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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). 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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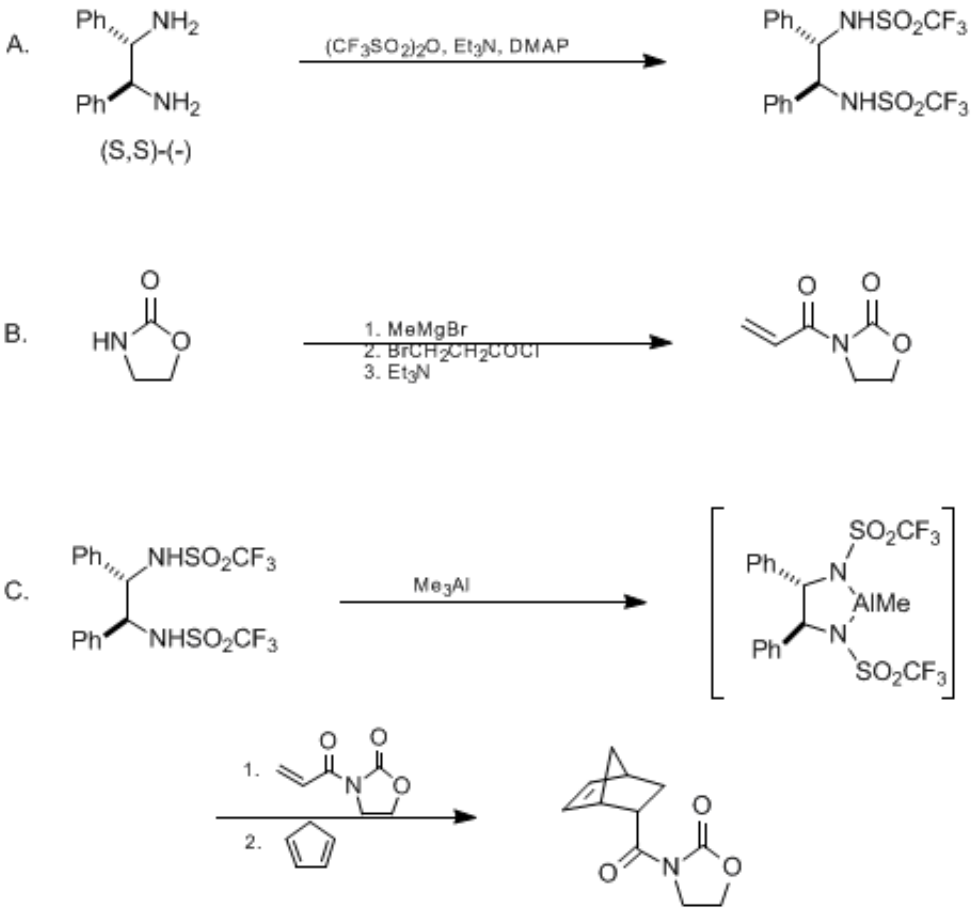
ENANTIOSELECTIVE, CATALYTIC DIELS-ALDER REACTION: (1S-endo)-3-(BICYCLO[2.2.1]HEPT-5-EN-2-YLCARBONYL)-2-OXAZOLIDINONE

[2-Oxazolidinone, 3-bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-, (1S-endo)-]



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1. Procedure

Caution! Dialkylzinc compounds, especially in undiluted form, are pyrophoric and must not be allowed to come into contact with air or moisture. These compounds should only be handled by individuals trained in their proper and safe use. [Note added January 2011]

A. *Bistriflamide of (1S,2S)-1,2-diphenylethylenediamine*. A 50-mL, one-necked, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 1.06 g (5 mmol) of (1S,2S)-1,2-diphenylethylenediamine,[3] 2.1 mL (15 mmol) of triethylamine (Note 1), 12.2 mg (0.1 mmol) of 4-dimethylaminopyridine (DMAP) (Note 2) and 25 mL of methylene chloride (Note 3). The mixture is stirred to dissolve the solids, cooled to –78°C with a solid carbon dioxide/acetone bath, and 3.39 g (12 mmol) of trifluoromethanesulfonic anhydride (Note 4) is added dropwise. The cooling bath is removed and the mixture is allowed to warm to ambient temperature over 30 min. The mixture is then poured into 4% aqueous sodium bicarbonate, the phases are separated, and the aqueous phase is washed with 15 mL of methylene chloride. The combined organic phases are washed with 1 N hydrochloric acid, with brine,

and then dried over anhydrous sodium sulfate and filtered. The filtrate is concentrated under reduced pressure and the residue is subjected to flash chromatography[4] on 100 g of silica gel (Note 5) (15% ethyl acetate-hexane, v/v) to give 1.64 g (69%) of the bistriflamide of (1S,2S)-1,2-diphenylethylenediamine as colorless crystals, mp 213–214°C (Note 6).

