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Carbonyl-Olefin Metathesis for the Synthesis of Cyclic Olefins

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Graphical Abstract

Procedure (Note 1)

A. Geranyl bromide (2).

A flame-dried 250-mL round-bottomed flask was charged with a Teflon-coated magnetic stir bar (egg-shaped, 4 cm length $\times$ 1.5 cm diameter), geraniol **1** (30.00 g, 194 mmol, 1.0 equiv.) and anhydrous THF (130 mL) (Note 2). The flask is equipped with a flame-dried 125-mL pressure-equalizing addition funnel fitted with a rubber septum and nitrogen inlet. Phosphorus tribromide (9.1 mL, 96.8 mmol, 0.5 equiv.) and anhydrous THF (10 mL) are added. The flask containing the geraniol solution is immersed in an ice/water bath and the phosphorus tribromide solution is added dropwise under stirring over 40 min (Figure 1).

After the addition is complete, the pale-yellow homogeneous solution was stirred in the ice bath for 1 h (full conversion of starting material judged by TLC) under an atmosphere of nitrogen (Note 3). The reaction mixture was poured carefully into a 1-L Erlenmeyer flask fitted with a Teflon-coated magnetic stir bar (5 cm length $\times$ 1 cm diameter) containing cold (0°C) deionized water (200 mL). The reaction flask was rinsed with hexanes (3 $\times$ 10 mL) during the transfer step. After stirring for 10 min, the biphasic mixture was transferred to a 500-mL separatory funnel, and the Erlenmeyer flask was rinsed with hexanes (3 $\times$ 10 mL), which is added to the separatory funnel. The aqueous layer was separated and

extracted with hexanes (3× 200 mL). The combined organic layers were dried over Na₂SO₄ (75 g), filtered and concentrated under reduced pressure with a rotary evaporator (100 mbar, bath temperature 40°C). The residue (clear oil) was transferred into a 100-mL round-bottomed flask and distilled using a short-path distillation apparatus under vacuum (2.1 mbar) (Figure 2). The fraction distilling at 63–69°C is collected after a forerun (~2 mL), which is discarded, to afford geranyl bromide **2** as colorless oil (34.9–36.3 g, 83–86%) (Note 4).

B. 2,6-dimethyl-1-phenyl-2-vinylhept-5-en-1-one (**3**).

A flame-dried 1-L three-necked, round-bottomed flask is fitted with a Teflon-coated magnetic stir bar (egg-shaped, 4 cm length × 1.5 cm diameter) and equipped with a rubber septum with nitrogen inlet. A flame-dried 125-mL pressure-equalizing addition funnel containing a solution of geranyl bromide **2** (27.8 mL, 140 mmol, 1.25 equiv.) in anhydrous THF (30 mL) is attached to the reaction flask and sealed with a rubber septum. The three-necked flask was charged with activated zinc powder (18.31 g, 280 mmol, 2.5 equiv.) (Note 5), lithium chloride (6.65 g, 157 mmol, 1.4 equiv.) and anhydrous THF (530 mL) before being sealed with a rubber septum. The flask is immersed in a room temperature water bath and the geranyl bromide solution is added dropwise over 10 min to the vigorously stirred suspension. After complete addition, the grey, heterogeneous mixture was stirred for 1.5 h under an atmosphere of nitrogen at ambient temperature (full consumption of starting material by TLC) (Note 6), at which time stirring was stopped and excess zinc allowed to settle. A flame-dried 1-L round-bottomed flask is fitted with a rubber septum with nitrogen inlet after being charged with a Teflon-coated magnetic stir bar (egg-shaped, 4 cm length × 1.5 cm diameter), benzoyl chloride (13.0 mL, 112 mmol, 1.0 equiv.) and anhydrous THF (110 mL).

