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Synthesis of 3,4-disubstituted 2(1*H*)-quinolinones via intramolecular Friedel–Crafts reaction of *N*-arylamides of Baylis–Hillman adducts

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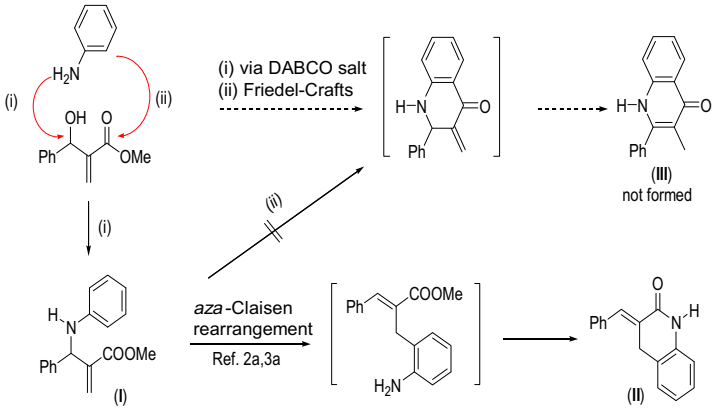
ABSTRACT

3,4-Disubstituted 2(1*H*)-quinolinones were synthesized starting from the Baylis–Hillman adducts via the following sequential processes: (i) hydrolysis of the Baylis–Hillman adduct to acid, (ii) EDC coupling with anilines, (iii) H_2SO_4-assisted intramolecular Friedel–Crafts cyclization, and the final (iv) DBU-mediated isomerization.

Recently, Baylis–Hillman adducts have been used for the synthesis of many heterocyclic compounds.[1–3] Among them, the synthesis of quinolone derivatives has received much attention due to the importance of these compounds.[2,3] Most of the reported syntheses of quinolone and its derivatives used the Baylis–Hillman adducts of 2-nitrobenzaldehydes as starting materials.[2b–e] The construction of quinolone ring was finally carried out by the condensation reaction between the carbonyl group and amino group, made by in situ reduction of the nitro group.[2b–e]

Modified Baylis–Hillman adducts with anilines, *aza*-Baylis–Hillman adducts, have also been used for the synthesis of quinolone derivatives.[2a,3a–c] As an example, *N*-phenyl *aza*-Baylis–Hillman adduct (**I**) produced 2(1*H*)-quinolinone (**II**) via the first *aza*-Claisen rearrangement and the following cyclization with PPA (polyphosphoric acid)[3a] or TFA (Scheme 1).[2a] We and others did not observe the formation of 4(1*H*)-quinolinone (**III**), which could be formed via the Friedel–Crafts type cyclization of (**I**) and the following double bond isomerization process (Scheme 1).



Scheme 1.

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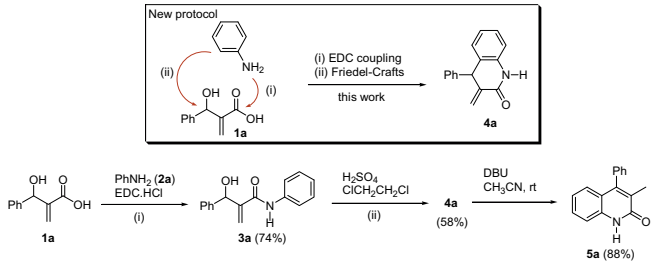


Scheme 2.

