 4.90; O, 28.18.

Step 3
Deprotection of *N*-Boc-Amines; General Procedure[19] The substrate (1.0 mmol) was dissolved in MeOH (20 mL) and TMSCl (217 mg, 2.0 mmol) was added. The mixture was kept at reflux temperature for 3 h. After the evaporation of the solvent under reduced pressure, the amine hydrochloride derivative was isolated in quantitative yields. Spectroscopic and analytical data of **1b**, **2b**, and **3b** were accord with authentic samples. Compound **3b**, quantitative yield.

2) alternative preparation shown, reusable reagent, key step, green chemistry-reagent, regioselective, solid-supported reaction, solid-supported reagent, Reactants: 2, Reagents: 4, Solvents: 3, Steps: 3, Stages: 4, Most stages in any one step: 2

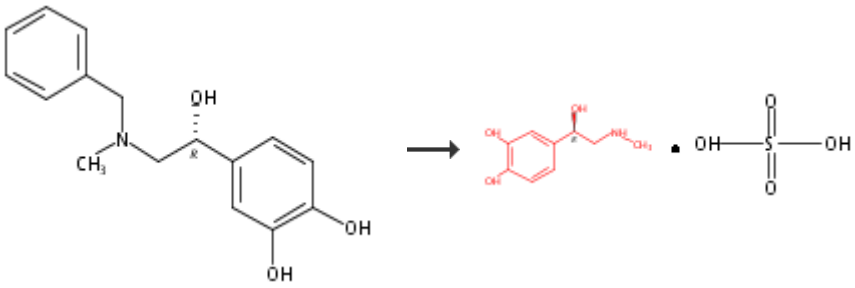
References

A new and efficient route for the synthesis of naturally occurring catecholamines

By Bernini, Roberta et al

From Synthesis, (22), 3838-3842; 2009

31. Single Step



75%

Overview

Steps/Stages

1.1 R:H_2SO_4, C:[RhCl(COD)]$_2$, C:122709-72-2, S:H_2O

1.2 R:H_2

Notes

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

References

Three-step stereoselective process for the production of adrenalin from N-benzyladrenalone

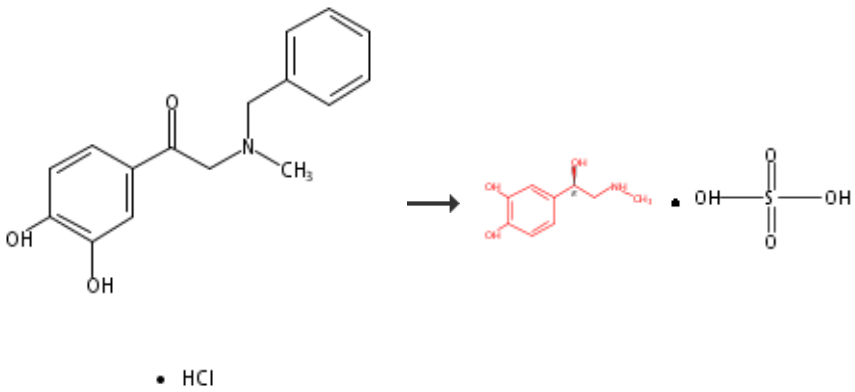
By Klingler, Franz Dietrich and Wolter, Lienhard

From Ger., 19938709, 18 Jan 2001

Experimental Procedure

Benzyl adrenaline 2 is dissolved in 10 ml of water and about 5 ml of 18% sulfuric acid (pH 5.5), approximately 50 mg of palladium-carbon (10%) are added and hydrogenated at 60°C and 2 HPa hydrogen pressure. The mixture is then concentrated to about half its volume, with about 20 ml of methanol is added and cooled. The crystalline product (adrenaline sulphate 3) is filtered and dried. Yield over all steps together: about 4.5 g (about 75%), opt. Purity: > 98% ee (HPLC), chem. Purity: > 98% (HPLC).

