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A Three-Step Route to a Tricyclic Steroid Precursor

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Abstract

2-Alkyl cyclohexenones are useful intermediates for organic synthesis. The Wittig reaction of a series of aldehydes with (cyclopropylmethyl)triphenylphosphonium bromide delivered the corresponding alkenyl cyclopropanes. UV irradiation in the presence of $\text{Fe}(\text{CO})_5$ converted the alkenyl cyclopropanes to the 2-substituted cyclohexenones. This approach enabled a three-step synthesis of the tricyclic core of estrone methyl ether.

Introduction

Estrone **1** and estradiol **2** (Eq. 1), important hormones that control the menstruation cycle of mammals, are an attractive research area due to their high biological activity and many pharmaceutical applications. A variety of synthetic strategies have been published for the synthesis of estrone and its derivatives.¹ The first total synthesis of estrone was published in 1948 by Anner and Miescher.^{1a} The tricyclic phenanthrenone core **3** played a key role in that synthesis and is a potentially useful intermediate for steroid syntheses.²

(1)

We envisioned (Scheme 1) that aldehyde **4a** could be homologated to the corresponding alkenyl cyclopropane by Wittig reaction with the commercially available (cyclopropylmethyl)-triphenylphosphonium bromide **5**.³ UV irradiation of the alkenyl cyclopropane **6a** so prepared in the presence of $\text{Fe}(\text{CO})_5$ under a CO atmosphere⁴ would then lead to the corresponding cyclohexenone **7a**. Acid catalyzed cyclization would then deliver the tricyclic ketone **3**, in just three steps from the commercial aldehyde **4a**.

Results and Discussion

2-Alkyl cyclohexenones are important intermediates for target-directed synthesis.⁵ While several methods have been developed to prepare such cyclohexenones, these routes tend to be either low yielding or multi-stepped.⁶ There were two challenges to be overcome in developing

the route to 2-alkylcyclohexenones outlined in Scheme 1: Development of the Wittig reaction, and optimization of the Fe-mediated cyclocarbonylation.

Development of the Wittig Reaction

We initially performed the Wittig reaction utilizing one equivalent of commercial (cyclopropylmethyl)triphenylphosphonium bromide and one equivalent of potassium *t*-butoxide at cryogenic temperatures. This protocol led to modest yields, with some unreacted aldehyde. During optimization, we found that increasing both base and phosphonium salt to a slight excess increased conversion. While maintaining the slight excess of phosphonium bromide, we doubled the amount of base, which led to complete conversion and high yields. Finally, we found that the reaction could be carried out at room temperature. The products (Table 1) were isolated as a mixture of both the *Z* and *E* isomers of the alkenyl cyclopropane, which was of no consequence for the subsequent cyclocarbonylation.

Optimization of the Fe-Mediated Cyclocarbonylation

We initiated carbonylation studies using the conditions that we had previously developed.⁶ We found that using less than one equivalent of Fe(CO)₅ reduced the conversion rate, while adding greater than two equivalents did not lead to significantly higher conversions. Increasing the concentration of the solution typically lowered conversion. We did find that the conversion and yield improved when the mixture was agitated periodically, providing for an exchange between the product and starting material forming the thin film that was being irradiated. We maintained a CO atmosphere in each of the runs, even though CO is formed during the irradiation of the Fe(CO)₅.

During the carbonylation of **6d**, we observed a significantly lower conversion of the alkenyl cyclopropane to the cyclohexenone **7d**. It was our hypothesis that the steric bulk of the molecule hindered the carbonylation. When we ran the photolysis without autocooling and so warmer, the conversion improved significantly. This two-step conversion appears to be a versatile and convenient way to prepare 2-alkyl cyclohexenones from the corresponding aldehydes.⁷

Cyclization of the Enone

We envisioned (Scheme 2) that a variety of Lewis acids could effect the cyclization of the enone **3**.^{5b,9} We initiated our studies with BF₃·OEt₂ and TiCl₄. While both Lewis acids were efficient in forming the tricyclic ring, BF₃·OEt₂ was milder in its reaction with the cyclohexenone, leading to less decomposition and thus higher yield. We found that by adding the Lewis acid slowly at 0°C, we could also minimize decomposition.

The tricyclic ketone was approximately a 1:1 mixture of *trans* and *cis* diastereomers **3** and **8**. As had been described², the *trans* diastereomer **3** could be separated by fractional crystallization. Alternatively, the two diastereomers could be efficiently separated by column chromatography. The isolated *cis* diastereomer **8** could then be epimerized to the 1:1 mixture by heating to reflux with K₂CO₃ in THF. Using this approach, one could prepare gram quantities of the crystalline *trans* ketone **3**.

