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Tetrahedron Letters
Tetrahedron Letters 45 (2004) 7409–7413

Synthesis of 4b,5,10a,11-tetrahydroindeno[1,2-*b*]-quinolin-10-ones from Baylis–Hillman adducts

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Received 30 June 2004; revised 9 August 2004; accepted 13 August 2004

Abstract—We developed an efficient synthetic method for indenoquinoline skeletons from Baylis–Hillman adducts. 4b,5,10a,11-Tetrahydroindeno[1,2-*b*]quinolin-10-ones and 7*H*-indeno[2,1-*c*]quinolines were prepared from Baylis–Hillman adducts in polyphosphoric acid.

Recently, Basavaiah et al. have reported the synthesis of 3-benzylidenechroman-4-ones from Baylis–Hillman adducts via the Friedel–Crafts acylation reaction as the key step.[1] During the continuing efforts for the construction of various types of heterocyclic compounds from Baylis–Hillman adducts,[2] we envisioned that we could synthesize the 7*H*-indeno[2,1-*c*]quinoline ring system from the Baylis–Hillman adducts via successive Friedel–Crafts type reaction (Scheme 1). As shown, Friedel–Crafts acylation of cinnamic acid derivative to form 3-benzylidene-2,3-dihydro-4(1*H*)quinolone and the following dehydrative cyclization would furnish the desired 7*H*-indeno[2,1-*c*]quinoline.

Indenoquinoline derivatives[3–6] showed a wide range of biological activities such as 5-HT-receptor binding activity,[3b] anti-inflammatory activity,[4c] and also act as antitumor agents,[3c,5b,d] inhibitor for steroid reductase,[3d] acetylcholonesterase inhibitors,[5e] and antimalarials.[5a] These compounds are frequently synthesized via the aza-Bergman cyclization[5c] or via the imino Diels–Alder reaction.[4a,b]

The required starting materials **3a**–**e** were prepared in moderate to good yields as shown in Scheme 2 by simply heating the corresponding anilines **2** and the acetates of the Baylis–Hillman adducts **1** in THF for 14–18 h. *E*-form of **3** was generated as the major product as reported in a similar system[2,7] and we could isolate the *E*-form in pure state. The carboxylic acid derivatives **4a**–**e** were made by KOH-assisted hydrolysis of **3a**–**e** (Scheme 2).[7]

With **3** and **4** in our hands we examined the possibility for the synthesis of 7*H*-indeno[2,1-*c*]quinoline derivatives. Initially, we examined the reaction of **3a** in various reaction conditions. As examples, we examined the following conditions including heating in TFA, heating in CH_2Cl_2 in the presence of TFAA,[1] heating in benzene with H_2SO_4, and heating in PPA. Among the examined reaction conditions we found some major components on TLC when we conducted the reaction in polyphosphoric acid (PPA) at around 120 °C.[8] We isolated three compounds, and after careful examination of the spectroscopic data, we finally found that the compounds have the structures of **6a** (3%), **7a** (62%), and **8a** (4%) (Scheme 3).[9]

The structure of **7a** was confirmed by ^1H, ^{13}C, IR, mass, and NOE experiments (Fig. 1).[9] Irradiation of the proton H_a ($\delta = 4.65$ ppm) showed increments of the intensities of H_b and H_e in 1.9% and 1.1%, respectively. Irradiation of the H_b proton ($\delta = 3.21$ ppm) showed enhancements of the intensities of H_a and H_c in 2.4% and 1.6%, respectively. From the NOE experiments, we could conclude that the stereochemistry of ring junction of **7a** as *cis*. In the ^1H NMR spectrum of **8a**, singlet of H-6 appeared at 9.14 ppm. One doublet and two doublets of doublet (presumably corresponding to H-1, H-11, H-4) appeared at 8.43, 8.24, and 8.69 ppm, respectively. Other peaks were overlapped and appeared at around 7.46–7.78 ppm. The postulated reaction mechanism

