Organic Syntheses

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). 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.

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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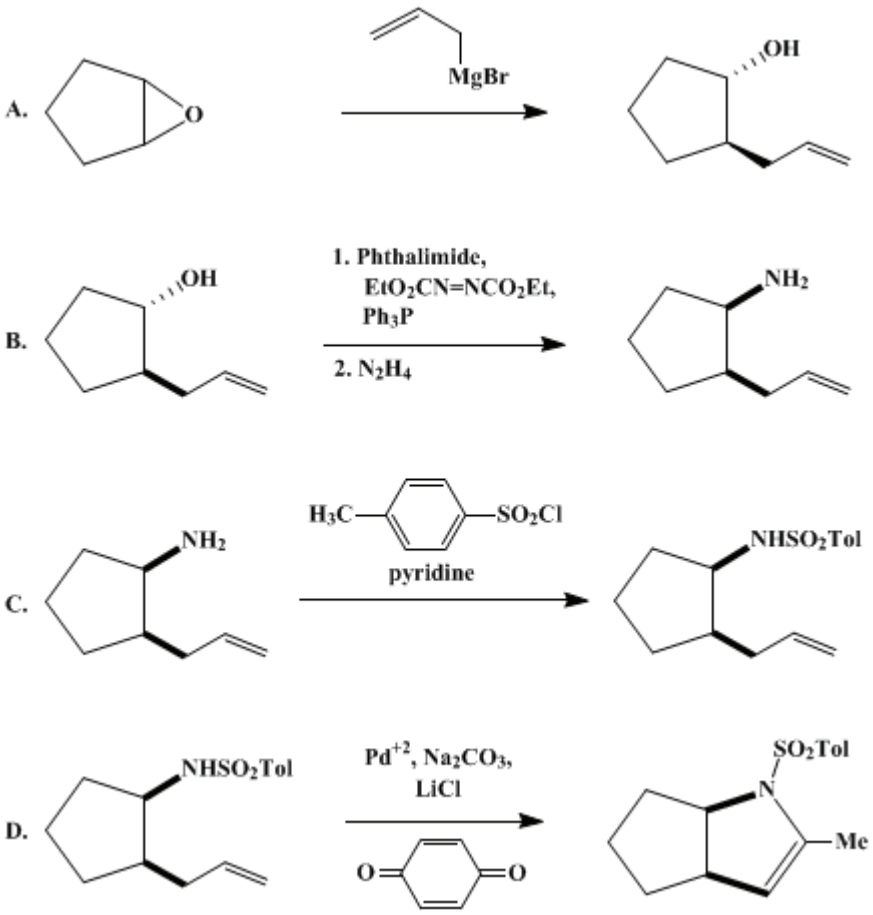
cis-*N*-TOSYL-3-METHYL-2-AZABICYCLO[3.3.0]OCT-3-ENE

[Cyclopenta[*b*]pyrrole, 1,3a,4,5,6,6a-hexahydro-2-methyl-1-[4-methylphenyl) sulfonyl]-, *cis*-]



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1. Procedure

A. *trans-2-(2-Propenyl)cyclopentanol*. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, reflux condenser with a stopcock, and a 250-mL addition funnel is charged with 18.3 g (750 mmol) of magnesium turnings (Note 1). The system is evacuated and placed under argon, then 100 mL of ethyl ether (Note 2) is added to the system via cannula. The system is placed in an ice–water bath, and 2 mL of allyl bromide (Note 3) is added via syringe to the magnesium suspension to initiate Grignard formation. The addition funnel is charged with 45.5 g (375 mmol) of allyl bromide and 30 mL of ethyl ether. Another 100 mL of ethyl ether is added to the reaction flask. Stirring is begun, and the allyl bromide–ethyl ether mixture is added dropwise to the cooled reaction flask over a period of about 2 hr. After the addition is complete, the dark-gray solution is stirred for several hours at ambient temperature (Note 4). Meanwhile, a 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a reflux condenser with a stopcock, and a 60-mL addition funnel is evacuated and placed under argon. The Grignard solution is transferred, via a cannula, into the flask, and 16.8 g (200 mmol) of cyclopentene oxide (Note 5) is placed in the addition funnel. While the solution is stirred, the epoxide is added dropwise to the Grignard reagent at a rate sufficient to maintain a mild reflux. After the solution is stirred for several hours or overnight, the flask containing the dark