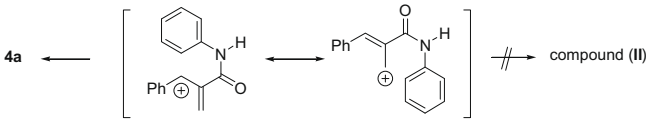
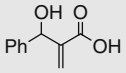
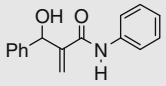
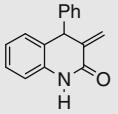
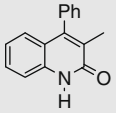
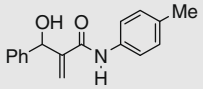
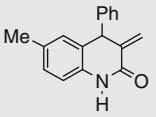
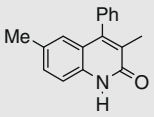
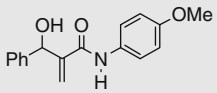
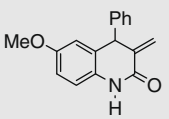
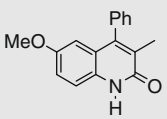
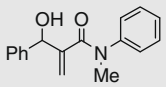
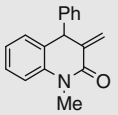
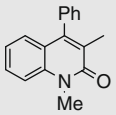
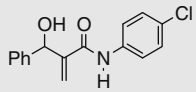
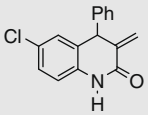
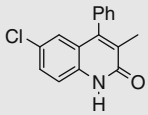
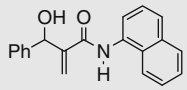
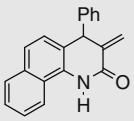
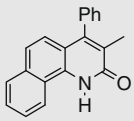
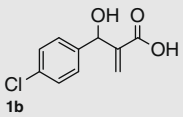
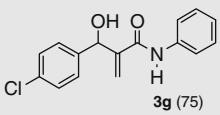
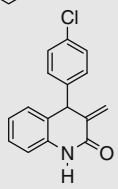
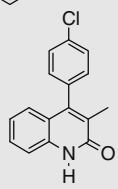
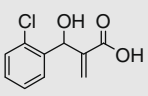
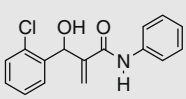
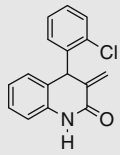
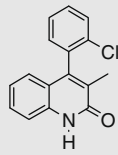


Figure 1.

Based on the importance of quinolone derivatives[2–4] and the synthetic potential of the Friedel–Crafts reaction in Baylis–Hillman chemistry,[5] we decided to develop a new methodology for this class of compounds. *Aza*-Claisen rearrangement of (**I**) occurred more preferentially than the intramolecular Friedel–Crafts cyclization,[2a,3a] thus we changed our protocol as in Scheme 2: first amide C–N bond formation via EDC [*N*-ethyl-*N*-(3-dimethylaminopropyl)carbodiimide] coupling between the Baylis–Hillman acid **1a** and aniline (path i), and the following H_2SO_4-catalyzed intramolecular Friedel–Crafts reaction (path ii). We expected that the intramolecular Friedel–Crafts type cyclization could be suc-

Table 1
Synthesis of 3-methylene dihydroquinolones **4** and 3-methylquinolones **5**

Entry	Acid **1**	Amine **2**	B–H amide **3**[a] (%)	Product **4**[b] (%)	Product **5**[c] (%)
1	 **1a**	Aniline (**2a**)	 **3a** (74)	 **4a** (58)	 **5a** (88)
2	**1a**	4-Methylaniline (**2b**)	 **3b** (70)	 **4b** (54)	 **5b** (83)
3	**1a**	4-Methoxtaniline (**2c**)	 **3c** (60)	 **4c** (57)	 **5c** (80)
4	**1a**	N-Methylaniline (**2d**)	 **3d** (71)	 **4d** (91)	 **5d** (99)
5	**1a**	4-Chloroaniline (**2a**)	 **3e** (59)	 **4e** (43)	 **5e** (85)
6	**1a**	1-Napthylamine (**2f**)	 **3f** (63)	 **4f** (60)	 **5f** (87)
7	 **1b**	**2a**	 **3g** (75)	 **4g** (69)	 **5g** (80)
8	 **1c**	**2a**	 **3h** (61)	 **4h** (44)	 **5h** (82)

