2. Single Step

Overview

Steps/Stages

1.1 \( R: \text{Disodium carbonate, } S: (\text{CH}_2\text{OH})_2 \)

Notes

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

References

Acrylamide derivatives as antiallergic agents.
2. Synthesis and structure activity relationships of N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(3-pyridyl)acrylamides

By Nishikawa, Yoshinori et al

From Journal of Medicinal Chemistry, 32(3), 583-93; 1989

4. Single Step

Overview

Steps/Stages

1.1 \( R: \text{Cl(O=)CC(=O)Cl, } C: \text{DMF, } S: \text{CH}_2\text{Cl}_2, \text{0°C} \rightarrow \text{rt} \)

1.2 \( R: \text{C}_5\text{H}_5\text{N, } S: \text{THF, MeCN, 3 h, -55°C} \rightarrow \text{rt; rt} \rightarrow -78°C \)

1.3 \( R: (\text{t-BuO})_3\text{AlH} \cdot \text{Li, } C: \text{CuI, } S: \text{THF, < -70°C; 0.5 h, < -70°C} \)

1.4 \( R: \text{HCl, } S: \text{H}_2\text{O, < -70°C} \)

Notes

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

References

Preparation of substituted 4-aryl-4H-pyrrolo[2,3-h]chromenes and analogs as activators of caspases and inducers of apoptosis and their uses against cancer and other disorders

By Cai, Sui Xiong et al

From PCT Int. Appl., 2003097806, 27 Nov 2003
6. 2 Steps

**Overview**

**Steps/Stages**

1.1 R:C_{5}H_{5}N
2.1 R:Disodium carbonate, S:(CH_{2}OH)_{2}

**Notes**

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

**References**

Acrylamide derivatives as antiallergic agents.
2. Synthesis and structure activity relationships of N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-[(3-pyrindyl)acrylamides

By Nishikawa, Yoshinori et al
From Journal of Medicinal Chemistry, 32(3), 583-93; 1989

7. 2 Steps

**Overview**

**Steps/Stages**

**Notes**

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

**References**

Acrylamide derivatives as antiallergic agents.
2. Synthesis and structure activity relationships of N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-[(3-pyrindyl)acrylamides

By Nishikawa, Yoshinori et al
From Journal of Medicinal Chemistry, 32(3), 583-93; 1989
1.1 R:POCl₃, S:CH₂Cl₂
1.2 S:CH₂Cl₂
2.1 R:S, S:Naphthalene

References

**Synthesis of substituted 3-pyridinecarboxaldehydes**
By Comins, Daniel L. and Herrick, James J.
From Heterocycles, 26(8), 2159-64; 1987

8. 3 Steps

**Overview**

**Steps/Stages**

<table>
<thead>
<tr>
<th>Step</th>
<th>Reactants</th>
<th>Reagents</th>
<th>Solvents</th>
<th>Stages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>R:NaBH₄, S:MeOH</td>
<td>-78°C; -78°C; 0.5 h, rt</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>1.2</td>
<td>R:H₂O</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.1</td>
<td>R:POCl₃, S:CH₂Cl₂</td>
<td>0°C; 25 min, 0°C</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>2.2</td>
<td>S:CH₂Cl₂</td>
<td>0°C; 2 h, rt; 40 min, reflux; reflux → 0°C</td>
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<td></td>
</tr>
<tr>
<td>2.3</td>
<td>R:AcOK, S:H₂O</td>
<td>0°C; 20 min, reflux</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1</td>
<td>R:S, S:Naphthalene</td>
<td>2 h, reflux; reflux → rt</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes**

2) regioselective, in-situ generated reagent in stage 1, 3) sublimed sulfur used, Reactants: 3, Reagents: 5, Solvents: 4, Steps: 3, Stages: 6, Most stages in any one step: 3

**References**

**Preparation of spiroindolinone derivatives as antiproliferative and anticancer agents**
By Chen, Li et al
From U.S. Pat. Appl. Publ., 20080009486, 10 Jan 2008

**Experimental Procedure**

**Step 1**
Preparation of intermediate 3-chloro-2H-pyridine-1-carboxylic acid phenyl ester. To a solution of 3-chloro-pyridine (6.0 g, 53 mmol) in methanol (50 mL) was added NaBH₄ (2.6 g, 69 mmol) at -78 °C., following addition of phenyl chloroformate (8.3 g, 53 mmol) at same temperature. The mixture was stirred at r.t. for 0.5 h. Then water (200 mL) was added slowly into the solution. The precipitate was collected by filtration to give crude product (Yield: 8.2 g, 67%). m/z (M+H)+: 236
Step 2
Preparation of intermediate 3-chloro-5-formyl-2H-pyridine-1-carboxylic acid phenyl ester. Phosphorus oxychloride (5.4 g, 57.9 mmol) was added slowly to a stirred solution of DMF (8.9 ml., 116 mmol) in dichloromethane (10 mL) at 0 °C. After addition, the solution was stirred at same temperature for 25 min., then transferred a solution of 3-chloro-2H-pyridine-1-carboxylic acid phenyl ester (5.67 g, 26.3 mmol) in anhydrous dichloromethane (50 mL) at 0 °C. The ice bath was removed and stirring was continued at r.t. for 2 h, then the mixture was refluxed for 40 min. After the mixture was cooled to 0 °C., an aqueous solution of KOAc (15 g, 153 mmol) in water (50 mL) was added slowly. The mixture was refluxed for 20 min., organic layer was separated, and aqueous layer was extracted with dichloromethane (50 mL). The organic layers were combined, washed with saturated NaHCO₃, water and brine then dried over MgSO₄, concentrated to give the crude product (Yield: 6.7 g). m/z (M+H)+: 264

Step 3
Preparation of intermediate 5-chloro-pyridine-3-carbaldehyde. The mixture of 3-chloro-5-formyl-2H-pyridine-1-carboxylic acid phenyl ester (2.3 g, 8.8 mmol), sublimed sulfur (0.29 g, 9 mmol) and naphthalene (6 g) was refluxed under an argon atmosphere for 2 h. After the reaction was complete, the mixture was cooled to r.t., dissolved in ethyl ether (30 mL), and extracted with aqueous 10% HCl. The combined acid extracts were washed with ethyl ether (20 mL) and cooled to 0 °C. Dichloromethane (30 mL) was added and "pH" of the mixture was adjusted to be basic with 25% aqueous NaOH, and the mixture was extracted with dichloromethane (20 mL). The combined organic phase was washed with brine, dried over K₂CO₃, filtered, and concentrated to give a brown solid. (0.8 g, 76%). m/z (M+H)+: 142

References
Acrylamide derivatives as antiallergic agents.
2. Synthesis and structure activity relationships of N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(3-pyridyl)acrylamides
By Nishikawa, Yoshinori et al
From Journal of Medicinal Chemistry, 32(3), 583-93; 1989

Overview
Steps/Stages
1.1 R:N₂H₄
2.1 R:C₆H₅N
3.1 R:Disodium carbonate, S:(CH₂OH)₂

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

References
Acrylamide derivatives as antiallergic agents.
2. Synthesis and structure activity relationships of N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(3-pyridyl)acrylamides
By Nishikawa, Yoshinori et al
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Overview

Steps/Stages

1.1 R:NaBH₄, S:MeOH
2.1 R:POCl₃, S:CH₂Cl₂
2.2 S:OH₂Cl₂
3.1 R:S, S:Naphthalene

Notes

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

References

Synthesis of substituted 3-pyridinecarboxaldehydes
By Comins, Daniel L. and Herrick, James J.
From Heterocycles, 26(8), 2159-64; 1987