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An Efficient Synthesis of Poly-Substituted Phenols and Pyridines from Morita-Baylis-Hillman Acetates and Diethyl Oxalacetate

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Various phenol derivatives were synthesized in a one-pot reaction from MBH acetates and sodium diethyl oxalacetate *via* a [4C+2C] cyclization protocol. In addition, some pyridine derivatives could also be synthesized using the same starting materials, by isolating the S_N2' reaction intermediate and performing the cyclization with NH_4OAc.

Key Words : Phenols, Pyridines, Morita-Baylis-Hillman acetates, Diethyl oxalacetate

Introduction

Morita-Baylis-Hillman (MBH) adducts[1] have been used for the synthesis of various aromatic compounds including phenols[2] and pyridines.[3,4] Poly-substituted phenols and pyridines are important due to their abundance in nature and biologically active substances.[5-7]

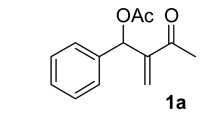
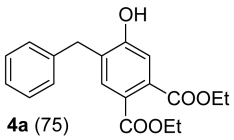
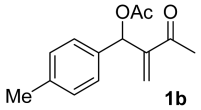
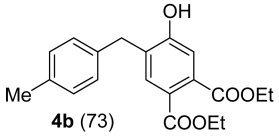
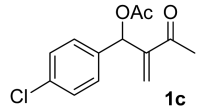
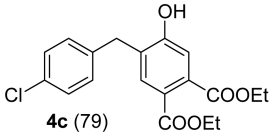
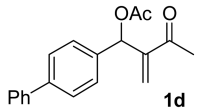
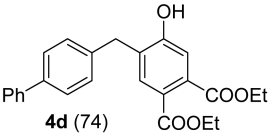
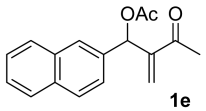
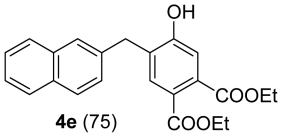
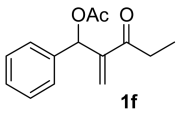
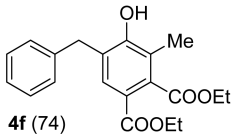
MBH adducts of methyl vinyl ketone could be used as a four-carbon source to form phenol derivative in the reaction with a two-carbon unit such as ketone bearing an α-proton *via* the [4C+2C] cyclization protocol.[2e] As shown in Scheme 1, a sequential S_N2' reaction between MBH acetate **1a** and sodium diethyl oxalacetate (**2a**) to form **3a**, dehydrative cyclization to form an intermediate **I**, and a final isomerization could produce phenol derivative **4a**.

Results and Discussion

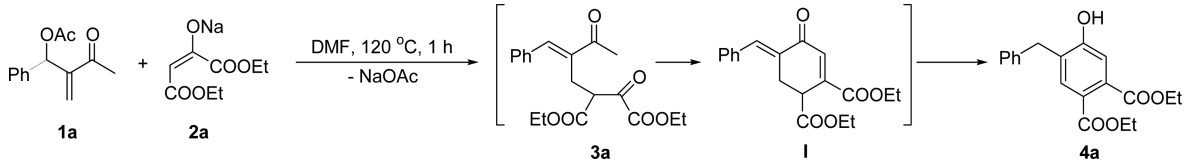
Thus, we examined the reaction of **1a** and **2a** in DMF at 120 °C for 1 h. To our delight, phenol **4a** was obtained in good yield (75%) in a one-pot reaction.[8] Encouraged by the successful results, various MBH acetates **1b-f** were prepared and the syntheses of phenol derivatives **4b-f** were carried out under the same reaction conditions. The results are summarized in Table 1. The reactions of MBH acetates **1b-e** and **2a** produced **4b-e** in good yields (73-79%, entries 2-5). The reaction of **1f**, derived from ethyl vinyl ketone, gave poly-substituted phenol **4f** in a similar yield (74%, entry 6).

