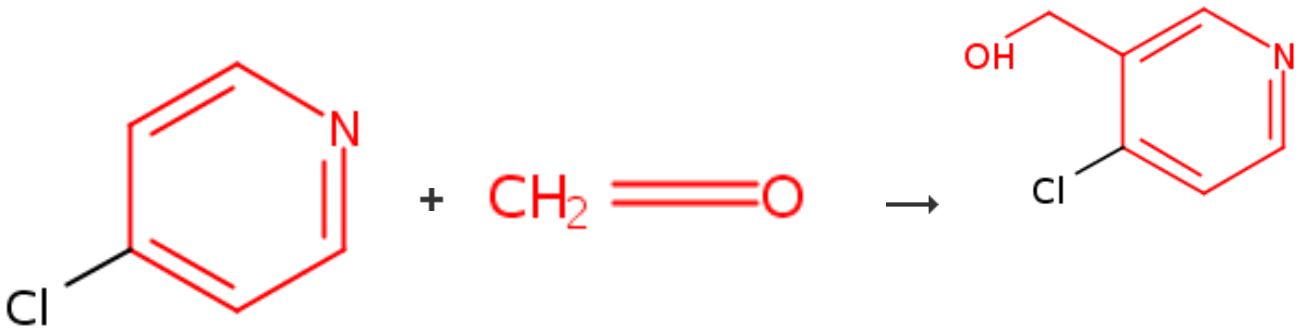
1. Single Step



- HCl

85%

Overview

Steps/Stages

1.1 R:LiN(Pr-*i*)$_2$, S:THF
1.2 S:DMF
1.3 S:H_2O

1.4 R:HCl, S:CH_2Cl_2

Notes

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

References

A practical synthesis of 4-chloro-3-(hydroxymethyl)pyridine by regioselective one-pot lithiation/formylation/reduction of 4-chloropyridine

By Albanese, Domenico et al

From Synthesis, (8), 1294-1296; 1999

Experimental Procedure

4-Chloro-3-formylpyridine (8) A 500 mL 4-necked round bottomed flask was dried at 110 °C for 1 h and then allowed to cool to r.t. under argon. The flask was assembled with a mechanical stirrer, an argon inlet, a rubber septum and a dropping funnel with a pressure-equalizing side tube. The apparatus was cooled to -78 °C with a dry ice-acetone bath and a 2 M LDA solution in THF (58 mL, 0.116 mol) was introduced via a cannula and vigorously stirred under argon for 10 minutes. A solution of 4-chloropyridine (**4**; 11.94 g, 0.105 mol) in anhyd THF (50 mL) was added dropwise over 15 min and the mixture became orange/brick red coloured. After stirring for 1 h at -78 °C, anhyd DMF (10 mL, 0.129 mol) was added by a syringe over 12 min and the mixture was stirred for 1 h. The conversion of the substrate **4** into the aldehyde **8** was monitored by ^{1}H NMR analysis as follows. A sample (200 mL) was diluted with Et_2O (200 mL) and hydrolyzed with H_2O (200 mL), the organic phase was separated, dried over molecular sieves (0.4 nm) and evaporated at 30 °C, diluted with $CDCl_3$ (0.7 mL) and its ^{1}H NMR spectrum was recorded. **4-Chloro-3-(hydroxymethyl)pyridine Hydrochloride (9)** After completion of the formylation, an aqueous solution (40% w/v) of formaldehyde (12 mL, 0.158 mol) was added at once, the temperature was allowed to rise to 25 °C and the mixture was vigorously stirred at this temperature for 90 minutes. The liquid phase was decanted and the remaining solid was washed with CH_2Cl_2 (2 x 20 mL) by decanting the CH_2Cl_2. The organic-aqueous mixture thus obtained was evaporated at 50 °C under vacuum (20 mbar) then at 20 °C (0.001 mbar). The residue was dissolved in CH_2Cl_2 (150 mL) and washed with H_2O (4 x 20 mL) and half saturated NaCl solution (40 mL), dried ($MgSO_4$) and evaporated under vacuum to 70 mL This solution was cooled in an ice bath to 0 °C and anhyd gaseous HCl was bubbled in for 15 minutes. After 3-4 min light brown crystals formed and were filtered after 30 min, washed with ice cold CH_2Cl_2 (20 mL) and dried under vacuum (20 mbar) at 40 °C. **4-Chloro-3-(hydroxymethyl)pyridine Hydrochloride (9)** Yield: 16.0 g (85%). mp 145 °C. ^{1}H NMR (DMSO-d_6): δ = 4.67 (s, 2 H), 6.12 (br s, 2 H), 8.18 (d, 1 H, *J* = 6.1 Hz), 8.79 (s, 1 H), 8.83 (d, 1 H, *J* = 6.1 Hz).

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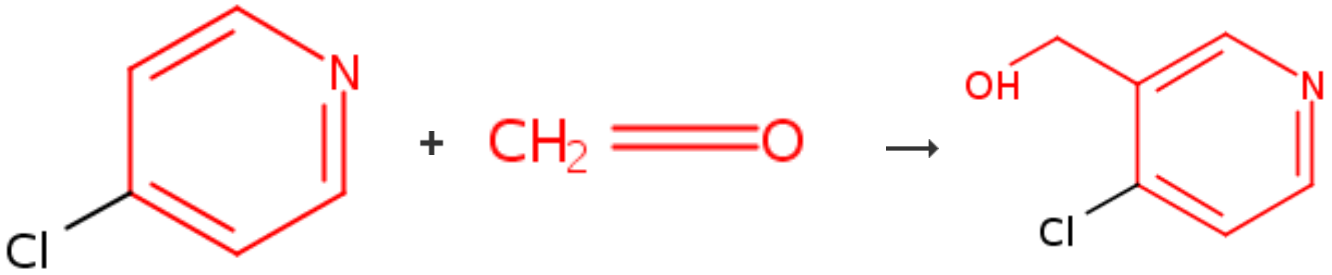
2. 2 Steps



Overview

Steps/Stages

1.1 R:LiN(Pr-*i*)$_2$, S:THF
1.2 S:DMF
1.3 S:H_2O

1.4 R:HCl, S:CH_2Cl_2

2.1 R:K_2CO_3, S:H_2O

Notes

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

References

A practical synthesis of 4-chloro-3-(hydroxymethyl)pyridine by regioselective one-pot lithiation/formylation/reduction of 4-chloropyridine

By Albanese, Domenico et al

From Synthesis, (8), 1294-1296; 1999

Experimental Procedure

Step 1

4-Chloro-3-formylpyridine (8) A 500 mL 4-necked round bottomed flask was dried at 110 °C for 1 h and then allowed to cool to r.t. under argon. The flask was assembled with a mechanical stirrer, an argon inlet, a rubber septum and a dropping funnel with a pressure-equalizing side tube. The apparatus was cooled to -78 °C with a dry ice-acetone bath and a 2 M LDA solution in THF (58 mL, 0.116 mol) was introduced via a cannula and vigorously stirred under argon for 10 minutes. A solution of 4-chloropyridine (**4**; 11.94 g, 0.105 mol) in anhyd THF (50 mL) was added dropwise over 15 min and the mixture became orange/brick red coloured. After stirring for 1 h at -78 °C, anhyd DMF (10 mL, 0.129 mol) was added by a syringe over 12 min and the mixture was stirred for 1 h. The conversion of the substrate **4** into the aldehyde **8** was monitored by ^{1}H NMR analysis as follows. A sample (200 mL) was diluted with Et_2O (200 mL) and hydrolyzed with H_2O (200 mL), the organic phase was separated, dried over molecular sieves (0.4 nm) and evaporated at 30 °C, diluted with $CDCl_3$ (0.7 mL) and its ^{1}H NMR spectrum was recorded. **4-Chloro-3-(hydroxymethyl)pyridine Hydrochloride (9)** After completion of the formylation, an aqueous solution (40% w/v) of formaldehyde (12 mL, 0.158 mol) was added at once, the temperature was allowed to rise to 25 °C and the mixture was vigorously stirred at this temperature for 90 minutes. The liquid phase was decanted and the remaining solid was washed with CH_2Cl_2 (2 x 20 mL) by decanting the CH_2Cl_2. The organic-aqueous mixture thus obtained was evaporated at 50 °C under vacuum (20 mbar) then at 20 °C (0.001 mbar). The residue was dissolved in CH_2Cl_2 (150 mL) and washed with H_2O (4 x 20 mL) and half saturated NaCl solution (40 mL), dried ($MgSO_4$) and evaporated under vacuum to 70 mL This solution was cooled in an ice bath to 0 °C and anhyd gaseous HCl was bubbled in for 15 minutes. After 3-4 min light brown crystals formed and were filtered after 30 min, washed with ice cold CH_2Cl_2 (20 mL) and dried under vacuum (20 mbar) at 40 °C. **4-Chloro-3-(hydroxymethyl)pyridine Hydrochloride (9)** Yield: 16.0 g (85%). mp 145 °C. ^{1}H NMR (DMSO-d_6): δ = 4.67 (s, 2 H), 6.12 (br s, 2 H), 8.18 (d, 1 H, *J* = 6.1 Hz), 8.79 (s, 1 H), 8.83 (d, 1 H, *J* = 6.1 Hz).

Step 2

Genertion of 4-Chloro-3-(hydroxymethyl)pyridine (6) from the Hydrochloride 9 A sample of the hydrochloride **9** was dissolved in cold H_2O and neutralized with 1 equivalent of $KHCO_3$. The free base **6** was recovered by extraction with CH_2Cl_2, drying ($MgSO_4$) and evaporation of the solvent under vacuum. Quantitative yield. mp 82-83 °C. ^{1}H NMR ($CDCl_3$/TMS): δ = 2.69 (br s, 1 H), 4.81 (s, 2 H), 7.29 (d, 1 H, *J* = 5.3 Hz), 8.40 (d, 1 H, *J* = 5.3 Hz), 8.65 (s, 1 H). GC/MS (EI): m/z = 144. Anal. calcd for C_6H_6ClNO: C, 50.19; H, 4.21; N, 9.76. Found: C, 50.11; H, 4.26; N, 9.85.