The benzoyl chloride containing flask is immersed in an ice/water bath and the supernatant zinc reagent solution is added via a cannula over 10 min at a rate that kept the internal temperature below 10°C. After addition is complete, the flask remained in the ice/water bath and the slightly cloudy solution is stirred for 20 min under an atmosphere of nitrogen (full conversion of starting material judged by TLC) (Note 7). Then an aqueous saturated NH₄Cl solution (100 mL) and deionized water (100 mL) were added sequentially. After the ice/water bath was removed and the mixture stirred for 10 min, the biphasic mixture was transferred to a 1-L separatory funnel and the reaction flask rinsed with EtOAc (3× 10 mL), which was added to the separatory funnel. The aqueous layer was separated, extracted with EtOAc (3× 200 mL) and the combined organic layers concentrated under reduced pressure with a rotary evaporator (100 mbar, bath temperature 40°C). The oily residue was taken up in EtOAc (250 mL) and washed with deionized water (50 mL), an aqueous 1 M NaOH (3× 50 mL) and brine (50 mL) (Note 8). The organic layer was dried over Na₂SO₄ (75 g), filtered and concentrated under reduced pressure with a rotary evaporator (100 mbar, bath temperature 40°C) and then with a vacuum pump (2.1 mbar) to afford aryl ketone **3** as pale-yellow oil (~31 g), which was used for the next step without further purification (Note 9).

C. (5-methyl-5-vinylcyclopent-1-en-1-yl)benzene (4).

A flame-dried 1-L round-bottomed flask was fitted with a Teflon-coated magnetic stir bar (egg-shaped, 4 cm length $\times$ 1.5 cm diameter) and charged with iron(III) chloride (908 mg, 5.6 mmol, 0.05 equiv.) (Note 10), which is immediately suspended in anhydrous CH_2Cl_2 (370 mL) (Note 11).

The flask was equipped with a flame-dried 125-mL pressure-equalizing addition funnel containing a solution of aryl ketone **3** (Note 12) in anhydrous CH_2Cl_2 (80 mL) and the apparatus sealed with a rubber septum with nitrogen inlet. The aryl ketone solution was added to the suspension of FeCl_3 over 2 min and the resulting dark-brown solution stirred at ambient temperature for 2.5 h (full consumption of starting material by TLC) (Note 13) (Figure 4). The reaction mixture was passed through a short silica plug (200 g silica gel equilibrated in CH_2Cl_2 in a glass column with 8.5 cm diameter) positioned over a 2-L round-bottomed flask and the plug rinsed with CH_2Cl_2 (750 mL) applying a brief positive pressure to move the solution through the silica gel (Figure 5).

The eluent is concentrated under reduced pressure with a rotary evaporator (100 mbar, bath temperature 40°C). The residual orange oil is transferred to a 100-mL round-bottomed flask and distilled using a short-path distillation apparatus under vacuum (2.1 mbar) (Note 14). The fraction distilling at 85–90°C is collected after a forerun (~2 mL), which is discarded, to afford cyclopentene **4** as colorless oil (11.92–14.40 g, 58–70% over two steps) (Note 15).

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of “Prudent Practices in the Laboratory” (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at <https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical>. See also “Identifying and Evaluating Hazards in Research Laboratories” (American Chemical Society, 2015) which is available via the associated website “Hazard Assessment in Research Laboratories” at <https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html>. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with geraniol, tetrahydrofuran (THF), phosphorus tribromide (PBr_3), hexane, ethyl acetate, sodium sulfate (Na_2SO_4), zinc, lithium chloride, benzoyl chloride, ammonium chloride, sodium hydroxide, sodium chloride, iron(III) chloride (FeCl_3), silica and dichloromethane (CH_2Cl_2), as well as the proper procedures for vacuum distillation.

