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An expedient synthesis of poly-substituted naphthalenes: consecutive Michael, intramolecular aldol, and decarboxylative Michael cascade of δ-ketonitriles

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ABSTRACT

An efficient synthetic method was developed for poly-substituted naphthalenes via the multi-step, one-pot domino reaction of δ-ketonitriles involving a sequential Michael addition, intramolecular aldol, lactonization, decarboxylative Michael addition, and elimination processes.

Regioselective synthesis of naphthalenes has been and continues to be of great interest in organic synthesis.[1,2] A new synthetic procedure is still highly desired due to the abundance of the skeleton in many biologically important natural products. Recently, we reported the synthesis of 1-arylisoquinoline derivatives via the indium-mediated Barbier-type allylation of nitrile group of δ-ketonitrile **1a** (Scheme 1).[3] The starting material **1a** was easily prepared by the S_NAr reaction of 2-fluorobenzophenone with methyl cyanoacetate.[3] During the studies we thought that **1a** could be used for the synthesis of naphthalene **10a** via the sequential Michael addition to methyl acrylate (**2a**), intramolecular aldol condensation, and elimination of HCN (vide infra, Scheme 2). However, compound **10a** was not formed in any trace amounts, and the major product was compound **3a**, unexpectedly.

Initially we carried out the reaction of **1a** with 3.0 equiv of methyl acrylate (**2a**) and obtained moderate yield of **3a** (41%).[4] However, the yield of **3a** increased to 61%, as shown in Scheme 1, when we used 5.0 equiv of **2a**.[4,5] The mechanism for the formation of **3a** could be proposed as shown in Scheme 2: (i) Michael addition of **1a** to **2a** produced **4a**, (ii) intramolecular aldol-type cyclization to **5a**, (iii) lactonization to tricyclic intermediate **6a**,[6] (iv) base-mediated decarboxylative Michael addition[7,8] to methyl acrylate via **7a** to produce **8a**, and (v) E2 elimination of HCN to give naphthalene **3a**. As shown in Scheme 1, compounds **4a** (3%), **8a** (7%), and **9a** (4%) were isolated together in low yields, and the results supported the proposed mechanism. Compound **9a** might be formed via the aerobic oxidation of **7a**. We obtained **3a** in 65% yield under the same conditions (Cs_2CO_3, reflux) from **4a** which was obtained by the reaction of **1a** and **2a** under mild conditions (K_2CO_3, 50 °C),[4] as shown in Scheme 3.

Encouraged by the results, we examined the reactions of **1a** with various Michael acceptors including ethyl acrylate (**2b**), phenyl vinyl sulfone (**2c**), acrylonitrile (**2d**), and methyl vinyl ketone (**2e**). When we used **2b** and **2c**, the corresponding naphthalenes **3b** and **3c** were obtained in moderate yields (entries 2 and 3 in Table 1). However, the reactions with **2d** and **2e** showed the formation of many intractable complex mixtures.[9] The reactions of other δ-ketonitriles **1b–d** and **2a** afforded the corresponding naphthalenes (**3a**, **3d**, and **3e**) in moderate yields (entries 4–6). The formation of **3a** from **1b** and **2a** (entry 4) supported again the proposed mechanism in Scheme 2. It is interesting to note that the reaction of **1e** (entry 7) afforded **3a** by following the mechanism proposed in Scheme 4. Compound **1e** has two acidic benzylic protons and Michael addition occurred two times to produce **11**, which produced **3a** via dehydrative cyclization and elimination of HCN.

As a synthetic application of the synthesized naphthalene, we examined the Friedel–Crafts reaction of **3a**, as shown in Scheme 5. Hydrolysis of **3a** (LiOH, aq THF) afforded the corresponding diacid in 92%. Treatment of this crude diacid with H_2SO_4 (10 equiv) in 1,2-dichloroethane afforded fluorenone derivative **12** and perinaphthenone derivative **13**.[5,10] When the reaction stopped after 6 h, compounds **12** and **13** were isolated in 80% and 5%,

