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# Efficient synthesis of 2- and 3-substituted indenes from 2-bromobenzyl bromide through an enolate alkylation/Cr(II)/Ni(II)-mediated carbonyl addition sequence

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**Abstract**

An efficient new synthesis of 2- and 3-substituted indenes has been developed based on the nickel-catalyzed chromium(II)-promoted addition of aryl bromides to a tethered ketone carbonyl. Several tethered bromoaryl ketones were prepared through enolate alkylation of acyclic or cyclic ketones with 2-bromobenzyl bromide. Nozaki–Takai–Hiyama–Kishi closure of the resulting bromoaryl ketones followed by acid promoted dehydration gave substituted indenes in overall yields for the three-step sequence ranging from 29 to 58%. © 1999 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

Substituted indenes have become quite important as ligands in tailored metallocene complexes,[1] especially complexes of the group 4 metallocenes used to catalyze olefin polymerization.[2] In addition to methods for producing indenes substituted on positions 4–7,[3] several synthetic sequences for producing 1- (or 3-) and 2-substituted indenes have been reported. Previous methods for the preparation of 1- or 3-substituted indenes include alkylation of indenyl anions at the 1-position[4] or addition of organometals to 1-indanone followed by dehydation.[5] Preparations of 2-substituted indenes include addition of organometals to 2-indanone followed by dehydration,[5,6] cross coupling of Grignard reagents with 2-bromoindene,[7] and Friedel–Crafts sequences to generate 2-substituted 1-indanones which can be reduced and dehydrated.[8] Methods for the preparation of 2,3-disubstitued indenes generally require the preparation of 2-substituted indenes followed by alkylation at the 1-position.[9] In order to improve upon

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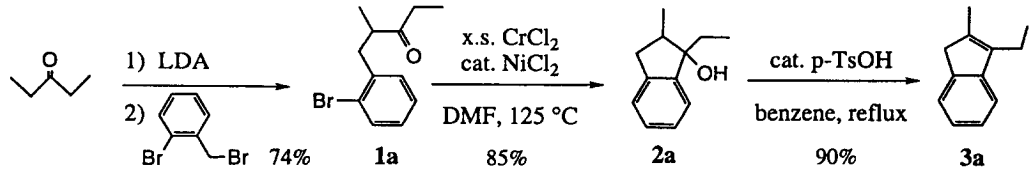
the lengthy and non-general known syntheses of 2,3-disubstituted indenes, we have developed and describe herein a nicely general three-step preparation of substituted indenes starting from 2-bromobenzyl bromide and ketones based on an extension of the Nozaki–Takai–Hiyama–Kishi Ni(II)/Cr(II)-mediated coupling of aryl halides with carbonyls.[10,11]

## 2. Results and discussion

The use of chromium(II) with catalytic nickel to couple aryl halides with aldehydes to form benzyl alcohols has been previously established to work especially well with aryl iodides or aryl triflates and less well with aryl bromides.[11] Coupling with ketones in place of the aldehydes has not been established. Our extension of this method to include intramolecular additions to ketones is illustrated starting with 3-pentanone in Scheme 1.[12] The lithium enolate of the ketone was alkylated by 2-bromobenzyl bromide to form the tethered bromoaryl ketone **1a** which could be cyclized in the presence of excess $CrCl_2$ and catalytic $NiCl_2$ at 125°C overnight in DMF to produce the substituted 1-indanol **2a** in very good yield. Dehydration of the benzylic alcohol in the presence of catalytic *p*-toluenesulfonic acid readily afforded the disubstituted indene **3a**.




Scheme 1.

Additional examples of this synthetic sequence showing the conversion of acyclic and cyclic ketones to substituted indenes are shown in Table 1.[13] In each case, the Nozaki–Takai–Hiyama–Kishi coupling reaction between aryl bromides and ketone carbonyls (even the hindered carbonyl in **2b**) proceeded in moderate to good yields. Generally, some traces of the indenes were observed in the carbonyl addition step, indicating the ability of the benzylic alchohols to dehydrate under these reaction conditions. In the case of cycloheptananone, the amount of dehydration was very significant during the carbonyl addition reaction and the crude alcohol **2e** was directly dehydrated to give indene **3e**. The ease with which one can make homologous series is nicely demonstrated in the synthesis of the annulated indenes **3d–3f** from cyclopentanone to cycloheptanone.

In conclusion, an efficient synthesis of substituted indenes has been developed which should enable better access to a wider range of indenes for incorporation as ligands in organometallic complexes.

