



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at [http://www.nap.edu/catalog.php?record\\_id=12654](http://www.nap.edu/catalog.php?record_id=12654)). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

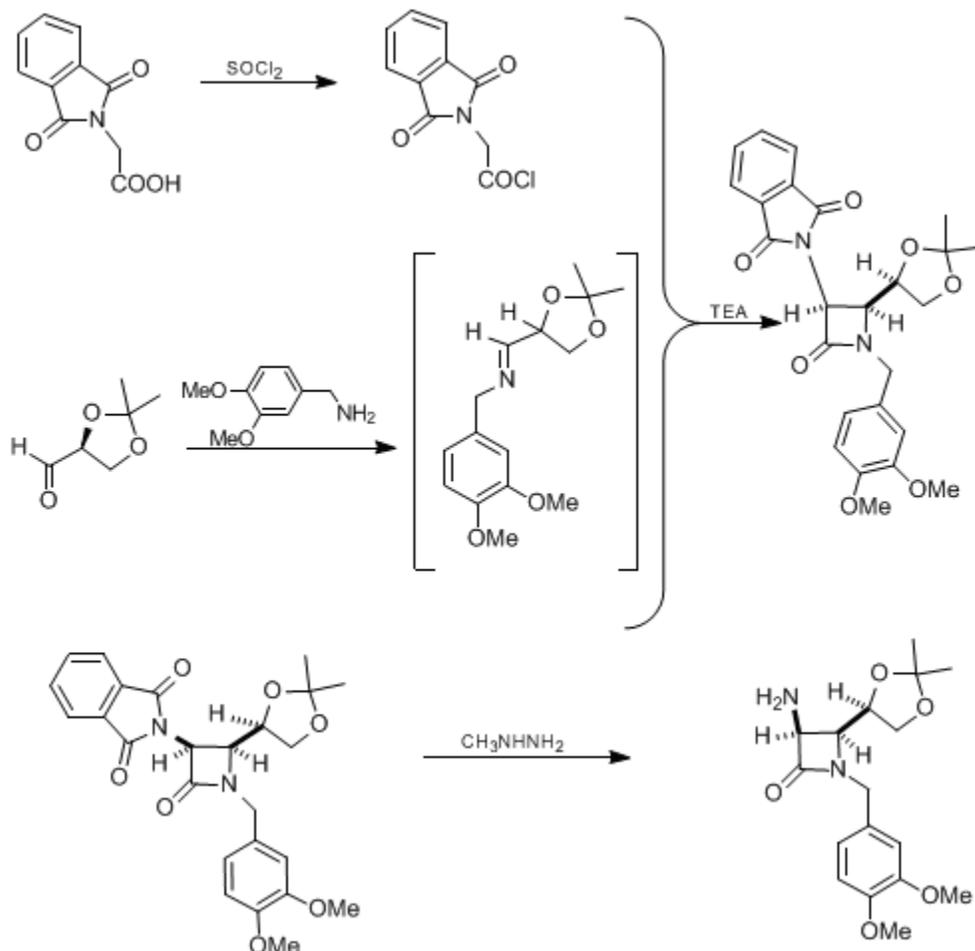
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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**(3*S*,4*S*)-3-AMINO-1-(3,4-DIMETHOXYBENZYL)-4-[(*R*)-2,2-DIMETHYL-1,3-DIOXOLAN-4-YL]-2-AZETIDINONE**

**[2-Azetidinone, 3-amino-1-[(3,4-dimethoxyphenyl)methyl]-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-, [3*S*-[3*a*,4*a*(*S*<sup>\*</sup>)]]-**



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## 1. Procedure

A. *Phthalylglycyl chloride*. *Phthalylglycine* (102.5 g, 0.5 mol; (Note 1)) is placed in a 750-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a reflux condenser (Note 2). *Thionyl chloride* (109 mL, 1.5 mol, (Note 3)) is added in one portion and the resulting suspension is stirred at reflux for 18 hr. The reaction mixture is cooled to room temperature before removing excess *thionyl chloride* under reduced pressure (Note 4). The residue is suspended in *ether* (100 mL, (Note 5)) and stirred for 1 hr at 0°C. The crystals are filtered by suction using a Büchner funnel (Note 6), washed with cold *ether* (50 mL), and dried under vacuum. Approximately 100 g of *phthalylglycyl chloride* (90% based on *phthalylglycine*) is obtained (Note 7).