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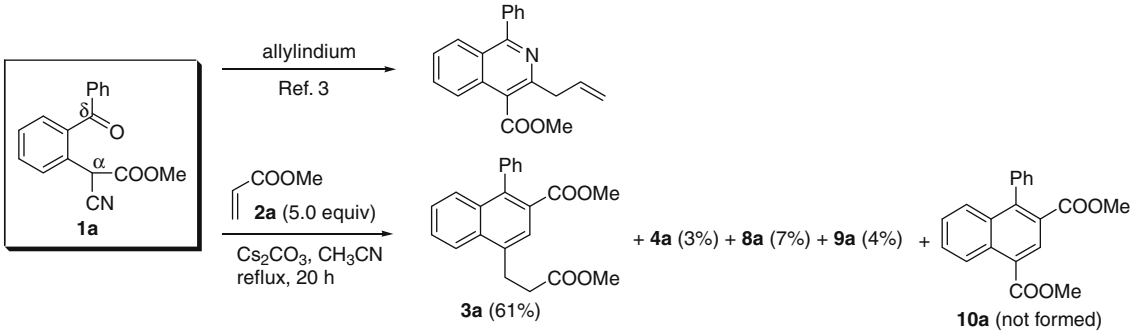
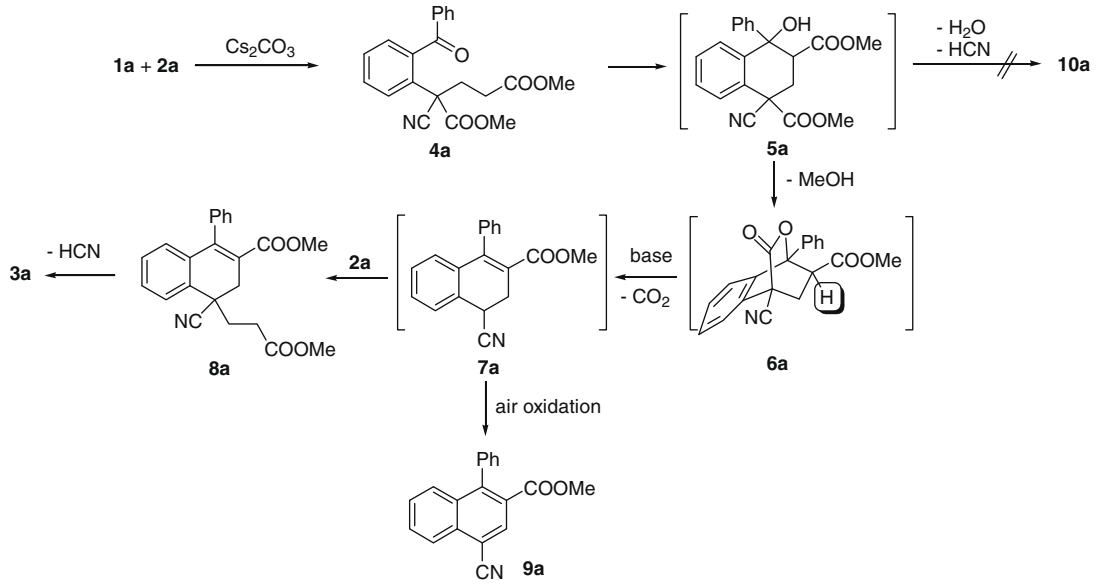
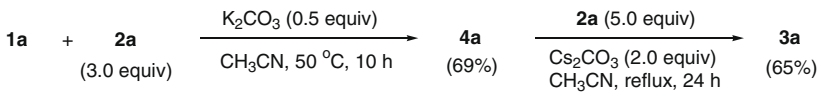


Scheme 1.



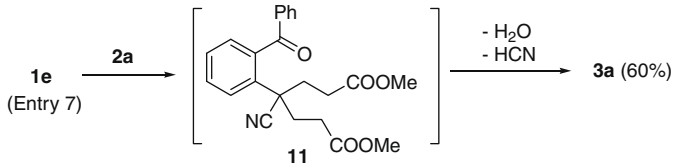
Scheme 2.



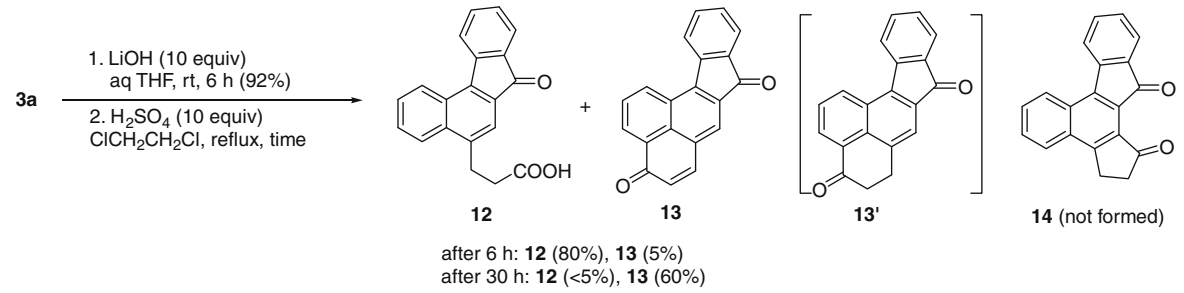
Scheme 3.

respectively. When we run the reaction for longer time (30 h), the amount of **13** increased to 60%. Compound **13** might be formed via the air oxidation of **13'** which was formed by the Friedel–Crafts reaction of **12**. We could not detect the formation of **14** in the reaction.