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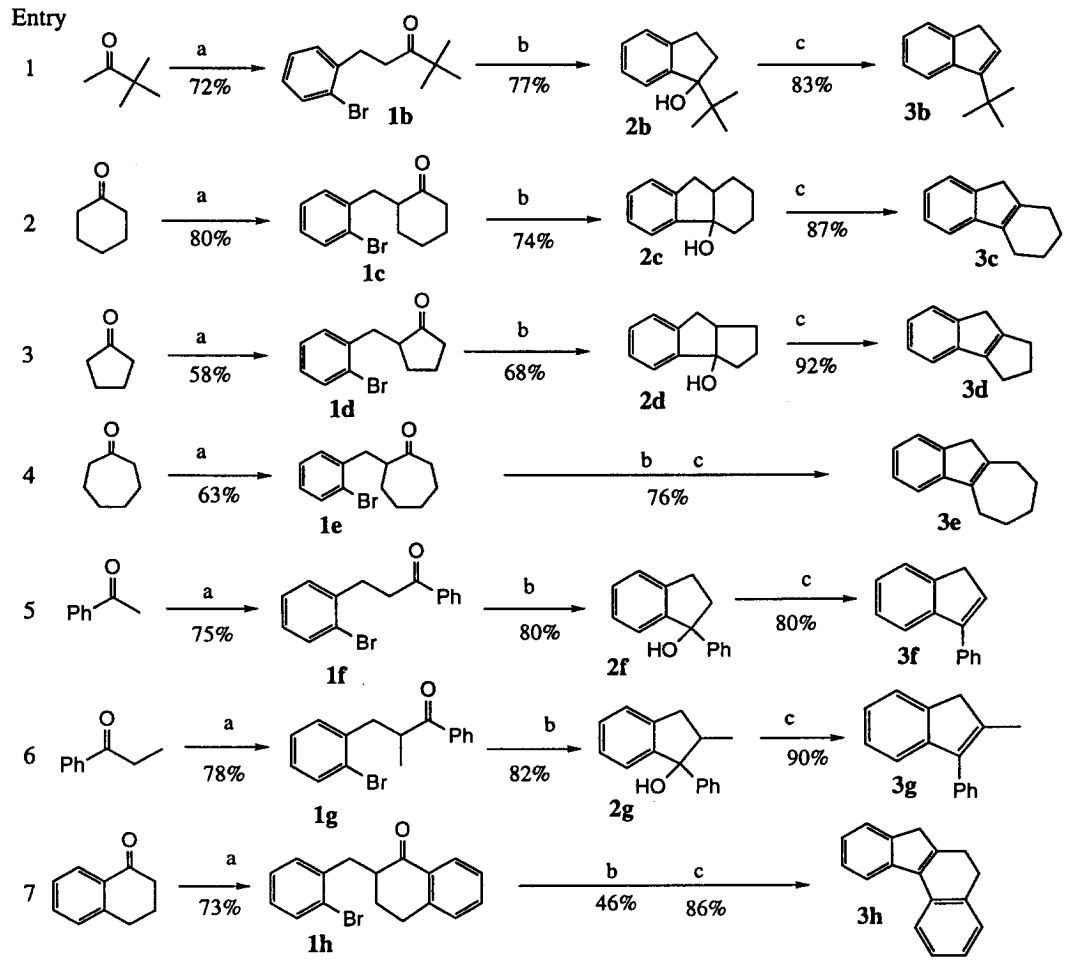
Table 1
Conversion of ketones to substituted indenes using Cr(II)/Ni(II)-mediated coupling




a LDA, 2-bromobenzyl bromide in THF. b $CrCl_2$ (cat. $NiCl_2$) in DMF. c cat. p-toluenesulfonic acid hydrate in benzene