B. *(3*S*,4*S*)-3-Amino-1-(3,4-dimethoxybenzyl)-4-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-azetidinone*. An aqueous solution of crude *L-(S)-glyceraldehyde acetone*<sup>2</sup> (estimated content, 190 mmol) is placed in a 1000-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar (32 mm) and a

100-mL, pressure-equalizing dropping funnel that is connected to an argon flow line. Dichloromethane (200 mL, (Note 5)) is added to the aqueous solution and the dropping funnel is charged with a solution of 3,4-dimethoxybenzylamine (31.1 g, 0.186 mol, (Note 8)) in dichloromethane (50 mL). The flask is flushed with argon and an argon atmosphere is maintained throughout the entire reaction sequence until the final work up. The solution is vigorously stirred and cooled to 10°C with an ice-water bath. The solution of 3,4-dimethoxybenzylamine is added dropwise over 5 min, the mixture is stirred for 20 min and then transferred into a 1000-mL separatory funnel. The organic phase is separated and the aqueous layer is extracted with dichloromethane (2 × 100 mL). The combined organic layers are collected in a 1000-mL Erlenmeyer flask and dried over magnesium sulfate under argon. After the magnesium sulfate is removed by filtration and thoroughly washed with three 100-mL portions of dichloromethane, the filtrate is placed in a 1000-mL, round-bottomed flask and concentrated to about 100 mL (Note 9). The solution is transferred to a 500-mL, two-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a thermometer, and a 250-mL, pressure-equalizing dropping funnel connected to an argon flow line. The solution is cooled to 0°C (ice-methanol bath) and treated with triethylamine (33.5 mL, 0.24 mol, (Note 10)). The dropping funnel is filled with a solution of phthalylglycyl chloride (41.5 g, 0.186 mol) in dichloromethane (75 mL). This solution is added dropwise over 45 min. The reaction mixture is stirred for 1 hr at room temperature, then transferred to a 1000-mL separatory funnel before sequentially washing with water (2 × 200 mL), cold 2 N hydrochloric acid (100 mL), saturated, aqueous sodium bicarbonate solution (100 mL), and brine (100 mL). The organic phase is dried over a mixture of magnesium sulfate and Fuller's earth (Fluka), filtered, and evaporated under reduced pressure. The resulting yellow syrup (72 g, 0.154 mol, 82% from 3,4-dimethoxybenzylamine, (Note 11)) is dissolved in 1,2-dichloroethane (200 mL, (Note 5)), treated with N-methylhydrazine (8.9 mL, 0.170 mol, (Note 12)) and refluxed for 60–80 min. The resulting suspension is cooled to room temperature and filtered by suction using a Büchner funnel. The crystals are thoroughly washed with two 100-mL portions of 1,2-dichloroethane and discarded. The combined organic solutions are evaporated to a heavy syrup under reduced pressure. The residue is dissolved in ethyl acetate (400 mL) and sequentially washed with water (2 × 150 mL) and aqueous 10% sodium chloride solution. The organic layer is dried over magnesium sulfate, filtered by suction using a Büchner funnel and evaporated. The resulting crystals are recrystallized from ethyl acetate/hexane (2:1). Approximately 30–32 g of (3*S*,4*S*)-3-amino-1-(3,4-dimethoxybenzyl)-4-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-azetidinone are obtained (49–52% from 3,4-dimethoxybenzylamine; 54% from 5,6-*O*-isopropylidene-*L*-gulono-1,4-lactone<sup>2</sup>) as pale yellow crystals, mp. 101–103°C (Note 13).

## 2. Notes

1. Phthalylglycine was purchased from Fluka A.G and used without any purification.
2. The gas released during the reaction should be vented through a calcium chloride trap to the back of an efficient hood.
3. Thionyl chloride of technical grade was distilled prior to use.
4. The submitters used the following conditions: rotatory evaporator; water bath temperature, 60°C; pressure, 120 mm then 60 mm.
5. Diethyl ether, dichloromethane, and dichloroethane puriss p.a. were used as purchased from Fluka A.G.
6. The submitters filtered the suspension under a stream of argon.
7. Phthalylglycyl chloride is a colorless powder. It can be stored for several weeks at room temperature in the absence of moisture and air, mp 85–87°C (lit.<sup>3</sup> 85–86°C).
8. 3,4-Dimethoxybenzylamine was purchased from Aldrich Chemical Company, Inc., and used without any purification. It is air sensitive and decomposes on standing into a white solid (3,4-dimethoxybenzoic acid). The success of the cycloaddition depends on having stoichiometric quantities of reagents. The quantity of 3,4-dimethoxybenzylamine added (less than one equivalent) is related to the average quantity of glyceraldehyde acetonide present in the crude aqueous solution.
9. The submitters used the following conditions: rotatory evaporator, water bath temperature, 35°C; pressure: 500 mm. The quality of the imine solution is determined in the following way: an aliquot of the dichloromethane solution is further evaporated under reduced pressure and analyzed by <sup>1</sup>H NMR (CDCl<sub>3</sub>). The ratio of integral value (height in mm) of the signal of the imine proton at δ 7.8 ppm to the signal of the three aromatic protons at δ 6.85 ppm gives a fairly good idea of the course of the reaction. The presence of an excess of 3,4-dimethoxybenzylamine in the solution leads to the formation of an

insoluble by-product resulting from the reaction of 3,4-dimethoxybenzylamine with phthalimidoacetyl chloride. It renders the final purification more tedious.