Keywords: Tetrahydroindeno[1,2-*b*]quinolin-10-ones; 7*H*-Indeno[2,1-*c*]-quinolines; Baylis–Hillman adducts; Polyphosphoric acid.
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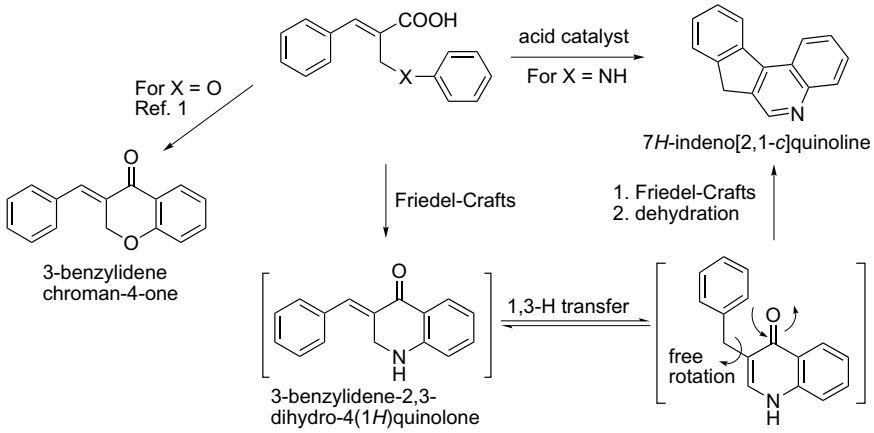
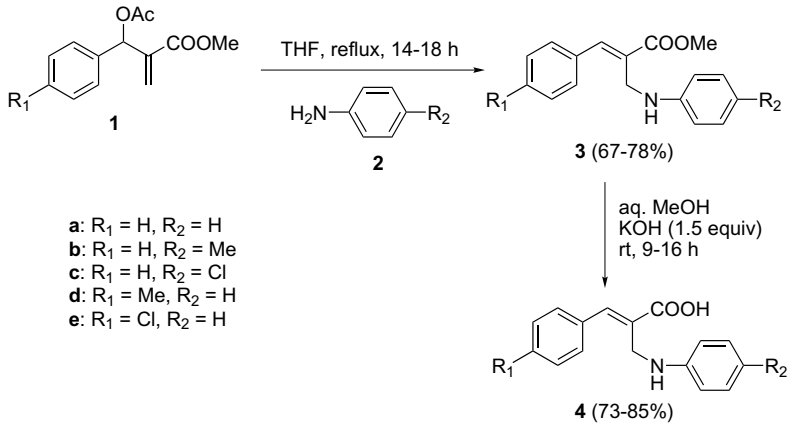
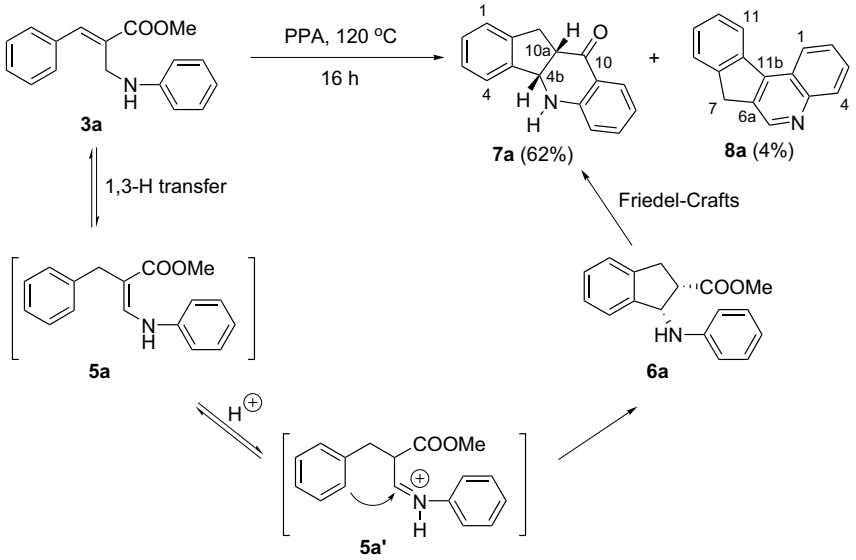
doi:10.1016/j.tetlet.2004.08.075