gray reaction mixture is placed in an ice–water bath, and excess Grignard reagent is hydrolyzed with 40 mL of a saturated aqueous ammonium chloride solution. The fine white precipitate is allowed to settle (Note 6), and the liquid is decanted into a 500-mL separatory funnel. The precipitate is washed with ethyl ether (4 × 50 mL) (Note 7), and all the ethyl ether solutions are combined, washed with saturated aqueous sodium bicarbonate solution (3 × 20 mL), then with saturated aqueous sodium chloride (2 × 20 mL). The aqueous layers are combined and washed with ethyl ether (2 × 20 mL). The ether layers are combined and dried over anhydrous potassium carbonate. The desiccant is removed by gravity filtration, and the solvent removed under reduced pressure to give 24.1–26.4 g (96–105%) of a yellow oil. Distillation (43°C, 0.250 mm) yields **1** (19.8–23.0 g, 78–91%) as a clear, colorless oil (Note 8).

B. *cis-2-(2-Propenyl)cyclopentylamine*. A 1000-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, two addition funnels, and a stopcock is charged with 41.5 g (158 mmol) of triphenylphosphine (Note 9) and 23.3 g (158 mmol) of phthalimide (Note 10). The system is evacuated and placed under argon. To one addition funnel, 20.0 g (158 mmol) of *trans*-2-(2-propenyl) cyclopentanol is added; 27.5 g (158 mmol) of diethyl azodicarboxylate (Note 11) is added to the other. Tetrahydrofuran, 500 mL (Note 12), is added to the flask via cannula, and stirring is begun. The substrate and diethyl azodicarboxylate are simultaneously added dropwise, slowly over about 30 min (Note 13), with stirring; the solution turns clear and yellow (Note 14). The reaction is permitted to proceed for 2 days at room temperature; the solution is then transferred to a 1000-mL, one-neck, round-bottomed flask, and the solvent is removed under reduced pressure, to leave a yellow–white semisolid. A magnetic stirring bar is added to the flask and the semisolid is taken up in 250 mL of reagent-grade methyl alcohol. To this, 10.1 g (316 mmol) of hydrazine (Note 15) is added. A reflux condenser is attached to the flask, stirring is begun, and the system is brought to reflux (Note 16). A large amount of clumpy white solid forms in a yellow-to-orange solution. After 4 hr at reflux, the solution is allowed to cool to room temperature; a mixture of 20 mL of hydrochloric acid (Note 17) and 65 mL of methyl alcohol is added, and the system is refluxed overnight. The resulting reaction mixture is filtered to remove the precipitate, and the solvent is removed under reduced pressure to yield a white-to-pink solid, which is taken up in 800 mL of water and 28 mL of hydrochloric acid. The solution is filtered, and the solid washed with water (2 × 200 mL) and hydrochloric acid (20 mL). The liquids are combined, placed in a 2000-mL separatory funnel, and washed with chloroform (3 × 250 mL), and ethyl ether (1 × 250 mL). The aqueous layer is transferred to a 2000-mL Erlenmeyer flask and cooled in an ice–water bath. A saturated aqueous sodium hydroxide solution is used to make the solution basic, to approximately pH 14, whereupon the solution turns dark olive green. The basic solution is extracted with ethyl ether (10 × 250 mL or by continuous extraction overnight) and the combined organic layers are dried over a mixture of anhydrous sodium sulfate and anhydrous potassium carbonate. Filtration and solvent removal at atmospheric pressure yields a green–yellow oil. Distillation (52–58°C, 8–11 mm) gives **2** (11.8–12.5 g, 60–63%) as a clear, colorless oil (Note 18).

C. *cis-1-N-Tosyl-2-(2-propenyl)cyclopentylamine*. A 100-mL, one-necked, round-bottomed flask equipped with a sidearm, a magnetic stirring bat, stopcock, and a serum cap on the sidearm, is charged with 8.00 g (64 mmol) of *cis*-2-(2-propenyl)cyclopentylamine. The system is evacuated and placed under argon. Via cannula, 50 mL of pyridine (Note 19) is added. The flask is cooled in an ice–water bath, the stopcock removed, 12.58 g (66 mmol) of *p*-toluenesulfonyl chloride (Note 20) is added to the reaction mixture, and the stopcock replaced. The reaction mixture immediately turns orange; it is allowed to stir at 0°C overnight, during which time the reaction mixture turns deep purple. The reaction mixture is then poured into a separatory funnel, 60 mL of distilled technical grade ethyl acetate is added, and the solution is washed with 100-mL portions of 1 : 1 2 N HCl: saturated aqueous sodium chloride until the washings are acidic. The organic layer is washed with saturated aqueous sodium chloride (2 × 60 mL), and dried over anhydrous magnesium sulfate. Gravity filtration and solvent removal under reduced pressure yield a dark red–brown solid. This is purified by recrystallization from 250 mL of ethyl alcohol: water (4 : 1); crystallization is completed in the refrigerator to give **3** (12.7–13.9 g, 71–78%) as off-white plates, mp 109–110°C (Note 21).

