

**C Step1** **Ground Truth**

- :1.68 ml of triethylamine added to a solution;
- :60 ml of ethyl acetate;
- :0.96 ml of 2-chloroacetyl chloride added;
- :Reaction mixture stirred at room temperature for 1 hour;
- :Mixed with water;
- :Aqueous mixture extracted with ethyl acetate;
- :Extract concentrated by evaporation under reduced pressure;
- :Concentrate purified by column chromatography through silica gel;
- :3.00 g of 3-(4-piperidinomethyl-2-pyridyloxy)propylamine;
- :3.40 g (87% yield) of the title compound obtained as an oil;

**C Step2**

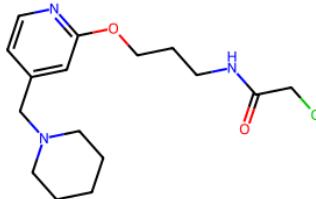
- :Start with phenol as a precursor;
- :Perform under a fume hood;
- :Reaction time: 1 hour;
- :Add concentrated nitric acid under stirring (500 RPM) at 25°C;

**C Step3**

- :Use 2-nitrophenol;
- :Add to formaldehyde in water (1:1.5 ratio);
- :Stir at room temperature (25°C) for 6 hours;

**C Step4**

- :Dissolve 2-nitrophenylmethanol in dichloromethane or DMSO;
- :Maintain temperature at 0°C;
- :Reaction time: 2 hours;
- :Add dimethyl sulfate under stirring (500 RPM);



N-[3-(4-Piperidinomethyl-2-pyridyloxy)propyl]-2-chloroacetamide

**C Step1**

- :Mix in dichloromethane;
- :Start with N-(tert-butoxycarbonyl)-3-[4-(2-pyridyl)-piperidin-1-yl]propylamine and 2-chloroacetic acid as precursors;
- :Stir at 25°C for 1 hour (600 RPM);

**C Step2**

- :Workup the reaction mixture;

**C Step3**

- :Concentrate the solution under reduced pressure;

**C Step4**

- :Extract with dichloromethane and water;
- :Dry organic layer over sodium sulfate;

**C Step5**

- :Filter to remove drying agent and impurities;

**C Step6**

- :Concentrate again to remove remaining solvent;

**C Step7**

- :Purify using column chromatography;

**C Step 1: Dissolving the starting materials**

- :Combine starting materials;
- :2-chloroacetyl chloride;
- :Use flask with magnetic stirrer;
- :3-(4-Piperidinomethyl-2-pyridyloxy)propylamine;
- :In suitable solvent (e.g., methanol, dioxane);

**C Step 2: Addition of reagents**

- :Deprotect the amine;
- :Add dropwise under stirring conditions;
- :Add reagents (e.g., sodium hydroxide);

**C Step 3: Reaction**

- :Stir for specific time (4-6 hours);
- :Controlled temperature (room temperature or up to 80°C);

**C Step 4: Workup**

- :Isolate product;
- :Dilute with water;
- :Workup techniques (extraction, filtration, evaporation);
- :Extract with organic solvent (e.g., ethyl acetate, chloroform);
- :Filtration (vacuum filtration);
- :Evaporation (rotary evaporator);

**C Step 5: Purification**

- :Further purification;
- :Remove unreacted materials or by-products;
- :Recrystallization or column chromatography;

**C Step1**

- :React with 2-chloroacetyl chloride in pyridine;
- :Room temperature or lower;
- :Neutralize with acid;

**C Step2**

- :Prepare intermediate chlorohydrin;
- :React chlorohydrin with piperidine;
- :Conditions: Below -10°C, preferably -20°C to -60°C;

**C Step1**

- :React with 2-chloroacetyl chloride in pyridine;
- :Room temperature or lower;
- :Neutralize with acid;

**C Step2**

- :Prepare intermediate chlorohydrin;
- :React chlorohydrin with piperidine;
- :Conditions: Below -10°C, preferably -20°C to -60°C;

**C Step 1: Synthesis of 4-piperidinomethyl-2-pyridyloxy**

- :Dissolve 2-pyridyl methanol in DCM;
- :Add paraformaldehyde and piperidine;
- :Monitor reaction progress with TLC;
- :Dilute with DCM and wash with water;
- :Dry organic layer over anhydrous sodium sulfate;
- :Concentrate in vacuo to get crude product;
- :Purify by column chromatography to obtain 4-piperidinomethyl-2-pyridyloxy;
- :2-pyridyl methanol (2.0 g, 17.4 mmol);
- :Piperidine (1.9 mL, 19.1 mmol);
- :Paraformaldehyde (1.3 g, 43.2 mmol);
- :Dichloromethane (DCM, 20 mL);
- :Glacial Acetic Acid (2 mL);
- :Stir at room temperature (25°C) for 24 hours at 200 rpm;

**C Step 2: Synthesis of N-[3-(4-Piperidinomethyl-2-pyridyloxy)propyl]-2-chloroacetamide**

- :Dissolve 4-piperidinomethyl-2-pyridyloxy in DCM;
- :Add 3-chloropropylamine hydrochloride and NaHCO<sub>3</sub>;
- :Dilute with DCM and wash with water;
- :Dry organic layer over anhydrous sodium sulfate;
- :Concentrate in vacuo to get intermediate product;
- :Monitor reaction with TLC;
- :Dilute with DCM and wash with water;
- :Dry organic layer over anhydrous sodium sulfate;
- :Concentrate in vacuo to get crude product;
- :4-piperidinomethyl-2-pyridyloxy (1.0 g, 4.48 mmol);
- :3-chloropropylamine hydrochloride (1.15 g, 8.96 mmol);
- :Sodium bicarbonate (NaHCO<sub>3</sub>, 1.89 g, 22.4 mmol);
- :Dichloromethane (DCM, 20 mL);
- :2-chloroacetyl chloride (0.52 mL, 6.72 mmol);
- :Stir at room temperature (25°C) for 24 hours at 200 rpm;
- :Add 2-chloroacetyl chloride and stir at room temperature (25°C) for 12 hours at 200 rpm;
- :Purify by column chromatography to obtain N-[3-(4-Piperidinomethyl-2-pyridyloxy)propyl]-2-chloroacetamide;

**(C) Step1** **Ground Truth**

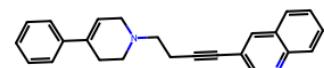
- :Catalytic amount of 4-dimethylaminopyridine;
- :Cool to 0°C;
- :Stir at 0°C for 18 hours;
- :Concentrated under reduced pressure;
- :A solution of the alcohol prepared in Step (a) (1.98 g, 0.01 mol);
- :N,N-diisopropylethylamine (3.5 mL, 0.02 mol);
- :Add methanesulfonyl chloride (0.8 mL, 0.0105 mol) dropwise;

**(C) Step2**

- :Heat at 40°C for 5 hours;
- :Remove solvent under reduced pressure;
- :Residue taken up in dimethylformamide (20 mL);
- :Add 4-phenyl-1,2,3,6-tetrahydropyridine (2.41 g, 0.015 mol);
- :Add sodium bicarbonate (3.4 g, 0.04 mol);

**(C) Step3**

- :Partition between 50 mL of ethyl acetate and 50 mL of water;
- :Extract aqueous layer with 50 mL of ethyl acetate;
- :Dry combined organic layers with sodium sulfate;
- :Remove solvent in vacuo;
- :Chromatograph (silica gel, 2% methanol/98% dichloromethane);



3-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]quinoline

**(C) Step1** **1**

- :to a 250-cm<sup>3</sup> flask with a magnetic stirrer;
- :Add 0.01 mole of 3-methyl-6-{3-[4-(3-trifluoromethylphenyl)-1-piperazinyl]-1-oxopropyl}benzoxazolinone;

**(C) Step2**

- :Dissolve the compound in 200 cm<sup>3</sup> of methanol;

**(C) Step3**

- :Slowly add 0.02 mole of sodium borohydride;
- :Maintain stirring for 4 hours at room temperature;

**(C) Step4**

- :Evaporate the reaction medium on a water bath under vacuum;
- :Take up the residue with water;
- :Extract several times with chloroform;

**(C) Step5**

- :Filter the extracts;
- :Evaporate them to dryness on a water bath under vacuum;

**(C) Step6**

- :Recrystallize the product in ethanol;
- :To yield 3-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]quinoline;

**(C) Conditions**

- :Room temperature;
- :Reaction under stirring;
- :In a flask with a magnetic stirrer;
- :In the presence of a solvent (methanol);

**(C) Chemicals**

- :Methanol: acts as a solvent;
- :Sodium borohydride: acts as a reducing agent;
- :Chloroform: used for the extraction process;
- :Ethanol: used for recrystallization;

**(C) Workup1**

- :Evaporation of the reaction medium on a water bath under vacuum;

**(C) Workup2**

- :Residue taken up with water;
- :Extracted several times with chloroform;

**(C) Workup3**

- :Filtration of the extracts;

**(C) Workup4**

- :Evaporation to dryness on a water bath under vacuum;

**(C) Workup5**

- :Recrystallization in ethanol;

**(C) Step 1: Preparing 4-phenyl-1(2H)-pyridinyl** **2**

- :Put 1g of Phenylboronic acid into a round-bottom flask;
- :Introduce 1.5g of Cs<sub>2</sub>CO<sub>3</sub> to act as a base;
- :Add 10ml of 1,2-Dibromobenzene to the mixture;
- :Pour in 100ml of Ethanol as the solvent;
- :Heat the mixture to reflux at 80°C for 24 hours;
- :After 24 hours, cool the mixture to room temperature;
- :Filter the solid and wash it with cold ethanol;
- :Obtain the product after drying under vacuum at 40°C for 5 hours;
- :Add 1g of Pd(PPh<sub>3</sub>)<sub>4</sub> to the flask as a catalyst;

**(C) Step 2: Preparing 1-butynyl bromide**

- :Put 10ml of 1-Butyne in a flask;
- :Add 20ml of Hydrobromic Acid in the flask;
- :Stir the mixture at 500 rpm at room temperature for 3 hours;
- :Separate the aqueous layer to obtain 1-butynyl bromide;

**(C) Step 3: Coupling 4-phenyl-1(2H)-pyridinyl with 1-butynyl bromide**

- :Introduce 1.5g of Cs<sub>2</sub>CO<sub>3</sub> as a base;
- :Add 100ml of DMF as the solvent;
- :Stir the mixture at 500 rpm at 80°C for 24 hours;
- :Cool down the mixture and filter out the solid;
- :Recrystallize the solid in ethanol to get the product;
- :Add 1g of 4-phenyl-1(2H)-pyridinyl and 1g of 1-Butynyl bromide in a flask;
- :Add 1g of Pd(PPh<sub>3</sub>)<sub>4</sub> as a catalyst;

**(C) Step 4: Making 3-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]quinoline**

- :Add 1g of the synthesized compound and 10ml of quinoline in a flask;
- :Put in 10ml of concentrated sulfuric acid as a catalyst;
- :Heat the mixture to reflux at 100°C for 24 hours;
- :Cool down the mixture and neutralize the acid with a base;
- :Obtain the final product 3-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]quinoline;

**(C) Workup** **4**

- :Separate the two layers by decantation;
- :Dry the aqueous layer over anhydrous magnesium sulfate;
- :Filter off the drying agent;
- :Evaporate the filtrate;
- :Obtain 0.3 g of crude product as an oil;
- :Take up in ether (about 5 ml) or dissolve in methylene chloride or chloroform for subsequent use without isolation;

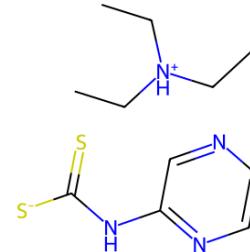
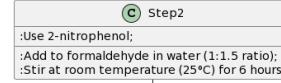
**(C) Conditions**

- :Heat at reflux for ten hours;
- :Nitrogen gas is evolved during the reaction;
- :Add silver(I) oxide (4.7 g, about 34 mmol) in water with stirring at room temperature;
- :Add quinoline-3-carbonitrile (5g, about 38 mmol), phenylacetylene (2 g, about 20 mmol), potassium carbonate (4 g), and tetrabutylammonium bromide (0.8 g);

**(C) AdditionalNotes**

- :Quinoline-3-carbonitrile can be obtained from quinoline according to known methods;
- :Chlorobenzene can be used instead of phenylacetylene;
- :The temperature may range from slightly below room temperature up to mild reflux conditions;
- :The reaction medium may contain organic solvents such as tetrahydrofuran, dioxane, etc.;

Ground Truth	
:In a 100-ml flask;	
:50 ml of ethyl acetate;	
:Added dropwise with stirring over a 5-min period on a water bath;	
:Stirred at 60°C for 5 hr;	
:10 ml of hexane added;	
:Allowed to stand overnight at room temperature to precipitate yellow crystals;	
:Crystals separated from the solution by filtration;	
:Washed with 5 ml of ethyl acetate;	
:Yield 31%;	
:4.9 g (50 mmol) of 3-aminopyrazine;	
:4.5 g (59 mmol) of carbon disulfide;	
:6.5 g (64 mmol) of triethylamine;	
:Obtained 4.3 g of triethylammonium N-(2-pyrazinyl)-dithiocarbamate (Intermediate II-1);	
:Mp 113–116°C (dec);	



triethylammonium N-(2-pyrazinyl)-dithiocarbamate

#### Step 1

4

- :Allow the mixture to warm up to room temperature and stand overnight;
- :Dissolve pyrazine-2-carbonyl chloride ( $C_5H_3ClN_2O$ ) in dry tetrahydrofuran (THF) under nitrogen;
- :Add diethylamine ( $C_4H_11N$ ) dropwise at 0°C with stirring;

#### Step 2

- :Add triethylamine ( $(C_2H_5)_3N$ ) to the solution;
- :Collect precipitated N-(2-pyrazinyl)-dithiocarbamate by filtration;