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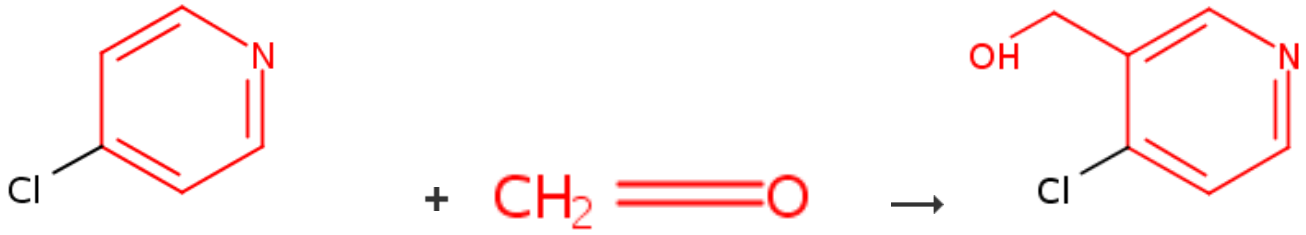
3. 2 Steps



- HCl
- HCl

[Step 2.3]

Overview

Steps/Stages

1.1 R:K_2CO_3, S:H_2O

2.1 R:LiN(Pr-*i*)$_2$, S:THF
2.2 S:DMF
2.3 S:H_2O

2.4 R:HCl, S:CH_2Cl_2

Notes

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

References

A practical synthesis of 4-chloro-3-(hydroxymethyl)pyridine by regioselective one-pot lithiation/formylation/reduction of 4-chloropyridine

By Albanese, Domenico et al

From Synthesis, (8), 1294-1296; 1999

Experimental Procedure

Step 1

4-Chloropyridine (4) To a solution of $KHCO_3$ (20 g, 0.2 mol) in distilled H_2O (40 mL) cooled at 0 °C was added portionwise 4-chloropyridine hydrochloride (30 g, 0.2 mol) over 10 minutes. The heterogeneous mixture was extracted with CH_2Cl_2 (5 x 30 mL). The combined organic phases were washed with brine (10 mL) and dried ($MgSO_4$). After evaporation of the solvent under vacuum (40 mbar) at 20 °C, the free base **4** was obtained. (21.86 g, 96%) as an oil. ^{1}H NMR ($CDCl_3$/TMS): δ = 7.25 (d, 2 H, *J* = 4.8 Hz), 8.46 (d, 2 H, *J*= 4.8 Hz). ^{1}H NMR (DMSO-d_6/TMS): δ = 7.45 (dd, 2 H, *J* = 1.5, 4.6 Hz), 8.54 (dd, 2 H, *J* = 1.5, 4.6 Hz).

Step 2

4-Chloro-3-formylpyridine (8) A 500 mL 4-necked round bottomed flask was dried at 110 °C for 1 h and then allowed to cool to r.t. under argon. The flask was assembled with a mechanical stirrer, an argon inlet, a rubber septum and a dropping funnel with a pressure-equalizing side tube. The apparatus was cooled to -78 °C with a dry ice-acetone bath and a 2 M LDA solution in THF (58 mL, 0.116 mol) was introduced via a cannula and vigorously stirred under argon for 10 minutes. A solution of 4-chloropyridine (**4**; 11.94 g, 0.105 mol) in anhyd THF (50 mL) was added dropwise over 15 min and the mixture became orange/brick red coloured. After stirring for 1 h at -78 °C, anhyd DMF (10 mL, 0.129 mol) was added by a syringe over 12 min and the mixture was stirred for 1 h. The conversion of the substrate **4** into the aldehyde **8** was monitored by ^{1}H NMR analysis as follows. A sample (200 mL) was diluted with Et_2O (200 mL) and hydrolyzed with H_2O (200 mL), the organic phase was separated, dried over molecular sieves (0.4 nm) and evaporated at 30 °C, diluted with $CDCl_3$ (0.7 mL) and its ^{1}H NMR spectrum was recorded. **4-Chloro-3-(hydroxymethyl)pyridine Hydrochloride (9)** After completion of the formylation, an aqueous solution (40% w/v) of formaldehyde (12 mL, 0.158 mol) was added at once, the temperature was allowed to rise to 25 °C and the mixture was vigorously stirred at this temperature for 90 minutes. The liquid phase was decanted and the remaining solid was washed with CH_2Cl_2 (2 x 20 mL) by decanting the CH_2Cl_2. The organic-aqueous mixture thus obtained was evaporated at 50 °C under vacuum (20 mbar) then at 20 °C (0.001 mbar). The residue was dissolved in CH_2Cl_2 (150 mL) and washed with H_2O (4 x 20 mL) and half saturated NaCl solution (40 mL), dried ($MgSO_4$) and evaporated under vacuum to 70 mL This solution was cooled in an ice bath to 0 °C and anhyd gaseous HCl was bubbled in for 15 minutes. After 3-4 min light brown crystals formed and were filtered after 30 min, washed with ice cold CH_2Cl_2 (20 mL) and dried under vacuum (20 mbar) at 40 °C. **4-Chloro-3-(hydroxymethyl)pyridine Hydrochloride (9)** Yield: 16.0 g (85%). mp 145 °C. ^{1}H NMR (DMSO-d_6): δ = 4.67 (s, 2 H), 6.12 (br s, 2 H), 8.18 (d, 1 H, *J* = 6.1 Hz), 8.79 (s, 1 H), 8.83 (d, 1 H, *J* = 6.1 Hz).

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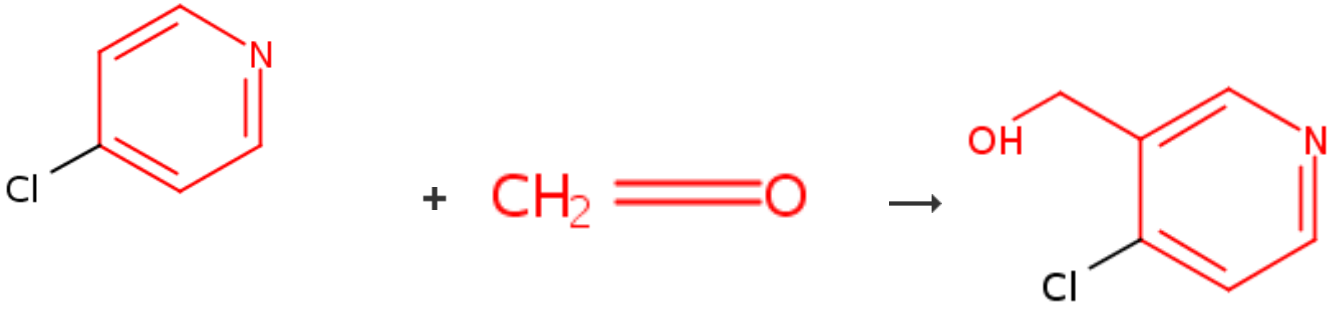
4. 3 Steps



- HCl

[Step 2.3]

Overview

Steps/Stages

1.1 R:K_2CO_3, S:H_2O

2.1 R:LiN(Pr-*i*)$_2$, S:THF
2.2 S:DMF
2.3 S:H_2O

2.4 R:HCl, S:CH_2Cl_2

3.1 R:K_2CO_3, S:H_2O

Notes

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

References

A practical synthesis of 4-chloro-3-(hydroxymethyl)pyridine by regioselective one-pot lithiation/formylation/reduction of 4-chloropyridine

By Albanese, Domenico et al

From Synthesis, (8), 1294-1296; 1999

Experimental Procedure

Step 1

4-Chloropyridine (4) To a solution of $KHCO_3$ (20 g, 0.2 mol) in distilled H_2O (40 mL) cooled at 0 °C was added portionwise 4-chloropyridine hydrochloride (30 g, 0.2 mol) over 10 minutes. The heterogeneous mixture was extracted with CH_2Cl_2 (5 x 30 mL). The combined organic phases were washed with brine (10 mL) and dried ($MgSO_4$). After evaporation of the solvent under vacuum (40 mbar) at 20 °C, the free base **4** was obtained. (21.86 g, 96%) as an oil. ^{1}H NMR ($CDCl_3$/TMS): δ = 7.25 (d, 2 H, *J* = 4.8 Hz), 8.46 (d, 2 H, *J*= 4.8 Hz). ^{1}H NMR (DMSO-d_6/TMS): δ = 7.45 (dd, 2 H, *J* = 1.5, 4.6 Hz), 8.54 (dd, 2 H, *J* = 1.5, 4.6 Hz).

Step 2
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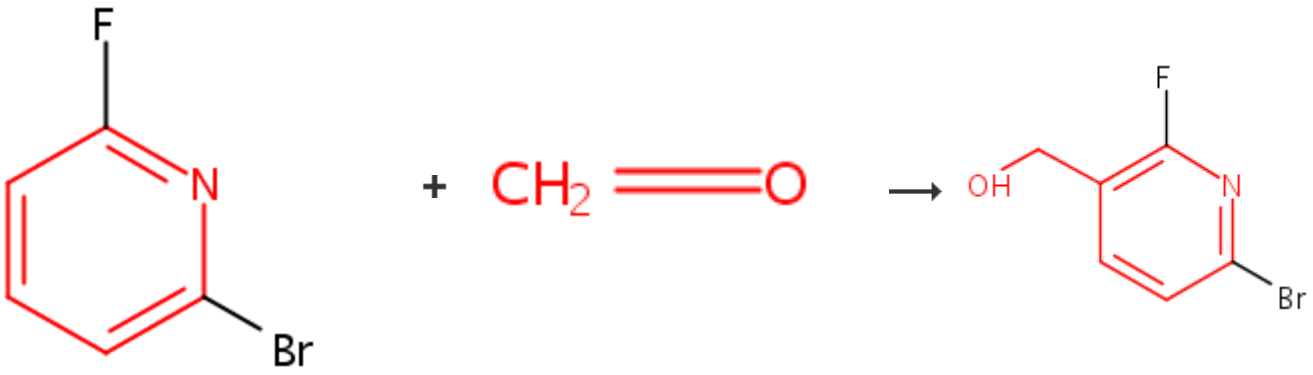
5. Single Step



36%

Overview

Steps/Stages

1.1 R:LiN(Pr-*i*)$_2$, S:THF, S:Me(CH$_2$)$_4$Me, -78°C; 2.5 h, -78°C
1.2 -78°C; -78°C → rt; overnight, rt

1.3 R:H_2O

Notes

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

References

5-Azaindazole compounds as Pim kinase inhibitors and their preparation

By Do, Steven et al

From U.S. Pat. Appl. Publ., 20140005168, 02 Jan 2014

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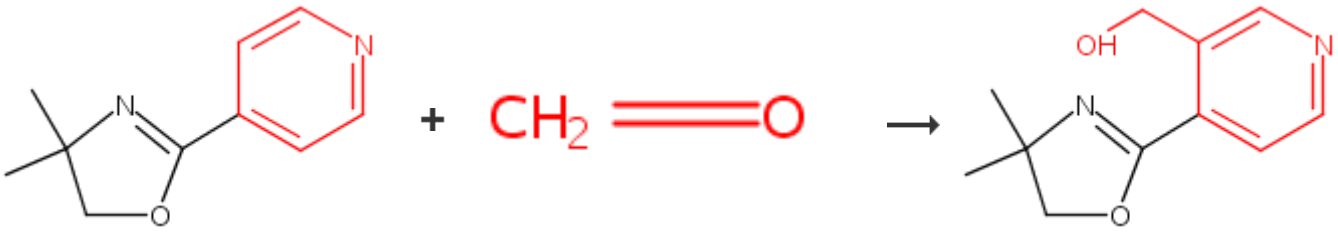
6. Single Step



33%

Overview

Steps/Stages

1.1 R:MeLi, S:THF

Notes

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

References

The synthesis of pyrido-oxepino indoles (MSc Thesis)

By Beal, Michael G.

