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Synthesis of bicyclo[5.3.0]azulene derivatives

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Abstract

Azulene has been recognized for its application in medicinal therapy against inflammation. Recently, azulene analogs have been used in optical technology. Nevertheless, synthesis of this family of compounds is always associated with multiple challenges. In this protocol, we describe a time-efficient and cost-effective procedure for the preparation of azulene derivatives from 2-hydroxycyclohepta-2,4,6-trienone (tropolone), a readily available starting material. The technique illustrated here involves a cycloaddition reaction of a lactone with the *in situ*-generated vinyl ether from 2,2-dimethoxypropane during the thermolysis reaction. The three-step synthesis should take <4 d, resulting in an overall yield of 74% with a final step yield of 91%.

INTRODUCTION

Azulene derivatives have many useful applications. It has a brilliant blue color, and the tuning of its optical properties has led to many azulenetic chromophores. Some of the most notable and useful derivatives of azulene are those that absorb in the near-infrared region (NIR) of the electromagnetic spectrum¹. NIR-absorbing compounds are useful imaging agents as they allow for imaging of deeper tissue because they absorb light in the ‘NIR window,’ a region of the spectrum (650–900 nm) where hemoglobin and water have their lowest absorption coefficients². Azulene derivatives have also found use as building blocks for potent pharmaceuticals. Modifications of the five- and seven-membered rings have led to the development of compounds that were found to have antioxidant, antiallergenic, antiarrhythmic, anticancer and local anesthetic activities³. Non-benzenoid bicyclic azulenes are also important intermediates in the synthesis of various useful compounds for mechanistic studies of cyclic conjugations and high-technology applications⁴. The utility of azulene derivatives is largely because of their inimitable structure of a bicyclic hydrocarbon containing asymmetric pi electrons, which result in a cyclopenta-dienyl anion and a tropylium cation. Although such a separation of charges occurs only to a slight extent, it has a very marked effect on the physical and chemical properties of azulene⁵. For instance, the cyclopentadiene of azulene is very reactive toward electrophilic substitution reactions. The

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AUTHOR CONTRIBUTIONS

D.D.N. performed the synthesis with some literature discussions and contributions from M.N.; W.P., R.P. and J.C.G. supervised the work. W.P. and D.D.N. prepared the manuscript.

aromaticity of this five-membered ring of azulene has been the subject of several important modifications, namely Friedel–Crafts acylations⁶, Mannich aminomethylations⁷, condensations⁸ and Vilsmeier formylations^{6,9,10}, among others. On the other hand, the tropylium cation is suitable for use in nucleophilic reactions and is a subject of interest representing a class of nonbenzenoid aromatic compounds^{11,12}.

Given its primary role in a number of leading research efforts, synthetic strategies for synthesizing azulene and its derivatives will remain the subject of much attention. Azulene can be obtained by dehydrogenation of bicyclo[5.3.0]decane or from various bicyclo[5.3.0]decenes in the presence of palladium catalysts⁵. These reactions usually require harsh conditions, result in low yields and must overcome a significant obstacle: the rareness of the starting materials. These drawbacks have necessitated the development of alternative techniques for generating azulene. Hafner and Meinhardt¹³ reported a four-step synthesis of azulene, in which a Mannich reaction was carried out on cyclopentadiene and pentamethinecyanine. In this approach, the amino fulvene is cyclized to the azulene system after a second amine elimination in the last step. Another approach for the synthesis of azulene is through the intramolecular carbene addition to the 1, 2 position of a benzene ring¹⁴. The transient formation of norcaradiene facilitates the ring opening of the bicyclo trienone, which forms azulene after dehydration. Using another approach, the [8+2]-cycloaddition reaction was carried out between heptafulvene and dimethyl acetylene dicarboxylate¹⁵. However, this reaction is impractical given the difficulties associated with obtaining the starting materials, specifically heptafulvene is very unstable¹⁶. Wang *et al.*¹⁷ recently reported the synthesis of azulene analogs by condensation of cyclohepta[*b*]furan-2-one with *in situ*-generated enamine in the presence of molecular sieves. Under optimized conditions, these procedures generate azulene analogs with 79% yield compared with 91% obtained through our protocol.