#### Step 3

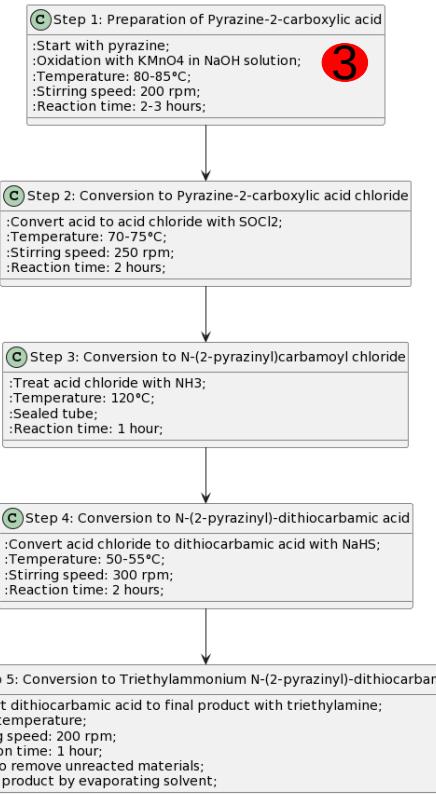
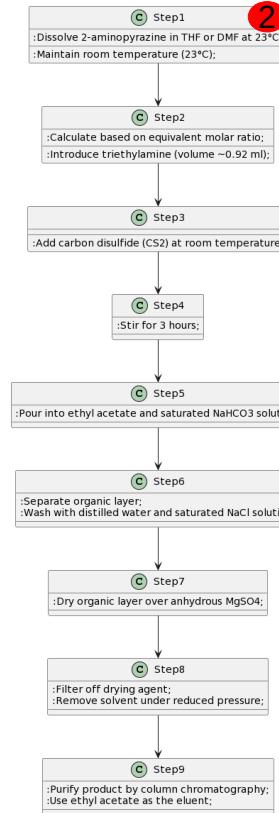
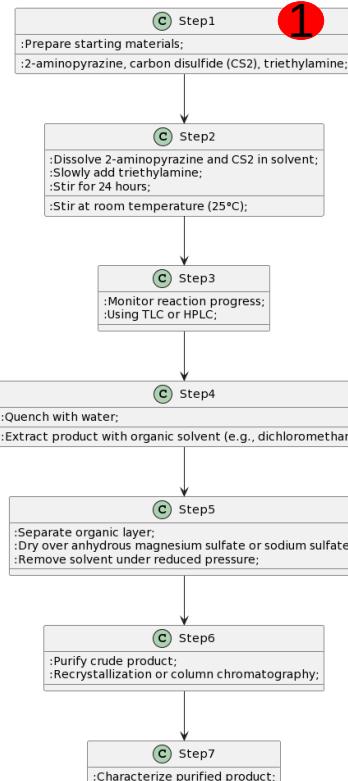
- :Evaporate filtrate under reduced pressure at 40°C to remove tetrahydrofuran;
- :Dissolve residue in water and acidify with concentrated hydrochloric acid;
- :Extract aqueous acidic solution three times with chloroform, methylene chloride, or ethyl acetate;

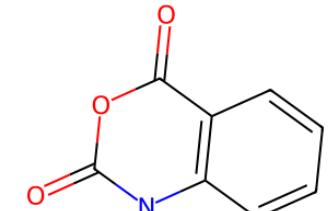
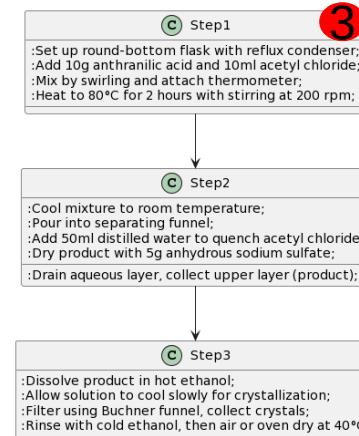
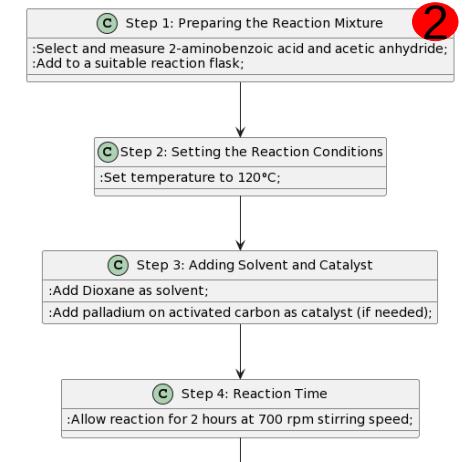
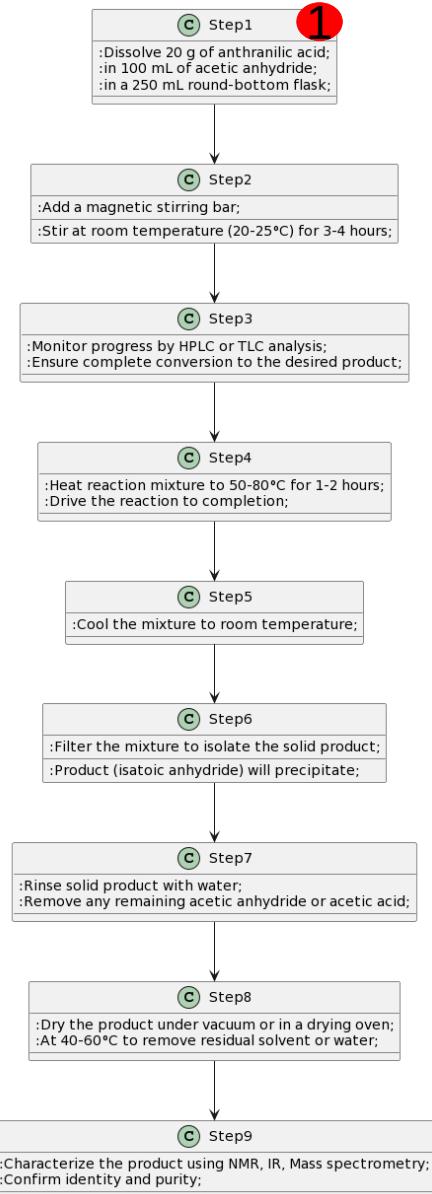
#### Step 4

- :Dry organic layer over magnesium sulfate or sodium sulfate;
- :Filter and evaporate under reduced pressure;

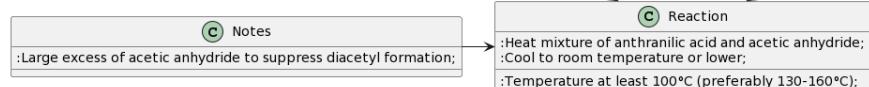
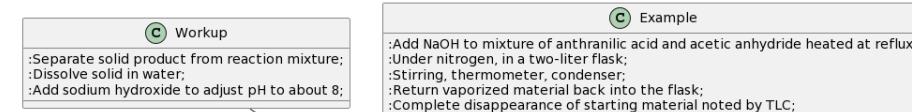
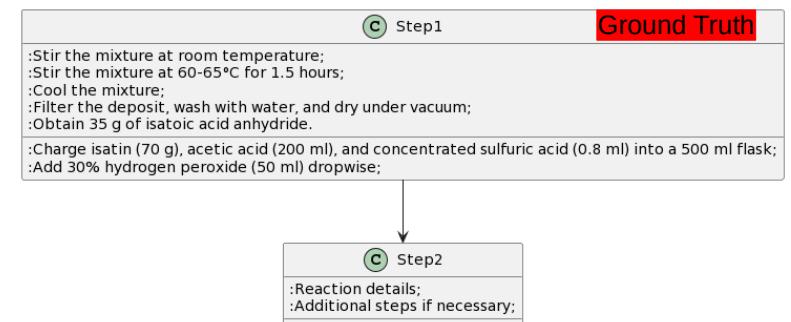
#### Step 5

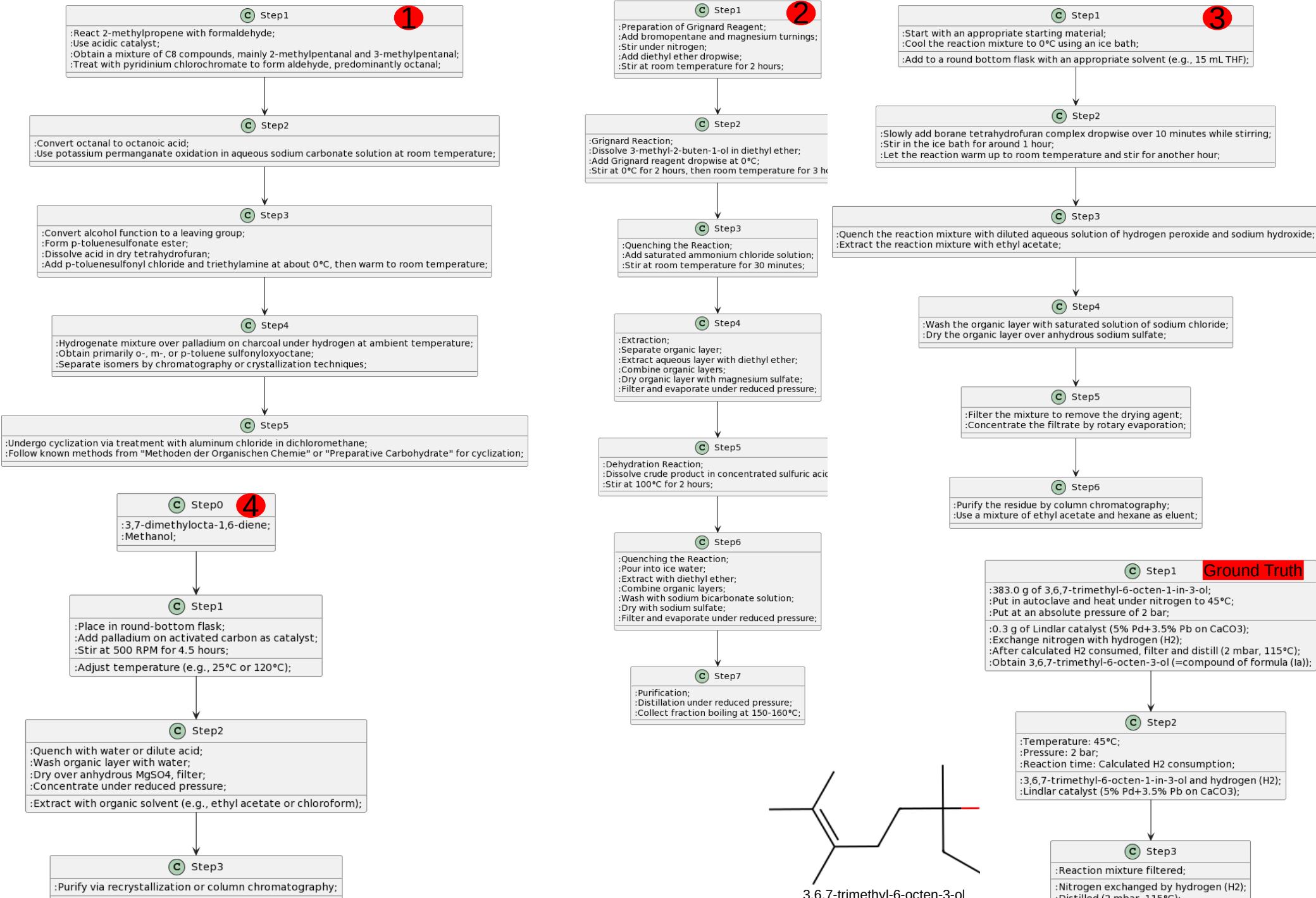
- :Recrystallize resulting solid from ethanol-water mixture as hydrochloride salt (Option 6a);
- :Treat with base (e.g., sodium bicarbonate) followed by careful evaporation for residual solvent (Option 6b);

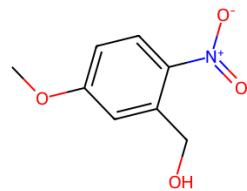




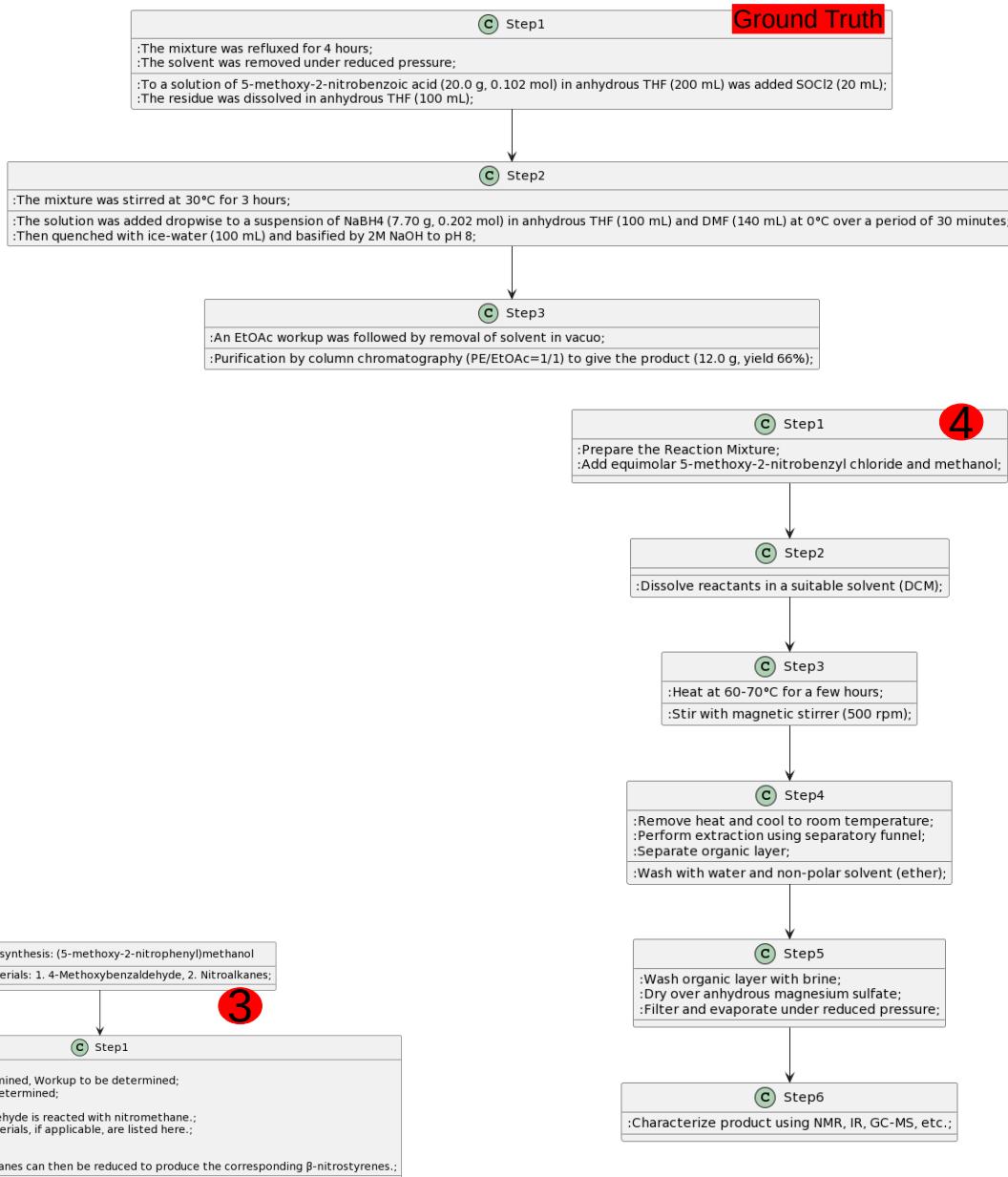
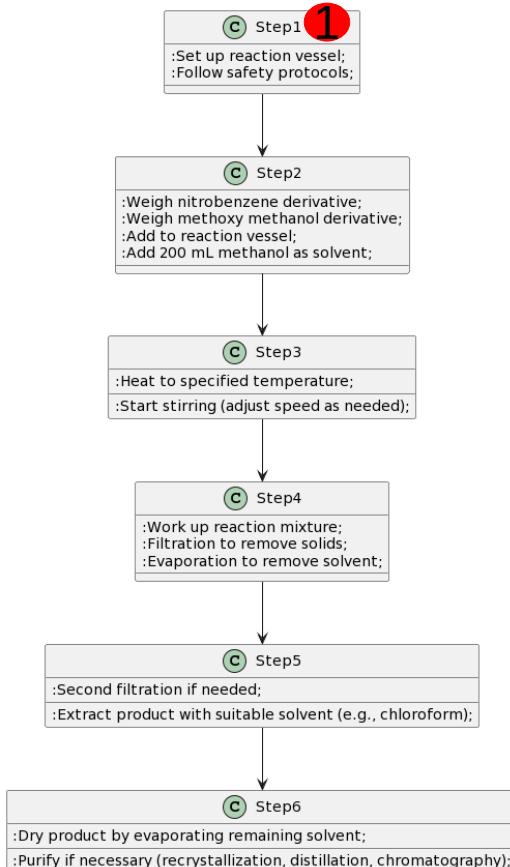
isatoic acid anhydride