In summary, we disclosed an efficient synthesis of poly-substituted naphthalenes via the multi-step, one-pot domino reaction of δ-ketonitriles involving a sequential Michael addition, intramolecular aldol, lactonization, decarboxylative Michael addition, and elimination processes.

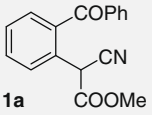
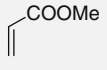
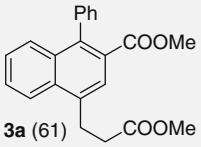
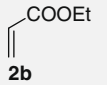
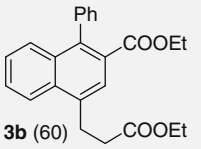
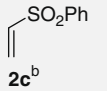
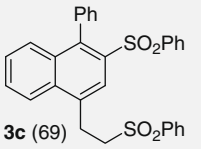
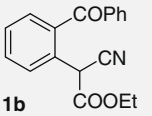
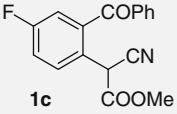
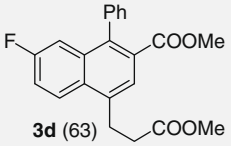
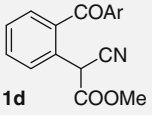
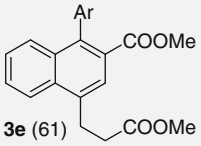
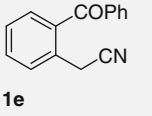


Scheme 4.



Scheme 5.

Table 1
Synthesis of poly-substituted naphthalenes[a]

Entry	Substrate **1**	Substrate **2**	Product (%)
1	 **1a**	 **2a**	 **3a** (61)
2	**1a**	 **2b**	 **3b** (60)
3	**1a**	 **2c**[b]	 **3c** (69)
4	 **1b**	**2a**	**3a** (57)
5	 **1c**	**2a**	 **3d** (63)
6[c]	 **1d**	**2a**	 **3e** (61)
7	 **1e**	**2a**	**3a** (60)

[a] Conditions: **1** (1.0 mmol), **2** (5.0 equiv), Cs_2CO_3 (2.0 equiv, CH_3CN, reflux, 20 h (8 h for entry 3).
[b] 3.0 equiv of **2c**.
[c] Ar is 4-methoxyphenyl.