From null, , No pp.; 1980

Experimental Procedure

Preparation of 3-hydroxymethyl pyridyl oxazoline (81): Pyridyl oxazoline (2.64 g) was dissolved in dry THF (100 mL) in a nitrogen atmosphere, and the solution brought to -78 degC. Methyl lithium solution (1.5 M, 10 mL) was introduced via a syringe to the magnetically stirred solution, whereupon the reaction mixture turned yellow. One hour after addition of the methyl lithium (MeLi), the acetone/dry ice bath (keeping the reaction at -78 degC) was replaced by an ice bath to bring the reaction to 0 degC. Having been at 0 degC for one hour, formaldehyde vapour was bubbled through the (now deep red/orange coloured) reaction mixture. When the reaction had turned pale yellow, and it had been ascertained that formaldehyde vapour was being expelled from the nitrogen outlet tube of the apparatus, formaldehyde production (by the heating of a flask of paraformaldehyde) was brought to a halt. The THF was evaporated, a small amount of water added to the remaining yellow solid, and a chloroform extraction performed. The chloroform layers were dried and evaporated to leave a brown oil, which crystallised at 0.5 mm Hg pressure (2.11g, 68 %). This was re-crystallised from 60-80 petroleum ether, giving off-white crystals of pure 3-hydroxymethyl pyridyl oxazoline (1.01 g, 33 %). mp 99-103 degC.

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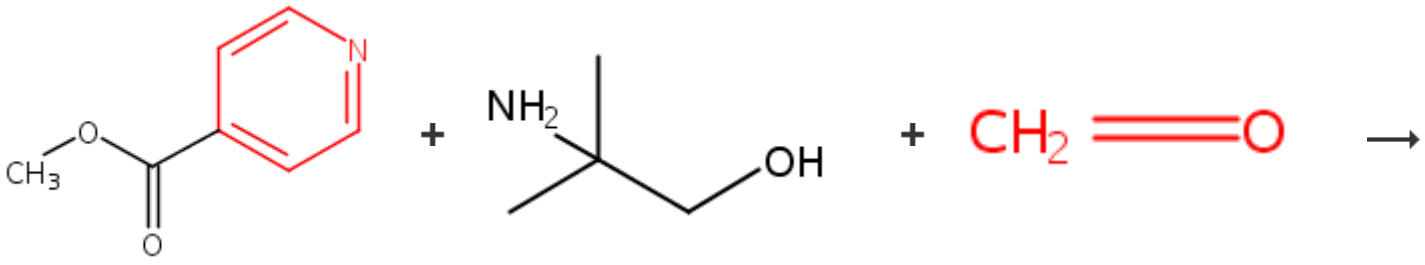
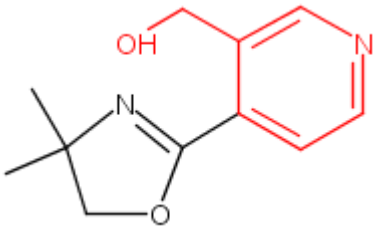
7. 2 Steps



[Step 2.1]



Overview

Steps/Stages

1.1 S:PhMe

2.1 R:MeLi, S:THF

Notes

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

References

The synthesis of pyrido-oxepino indoles (MSc Thesis)

By Beal, Michael G.

From null, , No pp.; 1980

Experimental Procedure

Step 1

Preparation of 2-(3-hydroxymethyl-4-pyridyl)-4,4-dimethyl-2-(oxazoline(or pyridyl oxazoline)) (79): Methyl isonicotinate (49 g) was dissolved in toluene (100 mL), 2-amino-2-methyl propan-1-ol (31 g) added, then the mixture heated at reflux under a Dean-Stark head for 4 days (approximately 96 hr). Water and methanol produced in the reaction were occasionally run off from the apparatus. After 4 days the reaction mixture was a black tar, which was distilled at 92-94 degC (1 mm Hg) to give yellow crystals of crude pyridyl oxazoline (46 g, 72 %). The crude product was re-crystallised from 60-80 petroleum ether to give off-white crystals of pure compound (40 g, 62 %). mp 51-54 degC. Rf = 0.31 (Solvent system: ethyl acetate:ethanol, 10:1).

Step 2

Preparation of 3-hydroxymethyl pyridyl oxazoline (81): Pyridyl oxazoline (2.64 g) was dissolved in dry THF (100 mL) in a nitrogen atmosphere, and the solution brought to -78 degC. Methyl lithium solution (1.5 M, 10 mL) was introduced via a syringe to the magnetically stirred solution, whereupon the reaction mixture turned yellow. One hour after addition of the methyl lithium (MeLi), the acetone/dry ice bath (keeping the reaction at -78 degC) was replaced by an ice bath to bring the reaction to 0 degC. Having been at 0 degC for one hour, formaldehyde vapour was bubbled through the (now deep red/orange coloured) reaction mixture. When the reaction had turned pale yellow, and it had been ascertained that formaldehyde vapour was being expelled from the nitrogen outlet tube of the apparatus, formaldehyde production (by the heating of a flask of paraformaldehyde) was brought to a halt. The THF was evaporated, a small amount of water added to the remaining yellow solid, and a chloroform extraction performed. The chloroform layers were dried and evaporated to leave a brown oil, which crystallised at 0.5 mm Hg pressure (2.11g, 68 %). This was re-crystallised from 60-80 petroleum ether, giving off-white crystals of pure 3-hydroxymethyl pyridyl oxazoline (1.01 g, 33 %). mp 99-103 degC.

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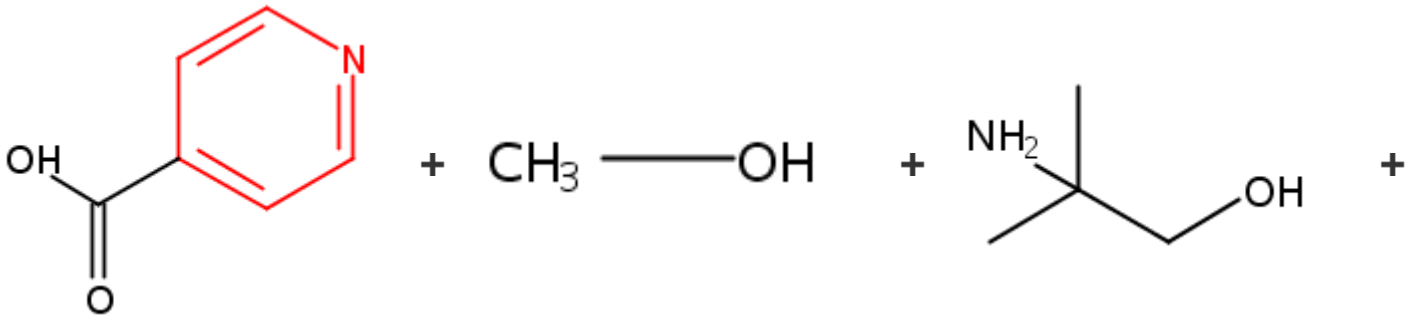
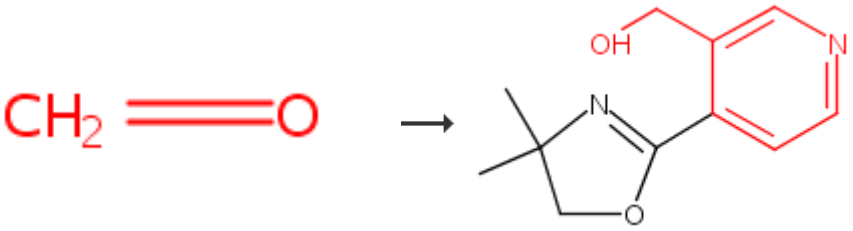
8. 3 Steps



[Step 2.1]



[Step 3.1]

Overview

Steps/Stages

1.1 R:$SOCl_2$

1.2 R:K_2CO_3, S:H_2O, S:MeOH
2.1 S:PhMe

3.1 R:MeLi, S:THF

Notes

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

References

The synthesis of pyrido-oxepino indoles (MSc Thesis)

By Beal, Michael G.

From null, , No pp.; 1980

Experimental Procedure

Step 1
Preparation of methyl isonicotinate (93): Thionyl chloride (200 mL) was added with care to isonicotinic acid (50 g). The reaction was then heated at reflux for 1.5 hours. The excess thionyl chloride was then distilled to leave yellow/brown crystals of isonicotinic acid chloride hydrochloride. Excess dry, distilled methanol was then added slowly to dissolve this hydrochloride, being accompanied by vigorous effervescence. This mixture was then refluxed for one hour. Having cooled down, the excess methanol was evaporated to leave an off-white solid (methyl isonicotinate hydrochloride). This solid was dissolved in distilled water and the solution neutralised with potassium carbonate, whence a pale brown oil separated. The mixture was extracted with ether and the etherial extracts were dried and evaporated to give the ester as a pale brown oil, (53 g, 96 %). The ester was distilled (20 mm Hg) at 124 degC to yield (48.6 g, 87 %). Rf = 0.5 (Solvent system: ethyl acetate:ethanol, 10:1).

Step 2
Preparation of 2-(3-hydroxymethyl-4-pyridyl)-4,4-dimethyl-2-(oxazoline(or pyridyl oxazoline)) (79): Methyl isonicotinate (49 g) was dissolved in toluene (100 mL), 2-amino-2-methyl propan-1-ol (31 g) added, then the mixture heated at reflux under a Dean-Stark head for 4 days (approximately 96 hr). Water and methanol produced in the reaction were occasionally run off from the apparatus. After 4 days the reaction mixture was a black tar, which was distilled at 92-94 degC (1 mm Hg) to give yellow crystals of crude pyridyl oxazoline (46 g, 72 %). The crude product was re-crystallised from 60-80 petroleum ether to give off-white crystals of pure compound (40 g, 62 %). mp 51-54 degC. Rf = 0.31 (Solvent system: ethyl acetate:ethanol, 10:1).

Step 3
Preparation of 3-hydroxymethyl pyridyl oxazoline (81): Pyridyl oxazoline (2.64 g) was dissolved in dry THF (100 mL) in a nitrogen atmosphere, and the solution brought to -78 degC. Methyl lithium solution (1.5 M, 10 mL) was introduced via a syringe to the magnetically stirred solution, whereupon the reaction mixture turned yellow. One hour after addition of the methyl lithium (MeLi), the acetone/dry ice bath (keeping the reaction at -78 degC) was replaced by an ice bath to bring the reaction to 0 degC. Having been at 0 degC for one hour, formaldehyde vapour was bubbled through the (now deep red/orange coloured) reaction mixture. When the reaction had turned pale yellow, and it had been ascertained that formaldehyde vapour was being expelled from the nitrogen outlet tube of the apparatus, formaldehyde production (by the heating of a flask of paraformaldehyde) was brought to a halt. The THF was evaporated, a small amount of water added to the remaining yellow solid, and a chloroform extraction performed. The chloroform layers were dried and evaporated to leave a brown oil, which crystallised at 0.5 mm Hg pressure (2.11g, 68 %). This was re-crystallised from 60-80 petroleum ether, giving off-white crystals of pure 3-hydroxymethyl pyridyl oxazoline (1.01 g, 33 %). mp 99-103 degC.