We describe herein a robust protocol for synthesizing azulene derivatives from commercially available starting materials. The procedures described have been investigated and optimized over the course of many years to achieve high reaction yield and reproducibility^{18,19}. The key step in this short three-step synthesis is the [8+2]-cycloaddition reaction that is carried out under high temperature and pressure²⁰.

Experimental design

The following protocol is the general procedure used for synthesizing methyl 2-methylazulene-1-carboxylate. It is optimized for reactions up to the 10-mmol scale. Detailed reaction conditions, setups and purification of the products by column chromatography are described. Although the reactions use anhydrous solvents in the presence of a static argon atmosphere, the starting materials are not particularly sensitive to air; therefore, no intensive care is required.

As shown in Figure 1, the [8+2]-cycloaddition reaction requires special attention to detail due to the explosive nature of the reaction. The sealed tube is not only heated at high temperature, but high pressure is also generated through the production of CO₂ gas during the reaction (Fig. 2).

MATERIALS

REAGENTS

Tropolone, 98% purity (Sigma-Aldrich, cat. no. T89702) ! **CAUTION** Irritant, may be harmful if swallowed, inhaled or absorbed through the skin. Irritating to the eyes.

p-Toluenesulfonyl chloride (Sigma-Aldrich, cat. no. 240877) ! **CAUTION** Irritant, may be harmful if swallowed, inhaled or absorbed through the skin. Causes eye burns.

Triethylamine (Sigma-Aldrich, cat. no. 471283) ! **CAUTION** Highly flammable, avoid contact, may cause eye, skin and respiratory tract irritation. May be harmful if swallowed. Target organs are the heart, liver, kidney and the central nervous system.

Dimethyl malonate (Sigma-Aldrich, cat. no. 136441) ! **CAUTION** Irritant, avoid contact with the eyes, skin, and respiratory tract. Risk of serious damage to the eyes.

Sodium methoxide (Fluka, cat. no. 71750) ! **CAUTION** Pyrophoric, highly flammable and corrosive. Reacts violently with water. Avoid contact, causes burns to the skin and the eyes, and inhalation and ingestion hazard.

2,2-Dimethoxypropane (Sigma-Aldrich, cat. no. D136808) ! **CAUTION** Avoid contact, may cause eye, skin, and respiratory tract irritation. May be harmful if swallowed.

Magnesium sulfate, anhydrous (Fisher Scientific, cat. no. M65-500) ! **CAUTION** Avoid contact, may cause eye, skin, and respiratory tract irritation.

Silica gel (Sigma-Aldrich, cat. no. 236837, Davisil, Grade 645, pore size 150 Å, 60–100 mesh) ! **CAUTION** Do not breathe dust, a known carcinogen.

Toluene, anhydrous, 99.8% purity (Sigma-Aldrich, cat. no. 244511) ! **CAUTION** Teratogen, flammable liquid, avoid contact, may cause eye, skin, and respiratory tract irritation.

Methanol, anhydrous, 99.8% purity (Sigma-Aldrich, cat. no. 322415) or purified through the purification system noted in EQUIPMENT. ! **CAUTION** Avoid skin contact and inhalation; flammable liquid and vapor; and poisonous.

Methylene chloride, anhydrous, 99.8% purity (Sigma-Aldrich, cat. no. 270997) or purified through the purification system noted in EQUIPMENT ! **CAUTION** A known carcinogen, avoid skin contact and inhalation, environmental toxin.

Hexanes (Fisher Scientific, cat. no. H292-20) ! **CAUTION** Highly flammable, avoid long-term exposure and environmental toxin.

EQUIPMENT

Tygon tubing (Nalgene 1/4 inch i.d.; Fisher Scientific)

Teflon-coated stir bars, assorted sizes and styles (Fisher Scientific)

Glass syringes, various sizes (Hamilton or Popper & Sons)

Stainless steel lure lock needles, various sizes (Popper & Sons)

Single-necked round-bottom flasks, various sizes (Chemglass or Wilmad)

Separatory funnels, 150 and 250 ml (Pyrex)

Septum stopper, sleeve type for 14/20 and 24/40 joints (Chemglass, cat. no. CG-3022-24 or CG-3022-08)

Erlenmeyer flask, 225 and 500 ml (Kimax)