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12. The synthetic procedure for the preparation of **3a** was used as a general procedure for the other examples in Table 1. Synthesis of 1-(2′-bromophenyl)-2-methyl-3-pentanone (**1a**): A 100 ml Schlenk flask was charged under nitrogen with tetrahydrofuran (25 mL) and diisopropylamine (1.50 ml, 10.7 mmol). A solution of *n*-butyllithium (2.5 M in hexane, 10 mmol) was added dropwise at −78°C. The solution was warmed to 0°C over 15 min and stirred at this temperature for 15 min. 3-Pentanone (0.90 ml, 8.5 mmol) was added slowly at −78°C. The mixture was stirred for 1.5 h from −78°C to −20°C to form the enolate. 2-Bromobenzyl bromide (3.50 g, 14.0 mmol) in tetrahydrofuran (10 mL) was added rapidly at −78°C. The reaction mixture was allowed to reach room temperature and stirred for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The two layers were separated, and the aqueous layer was extracted with portions of ethyl ether. The combined organic layer was washed with water and brine and dried over anhydrous magnesium sulfate, evaporated and purified by chromatography ($SiO_2$, petroleum ether/ethyl ether) to give **1a** as colorless liquid (1.60 g, 74%). Synthesis of 1-hydroxyl-1-ethyl-2-methyl-2,3-dihydroindene (**2a**): To a stirred suspension of chromium(II) chloride (Aldrich, 1.08 g, 9.6 mmol) and nickel chloride (13 mg, 0.10 mmol) in *N,N*-dimethylformamide (10 mL) was added a solution of 1-(2′-bromophenyl)-2-methyl-3-pentanone (**1a**) (0.78 g, 0.31 mmol) in DMF (4 mL) at room temperature under argon atmosphere. After being stirred at 125°C for 12 h, the mixture was cooled to room temperature, water (15 ml) was added and the mixture was extracted with diethyl ether. The combined organic portion was dried over anhydrous magnesium sulfate and concentrated. Purification of the crude product by chromatography ($SiO_2$, PE/diethyl ether) gave 1-hydroxyl-1-ethyl 2-methyl-2,3-dihydroindene (**2a**) (0.46 g, 85%). Synthesis of 3-ethyl-2-methyl-1*H*-indene (**3a**): To a solution of 1-hydroxyl-1-ethyl-2-methyl-2,3-dihydroindene (**2a**) (200 mg, 1.13 mmol) in benzene (10 mL) was added a few crystals of *p*-toluenesulfonic acid hydrate. After the solution was refluxed for 3 h, it was cooled to room temperature and washed with a saturated solution of $NaHCO_3$ (5 mL) followed by water. The organic layer was dried over anhydrous magnesium sulfate, evaporated and purified by chromatography ($SiO_2$, PE) to give the 3-ethyl-2-methyl-1*H*-indene (**3a**) as a colorless liquid (160 mg, 90%).
13. Each of the compounds **1–3** was characterized by spectroscopic methods. Selected data for the indenes **3a–3h** are given here. **3a**:[9] MS (EI, 70 eV, rel.%) 158 (59, $M^+$), 143 (100), 128 (78); $^1H$ NMR (300 MHz, $CDCl_3$) δ: 7.46 (d, J=8 Hz, 1H), 7.34 (m, 2H), 7.20 (m, 1H), 3.35 (s, 2H), 2.62 (q, J=7 Hz, 2H), 2.16 (s, 3H), 1.23 (t, J=7 Hz, 3H). **3b**: [Demlow, E. V.; Bollmann, C. *Tetrahedron Lett.* **1991**, *32*, 5773.] $^1H$ NMR (300 MHz, $CDCl_3$) δ: 7.68 (d, J=8 Hz, 1H), 7.51 (d, J=8 Hz, 1H), 7.32 (dd, J=8, 8 Hz, 1H), 7.21 (dd, J=8, 8 Hz, 1H), 6.25 (br s, 1H), 3.32 (s, 2H), 1.43 (s, 9H). **3c**: [Smith, W. K.; Hardin, J. N.; Rabideau, P. W. *J. Org. Chem.* **1990**, *55*, 5301.] MS (EI, 70 eV, rel.%) 170 (92, $M^+$), 141 (100), 115 (42); $^1H$ NMR (300 MHz, $CDCl_3$) δ: 7.02–7.16 (m, 4H), 2.97 (s, 2H), 2.25 (m, 2H), 2.17 (m, 2H), 2.09 (m, 2H). **3d**: MS (EI, 70 eV, rel.%) 156 (60, $M^+$), 141 (38), 128 (100); $^1H$ NMR (300 MHz, $CDCl_3$) δ: 7.03–7.18 (m, 4H), 3.02 (s, 2H), 2.52 (m, 2H), 2.30 (m, 2H), 1.75 (m, 2H), 1.5–1.7 (m, 4H). **3e**: [Parham, W. E.; Egberg, D. C. *J. Org. Chem.* **1972**, *37*, 1545.] MS (EI, 70 eV, rel.%) 184 (73, $M^+$), 169 (24), 141 (100), 115 (68); $^1H$ NMR (300 MHz, $CDCl_3$) δ: 7.38 (d, J=8 Hz, 1H), 7.1–7.3 (m, 3H), 3.24 (s, 2H), 2.45 (m, 4H), 1.85 (m, 4H). **3f**: [Foster, P.; Chien, J. C. W.; Rausch, M. D. *Organometallics* **1996**, *15*, 2404.] MS (EI, 70 eV, rel.%) 192 (15, $M^+$), 178 (100), 152 (22); $^1H$ NMR (300 MHz, $CDCl_3$) δ: 7.0–7.5 (m, 10H), 6.34 (s, 1H), 3.15 (s, 2H). **3g**: [Jayamani, M.; Pant, N.; Ananthan, S.; Narayanan, K.; Pillai, C. N. *Tetrahedron* **1986**, *42*, 4325.] MS (EI, 70 eV, rel.%) 206 (100, $M^+$), 191 (76), 128 (23); $^1H$ NMR (300 MHz, $CDCl_3$) δ: 7.1–7.5 (m, 9H), 3.98 (s, 2H), 1.90 (s, 3H). **3h**: [Kiesele, H. *Angew. Chem., Int. Ed. Engl* **1983**, *22*, 254; *Angew. Chem. Suppl.* **1983**, 210.] MS (EI, 70 eV, rel.%) 218 (100, $M^+$), 215 (56), 202 (44), 91 (53); $^1H$ NMR (300 MHz, $CDCl_3$) δ: 7.0–7.5 (m, 8H), 3.10 (s, 2H), 2.65 (m, 2H), 2.24 (m, 2H).