Acknowledgments

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References and notes

1. For our recent synthesis of naphthalene derivatives, see: (a) Lee, K. Y.; Kim, S. C.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 977–980. and further references cited therein; (b) Gowrisankar, S.; Kim, K. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2008**, *29*, 2537–2539; (c) Im, Y. J.; Lee, K. Y.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2002**, *43*, 4675–4678; (d) Gowrisankar, S.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 3105–3108; (e) Im, Y. J.; Chung, Y. M.; Gong, J. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 787–788.
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3. Kim, S. H.; Lee, H. S.; Kim, K. H.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 6476–6479.
4. When we used 3.0 equiv of methyl acrylate, the yield of **3a** decreased to 41% whereas the yield of **4a** increased to 10%. When we used K_2CO_3 (2.0 equiv) instead of Cs_2CO_3 in the reaction of **1a** and **2a**, product **3a** was not formed at all, instead compounds **4a** (26%) and **8a** (33%) were isolated. Compound **4a** was prepared as the major product (69%) under the influence of K_2CO_3 (0.5 equiv) at 50 °C (10 h).
5. *Typical procedure for the synthesis of compound* **3a**: A stirred mixture of **1a** (279 mg, 1.0 mmol),[3] **2a** (430 mg, 5.0 mmol), and Cs_2CO_3 (652 mg, 2.0 mmol) in acetonitrile (2.0 mL) was heated to reflux for 20 h. After the usual aqueous workup and column chromatographic purification process (hexanes/CH_2Cl_2/EtOAc, 10:1:1), we obtained **3a** (212 mg, 61%), **4a** (11 mg, 3%), **8a** (26 mg, 7%), and **9a** (11 mg, 4%). Other compounds were prepared similarly and the selected spectroscopic data of **3a**, **4a**, **8a**, **9a**, **3c**, **12**, and **13** are as follows:
Compound **3a**: 61%; colorless oil; IR (film) 1736, 1730, 1433, 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.83 (t, J = 7.8 Hz, 2H), 3.49 (t, J = 7.8 Hz, 2H), 3.60 (s, 3H), 3.74 (s, 3H), 7.25–7.30 (m, 2H), 7.39–7.50 (m, 4H), 7.57–7.64 (m, 2H), 7.80 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.08, 34.75, 51.77, 51.90, 123.30, 125.25, 126.23, 127.26, 127.62, 127.63, 127.83, 128.81, 129.65, 132.96, 133.04, 136.29, 139.01, 140.50, 168.62, 173.23; ESIMS m/z 371 (M^++Na). Anal. Calcd for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.66; H, 5.92.
Compound **4a**: 3%; colorless oil; IR (film) 2243, 1744, 1736, 1366, 1229 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.45–2.93 (m, 4H), 3.65 (s, 3H), 3.66 (s, 3H), 7.44–7.50 (m, 4H), 7.58–7.65 (m, 2H), 7.75–7.83 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.28, 32.18, 51.78, 51.89, 53.75, 118.15, 128.09, 128.42, 128.88, 130.47, 131.23, 131.38, 133.44, 133.91, 136.93, 136.97, 167.41, 172.01, 197.28; ESIMS m/z 388 (M^++Na).
Compound **8a**: 7%; white solid, mp 125–126 °C; IR (KBr) 2224, 1730, 1705, 1221 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.16–2.26 (m, 1H), 2.36–2.47 (m, 2H), 2.57–2.67 (m, 1H), 3.18 (d, J = 16.5 Hz, 1H), 3.25 (d, J = 16.5 Hz, 1H), 3.52 (s, 3H), 3.61 (s, 3H), 6.85 (dd, J = 7.5 and 1.2 Hz, 1H), 7.13–7.16 (m, 2H), 7.23 (td, J = 7.5 and 1.2 Hz, 1H), 7.35–7.45 (m, 4H), 7.61 (ddd, J = 7.5, 1.2, and 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.19, 31.42, 34.40, 41.01, 51.74, 51.86, 121.85, 122.16, 126.33, 127.80, 128.13, 128.56, 128.74, 129.60, 129.87, 133.20, 133.28, 137.68, 145.46, 167.51, 172.23; ESIMS m/z 398 (M^++Na).
Compound **9a**: 4%; white solid, mp 147–149 °C; IR (KBr) 2241, 1726, 1437, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.65 (s, 3H), 7.26–7.29 (m, 2H), 7.48–7.59 (m, 4H), 7.65–7.69 (m, 1H), 7.75–7.80 (m, 1H), 8.31–8.34 (m, 1H), 8.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.40, 110.20, 117.16, 125.25, 127.51, 128.11, 128.12, 128.15, 128.79, 129.03, 130.03, 132.44, 132.65, 133.31, 137.41, 146.85, 166.67; ESIMS m/z 310 (M^++Na).
Compound **3c**: 69%; white solid, mp 176–177 °C; IR (KBr) 1447, 1306, 1146 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.56–3.76 (m, 4H), 6.82–6.85 (m,