Scheme 1. Synthetic rationale for 7*H*-indeno[2,1-*c*]quinoline.



Scheme 2. Synthesis of starting materials **3** and **4**.



Scheme 3. Synthesis of indenoquinolines **7a** and **8a**.

for the formation of **6a** and **7a** is depicted in Scheme 3. The double bond of **3a** can be isomerized to form **5a** as already reported in similar systems by us and other groups.[10] In our acidic medium, **5a** can be protonated to generate the corresponding iminium ion **5a**′. The intramolecular aromatic Mannich type reaction[11] of **5a**′ furnished **6a**, which can be converted to the 4b,5,10a,11-tetrahydroindeno[1,2-*b*]quinolin-10-one

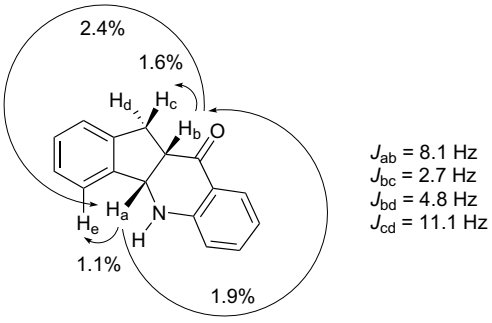
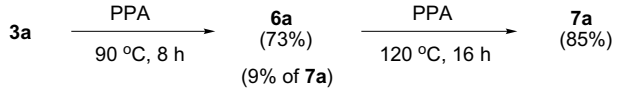


Figure 1. NOE and coupling constant data of **7a**.

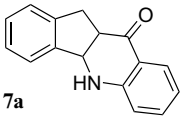
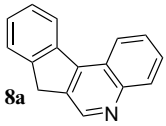
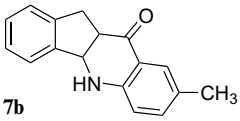
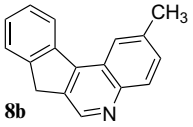
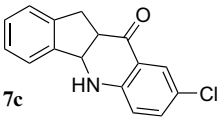
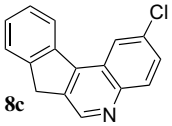
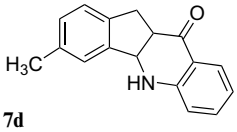
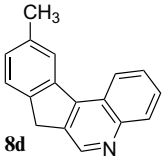
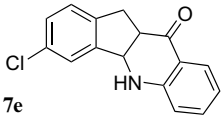
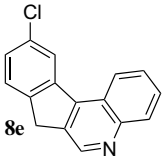
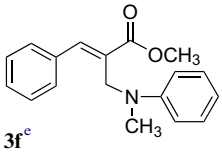
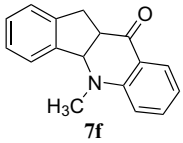
(**7a**) via the following Friedel–Crafts acylation. The formation and isolation of **6a** provided us with definite proof for the reaction mechanism of **7a**. In a suitably controlled reaction conditions (PPA, 90 °C, 8 h) we obtained the intermediate **6a** as the major product (73%) together with 9% of **7a**. From the reaction of **6a** at elevated temperature (120 °C, 16 h) the formation of **7a** from **6a** could be confirmed as in Scheme 4.



Scheme 4.