D. *cis-N-Tosyl-3-methyl-2-azabicyclo[3.3.0]oct-3-ene*. A 500-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and reflux condenser is charged with 5.159 g (18.49 mmol) of *cis*-1-*N*-tosyl-2-(2-propenyl)cyclopentylamine, 1.998 g (18.49 mmol) of *p*-benzoquinone (Note 22),

0.096 g (0.370 mmol, 2 mol%) of $PdCl_2(CH_3CN)_2$ (Note 23), 3.920 g (92.46 mmol, 500 mol%) of lithium chloride (Note 24), and 1.960 g (18.49 mmol) of sodium carbonate (Note 25). Tetrahydrofuran (100 mL) (Note 12) is added and stirring is begun. The yellow–orange solution is heated at reflux until thin-layer chromatography (3 : 1 hexane : ethyl acetate, SiO_2) shows that no starting material remains (about 3–4 hr); it is then poured into a 500-mL separatory funnel and 100 mL of ethyl acetate is added. This is washed with 100-mL portions of 1 : 1 saturated aqueous sodium chloride : sodium hydroxide (1%) until the aqueous layer is clear; then the yellow–green organic layer is washed with saturated aqueous sodium chloride (2 × 50 mL). The organic layer is dried over anhydrous magnesium sulfate, filtered by gravity, and passed through a short column (approximately 5 cm) of neutral alumina, and the column is washed with 100 mL of ethyl acetate. The combined solvents are removed under reduced pressure to give 4.9–5.1 g (94–99%) of a tan solid. The product is recrystallized from 100 mL of methyl alcohol : water (4 : 1) to yield **4** (3.9–4.45 g, 76–87%) as white needles, mp 91–92°C (Note 26) and (Note 27).

2. Notes

1. Magnesium turnings, purified for Grignard reactions, are purchased from J. T. Baker Chemical Company and used without further purification.
2. Ethyl ether is freshly distilled from sodium/benzophenone ketyl at atmospheric pressure under nitrogen.
3. Allyl bromide, purchased from Aldrich Chemical Company, Inc., is distilled and stored in a brown bottle away from light.
4. Successful reactions have been run with this induction period lasting from 1 hr to overnight.
5. Cyclopentene oxide is purchased from Arapahoe Chemicals, Boulder, CO, and used without purification. The checkers bought cyclopentene oxide from Lancaster Synthesis.
6. The fine precipitate may take several hours to settle. Filtration is often ineffective, but settling can be accelerated by centrifuging.
7. Since the efficiency of this washing is dependent on the degree of settling, the checkers recommend that washing with 50-mL batches of ether be continued until the smell of the alcohol is no longer detectable on a sample of the dry salts.
8. The spectral properties are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.0–2.4 (m, 9 H); 3.0–3.3 (br s, 1 H, O-H); 3.7–4.1 (m, 1 H, CH-O); 4.8–5.3 (m, 2 H, $=CH_2$); 5.5–6.2 (m, 1 H, -CH=).
9. Anhydrous triphenylphosphine is purchased from Sigma Chemical Company and is used without further purification
10. Phthalimide, 98%, is purchased from Aldrich Chemical Company, Inc. and is used without further purification.
11. Diethyl azodicarboxylate is purchased from Aldrich Chemical Company, Inc. and is used without further purification.
12. Tetrahydrofuran is freshly distilled from sodium/benzophenone ketyl at atmospheric pressure under nitrogen.
13. Too rapid a rate of addition may cause the solution to boil.
14. The solution does not become homogeneous until it is warmed by the heat of the reaction.
15. Anhydrous hydrazine, ≥97%, is purchased from Matheson, Coleman and Bell, No wood, OH 45212 and is used without further purification.
16. *Caution! Because of the dangerous nature of hydrazine, a safety shield should always be in place during this reaction.*
17. ACS reagent hydrochloric acid is purchased from Fisher Scientific Company and used without further purification.
18. The spectral properties are as follows: ^{1}H NMR ($CDCl_3$) δ: 0.8 (s, 2 H, NH_2); 1.3–2.4 (m, 9 H, CH_2, CH); 3.1–3.4 (m, 1 H, HC-N); 4.8–5.2 (m, 2 H, $=CH_2$); 5.4–6.1 (m, 1 H, HC=).
19. Pyridine is distilled from CaH_2 and stored over CaH_2 under argon.
20. *p*-Toluenesulfonyl chloride is purchased from J. T. Baker Chemical Company and purified by dissolving 20 g in 50 mL of chloroform, adding 250 mL of hexane, filtering, and removing solvent under reduced pressure.[2]
21. The spectral properties are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.0–2.3 (m, 9 H, CH_2, CH); 2.41 (s, 3 H, CH_3); 3.4–3.8 (m, 1 H, CHN); 4.7–5.1 (m, 3 H, $=CH_2$, NH); 5.2–6.1 (m, 1 H, =CH); 7.25 (d, 2 H, J = 8, ArH); 7.8 (d, 2 H, J = 8 ArH).