32. 2 Steps



• HCl

Overview

Steps/Stages

Notes

1.1 R:Et_3N, C:$[RhCl(COD)]_2$, C:122709-72-2, S:MeOH

1.2 R:H_2

2.1 R:H_2SO_4, C:$[RhCl(COD)]_2$, C:122709-72-2, S:H_2O

2.2 R:H_2

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

References

Three-step stereoselective process for the production of adrenalin from N-benzyladrenalone

By Klingler, Franz Dietrich and Wolter, Lienhard

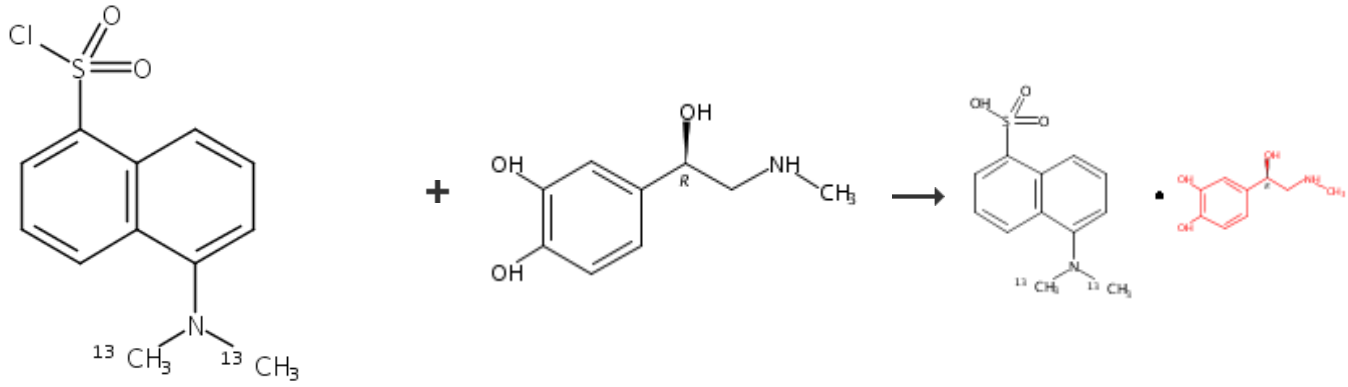
From Ger., 19938709, 18 Jan 2001

Experimental Procedure

Step 1
Preparation of adrenaline. 7.4 g benzyladrenalone hydrochloride 1 was dissolved in about 60 ml of methanol (degassed), mixed with 0.07 ml of triethylamine and 10 ml of catalyst solution (corresponding to 6 mg $(RhCODCl)_2$ and 8.2 mg of RR-MCCPM) and hydrogenated at about 50°C and about 20 HPa hydrogen pressure. After the reaction was completed, the methanol was largely distilled, mixed with about 30 ml of water and about 0.5 g of activated charcoal, stirred for 30 min and filtered. Then N-benzyladrenaline 2 was precipitated with 10 ml of water and about 15 ml of methanol and by addition of about 4 ml of ammonia (about 25%) and filtered. (R. T.) Yield 6 g = 90%.

Step 2
Benzyl adrenaline 2 is dissolved in 10 ml of water and about 5 ml of 18% sulfuric acid (pH 5.5), approximately 50 mg of palladium-carbon (10%) are added and hydrogenated at 60°C and 2 HPa hydrogen pressure. The mixture is then concentrated to about half its volume, with about 20 ml of methanol is added and cooled. The crystalline product (adrenaline sulphate 3) is filtered and dried. Yield over all steps together: about 4.5 g (about 75%), opt. Purity: > 98% ee (HPLC), chem. Purity: > 98% (HPLC).