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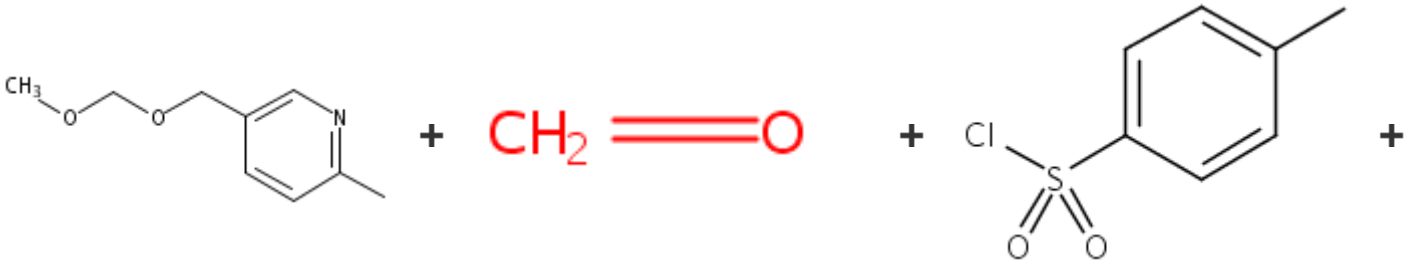
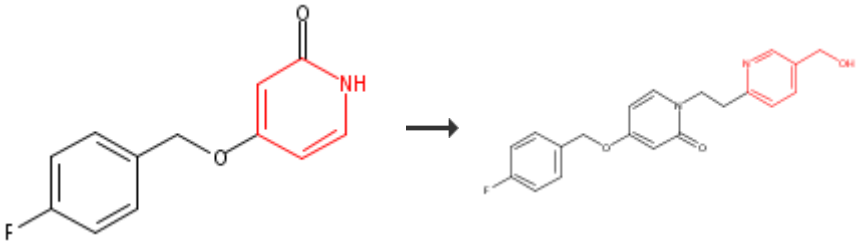
9. 4 Steps



[Step 2.1]



[Step 3.1]

Overview

Steps/Stages

1.1 S:H_2O, 17 h, 150°C

2.1 R:Et_3N, C:4-DMAP, 14 h, 0°C → rt

3.1 R:K_2CO_3, S:DMF, 2-17 h, 80°C

4.1 R:HCl, S:H_2O, S:THF, 2-18 h, rt

Notes

3) alternative method shown, 4) alternative method shown, Reactants: 4, Reagents: 3, Catalysts: 1, Solvents: 3, Steps: 4, Stages: 4, Most stages in any one step: 1

References

Discovery of novel phenethylpyridone derivatives as potent melanin-concentrating hormone 1 receptor antagonists

By Ando, Makoto et al

From Bioorganic & Medicinal Chemistry Letters, 19(17), 5186-5190; 2009

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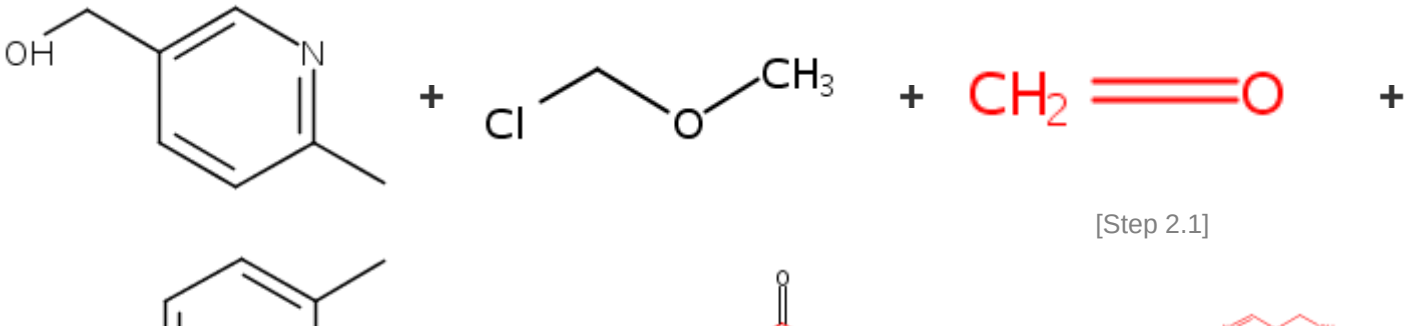
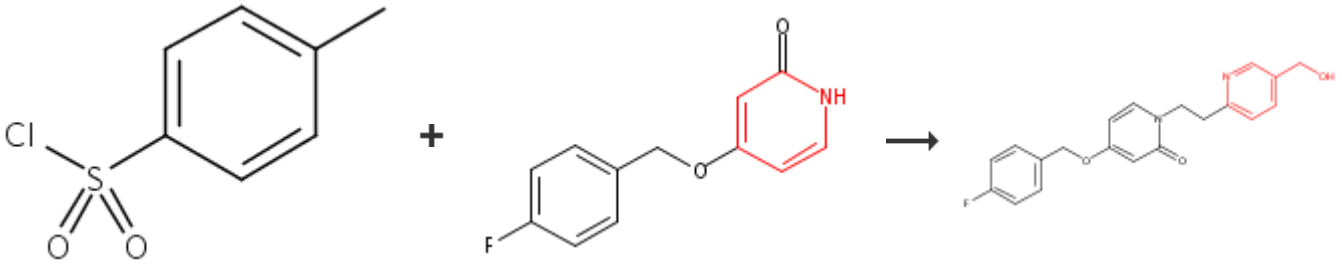
10. 5 Steps



[Step 2.1]



[Step 3.1] [Step 4.1]

Overview

Steps/Stages

1.1 R:NaH, S:DMF, 30 min, -20°C
2.1 S:H_2O, 17 h, 150°C

3.1 R:Et_3N, C:4-DMAP, 14 h, 0°C → rt

4.1 R:K_2CO_3, S:DMF, 2-17 h, 80°C

5.1 R:HCl, S:H_2O, S:THF, 2-18 h, rt

Notes

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

References

Discovery of novel phenethylpyridone derivatives as potent melanin-concentrating hormone 1 receptor antagonists

By Ando, Makoto et al

From Bioorganic & Medicinal Chemistry Letters, 19(17), 5186-5190; 2009

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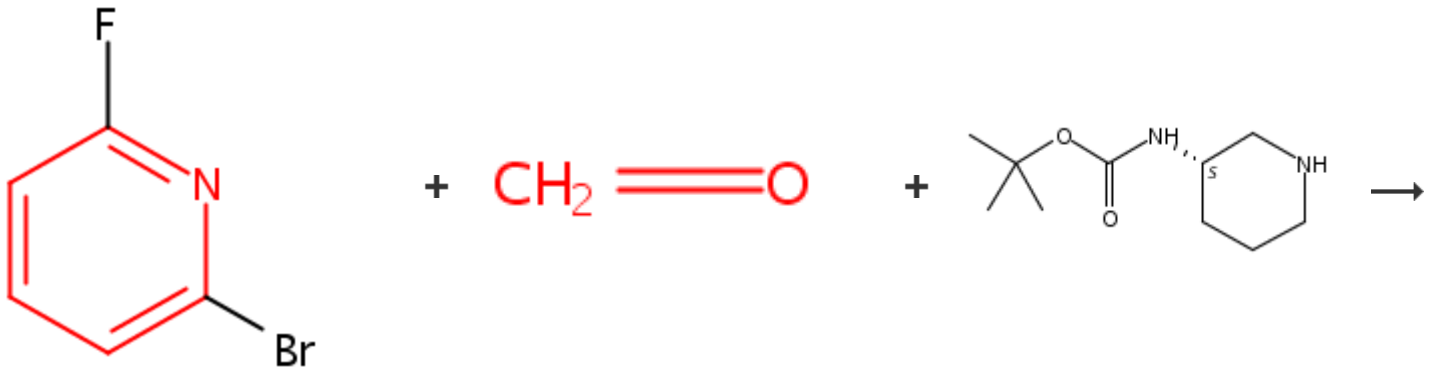
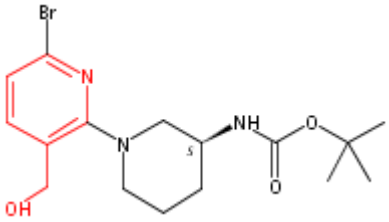
11. 2 Steps



[Step 2.1]



Overview

Steps/Stages

1.1 R:LiN(Pr-*i*)$_2$, S:THF, S:Me$(CH_2)_4$Me, -78°C; 2.5 h, -78°C
1.2 -78°C; -78°C → rt; overnight, rt

1.3 R:H_2O

2.1 R:N-Methylmorpholine, S:NMP, 4 h, 130°C

Notes

1) regioselective, paraformaldehyde used, 2) sealed tube used, Reactants: 3, Reagents: 3, Solvents: 3, Steps: 2, Stages: 4, Most stages in any one step: 3

References

5-Azaindazole compounds as Pim kinase inhibitors and their preparation

By Do, Steven et al

From U.S. Pat. Appl. Publ., 20140005168, 02 Jan 2014

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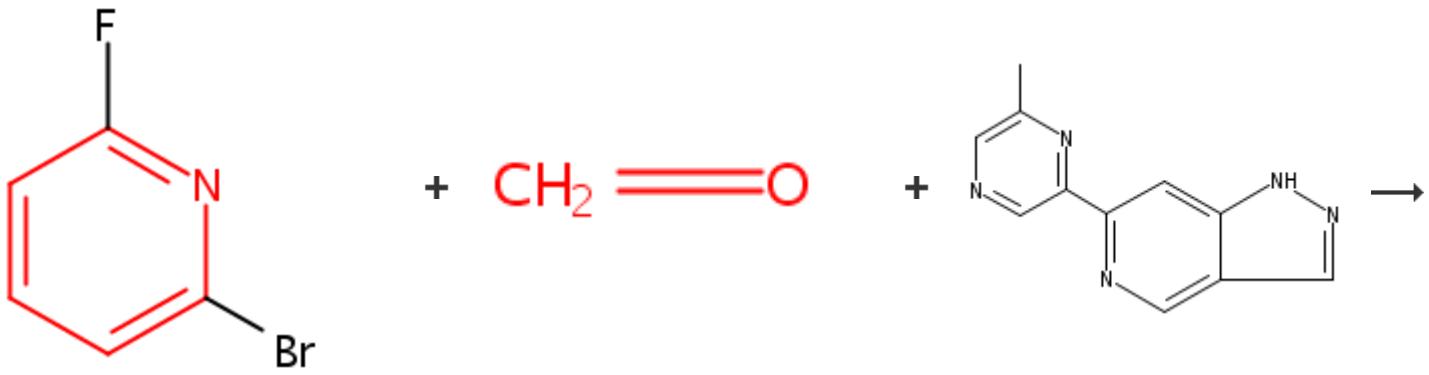
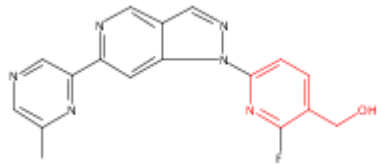
12. 2 Steps