22. *p*-Benzoquinone, ≥98%, is purchased from the Aldrich Chemical Company, Inc., sublimed at 60° C/15 mm, and stored under argon. The checkers used it as supplied.
23. Palladium(II) chloride–acetonitrile complex is formed by placing 8.00 g of $PdCl_2$ in 200 mL of acetonitrile and stirring for 2 days or refluxing for 3 hr. The complex (11.43 g, 97.8%) is collected by filtration, washed, and dried.
24. Lithium chloride is purchased from Fisher Scientific Company and used without further purification.
25. Sodium carbonate is purchased from Aldrich Chemical Company, Inc. and used without further purification.
26. The spectral properties are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.40–2.00 (m, 6 H, CH_2); 2.10 (m, 3 H, CH_3C=); 2.40 (s, 3 H, $ArCH_3$); 2.80–3.20 (m, 1 H) 4.20–4.50 (m, 1 H, CHN); 4.70 (m, 1 H, CH=); 7.30 (d, 2 H, J = 8, ArH); 7.70 (d, 2 H, J = 8, ArH).
27. The checkers also carried out the entire sequence on three times the scale with slightly better yields.

3. Discussion

Synthesis of the title compound is representative of a number of syntheses of non-aromatic nitrogen heterocycles via Pd(II)-catalyzed amination of olefins.[3] These tosylated enamines are not readily available by standard synthetic methods and show potential for further functionalization of the heterocycle.[4] The saturated amine can be synthesized from the title compound by hydrogenation of the double bond followed by photolytic deprotection.[3]

In terms of cost, the effectiveness of the catalytic cycle in the ring closure makes this process economical in palladium. The first three steps in the reaction sequence—ring opening of an epoxide by a Grignard reagent,[5] conversion of an alcohol to an amine with inversion,[6] and sulfonamide formation from the amine[7]—are all standard synthetic processes.

References and Notes

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

benzophenone ketyl

Cyclopenta[b]pyrrole, 1,3a,4,5,6,6a-hexahydro-2-methyl-1-[4-methylphenyl)sulfonyl]-, cis-

cis-1-N-Tosyl-2-(2-propenyl)cyclopentylamine

ethyl alcohol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid,
HCl (7647-01-0)

ethyl acetate (141-78-6)

methyl alcohol (67-56-1)

ether,
ethyl ether (60-29-7)

ammonium chloride (12125-02-9)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

magnesium,
magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

Allyl bromide (106-95-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

pyridine (110-86-1)

sodium (13966-32-0)

palladium (7440-05-3)

Phthalimide (85-41-6)

hydrazine (302-01-2)

p-benzoquinone (106-51-4)

palladium(II) chloride (7647-10-1)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

diethyl azodicarboxylate (1972-28-7)

hexane (110-54-3)

Lithium chloride (7447-41-8)

argon (7440-37-1)

triphenylphosphine (603-35-0)

p-Toluenesulfonyl chloride (98-59-9)

tosyl-2-(2-propenyl)cyclopentylamine

Cyclopentene oxide (285-67-6)

cis-N-Tosyl-3-methyl-2-azabicyclo[3.3.0]oct-3-ene (81097-07-6)

trans-2-(2-Propenyl)cyclopentanol (74743-89-8)

cis-2-(2-Propenyl)cyclopentylamine (81097-02-1)