As a next trial, in order to find better conditions for the formation of **8a**, we examined a variety of conditions. As shown in Scheme 1, initially we expected that Friedel–Crafts acylation of **4a** might proceed without difficulty to produce 3-benzylidene-2,3-dihydro-4(1*H*) quinolone.[1] If the double bond of 3-benzylidene-2,3-dihydro-4(1*H*)quinolone (**4a**) could be isomerized into its

Table 1. Synthesis of **7a**–**f** and **8a**–**e**

Entry	**3** or **4**[a]	Conditions	Products	Yield (%), mp (°C)
1	**3a**	PPA 120 °C, 16 h	 **7a**  **8a**	**7a** (62), (149–150), **8a** (4)[b]
2	**4a**	PPA 170 °C, 1 h		**7a**,[c] **8a** (18)
3	**3b**	PPA 120 °C, 15 h	 **7b**  **8b**	**7b** (55), (144–145), **8b**[b,c]
4	**4b**	PPA 170 °C, 30 min		**7b** (4), **8b** (17)
5	**3c**	PPA 120 °C, 13 h	 **7c**  **8c**	**7c** (50), (182–183), **8c**[b,c]
6	**4c**	PPA 170 °C, 1 h		**7c** (3), **8c** (14)
7	**3d**	PPA 120 °C, 18 h	 **7d**  **8d**	**7d** (54), (156–157), **8d**[b,c]
8	**4d**	PPA 170 °C, 30 min		**7d** (4), **8d** (22)
9	**3e**	PPA 120 °C, 17 h	 **7e**  **8e**	**7e** (52), (103–104), **8e**[b,c]
10	**4e**	PPA 170 °C, 1 h		**7e**,[c] **8e** (13)
11	**3b**-*Z*[d]	PPA 120 °C, 15 h	**7b**	**7b** (57), (144–145), **8b**[c]
12	 **3f**[e]	PPA 120 °C, 15 h	 **7f**	**7f** (53), (150–151)

[a] *E*-isomer.
[b] Oil.
[c] Trace amounts on TLC observation.
[d] *Z*-isomer.
[e] *E*/*Z* = 4:1 mixture.

endo-position via 1,3-hydrogen shift under the acidic conditions,[10] then, the following Friedel–Crafts reaction and dehydration would afford the desired 7*H*-indeno-[2,1-*c*]quinoline (**8a**). But, unfortunately, the reaction of **4a** in PPA showed the formation of complex mixtures as compared in the reaction of **3a** in PPA (vide supra). When we used **4a** as the starting material we could obtain low yield of **7a** (<5%) and **8a** (18%) by using PPA at around 170 °C. Until now, this is the best result for the synthesis of **8a**. Some representative results for the synthesis of **7** and **8** are summarized in Table 1.

We used *para*-substituted arenes both at the Baylis–Hillman moiety and at the aniline moiety in order to produce only pure regioisomeric products. The stereochemistry of the double bond of starting materials are *E*-form in all cases except entry 11.[12] We separated the *Z*-form of **3b** and examined the reaction in PPA (entry 11). The reaction of **3b**-*Z* in PPA gave the same product **7b** in 57% yield as in the reaction of **3b**-*E* as expected. This means that the configuration of the double bond of **3** did not affect the whole reaction due to the involvement of the double bond isomerization step during the reaction. In another experiment, the reaction of **3f** (*E*/*Z* = 4:1 in this case, made from *N*-methylaniline) afforded the corresponding **7f** in a similar yield (53%, entry 12).

In summary, we have disclosed an efficient entry for the synthesis of valuable indenoquinoline skeletons from the easily available Baylis–Hillman adducts in PPA medium. We are currently searching the improved conditions for the synthesis of 7*H*-indeno[2,1-*c*]quinolines.

Acknowledgements

This work was supported by Korea Research Foundation Grant (KRF-2002-015-CP0215).