Overview

Steps/Stages

1.1 R:LiN(Pr-*i*)$_2$, S:THF, S:Me(CH$_2$)$_4$Me, -78°C; 2.5 h, -78°C

1.2 -78°C; -78°C → rt; overnight, rt

1.3 R:H$_2$O

2.1 R:Me$_2$NCH$_2$CH$_2$NH$_2$, R:K$_2$CO$_3$, C:CuI, S:Dioxane, overnight, 105°C

Notes

1) regioselective, paraformaldehyde used, 2) chemoselective, sealed tube used, Reactants: 3, Reagents: 4, Catalysts: 1, Solvents: 3, Steps: 2, Stages: 4, Most stages in any one step: 3

References

5-Azaindazole compounds as Pim kinase inhibitors and their preparation

By Do, Steven et al

From U.S. Pat. Appl. Publ., 20140005168, 02 Jan 2014

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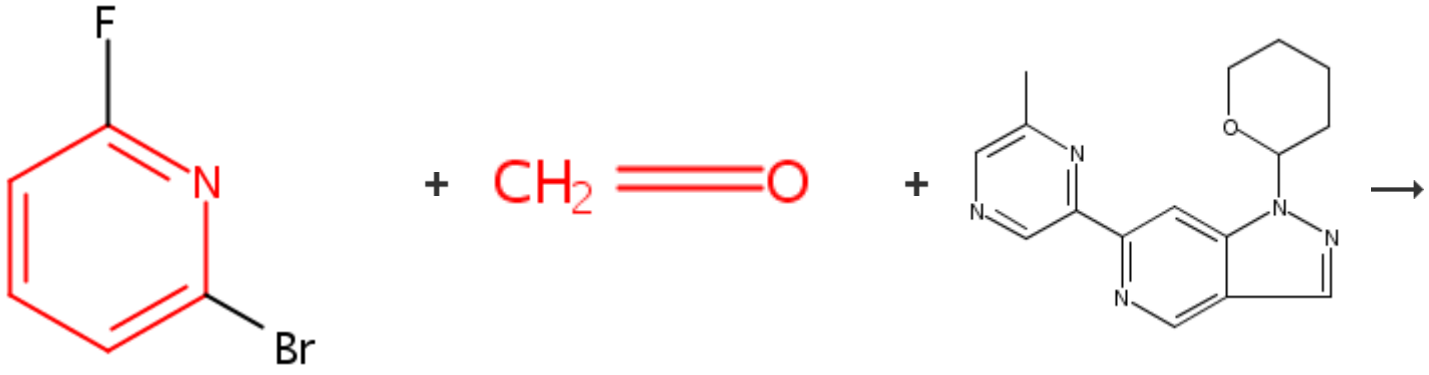
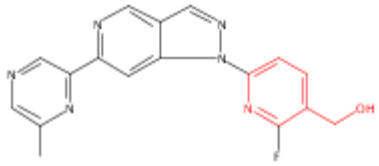
13. 3 Steps (Converging)





Overview

Steps/Stages

1.1 R:LiN(Pr-*i*)$_2$, S:THF, S:Me(CH$_2$)$_4$Me, -78°C; 2.5 h, -78°C
1.2 -78°C; -78°C → rt; overnight, rt

1.3 R:H$_2$O

1.1 R:HCl, S:MeOH, S:Dioxane, overnight, rt

2.1 R:Me$_2$NCH$_2$CH$_2$NH$_2$, R:K$_2$CO$_3$, C:CuI, S:Dioxane, overnight, 105°C

Notes

regioselective, paraformaldehyde used, chemoselective, sealed tube used, Reactants: 3, Reagents: 5, Catalysts: 1, Solvents: 4, Steps: 3, Stages: 5, Most stages in any one step: 3

References

5-Azaindazole compounds as Pim kinase inhibitors and their preparation

By Do, Steven et al

From U.S. Pat. Appl. Publ., 20140005168, 02 Jan 2014

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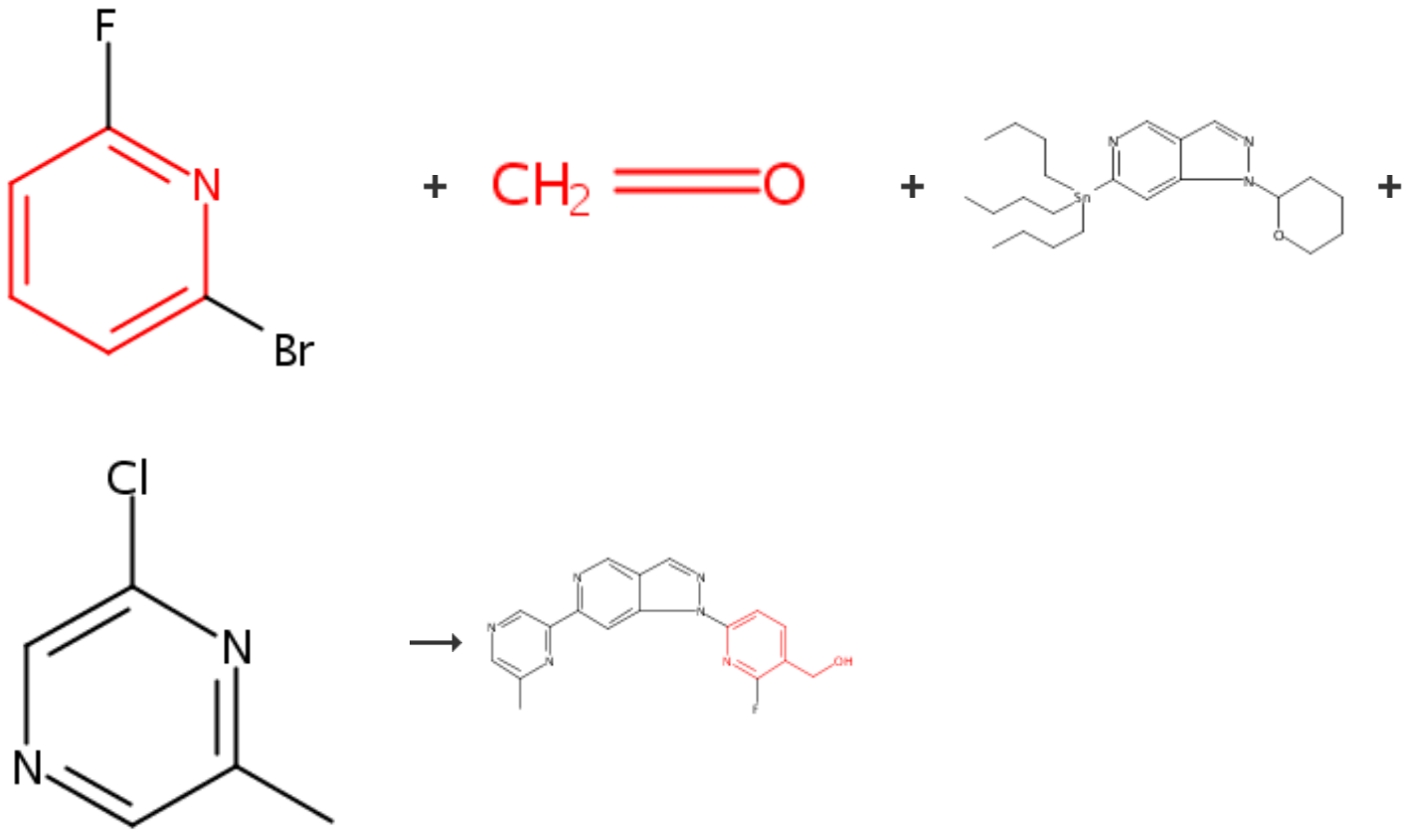
14. 4 Steps (Converging)



Overview

Steps/Stages

1.1 R:LiN(Pr-*i*)$_2$, S:THF, S:Me(CH$_2$)$_4$Me, -78°C; 2.5 h, -78°C
1.2 -78°C; -78°C → rt; overnight, rt

1.3 R:H$_2$O
1.1 C:Pd$_2$(dba)$_3$, C:(C$_6$H$_{11}$)$_3$P, S:AcNMe$_2$, overnight, 130°C

2.1 R:HCl, S:MeOH, S:Dioxane, overnight, rt

3.1 R:Me$_2$NCH$_2$CH$_2$NH$_2$, R:K$_2$CO$_3$, C:CuI, S:Dioxane, overnight, 105°C

Notes

regioselective, paraformaldehyde used, Stille coupling, chemoselective, sealed tube used, Reactants: 4, Reagents: 5, Catalysts: 3, Solvents: 5, Steps: 4, Stages: 6, Most stages in any one step: 3