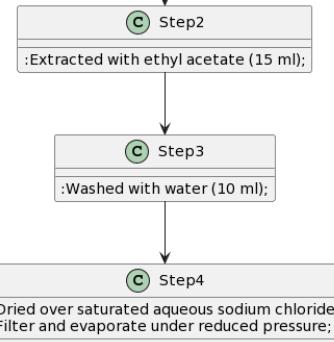
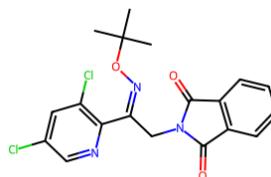
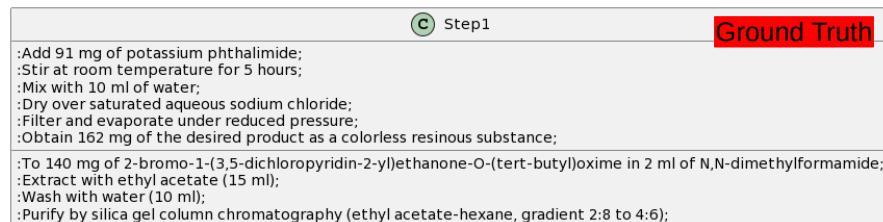




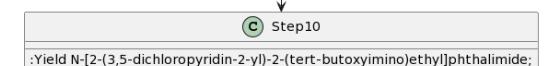
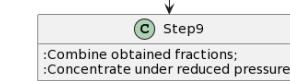
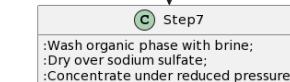
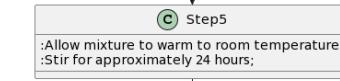
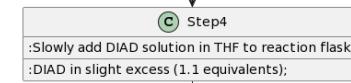
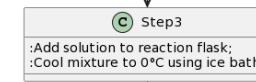
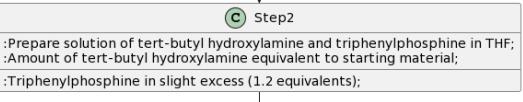
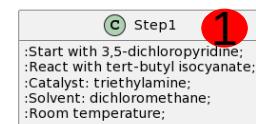
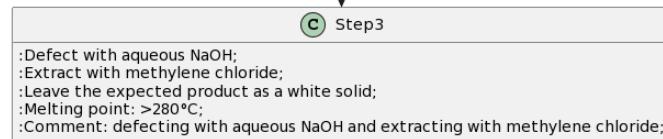
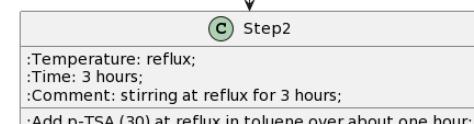
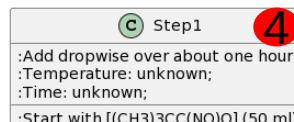
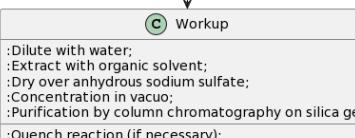
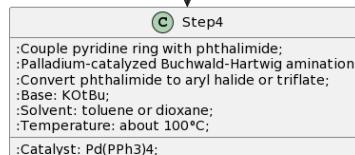
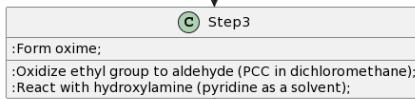
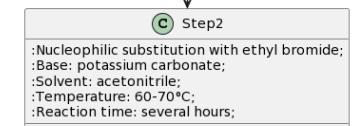
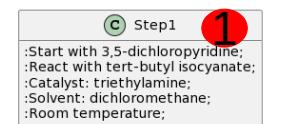
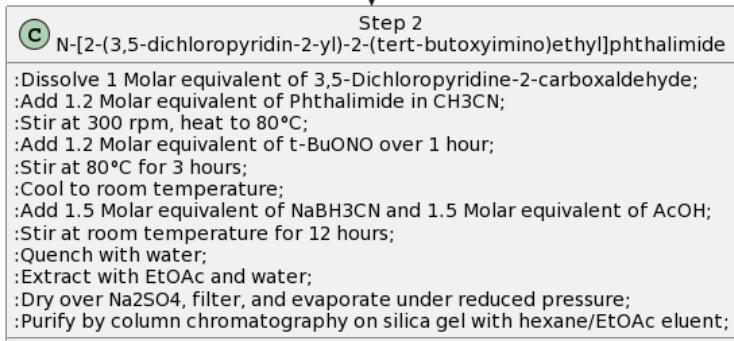
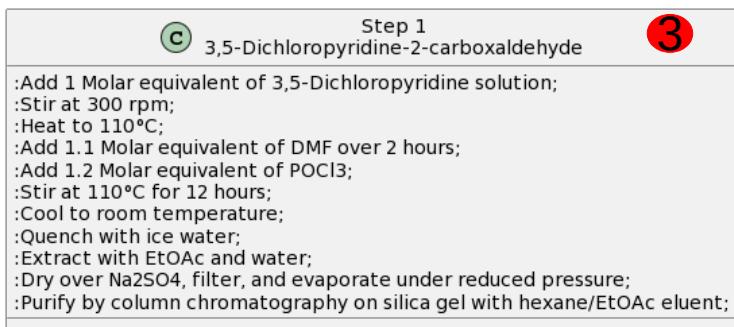
(5-methoxy-2-nitrophenyl)methanol

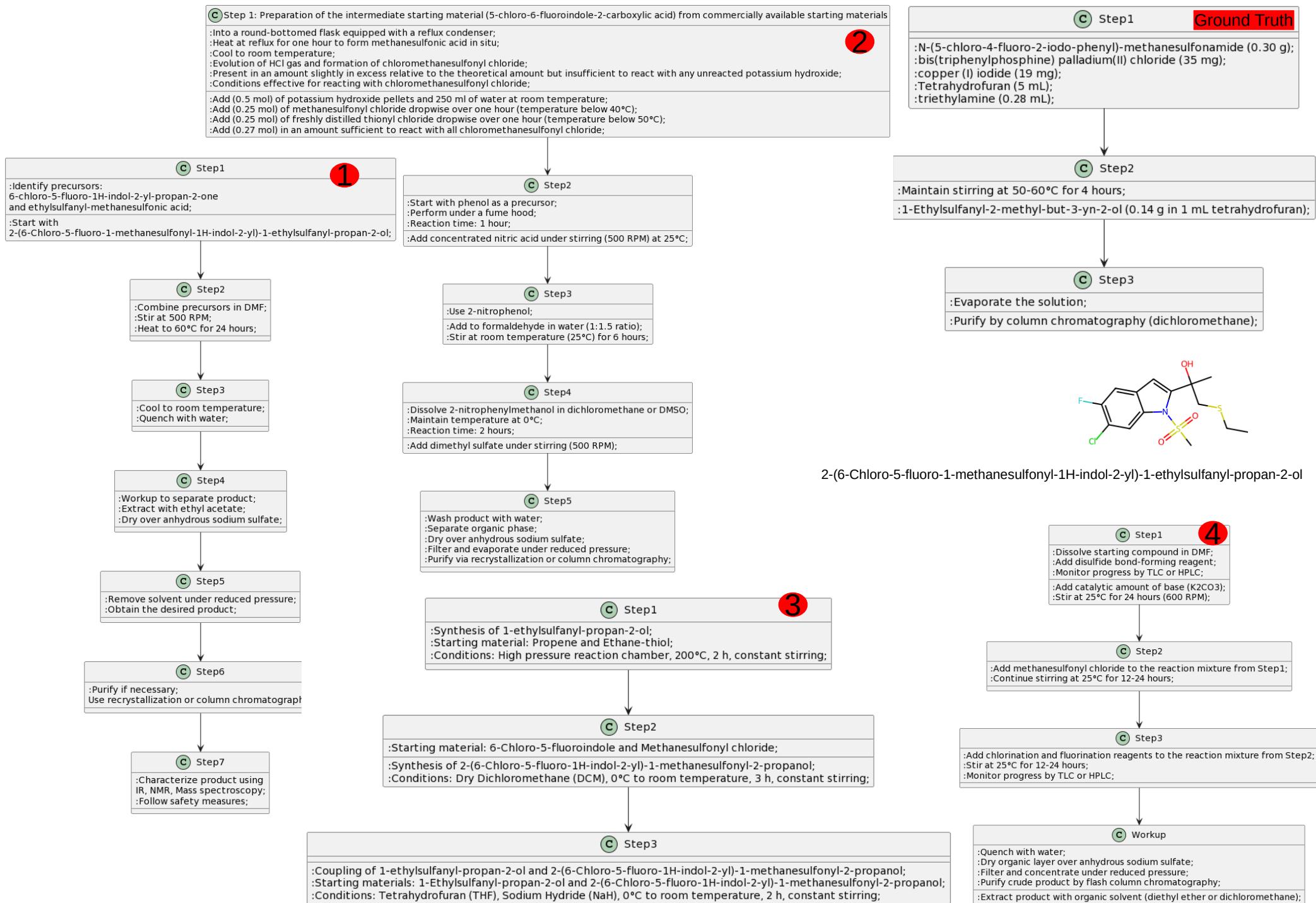


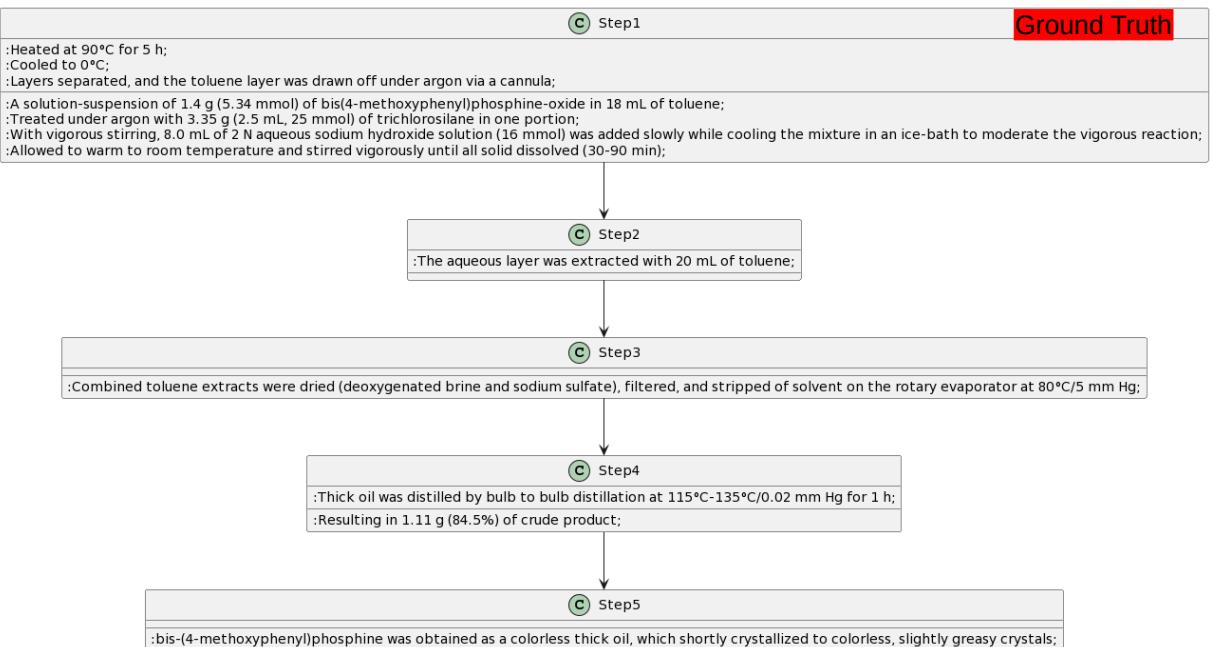
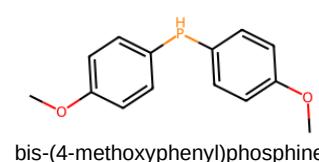
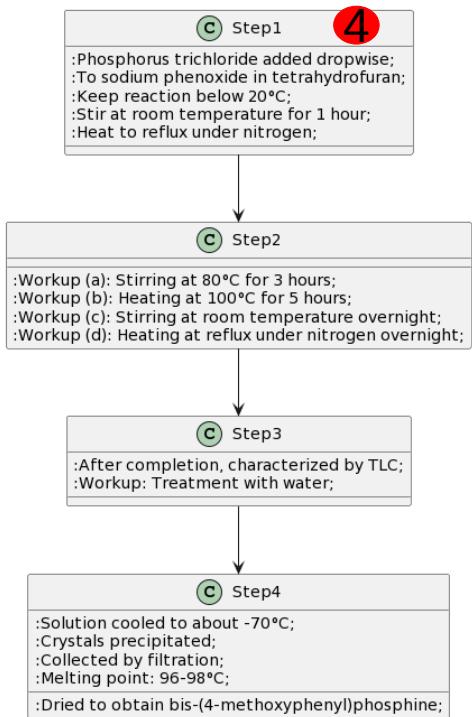
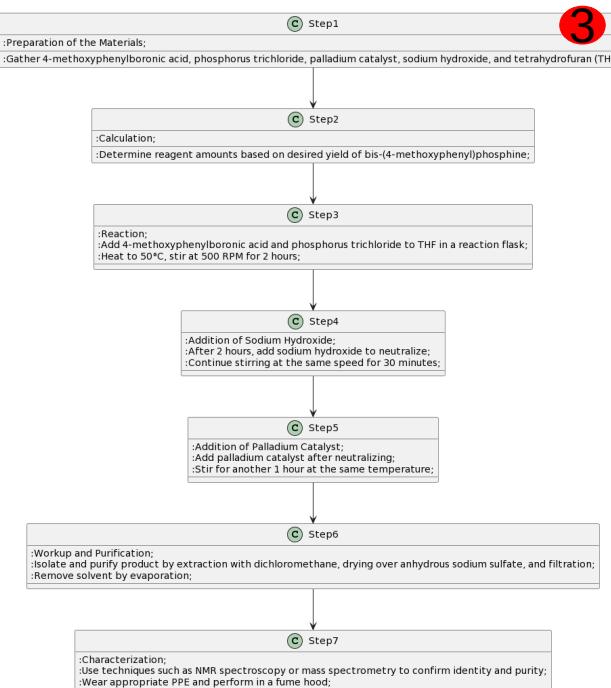
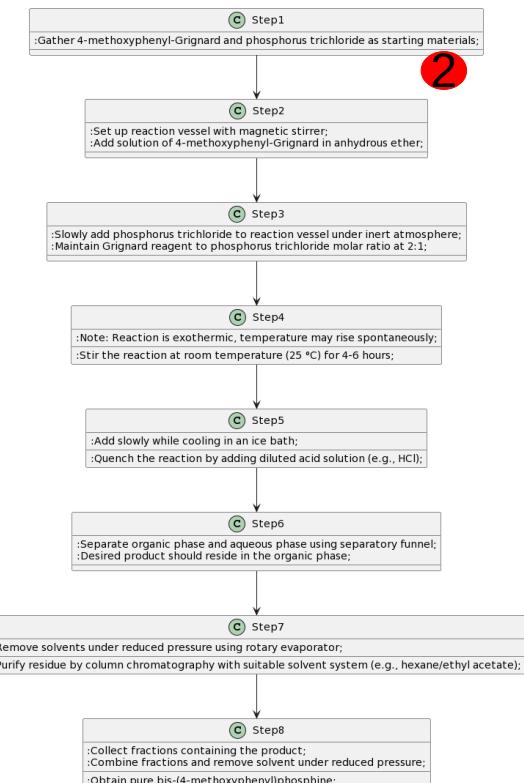
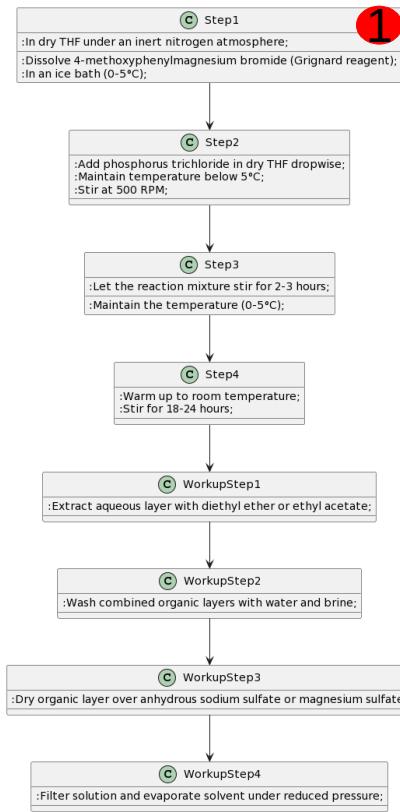
Conditions: Conditions to be determined;  
Temperature: Temperature to be determined;  
Notes: The reaction flask was heated on an oil bath for two hours at reflux using a condenser over the end of which was attached an adapter through which nitrogen gas could flow into the flask and into solution in order that there would not develop any explosive hydrogen gas upon contact between LiAlH<sub>4</sub> and water present in starting material or resulting product.;  
Notes: The solid remaining after filtration was washed three times by adding hexane or petroleum ether followed by swirling and decanting liquid from it. The filtrate was evaporated using rotary evaporation at reduced pressure whereby about one-fourth volume of methanol present therein distilled off first as expected but no additional pure product was obtained.;  
Inputs: reduction of β-nitrostyrenes with lithium aluminum hydride (LiAlH<sub>4</sub>);  
Notes: (LiAlH<sub>4</sub>) is a known reducing agent.;  
{N+}(=O)[O-].CO.C1=CC(=C=C1=

