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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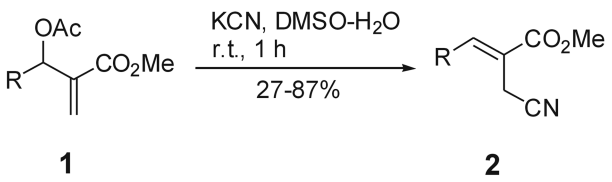
The Baylis-Hillman (BH) reaction[1] has been developed enormously over the past few years due to its wide applicability towards formation of multifunctional derivatives,[2] heterocycles[3] and natural products.[4] Aliphatic nitriles are potentially useful building block in organic synthesis due to the electron-withdrawing nature associated with the cyano group and the conversion of the cyano group into other functionalities.[5]

Much attention has recently been focussed on the S_N2' nucleophilic substitution of the Baylis-Hillman acetates.[6] 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 S_N2'-S_N2' reaction of BH acetates with KCN[7] and the other methods are Michael addition of KCN with *O*-*t*-butyldimethylsilyl BH adduct of piperonal,[8] and several S_N2' reaction of BH acetates of 2-azidobenzaldehyde with KCN by us.[3b]

As part of our continuing studies towards development of the BH chemistry,[9] 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/H_2O 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-methyleneprapanoates **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 ^{1}H NMR data of the vinyl peaks appeared at 7.70-8.03 ppm, which were well coincident with the reported data of similar compounds.[3b]



Scheme 1

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. H_2SO_4 at room temperature,[10] 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[11] and the Stobbe condensation route.[12]

In our work we found that use of acetic acid in the presence of $FeCl_3$[13] 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. $FeCl_3$ makes the nitrile group more electrophilic, then subsequent nucleophilic addition of acetic acid to the cyano group generates imidate **6**, which undergoes formation of lactam **7**, and cleavage of acetyl group by methanol gives succinimide **8**.

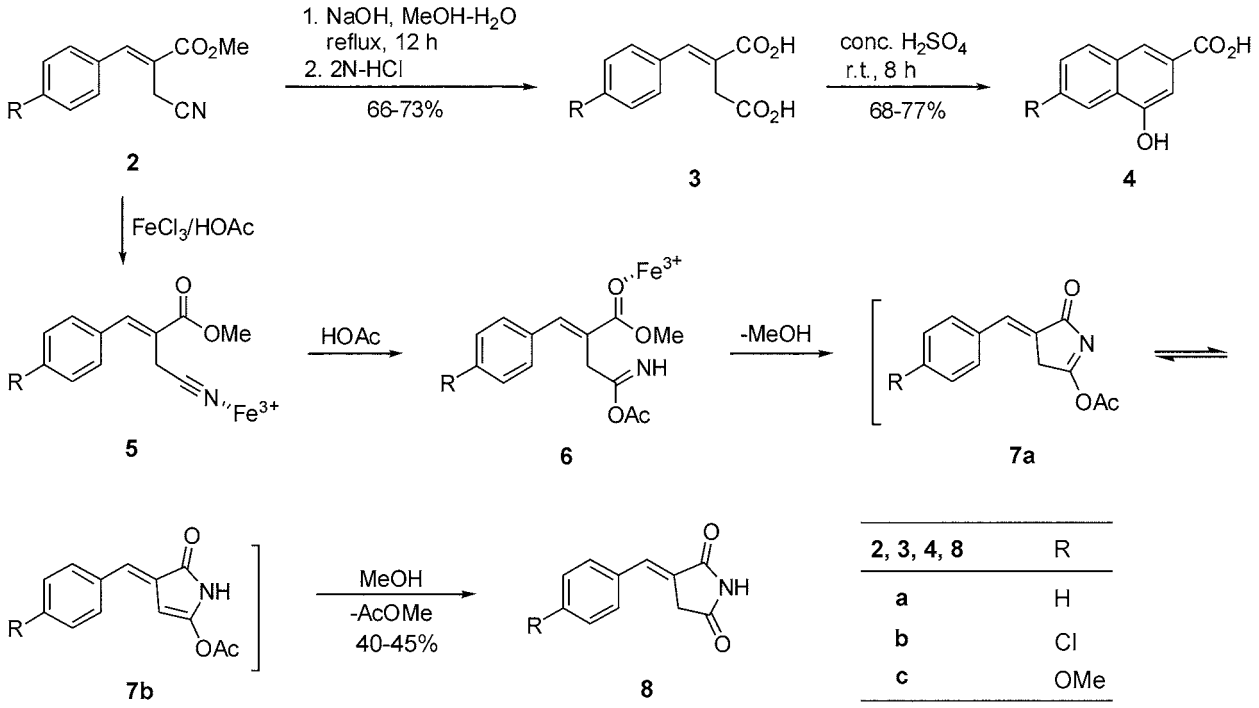
In summary, a simple synthesis of methyl 2-cyanomethylcinnamates from readily available Baylis-Hillman acetates and conversion to the several naphthalene and benzylidensuccinimide derivatives is disclosed.