References

5-Azaindazole compounds as Pim kinase inhibitors and their preparation

By Do, Steven et al

From U.S. Pat. Appl. Publ., 20140005168, 02 Jan 2014

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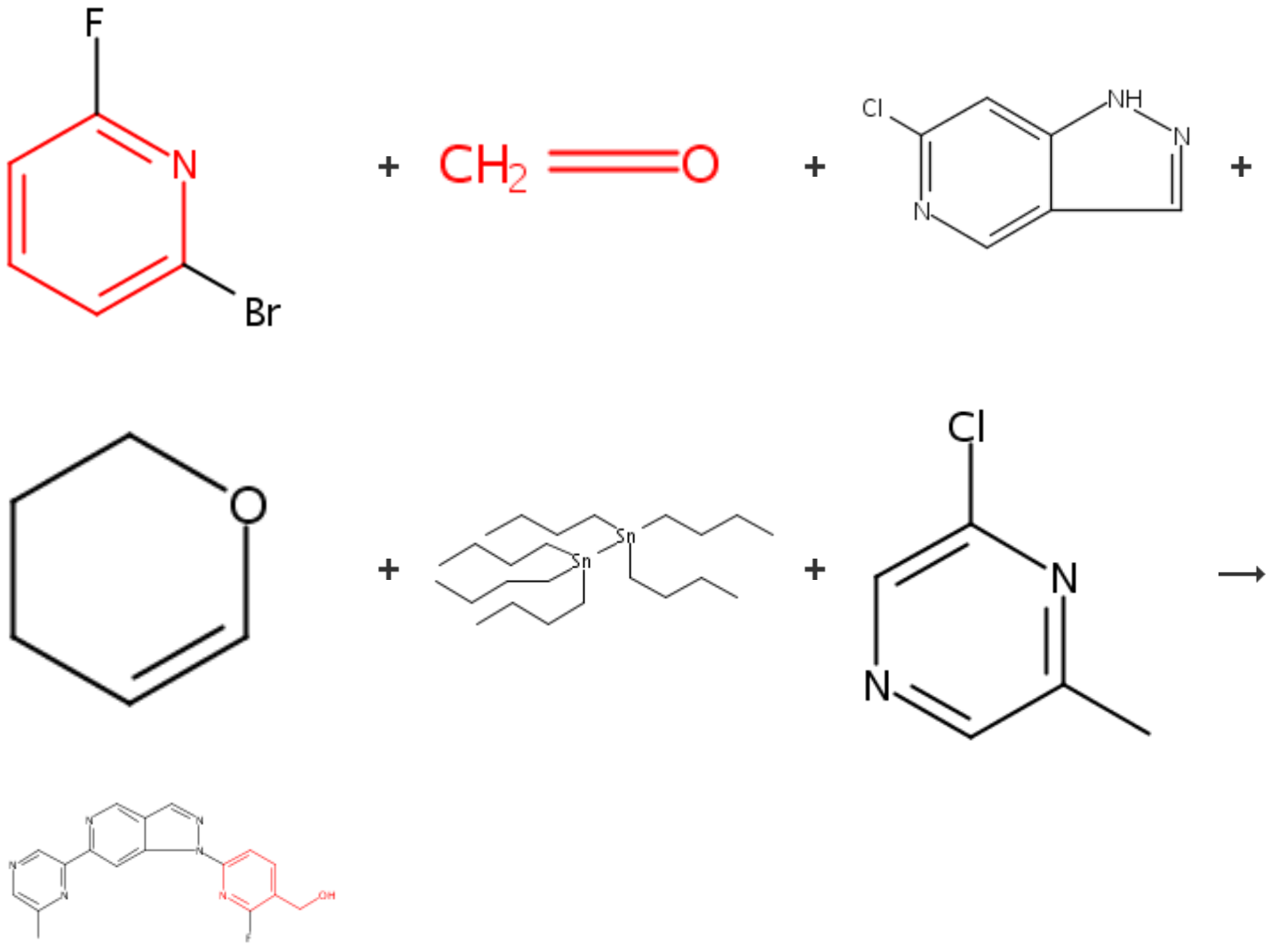
15. 6 Steps (Converging)



Overview

Steps/Stages

Notes

1.1 R:LiN(Pr-*i*)$_2$, S:THF, S:Me(CH$_2$)$_4$Me, -78°C; 2.5 h, -78°C
1.2 -78°C; -78°C → rt; overnight, rt

1.3 R:H_2O
1.1 C:*p*-MeC$_6$H$_4$SO$_3$H, S:Dioxane, overnight, 110°C; 110°C → rt

2.1 R:LiCl, C:Pd$_2$(dba)$_3$, C:(C$_6$H$_{11}$)$_3$P, S:Dioxane, overnight, 120°C
3.1 C:Pd$_2$(dba)$_3$, C:(C$_6$H$_{11}$)$_3$P, S:AcNMe$_2$, overnight, 130°C

4.1 R:HCl, S:MeOH, S:Dioxane, overnight, rt

5.1 R:Me$_2$NCH$_2$CH$_2$NH$_2$, R:K$_2$CO$_3$, C:CuI, S:Dioxane, overnight, 105°C

regioselective, paraformaldehyde used, sealed tube used, Stille coupling, chemoselective, sealed tube used, Reactants: 6, Reagents: 6, Catalysts: 4, Solvents: 5, Steps: 6, Stages: 8, Most stages in any one step: 3

References

5-Azaindazole compounds as Pim kinase inhibitors and their preparation

By Do, Steven et al

From U.S. Pat. Appl. Publ., 20140005168, 02 Jan 2014

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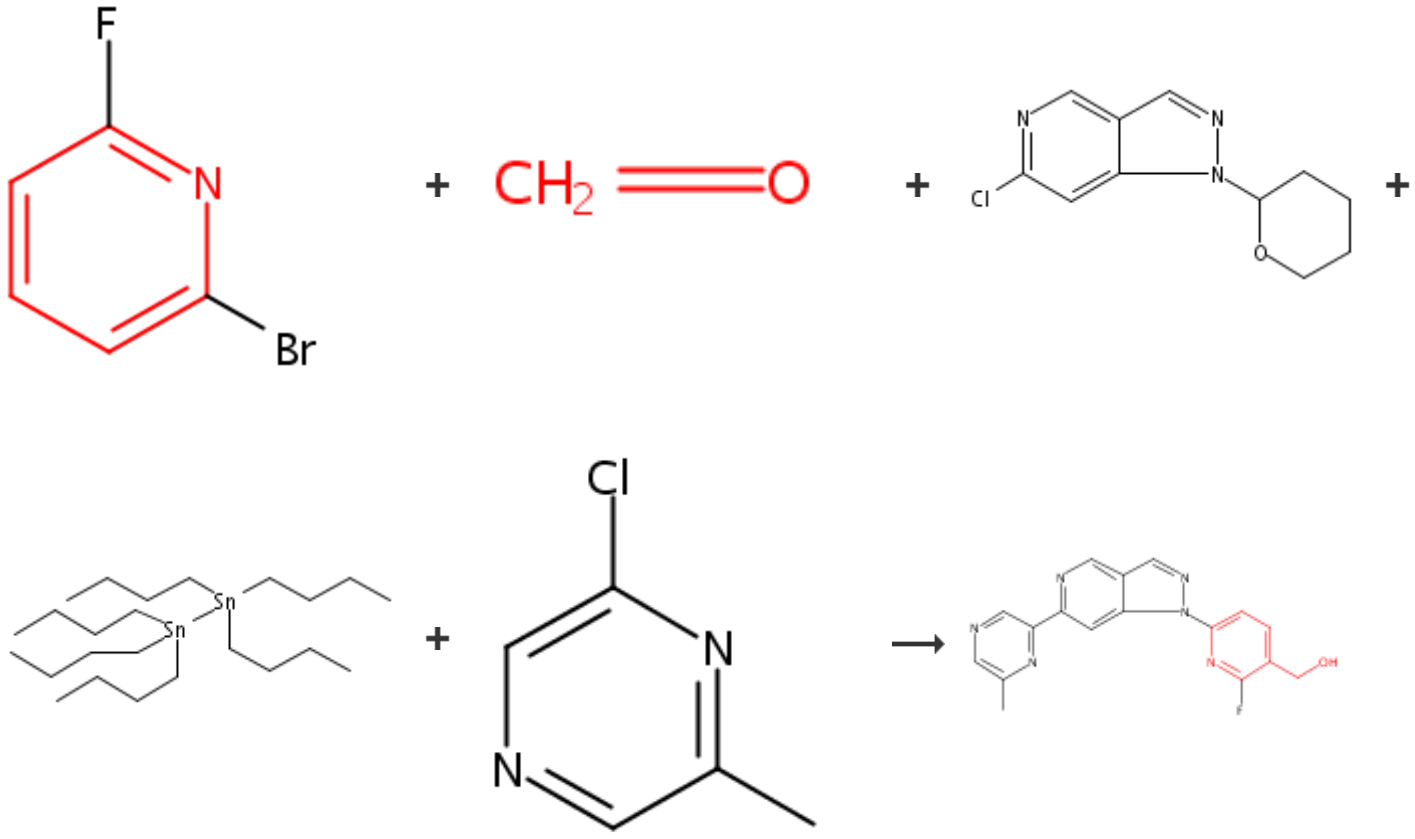
16. 5 Steps (Converging)



Overview

Steps/Stages

Notes

1.1 R:LiN(Pr-*i*)$_2$, S:THF, S:Me(CH$_2$)$_4$Me, -78°C; 2.5 h, -78°C
1.2 -78°C; -78°C → rt; overnight, rt

1.3 R:H$_2$O

1.1 R:LiCl, C:Pd$_2$(dba)$_3$, C:(C$_6$H$_{11}$)$_3$P, S:Dioxane, overnight, 120°C
2.1 C:Pd$_2$(dba)$_3$, C:(C$_6$H$_{11}$)$_3$P, S:AcNMe$_2$, overnight, 130°C

3.1 R:HCl, S:MeOH, S:Dioxane, overnight, rt

4.1 R:Me$_2$NCH$_2$CH$_2$NH$_2$, R:K$_2$CO$_3$, C:CuI, S:Dioxane, overnight, 105°C

regioselective, paraformaldehyde used, sealed tube used, Stille coupling, chemoselective, sealed tube used, Reactants: 5, Reagents: 6, Catalysts: 3, Solvents: 5, Steps: 5, Stages: 7, Most stages in any one step: 3

References

5-Azaindazole compounds as Pim kinase inhibitors and their preparation

By Do, Steven et al

From U.S. Pat. Appl. Publ., 20140005168, 02 Jan 2014

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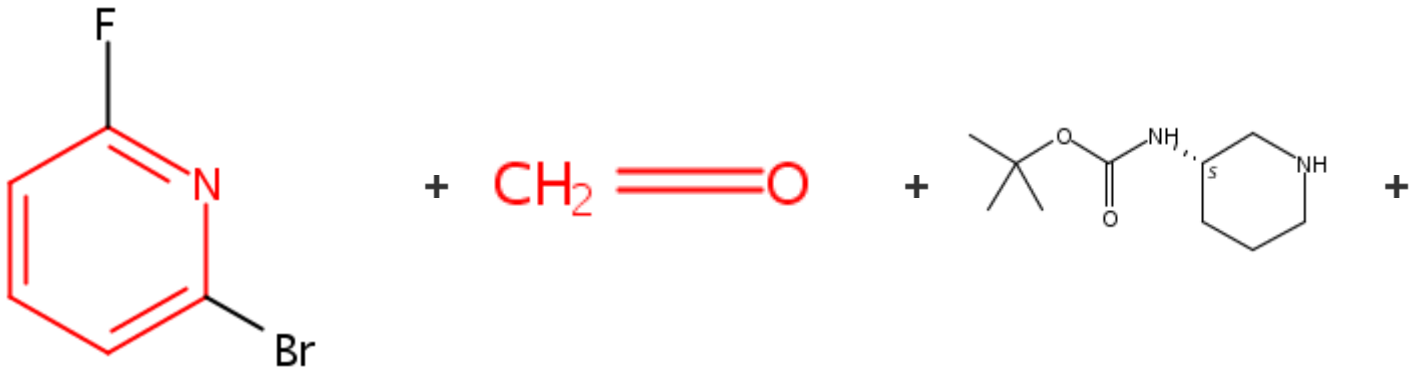
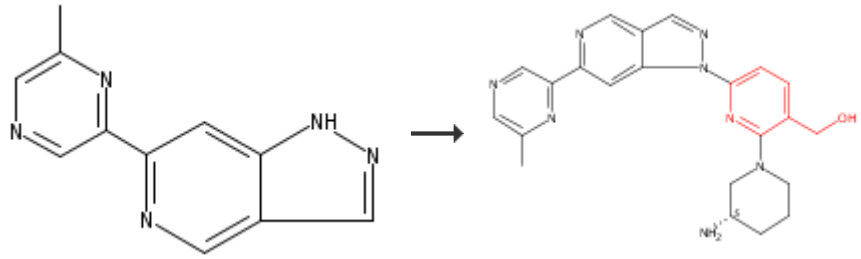
17. 3 Steps



