New substituted indene derivatives from bicyclic Baylis-Hillman acetate

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Abstract: A convenient protocol for the synthesis of highly functionalized indenes 4 has been developed. The coupling reaction of bicyclic Baylis-Hillman acetate 2 with nitroalkane salts in basic conditions led to the corresponding substituted indenes in good yields and high purity.

Keywords: Bicyclic Baylis-Hillman acetate; nitroalkanes; ethyl 1-alkylidene-1H-indene-2-carboxylates.

Introduction

The design of new molecules with indene ring is still an open challenge to organic chemists. These compounds are important model structures found in various natural products 1-3 and bioactive compounds 4-7 (Figure 1).

![Figure 1. Some indene skeletons related to various natural and pharmaceutical products](image)

Various indene-based molecules have shown a wide range of biological activities such as antimicrobial, 8 anti-inflammatory 9, aromatase inhibitory 10, cytotoxic activities 11, estrogen receptor modulators 12 and some anti-proliferative activities 13. In addition, indene derivatives are widely used as building blocks for the synthesis of functional materials 14 and metallocene complexes for olefin polymerization 15. Thus, the importance of indenes has stimulated much interest in the construction of indene system including the ring expansion of suitably substituted cyclopropanes, 16 tandem Friedel Crafts alkylation 17, [3+2] cycloadditions 18, C-H bond activation 19, C-C bond cleavage 20, thermal cascade reactions 21, ruthenium-mediated ring-closing metathesis 22, and skeletal rearrangement using some transition metals and Lewis and Brønsted acid catalysts 23-38. However, the above reported approaches suffer from low tolerance of functionality, the use of expensive transition metal catalysts and harsh reaction conditions. Accordingly, the search for an effective and inexpensive method for obtaining substituted indene derivatives is nowadays very sought. Herein, we report an efficient easy two-step synthesis of functionalized indenes 4 from the prepared bicyclic Baylis-Hillman acetate 2 (Scheme 1).

![Scheme 1. Retrosynthetic route to highly substituted indenes 4](image)

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Results and Discussion

Previously, we have described an efficient synthetic method to prepare substituted indenol derivatives following the coupling reaction of 1-hydroxy-1H-indene-2-carboxylic acid with alcohols in the presence of p-toluenesulfonic acid (PTSA) as a catalyst. Various analogues of indenol derivatives 1 have been reported to show a great ability to act as powerful synthons for the synthesis of various useful compounds. They were used as templates for the synthesis of various alkyl 1-acetoxy-1H-indene-2-carboxylates and various functionalized-1H-indene esters through S_N2'-type addition-elimination reaction as shown in Scheme 2.

Continuing with our efforts toward the functionalization of the bicyclic Baylis-Hillman acetate 2, we report herein the reactivity of the bicyclic Baylis-Hillman adduct 2b with nitroalkanes salts as nucleophilic reagents. Conjugate addition of nitroalkane to functional allyl acetates has been the subject of intensive work by our group. Based on the previous results achieved by our group and others, we further investigated the reactivity of allyl acetates 2b with nitronate anion generated from primary and secondary nitroalkanes toward the formation of highly substituted ethyl 1-alkylidene-1H-indene-2-carboxylates 4.

With the aim of developing the best reaction conditions for the coupling of allyl acetate 2b with nitroethane, several bases have been tested and the representative results are summarized in Table 1. No products were obtained following the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,4-diazabicyclo[2.2.2]octane (DABCO) in THF and CH3CN respectively or sodium ethoxide (EtONa) (Table 1, entries 1, 2 and 3). The best result was obtained when the allyl acetate (2 mmol) was treated with nitroethane (1.2 equiv.) in THF at room temperature in the presence of aqueous NaOH (0.6 M, 1.5 equiv.). The desired compound 4a was obtained in good yield (71%) (Scheme 3).