Experimental Section

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

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

Reactant	R	Product	Yield (%)	mp (°C)
1a	C_6H_5	**2a**	74	oil
1b	4-ClC_6H_4	**2b**	57	85 - 87
1c	4-$MeOC_6H_4$	**2c**	69	64 - 65
1d	4-$AcNHC_6H_4$	**2d**	64	163 - 165
1e	2-ClC_6H_4	**2e**	79	83 - 85
1f	3-$O_2NC_6H_4$	**2f**	33	88 - 90
1g	2,6-$Cl_2C_6H_3$	**2g**	65	102 - 104
1h	3,4-$MeOC_6H_3$	**2h**	87	97 - 99
1i	2,6-Cl_2-3-$O_2NC_6H_2$	**2i**	27	80 - 82



Scheme 2

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_2O (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_2Cl_2 (3 × 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 ($CDCl_3$) δ 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 °C; IR (KBr) 2253, 1713, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.51 (s, 2H), 3.90 (s, 3H), 7.34 (d, 2H, *J* = 8.5 Hz), 7.46 (d, 2H, *J* = 8.5 Hz), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$) 16.70, 52.72, 116.90, 122.48, 129.27, 130.40, 132.09, 135.92, 142.53, 165.85.

2c: 159 mg (69%); mp 64-65 °C; IR (KBr) 2245, 1711, 1628 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.57 (s, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 6.99 (d, 2H, *J* = 8.6 Hz), 7.39 (d, 2H, *J* = 8.6 Hz), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$) 16.92, 52.60, 55.37, 114.46, 117.47, 119.27, 126.07, 131.27, 143.65, 160.85, 166.52.

2d: 166 mg (64%); mp 163-165 °C; IR (KBr) 3424, 2248, 1693, 1669 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3H), 3.56 (s, 2H), 3.90 (s, 3H), 7.39 (d, 2H, *J* = 8.6 Hz), 7.58 (br s, 1H), 7.64 (d, 2H, *J* = 8.6 Hz), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$) 16.96, 24.68, 52.75, 117.41, 119.76, 120.56, 129.26, 130.45, 139.47, 143.38, 166.36, 168.58.

2e: 186 mg (79%); mp 83-85 °C; IR (KBr) 2251, 1716, 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.42 (s, 2H), 3.92 (s, 3H), 7.37-7.40 (m, 3H), 7.46-7.50 (m, 1H), 8.03 (s, 1H); ^{13}C NMR ($CDCl_3$) 17.04, 52.80, 116.94, 123.95, 127.13, 129.59, 129.93, 130.83, 132.35, 133.99, 141.13, 165.53.

2f: 81 mg (33%); mp 88-90 °C; IR (KBr) 2251, 1709, 1638, 1530, 1355 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.53 (s, 2H), 3.94 (s, 3H), 7.70-7.76 (m, 2H), 8.00 (s, 1H), 8.24-8.32 (m, 2H); ^{13}C NMR ($CDCl_3$) 16.63, 52.97, 116.36, 123.78, 124.13, 124.69, 130.17, 134.38, 135.22, 140.95, 148.41, 165.33.