2H), 7.18–7.44 (m, 10H), 7.53–7.75 (m, 4H), 8.00–8.06 (m, 3H), 8.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.18, 56.21, 122.87, 123.48, 127.07, 127.43, 127.51, 127.84, 128.10, 128.39, 128.84, 129.28, 129.48, 131.01, 132.50, 133.20, 134.02, 134.03, 134.18, 134.43, 136.52, 138.74, 140.89, 141.19; ESIMS *m*/*z* 535 (M^++Na). Anal. Calcd for $C_{30}H_{24}O_4S_2$: C, 70.29; H, 4.72 Found: C, 70.51; H, 4.94.
Compound **12**: 80%; orange solid, mp 234–235 °C; IR (KBr) 3447, 1709, 1209 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.69 (t, *J* = 7.5 Hz, 2H), 3.34 (t, *J* = 7.5 H, 2H), 7.36–7.41 (m, 1H), 7.56 (s, 1H), 7.60–7.65 (m, 2H), 7.73–7.76 (m, 2H), 8.17–8.20 (m, 1H), 8.26 (d, *J* = 7.5 Hz, 1H), 8.66–8.70 (m, 1H), 12.20 (br s, 1H); ^{13}C NMR (DMSO-d_6 + $CDCl_3$, 75 MHz) δ 28.18, 34.45, 119.45, 122.96, 123.67, 124.91, 125.40, 127.18, 128.26, 128.27, 129.04, 131.01, 134.14, 134.30, 135.78, 138.91, 141.40, 144.76, 174.44, 194.36; ESIMS *m*/*z* 325 (M^++Na). Anal. Calcd for $C_{20}H_{14}O_3$: C, 79.46; H, 4.67. Found: C, 79.17; H, 4.97.
Compound **13**: 5%; reddish solid, mp 282–284 °C (decomp.); IR (KBr) 1713, 1632, 1570, 1215 cm^{-1}; ^{1}H NMR (DMSO-d_6 + $CDCl_3$, 300 MHz) δ 6.71 (d, *J* = 9.6 Hz, 1H), 7.40–7.45 (m, 1H), 7.61 (td, *J* = 7.8 and 1.2 Hz, 1H), 7.71–7.77 (m, 2H), 7.90 (dd, *J* = 8.4 and 7.5 Hz, 1H), 7.91 (s, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 8.68 (dd, *J* = 7.2 and 1.2 Hz, 1H), 8.86 (dd, *J* = 8.4 and 1.2 Hz, 1H); ^{13}C NMR (DMSO-d_6 + $CDCl_3$, 75 MHz) δ 123.82, 124.15, 124.50, 127.53, 128.15, 128.37, 128.50, 129.83, 130.17, 131.19, 131.49, 131.72, 132.29, 133.99, 134.76, 141.53, 143.31, 145.86, 184.69, 192.54; ESIMS *m*/*z* 305 (M^++Na). Anal. Calcd for $C_{20}H_{10}O_2$: C, 85.09; H, 3.57. Found: C, 84.76; H, 3.89.

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8. The mechanism involving retro-Dields–Alder reaction of tricyclic compound **6a** to form the dihydronaphthalene derivative **7a** with loss of CO_2 could be ruled out. Similar cyclo-reversions have been reported to occur at high temperature (250–570 °C) under flash vacuum pyrolysis conditions, see: (a) Holland, J. M.; Jones, D. W. *J. Chem. Soc. (C)* **1970**, 536–540; (b) Spangler, R. J.; Beckmann, B. G.; Kim, J. H. *J. Org. Chem.* **1977**, *42*, 2989–2996.
9. In the reaction of **1a** and **2e**, we isolated low yields of 4-(3-acetyl-4-phenylnaphthalen-1-yl)butan-2-one (**3f**, 18%) and 3-acetyl-4-phenyl naphthalene-1-carbonitrile (**9f**, 5%).
Compound **3f**: 18%; colorless oil; IR (KBr) 1719, 1711, 1686, 1678, 1366, 1356 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.91 (s, 3H), 2.22 (s, 3H), 2.96 (t, *J* = 7.8 Hz, 2H), 3.42 (t, *J* = 7.8 Hz, 2H), 7.34–7.37 (m, 2H), 7.42–7.52 (m, 5H), 7.57–7.62 (m, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.54, 30.06, 30.70, 44.06, 123.49, 124.04, 126.40, 127.39, 128.15, 128.27, 128.52, 130.70, 132.42, 132.75, 137.17, 137.28, 137.70, 138.38, 204.92, 207.54; ESIMS *m*/*z* 339 (M^++Na).
Compound **9f**: 5%; white solid, mp 137–138 °C; IR (KBr) 2222, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.92 (s, 3H), 7.34–7.38 (m, 2H), 7.54–7.62 (m, 4H), 7.75–7.80 (m, 2H), 8.13 (s, 1H), 8.31–8.34 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.39, 110.47, 117.18, 125.38, 128.21, 128.32, 128.86, 129.09, 129.77, 130.13, 131.34, 131.96, 133.05, 136.76, 137.30, 143.48, 202.29; ESIMS *m*/*z* 294 (M^++Na).
10. For the synthesis and biological activities of similar fluorenone and perinaphthenone derivatives, see: (a) Zhang, X.; Larock, R. C. *Org. Lett.* **2005**, *7*, 3973–3976; (b) Waldo, J. P.; Zhang, X.; Shi, F.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 6679–6685. and further references cited therein; (c) Zhao, S.; Freeman, J. P.; Szmuszkovicz, J. *J. Org. Chem.* **1992**, *57*, 4051–4053.