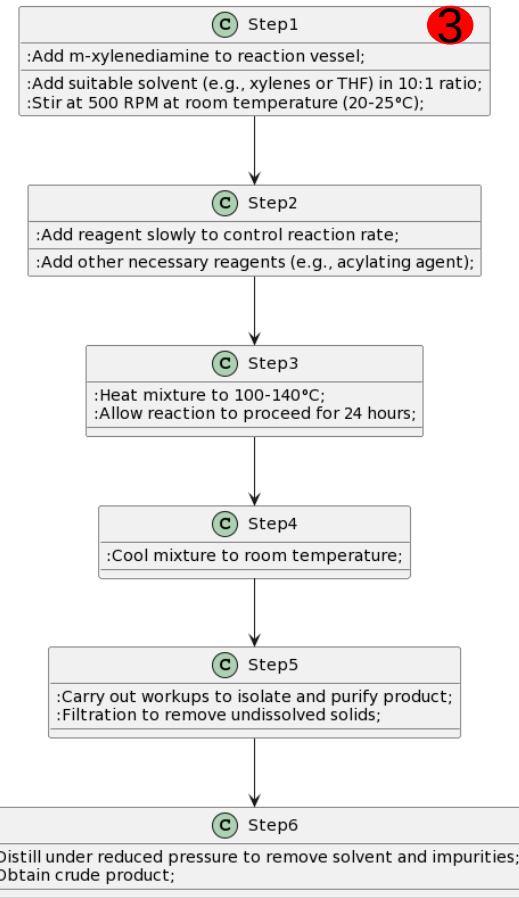
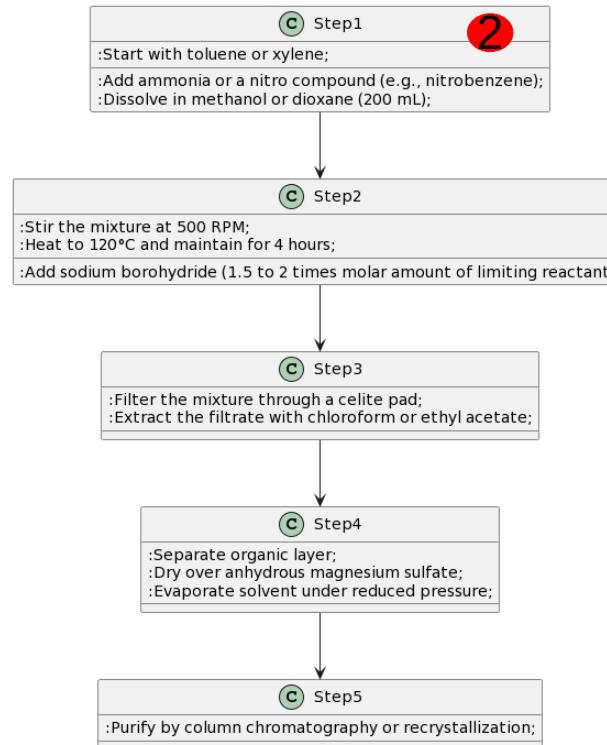
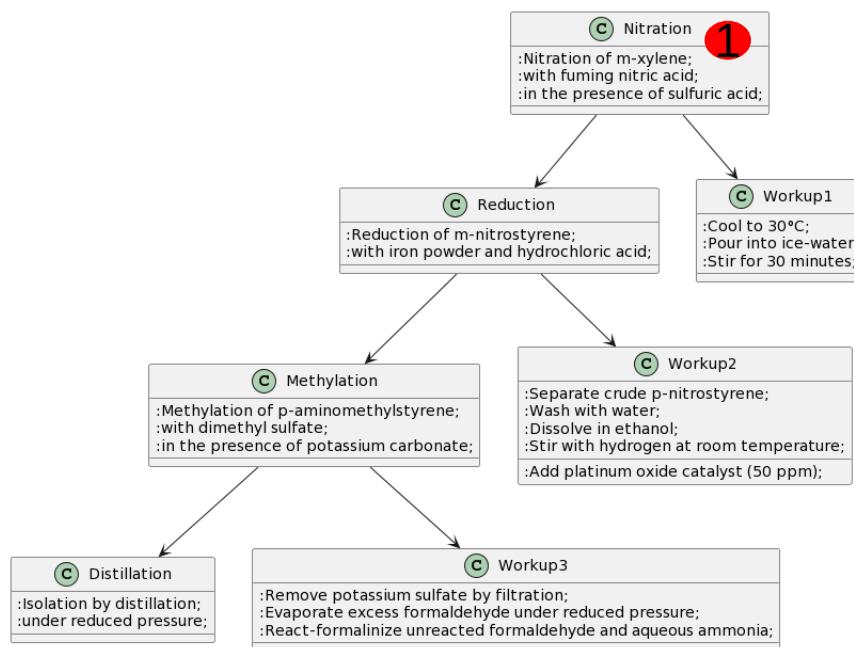


### N-[2-(3,5-dichloropyridin-2-yl)-2-(tert-butoxyimino)ethyl]phthalimide









**Ground Truth**

:Charge 0.76 g of dicobalt octacarbonyl, 1 g of isophthalonitrile, and 20 ml of m-xylene into a 100 ml eggplant-type flask;  
:Thoroughly replace air by introducing carbon monoxide through the gas inlet tube;  
:Heat in an oil bath at 160°C for 90 minutes under reflux with carbon monoxide passing through;  
:Cool to room temperature;  
:Transfer resulting precipitate into a 100 ml shaking-type autoclave with m-xylene;  
:Add 9 g of isophthalonitrile and 10 ml of m-xylene;  
:Replace gas with hydrogen;  
:Add 10 ml of liquid ammonia;  
:Hydrogenate isophthalonitrile at 100°C under an initially charged hydrogen pressure of 260 kg/cm<sup>2</sup> gage;  
:Complete reaction in 120 minutes, yielding m-xylenediamine (96.4%);

**C Step2**

:Wash product with water;  
:Separate organic phase;  
:Dry over anhydrous sodium sulfate;  
:Filter and evaporate under reduced pressure;  
:Purify via recrystallization or column chromatography;

**C Step 1: Preparation of m-dinitrobenzene** **4**

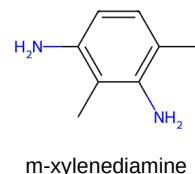
:1. Add 50 g of m-nitrochlorobenzene to a 500 mL round bottom flask;  
:4. Slowly add NaNO<sub>2</sub> solution to the flask, keep temperature < 20°C;  
:5. Stir the mixture for 2 hours at 20°C;  
:6. Allow the mixture to settle, the precipitate is m-dinitrobenzene.

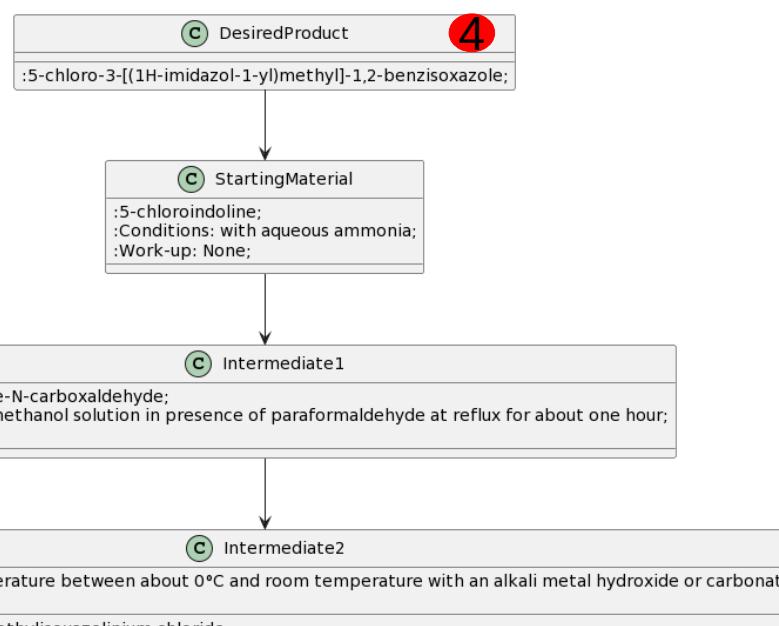
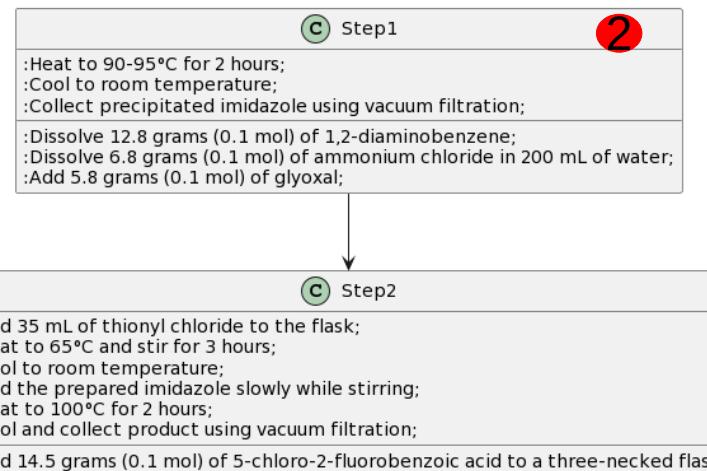
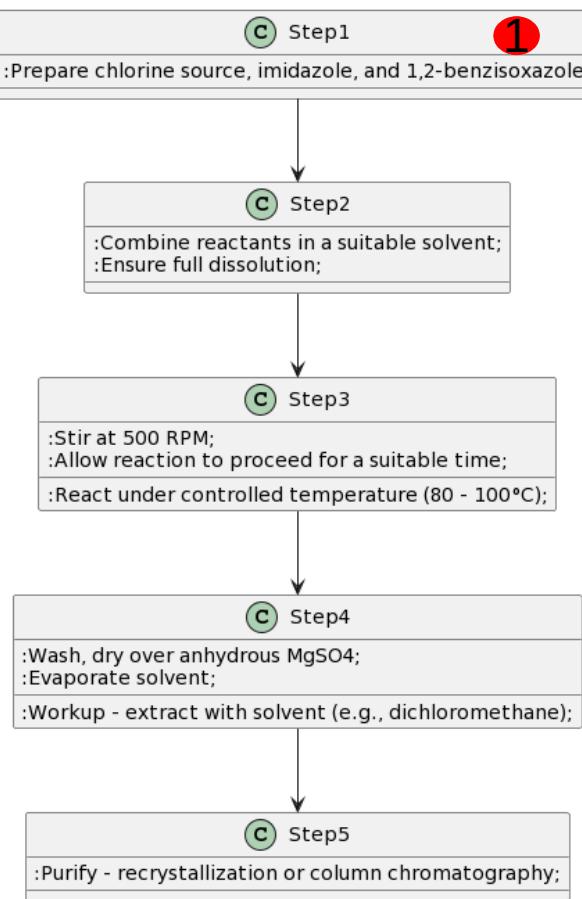
:2. Dissolve in 200 mL of 50% Hydrochloric acid (HCl) with stirring (200 rpm);  
:3. Dissolve 80 g of Sodium nitrite (NaNO<sub>2</sub>) in 200 mL of water;

**C Step 2: Reduction of m-dinitrobenzene to m-xylenediamine**

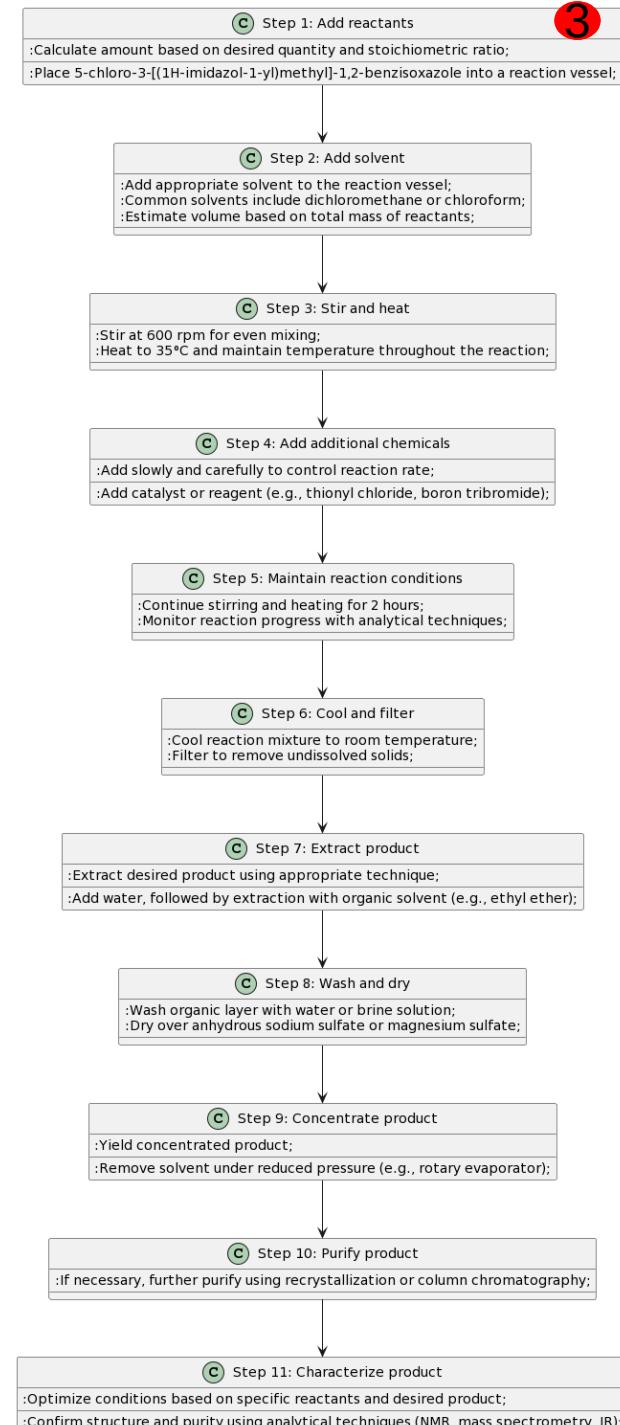
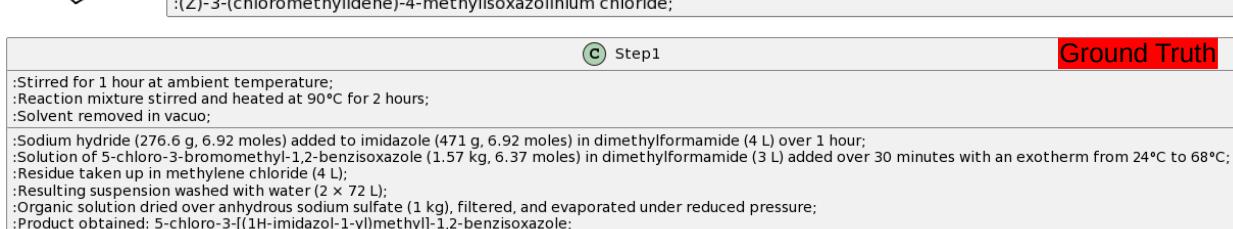
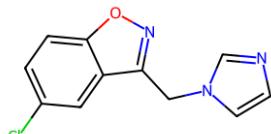
:1. In a 500 mL round bottom flask, add 50 g of m-dinitrobenzene from Step 1;  
:3. Add 10 g of Raney Nickel to the flask;  
:5. Stir at 500 rpm at 80°C for 4 hours;  
:6. Release pressure, carefully filter the mixture to remove Raney Nickel;  
:7. The filtrate contains m-xylenediamine, evaporate EtOH under reduced pressure.  
:Note: Perform in a closed system, under a hydrogen atmosphere, away from flames. Wear PPE, work in a well-ventilated area.

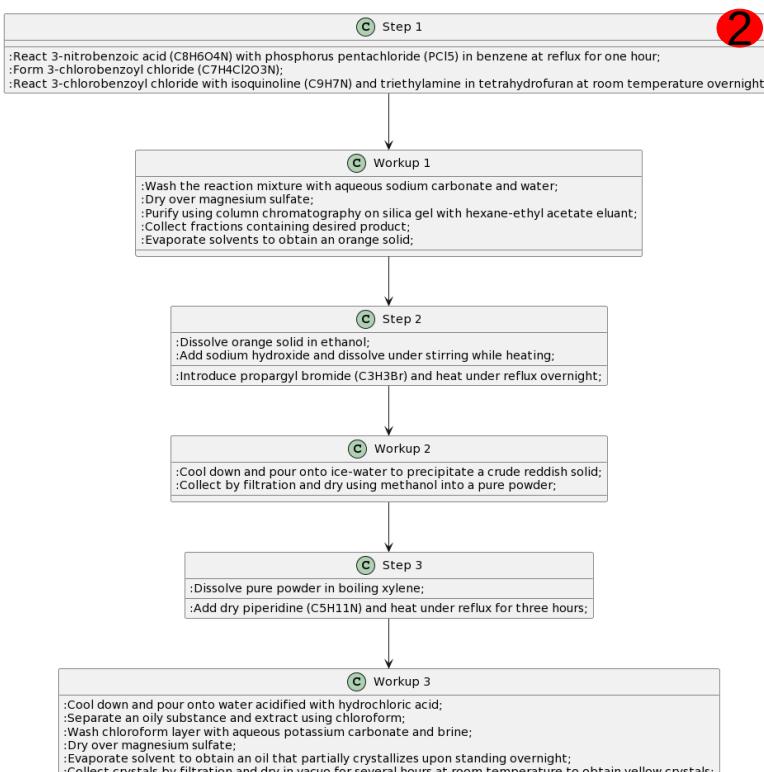
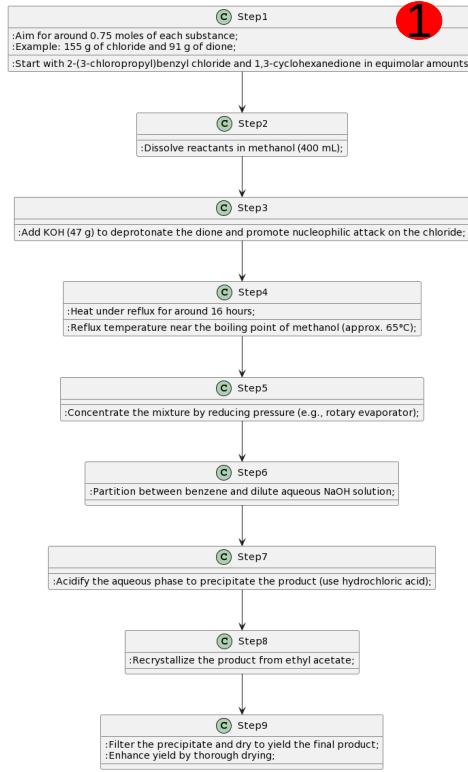
:2. Dissolve in 200 mL of absolute ethanol (EtOH);  
:4. Seal the flask, apply a hydrogen (H<sub>2</sub>) atmosphere at 5 atm pressure;





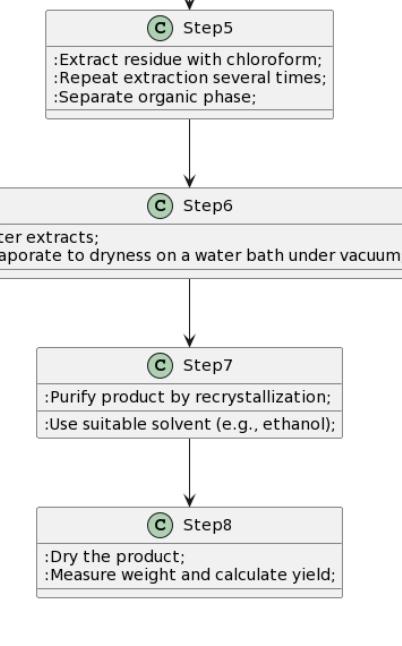
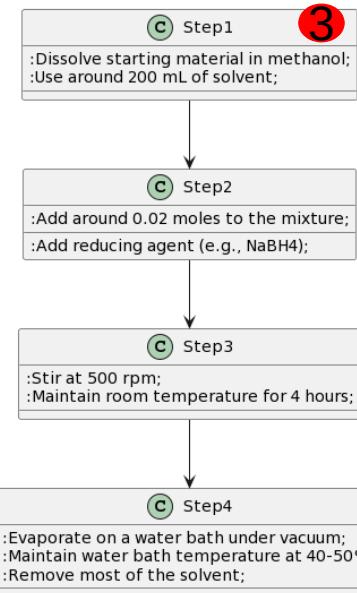
5-chloro-3-[(1H-imidazol-1-yl)methyl]-1,2-benzisoxazole



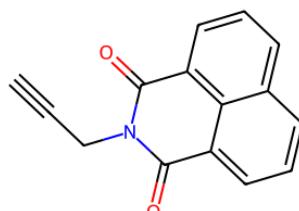


**Additional Information**  
:NMR;  
:DOSAGE;  
:TEMPERATURE;  
:STIRRING;

**Reaction Conditions**  
:React under reflux for one hour in benzene at 90°C;  
:Add isoquinoline dropwise over thirty minutes at about -20°C;  
:Stir for twelve to twenty-four hours at ambient temperature or slightly raised;  
:Add triethylamine;

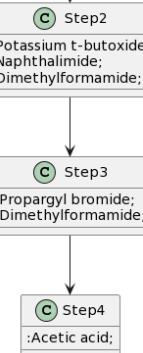


**Step 1**  
:Stir in the cold for 1 hour;  
:Allow the mixture to warm to room temperature;  
:Heat to 45°C for 45 minutes;  
:After cooling, add 15 mL of glacial acetic acid;  
:Product precipitated by addition of water;  
:Collect solids and recrystallize from ethyl acetate;  
  
:Potassium t-butoxide, 6.2 g (0.055 mol);  
:Add to a solution of 9.9 g (0.05 mol) of naphthalimide in 50 mL of dimethylformamide cooled to -20°C;  
:Add 5 mL (0.055 mol) of propargyl bromide in 20 mL of dimethylformamide;  
:Leave 10 g (84%) of colorless crystals of 2-(2-propynyl)-1H-benz[de]isoquinoline-1,3(2H)-dione with m.p. 235-237°C;



2-(2-propynyl)-1H-benz[de]isoquinoline-1,3(2H)-dione

### Ground Truth



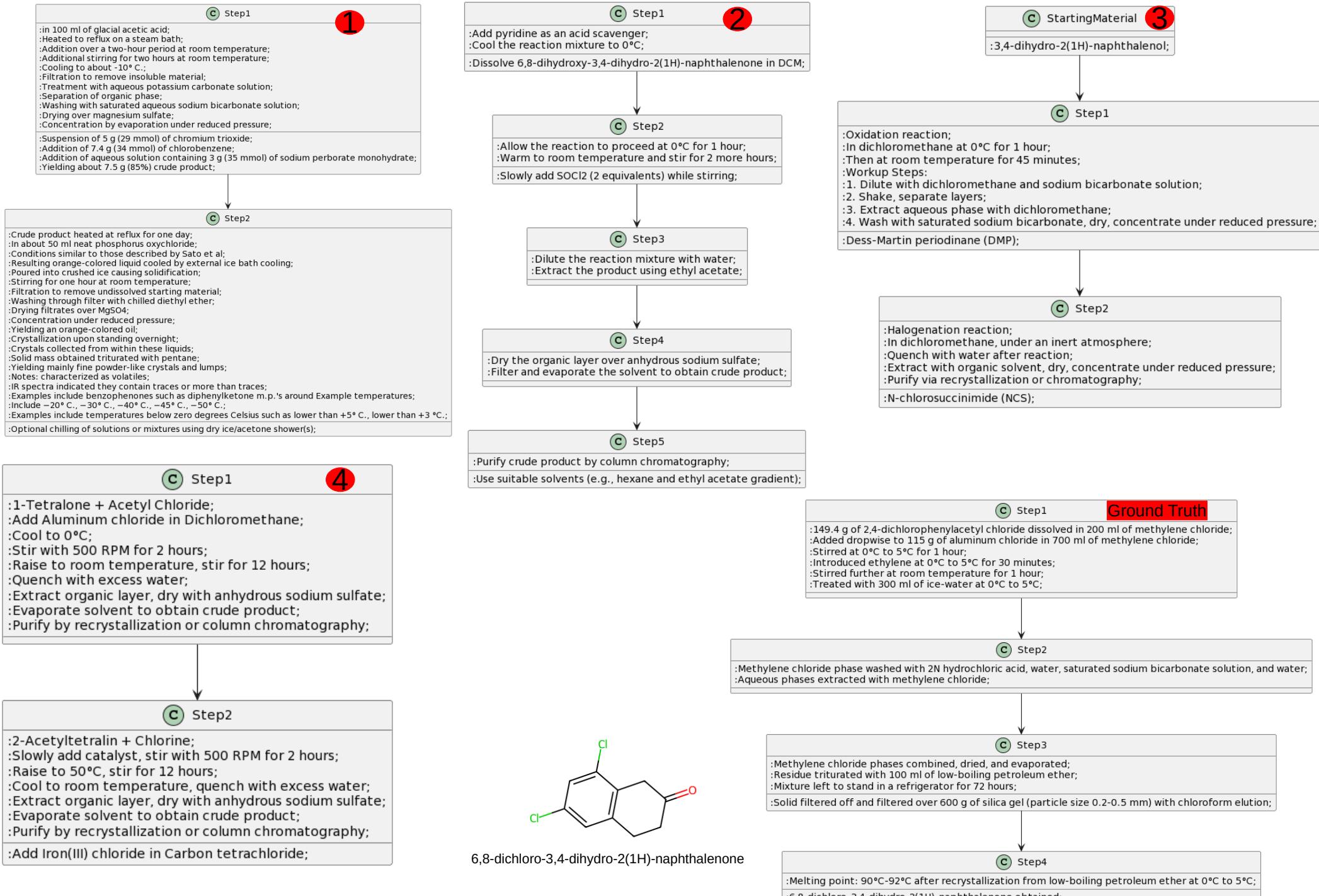
**Step 1: Preparation of 1H-benz[de]isoquinoline-1,3(2H)-dione**

1. Dissolve 1,2-dimethoxybenzene in dry DCM;
3. Reflux at 80°C for 2 hours;
4. Cool to room temperature and add 4-aminobenzoic acid;
5. Stir at room temperature for 30 minutes;
6. Quench with water and transfer to a separatory funnel;
7. Extract organic layer, wash with water and brine;
8. Dry over anhydrous sodium sulfate, filter, and evaporate.
2. Add  $P_2O_5$  slowly under stirring (20-25°C);

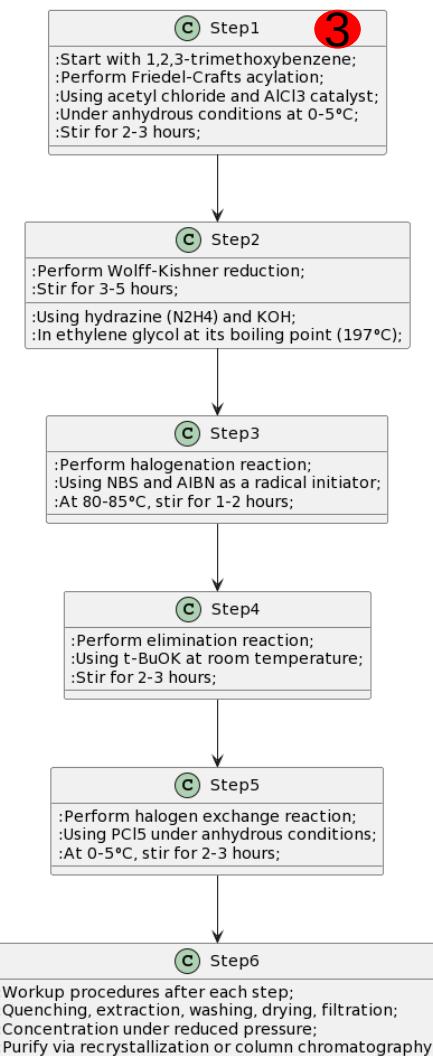
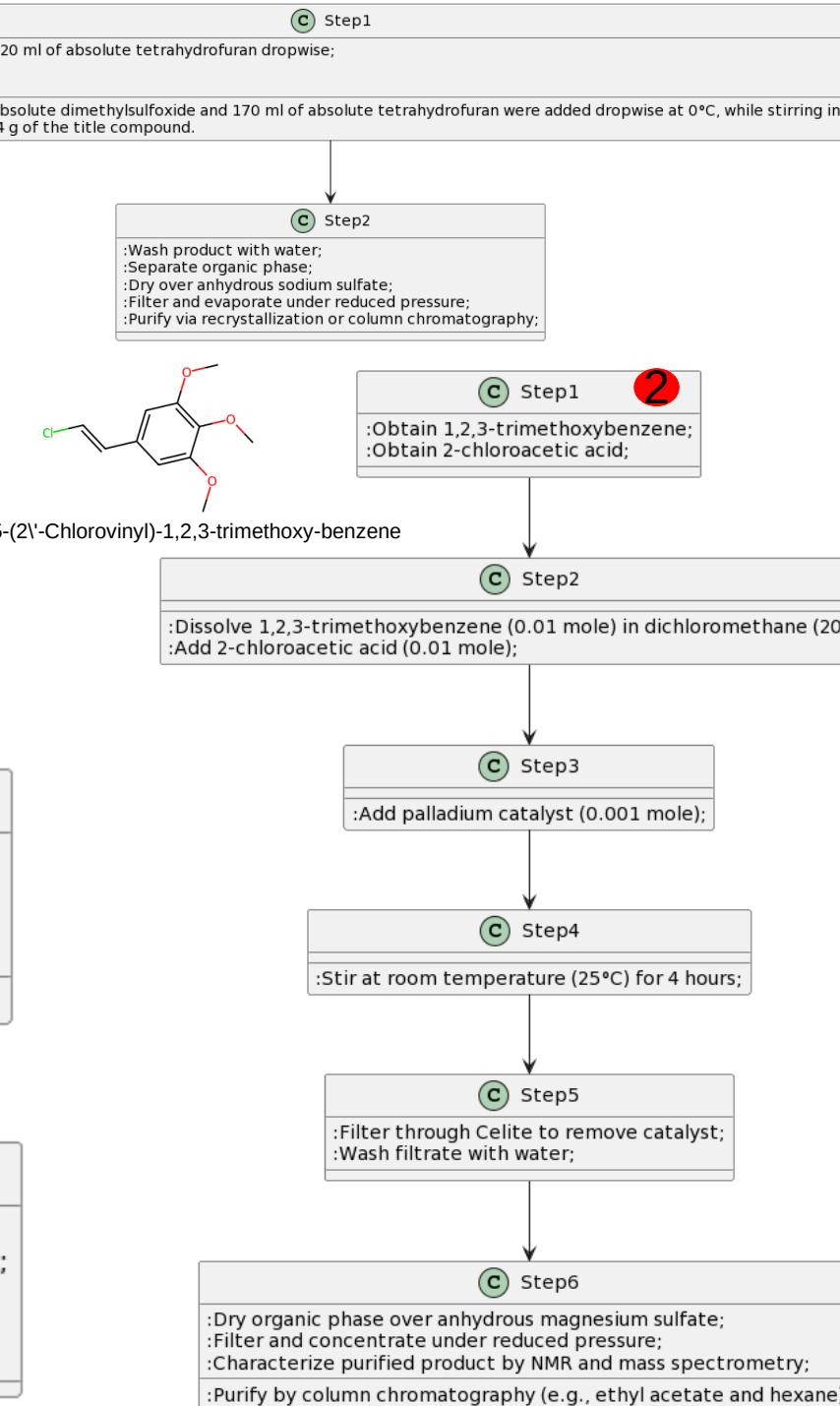
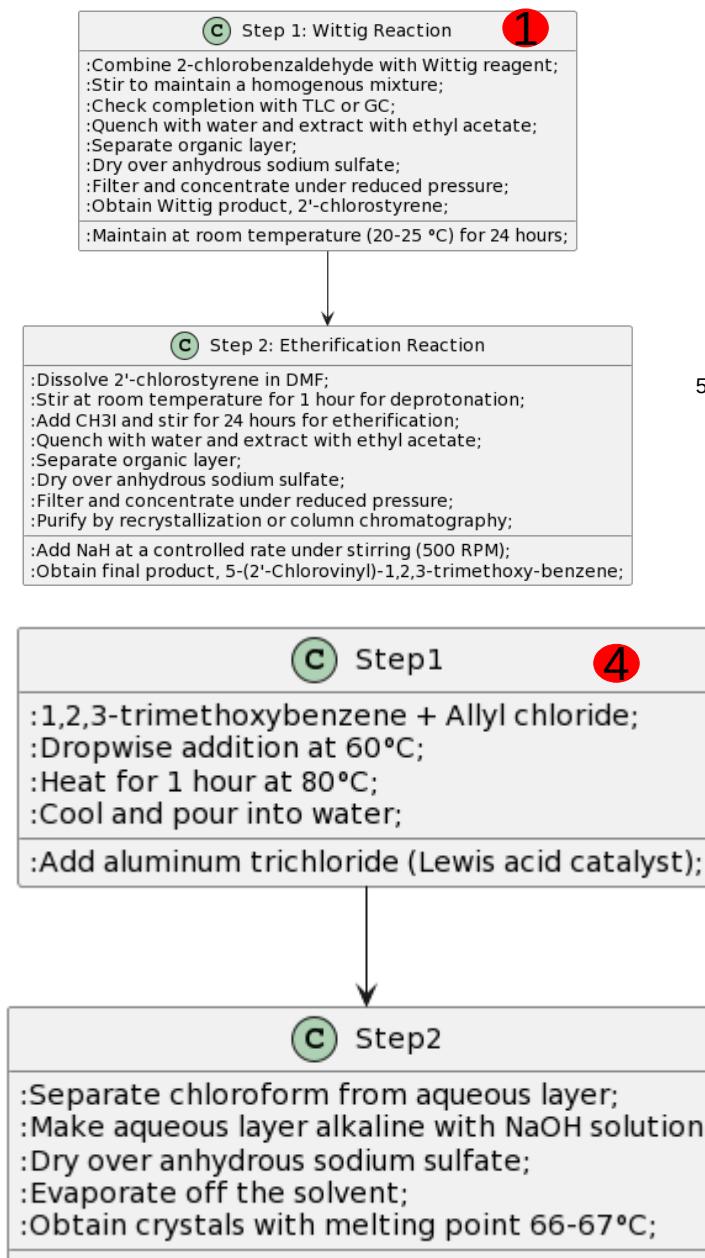
**Step 2: Preparation of 2-(2-propynyl)-1H-benz[de]isoquinoline-1,3(2H)-dione**

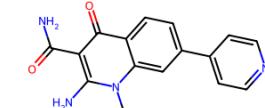
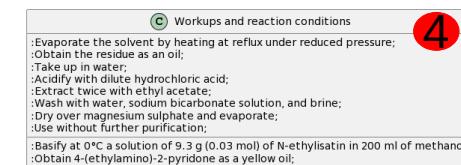
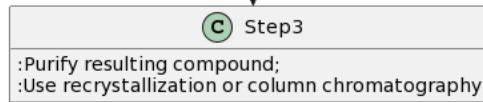
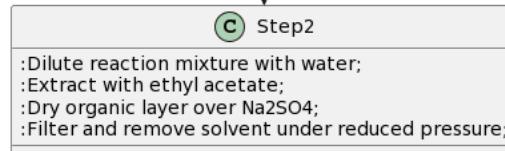
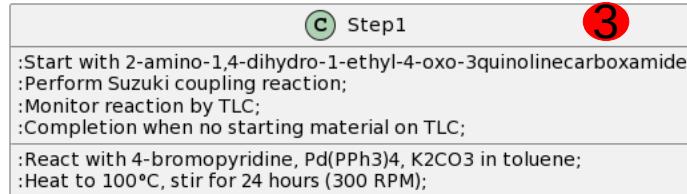
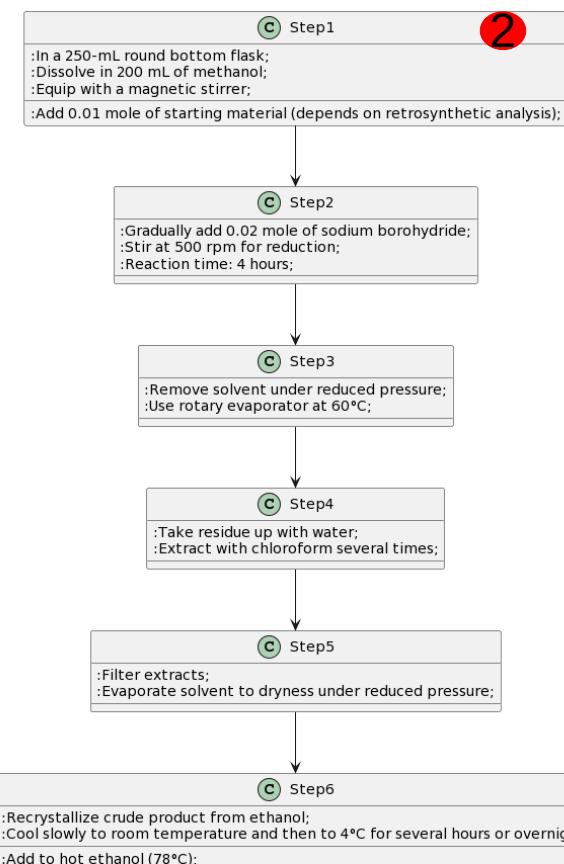
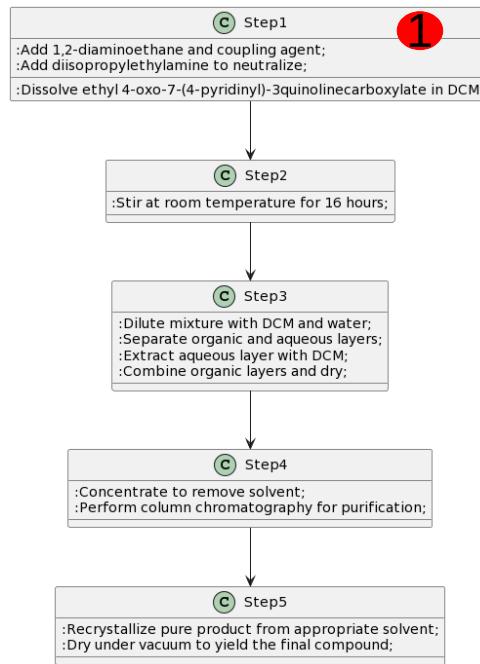
2. Add  $K_2CO_3$ , stir at room temperature for 30 minutes;
3. Cool in an ice bath and add propargyl bromide slowly;
4. Stir at room temperature for 6 hours;
5. Quench with water, extract organic layer;
6. Wash organic layer with water, then with brine;
7. Dry over anhydrous sodium sulfate, filter, and evaporate.
1. Dissolve 1H-benz[de]isoquinoline-1,3(2H)-dione in DMF;

4



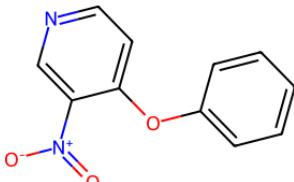
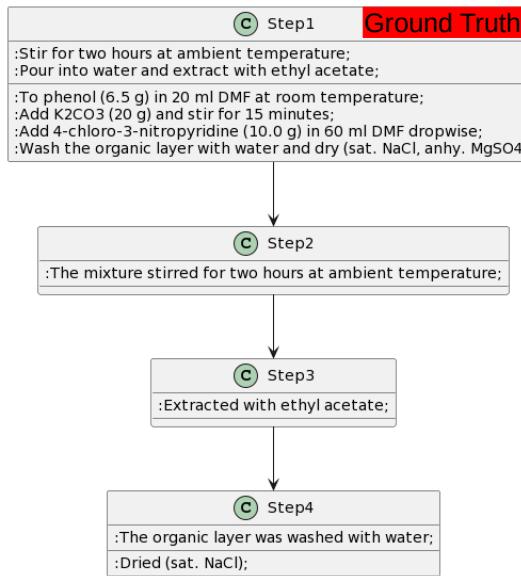
:After stirring for 30 minutes, add a solution of 5.48 g of 3,4,5-trimethoxybenzaldehyde in 20 ml of absolute tetrahydrofuran dropwise;  
 :Stir the mixture for 30 minutes at 0°C and then allow it to warm to room temperature;  
 :After about 4 hours, work up the reaction mixture as described in Example 5e;  
 :To a suspension of 11.94 g of (chloromethyl)-triphenylphosphonium chloride in 85 ml of absolute dimethylsulfoxide and 170 ml of absolute tetrahydrofuran were added dropwise at 0°C, while stirring in an atmosphere of dry nitrogen, 21.5 ml of n-butyllithium solution;  
 :Column chromatography of the raw product with petroleum ether/ether (2:1) yielded 4.64 g of the title compound.