2g: 175 mg (65%); mp 102-104 °C; IR (KBr) 2256, 1721, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 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 °C; IR (KBr) 2238, 1716, 1632 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 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.

2i: 85 mg (27%); mp 80-82 °C; IR (KBr) 2258, 1722,

1658, 1536, 1354 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.28 (s, 2H), 3.96 (s, 3H), 7.58 (d, 1H, J = 8.9 Hz), 7.70 (s, 1H), 7.87 (d, 1H, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) 17.44, 53.15, 115.16, 126.22, 127.12, 128.31, 128.85, 134.31, 136.66, 137.99, 147.26, 164.36.

Typical Procedure for the Preparation of Benzylidenesuccinic Acid 3a: A solution of NaOH (320 mg) in water (1 mL) was added to a solution of **2a** (201 mg, 1.0 mmol) in MeOH (3 mL), and the mixture was stirred and heated under reflux for 12 h. The solvent was removed *in vacuo*. The aqueous layer was acidified with 2 N-HCl and extracted with ether (3 × 25 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford a solid, which was crystallized with EtOAc/hexane to give 150 mg (73%) of **3a**; mp 186-187 °C (lit.[14a] 186-188 °C).

3b: 159 mg (66%); mp 191-192 °C (lit.[14b] 193-194 °C).

3c: 160 mg (68%); mp 185-187 °C (lit.[10c] 188-191 °C).

Typical Procedure for the Preparation of 4-Hydroxy-2-naphthoic Acid 4a: Benzylidenesuccinic acid **3a** (206 mg 1.0 mmol) was dissolved in conc. H_2SO_4 (464 mg) and stirred at room temperature for 8 h. The reaction mixture was carefully poured over cold water (1 mL) and allowed to crystallize overnight at 5 °C. The resulting crystals were filtered, washed with water, dried *in vacuo* and recrystallized from EtOH/H_2O to give 144 mg (77%) of **4a**; mp 223-224 °C. (lit.[10a] 225-226 °C). IR (KBr) 3447, 1656, 1579 cm^{-1}; ^1H NMR (DMSO-d_6) δ7.37 (s, 1H), 7.58 (m, 2H), 8.02 (m, 1H), 8.05 (s, 1H), 8.16 (m, 1H), 10.49 (s, 1H), 12.92 (br s, 1H); ^{13}C NMR (DMSO-d_6) 106.98, 121.34, 122.08, 126.72, 127.02, 127.06, 128.63, 129.08, 133.55, 153.43, 167.74.

4b: 155 mg (70%); mp 295-297 °C (lit.[10b] 297 °C).

4c: 149 mg (68%); mp 243-245 °C (lit.[10c] 243-246 °C).

Typical Procedure for the Preparation of Benzylidenesuccinimide 8a: To a stirred solution of cyanomethylpropenoate **2a** (402 mg, 2.0 mmol) in glacial HOAc (10 mL) was added $FeCl_3$ (649 mg, 4.0 mmol), and the mixture was heated under reflux for 10 h. After removal of the HOAc under vacuum, the residue was dissolved in $CHCl_3$ (30 mL), and the $CHCl_3$ layer was washed with aq. $NaHCO_3$ (20 mL) and H_2O (20 mL), successively. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford a solid, which was crystallized with MeOH to give 150 mg (40%) of **8a**; mp 197-199 °C. (lit.[11] 198-200 °C). IR (KBr) 3136, 1766, 1708, 1648 cm^{-1}; ^1H NMR ($CDCl_3$) 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); ^{13}C NMR (DMSO-d_6) 34.75, 126.99, 129.00, 130.13, 131.38, 131.54, 134.14, 171.91, 175.70.

8b: 200 mg (45%); mp 251-252 °C (lit.[15a] 251-252 °C).

8c: 194 mg (45%); mp 246-247 °C (lit.[15b] 246.6-247.2 °C).

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