[Step 2.1]



[Step 3.1]

Overview

Steps/Stages

1.1 R:LiN(Pr-*i*)$_2$, S:THF, S:Me(CH$_2$)$_4$Me, -78°C; 2.5 h, -78°C
1.2 -78°C; -78°C → rt; overnight, rt

1.3 R:H$_2$O

2.1 R:N-Methylmorpholine, S:NMP, 4 h, 130°C

3.1 R:Me$_2$NCH$_2$CH$_2$NH$_2$, R:K$_2$CO$_3$, C:CuI, S:Dioxane, overnight, 100°C; 100°C → rt

3.2 R:HCl, S:MeOH, S:Dioxane, overnight, rt

Notes

1) regioselective, paraformaldehyde used, 2) sealed tube used, 3) sealed, Reactants: 4, Reagents: 6, Catalysts: 1, Solvents: 5, Steps: 3, Stages: 6, Most stages in any one step: 3

References

5-Azaindazole compounds as Pim kinase inhibitors and their preparation

By Do, Steven et al

From U.S. Pat. Appl. Publ., 20140005168, 02 Jan 2014

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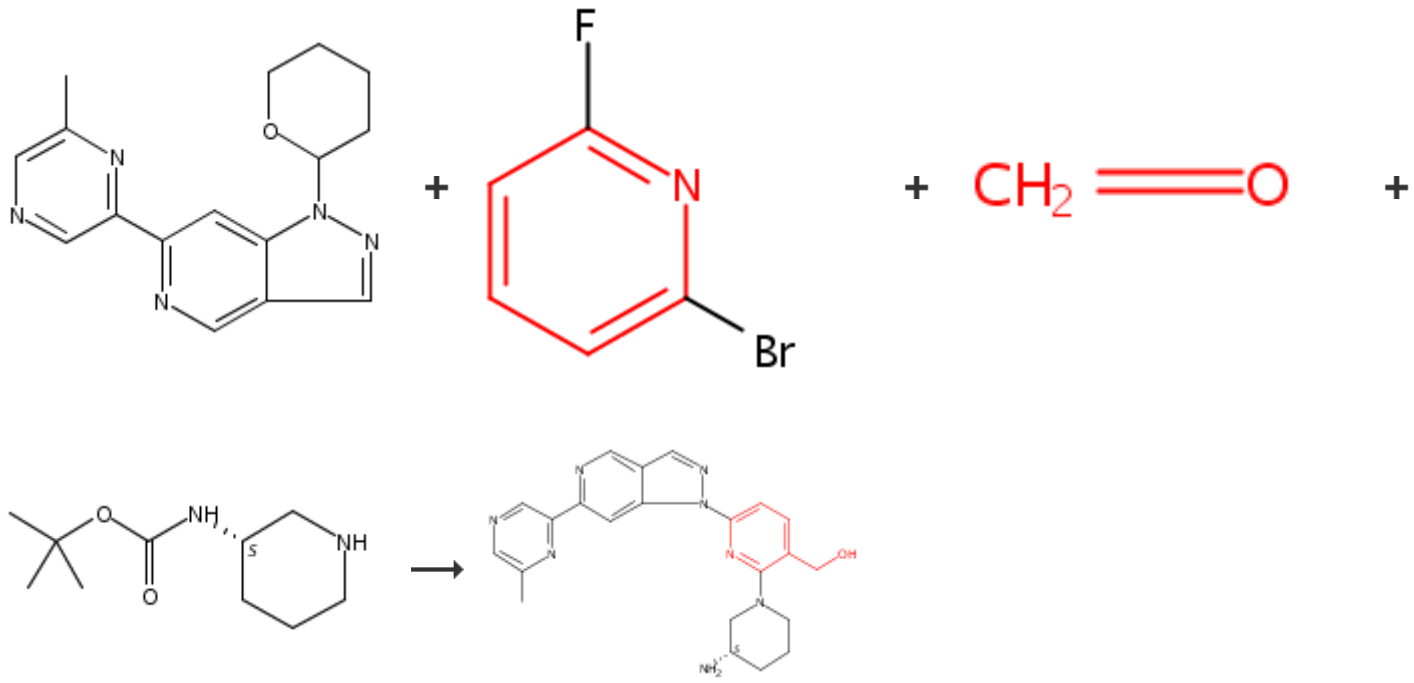
18. 4 Steps (Converging)



Overview

Steps/Stages

1.1 R:HCl, S:MeOH, S:Dioxane, overnight, rt

1.1 R:LiN(Pr-*i*)$_2$, S:THF, S:Me(CH$_2$)$_4$Me, -78°C; 2.5 h, -78°C
1.2 -78°C; -78°C → rt; overnight, rt

1.3 R:H$_2$O

2.1 R:N-Methylmorpholine, S:NMP, 4 h, 130°C

3.1 R:Me$_2$NCH$_2$CH$_2$NH$_2$, R:K$_2$CO$_3$, C:CuI, S:Dioxane, overnight, 100°C; 100°C → rt

3.2 R:HCl, S:MeOH, S:Dioxane, overnight, rt

Notes

regioselective, paraformaldehyde used, sealed tube used, sealed, Reactants: 4, Reagents: 6, Catalysts: 1, Solvents: 5, Steps: 4, Stages: 7, Most stages in any one step: 3

References

5-Azaindazole compounds as Pim kinase inhibitors and their preparation

By Do, Steven et al

From U.S. Pat. Appl. Publ., 20140005168, 02 Jan 2014

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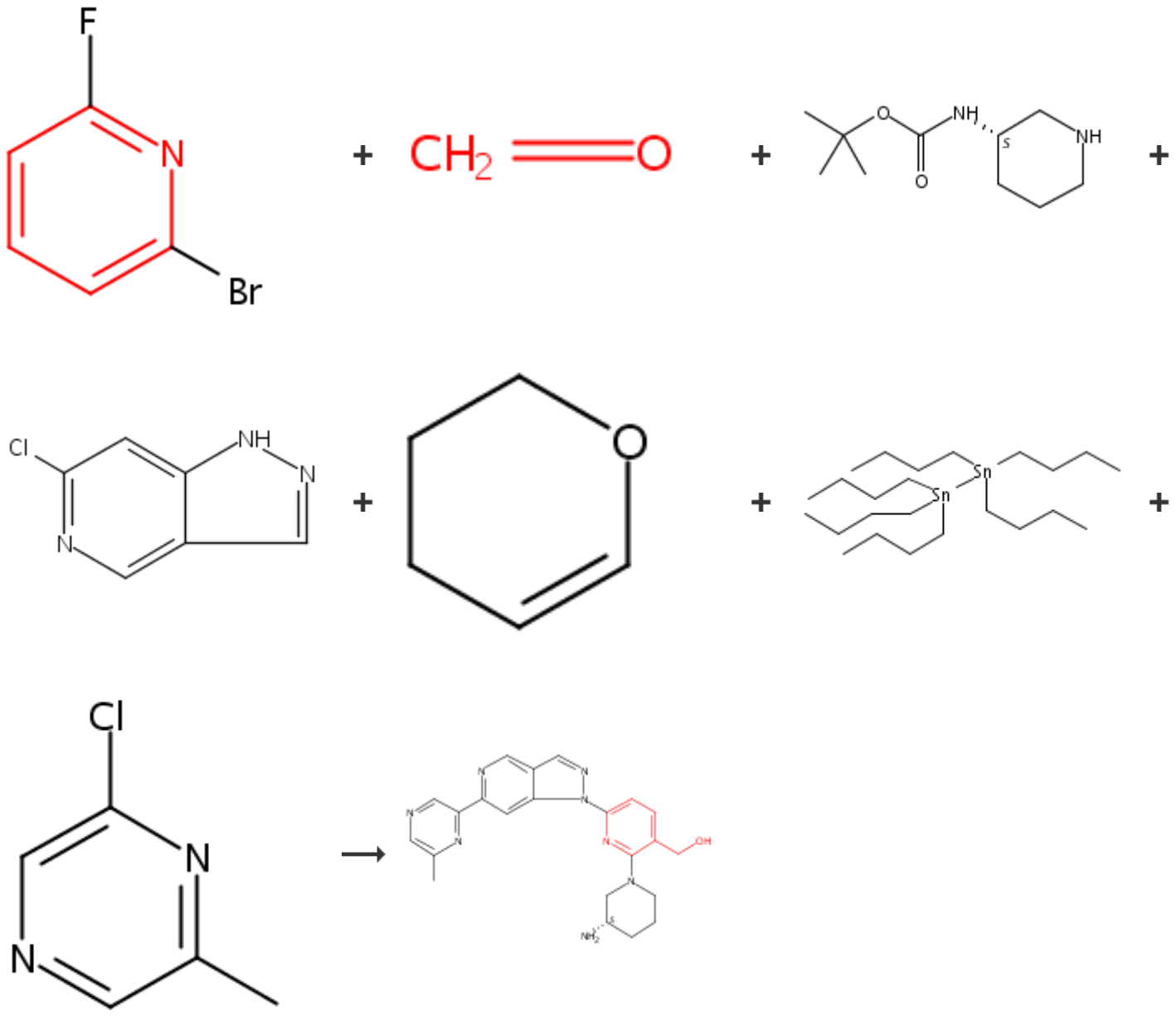
19. 7 Steps (Converging)



Overview

Steps/Stages

Notes

1.1 R:LiN(Pr-*i*)$_2$, S:THF, S:Me(CH$_2$)$_4$Me, -78°C; 2.5 h, -78°C
1.2 -78°C; -78°C → rt; overnight, rt

1.3 R:H$_2$O

2.1 R:N-Methylmorpholine, S:NMP, 4 h, 130°C
1.1 C:*p*-MeC$_6$H$_4$SO$_3$H, S:Dioxane, overnight, 110°C; 110°C → rt

2.1 R:LiCl, C:Pd$_2$(dba)$_3$, C:(C$_6$H$_{11}$)$_3$P, S:Dioxane, overnight, 120°C
3.1 C:Pd$_2$(dba)$_3$, C:(C$_6$H$_{11}$)$_3$P, S:AcNMe$_2$, overnight, 130°C