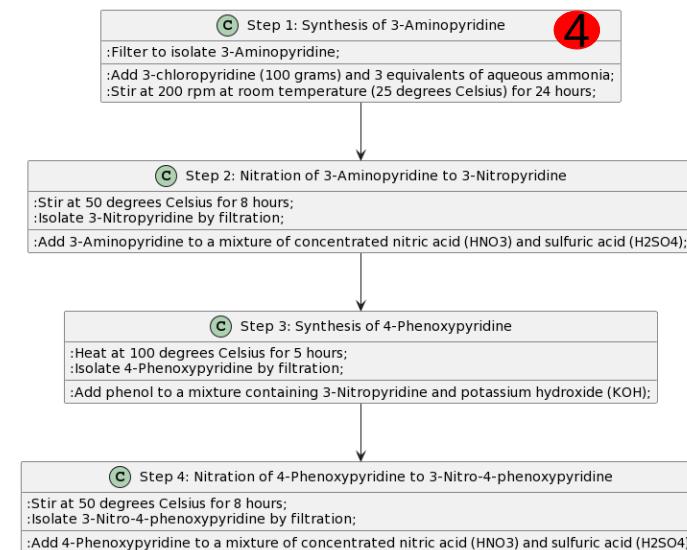
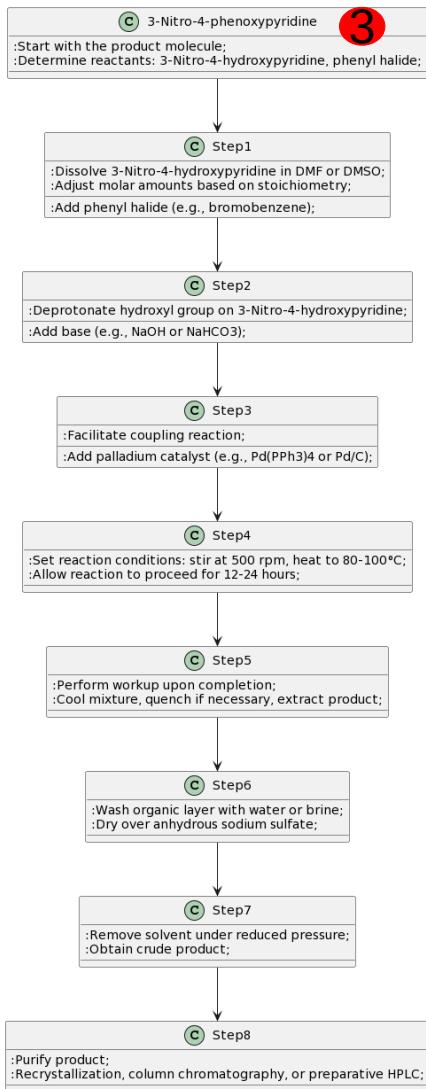
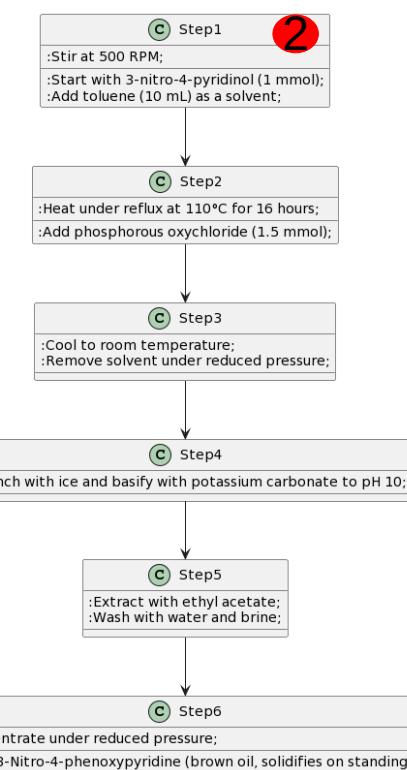
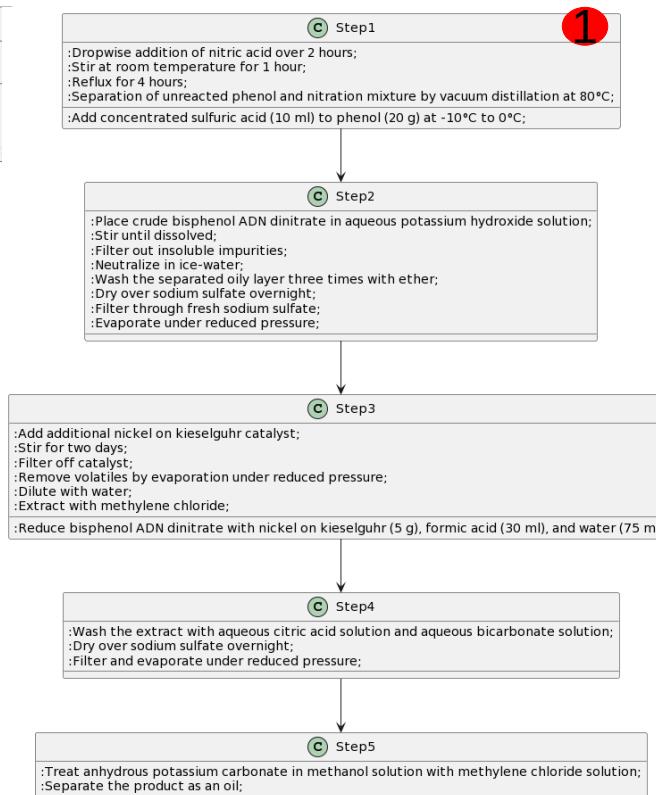


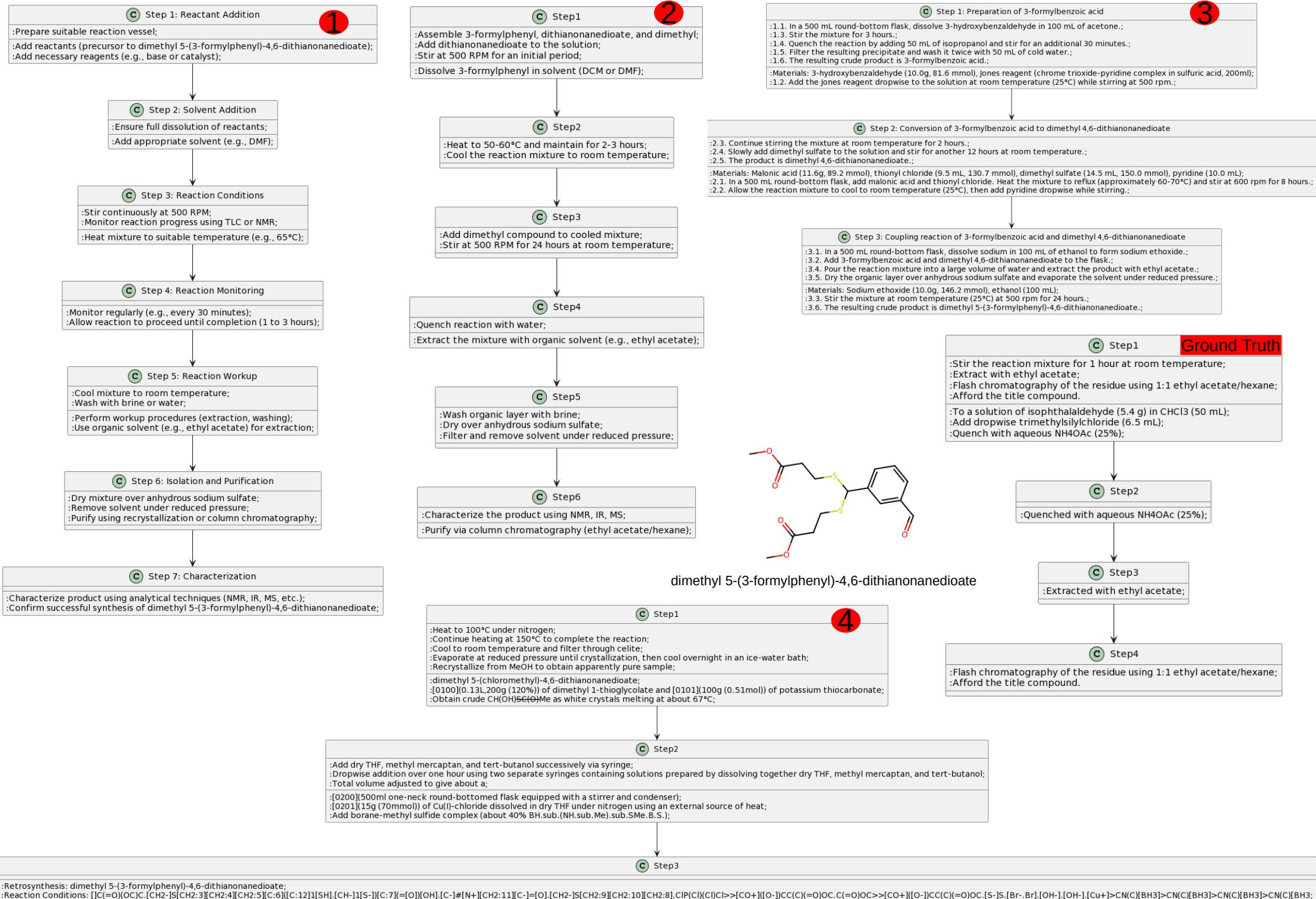
2-amino-1,4-dihydro-1-ethyl-4-oxo-7-(4-pyridinyl)-3quinolinicarboxamide