[a] Conditions: acid **1** (1.5 mmol), amine **2** (1.8 mmol), EDC·HCl (1.8 mmol), DMF, rt, 12 h.
[b] Conditions: amine **3** (1.0 mmol), H_2SO_4 (3.0 equiv), CH_2Cl_2, reflux, 20 min.
[c] Conditions: compound **4** (0.5 mmol), DBU (1.0 equiv), CH_3CN, rt, 30 min.

cessful due to the formation of stable benzylic carbocation although the aryl group of amide is not an electron-rich aryl moiety. Fortunately, intramolecular Friedel–Crafts reaction of amide **3a** produced expected methylene compound **4a** in moderate yield (58%) as shown in Scheme 2 in short time (20 min).[6] In the reaction, we did not observe the formation of compound (**II**), which could be formed via the Friedel–Crafts reaction of relatively unstable primary carbocation intermediate as demonstrated in Figure 1.

N-Arylamides of Baylis–Hillman adducts **3a**–**h** were synthesized from the reaction of acid **1a**–**c** and aniline derivatives **2a**–**f** by using EDC in good to moderate yields (59–75%).[6,7] The next Friedel–Crafts reaction was carried out in the presence of H_2SO_4 (3.0 equiv) in CH_2Cl_2 at refluxing temperature in short time (20 min). The yields of methylene compounds **4a**–**h** were moderate to good (43–91%).[6] This is the first successful result on the Friedel–Crafts cyclization involving the aryl moiety of *N*-arylamides of Baylis–Hillman adducts. Conversion of these *exo*-methylene compounds **4a**–**h** into their *endo*-isomers **5a**–**h** was carried out under the influence of DBU in CH_3CN in high yields (80–99%).[6] The results are summarized in Table 1.

As shown in entry 5, the yield of product **4e** was low (43%), presumably due to the presence of an electron-withdrawing chloro substituent as compared with entries 1–4. The reaction was influenced also by the steric crowdedness around the benzylic carbocation. When the aryl group of Baylis–Hillman adduct was *para*-chloro (entry 7), the yield of **4 g** was moderate (69%), while it was low (44%) with *ortho*-chloro derivative (entry 8).

In summary, we disclosed the synthesis of 3,4-disubstituted 2(1*H*)-quinolinones starting from the Baylis–Hillman adducts via the H_2SO_4-assisted intramolecular Friedel–Crafts cyclization as the key step. Friedel–Crafts cyclization involving the aryl moiety of *N*-arylamides of Baylis–Hillman adducts is unprecedented in Baylis–Hillman chemistry, and further studies are currently underway.