60-ml Coarse frit vacuum funnel (Pyrex, cat. no. 40–60)

Thin Layer Chromatography (TLC) plates (Sigma-Aldrich, cat. no. 60778)

Rotary evaporator with heating bath (Buchi, models R-205 and B-490)

Glass filter flasks, 250 and 500 ml (Pyrex, cat. no. 5340)

Filter paper, various sizes (Whatman)

Buchner filter funnels (CoorsTek, cat. no. 60239)

Ace pressure tube bushing type A, volume ~38 ml (Sigma-Aldrich, cat. no. Z181080)

Ace glass FETFE O-ring, size 110 (Sigma-Aldrich, cat. no. 7855-716)

Aldrich dual bank manifold with glass stopcocks (Sigma-Aldrich, cat. no. Z243574)

Optional

Weighted safety shield (Sigma-Aldrich, cat. no. Z231401)

Silicon oil (Sigma-Aldrich, cat. no. 175633)

Biotage purification system (model SP-1, SPX software v. 2.0 Build #4159) Optional

Flash columns (Biotage Si 25+M 1988-1 ~48 ml)

Pure Solv MD-5 Solvent Purification System (Innovative Technology) Optional

PROCEDURE

Synthesis of 7-oxocyclohepta-1,3,5-trienyl 4-methylbenzenesulfonate (1)

- 1| Weigh 5.3 g (43 mmol) of 2-hydroxycyclohepta-2,4,6-trienone (tropolone) and transfer into an oven-dried 500-ml round-bottomed flask that has been flushed with argon and equipped with a large Teflon-coated magnetic stir bar. Re-seal with a rubber septum.
- 2| Weigh 8.2 g (43 mmol) of 4-methylbenzene-1-sulfonyl chloride (tosyl chloride) and transfer into the same 500-ml round-bottomed flask (from Step 1) and re-seal with the rubber septum.
- 3| Add 60 ml of anhydrous methylene chloride into the same 500-ml round-bottomed flask (from Step 1) at room temperature (22–26 °C) and begin stirring the mixture with a magnetic stir plate to dissolve the tropolone and tosyl chloride. **▲ CRITICAL STEP** Steps 3 and 4 must be performed using inert gas techniques.

- 4| Add 4.4 g (6 ml, 43 mmol) of triethylamine dropwise to the stirring methylene chloride mixture through a glass syringe equipped with a 20-gauge stainless steel syringe needle. This should result in a yellow slurry. Add another 60 ml of methylene chloride to provide sufficient volume for stirring because of increased viscosity of the reaction mixture.
- 5| After stirring at room temperature for ~32 h under nitrogen or argon, add ice directly to the reaction mixture.
- 6| Transfer the reaction mixture to a 500-ml separation funnel and extract three times with 150 ml portions of methylene chloride. Combine the methylene chloride extracts and dry using anhydrous MgSO_4 for <10 min. Filter and concentrate the dried extracts under reduced pressure in a rotary evaporator (~1.0 mm Hg water bath at 30–40 °C for ~35 min) to yield a tan-colored solid that needs no further purification (11.8 g, 99%).

Synthesis of methyl 2-oxo-2H-cyclohepta[b]furan-3-carboxylate (2)

- 7| Weigh 11.8 g (43 mmol) of 7-oxocyclohepta-1,3,5-trienyl 4-methylbenzenesulfonate (**1**) and transfer into an oven-dried 250-ml round-bottomed flask, flask A, which has been flushed with argon and equipped with a large Teflon-coated magnetic stir bar and a rubber septum.
- ▲ **CRITICAL STEP** As the flask is cooled and after the addition of compound **1**, ensure to place an inert gas inlet into the septum of the flask so that ambient air is not drawn into the dried flask.
- 8| Add 9.8 ml (86 mmol) of dimethyl malonate into flask A through a 10-ml glass syringe equipped with a 20-gauge stainless steel syringe needle.
- 9| Weigh 4.62 g (86 mmol) of sodium methoxide and quickly transfer the powder into an oven-dried 100-ml round-bottomed flask, flask B, equipped with a medium Teflon-coated magnetic stir bar and seal with a rubber septum. Slowly add 50 ml of anhydrous methanol to the sodium methoxide and mix to dissolve.
- ! **CAUTION** Sodium methoxide is a dangerously caustic base; use proper safety equipment while handling.
- 10| Cool the flask A to 0 °C by immersing in an ice water bath.
- ▲ **CRITICAL STEP** Place an inert gas inlet into the septum of the flask so that ambient air is not drawn into the flask as it cools.
- 11| Once cooled, slowly add the contents of the flask B to the flask A dropwise through a 10-ml glass syringe equipped with a 20-gauge stainless steel syringe needle over the course of 15 min.
- 12| Once the addition is complete, leave the flask A immersed in the 0 °C ice water bath for 6 h, and then slowly allow the reaction mixture to warm to room temperature overnight.