33. Single Step



Overview

Steps/Stages **Notes**

1.1 S:H_2O, 60 min, 60°C, pH 9.4

1.2 R:$MeNH_2$, 30 min, 60°C

combinatorial, sodium carbonate buffered solution used, alternate unlabeled preparation also shown, Reactants: 2, Reagents: 1, Solvents: 1, Steps: 1, Stages: 2, Most stages in any one step: 2

References

Differential 12C-/13C-Isotope Dansylation Labeling and Fast Liquid Chromatography/Mass Spectrometry for Absolute and Relative Quantification of the Metabolome

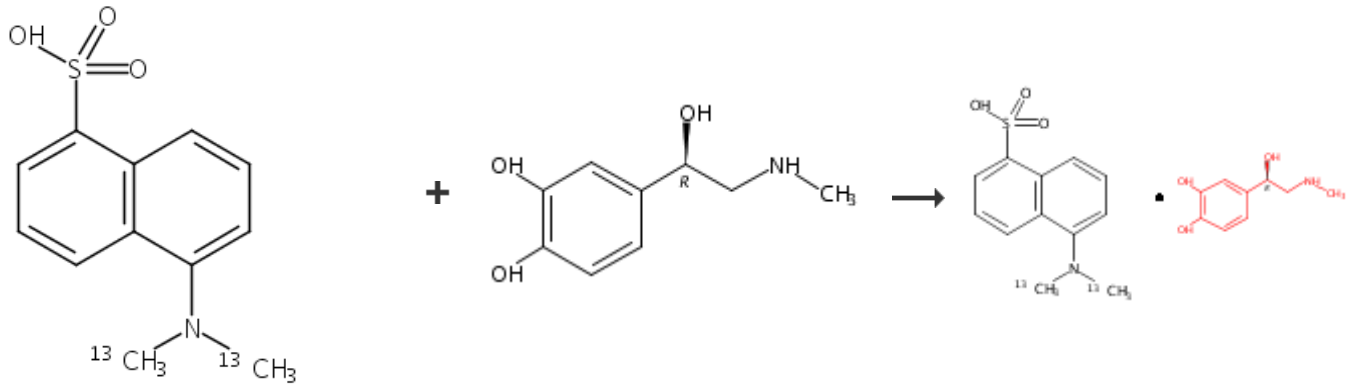
By Guo, Kevin and Li, Liang

From Analytical Chemistry (Washington, DC, United States), 81(10), 3919-3932; 2009

Experimental Procedure

General/Typical Procedure: **Dansylation Labeling Reaction.** Figure 1B shows the reaction scheme for dansylation of amine- and phenol-containing compounds. The frozen urine was thawed in an ice-bath and then centrifuged for 10 min at 12 000 rpm. About 100 μL of urine supernatant or amino acids, amine, and phenolic hydroxyl standard solutions were mixed with an equal volume of sodium carbonate/sodium bicarbonate buffer (0.5 mol/L, pH 9.4) in a reaction vial. The solutions were vortexed, spun down, and mixed with 100 μL of freshly prepared ^{12}C-dansyl chloride solution (20 mg/mL) (for light labeling) or ^{13}C-dansyl chloride (20 mg/mL) (for heavy labeling). The dansylation reaction was allowed to proceed for 60 min at 60 °C with shaking at 150 rpm in an Innova-4000 benchtop incubator shaker. After 60 min, mixtures were vortexed, spun down and 30 μL of methylamine (0.5 mol/L) was added to the reaction mixture to consume the excess dansyl chloride. The solutions were again vortexed and spun down. After an additional 30 min of 60 °C incubation, samples were then centrifuged. The ^{13}C-labeled mixtures were combined with their ^{12}C-labeled counterparts for MS analysis. The reaction vials were carefully washed twice using 50 μL of LC/MS grade MeOH, and the washing solution was added to the initial mixture to ensure dissolution and transfer of all products for MS analysis. The combined mixtures were centrifuged for 10 min at 12 000 rpm and were ready to be injected onto a RPLC column. Dns-epinephrine

34. 2 Steps



[Step 2.1]

Overview

Steps/Stages **Notes**

1.1 R:PCl_5, 2 h, 60°C

1.2 R:$NaHCO_3$, S:H_2O, neutralized

2.1 S:H_2O, 60 min, 60°C, pH 9.4

2.2 R:$MeNH_2$, 30 min, 60°C

2) combinatorial, sodium carbonate buffered solution used, alternate unlabeled preparation also shown, Reactants: 2, Reagents: 3, Solvents: 1, Steps: 2, Stages: 4, Most stages in any one step: 2

References

Differential 12C-/13C-Isotope Dansylation Labeling and Fast Liquid Chromatography/Mass Spectrometry for Absolute and Relative Quantification of the Metabolome

By Guo, Kevin and Li, Liang

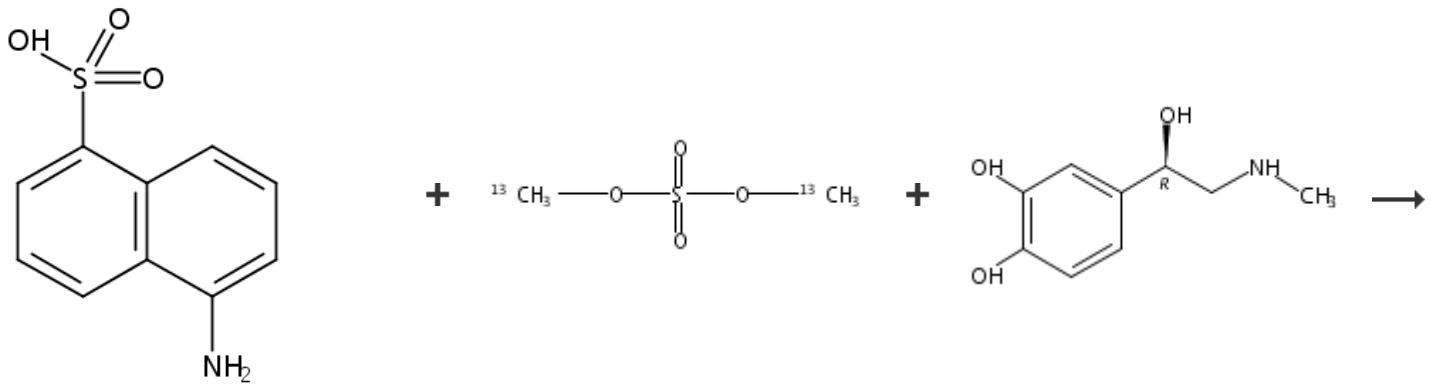
From Analytical Chemistry (Washington, DC, United States), 81(10), 3919-3932; 2009

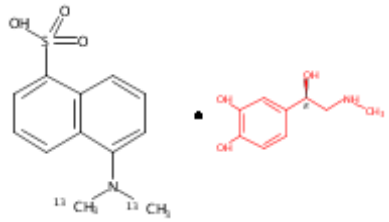
Experimental Procedure

Step 1
Under ice-cooling, 5-dimethylamino-naphthalene-1-sulfonic acid was ground into a powder and then mixed with 0.88 g of phosphorus pentachloride. To complete the reaction, the mixture was warmed to 60 °C for 2 h under the exclusion of moisture. About 12.5 mL of ice water was then poured in. After careful neutralization with 1.75 g of sodium bicarbonate, the product was extracted with Et_2O (4 × 6 mL). The organic layer was dried using sodium sulfate. The residue was purified by flush chromatography (silica gel, 20 cm × 3 cm, 60 mL of AcOEt) and further purified by a semipreparative Grace Apollo silica normal-phase HPLC column (10 mm × 150 mm, 5 μm particles). The resulting product of ^{13}C-dansyl chloride was then dried in a SpeedVac and stored in a -80 °C freezer. The purity and confirmation of ^{13}C-dansyl chloride was tested against the commercial ^{12}C-dansyl chloride using LC/FTICR MS. NMR was also used to characterize the reaction products and confirm the identity and purity of the final product. ^{13}C-dansyl chloride