During the reaction, we examined the preparation of an intermediate **3a**, as shown in Scheme 2, in order to synthesize poly-substituted pyridines (*vide infra*). The reaction of

Table 1. Synthesis of poly-substituted phenols from **1** and **2a**

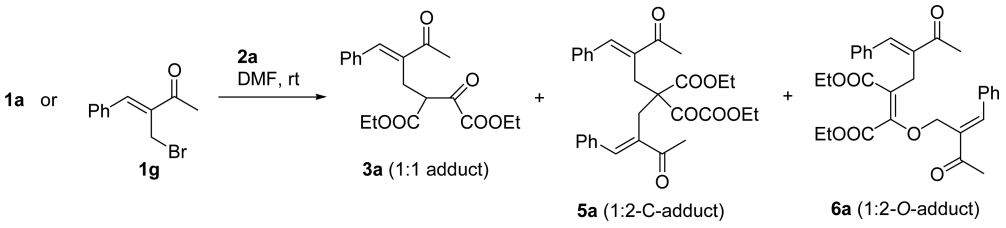
Entry	MBH acetate **1**	Phenol **4** (%)[a]
1	 **1a**	 **4a** (75)
2	 **1b**	 **4b** (73)
3	 **1c**	 **4c** (79)
4	 **1d**	 **4d** (74)
5	 **1e**	 **4e** (75)
6	 **1f**	 **4f** (74)

[a]Conditions: Substrate **1** (0.5 mmol), **2a** (1.1 equiv), DMF, 120 °C, 1 h.



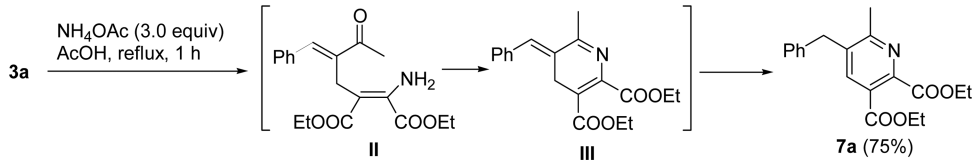
1a **2a** **3a** **I** **4a**

Scheme 1



1a + **2a** (1.1 equiv), DMF, rt, 12 h: **3a** (53%) + **5a** (17%) + **6a** (not observed)
1a + **2a** (3.0 equiv), DMF, rt, 12 h: **3a** (57%) + **5a** (10%) + **6a** (not observed)
1g + **2a** (1.1 equiv), DMF, rt, 5 h: **3a** (49%) + **5a** (4%) + **6a** (32%)

Scheme 2



Scheme 3

Table 2. Synthesis of poly-substituted pyridines

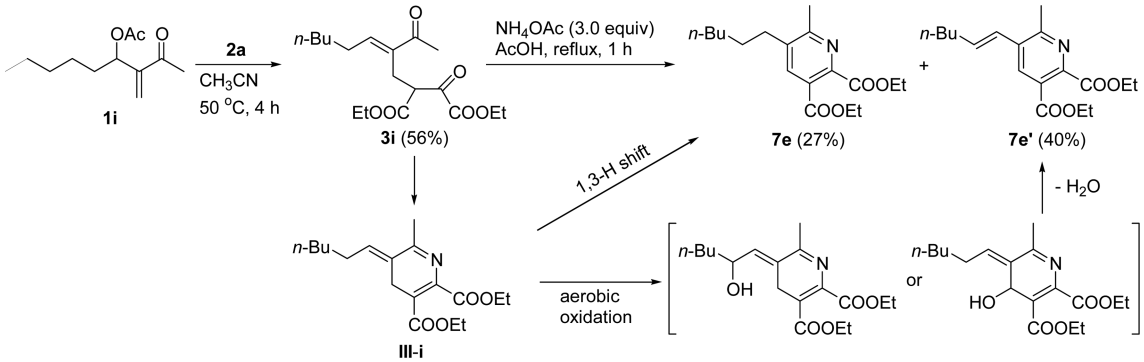
Entry	MBH acetate **1**	Compound **3** (%)[a]	Pyridine **7** (%)[b,c]
1	**1a**	**3a** (53)	**7a** (75)[b]
2	**1d**	**3d** (55)	**7b** (70)[b]
3	**1f**	**3f** (56)	**7c** (60)[b]
4	**1h**	**3h** (57)	**7d** (76)[c]

[a]Conditions: Substrate **1** (1.0 mmol), **2a** (1.1 equiv), DMF, rt, 12 h. [b]Conditions: Substrate **3** (0.4 mmol), NH4OAc (3.0 equiv), AcOH, reflux, 1 h. [c]Conditions: Substrate **3** (0.4 mmol), NH4OAc (20.0 equiv), AcOH, reflux, 18 h.