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9. Typical procedure for the synthesis of **6a**, **7a**, and **8a**: The reaction of **1a** and aniline (3 equiv) in refluxing THF (15 h) gave **3a** in 69% yield. A stirred solution of **3a** (534 mg, 2 mmol) in PPA (6 mL) was heated to 120 °C for 16 h. After pouring the reaction mixture into cold water the aqueous phase was neutralized cautiously with $NaHCO_3$. Extraction with ether, removal of solvent, and flash column chromatographic separation process (hexanes/ether, 2:1) gave **6a** (16 mg, 3%), **7a** (292 mg, 62%), and **8a** (18 mg, 4%).
Compound **6a**: ^{1}H NMR ($CDCl_3$) δ 2.97–3.04 (m, 1H), 3.57 (s, 3H), 3.32–3.60 (m, 2H), 3.95 (br s, 1H), 4.48 (d, J = 7.2 Hz, 1H), 6.55–6.62 (m, 2H), 6.72 (d, J = 7.5 Hz, 1H), 7.00 (t, J = 7.8 Hz, 1H), 7.11–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 41.90, 45.26, 46.83, 51.83, 114.40, 117.76, 122.52, 126.61, 127.30, 128.38, 128.93, 130.47, 143.86, 144.42, 173.45.
Compound **7a**: IR (neat) 3340, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.21 (ddd, J = 8.1, 4.8, and 2.7 Hz, 1H), 3.31 (dd, J = 11.1 and 4.8 Hz, 1H), 3.65 (br s, 1H), 3.74 (dd, J = 11.1 and 2.7 Hz, 1H), 4.65 (d, J = 8.1 Hz, 1H), 6.52 (dd, J = 7.8 and 1.2 Hz, 1H), 6.85 (td, J = 7.5 and 1.2 Hz, 1H), 7.01 (td, J = 7.8 and 1.2 Hz, 1H), 7.25–7.36 (m, 1H), 7.48–7.63 (m, 3H), 7.73 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 40.23, 44.35, 50.28, 115.90, 119.60, 123.28, 124.43, 126.25, 127.24, 127.74, 129.20, 135.26, 135.65, 146.54, 156.52, 207.77; EI-MS (70 eV) *m*/*z* (rel. intensity) 77 (12), 130 (31), 178 (14), 206 (24), 218 (30), 234 (67), 235 (M^+, 100).

Compound **8a**: ^{1}H NMR ($CDCl_3$) δ 4.08 (s, 2H), 7.46–7.58 (m, 2H), 7.65–7.78 (m, 3H), 8.24 (dd, J = 8.4 and 1.2 Hz, 1H), 8.43 (d, J = 7.5 Hz, 1H), 8.69 (dd, J = 8.4 and 1.2 Hz, 1H), 9.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 35.72, 123.65, 124.43, 124.64, 125.47, 126.83, 127.38, 128.22, 128.43, 130.51, 135.85, 140.70, 144.47, 144.97, 147.63, 147.91; MS (MALDI-TOF) 217.4 (M^+).

The other experiments were carried out analogously and the spectroscopic data of the prepared compounds are as follows.

Compound **7b**: IR (neat) 3344, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 3.17–3.22 (m, 1H), 3.26–3.31 (m, 1H), 3.52 (br s, 1H), 3.74 (dd, J = 11.1 and 2.7 Hz, 1H), 4.60 (d, J = 7.8 Hz, 1H), 6.44 (d, J = 7.8 Hz, 1H), 6.83 (dd, J = 7.8 and 1.5 Hz, 1H), 7.31–7.36 (m, 2H), 7.53–7.63 (m, 2H), 7.73 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.71, 40.29, 44.68, 50.26, 115.83, 123.24, 124.45, 126.26, 127.70, 127.86, 128.88, 129.60, 135.26, 135.70, 144.12, 156.55, 208.02; EI-MS (70 eV) *m/z* (rel. intensity) 144 (27), 234 (24), 248 (64), 249 (M^+, 100).

