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AN IMPROVED SYNTHESIS OF 2-(HYDROXYMETHYL)INDENE

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AN IMPROVED SYNTHESIS OF 2-(HYDROXYMETHYL)INDENE

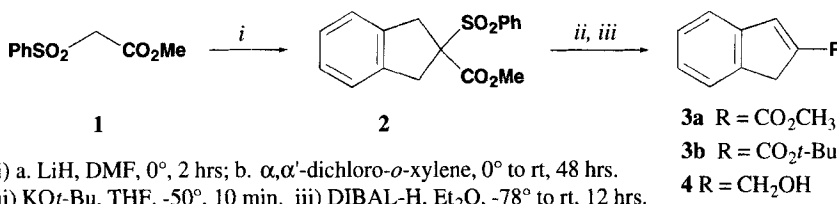
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Indene is an inherently difficult molecule to functionalize at its C(2) position. A number of synthetic strategies to prepare 2-substituted indenenes have been developed,¹ and among these various approaches, the introduction of the C-2 substituent generally precedes the indene ring formation.² Along these lines, we have found that the application of a 4+1 approach to indan ring construction has resulted in an improved synthesis of 2-(hydroxymethyl)indene (**4**). We report herein a three-step synthesis of the title compound from commercially available methyl phenylsulfonylacetate (**1**) in 77% overall yield.

We became interested in 2-(hydroxymethyl)indene as a potentially useful precursor of 2-indenyl ligands for *ansa*-metallocene synthesis.³ A recent synthesis of **4** has been reported by Murphy and Patterson from 1-indanone using a four-step reaction sequence to give **4** in 23% overall yield.⁴ Our previous experience using the phenylsulfonyl group to promote indan ring formation led us to explore a new route to **4**.⁵ The synthesis follows a path analogous to a previously reported



method⁶ for cyclopentadiene formation using a 4+1 approach to prepare the five-membered ring. No application of the method to indan ring formation had been previously examined.

Treatment of **1** with excess LiH in DMF followed by reaction with α,α'-dichloro-*o*-xylene resulted in efficient cyclization to give sulfone ester **2**. Dissolution of the crude reaction product in hot methanol followed by cooling was sufficient to afford pure **2** as needles in 81% yield. Indene formation via phenylsulfinate elimination⁷ was induced by treatment of **2** with a THF solution⁷ of KO*t*-Bu to give a mixture⁸ of methyl and *tert*-butyl esters **3a** and **3b**. The resultant crude mixture of esters was reduced directly by reaction with diisobutylaluminum hydride to give 2-(hydroxymethyl)indene in 95% yield from **2**.

In summary, we have described a facile synthesis of 2-(hydroxymethyl)indene. The synthesis is amenable to large scale preparation and does not require purifications involving column chromatography.

EXPERIMENTAL SECTION

DMF was distilled from magnesium sulfate and stored over 4 Å molecular sieves. THF and Et₂O were

distilled from Na^o-benzophenone ketyl immediately prior to use. NMR spectra were recorded with a General Electric QE-300 spectrometer (¹H at 300 MHz, ¹³C at 75 MHz). Infrared spectra were recorded on a Mattson FTIR 3000 spectrometer. Melting points are uncorrected. Elemental analyses were performed by Midwest Microlabs (Indianapolis, IN).

Preparation of 2-Carbomethoxy-2-phenylsulfonylindan (2).- To a stirred solution of methyl phenylsulfonylacetate (10.0 g, 46.7 mmol) in DMF (75 mL) at 0° was added in one portion LiH (1.11 g, 140 mmol). After stirring 2 hrs, α,α'-dichloro-*o*-xylene (9.40 g, 53.7 mmol) was added and the reaction mixture was allowed to warm to rt. The reaction was recooled to 0° after 48 hrs, quenched by the careful addition of saturated aqueous NH₄Cl, and then diluted with CH₂Cl₂ (150 mL) and H₂O (100 mL). The layers were separated and the aqueous phase was extracted with CH₂Cl₂. The combined organic extract was washed with H₂O, saturated brine, and dried (Na₂SO₄). The solvents were removed by rotary evaporation to afford the crude product. Recrystallization of the residue from methanol gave 12.0 g (81%) of **2** as a white solid, mp. 134.9-135.1°; IR (CHCl₃): 3071, 1736, 1324, 1251, 1155 cm⁻¹; ¹H NMR (CDCl₃): δ 3.68 (s, 3 H), 3.71 (d, *J* = 14.7 Hz, 2 H), 3.86 (d, *J* = 16.8 Hz, 2 H), 7.15 (m, 4 H), 7.54 (apparent t, *J* = 7.7 Hz, 2 H), 7.68 (apparent t, *J* = 7.3 Hz, 1 H), 7.85 (d, *J* = 7.5 Hz, 2 H); ¹³C NMR (CDCl₃): δ 38.4, 53.4, 78.9, 124.1, 127.2, 128.8, 129.7, 134.2, 136.4, 138.4, 168.5.