Conclusion

We expect that the aldehyde to 2-alkyl cyclohexenone conversion described here will make such cyclohexenones more readily available as intermediates for target-directed synthesis. We also envision that this facile new preparation of the ketone **3** will facilitate future steroid syntheses.

Experimental

1-(4-Cyclopropylbut-3-enyl)-3-methoxybenzene **6a**

Potassium t-butoxide (1.0 M solution in THF, 50 mL, 50 mmol) was added over 20 min to a suspension of (cyclopropylmethyl)triphenylphosphonium bromide (10.0 g, 25 mmol) in 25 mL of dry THF at 0°C. The external cooling was removed and the mixture was stirred for 30 min. The aldehyde **4a** (3.28 g, 20 mmol) was added, and the solution was stirred at rt for 1 h. The mixture was quenched with 1N HCl (50 mL) and then partitioned between water and EtOAc (3 × 100 mL). The combined organic extract was dried (MgSO₄) and concentrated. The residue was chromatographed to give the alkenyl cyclopropane **6a** (3.76 g, 93% yield, 77:23 *Z/E*) as an oil. TLC *R_f* = 0.62 (9:1 hexanes/EtOAc), ¹H NMR (*Z*) δ 7.19 (t, *J* = 7.8 Hz, 1H), 6.72-6.84 (m, 3H), 5.33-5.38 (m, 1H), 4.76 (t, *J* = 10.8 Hz, 1H), 3.79 (s, 3H), 2.61-2.72 (m, 2H), 2.44-2.52 (m, 2H), 1.44-1.53 (m, 1H), 0.63-0.72 (m, 2H), 0.27-0.31 (m, 2H); ¹³C NMR (*Z*) δ CH₃: 55.1 CH₂: 36.2, 29.4, 6.8 CH: 134.5, 129.2, 127.0, 120.9, 114.2, 111.0, 9.5 C: 159.6, 143.8; ¹H NMR (*E*) δ 7.19 (t, *J* = 7.8 Hz, 1H) 6.72-6.84 (m, 3H), 5.52-5.57 (m, 1H), 5.01 (dd, *J* = 15.2, 8.4 Hz, 1H), 3.79 (s, 3H), 2.61-2.72 (m, 2H), 2.25-2.32 (m, 2H), 1.30-1.36 (m, 1H), 0.63-0.72 (m, 2H), 0.27-0.31 (m, 2H); ¹³C NMR (*Z*) δ CH₃: 55.1 CH₂: 36.1, 29.4, 6.4 CH: 134.4, 129.2, 127.2, 120.9, 114.2, 111.0, 9.5 C: 159.6, 143.8; IR 2935, 1598, 1487, 1455, 1258 cm⁻¹; MS *m/z* (%) 202 (M, 30), 137 (65), 121 (100); HRMS: Calcd for C₁₄H₁₈O 202.1358, obsd 202.1360.

2-(3-Methoxyphenethyl)cyclohex-2-enone **7a**

To the alkenyl cyclopropane **6a** (202 mg, 1.0 mmol) in 15 mL of 2-propanol (0.075 M) was added Fe(CO)₅ (392 mg, 2.0 mmol). The reaction vessel was purged with CO, a CO balloon was attached, and the mixture was photolyzed for 8 h at room temperature in a Rayonet apparatus (300 nm) set for autocooling. The reaction was halted every 2 hours to agitate the tube inside the larger tube, after which photolysis was restarted. At the end of the irradiation, DBU (304 mg, 2.0 mmol) was added, and the mixture was stirred at room temperature for 1 h under nitrogen. The mixture was diluted with 40 mL of EtOAc and filtered through a small pad of packed silica gel and then subsequently concentrated. The residue was chromatographed to give 2 mg of unreacted **2a** and 202 mg of **7a** (89% yield based on **6a** not recovered) as an oil. TLC *R_f* = 0.17 (9:1 hexanes/EtOAc), ¹H NMR δ 7.16 (t, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 9.2 Hz, 1H), 6.81 (t, *J* = 9.2 Hz, 1H), 6.73 (m, 1H), 6.61 (m, 1H), 3.78 (s, 3H), 2.68 (m, 2H), 2.45 (m, 4H), 2.28 (m, 2H), 1.98 (m, 2H); ¹³C NMR δ CH₃: 55.4 CH₂: 38.7, 35.1, 31.7, 26.1, 23.1 CH: 149.6, 129.2, 121.0, 114.1, 111.2 C: 199.4, 159.5, 143.7, 139.2; IR 3442, 2960, 1734, 1206, 1099 cm⁻¹; MS *m/z* (%) 230 (M, 8), 221 (7), 163 (15), 135 (95), 107 (100); HRMS: Calcd for C₁₅H₁₈O₂ 231.1385, obsd 231.1391.