- 13| Precipitate the product by pouring the reaction mixture onto ice in an Erlenmeyer flask and pack the flask in ice.
- 14| Collect the yellow solid that has precipitated/crystallized in the Erlenmeyer flask using a Buchner funnel and filter paper (Whatman no. 1, 42.5 mm). More solid product can be collected by concentrating the filtrate on a rotary evaporator until solid forms and again pouring the resulting slurry over ice. Two to three crops of product are typically collected depending on how much starting material is used.
- 15| Combine the collected solid in a 20-ml glass scintillation vial and dry in a vacuum desiccator overnight to remove all solvent yielding a yellow solid that needs no further purification (7.2 g, 82%).

Synthesis of methyl 2-methylazulene-1-carboxylate (3)

- 16| Weigh 1.87 g (9.2 mmol) of methyl 2-oxo-2H-cyclohepta[b]furan-3-carboxylate (**2**) and transfer into an oven-dried Ace pressure tube using a glass funnel.
▲ CRITICAL STEP Ensure none of the solid gets into the grooves of the Teflon cap. The residual solid will prevent the cap from sitting properly and may cause an explosion once the tube is under pressure.
- 17| Add 5.7 ml (46.5 mmol) of 2,2-dimethoxypropane to the pressure tube through a 10-ml glass syringe equipped with a 20-gauge stainless steel needle, rinsing the residual solid into the tube.
- 18| Add 6 ml (56.5 mmol) of toluene to the pressure tube through a 10-ml glass syringe equipped with a 20-gauge stainless steel needle, by rinsing the remaining part of the residual solid into the tube.
- 19| Seal the tube with the Teflon cap and the FETFE O-ring (size 110) until the cap is finger tight (see Fig. 3).
▲ CRITICAL STEP Ensure the cap is not over tightened and that the FETFE O-ring is sitting properly in order to avoid a possible explosion due to excessive pressure during the reaction.
! CAUTION Do not fill the tube more than half full of solvent; this precaution will help prevent explosion.
- 20| Heat the pressure tube to 200 °C in a silicon oil bath heated with a ceramic hot-stir plate.
▲ CRITICAL STEP Ensure to calibrate the ceramic hot plate. Heat transfer from the hot plate to the silicon oil bath is not perfect. The actual oil bath temperature may be up to 200 °C lower than the setting on the hot plate.
! CAUTION Ensure to angle the tube away from the front of the hood and toward a corner. Place a blast shield in front of the reaction in case it happens to explode, this safeguard will prevent potential injury.
- 21| Heat the reaction for 24 h at 200 °C.

- 22| After the pressure tube has cooled, carefully open the Teflon cap pointing the tube away from one's body.
- 23| Pour the contents of the tube into an oven-dried 250-ml round-bottom flask and rinse the tube using 50–100 ml of methylene chloride.
- 24| Concentrate the reaction mixture under reduced pressure using a rotary evaporator to yield a violet-colored residue or solid.
- 25| Adsorb the residue or solid onto silica gel by dissolving the residue in 50 ml of methylene chloride and then add 10–15 g of dry silica gel. Concentrate the material using a rotary evaporator to provide a fine violet powder.
- 26| Pack the compound adsorbed onto the silica gel into the top of a flash chromatography column. Put the flash column into the pressure cylinder on a Biotage purification system and attach the solvent flow tubes to the cylinder according to the manufacturer's instructions.
- 27| Elute the product from the flash column using a gradient of 0–50% methylene chloride in hexanes over the course of 3,200 ml with a flow rate of 40 ml min⁻¹. The product elutes over a wide solvent range (1,375–2,800 ml).
- 28| Use TLC analysis to correctly identify compound **3** in fractions collected during Step 27. Carry out an analysis using an eluent in the ratio of 50:50 CH₂Cl₂/hexanes (*R_f* = 0.85).
- 29| Evaporate the solvent of the combined fractions using a rotary evaporator and by gently warming the external water bath to a maximum of 40 °C. Further dry the violet solid by placing it inside a desiccator connected to an in-house vacuum line to provide **3** as a violet-red solid (1.67 g, 91% yield from **2**).