2. Geraniol (>96.0%) was obtained from TCI America and used as received. Tetrahydrofuran was obtained from Fisher (Optima) and dried by being passed through columns of activated alumina under argon (using a JC-Meyer Solvent Systems). PBr_3 (99%) was obtained from Acros Organics and used as received.
3. The reaction progress was followed by TLC analysis on silica gel with 8:2 hexane/EtOAc as eluent and visualization with KMnO_4 . The starting material geraniol has $R_f = 0.47$ and the product geranyl bromide has $R_f = 0.95$.
4. The product **2** was characterized as follows: $^1\text{H NMR}$ (700 MHz; CDCl_3): $\delta = 5.53$ (td, $J = 8.4, 1.4$ Hz, 1H), 5.07 (tt, $J = 6.8, 1.6$ Hz, 1H), 4.03 (d, $J = 8.5$ Hz, 2H), 2.13 – 2.04 (m, 4H), 1.73 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); $^{13}\text{C NMR}$ (176 MHz; CDCl_3): $\delta = 143.8, 132.2, 123.7, 120.7, 39.7, 29.9, 26.3, 25.8, 17.9, 16.1$; **IR** (neat): $\nu = 2968, 2914, 2855, 1657, 1443, 1376, 1200, 1108, 984, 837$; **HRMS** (EI): m/z calcd. for $\text{C}_{10}\text{H}_{17}\text{Br}^+ [\text{M}^+]$: 216.0514; found: 216.0505. The purity was assessed as 97% by quantitative $^1\text{H NMR}$ using dimethyl terephthalate as internal standard.
5. Zn powder (99.3%) was obtained from Fischer Chemical and activated prior to use. For the reported scale, a 250-mL Erlenmeyer flask fitted with a Teflon-coated magnetic stir bar (5 cm length $\times$ 1 cm diameter) was charged with zinc powder (~25 g) and 1 M HCl (aq., 75 mL). The suspension was stirred for 10 min and filtered with a Buchner funnel and subsequently washed with 1 M HCl (aq., 2×50 mL), water (1×50 mL), ethanol (2×50 mL) and diethyl ether (2×50 mL) and the activated zinc powder dried under reduced pressure using a vacuum pump. LiCl (99%, for molecular biology) was obtained from Acros Organics and dried prior to use at 200°C under reduced pressure with a vacuum pump. Benzoyl chloride (99%) was obtained from Sigma Aldrich and distilled prior to use.
6. Full consumption of geranyl bromide was determined by TLC on silica gel with 100% hexane as eluent and visualization with KMnO_4 and UV light (254 nm). Geranyl bromide has $R_f = 0.48$.
7. The reaction progress was followed by TLC analysis on silica gel with 98:2 hexane/EtOAc as eluent and visualization with UV and ceric ammonium molybdate (CAM) stain. The starting material benzoyl chloride has $R_f = 0.59$ (no CAM activity) and the ketone product has $R_f = 0.41$ (blue with CAM).
8. A basic wash was necessary to remove any benzoic acid. A basic wash without prior removal of THF proved to be ineffective.
9. An analytically pure sample of **3** was obtained by purification by flash column chromatography (19:1 hexane/EtOAc). The pure compound was characterized as follows: $^1\text{H NMR}$ (700 MHz; CDCl_3): $\delta = 7.85$ (d, $J = 7.3$ Hz, 2H), 7.45 (t, $J = 7.4$ Hz, 1H), 7.37 (t, $J = 7.8$ Hz, 2H), 6.17 (dd, $J = 17.6, 10.7$ Hz, 1H), 5.25 – 5.20 (m, 2H), 5.02 (s, 1H), 1.96 – 1.91 (m, 2H), 1.80 – 1.73 (m, 2H), 1.62 (s, 3H), 1.44 (s, 3H), 1.38 (s, 3H); $^{13}\text{C NMR}$ (176 MHz; CDCl_3): $\delta = 204.8, 143.3, 137.8, 132.1, 131.7, 129.1, 128.1, 124.1, 114.9, 53.7, 39.1, 25.8, 23.1$,

23.0, 17.6; **IR** (neat): ν = 2970, 2929, 2858, 1677, 1630, 1445, 1176, 1002, 964, 917, 718, 694; **HRMS** (ESI+): m/z calcd. for $C_{17}H_{23}O^+$ [$M+H^+$]: 243.1743; found: 243.1741.