Acknowledgments

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6. *Typical experimental procedure for the synthesis of compounds **3a**, **4a**, and **5a***: To a stirred solution of **1a** (267 mg, 1.5 mmol) and aniline (**2a**, 167 mg, 1.8 mmol) in DMF (3 mL) was added EDC hydrochloride (343 mg, 1.8 mmol). After stirring at room temperature for 12 h, the reaction mixture was poured into water and extracted with EtOAc. Column chromatographic purification process (hexanes/EtOAc, 4:1) afforded pure amide **3a** (281 mg, 74%). To a stirred solution of compound **3a** (253 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added H_2SO_4 (294 mg, 3.0 mmol), and the reaction mixture was heated to reflux for 20 min. After the usual aqueous extractive workup and chromatographic purification process, (hexanes/EtOAc, 5:1) compound **4a** was isolated, 136 mg (58%). Compound **4a** (117 mg, 0.5 mmol) was dissolved in CH_3CN (3 mL) and was treated with DBU (76 mg, 0.5 mmol) at room temperature for 30 min. After the usual aqueous extractive workup and chromatographic purification process (hexanes/EtOAc, 2:1), compound **5a** was isolated, 103 mg (88%).[4a] Other compounds were synthesized similarly, and the representative spectroscopic data of **3a**, **4a**, **5a**, **5b**, and **5f** are as follows.
Compound **3a**: 74%; white solid; mp 133–135 °C; IR (KBr) 3315, 1658, 1531, 1442 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.54 (d, J = 4.5 Hz, 1H), 5.55 (s, 1H), 5.66 (d, J = 4.5 Hz, 1H), 6.11 (s, 1H), 7.06–7.12 (m, 1H), 7.26-7.48 (m, 9H), 8.34 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 74.73, 120.20, 123.04, 124.57, 126.03, 127.97, 128.61, 128.97, 137.44, 140.38, 145.36, 165.21; ESIMS m/z 254 (M^++1). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.96; H, 5.72.; N, 5.29.
Compound **4a:** 58%; white solid; mp 163–165 °C; IR (KBr) 1678, 1360, 1242 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.96 (s, 1H), 5.46 (dd, J = 2.4 and 1.2 Hz, 1H), 6.38 (t, J = 1.2 Hz, 1H), 6.83 (dd, J = 7.8 and 0.9 Hz, 1H), 6.96–7.01 (m, 1H), 7.06–7.08 (m, 1H), 7.13–7.33 (m, 6H), 8.09 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 49.63, 115.46, 123.30, 125.59, 125.61, 127.16, 127.91, 128.06, 128.84, 128.97, 136.11, 139.92, 141.71, 164.38; ESIMS m/z 236 (M^++1). Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.55; H, 5.79; N, 5.76.
Compound **5a**:[4a,4b] 88%; white solid; mp 226–227 °C; IR (KBr) 1651, 1431 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.10 (s, 3H), 7.03–7.09 (m, 2H), 7.23–7.27 (m, 2H), 7.41–7.56 (m, 5H), 12.57 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.28, 115.92, 121.07, 122.12, 126.68, 127.42, 127.92, 128.62, 128.76, 129.23, 136.98, 137.10, 148.78, 164.60; ESIMS m/z 236 (M^++1).
Compound **5b**: 83%; white solid; mp 210–212 °C; IR (KBr) 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.07 (s, 3H), 2.26 (s, 3H), 6.83 (s, 1H), 7.22–7.28 (m, 3H), 7.39 (d, J = 8.1 Hz, 1H) 7.44–7.56 (m, 3H), 12.28 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.33, 21.08, 115.74, 120.99, 126.25, 127.36, 127.86, 128.63, 128.76, 130.62, 131.62, 135.06, 137.14, 148.56, 164.28; 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, 82.07; H, 6.24; N, 5.37.
Compound **5f**: 87%; pale yellow solid; mp 275–277 °C; IR (KBr) 1633 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.18 (s, 3H), 7.10 (d, J = 8.7 Hz, 1H), 7.27–7.31 (m, 2H), 7.43–7.72 (m, 6H), 7.84 (dd, J = 8.1 and 1.2 Hz, 1H), 8.95 (d, J = 8.4 Hz, 1H), 12.38 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.31, 116.96, 121.68, 122.03, 122.44, 123.90, 126.70, 127.39, 127.56, 127.97, 128.41, 128.73, 128.78, 133.40, 133.62, 137.38, 149.85, 164.21; ESIMS m/z 286 (M^++1). Anal. Calcd for $C_{20}H_{15}NO$: C, 84.19; H, 5.30; N, 4.91. Found: C, 84.28; H, 5.52; N, 4.63.
7. For the coupling reaction with EDC, see: (a) Adam, W.; Groer, P.; Humpf, H.-U.; Saha-Moller, C. R. *J. Org. Chem.* **2000**, *65*, 4919–4922; (b) Holmes, C. P. *J. Org. Chem.* **1997**, *62*, 2370–2380; (c) Sheehan, J. C.; Cruickshank, P. A.; Boshart, G. L. *J. Org. Chem.* **1961**, *26*, 2525–2528.