Compound **7c**: IR (neat) 3340, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.18–3.31 (m, 1H), 3.26–3.32 (m, 1H), 3.68 (br s, 1H), 3.76 (dd, J = 11.1 and 2.7 Hz, 1H), 4.58 (d, J = 8.1 Hz, 1H), 6.46 (d, J = 8.4 Hz, 1H), 6.96 (dd, J = 8.1 and 2.1 Hz, 1H), 7.34–7.40 (m, 1H), 7.46 (dd, J = 2.4 and 0.6 Hz, 1H), 7.59–7.61 (m, 2H), 7.74 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 40.09, 44.19, 49.96, 117.01, 123.42, 123.96, 125.94, 126.19, 127.15, 128.04, 128.80, 135.47, 135.64, 145.13, 155.69, 207.18; EI-MS (70 eV) *m/z* (rel. intensity) 164 (32), 204 (26), 233 (24), 251 (21), 269 (M^+, 100).

Compound **7d**: IR (neat) 3363, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 3.19–3.24 (m, 1H), 3.28–3.34 (m, 1H), 3.62 (br s, 1H), 3.74 (dd, J = 10.8 and 2.7 Hz, 1H), 4.61 (d, J = 8.1 Hz, 1H), 6.52 (dd, J = 7.8 and 1.2 Hz, 1H), 6.84 (td, J = 7.2 and 1.2 Hz, 1H), 7.01 (td, J = 7.8 and 1.5 Hz, 1H), 7.37 (dd, J = 8.1 and 1.2 Hz, 1H), 7.47–7.53 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 20.98, 39.92, 44.47, 50.64, 115.89, 119.60, 123.18, 124.75, 125.93, 127.16, 129.17, 135.82, 136.56, 137.78, 146.49, 154.02, 207.87; EI-MS (70 eV) *m/z* (rel. intensity) 130 (31), 204 (17), 220 (17), 232 (39), 249 (M^+, 100).

Compound **7e**: IR (neat) 3351, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.20–3.31 (m, 2H), 3.63 (br s, 1H), 3.73 (dd, J = 10.8 and 2.4 Hz, 1H), 4.60 (d, J = 7.8 Hz, 1H), 6.52 (dd, J = 7.8 and 1.2 Hz, 1H), 6.85 (td, J = 7.8 and 1.2 Hz, 1H), 7.02 (td, J = 7.8 and 1.2 Hz, 1H), 7.43–7.53 (m, 3H), 7.66 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 39.88, 44.44, 50.74, 115.98, 119.75, 122.89, 123.89, 127.42, 127.54, 129.00, 134.15, 135.18, 137.02, 146.51, 154.56, 206.58; EI-MS (70 eV) *m/z* (rel. intensity) 130 (33), 204 (30), 233 (20), 252 (36), 269 (M^+, 100).

Compound **7f**: IR (neat) 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 3H), 3.02 (dd, J = 11.1 and 5.1 Hz, 1H), 3.09–3.15 (m, 1H), 3.51 (dd, J = 11.1 and 2.1 Hz, 1H), 4.55 (d, J = 8.1 Hz, 1H), 6.53 (dd, J = 8.1 and 0.9 Hz, 1H), 6.81 (td, J = 7.5 and 1.2 Hz, 1H), 7.05 (td, J = 7.8 and 1.5 Hz, 1H), 7.21–7.27 (m, 1H), 7.40–7.50 (m, 3H), 7.64 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 39.74, 41.09, 50.66, 53.99, 112.78, 119.35, 123.35, 126.34, 126.42, 127.78, 127.90, 128.98, 135.44, 136.02, 149.16, 156.78, 208.37; EI-MS (70 eV) *m/z* (rel. intensity) 144 (29), 178 (11), 204 (14), 220 (17), 232 (29), 249 (M^+, 100).