Step 2
General/Typical Procedure: **Dansylation Labeling Reaction.** Figure 1B shows the reaction scheme for dansylation of amine- and phenol-containing compounds. The frozen urine was thawed in an ice-bath and then centrifuged for 10 min at 12 000 rpm. About 100 μL of urine supernatant or amino acids, amine, and phenolic hydroxyl standard solutions were mixed with an equal volume of sodium carbonate/sodium bicarbonate buffer (0.5 mol/L, pH 9.4) in a reaction vial. The solutions were vortexed, spun down, and mixed with 100 μL of freshly prepared ^{12}C-dansyl chloride solution (20 mg/mL) (for light labeling) or ^{13}C-dansyl chloride (20 mg/mL) (for heavy labeling). The dansylation reaction was allowed to proceed for 60 min at 60 °C with shaking at 150 rpm in an Innova-4000 benchtop incubator shaker. After 60 min, mixtures were vortexed, spun down and 30 μL of methylamine (0.5 mol/L) was added to the reaction mixture to consume the excess dansyl chloride. The solutions were again vortexed and spun down. After an additional 30 min of 60 °C incubation, samples were then centrifuged. The ^{13}C-labeled mixtures were combined with their ^{12}C-labeled counterparts for MS analysis. The reaction vials were carefully washed twice using 50 μL of LC/MS grade MeOH, and the washing solution was added to the initial mixture to ensure dissolution and transfer of all products for MS analysis. The combined mixtures were centrifuged for 10 min at 12 000 rpm and were ready to be injected onto a RPLC column. Dns-epinephrine

35. 3 Steps





Overview

Steps/Stages

1.1 R:$NaHCO_3$, S:H_2O, rt; 30 min, cooled; 30 min, 80°C; 80°C → rt

1.2 R:HCl, S:H_2O, pH 4

2.1 R:PCl_5, 2 h, 60°C

2.2 R:$NaHCO_3$, S:H_2O, neutralized

3.1 S:H_2O, 60 min, 60°C, pH 9.4

3.2 R:$MeNH_2$, 30 min, 60°C

Notes

3) combinatorial, sodium carbonate buffered solution used, alternate unlabeled preparation also shown, Reactants: 3, Reagents: 4, Solvents: 1, Steps: 3, Stages: 6, Most stages in any one step: 2

References

Differential 12C-/13C-Isotope Dansylation Labeling and Fast Liquid Chromatography/Mass Spectrometry for Absolute and Relative Quantification of the Metabolome

By Guo, Kevin and Li, Liang

From Analytical Chemistry (Washington, DC, United States), 81(10), 3919-3932; 2009

Experimental Procedure

Step 1

Synthesis of Dansyl Chloride-$^{13}C_2$. The synthesis of ^{13}C-dansyl chloride as a derivatizing reagent was based on a two-step procedure described by Horner and Bergmann.[58,59] Figure 1A shows the synthesis scheme. In a 25 mL round-bottom flask, 0.78 g of 5-aminonaphthalene-1-sulfonic acid was added slowly in portions to 1.09 g of sodium bicarbonate in 3.5 mL of water. Then 0.77 mL of $^{13}C_2$-dimethyl sulfate was added dropwise over 30 min to the stirred ice-cooled solution. The solution was warmed to 80 °C in a hot water-bath for 30 min. After cooling to room temperature, 0.46 mL of concentrated hydrochloric acid was added to the solution, and the pH was adjusted to 4. The precipitated product, 5-dimethylamino-naphthalene-1-sulfonic acid was filtered, washed with a small quantity of water, dried in the air to a constant weight, and then further dried at 120 °C in an oven. 5-dimethylamino-naphthalene-1-sulfonic acid