10. Triethylamine (puriss. p.a.) was purchased from Fluka A.G. and used without any purification.

11. N-[(2R,3R)-cis-1-(3,4-Dimethoxybenzyl)-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-oxo-3-azetidiny]phthalimide can be purified at this stage by flash column chromatography (dichloromethane/ethyl acetate 9:1) but does not tend to crystallize. The <sup>1</sup>H NMR spectrum is as follows (CDCl<sub>3</sub>) δ: 1.23 and 1.35 (2 s, 2 × 3 H), 3.39 (dd, 1 H, J = 6.5, 8.5), 3.66 (dd, 1 H, J = 6.5, 8.5), 3.79 (dd, 1 H, J = 5, 9), 3.89 and 3.91 (2 s, 2 × 3 H), 4.32 and 4.81 (2 × d, 2 × 1 H, J = 15), 4.36 (dt, 1 H, J = 6.5 and 9), 5.30 (d, 1 H, J = 5), 6.82–6.93 (m, 3 H), 7.76–7.90 (m, 4 H).

12. N-Methylhydrazine was purchased from Fluka and was used without any purification. All the operations should be carried out under a well-vented hood since N-methylhydrazine is a carcinogen.

13. An analytically pure sample can be obtained after a further recrystallization from ethyl acetate (mp 106–107°C). The <sup>1</sup>H NMR spectrum is as follows (CDCl<sub>3</sub>) δ: 1.36 and 1.45 (2 s, 2 × 3 H), 1.86 (broad s, 2 H), 3.53 (t, 1 H, J = 7.5), 3.70 (dd, 1 H, J = 6, 10), 3.87 (2 s, 2 × 3 H), 4.06 and 4.80 (2 d, 2 × 1 H, J = 18), 4.15–4.30 (m, 3 H), 6.80–6.82 (m, 3 H).

### Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

### 3. Discussion

Monocyclic azetidinones are useful building blocks in organic synthesis. Besides the wide use in the syntheses of monobactam antibiotics and nuclear analogues of natural bicyclic β-lactam antibiotics,<sup>4</sup> new applications have appeared with the syntheses of unnatural α-amino acids, amino sugars<sup>5</sup> and inhibitors of elastase.<sup>6</sup>

These building blocks can be obtained either by the Miller cyclization of β-hydroxy-α-amino acids<sup>7</sup> or by the Staudinger reaction<sup>8,9</sup> ([2+2] ketene-imine cycloaddition). The procedure reported here follows the second route and has the advantages of being diastereospecific and to proceed in high yield. For a large scale preparation, the harmful and toxic N-methylhydrazine can be replaced by N,N-dimethyl-1,3-propanediamine.<sup>10</sup> Further transformations of the key intermediate have been reported elsewhere.<sup>8,11</sup>

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### References and Notes

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**Appendix**  
**Chemical Abstracts Nomenclature (Collective Index Number);**  
**(Registry Number)**

brine

glyceraldehyde acetonide

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether,  
diethyl ether (60-29-7)

thionyl chloride (7719-09-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

1,2-dichloroethane (107-06-2)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

N-methylhydrazine (60-34-4)

hexane (110-54-3)

triethylamine (121-44-8)

argon (7440-37-1)

dichloroethane (75-34-3)

N,N-dimethyl-1,3-propanediamine (109-55-7)

ketene-imine (18295-52-8)

3,4-dimethoxybenzoic acid (93-07-2)

Morin

(3S,4S)-3-Amino-1-(3,4-dimethoxybenzyl)-4-[(R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-azetidinone,  
2-Azetidinone, 3-amino-1-[(3,4-dimethoxyphenyl)methyl]-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-, [3S-

[3a,4a(S\*)]]- (159802-14-9)

Phthalylglycyl chloride (6780-38-7)

Phthalylglycine (4702-13-0)

3,4-dimethoxybenzylamine (5763-61-1)

5,6-O-isopropylidene-L-gulono-1,4-lactone

phthalimidoacetyl chloride

N-[(2R,3R)-cis-1-(3,4-Dimethoxybenzyl)-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-oxo-3-azetidiny] phthalimide (86418-70-4)

L-(S)-Glyceraldehyde acetonide (22323-80-4)