● TIMING

- Synthesis of (**1**): Steps 1–2, 5 min; Step 3, 1 min; Step 4, 20 min; Step 5, 32 h; and Step 6, 35–45 min. Total time: 33 h.
- Synthesis of (**2**): Steps 7–8, 10 min; Step 9, 10 min; Step 10, 10 min; Step 11, 15 min; Step 12, 18 h; Step 13, 30 min; Step 14, 25–35 min; and Step 15, 12 h. Total time: 32 h 45 min.
- Synthesis of (**3**): Steps 16–19, 20 min; Step 21, 24 h; Step 22, 30 min; Steps 23–24, 15 min; Step 25, 10 min; Step 26, 5 min; Step 27, 60–75 min; Step 28, 15–20 min; and Step 29, 4 h. Total time: 30 h 40 min.

ANTICIPATED RESULTS

Typical yields

Typical isolated yield for **1** is 90–99%, yields of 66–82% can be expected for the synthesis of **2** and 70–91% for **3** (yields improve with experience). The typical overall yield achieved by an experienced researcher for the three steps starting from tropolone is 74%.

Analytical data

Synthesis of 1, a tan solid (melting point (MP) =146 °C)—¹H NMR (400 MHz, CDCl₃): δ 2.43 (3H, s); 6.95 (1H, t, *J* = 10.1); 7.05 (1H, t, *J* = 10.9, 7.8); 7.12 (1H, d, *J* = 11.8); 7.18 (1H, m, *J* = 7.8, 4.9, 7.8); 7.32 (2H, d, *J* = 8.2); 7.43 (1H, d, *J* = 9.4); 7.905 (2H, d, *J* = 8.3).

MS (ESI) *m/e* calculated for C₁₄H₁₂O₄S: (*M*⁺ + 1) 277.0490, observed: 277.1159.

Synthesis of 2, a yellow solid (MP = 162 °C)—TLC (95:5 CH₂Cl₂/methanol): *R*_f = 0.76.

¹H NMR (300 MHz, CDCl₃): δ 3.89 (3H, s); 7.32 (1H, t, *J* = 8.9); 7.46 (2H, d, *J* = 8.5); 7.61 (1H, t, *J* = 9.9); 8.82 (2H, d, *J* = 11.4).

MS (ESI) *m/e* calculated for C₁₁H₈O₄: (*M*⁺ + 1) 205.0456, observed: 205.1024.

Synthesis of 3, a violet red solid (MP = 30–32 °C)—TLC (50:50 CH₂Cl₂/hexanes): *R*_f = 0.85.

¹H NMR (400 MHz, CDCl₃): δ 2.81 (3H, s); 3.95 (3H, s); 7.11 (1H, s); 7.37 (1H, t, *J* = 9.7 Hz); 7.48 (1H, t, *J* = 9.9);

7.67 (1H, t, *J* = 9.8); 8.26 (1H, d, *J* = 9.8); 9.47 (1H, d, *J* = 10).

MS (ESI) *m/e* calculated for C₁₃H₁₂O₂: (*M*⁺ + 1) 201.0871, observed: 201.1239.

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Figure 1. Synthesis scheme for the preparation of methyl 2-methylazulene-1-carboxylate (**3**). **(a)** Preparation of tosylated tropolone (**1**). **(b)** Ring-closing reaction to prepare lactone (**2**). **(c)** [8+2]-cycloaddition reaction. Reproduced with permission from reference 18.

Figure 2.
Proposed mechanism of [8+2]-cycloaddition.

Figure 3. Apparatus set up for the pressurized [8+2]-cycloaddition reaction to prepare the azulene derivative, **3**.