Compound **8b**: ^{1}H NMR ($CDCl_3$) δ 2.66 (s, 3H), 4.06 (s, 2H), 7.45–7.59 (m, 3H), 7.70 (d, J = 6.0 Hz, 1H), 8.12 (d, J = 6.0 Hz, 1H), 8.42–8.44 (m, 2H), 9.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.34, 35.92, 122.90, 124.64, 124.89, 125.66, 127.52, 128.28, 130.38, 130.87, 136.11, 136.98, 141.09, 143.98, 145.17, 146.71, 146.95; EI-MS (70 eV) *m/z* (rel. intensity) 115 (5), 189 (5), 202 (11), 216 (17), 231 (M^+, 100).

Compound **8c**: ^{1}H NMR ($CDCl_3$) δ 4.09 (s, 2H), 7.48–7.61 (m, 2H), 7.67–7.74 (m, 2H), 8.17 (d, J = 9.0 Hz, 1H), 8.37 (d, J = 7.2 Hz, 1H), 8.65 (d, J = 2.4 Hz, 1H), 9.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 35.73, 122.80, 124.19, 125.10, 125.56, 127.56, 128.55, 129.36, 132.02, 132.74, 136.69, 140.09, 143.80, 144.85, 146.30, 147.79; EI-MS (70 eV) *m/z* (rel. intensity) 94 (10), 125 (9), 189 (20), 216 (96), 251 (M^+, 100).

Compound **8d**: ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 3H), 4.03 (s, 2H), 7.31 (dd, J = 7.5 and 0.6 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.66–7.78 (m, 2H), 8.22–8.25 (m, 2H), 8.71 (dd, J = 8.4 and 1.2 Hz, 1H), 9.11 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.84, 35.35, 123.75, 124.71, 125.06, 125.10, 126.74, 128.39, 129.24, 130.50, 136.28, 137.05, 140.94, 142.13, 144.53, 147.67, 147.92; EI-MS (70 eV) *m/z* (rel. intensity) 101 (5), 189 (6), 202 (15), 216 (23), 231 (M^+, 100).

Compound **8e**: IR (neat) 2924, 1562, 1508 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.05 (s, 2H), 7.43–7.80 (m, 4H), 8.24 (d, J = 8.1 Hz, 1H), 8.37 (s, 1H), 8.58 (d, J = 8.1 Hz, 1H), 9.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 35.60, 123.52, 124.57, 124.73, 126.54, 127.46, 128.40, 128.93, 130.84, 133.58, 136.68, 142.52, 143.27, 143.54, 147.78, 148.11.

10. For the related isomerization phenomena, see: (a) Kim, J. N.; Kim, H. S.; Gong, J. H.; Chung, Y. M. *Tetrahedron Lett.* **2001**, *42*, 8341, and further references cited therein; (b) Diaba, F.; Houerou, C. L.; Grignon-Dubois, M.; Gerval, P. *J. Org. Chem.* **2000**, *65*, 907; (c) Diaba, F.; Lewis, I.; Grignon-Dubois, M.; Navarre, S. *J. Org. Chem.* **1996**, *61*, 4830; (d) Carelli, V.; Liberatore, F.; Tortorella, S. *Gazz. Chim. Ital.* **1983**, *113*, 569; (e) Minter, D. E.; Stotter, P. L. *J. Org. Chem.* **1981**, *46*, 3965; (f) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321; (g) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315; (h) Grignon-Dubois, M.; Diaba, F.; Grellier-Marly, M.-C. *Synthesis* **1994**, 800.
11. For the intramolecular aromatic Mannich type reaction, see: Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1007–1046.
12. As already published,[2,7] the S_N2' reaction of the Baylis–Hillman acetate and nucleophiles including aniline afforded the *E*-form product as the major component. The corresponding *Z*-form was generated in about 5–20% depending on the substrates. Thus, we scaled up the reaction and obtained the minor component **3b**-*Z*.