B. *Acryloyl-2-oxazolidinone (Note 7)*. A flame-dried, 1-L, one-necked, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 8.71 g (100 mmol) of 2-oxazolidinone (Note 2), flushed with argon (Note 8), and then 500 mL of tetrahydrofuran (Note 9) is introduced. The mixture is stirred to dissolve solids, cooled to 0°C, and 33.3 mL (100 mmol) of 3 M methylmagnesium bromide in ether (Note 2) is slowly added. After the solution is stirred for 10 min at 0°C, 11.6 mL (115 mmol) of 3-bromopropionyl chloride (Note 10) is added dropwise. The cooling bath is removed and the mixture is allowed to warm to ambient temperature over 30 min. The mixture is diluted with 600 mL of peroxide-free ether (Note 11) and washed with saturated aqueous ammonium chloride. The organic phase is dried over magnesium sulfate and filtered. To the filtrate, stirred at ambient temperature, is added 69 mL (500 mmol) of triethylamine (Note 1). A colorless precipitate forms immediately and the resulting slurry is stirred at ambient temperature for 3 hr, then poured into a 1:1 mixture of saturated aqueous ammonium chloride and 1 N aqueous hydrochloric acid. The aqueous layer is extracted with 200 mL of peroxide-free ether (Note 11), and the combined organic phases are dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue is subjected to flash chromatography[4] on 150 g of silica gel (Note 5) (35% ethyl acetate-hexane, v/v) to give 5.81 g (41%) of acryloyl-2-oxazolidinone as colorless crystals, mp 82–83°C (Note 12).

C. *Diels-Alder reaction*. All reagents and glassware are dried rigorously. A flame-dried, 250-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar and a reflux condenser, is charged with 1.31 g (2.75 mmol) of bistriflamide of (1S,2S)-1,2-diphenylethylenediamine (dried at 80°C and 1 mm) and placed under dry argon (Note 8). 1,2-Dichloroethane (20 mL) (Note 13) is added, the mixture is heated to 80°C with stirring to effect solution, cooled to ambient temperature, and treated dropwise with 1.37 mL (2.74 mmol) of 2 M trimethylaluminum in toluene (Note 2). After the evolution of gases ceases, the homogeneous mixture is heated to 80°C (oil bath) for 3 hr. The heating bath is removed, the mixture is cooled to ambient temperature, the reflux condenser is replaced by a glass stopper, and the solvent is removed under reduced pressure (oil pump) that is maintained for an additional 30 min. The resulting solid is dissolved in 10 mL of dry methylene chloride (Note 3) and overlayered with 50 mL of dry heptane. Colorless crystals are deposited after 20 hr. The supernatant liquid is drawn off by syringe and the residual solid is dissolved in 50 mL of methylene chloride (Note 3). The solution is cooled to −78°C and a solution of 7.76 g (55 mmol) of acryloyl-2-oxazolidinone in 50 mL of methylene chloride (Note 3) is introduced through a cannula. The mixture is stirred for 5 min at −78°C and then 5.7 mL (71 mmol) of neat, cold (−78°C) cyclopentadiene (Note 14) is slowly introduced through a cannula (Note 15) along the cooled sides of the flask. Stirring is continued for another 15 min. The mixture is poured into 1 N aqueous hydrochloric acid, the phases are separated, and the aqueous phase is washed with 25 mL of methylene chloride. The combined organic phases are washed successively with aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate is concentrated under reduced pressure and the residue is subjected to flash chromatography[4] on 150 g of silica gel (Note 5) (hexane-ethyl acetate 2:1, v/v) to give 10.1 g (89%) of the cycloadduct as colorless crystals, mp 68–69°C (Note 16) and (Note 17).

2. Notes

1. Triethylamine (99+%) was purchased from the Aldrich Chemical Company, Inc., and stored over sodium hydroxide.
2. 4-Dimethylaminopyridine (DMAP) (99%), 2-oxazolidinone (98%), methylmagnesium bromide (3 M in ether), and trimethylaluminum (2 M in toluene) were purchased from the Aldrich Chemical Company, Inc., and used as received.
3. Methylene chloride (A.C.S. reagent) was distilled from calcium hydride prior to use.
4. Trifluoromethanesulfonic anhydride was purchased from the Aldrich Chemical Company, Inc., and used as received. It can also be prepared from the acid according to the *Organic Syntheses* procedure.[5]
5. Kieselgel 60 (230–400 mesh) was purchased from EM Science, an affiliate of E. Merck, Darmstadt.

6. The product has the following properties: $[\alpha]_D$ –6.6° ($CHCl_3$, *c* 1.4); ^1H NMR ($CDCl_3$) δ: 4.81 (s, 2 H), 6.80 (bs, 2 H), 7.25 (6 H), 7.0 (4 H); ^{13}C NMR ($CDCl_3$) δ: 63.7, 127.0, 129.1 (2 C), 135.1.