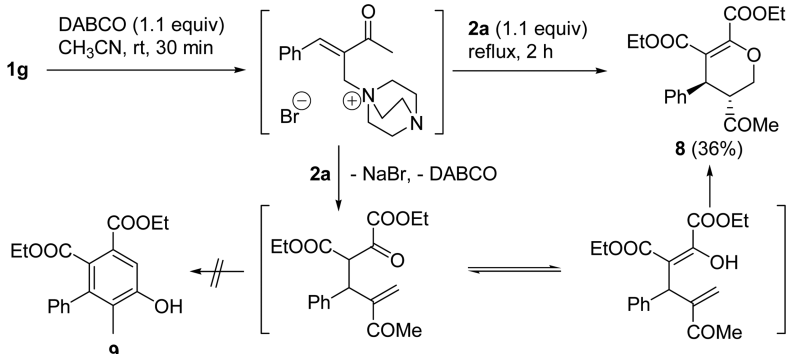
1a and **2a** (1.1 equiv) in DMF at room temperature for 12 h afforded **3a** in moderate yield (53%) along with 1:2 adduct **5a** (17%).[9] The yield of **3a** increased slightly by using an excess amount (3.0 equiv) of **2a**. When we used MBH bromide **1g** instead of MBH acetate **1a**, desired compound **3a** was obtained in a similar yield (49%) along with 1:2 adduct **6a** (32%).[10]

With this compound **3a** in our hand, the synthesis of pyridine **7a** was examined in the presence of NH_4OAc (3.0 equiv), as shown in Scheme 3. To our delight, poly-substituted pyridine **7a** was formed in good yield (75%) *via* the plausible intermediates **II** and **III**.[11] For the synthesis of pyridine, MBH adduct served a three-carbon unit, and the pyridine ring was constructed by the [3C+2C+1N] cyclization protocol.[3c]

Encouraged by the results, **3d**, **3f** and **3h** were prepared according to Scheme 2, and the syntheses of pyridine derivatives were carried out as summarized in Table 2. Pyridines **7b** and **7c** were obtained in good yields (60-70%). 2-Hydroxypyridine **7d** was synthesized under the similar reaction conditions in good yield (76%) from ester derivative **3h**, which was made from the MBH acetate of methyl acrylate **1h**. For the synthesis of **7d**, an excess amount (20 equiv) of NH_4OAc and a long reaction time (18 h) were required.[4a] In



Scheme 4



Scheme 5

addition the synthesis of *n*-hexyl-substituted pyridine **7e** was examined, as shown in Scheme 4. The reaction of **3i**[12] and NH_4OAc afforded **7e** (27%) along with a hexenyl-substituted pyridine **7e'** (40%) under the same reaction conditions. The pyridine **7e'** might be produced *via* the aerobic oxidation of an intermediate **III-i** and the following acid-catalyzed dehydration, as previously observed in a similar case.[2c,3c]

As a last examination, we carried out the reaction of a DABCO salt of MBH bromide **1g** and **2a**, as shown in Scheme 5. The reaction of **1g** and DABCO in CH_3CN at room temperature produced the corresponding DABCO salt quantitatively.[13] To the reaction mixture, **2a** was added and the reaction mixture was heated to reflux for 2 h. 3,4-Dihydro-2*H*-pyran derivative **8** was obtained in moderate yield (36%),[14] *via* an intramolecular conjugate addition of the enol intermediate, as already reported in a similar case.[15] Polysubstituted phenol **9** was not formed at all.

In summary, various phenol derivatives were synthesized in a one-pot reaction from MBH acetates and sodium diethyl oxalacetate *via* a [4C+2C] cyclization protocol. In addition, some pyridine derivatives could also be synthesized using the same starting materials, by isolating the S_N2' reaction intermediate and performing the cyclization with NH_4OAc.

Experimental Section

Typical Procedure for the Synthesis of 4a. A mixture of **1a** (109 mg, 0.5 mmol) and **2a** (116 mg, 0.55 mmol) in DMF (1.0 mL) was stirred at 120 °C for 1 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/EtOAc, 4:1), compound **4a** was obtained as pale yellow oil, 123 mg (75%). Other compounds were synthesized similarly, and the spectroscopic data of **4a-f** are as follows.

Compound 4a: 75%; pale yellow oil; IR (film) 3364, 1716, 1609, 1303, 1133, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (t, *J* = 7.2 Hz, 3H x 2), 3.98 (s, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 6.87 (br s, 1H), 7.06 (s, 1H), 7.16-7.28 (m, 5H), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.94, 14.10, 35.81, 61.37, 61.97, 115.63, 122.60, 126.42, 128.57, 128.68, 130.01, 132.50, 133.25, 139.02, 156.90, 166.90, 168.96; ESIMS *m/z* 329 [M^++H]. Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.76; H, 6.03.

Compound 4b: 73%; pale yellow oil; IR (film) 3372, 1718, 1608, 1305, 1133 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (t, *J* = 7.2 Hz, 3H x 2), 2.30 (s, 3H), 3.95 (s, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 6.68 (br s, 1H), 7.06 (s, 1H), 7.07 (s, 4H), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.95, 14.11, 20.98, 35.48, 61.36, 61.93, 115.68, 122.66, 128.52, 129.32, 130.17, 132.45, 133.18, 135.80, 136.03, 156.89, 166.92, 168.91; ESIMS *m/z* 343 [M^++H].

Compound 4c: 79%; colorless oil; IR (film) 3365, 1718, 1609, 1303, 1133 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.33 (t, *J* = 7.2 Hz, 3H x 2), 3.94 (s, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.33 (q, *J* = 7.2 Hz, 2H), 6.63 (br s, 1H), 7.05 (s, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.95, 14.13, 35.16, 61.43, 62.06, 115.59, 122.76, 128.60, 129.58, 130.01, 132.15, 132.43, 133.43, 137.64, 156.65, 166.68, 168.92; ESIMS *m/z* 363 [M^++H], 365 [M^++H+2].

Compound 4d: 74%; colorless oil; IR (film) 3359, 1719, 1608, 1304, 1133 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (t, *J* = 7.2 Hz, 3H x 2), 4.02 (s, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 4.33 (q, *J* = 7.2 Hz, 2H), 6.81 (br s, 1H), 7.09 (s, 1H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.28-7.56 (m, 7H), 7.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.94, 14.11, 35.46, 61.40, 62.01, 115.66, 122.64, 126.96, 127.11, 127.28, 128.69, 129.06, 129.91, 132.53, 133.31, 138.14, 139.34, 140.81, 156.90, 166.87, 168.99; ESIMS *m/z* 405 [M^++H].

Compound 4e: 75%; pale yellow solid, mp 148-150 °C; IR (KBr) 3370, 1715, 1608, 1305, 1133 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 4.06 (s, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 6.62 (br s, 1H), 7.01 (s, 1H), 7.23 (dd, *J* = 8.4 and 1.2 Hz, 1H), 7.30-7.40 (m, 2H), 7.53 (s, 1H), 7.57 (s, 1H), 7.61-7.73 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.94, 14.10, 36.02, 61.39, 61.96, 115.73, 122.77, 125.51, 126.07, 126.86, 127.17, 127.54, 127.59, 128.28, 129.77, 132.20, 132.61, 133.37, 133.52, 136.49, 156.95, 166.89, 168.83; ESIMS *m/z* 379 [M^++H].

Compound 4f: 74%; pale yellow oil; IR (film) 3436, 1715, 1575, 1314, 1199 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.34 (t, *J* = 7.2 Hz, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 2.16 (s, 3H), 4.01 (s, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.42 (q, *J* = 7.2 Hz, 2H), 5.34 (br s, 1H), 7.16-7.34 (m, 5H), 7.75 (s, 1H); ^{13}C

NMR ($CDCl_3$, 75 MHz) δ 12.39, 14.07, 14.20, 36.77, 61.08, 61.51, 119.66, 121.81, 126.54, 126.94, 128.46, 128.92, 130.91, 136.28, 138.20, 156.18, 165.50, 169.33; ESIMS *m/z* 343 [M^++H]. Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.03; H, 6.74.

Typical Procedure for the Synthesis of 3a. A mixture of **1a** (218 mg, 1.0 mmol) and **2a** (231 mg, 1.1 mmol) in DMF (1.5 mL) was stirred at room temperature for 12 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/CH_2Cl_2/EtOAc, 10:1:1), compound **3a** was obtained as colorless oil, 183 mg (53%) along with **5a** (43 mg, 17%). Other compounds were synthesized similarly, and the spectroscopic data of **3a**, **5a**, **6a**, **3d**, **3f** and **3h** are as follows.

Compound 3a: 53%; colorless oil; IR (film) 1754, 1731, 1666, 1251 cm-^{1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.08 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 2.38 (s, 3H), 3.06 (dd, *J* = 14.1 and 8.1 Hz, 1H), 3.18 (dd, *J* = 14.1 and 7.2 Hz, 1H), 3.95-4.04 (m, 3H), 4.20 (q, *J* = 7.2 Hz, 2H), 7.25-7.38 (m, 5H), 7.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.85, 13.88, 24.26, 25.79, 53.48, 61.62, 62.68, 128.73, 129.01, 129.06, 134.72, 138.20, 142.81, 159.56, 168.31, 187.87, 200.05; ESIMS *m/z* 347 [M^++H].

Compound 5a: 17%; colorless oil; IR (film) 1730, 1668, 1239 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 2.01 (s, 6H), 3.01 (d, *J* = 14.7 Hz, 2H), 3.31 (d, *J* = 14.7 Hz, 2H), 3.88 (q, *J* = 7.2 Hz, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 7.25 (s, 2H), 7.26-7.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.59, 13.92, 25.53, 29.44, 58.76, 61.51, 62.27, 128.58, 128.73, 129.41, 135.35, 138.31, 142.10, 159.71, 170.25, 186.56, 200.73; ESIMS *m/z* 505 [M^++H].

Compound 6a: 32%; pale yellow oil; IR (film) 1731, 1670, 1627, 1299, 1102 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 2.38 (s, 3H x 2), 3.65 (s, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.74 (s, 2H), 7.27-7.58 (m, 11H), 7.71 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.88, 13.95, 24.48, 25.90, 26.12, 60.82, 61.64, 63.84, 118.76, 128.35, 128.47, 128.76, 129.39, 129.86, 129.92, 133.98, 134.79, 135.27, 138.84, 140.07, 145.57, 150.56, 162.96, 166.99, 197.98, 199.35; ESIMS *m/z* 527 [M^++Na].

Compound 3d: 55%; colorless oil; IR (film) 1740, 1731, 1665, 1253, 1096 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16 (t, *J* = 7.2 Hz, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 2.47 (s, 3H), 3.19 (dd, *J* = 14.1 and 8.4 Hz, 1H), 3.33 (dd, *J* = 14.1 and 6.9 Hz, 1H), 4.04-4.16 (m, 3H), 4.29 (q, *J* = 7.2 Hz, 2H), 7.34-7.41 (m, 1H), 7.42-7.50 (m, 4H), 7.57-7.69 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.88, 13.90, 24.41, 25.81, 53.54, 61.68, 62.72, 127.01, 127.37, 127.83, 128.91, 129.80, 133.60, 138.10, 140.01, 141.86, 142.40, 159.60, 168.38, 187.91, 200.03; ESIMS *m/z* 423 [M^++H].

Compound 3f: 56%; colorless oil; IR (film) 1731, 1668, 1259 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H), 1.33 (t, *J* = 7.2 Hz, 3H), 2.83 (q, *J* = 7.2 Hz, 2H), 3.14 (dd, *J* = 14.4 and 7.8 Hz, 1H), 3.25 (dd, *J* = 14.4 and 7.8 Hz, 1H), 4.01-4.11 (m, 3H), 4.27 (q, *J* = 7.2 Hz, 2H), 7.27-7.45 (m, 5H), 7.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.63, 13.85, 13.88, 24.48, 30.61, 53.45, 61.59, 62.65, 128.70, 128.85, 129.02, 134.87, 137.76, 141.34, 159.60, 168.36, 187.94, 202.64; ESIMS *m/z* 361 [M^++H].

Compound 3h: 57%; colorless oil; IR (film) 1731, 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (t, *J* = 7.2 Hz, 3H), 1.33 (t, *J* = 7.2 Hz, 3H), 3.17 (dd, *J* = 14.7 and 7.8 Hz, 1H), 3.30 (dd, *J* = 14.7 and 7.8 Hz, 1H), 3.81 (s, 3H), 4.01-4.12 (m, 2H), 4.25 (t, *J* = 7.8 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 7.28-7.46 (m, 5H), 7.80 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.82, 13.88, 25.22, 52.16, 53.51, 61.71, 62.74, 128.46, 128.63, 128.78, 129.09, 134.78, 142.19, 159.66, 167.95, 168.31, 188.03; ESIMS *m/z* 363 [M^++H].

Compound 3i: 56%; colorless oil; IR (film) 2932, 1755, 1731, 1667, 1259, 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, *J* = 6.9 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.27-1.40 (m, 4H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.40-1.49 (m, 2H), 2.22-2.30 (m, 2H), 2.29 (s, 3H), 2.90 (d, *J* = 7.5 Hz, 2H), 4.06 (t, *J* = 7.5 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 6.73 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.90 (2C), 13.93, 22.41, 23.93, 25.38, 28.41, 29.06, 31.54, 53.48, 61.57, 62.71, 137.60, 147.41, 159.81, 168.53, 188.34, 199.37; ESIMS *m/z* 341 [M^++H].

Typical Procedure for the Synthesis of 7a. A mixture of **3a** (138 mg, 0.4 mmol) and NH_4OAc (92 mg, 1.2 mmol) in AcOH (1.0 mL) was heated to reflux for 1 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/EtOAc, 8:1), compound **7a** was obtained as pale yellow oil, 98 mg (75%). Other compounds were synthesized similarly, and the spectroscopic data of **7a-d** are as follows.

Compound 7a: 75%; pale yellow oil; IR (film) 1728, 1307, 1151 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (t, *J* = 7.2 Hz, 3H), 1.41 (t, *J* = 7.2 Hz, 3H), 2.55 (s, 3H), 4.05 (s, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 4.45 (q, *J* = 7.2 Hz, 2H), 7.06-7.11 (m, 2H), 7.20-7.34 (m, 3H), 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.98, 14.00, 22.71, 38.48, 61.73, 62.05, 123.32, 126.71, 128.57, 128.74, 135.71, 137.73, 138.52, 149.19, 160.96, 165.22, 166.83; ESIMS *m/z* 328 [M^++H]. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.93; H, 6.62; N, 4.14.

Compound 7b: 70%; pale yellow oil; IR (film) 1727, 1307, 1151 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (t, *J* = 7.2 Hz, 3H), 1.41 (t, *J* = 7.2 Hz, 3H), 2.58 (s, 3H), 4.08 (s, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 4.45 (q, *J* = 7.2 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 7.30-7.37 (m, 1H), 7.39-7.46 (m, 2H), 7.51-7.59 (m, 4H), 7.95 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.98, 14.01, 22.76, 38.13, 61.76, 62.07, 123.35, 126.93, 127.26, 127.41, 128.72, 128.98, 135.61, 136.77, 138.55, 139.66, 140.51, 149.24, 161.00, 165.22, 166.83; ESIMS *m/z* 404 [M^++H]. Anal. Calcd for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.46; H, 6.57; N, 3.28.

Compound 7c: 60%; colorless oil; IR (film) 1731, 1592, 1454, 1301, 1152, 1041 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, *J* = 7.5 Hz, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.41 (t, *J* = 7.2 Hz, 3H), 2.85 (q, *J* = 7.5 Hz, 2H), 4.08 (s, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 4.45 (q, *J* = 7.2 Hz, 2H), 7.06-7.11 (m, 2H),

7.19-7.34 (m, 3H), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.94, 14.01, 14.04, 28.46, 37.92, 61.71, 62.00, 122.89, 126.70, 128.60, 128.74, 134.92, 138.38, 139.03, 149.60, 165.25, 165.43, 167.09; ESIMS *m/z* 342 [M^++H].

Compound 7d: 76%; pale yellow solid, mp 174-176 °C; IR (KBr) 3392, 1727, 1651 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, *J* = 7.2 Hz, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 3.88 (s, 2H), 4.27 (q, *J* = 7.2 Hz, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 7.20-7.34 (m, 5H), 7.44 (s, 1H), 11.91 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.91, 13.95, 35.87, 61.74, 63.11, 111.92, 126.63, 128.64, 129.09, 135.71, 136.83, 137.20, 138.09, 161.31, 162.90, 164.63; ESIMS *m/z* 330 [M^++H].

Compound 7e: 27%; colorless oil; IR (film) 2930, 1728, 1304, 1151 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.26-1.40 (m, 6H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.53-1.64 (m, 2H), 2.60 (s, 3H), 2.66 (t, *J* = 7.8 Hz, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 4.44 (q, *J* = 7.2 Hz, 2H), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.01 (2C), 14.06, 22.13, 22.52, 29.05, 29.41, 31.54, 32.40, 61.78, 62.15, 123.38, 137.72, 137.87, 148.27, 160.10, 165.36, 166.70; ESIMS *m/z* 322 [M^++H]. Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.51; H, 8.34; N, 4.19.

Compound 7e': 40%; colorless oil; IR (film) 2929, 1728, 1306, 1260, 1149 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, *J* = 7.2 Hz, 3H), 1.32-1.54 (m, 4H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.39 (t, *J* = 7.2 Hz, 3H), 2.27 (dq, *J* = 6.9 and 1.2 Hz, 2H), 2.62 (s, 3H), 4.37 (q, *J* = 7.2 Hz, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 6.27 (dt, *J* = 15.9 and 6.9 Hz, 1H), 6.50 (d, *J* = 15.9 Hz, 1H), 8.11 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.87, 14.01, 14.07, 22.23, 22.75, 31.13, 33.07, 61.79, 62.07, 123.94, 124.40, 133.68, 133.97, 137.55, 148.40, 158.26, 165.57, 166.69; ESIMS *m/z* 320 [M^++H]. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.74; H, 7.95; N, 4.14.

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9. The result stated that the cyclization of **3a** to phenol **4a** occurred readily at 120 °C (Scheme 1 and Table 1); however, a second alkylation of **3a** with **1a** to form 1:2 adduct **5a** proceeds slowly to some extent (17%) at room temperature.
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11. A direct one-pot synthesis of pyridine **7a** was examined. The reaction of **1a** and **2a** (3.0 equiv) in the presence of NH_4OAc (4.0 equiv) in AcOH under refluxing conditions for 3 h produced **7a**; however, the yield was quite low (< 10%).
12. The compound **3i** was prepared from **1i** and **2a** in CH_3CN (50 °C, 4 h) in 56% yield. We also examined the synthesis of phenol derivative from **1i** and **2a** (DMF, 120 °C, 1 h); however, a severe decomposition was observed.
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14. An appreciable amount of intractable side products was formed, and the corresponding *cis*-form of **8** was also formed in trace amount, but it was not isolated. The spectroscopic data of **8** was as follows: colorless oil; IR (film) 1744, 1712, 1637, 1368, 1285 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 2.13 (s, 3H), 2.79 (app q, J = 3.9 Hz, 1H), 3.92 (q, J = 7.2 Hz, 2H), 4.07 (dd, J = 11.4 and 3.3 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 4.32-4.39 (m, 2H), 7.13-7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.70, 13.86, 28.69, 38.43, 53.11, 60.69, 62.14, 64.19, 108.44, 127.14, 127.78, 128.75, 142.12, 153.10, 163.06, 165.66, 205.26; ESIMS *m/z* 347 [M^++H].
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