Table 1. Use of various bases in the synthesis of indene 4a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>T °C</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DBU</td>
<td>THF</td>
<td>25</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>DABCO</td>
<td>CH3CN</td>
<td>50</td>
<td>16</td>
<td>Mixture</td>
</tr>
<tr>
<td>3</td>
<td>EtONa</td>
<td>EtOH</td>
<td>25</td>
<td>76</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>K2CO3</td>
<td>THF-H2O</td>
<td>25</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>NaOH (0.6 M)</td>
<td>THF</td>
<td>0-25</td>
<td>48</td>
<td>71</td>
</tr>
</tbody>
</table>

Under the optimized reaction conditions described above, we intended to extend this reaction to a variety of aliphatic nitroalkanes. Different ethyl (E/Z)-1-alkylidene-1H-indene-2-carboxylates 4a-e were synthesized in moderate to good yields (Scheme 4, Table 2). The use of secondary nitroalkane (entry 3) under the same reaction conditions, led to the desired compound 4 in low yield (35%) (Scheme 4).
Ethyl 1-alkylidene-1H-indene-2-carboxylates 4a-e were obtained as a mixture of two stereoisomers (E, Z). The structures of 4a-e were established on the basis of their 1H and 13C NMR spectra and by heteronuclear multiple bond correlation (HMBC). Their stereochemistry was clearly assigned on the basis of NOESY experiments.

Conclusion

In summary, we have developed an efficient two-step protocol for the efficient synthesis of new functionalized ethyl 1-alkylidene-1H-indene-2-carboxylates 4 following the coupling reaction of bicyclic Baylis-Hillman acetate 2 with nitroalkane salts. The described approach can be explored for the synthesis of new functional indene derivatives as new candidates for biological evaluations, ligand precursors for metallocene catalyst systems and functional materials.

Experimental Section

All commercially available chemicals and reagents were used without further purification. 1H-NMR and 13C-NMR spectra were recorded on Bruker AMX 300 spectrometer working at 300 MHz and 75 MHz respectively for the proton and 13C with CDCl3 as solvent and TMS as the internal standard. The chemical shifts (δ) and coupling constants (J) are, respectively, expressed in parts per million (ppm) and Hertz (Hz). All NMR spectra were acquired at room temperature. Assignments of proton (1H-NMR) and carbon (13C-NMR) signals were secured by DEPT 135, NOESY, HMOC and HMBC experiments. All reactions were monitored by TLC on silica gel plates (Fluka Kieselgel 60 F254, Merck) eluting with the solvents indicated, visualized by a 254 nm UV lamp and aqueous potassium permanganate solution. For column chromatography, Fluka Kieselgel 70-230 mesh was used. Multiplicity of peaks is indicated by the following: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra were recorded on an Equinox 55 spectrophotometer. High-Resolution Mass Spectrometry (HRMS) analyses were performed with a Maldi-TOF-TOF technique on a Bruker Autoflex III Smartbeam.

Procedure for the synthesis of alkyl 1-acetoxy-1H-indene-2-carboxylates 2a-e

To a mixture of alcohol 1 (5 mmol), acetic anhydride (25 mmoles) in 40 mL of anhydrous ether cooled at 0 °C under stirring in nitrogen atmosphere, was added a drop of concentrated sulfuric acid. After completion of the reaction, the mixture was hydrolyzed with ice water and extracted with ether (3 x 20 mL). The organic layers were washed successively with sodium hydroxide solution (1.5 M) and brine until neutral pH then dried over MgSO4 and concentrated in vacuo. After evaporating the solvent, the residue obtained was purified on silica gel column chromatography (Hexane/AcOEt, 7:3).

Ethyl 1-acetoxy-1H-indene-2-carboxylic acid (2b)

White solid, yield: (80%), mp 74-76 °C. IR (ATR): 1708, 1246 cm⁻¹; 1H-NMR (300 MHz, CDCl3): 7.67 (s, 1H, H(IR)); 7.48-7.51 (m, 4H, CH); 4.28 (q, 2H, J = 7.5 Hz, OCH2); 2.17 (s, 3H, CH3); 1.33 (t, 3H, J = 7.5 Hz, CH3); 13C-NMR (75 MHz, CDCl3): 170.8 (CO); 163.2 (CO); 143.8 (=CH); 143.6 (CAr); 140.2 (CAr); 136.7 (=C); 129.3 (CHAr); 129.0 (CHAr); 124.9 (CHAr); 123.8 (CHAr); 74.5 (=CH); 60.5 (OCH2); 29.7 (CH3); 14.2 (CH3). HRMS calculated for C14H14O2Na [M+Na]+ 269.07843, found 269.07800.
General procedure for the synthesis of ethyl (E/Z)-1-alkylidene-1H-indene-2-carboxylates 4a-e.