4.1 R:HCl, S:MeOH, S:Dioxane, overnight, rt

5.1 R:Me$_2$NCH$_2$CH$_2$NH$_2$, R:K$_2$CO$_3$, C:CuI, S:Dioxane, overnight, 100°C; 100°C → rt

5.2 R:HCl, S:MeOH, S:Dioxane, overnight, rt

regioselective, paraformaldehyde used, sealed tube used, sealed tube used, Stille coupling, sealed, Reactants: 7, Reagents: 7, Catalysts: 4, Solvents: 6, Steps: 7, Stages: 10, Most stages in any one step: 3

References

5-Azaindazole compounds as Pim kinase inhibitors and their preparation

By Do, Steven et al

From U.S. Pat. Appl. Publ., 20140005168, 02 Jan 2014

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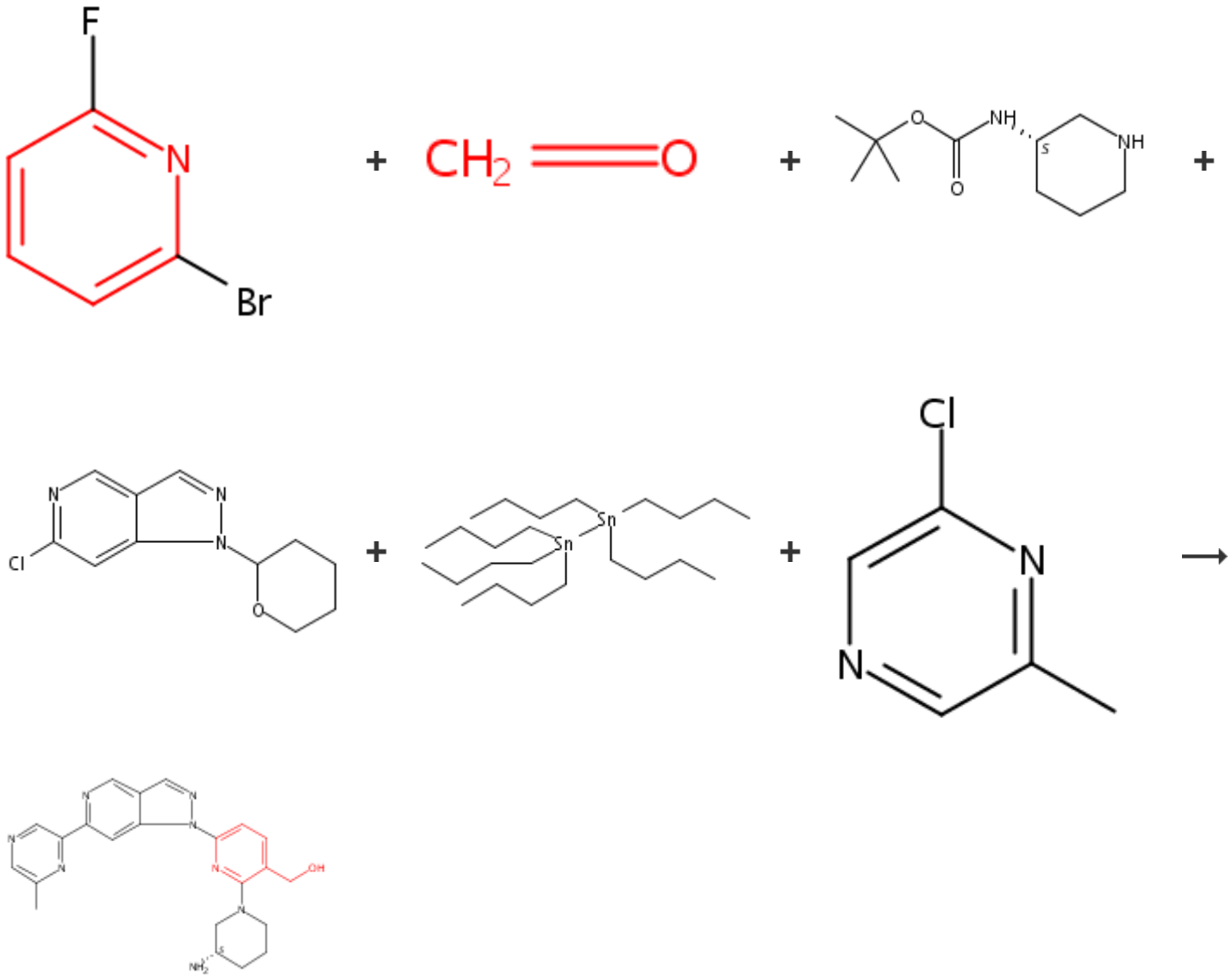
20. 6 Steps (Converging)



Overview

Steps/Stages

1.1 R:LiN(Pr-*i*)$_2$, S:THF, S:Me(CH$_2$)$_4$Me, -78°C; 2.5 h, -78°C
1.2 -78°C; -78°C → rt; overnight, rt

1.3 R:H_2O

2.1 R:N-Methylmorpholine, S:NMP, 4 h, 130°C

1.1 R:LiCl, C:$Pd_2(dba)_3$, C:$(C_6H_{11})_3P$, S:Dioxane, overnight, 120°C
2.1 C:$Pd_2(dba)_3$, C:$(C_6H_{11})_3P$, S:$AcNMe_2$, overnight, 130°C

3.1 R:HCl, S:MeOH, S:Dioxane, overnight, rt

4.1 R:$Me_2NCH_2CH_2NH_2$, R:K_2CO_3, C:CuI, S:Dioxane, overnight, 100°C; 100°C → rt

4.2 R:HCl, S:MeOH, S:Dioxane, overnight, rt

Notes

regioselective, paraformaldehyde used, sealed tube used, sealed tube used, Stille coupling, sealed, Reactants: 6, Reagents: 7, Catalysts: 3, Solvents: 6, Steps: 6, Stages: 9, Most stages in any one step: 3

References

5-Azaindazole compounds as Pim kinase inhibitors and their preparation

By Do, Steven et al

From U.S. Pat. Appl. Publ., 20140005168, 02 Jan 2014

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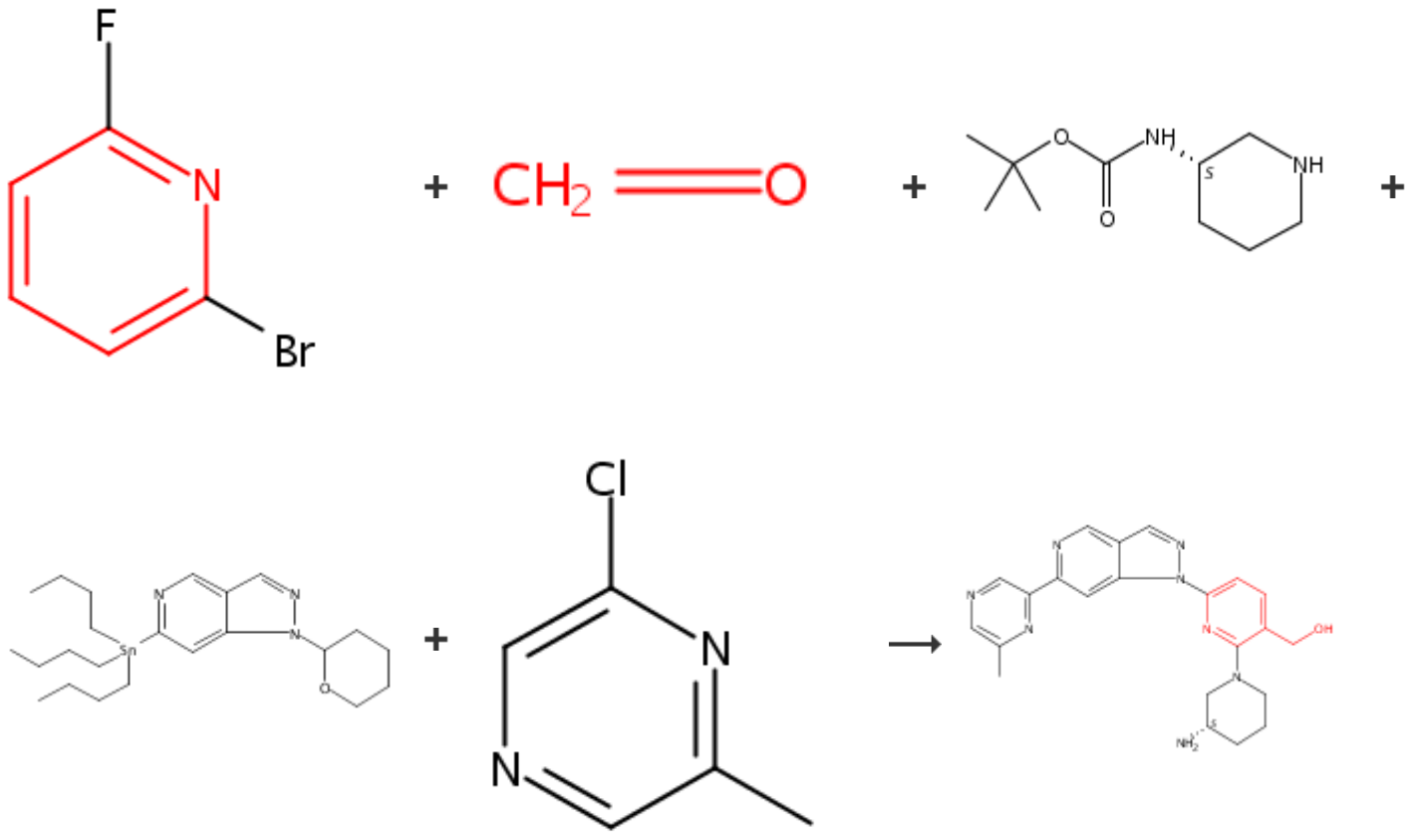
21. 5 Steps (Converging)



Overview

Steps/Stages

Notes

1.1 R:LiN(Pr-*i*)$_2$, S:THF, S:Me(CH$_2$)$_4$Me, -78°C; 2.5 h, -78°C
1.2 -78°C; -78°C → rt; overnight, rt

1.3 R:H$_2$O

2.1 R:N-Methylmorpholine, S:NMP, 4 h, 130°C
1.1 C:Pd$_2$(dba)$_3$, C:(C$_6$H$_{11}$)$_3$P, S:AcNMe$_2$, overnight, 130°C

2.1 R:HCl, S:MeOH, S:Dioxane, overnight, rt

3.1 R:Me$_2$NCH$_2$CH$_2$NH$_2$, R:K$_2$CO$_3$, C:CuI, S:Dioxane, overnight, 100°C; 100°C → rt

3.2 R:HCl, S:MeOH, S:Dioxane, overnight, rt

regioselective, paraformaldehyde used, sealed tube used, Stille coupling, sealed, Reactants: 5, Reagents: 6, Catalysts: 3, Solvents: 6, Steps: 5, Stages: 8, Most stages in any one step: 3

References

5-Azaindazole compounds as Pim kinase inhibitors and their preparation

By Do, Steven et al

From U.S. Pat. Appl. Publ., 20140005168, 02 Jan 2014

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