7-Methoxy-2,3,4,4a,10,10a-hexahydrophenanthren-1(9H)-one **3** and **8**

BF₃·OEt₂ (1.0 M solution in CH₂Cl₂, 2 mL, 2 mmol) was added over 5 min to cyclohexenone **7a** (230 mg, 1.0 mmol) in 5 mL of dry CH₂Cl₂ (0.20 M) at 0°C. The solution was stirred at rt for 3 h, quenched with water (5 mL), and then partitioned between water and methylene chloride. The combined organic extract was dried (MgSO₄) and concentrated. The residue was chromatographed using 80:20 PE:MTBE as an elution solvent to give the phenanthrenone **3** (92 mg, 40% yield) as a solid and phenanthrenone **8** (90 mg, 38% yield, 78% yield overall) as an oil. The *cis* diastereomer **8** (85 mg, 0.37 mmol) was then heated to reflux with a suspension of K₂CO₃ (690 mg, 5 mmol) in dry THF (2 mL) overnight to epimerize the phenanthrenone to a 1:1 mixture of diastereomers. For phenanthreneone **3**: mp = 106-109°C, TLC *R_f* = 0.45 (8:2 hexanes/EtOAc (double elution)). ¹H NMR δ 7.23 (d, *J* = 9 Hz, 1H), 6.75 (dd, *J* = 9, 3 Hz, 1H), 6.66 (d, *J* = 3 Hz, 1H), 3.78 (s, 3H), 2.84 (m, 2H), 2.73 (td, *J* = 12, 3 Hz, 1H), 2.61 (m, 1H), 2.41-2.53 (m, 2H), 2.35 (td, *J* = 12, 3 Hz, 1H), 2.18-2.30 (m, 2H), 1.86 (tdd, *J* = 13, 5, 4 Hz, 1H), 1.61-1.77 (m, 2H); ¹³C NMR δ CH₃: 55.2 CH₂: 44.3, 30.5, 29.3, 26.3, 21.7 CH: 138.0,

113.8, 112.0, 52.7, 44.3; C: 212.0, 157.8, 138.0, 131.2, 126.9; IR 1720, 1615 cm^{-1} ; MS m/z (%) 230 (M, 100), 213 (55), 187 (30), 160 (25), 135 (43); HRMS: Calcd for $\text{C}_{14}\text{H}_{18}\text{O}$ 230.1307, obsd. 230.1302; For phenanthrenone **8**: TLC R_f = 0.42 (8:2 hexanes/EtOAc (double elution)), ^1H NMR δ 7.05 (d, J = 9 Hz, 1H), 6.75 (dd, J = 9, 3 Hz, 1H), 6.62 (d, J = 3 Hz, 1H), 3.78 (s, 3H), 2.84 (m, 2H), 2.73 (td, J = 12, 3 Hz, 1H), 2.61 (m, 1H), 2.41-2.53 (m, 2H), 2.35 (td, J = 12, 3 Hz, 1H), 2.18-2.30 (m, 2H), 1.86 (tdd, J = 13, 5, 4 Hz, 1H), 1.61-1.77 (m, 2H); ^{13}C NMR δ CH_3 : 55.6 CH_2 : 38.8, 30.7, 29.0, 24.5, 22.6 CH: 129.7, 113.6, 112.7, 50.6, 40.4; C: 214.4, 157.8, 137.0, 131.2, 126.9; IR 1720, 1615 cm^{-1} ; MS m/z (%) 230 (M, 100), 213 (4), 187 (40), 159 (35), 147 (31), 121 (19); HRMS: Calcd for $\text{C}_{14}\text{H}_{18}\text{O}$ 230.1307, obsd 230.1302.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Scheme 2.

Table 1

Wittig Reaction and Carbonylation

Entry	Aldehyde	Wittig Yield (%)	Cyclohexenone	Carbonylation Yield (%)
1	<p>4a</p>	93	<p>7a</p>	89
2	<p>4b</p>	84	<p>7b</p>	89
3	<p>4c</p>	78	<p>7c</p>	86
4	<p>4d</p>	98	<p>7d</p>	72 ^{a,b}
5	<p>4e</p>	89	<p>7e</p>	86
6	<p>4f</p>	88	<p>7f</p>	85

^a Autocooling in Rayonet was turned off.

^b For a previous preparation of **3d**, see ^{ref 8}.