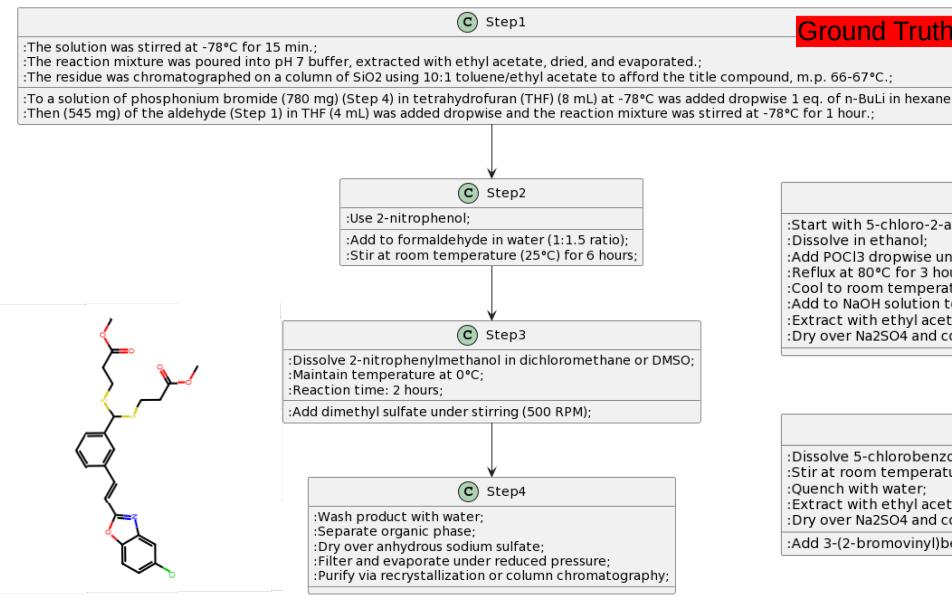




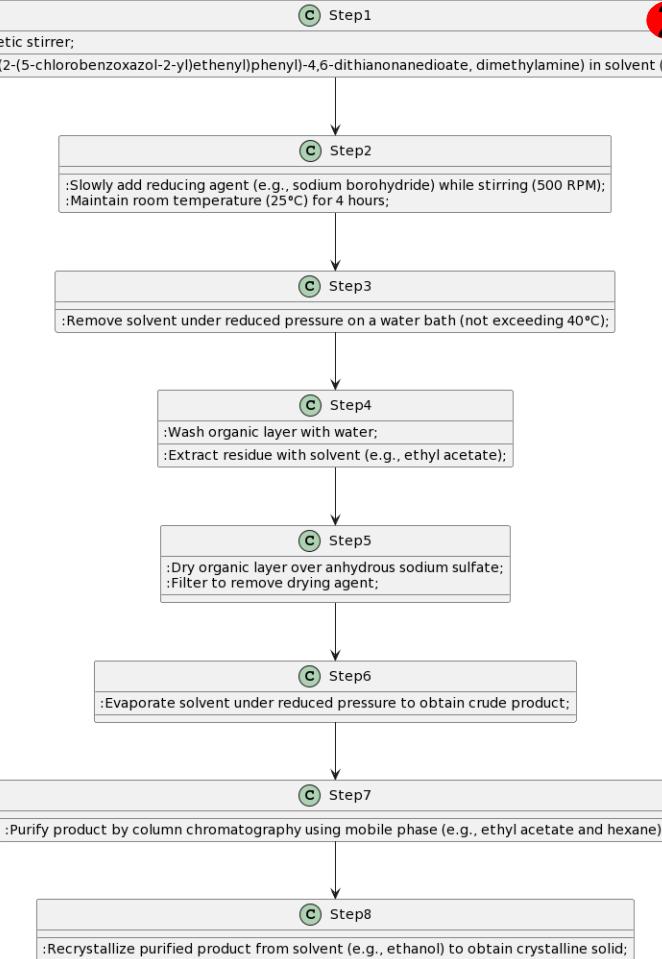
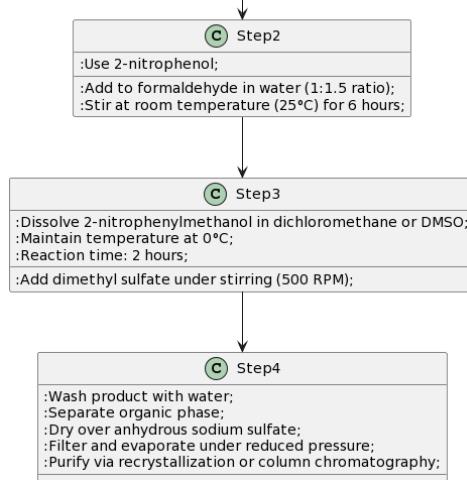
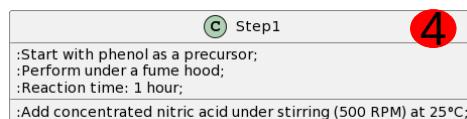
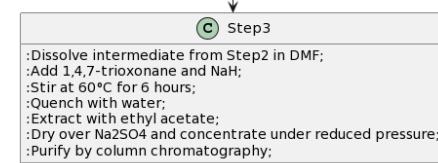
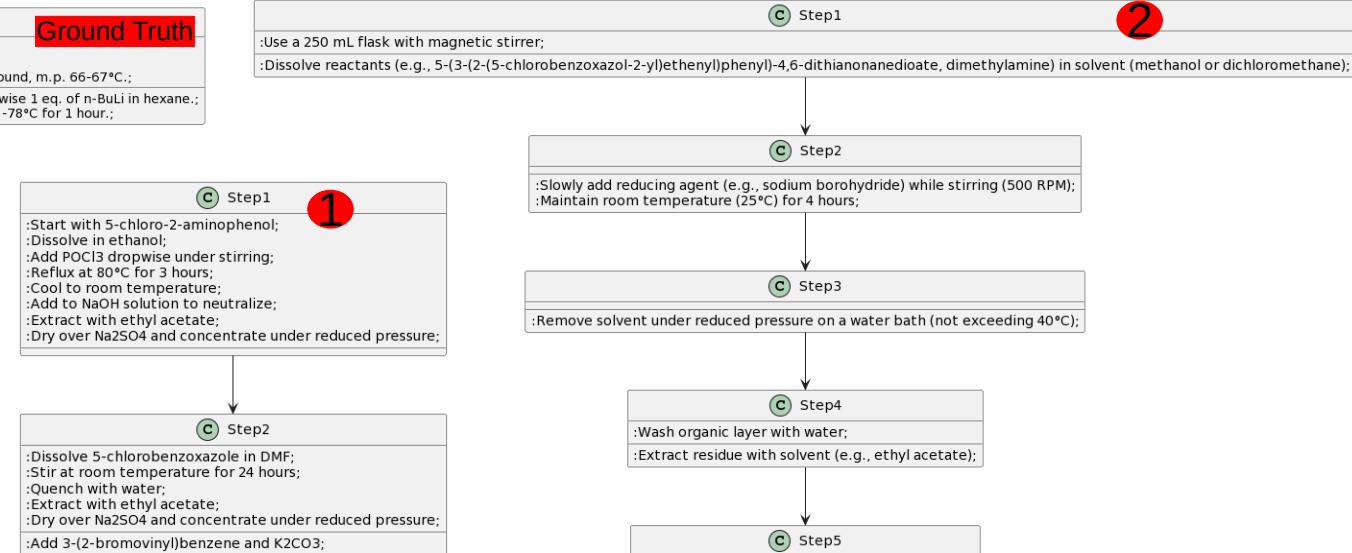
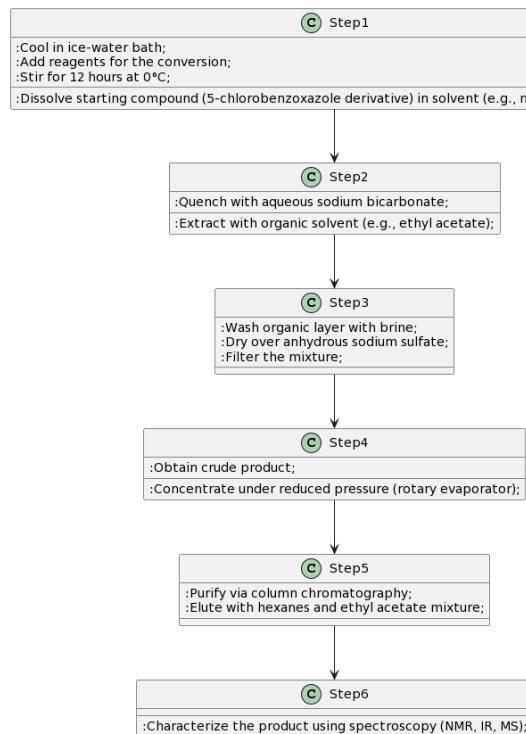
3-Nitro-4-phenoxypyridine

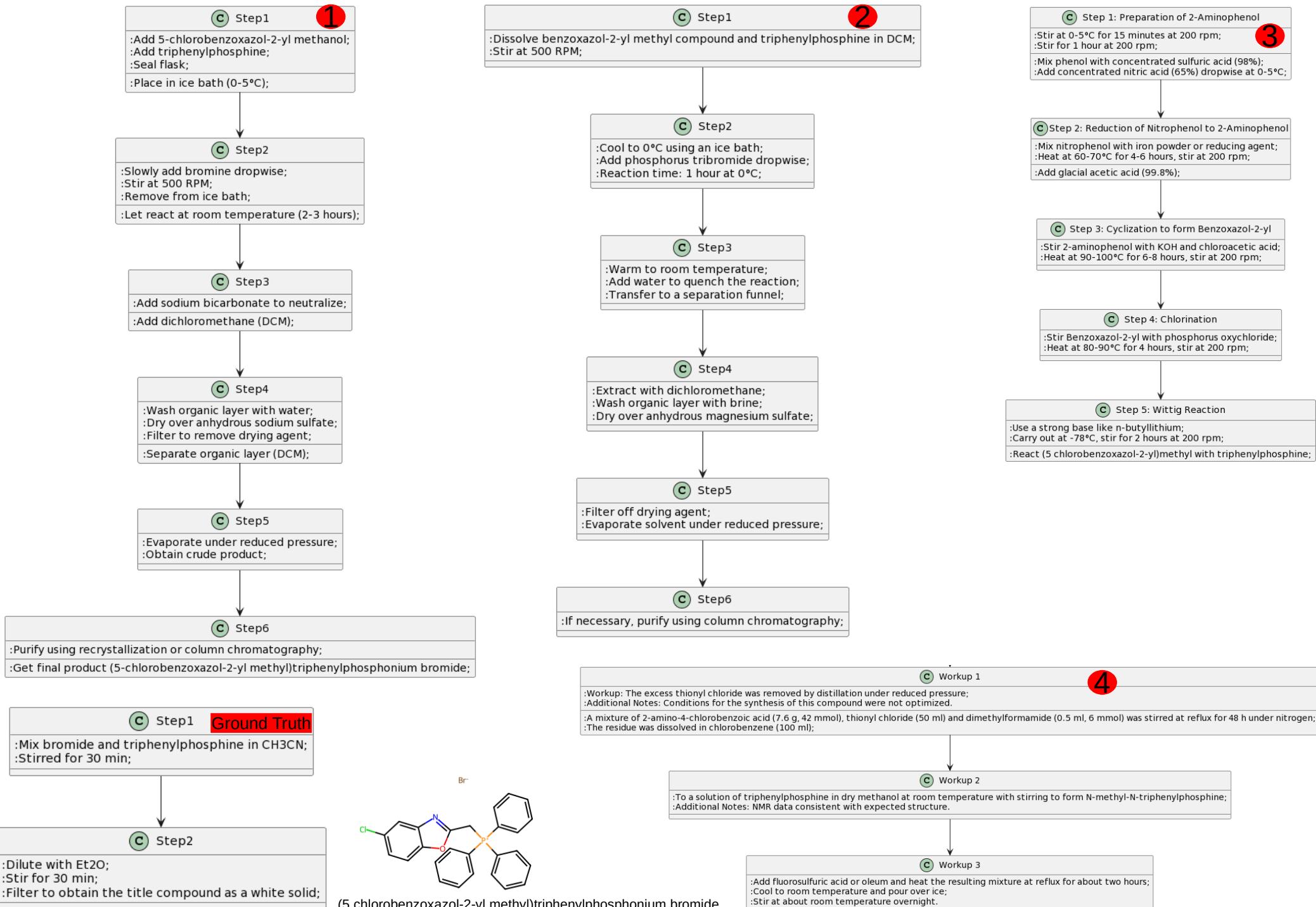


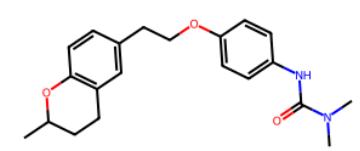
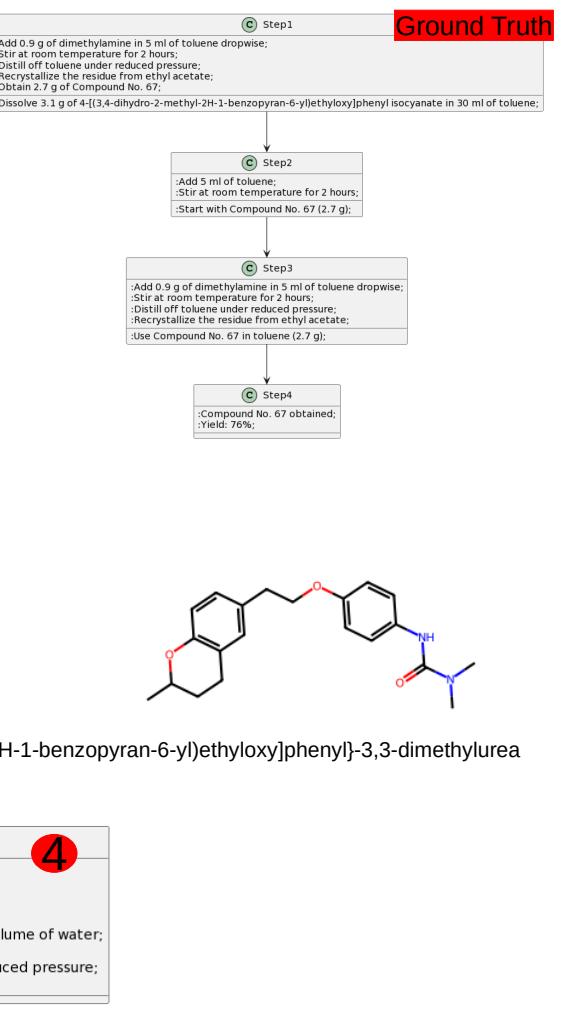
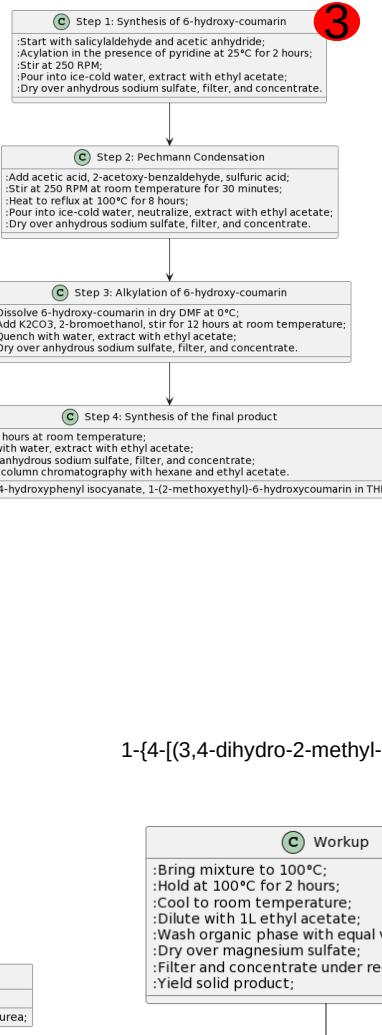
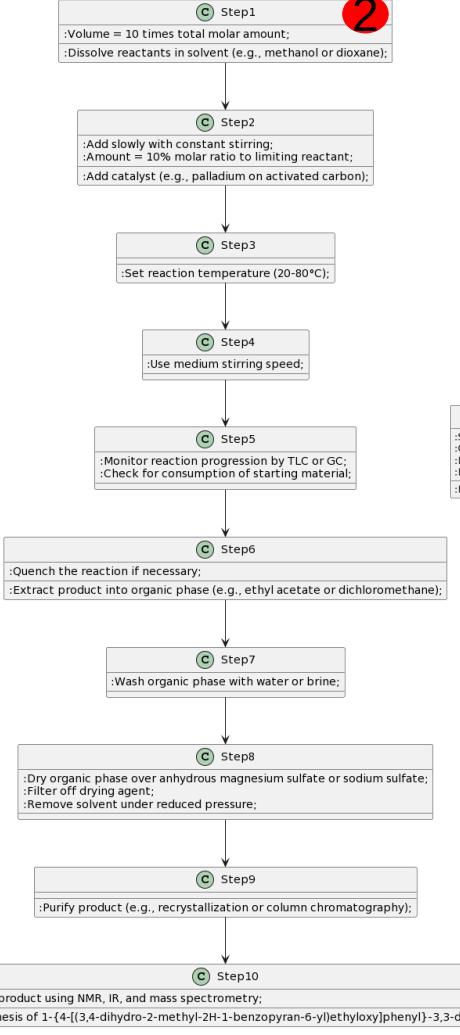
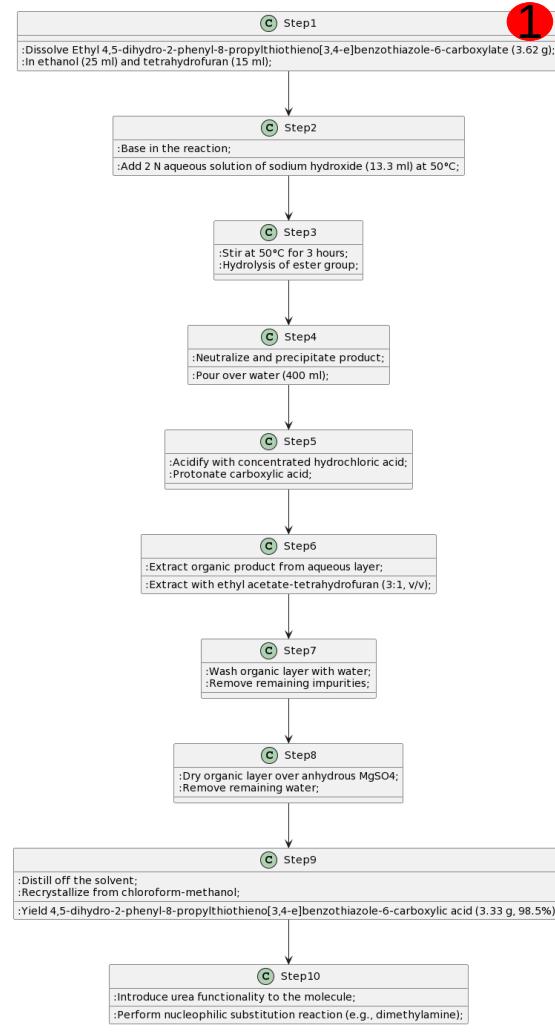




### Dimethyl 5-(3-(2-(5-chlorobenzoxazol-2-yl)ethenyl)phenyl)-4,6-dithianonanedioate







1-{4-[{(3,4-dihydro-2-methyl-2H-1-benzopyran-6-yl)ethoxy}phenyl]-3,3-dimethylurea}