7. This procedure is essentially the same as that described in the literature.[6]
8. This procedure involves three consecutive evacuations of the flask and fillings with dry argon.
9. Reagent grade tetrahydrofuran, purchased from J. T. Baker Chemical Company, was freshly distilled from sodium metal and benzophenone.
10. 3-Bromopropionyl chloride (tech) was purchased from the Aldrich Chemical Company, Inc., and distilled prior to use.
11. Anhydrous diethyl ether was freshly distilled from sodium metal and benzophenone.
12. The product has the following properties: R_f = 3.1 (35% ethyl acetate in hexane, v/v); IR cm^{-1}: 1785, 1675, 1419, 1396, 1321, 1258, 1220, 1024, 1008, 982, 752; ^1H NMR ($CDCl_3$) δ: 4.09 (t, 2 H, J = 8.0), 4.45 (t, 2 H, J = 8.0), 5.90 (dd, 1 H, J = 10.4, 1.6), 6.56 (dd, 1 H, J = 17.1, 1.6), 7.49 (dd, 1 H, J = 17.1, 10.4); ^{13}C NMR ($CDCl_3$) δ: 42.6, 62.1, 127.0, 131.6, 153.6, 165.0.
13. 1,2-Dichloroethane (99%, A.C.S. reagent) was freshly distilled from calcium hydride.
14. Cyclopentadiene was prepared by thermal cracking of dicyclopentadiene available from the Aldrich Chemical Company, Inc., following the literature procedure.[7]
15. Because of the high rate of the cycloaddition reaction it is very important that the cyclopentadiene solution enter the reaction flask and mix with the acrylate solution at as low a temperature as possible. For this reason it is beneficial to use a short cannula and to introduce the cyclopentadiene solution onto the wall of the flask that is deeply immersed in a solid CO_2 bath.
16. The product has the following properties: $[\alpha]_D$ –152.0° ($CHCl_3$, *c* 1.5; ee 89%), (lit.[7] $[\alpha]_D$ –65° ($CHCl_3$, *c* 1.5; ee 38%); R_f = 0.23 (hexane-ethyl acetate 2:1, v/v); IR cm^{-1}: 2975, 1775, 1696, 1386, 1337, 1279, 1253, 1226, 1111, 1039, 761, 704; ^1H NMR ($CDCl_3$) δ: 1.39–1.50 (m, 3 H), 1.95 (ddd, 1 H, J = 12.6, 9.3, 3.7), 2.93 (m, 1 H), 3.30 (m, 1 H), 3.91–4.00 (m, 3 H), 4.35–4.41 (m, 2 H), 5.87 (dd, 1 H, J = 5.5, 2.8), 6.24 (dd, 1 H, J = 5.5, 3.1); ^{13}C NMR ($CDCl_3$) δ: 29.5, 42.9 (2 C), 43.2, 46.4, 50.2, 61.9, 131.6, 138.1, 153.4, 174.7.
17. The endo-exo selectivity of the cycloaddition reaction is higher than 50:1, since no signals corresponding to the exo product are observed in the 500 MHz ^1H NMR spectrum of the crude or chromatographed product. The optical purity is 89% ee based on comparison with an authentic sample and the literature data.[8] The optical purity is confirmed by a 500 MHz ^1H NMR spectrum of the corresponding Mosher ester prepared in two steps: 1. Lithium aluminum hydride ($LiAlH_4$) reduction in tetrahydrofuran at room temperature; 2. esterification of the resulting primary alcohol with (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[9] in the presence of triethylamine and DMAP in methylene chloride at room temperature.

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

The design and application of chiral, non-racemic Lewis acids for the asymmetric Diels-Alder reaction has recently been a subject of considerable interest.[10 11] Several methods have been developed in many laboratories[8,12 13 14 15 16 17 18 19 20 21 22 23 24] but catalysts are still needed that are more efficient in governing the stereochemical course of the cycloaddition reaction.

This procedure describes the preparation and application of an effective chiral catalyst for the enantioselective Diels-Alder reaction.[25] The catalyst is derived from optically active 1,2-

diphenylethylenediamine, the preparation of which (either antipode) is described (p. 387). The aluminum-based Lewis acid also catalyzes the cycloaddition of crotonoyl oxazolidinones with cyclopentadiene,[25] and acryloyl derivatives with benzyloxymethylenecyclopentadiene. The latter reaction leads to optically pure intermediates for synthesis of prostaglandins.[25]

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

silica gel

brine

2-Oxazolidinone, 3-bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-, (1S-endo)-

Bistriflamide of (1S,2S)-1,2-diphenylethylenediamine

DMAP

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether,
diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

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

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

methylmagnesium bromide (75-16-1)

Tetrahydrofuran (109-99-9)

heptane (142-82-5)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

triethylamine (121-44-8)

CYCLOPENTADIENE (542-92-7)

dicyclopentadiene (77-73-6)

argon (7440-37-1)

2-Oxazolidinone (497-25-6)

calcium hydride (7789-78-8)

ethyl acetate-hexane (2639-63-6)

Trifluoromethanesulfonic anhydride (358-23-6)

trimethylaluminum (75-24-1)

4-dimethylaminopyridine (1122-58-3)

(1S,2S)-1,2-diphenylethylenediamine (35132-20-8)

Acryloyl-2-oxazolidinone (2043-21-2)

3-bromopropionyl chloride (15486-96-1)

1,2-diphenylethylenediamine

benzyloxymethylenecyclopentadiene

(1S-endo)-3-(Bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-2-oxazolidinone (109299-97-0)

(R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride