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ScienceDirect
Tetrahedron 64 (2008) 103–109
Tetrahedron
www.elsevier.com/locate/tet

Synthesis of poly-substituted benzenes starting from Baylis–Hillman adducts: DBU-assisted unusual dehydrogenation

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Received 12 October 2007; received in revised form 19 October 2007; accepted 19 October 2007
Available online 22 October 2007

Abstract

Poly-substituted benzenes were synthesized in moderate yields starting from the Baylis–Hillman adducts. The synthesis was carried out by two steps via first synthesis of cyclohexene intermediates and the following DBU-assisted unusual dehydrogenation.

Keywords: Baylis–Hillman adducts; Poly-substituted benzenes; DBU; Dehydrogenation

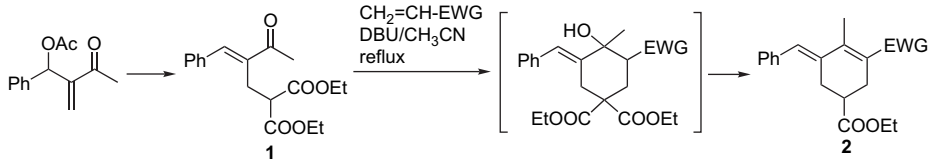
1. Introduction

Recently various aromatic and hetero-aromatic compounds[1] have been synthesized from the Baylis–Hillman adducts including poly-substituted benzenes,[1d,e,f] phenols,[1g,h] naphthalenes,[1i–k] and pyridines.[1l] Based on the importance of poly-substituted aromatic and heterocyclic compounds the syntheses of these compounds can be regarded as the most fruitful chemical transformations in Baylis–Hillman chemistry. Very recently we reported an interesting base-catalyzed domino process for the synthesis of 3-benzylidenecyclohexenes **2** as in Scheme 1.[2]

During our continuous studies on the synthesis of 3-benzylidenecyclohexenes we tried the synthesis of nitrile-containing cyclohexene **2a** by following the procedure in Scheme 2 (vide infra). The synthesis of cyclohexene **2a** was carried out similarly as in our previous paper[2] in 62% isolated yield from the reaction of **1a** and MVK (methyl vinyl ketone) under DBU/CH_3CN conditions, however, we observed a trace amount of non-polar compound on TLC and it was found as a tetra-substituted benzene derivative **3a** (3–5%), to our surprise. In this paper we wish to report the results on the regioselective synthesis of poly-substituted benzenes starting from the Baylis–Hillman adducts via the corresponding 3-benzylidenecyclohexene intermediates.

2. Results and discussion

From the unexpected formation of **3a** we reasoned that we could find effective conditions, which provide tetra-substituted



Scheme 1.

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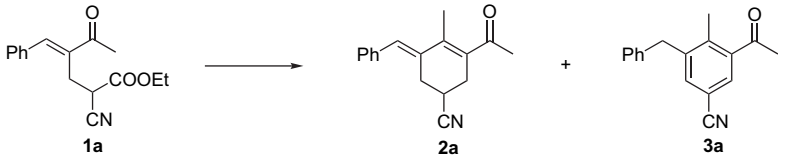
0040-4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.10.068



MVK (2.0 equiv), DBU (2.0 equiv), CH_3CN, reflux, 24 h: **2a** (62%), **3a** (trace)
MVK (2.0 equiv), DBU (2.0 equiv), DMF, rt (30 min), 130-140 °C (2 h): **2a** (18%), **3a** (48%)

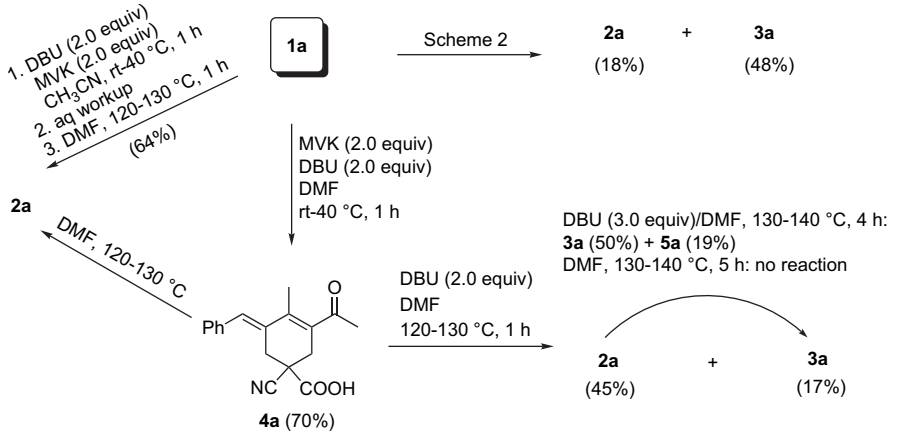
Scheme 2.

benzenes in reasonable yields. However, many trials were found to be ineffective (vide infra). As some examples, the reaction of **2a** with Pd/C in decaline at refluxing temperature[3] or DDQ oxidation[4] in benzene was ineffective. After many trials we found that direct one-pot reaction of **1a** and MVK in the presence of DBU in DMF could afford **3a** up to 48% yield when we raised the reaction temperature to 130–140 °C as shown in Scheme 2, fortunately.

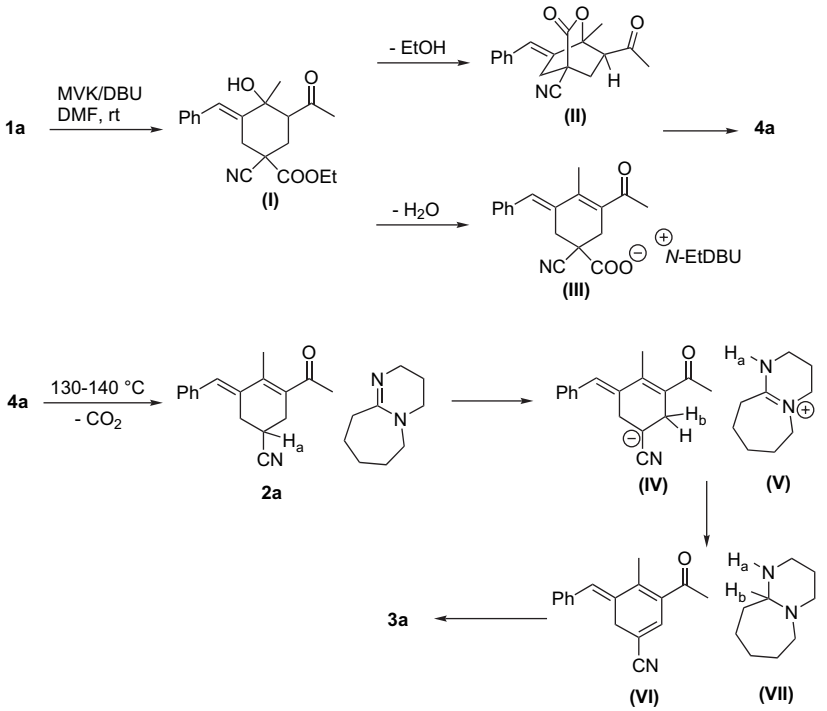
When the reaction of **1a** was carried out under nitrogen atmosphere in DMF at 130–140 °C, we also observed the formation of **3a** in a similar yield. Thus the formation of **3a** could not be explained by simple air oxidation process. Thus we examined the reaction carefully (Scheme 3) and we could propose a tentative mechanism for the formation of **3a** (Scheme 4, vide infra). The reaction of **1a** and MVK in the presence of DBU in DMF at rt–40 °C afforded cyclohexene carboxylic acid **4a** in 70% yield (Scheme 3). The compound **4a** was converted to **2a** almost quantitatively by simply heating (120–130 °C) in DMF in the absence of DBU by decarboxylation. When the reaction of **1a** and MVK was carried out in CH_3CN instead of DMF at rt–40 °C, we again observed the formation of compound **4a** as the major product, which was converted to **2a** by heating in DMF after aqueous workup (64% from **1a**). *From the experiments we came to know that the reaction of **1a** and MVK at low temperature (<40 °C) produced **4a** as an intermediate, which can be changed into **2a** thermally without the aid of DBU*. However, the reaction of **4a** in DMF in the presence of DBU at slightly lower temperature gave a mixture of **2a** (45%) and **3a** (17%). In addition, the reaction of **2a** in the presence of excess DBU (3.0 equiv) in DMF at 130–140 °C afforded **3a** (50%) and 19% of amide compound **5a** (entry 1 in Table 2, vide infra),[5] while the reaction in the absence of DBU did not produce any trace amounts of **3a**. *From the results we thought the formation of benzene derivative **3a** could be effective in the presence of excess amounts of DBU at high temperature*.

In order to find optimized conditions for the synthesis of poly-substituted benzenes we examined the reaction of **2a**[6] under a variety of conditions as summarized in Table 1.[7] As shown in Table 1, amidine bases such as DBU, DBN, and TBD (1,5,7,-triazabicyclo[4,4,0]dec-5-ene) showed good results (entries 1–3). On the other hand DABCO, piperidine, and TBAF[7b] were completely ineffective (entries 4, 5, and 7). It is interesting to note that the conditions using K_2CO_3 produced about 20% of aromatized compounds (entry 6). As demonstrated in entries 8–11, the use of CH_3CN as solvent, insufficient amounts of DBU or lower temperature were all less effective to produce the aromatized compound. *From the experiments we obtained the following insights: (i) strong amine bases having amidine functionality were effective for the dehydrogenation of **2a**, (ii) the optimum conditions would be the application of DBU (3.0 equiv) in DMF at elevated temperature (130–140 °C)*.

Thus, we prepared various cyclohexene derivatives **2b–g** by using the same procedure of **2a** (Scheme 2, CH_3CN, DBU, reflux, 1–24 h) as in our previous paper.[2] With these cyclohexenes, we examined the synthesis of poly-substituted benzene derivatives and the results are summarized in Table 2. As described above we obtained **3a** (50%) and the amide compound **5a** (19%) from **2a** under the optimized conditions (entry 1).



Scheme 3.



Scheme 4.

Similarly, **3b** (36%) and **5b** (27%) were isolated from the reaction of **2b** (entry 2). The reaction of **2c** under the same conditions produced three types of compounds, **3c**, **5c** (hydrolyzed compound), and **6c**.[8] The compound **6c** must be the result of decarboxylation of **5c** and this was observed in other cases of ester-containing substrates **2d** and **2e** (entries 4 and 5) although the ratios were slightly different (vide infra). The formation of hydrolyzed compounds **5c** and **5e** could be explained by the reported DBU-assisted hydrolysis mechanism.[9] DBU attacks the alkyl group of ester moiety liberating the corresponding carboxylate salt, which converted into its acid form during the workup stage. The DBU-promoted hydrolysis of ester group was more effective for the methyl ester than the ethyl ester (entries 3 and 4).[9] As shown in entries 6 and 7, somewhat complex mixtures were observed for the substrates containing two-hydrolyzable substituents. From the reaction of **2f** we isolated **3f** in low yield (23%) and we observed the formation of many intractable polar compounds. Similarly we isolated **3g** and **6g** in low yields from the reaction of **2g** (entry 7).

Table 1
Optimization of the reaction conditions for the conversion of **2a** to **3a**

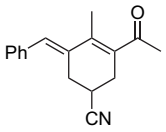
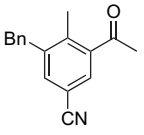
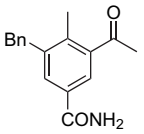
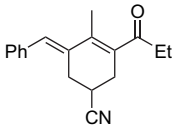
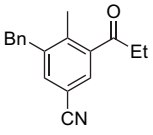
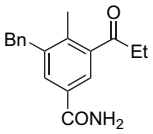
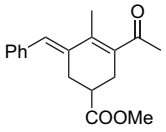
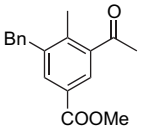
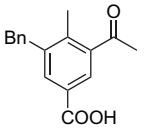
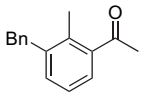
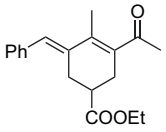
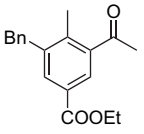
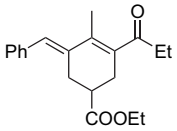
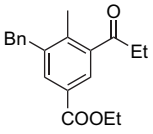
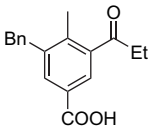
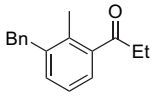
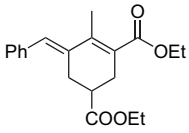
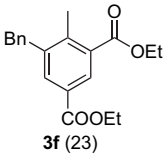
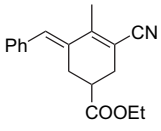
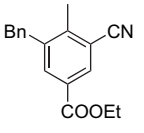
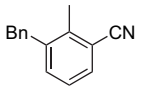
Entry	Conditions	Products (**3a**/**5a**)
1	DBU (3.0 equiv), DMF, 130–140 °C, 4 h	50/19
2	DBN (3.0 equiv), DMF, 130–140 °C, 8 h	40/26
3	TBD (3.0 equiv),[a] DMF, 130–140 °C, 2 h	49/7
4	DABCO (3.0 equiv), DMF, 130–140 °C, 3 h	nd[b]
5	Piperidine (3.0 equiv), DMF, 130–140 °C, 16 h	nd[b]
6	K_2CO_3 (3.0 equiv), DMF, 130–140 °C, 18 h	15/5
7	TBAF (3.0 equiv), THF, reflux, 16 h	nd[b]
8	DBU (3.0 equiv), CH_3CN, reflux, 22 h	2/0 (78% **2a**)
9	DBU (3.0 equiv), DMF, 70–80 °C, 22 h	23/5 (37% **2a**)
10	DBU (0.1 equiv), DMF, 130–140 °C, 16 h	9/0 (74% **2a**)
11	DBU (10.0 equiv), neat, 130–140 °C, 2 h	25/30

[a] 1,5,7-Triazabicyclo[4,4,0]dec-5-ene.
[b] Not detected.

The reaction mechanisms for the formation of **4a** from **1a** and the dehydrogenation of **4a** to **3a** could be postulated tentatively as shown in Scheme 4 based on the experimental results (vide supra). The reaction of **1a** and MVK produced the corresponding cyclohexane intermediate (**I**) via the sequential Michael–aldol process as in our previous paper.[2] The intermediate (**I**) could be converted into the cyclohexene derivative **4a** via the bicyclic lactone intermediate (**II**). Otherwise, dehydration of (**I**) and the following DBU-assisted hydrolysis[9] via the intermediate (**III**) could also produce **4a**. Decarboxylation of **4a** at elevated temperature produced **2a**, which could be dehydrogenated by DBU by the following process: (i) deprotonation of H_a of **2a** by DBU to give (**IV**) and amidinium salt (**V**), (ii) hydride (H_b) transfer from (**IV**) to the amidinium salt (**V**) to give (**VI**) and (**VII**), and finally (iii) double bond migration to the final aromatic compound **3a**. Although the reaction mechanism is not clear at this stage we prepared poly-substituted aromatic compounds in moderate yields by using the Baylis–Hillman acetates as the starting materials.[10]

In summary, we disclosed the synthesis of poly-substituted benzene derivatives starting from Baylis–Hillman adducts via the combination of domino process for the cyclohexene intermediates and the following DBU-assisted unusual dehydrogenation process. Further studies on the mechanism of DBU-assisted unusual dehydrogenation and the synthetic applications are actively underway.

Table 2
Synthesis of poly-substituted benzene derivatives **3a–g**

Entry	Substrate[a]	Conditions	Products (%)		
1	 **2a**	DBU (3.0 equiv), DMF, 130–140 °C, 4 h	 **3a** (50)	 **5a** (19)	
2	 **2b**	DBU (3.0 equiv), DMF, 130–140 °C, 4 h	 **3b** (36)	 **5b** (27)	
3	 **2c**	DBU (5.0 equiv), DMF, 130–140 °C, 6 h	 **3c** (5)	 **5c** (50)	 **6c** (16)
4	 **2d**	DBU (5.0 equiv), DMF, 130–140 °C, 12 h	 **3d** (35)	**5c** (39)	**6c** (8)
5	 **2e**	DBU (5.0 equiv), DMF, 140–150 °C, 12 h	 **3e** (44)	 **5e** (11)	 **6e** (11)
6	 **2f**	DBU (5.0 equiv), DMF, 140–150 °C, 22 h	 **3f** (23)	[b,c]	
7	 **2g**	DBU (5.0 equiv), DMF, 130–140 °C, 3 h	 **3g** (40)	[b,c]	 **6g** (3)

[a] Starting materials **2c–g** were prepared according to the previous paper.[2] Starting materials **2a** and **2b** were prepared as: (i) **1a**, MVK or EVK (2.0 equiv), DBU (2.0 equiv), CH_3CN, 40 °C, 1 h, (ii) aqueous extractive workup, (iii) DMF, 120–130 °C, 1 h; **2a** (64%), **2b** (60%).
[b] Starting materials were recovered (17% of **2f** in entry 6, 21% of **2g** in entry 7).
[c] Intractable many hydrolyzed compounds were formed.

3. Experimental

3.1. General procedure

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. The signal positions are reported in parts per million relative to TMS (δ scale) used as an internal standard. IR spectra are reported in cm^{-1}. Mass spectra were obtained from the Korea Basic Science Institute (Gwangju branch). Melting points are uncorrected. The elemental analyses were carried out at Korea Research Institute of Chemical Technology, Taejeon, Korea. All reagents were purchased from commercial sources and used without further treatment. The separations were carried out by flash column chromatography over silica gel (230–400 mesh ASTM). Organic extracts were dried over anhydrous $MgSO_4$ and the solvents were evaporated on a rotary evaporator under water aspirator pressure.

3.2. Typical procedure for the synthesis of compound *2a*

The compound **2a** was prepared in 62% yield by using the reported method,[2] otherwise the compound **2a** was also

prepared as follows. To a stirred solution of **1a** (542 mg, 2.0 mmol) in CH_3CN (3 mL) was added DBU (608 mg, 4.0 mmol) and methyl vinyl ketone (280 mg, 4.0 mmol) at room temperature and stirred at around 40 °C for 1 h. The reaction mixture was poured into cold HCl solution and extracted with ether, dried with $MgSO_4$ and removal of solvent afforded crude **4a**. This oily residue was dissolved in DMF (3 mL) and heated to 120–130 °C for 1 h. After usual aqueous workup and column chromatographic purification process (hexanes/EtOAc, 7:1) we obtained pure **2a** (301 mg, 64%) as a white solid. Compound **2b** was synthesized similarly in 60% yield and other starting materials **2c–g** were prepared as reported.[2]

3.2.1. Compound *2a*

Yield 64%; white solid; mp 59–61 °C; IR (film) 2925, 2241, 1685, 1444, 1354, 1228 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.09 (s, 3H), 2.36 (s, 3H), 2.70–2.93 (m, 4H), 3.04 (dd, J=14.1 and 2.4 Hz, 1H), 6.94 (s, 1H), 7.23–7.32 (m, 3H), 7.36–7.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.17, 25.26, 29.70, 30.06, 30.29, 121.08, 127.52, 128.39, 129.15, 130.75, 133.16, 134.13, 134.95, 136.48, 203.98; ESIMS *m/z* 252 (M^++1). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.07; H, 6.99; N, 5.30.

3.2.2. Compound *2b*

Yield 60%; colorless oil; IR (film) 2933, 2241, 1689, 1450, 1186 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (t, J=7.2 Hz, 3H), 2.01 (s, 3H), 2.63 (q, J=7.2 Hz, 2H), 2.68–2.93 (m, 4H), 3.03 (dd, J=14.1 and 2.4 Hz, 1H), 6.88 (s, 1H), 7.22–7.31 (m, 3H), 7.35–7.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.85, 16.12, 25.22, 29.64, 30.24, 35.43, 121.09, 127.39, 128.34, 129.10, 129.97, 132.90, 133.25, 134.44, 136.47, 207.82; ESIMS *m/z* 266 (M^++1). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.22; H, 7.51; N, 5.11.

3.3. Synthesis of compound *4a*

To a stirred solution of **1a** (542 mg, 2.0 mmol) in DMF (3 mL) was added DBU (608 mg, 4.0 mmol) and methyl vinyl ketone (280 mg, 4.0 mmol) at room temperature and stirred at around 40 °C for 1 h. After usual aqueous workup and column chromatographic purification process (hexanes/EtOAc, 1:1) we obtained pure **4a** (414 mg, 70%) as a white solid.

3.3.1. Compound *4a*

Yield 70%; white solid; mp 100–102 °C; IR (KBr) 3500, 2927, 2594, 2247, 1714, 1680, 1633, 1373, 1259, 1232 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.13 (s, 3H), 2.38 (s, 3H), 2.86–3.00 (m, 3H), 3.31 (d, J=15.0 Hz, 1H), 7.05 (s, 1H), 7.25–7.40 (m, 5H), 8.89 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.11, 30.08, 33.23, 34.07, 43.02, 118.74, 127.52, 128.41, 129.16, 132.04, 132.20, 132.65, 135.02, 136.41, 169.55, 203.84; ESIMS *m/z* 296 (M^++1). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.02; H, 5.69; N, 4.68.

3.4. Typical procedure for the synthesis of compound *3a*

To a stirred solution of **2a** (251 mg, 1.0 mmol) in DMF (1 mL) was added DBU (457 mg, 3.0 mmol) and heated to 130–140 °C for 4 h. The reaction mixture was poured into cold HCl solution and extracted with ether, dried with $MgSO_4$, removal of solvent and column chromatographic purification process (hexanes/EtOAc, 7:1) we obtained pure **3a** (125 mg, 50%) and **5a** (51 mg, 19%). Other compounds **3b–g**, **5b–e**, and **6c–g** were prepared similarly and the spectroscopic data are as follows.

3.4.1. Compound *3a*

Yield 50%; colorless oil; IR (film) 3028, 2924, 2229, 1695, 1452, 1358 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.38 (s, 3H), 2.58 (s, 3H), 4.04 (s, 2H), 7.06–7.09 (m, 2H), 7.22–7.35 (m, 3H), 7.44 (d, J=1.5 Hz, 1H), 7.69 (d, J=1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.83, 30.38, 39.34, 109.66, 118.22, 126.75, 128.65, 128.83, 129.39, 134.96, 138.02, 141.01, 141.26, 142.56, 201.57; ESIMS *m/z* 250 (M^++1). Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.72; H, 6.11; N, 5.50.

3.4.2. Compound *5a*

Yield 19%; white solid; mp 144–146 °C; IR (film) 3361, 3186, 1689, 1658, 1618, 1412 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 3H), 2.60 (s, 3H), 4.09 (s, 2H), 6.00 (br s, 2H), 7.07–7.10 (m, 2H), 7.21–7.29 (m, 3H), 7.62 (s, 1H), 7.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.69, 30.48, 39.66, 125.43, 126.41, 128.53, 128.64, 130.58, 130.95, 138.98, 139.76, 140.90, 141.22, 168.60, 203.11; ESIMS *m/z* 268 (M^++1). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.53; H, 6.51; N, 5.21.

3.4.3. Compound *3b*

Yield 36%; colorless oil; IR (film) 2924, 2227, 1699, 1495, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, J=7.2 Hz, 3H), 2.32 (s, 3H), 2.85 (q, J=7.2 Hz, 2H), 4.04 (s, 2H), 7.07–7.10 (m, 2H), 7.22–7.35 (m, 3H), 7.42 (d, J=1.5 Hz, 1H), 7.59 (d, J=1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.05, 16.77, 36.15, 39.33, 109.68, 118.30, 126.76, 128.50, 128.68, 128.84, 135.54, 138.04, 140.40, 141.91, 142.40, 205.24; ESIMS *m/z* 264 (M^++1). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.34; H, 6.61; N, 5.04.

3.4.4. Compound *5b*

Yield 27%; white solid; mp 134–136 °C; IR (film) 3354, 3197, 2925, 1660, 1614, 1454, 1390 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.81 (t, J=7.2 Hz, 3H), 2.29 (s, 3H), 2.89 (q, J=7.2 Hz, 2H), 4.07 (s, 2H), 6.10 (br s, 2H), 7.07–7.10 (m, 2H), 7.18–7.31 (m, 3H), 7.61 (d, J=1.8 Hz, 1H), 7.83 (d, J=1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.16, 16.60, 36.10, 39.64, 124.48, 126.40, 128.55, 128.63, 130.46 (2C), 138.99, 139.18, 141.07, 141.53, 168.71, 206.73; ESIMS *m/z* 282 (M^++1). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.63; H, 6.79; N, 4.84.

3.4.5. Compound ***3c***

Yield 5%; colorless oil; IR (film) 2918, 1722, 1693, 1433, 1315, 1227 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 3H), 2.60 (s, 3H), 3.92 (s, 3H), 4.09 (s, 2H), 7.07–7.10 (m, 2H), 7.17–7.30 (m, 3H), 7.94 (d, J=1.5 Hz, 1H), 8.13 (d, J=1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.84, 30.39, 39.73, 52.23, 126.34, 127.44, 127.47, 128.49, 128.63, 133.52, 139.14, 140.54, 141.14 (2C), 166.44, 202.77; ESIMS *m/z* 283 (M^++1).

3.4.6. Compound ***5c***

Yield 50% (from **2c**); white solid; mp 158–160 °C; IR (film) 3026, 2922, 2627, 1691, 1603, 1415, 1309, 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.38 (s, 3H), 2.62 (s, 3H), 4.10 (s, 2H), 7.07–7.11 (m, 2H), 7.15–7.39 (m, 3H), 7.99 (d, J=1.8 Hz, 1H), 8.19 (d, J=1.8 Hz, 1H), 9.12 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.94, 30.35, 39.69, 126.39, 126.53, 127.99, 128.50, 128.62, 133.95, 138.93, 140.58, 141.40, 142.24, 171.25, 202.74; ESIMS *m/z* 269 (M^++1). Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.23; H, 6.22.

3.4.7. Compound ***6c***

Yield 16% (from **2c**); colorless oil; IR (film) 2924, 1687, 1495, 1450, 1352, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.32 (s, 3H), 2.56 (s, 3H), 4.04 (s, 2H), 7.08–7.11 (m, 2H), 7.16–7.30 (m, 5H), 7.42–7.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.38, 30.46, 39.64, 125.40, 126.10, 126.27, 128.47, 128.62, 132.83, 135.33, 139.81, 140.47, 140.59, 203.83; ESIMS *m/z* 225 (M^++1). Anal. Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.77; H, 6.98.

3.4.8. Compound ***3d***

Yield 35%; colorless oil; IR (film) 2924, 1718, 1691, 1367, 1313, 1225, 1146 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.39 (t, J=7.2 Hz, 3H), 2.35 (s, 3H), 2.60 (s, 3H), 4.09 (s, 2H), 4.38 (q, J=7.2 Hz, 2H), 7.07–7.10 (m, 2H), 7.17–7.30 (m, 3H), 7.95 (d, J=1.5 Hz, 1H), 8.12 (d, J=1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.28, 16.80, 30.38, 39.72, 61.16, 126.28, 127.38, 127.77, 128.43, 128.54, 133.50, 139.15, 140.52, 140.94, 140.98, 165.94, 202.84; ESIMS *m/z* 297 (M^++1). Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.83; H, 7.01.

3.4.9. Compound ***3e***

Yield 44%; colorless oil; IR (film) 2979, 1718, 1697, 1454, 1369, 1300, 1217 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19 (t, J=7.2 Hz, 3H), 1.39 (t, J=7.2 Hz, 3H), 2.29 (s, 3H), 2.90 (q, J=7.2 Hz, 2H), 4.08 (s, 2H), 4.37 (q, J=7.2 Hz, 2H), 7.07–7.10 (m, 2H), 7.17–7.30 (m, 3H), 7.93 (d, J=1.5 Hz, 1H), 8.02 (d, J=1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.46, 14.58, 17.00, 36.27, 40.00, 61.41, 126.57, 126.72, 128.10, 128.75, 128.84, 133.31, 139.47, 140.58, 141.10, 141.46, 166.28, 206.70; ESIMS *m/z* 311 (M^++1). Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.54; H, 7.03.

3.4.10. Compound ***5e***

Yield 11%; white solid; mp 142–145 °C; IR (film) 3030, 2925, 2856, 1695, 1608, 1460, 1410, 1294, 1228 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, J=7.2 Hz, 3H), 2.33 (s, 3H), 2.92 (q, J=7.2 Hz, 2H), 4.09 (s, 2H), 7.08–7.11 (m, 2H), 7.18–7.36 (m, 3H), 7.96 (d, J=1.5 Hz, 1H), 8.08 (d, J=1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.18, 16.85, 35.99, 39.69, 126.39, 126.57, 127.04, 128.53, 128.63, 133.47, 138.98, 141.20, 141.24, 141.53, 170.87, 206.27; ESIMS *m/z* 283 (M^++1). Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.50; H, 6.63.

3.4.11. Compound ***6e***

Yield 11%; colorless oil; IR (film) 2924, 1691, 1450, 1267, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18 (t, J=7.2 Hz, 3H), 2.26 (s, 3H), 2.86 (q, J=7.2 Hz, 2H), 4.03 (s, 2H), 7.09–7.12 (m, 2H), 7.15–7.36 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.33, 16.30, 36.04, 39.64, 125.26, 125.43, 126.10, 128.48, 128.67, 132.25, 134.63, 139.86, 140.45, 141.12, 207.46; ESIMS *m/z* 239 (M^++1). Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.43; H, 7.53.

3.4.12. Compound ***3f***

Yield 23%; colorless oil; IR (film) 2981, 1720, 1452, 1367, 1317, 1228 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.38 (t, J=7.2 Hz, 3H), 1.39 (t, J=7.2 Hz, 3H), 2.45 (s, 3H), 4.10 (s, 2H), 4.37 (q, J=7.2 Hz, 4H), 7.06–7.09 (m, 2H), 7.16–7.29 (m, 3H), 7.97 (d, J=1.5 Hz, 1H), 8.33 (d, J=1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.21, 14.27, 16.94, 39.79, 61.06, 61.17, 126.24, 127.83, 128.40, 128.51, 129.35, 132.45, 133.94, 139.23, 140.57, 142.87, 165.95, 167.88; ESIMS *m/z* 327 (M^++1). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.98; H, 7.01.

3.4.13. Compound ***3g***

Yield 40%; colorless oil; IR (film) 2981, 2227, 1722, 1452, 1367, 1306, 1217 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.39 (t, J=7.2 Hz, 3H), 2.50 (s, 3H), 4.08 (s, 2H), 4.38 (q, J=7.2 Hz, 2H), 7.05–7.08 (m, 2H), 7.22–7.32 (m, 3H), 8.03 (d, J=1.5 Hz, 1H), 8.19 (d, J=1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.22, 18.17, 39.55, 61.53, 114.28, 117.68, 126.66, 128.42, 128.75, 129.08, 132.08, 134.98, 138.21, 140.89, 145.44, 164.85; ESIMS *m/z* 280 (M^++1). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.57; H, 6.38; N, 4.89.

3.4.14. Compound ***6g***

Yield 3%; colorless oil; IR (film) 2925, 2856, 2227, 1728, 1450, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.46 (s, 3H), 4.02 (s, 2H), 7.06–7.09 (m, 2H), 7.19–7.37 (m, 5H), 7.50–7.53 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.68, 39.45, 113.69, 118.59, 126.38, 126.45, 128.58, 128.65, 130.94, 134.31, 138.84, 140.40, 140.54; ESIMS *m/z* 208 (M^++1).

Acknowledgements

This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD, KRF-2006-311-C00384). Spectroscopic data were obtained from the Korea Basic Science Institute, Gwangju branch.

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5. The reaction of benzonitrile and DBU (3.0 equiv) in DMF produced 15–20% of benzamide (130–140 °C, 16 h). The reaction of **3a** under the same conditions gave 25–30% of **5a** (6 h).
6. Starting material **2a** was prepared in 62% yield from **1a** by using the method in Scheme 2, or in 64% yield by following the sequence in Scheme 3 more easily.
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8. The formation of **6c**, **6e**, and **6g** could be explained by the decarboxylation of the corresponding benzoic acid derivatives via the S_E1 type mechanism, please see: Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons: New York, NY, 2002; pp 732–733.
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10. We tried isolation of the side product **VII** in Scheme 4. Although we obtained small amounts of plausible 1,8-diazabicyclo[5.4.0]undecane (**VII**), unfortunately, it is not clear at this stage due to the contamination of DBU and some other polar impurities in the sample in ^{1}H NMR spectrum.