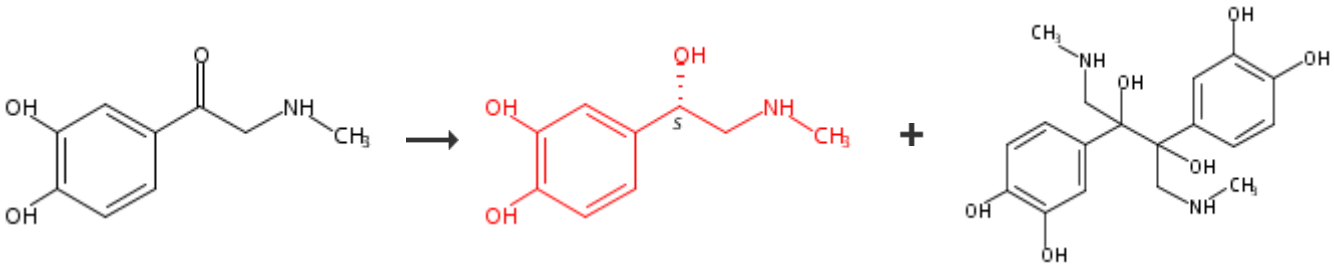
Step 2

Under ice-cooling, 5-dimethylamino-naphthalene-1-sulfonic acid was ground into a powder and then mixed with 0.88 g of phosphorus pentachloride. To complete the reaction, the mixture was warmed to 60 °C for 2 h under the exclusion of moisture. About 12.5 mL of ice water was then poured in. After careful neutralization with 1.75 g of sodium bicarbonate, the product was extracted with Et_2O (4 × 6 mL). The organic layer was dried using sodium sulfate. The residue was purified by flush chromatography (silica gel, 20 cm × 3 cm, 60 mL of AcOEt) and further purified by a semipreparative Grace Apollo silica normal-phase HPLC column (10 mm × 150 mm, 5 µm particles). The resulting product of ^{13}C-dansyl chloride was then dried in a SpeedVac and stored in a -80 °C freezer. The purity and confirmation of ^{13}C-dansyl chloride was tested against the commercial ^{12}C-dansyl chloride using LC/FTICR MS. NMR was also used to characterize the reaction products and confirm the identity and purity of the final product. ^{13}C-dansyl chloride

Step 3

General/Typical Procedure: **Dansylation Labeling Reaction.** Figure 1B shows the reaction scheme for dansylation of amine- and phenol-containing compounds. The frozen urine was thawed in an ice-bath and then centrifuged for 10 min at 12 000 rpm. About 100 μL of urine supernatant or amino acids, amine, and phenolic hydroxyl standard solutions were mixed with an equal volume of sodium carbonate/sodium bicarbonate buffer (0.5 mol/L, pH 9.4) in a reaction vial. The solutions were vortexed, spun down, and mixed with 100 μL of freshly prepared ^{12}C-dansyl chloride solution (20 mg/mL) (for light labeling) or ^{13}C-dansyl chloride (20 mg/mL) (for heavy labeling). The dansylation reaction was allowed to proceed for 60 min at 60 °C with shaking at 150 rpm in an Innova-4000 benchtop incubator shaker. After 60 min, mixtures were vortexed, spun down and 30 μL of methylamine (0.5 mol/L) was added to the reaction mixture to consume the excess dansyl chloride. The solutions were again vortexed and spun down. After an additional 30 min of 60 °C incubation, samples were then centrifuged. The ^{13}C-labeled mixtures were combined with their ^{12}C-labeled counterparts for MS analysis. The reaction vials were carefully washed twice using 50 μL of LC/MS grade MeOH, and the washing solution was added to the initial mixture to ensure dissolution and transfer of all products for MS analysis. The combined mixtures were centrifuged for 10 min at 12 000 rpm and were ready to be injected onto a RPLC column. Dns-epinephrine

36. Single Step



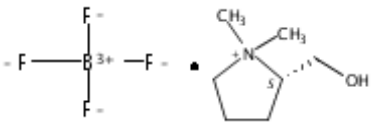
90% 5%

Overview

Steps/Stages

1.1 R:Bu_4N^+ BF_4^-

R:



S:Me_2CHOH, S:DMF, rt

Notes

electrochemical, cathode - mercury pool, anode - Pt foil, stereoselective, Reactants: 1, Reagents: 2, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

