Synthesis of Methyl (E)-2-Cyanomethylcinnamates Derived from Baylis-Hillman Acetates and Conversion into Several 4-Hydroxy-2-naphthoic Acids and Benzylidenesuccinimides

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The Baylis-Hillman (BH) reaction has been developed enormously over the past few years due to its wide applicability towards formation of multifunctional derivatives, heterocycles and natural products. Aliphatic nitriles are potentially useful building block in organic synthesis due to the electron-withdrawing nature associated with the cyano group and the conversion of the cyano group into other functionalities.

Much attention has recently been focussed on the SN1' nucleophilic substitution of the Baylis-Hillman acetates. Among them only limited approaches to the cyanation of BH adducts are known in the literature. The one method is to access ethyl 3-cyano-2-methylcinnamates through DABCO assisted the successive SN2'-SN2' reaction of BH acetates with KCN and the other methods are Michael addition of KCN with O-t-butyldimethylsilyl BH adduct of piperonal, and several SN2' reaction of BH acetates of 2-azidobenzaldehyde with KCN by us.

As part of our continuing studies towards development of the BH chemistry, we desired to have the cyano group at the allylic position of the 3-aryl-2-propenoates. In principle, such nitrile compounds might be extended further towards the building of naphthalene and succinimide derivatives.

Treatment of BH acetate 1a with KCN in DMSO/H2O at room temperature for 1 h afforded 2-cyanomethylcinnamic acid methyl ester (2a) in 74% yield. This success led us to transform a variety of methyl 3-acetoxy-3-aryl-2-methyl-2-propenoates 1b-i into methyl (E)-3-aryl-2-cyanomethyl-2-propenoates 2b-i stereoselectively under the similar reaction conditions (Scheme 1, Table 1). The E-geometry of the olefinic bond was established on the basis of 1H NMR data of the vinyl peaks appeared at 7.70-8.03 ppm, which were well coincident with the reported data of similar compounds.

To confirm the synthetic efficacy of (E)-3-aryl-2-cyanomethyl-2-propenoates 2, we prepared several known 4-hydroxy-2-naphthoic acids 4a-c by dehydration of (E)-benzylidenesuccinic acids 3a-c with conc. H2SO4 at room temperature, which were obtained from the hydrolysis of 2a-c under basic conditions. Also, we examined the feasibility of transforming several cyanomethylcinnamates 2a-c into the corresponding benzylidenesuccinimides 8a-c by using nitrile group transformation strategy. Several methods for the synthesis of benzylidenesuccinimides involve the Wittig reaction of triphenylphosphoranylidenesuccinimides with aromatic aldehydes and the Stobbe condensation route.

In our work we found that use of acetic acid in the presence of FeCl3 at reflux temperature led to the desired benzylidenesuccinimides in 40-45% yields. The plausible mechanism for the formation of imide 8a-c can be thought as shown in Scheme 2. FeCl3 makes the nitrile group more electrophilic, then subsequent nucleophilic addition of acetic acid to the cyano group generates imidate, which undergoes formation of lactam, and cleavage of acetyl group by methanol gives succinimide.

In summary, a simple synthesis of methyl 2-cyanomethylcinnamates from readily available Baylis-Hillman acetates and conversion to the several naphthalene and benzylidenesuccinimide derivatives is disclosed.

**Experimental Section**

Silica gel 60 (70-230 mesh ASTM) used for column chromatography.

**Table 1.** Methyl (E)-3-Aryl-2-cyanomethyl-2-propenoates 2

<table>
<thead>
<tr>
<th>Reactant</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>C6H5</td>
<td>2a</td>
<td>74</td>
<td>oil</td>
</tr>
<tr>
<td>1b</td>
<td>4-ClC6H4</td>
<td>2b</td>
<td>57</td>
<td>85 - 87</td>
</tr>
<tr>
<td>1c</td>
<td>4-4MeOC6H4</td>
<td>2c</td>
<td>69</td>
<td>64 - 65</td>
</tr>
<tr>
<td>1d</td>
<td>4-AcNHOC6H4</td>
<td>2d</td>
<td>64</td>
<td>163 - 165</td>
</tr>
<tr>
<td>1e</td>
<td>2-CIC6H4</td>
<td>2e</td>
<td>79</td>
<td>83 - 85</td>
</tr>
<tr>
<td>1f</td>
<td>3-O2NC6H4</td>
<td>2f</td>
<td>33</td>
<td>88 - 90</td>
</tr>
<tr>
<td>1g</td>
<td>2,6-Cl2C6H4</td>
<td>2g</td>
<td>65</td>
<td>102 - 104</td>
</tr>
<tr>
<td>1h</td>
<td>3,4-MeOC6H3</td>
<td>2h</td>
<td>87</td>
<td>97 - 99</td>
</tr>
<tr>
<td>1i</td>
<td>2,6-Cl3-3-O2NC6H2</td>
<td>2i</td>
<td>27</td>
<td>80 - 82</td>
</tr>
</tbody>
</table>
chromatography was supplied by E. Merck. Analytical thin layer chromatography (TLC) was carried out on Merck silica gel 60 F254 TLC plates. Melting points were taken using an Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet Magna 550 FTIR spectrometer. The $^1$H and $^{13}$C NMR spectra were measured on a Gemini 300 spectrometer using CDCl$_3$ or DMSO-d$_6$. All chemical shifts are reported in ppm relative to TMS and coupling constants (J) are expressed in Hz.