10. $FeCl_3$ (98%) was obtained from Strem Chemicals and used as received. Anhydrous CH_2Cl_2 was obtained from Fisher (Stabilized/Certified ACS) and dried by being passed through columns of activated alumina under argon (using a JC-Meyer Solvent Systems).
11. $FeCl_3$ was weighed out onto a metal spatula (1.5 cm width) and washed into the round-bottomed flask using CH_2Cl_2 .
12. All crude material obtained from the previous step was used.
13. The reaction progress was followed by TLC analysis on silica gel with 19:1 hexane/EtOAc as eluent and visualization with UV light. The starting material aryl ketone **3** has R_f = 0.38 and the product cyclopentene **4** has R_f = 0.62. Note: A side product with the same R_f value as starting material was observed by TLC during the course of the reaction.
14. The same distillation setup as displayed in Figure 2 was used.
15. The product **4** was characterized as follows: **1H NMR** (700 MHz; $CDCl_3$): δ = 7.42 (d, J = 7.5 Hz, 2H), 7.27 (t, J = 7.6 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 6.08 (dd, J = 17.5, 10.6 Hz, 1H), 6.05 (t, J = 2.6 Hz, 1H), 5.12 – 5.03 (m, 2H), 2.48 – 2.40 (m, 1H), 2.42 – 2.34 (m, 1H), 2.03 – 1.99 (m, 1H), 1.92 – 1.86 (m, 1H), 1.32 (s, 3H); **^{13}C NMR** (176 MHz; $CDCl_3$): δ = 149.0, 146.0, 137.1, 128.9, 128.0, 127.2, 126.8, 111.4, 52.4, 42.1, 29.7, 23.5; **IR** (neat): ν = 3081, 3053, 2957, 2929, 2845, 1634, 1492, 1444, 1370, 1075, 1000, 909, 828, 758, 695; **HRMS** (EI): m/z calcd. for $C_{14}H_{16}^+$ [M^+]: 184.1252; found: 184.1254. The purity was assessed as 97% by quantitative 1H NMR using dimethyl terephthalate as internal standard.

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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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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Discussion

The carbonyl-olefin metathesis reaction is characterized by the exchange of double-bonded atoms in a carbonyl and an olefin to form a new carbonyl and a new olefin. The most common protocol for this reaction involves using precious metal alkylidenes as reagents that provide ring-closing carbonyl olefin metathesis products with a corresponding amount of a catalytically inactive metal-oxo by-product.^{2,3} Our lab recently developed a carbonyl-olefin metathesis reaction relying on FeCl₃ as an environmentally benign Lewis acid catalyst that allows for the synthesis of cyclic olefins under mild conditions.⁴⁻⁶ The reported method is operationally facile and employs catalyst loadings as low as 5 mol%. Notably, the reaction occurs at ambient temperature, utilizes a cheap, abundant metal salt as a catalyst, and produces an easily removable, organic compound as the sole by-product. Table 1 demonstrates a small selection of the broad substrate scope for the carbonyl-olefin metathesis reaction. Generally, aromatic ketones with electron-donating or withdrawing groups are converted to the corresponding cyclopentene products in good to excellent yields. Furthermore, the reaction protocol allows for efficient access to cyclohexenes and structurally complex motifs such as tricycles and spirocycles.

In this work, we report a carbonyl-olefin metathesis protocol that provides an operationally simple and easily scalable synthesis of cyclic olefin **4**. We demonstrate, that the required starting material for the carbonyl-olefin metathesis can be prepared from readily accessible and cheap reagents allowing for rapid access to large quantities of compound. The carbonyl-olefin metathesis as a key transformation was carried out on 30 g-scale using FeCl₃ as a cheap and environmentally benign Lewis acid catalyst. Notably, the reported protocol gives the desired product in good yield and excellent purity. This manuscript demonstrates the potential of carbonyl-olefin metathesis as an economical and sustainable approach for the synthesis of cyclic olefins.

Appendix: Chemical Abstracts Nomenclature (Registry Number)

Geraniol: 2, 6-Octadien-1-ol, 3,7-dimethyl-, (2*E*)-; (106-24-1)

Phosphorus tribromide: Phosphorous tribromide; (7789-60-8)

Zinc; Zinc; (7440-66-6)

Lithium chloride: Lithium chloride; (7447-41-8)

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Figure 1:
Addition of phosphorus tribromide to geraniol.

Figure 2:
Distillation Apparatus for distillation of geranyl bromide 2.

Figure 3:
Preparation of allyl zinc reagent (left) and addition of allyl zinc reagent to benzoyl chloride via cannula (right).

Figure 4:
Color change before (left) and after (right) addition of aryl ketone 3 to FeCl_3 suspension.

Figure 5:
Silica plug before (left) and after (right) filtration and rinsing.

Table 1:

Scope of the iron(III)-catalyzed carbonyl-olefin metathesis reaction.

Selected Examples

* Conditions: ketone (1 equiv.), FeCl_3 (5 mol%), dichloroethane (0.1–0.01 M), rt, 1–24 h.