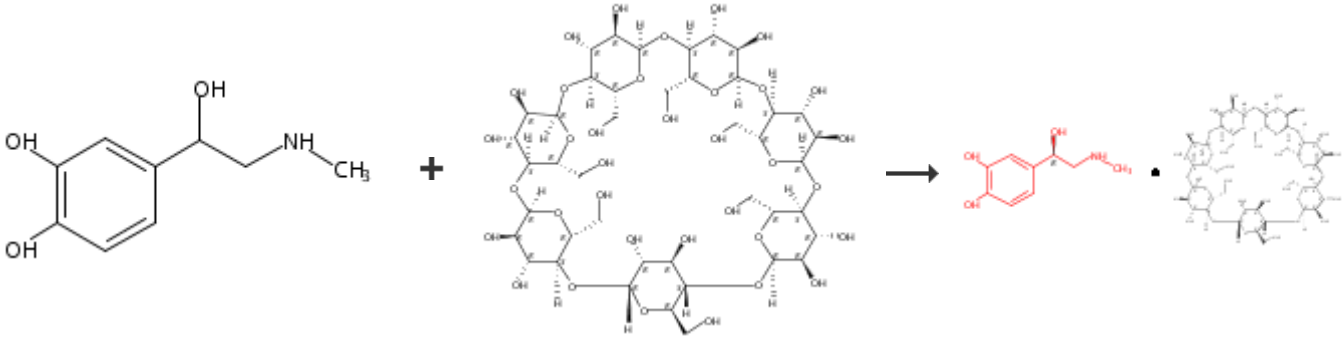
References

Electroreductive generation of (S)-(+)-N,N-dimethyl-2-(hydroxymethyl)-pyrrolidinium mercury compound for enantioselective synthesis of 2-amino-1-alkyl/aryl ethanols

By Yadav, Ashok K. and Manju, Meera

From Indian Journal of Chemistry, Section B: Organic Chemistry Including Medicinal Chemistry, 45B(12), 2770-2772; 2006