Anal. Calcd for C₁₇H₁₆O₄S: C, 64.54; H, 5.10. Found: C, 64.55; H, 5.01.

Preparation of 2-(Hydroxymethyl)indene (4).- To a stirred solution of **2** (6.0 g, 19.0 mmol) in THF (70 mL) at -50° was added rapidly a solution of KO^{*t*}-Bu (70 mL, 1.0 M in THF, 70 mmol). On complete addition, the reaction mixture was stirred for 10 min and then quenched by addition of saturated aqueous NH₄Cl (150 mL). The quenched reaction was diluted with EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic extract was washed with H₂O, saturated brine, and dried (MgSO₄). Removal of the solvents under reduced pressure afforded the crude product as a mixture of methyl and *tert*-butyl esters. A small quantity of the mixture was purified by silica gel column chromatography (hexane:ethyl acetate, 98:2) to give pure samples of each ester as white solids, **3a**: mp. 82.3-82.8°, lit.⁴ 36-38°, lit.⁹ 82.0-83.5°; IR (CHCl₃): 3000, 1699, 1249 cm⁻¹; ¹H NMR (CDCl₃): δ 3.69 (apparent d, *J* = 1.5 Hz, 2 H), 3.85 (s, 3 H), 7.34 (m, 2 H), 7.51 (m, 2 H), 7.73 (m, 1 H); ¹³C NMR (CDCl₃): δ 38.2, 51.4, 123.2, 124.1, 126.7, 127.4, 136.9, 141.0, 142.5, 144.6, 165.2; **3b**: mp. 68.7-69.0°; IR (CHCl₃): 3004, 1704, 1253 cm⁻¹; ¹H NMR (CDCl₃): δ 1.56 (s, 9 H), 3.64 (apparent d, *J* = 2.1 Hz, 2 H), 7.31 (m, 2 H), 7.49 (m, 2 H), 7.62 (m, 1 H); ¹³C NMR (CDCl₃): δ 28.2, 38.3, 80.3, 123.0, 124.1, 126.7, 127.1, 139.2, 140.0, 142.8, 144.6, 164.4.

Anal. Calcd for C₁₄H₁₆O₂: C, 77.74; H, 7.46. Found: C, 77.49; H, 7.42.

The crude ester mixture was dissolved in Et₂O (100 mL) and cooled to -78°. To the solution was added dropwise diisobutylaluminum hydride (50.5 mL of a 1.0 M solution in hexane, 50.5 mmol). The reaction was allowed to warm to room temperature and stirred 12 hrs. The reaction was quenched by slowly pouring the reaction mixture into an Erlenmeyer flask containing a vigorously stirred solution of 3 M NaOH (120 mL). The layers were separated and the aqueous phase was extracted with additional portions of Et₂O. The aqueous layer was then neutralized with 10% HCl and

extracted with EtOAc. The combined organic extract was washed with saturated brine and dried (MgSO_4). Removal of the solvents by rotary evaporation afforded 2.65 g (95%) of **4** as a pale yellow solid, mp. 49.9-50.6°, lit.¹⁰ 43-44°; IR (CHCl_3): 3307, 3070, 2908, 1094 cm^{-1} ; ^1H NMR (CDCl_3): δ 3.42 (s, 2 H), 4.58 (s, 2 H), 6.75 (s, 1 H), 7.15-7.43 (m, 4 H); ^{13}C NMR (CDCl_3): δ 38.8, 61.7, 120.7, 123.7, 124.4, 126.3, 127.4, 143.2, 144.5, 148.6.

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