**Typical Procedure for the Preparation Methyl (E)-3-Aryl-2-cyanomethyl-2-propenoate 2a:** To a stirred solution of 1a (234 mg, 1.0 mmol) in 1:1 DMSO-H$_2$O (6 mL) was added KCN (98 mg, 1.5 mmol) at room temperature. After stirring at the same temperature for 1 h, the reaction mixture was diluted with water (10 mL) and extracted with CH$_2$Cl$_2$ ($3 \times 15$ mL). The combined organic layers were dried over anhydrous MgSO$_4$ and the solvent was evaporated in vacuo. The resulting mixture was chromatographed on silica gel eluting with hexane/EtOAc (6:1) to afford 149 mg (74%) of 2a as a liquid; IR (neat) 2250, 1710, 1637 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 3.54 (s, 2H), 3.90 (s, 3H), 7.39-7.51 (m, 5H), 7.98 (s, 1H); $^{13}$C NMR (CDCl$_3$) 16.92, 52.72, 117.31, 121.81, 129.03, 129.69, 130.66, 133.69, 144.02, 166.16.

The spectroscopic data of the synthesized compounds are as follows.

- **2b:** 135 mg (57%); mp 85-87 ºC; IR (KBr) 2253, 1710, 1637 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 3.54 (s, 2H), 3.90 (s, 3H), 7.39-7.51 (m, 5H), 7.98 (s, 1H); $^{13}$C NMR (CDCl$_3$) 16.92, 52.72, 117.31, 121.81, 129.03, 129.69, 130.66, 133.69, 144.02, 166.16.

- **2c:** 159 mg (69%); mp 64-65 ºC; IR (KBr) 2256, 1722, 1650 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 3.26 (s, 2H), 3.94 (s, 3H), 7.28-7.42 (m, 3H), 7.74 (s, 1H); $^{13}$C NMR (CDCl$_3$) 17.38, 52.87, 115.76, 126.89, 128.33, 130.62, 131.52, 133.99, 138.34, 164.89.

- **2h:** 227 mg (87%); mp 97-99 ºC; IR (KBr) 2258, 1722, 1650 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 3.26 (s, 2H), 3.94 (s, 3H), 7.28-7.42 (m, 3H), 7.74 (s, 1H); $^{13}$C NMR (CDCl$_3$) 17.38, 52.87, 115.76, 126.89, 128.33, 130.62, 131.52, 133.99, 138.34, 164.89.

- **2i:** 85 mg (27%); mp 80-82 ºC; IR (KBr) 2258, 1722, 1650 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 3.58 (s, 2H), 3.89 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 6.94-6.97 (m, 2H), 7.05 (dd, 1H, $J$ = 8.2 and 1.8 Hz), 7.91 (s, 1H); $^{13}$C NMR (CDCl$_3$) 17.02, 52.62, 55.86, 55.99, 111.19, 112.19, 117.53, 119.62, 122.96, 126.36, 143.98, 149.06, 150.43, 166.44.
filtered, washed with water, dried. The mixture was stirred at room temperature for 8 h. After removal of HOAc, the residue was dissolved in CHCl3 (30 mL), and the CHCl3 layer was washed with aq. NaHCO3 (20 mL), dried over anhydrous MgSO4 and concentrated under vacuum, the residue was dissolved in CHCl3 (30 mL), and the CHCl3 layer was washed with aq. NaHCO3 (20 mL), dried over anhydrous MgSO4 and concentrated under vacuum to give 150 mg (40%) of succinic Acid 3a; mp 197-199 °C. (lit.4 198-200 °C). IR (KBr) 3216, 1708, 1648 cm−1; 1H NMR (CDCl3) δ 3.64 (d, 2H, J = 2.4 Hz), 7.45-7.50 (m, 5H), 7.62 (t, 1H, J = 2.4 Hz), 8.19 (br s, 1H); 13C NMR (CDCl3-d6) 34.75, 126.99, 129.00, 130.13, 131.38, 131.54, 134.17, 171.91, 175.70. 

8b: 200 mg (45%); mp 251-252 °C (lit.2 251-252 °C).

8c: 194 mg (45%); mp 246-247 °C (lit.2 246.6-247.2 °C).

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References and Notes