37. Single Step



Overview

Steps/Stages

1.1

Notes

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

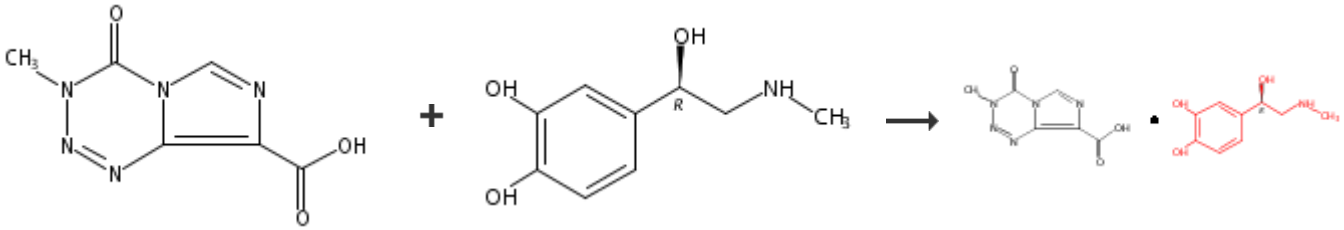
References

Effect of β-cyclodextrins on solubility and oxidation of epinephrine

By Tomono, Kazuo et al

From Yakuzaigaku, 51(2), 129-34; 1991

38. Single Step



Overview

Steps/Stages

1.1 S:H_2O, 15-20°C

Notes

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

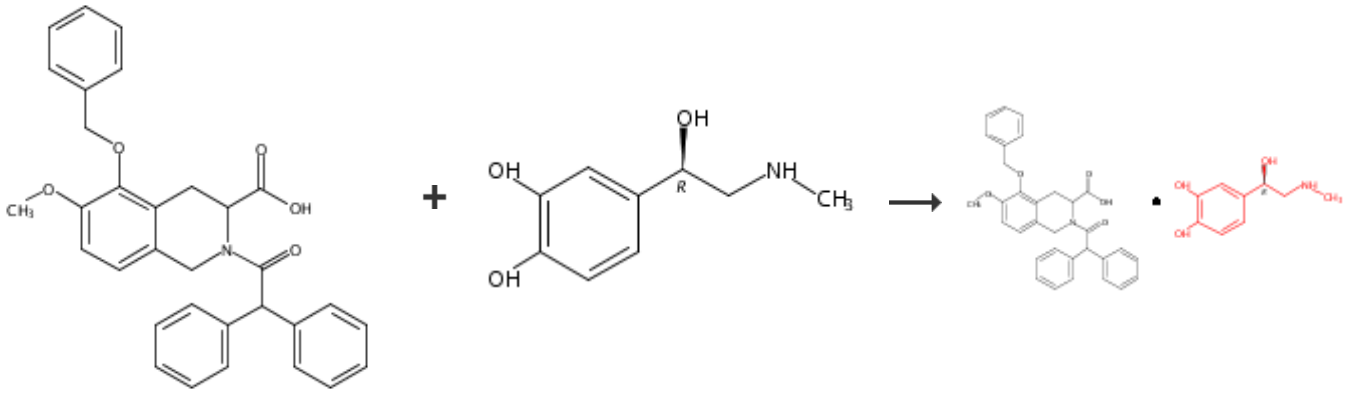
References

Preparation of water-soluble temozolomide-8-carboxylic acid derivatives as antitumor agents

By Wang, Yongfeng

From Faming Zhuanli Shenqing, 1948313, 18 Apr 2007

39. Single Step



Overview

Steps/Stages

1.1 S:EtOH, rt → 50°C; 21 h, 50°C → 5°C

Notes

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

References

Preparation of sodium salt and solvates of (S)-2-(diphenylacetyl)-1,2,3,4-tetrahydro-6-methoxy-5-(phenylmethoxy)-3-isoquinolinecarboxylic acid

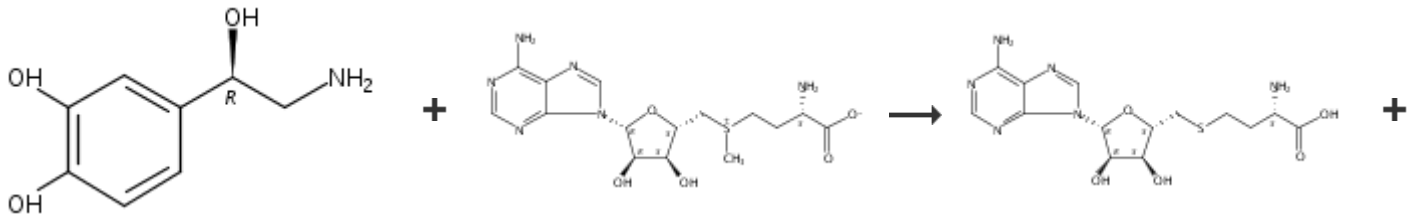
By McCarthy, Thomas David et al

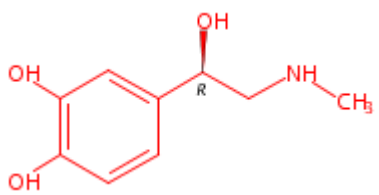
From PCT Int. Appl., 2012010843, 26 Jan 2012

Experimental Procedure

General/Typical Procedure: All the chiral bases were made up to 0.5 molar concentrations in ethanol. Those that would not dissolve in ethanol were added as solids, using the masses given, so that 1.05 molar equivalents of the bases were added to each sample of the free acid. The solutions were heated to 50°C with stirring and cooled to 5°C over twenty-one hours. The results are shown in Table 1. Samples 7 and 9 recrystallized on cooling. Those that did not recrystallize were sonicated for ten minutes, and then stored in a shaker at 25°C overnight. Samples 4, 6, 12 and 19 were added as solids and did not dissolve fully at 50°C, so were matured at 25°C. Final product

40. Single Step





Overview

Steps/Stages

1.1 C:9037-68-7, S:H_2O

Notes

biotransformation, enzymic, buffered soln., immobilized enzyme reactor used, phenylethanolamine N-methyltransferase used, Reactants: 2, Catalysts: 1, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Biosynthesis in an on-line immobilized-enzyme reactor containing phenylethanolamine N-methyltransferase in single-enzyme and coupled-enzyme formats

By Markoglou, Nektaria and Wainer, Irving W.

From Journal of Chromatography A, 948(1-2), 249-256; 2002