A solution of aqueous NaOH (3 mmol, 0.6 M) was added dropwise over a period of 30 min to an ice-cold solution of allyl acetate 2b (2 mmol) and nitroalkane (2.4 mmol) in THF (5 mL). The resulting mixture was stirred at room temperature until total substitution of 2b. The mixture was hydrolyzed with water then extracted with ether (3×15 mL). The combined organic layers were washed with brine then dried over MgSO₄ and concentrated in vacuo. The obtained liquid was purified by flash chromatography (Hexane/AcOEt, 9:1) to provide pure ethyl (E/Z)-1-alkylidene-1H-indene carboxylates 4. The mixture of 4Z-indene isomers 4 cannot be separated by column chromatography.

Ethyl (E/Z)-1-ethylidene-1H-indene-2-carboxylate (4a)

Fluorescent yellow oil, yield: 71%, ¹H-NMR (300 MHz, CDCl₃): 7.78 (s, 1H, Hetylenic); 7.47-7.26 (m, 4H, HAr); 7.67, 7.02 (2q, 1H, J = 7.5 Hz, J = 6 Hz, Hetylenic); 4.31 (q, 2H, J = 7.5 Hz, OCH₂); 2.41 (d, 3H, J = 6 Hz, CH₃); 1.37 (t, 3H, J = 7.5 Hz, CH₂); ¹³C-NMR (75 MHz, CDCl₃): 164.8 (CO); 141.4 (=CH); 140.3 (=C); 139.5 (=CH); 137.3 (=C); 130.1 (=C); 132.5 (=C); 127.3 (CHAr); 124.4 (CHAr); 122.4 (CHAr), 118.9 (CHAr); 60.1 (OCH₂); 16.2 (CH₂); 14.3 (CH₃). HRMS calculated for C₁₇H₁₆O₂Na [M+Na]⁺ 237.0891, found 237.0892.

Ethyl (Z/E)-1-propylidene-1H-indene-2-carboxylate (4b)

Fluorescent yellow oil. Yield: 63%, ¹H-NMR (300 MHz, CDCl₃): 7.82 (s, 1H, Hetylenic); 7.65-7.25 (m, 4H, HAr); 7.54, 6.87 (2t, 1H, J = 9 Hz, J = 6 Hz, Hetylenic); 4.31 (q, 2H, J = 7 Hz, OCH₂); 2.85 (q, 2H, J = 7 Hz, CH₂); 1.37 (t, 3H, J = 7 Hz, CH₂); 1.20 (t, 3H, J = 7.5 Hz, CH₃); ¹³C-NMR (75 MHz, CDCl₃): 164.7 (CO); 141.4 (=CH); 140.3 (=C); 138.5 (=CH); 137.2 (=C); 136.2 (=C); 130.1 (=C); 127.7 (CHAr), 127.2 (CHAr), 124.4 (CHAr); 122.5 (CHAr); 60.1 (OCH₂); 23.6 (CH₂); 14.3 (CH₃); 13.7 (CH₄). HRMS calculated for C₁₇H₁₉O₂Na [M+Na]⁺ 279.1361, found 279.1363.

Ethyl (Z/E)-1-pentylidene-1H-indene-2-carboxylate (4c)

Fluorescent yellow oil. Yield: 52%, ¹H-NMR (300 MHz, CDCl₃): 7.80 (s, 1H, Hetylenic); 7.65-7.27 (m, 4H, HAr); 7.58, 6.90 (2t, 1H, J = 9 Hz, J = 7.5 Hz, Hetylenic); 4.32 (q, 2H, J = 7 Hz, OCH₂); 2.84 (q, 2H, J = 7 Hz, CH₂); 1.70-1.45 (m, 2H, CH₂); 1.43-1.35 (m, 2H, CH₂); 1.21 (t, 3H, J = 7.5 Hz, CH₃); 0.97 (t, 3H, J = 7.5 Hz, CH₃); ¹³C-NMR (75 MHz, CDCl₃): 164.8 (CO); 143.0 (=CH); 140.2 (=C); 138.4 (=CH); 137.6 (=C); 136.4 (=C); 129.9 (=C); 127.6 (CHAr), 127.2 (CHAr), 124.3 (CHAr), 123.2 (CHAr), 60.1 (OCH₂); 31.4 (CH₂); 29.7 (CH₂); 22.5 (CH₂); 14.3 (CH₃); 14.1 (CH₄). HRMS calculated for C₁₇H₂₈O₂Na [M+Na]⁺ 301.8024, found 301.8024.

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