Facile Synthesis of 3-Substituted 2(1*H*)-Quinolinones from the Baylis-Hillman Adducts of 2-Nitrobenzaldehydes

Ka Young Lee and Jae Nyoung Kim*

Department of Chemistry and Institute of Basic Science, Chonnam National University, Kwangju 500-757, Korea
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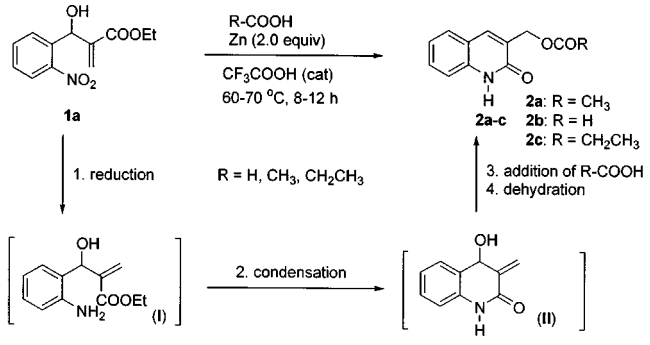
The Baylis-Hillman reaction is a useful carbon-carbon bond-forming method from activated vinyls and carbonyl compounds.[1] Chemical transformation of the Baylis-Hillman adducts or their derivatives into useful heterocyclic compounds have been studied recently by us and other groups.[2,3] Especially, conversion of the Baylis-Hillman adducts derived from 2-nitrobenzaldehydes into quinoline skeleton is a useful entry for the quinoline chemistry.[3]

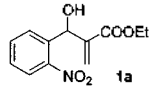
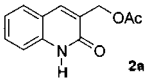
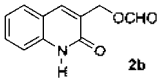
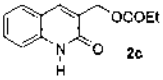
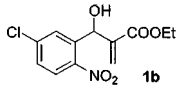
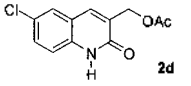
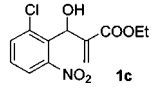
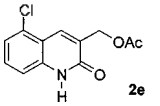
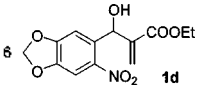
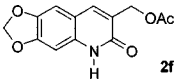
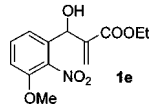
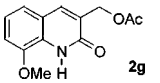
We have reported on the synthesis of quinoline *N*-oxides and quinoline derivatives from the Baylis-Hillman adducts of 2-nitrobenzaldehydes.[3a,3b] Kaye *et al.* have reported on the synthesis of quinoline skeleton from the Baylis-Hillman adducts recently.[3c,3d] The 2(1*H*)-quinolinone ring system is found in many biologically important compounds.[4] Thus, the development of a new method for the synthesis of 2(1*H*)-quinolinone ring system is important until now.[4] In these respects, we intended to examine the synthesis of 2(1*H*)-quinolinone ring system from the appropriate Baylis-Hillman adduct by the reduction of the nitro functionality into amino group followed by condensation sequence.

Among the various examined reduction conditions, the use of zinc dust in acetic acid in the presence of catalytic amounts of trifluoroacetic acid was found to meet our requirement. Thus, we would like to publish our preliminary results herein. The reaction of the Baylis-Hillman adduct **1a** and zinc (2.0 equiv) in acetic acid in the presence of catalytic amounts of trifluoroacetic acid (0.2 equiv) at 60-70 °C gave the 3-acetoxymethyl-2(1*H*)-quinolinone (**2a**) in 74% isolated yield (Scheme 1).[5] Without the use of trifluoroacetic acid long reaction time was needed and the yield of **2a** decreased. The same reaction in formic acid afforded the corresponding formyloxymethyl derivative **2b** in a similar yield (entry 2, 68%). Similarly, propionyl derivative **2c** was obtained in propionic acid (entry 3). The other results are summarized in Table 1.



Scheme 1

Table 1. Synthesis of 3-substituted 2(1*H*)-quinolinones **2a-g**

Entry	B-H adduct	Conditions	Product	% yield[a]
1	 **1a**	AcOH CF_3COOH (cat) Zn (2.0 equiv) 60-70 °C, 8 h	 **2a**	74[b] (183-185)
2	**1a**	HCOOH CF_3COOH (cat) Zn (2.0 equiv) 60-70 °C, 8 h	 **2b**	68 (187-189)
3	**1a**	CH_3CH_2COOH CF_3COOH (cat) Zn (2.0 equiv) 60-70 °C, 8 h	 **2c**	52 (169-170)
4	 **1b**	AcOH CF_3COOH (cat) Zn (2.0 equiv) 60-70 °C, 10 h	 **2d**	70 (229-230)
5	 **1c**	AcOH CF_3COOH (cat) Zn (2.0 equiv) 60-70 °C, 12 h	 **2e**	64 (181-183)
6	 **1d**	AcOH CF_3COOH (cat) Zn (2.0 equiv) 60-70 °C, 12 h	 **2f**	58 (227-228)
7	 **1e**	AcOH CF_3COOH (cat) Zn (2.0 equiv) 60-70 °C, 12 h	 **2g**	51[c] (170-172)

[a]Mp was written in parenthesis. [b]The use of iron powder instead of zinc gave similar result. [c]Unknown side products were observed.

The reaction mechanism is thought to be as follows as shown in Scheme 1: (1) Reduction of the nitro functionality of **1a** gives the amino derivative (**I**), (2) intramolecular condensation affords the intermediate (**II**), and finally (3) addition of carboxylic acid followed by dehydration gives the desired product **2a-c**.

As a conclusion, we disclosed on the facile one-pot preparation method of 3-substituted 2(1*H*)-quinolinones from the Baylis-Hillman adducts of 2-nitrobenzaldehydes.

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References and Notes

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4. (a) Jones, G. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 5, pp 167-243. (b) Balasubramanian, M.; Keay, J. G. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 5, pp 245-300.
5. Typical procedure for the synthesis of **2a**: A stirred suspension of **1a** (251 mg, 1.0 mmol) and zinc (130 mg, 2.0 mmol) in acetic acid (2 mL) was added CF_3COOH (23 mg, 0.2 mmol) and heated to 60-70 °C for 8 h. After appropriate workup process and column chromatographic purification (hexane:ether = 1:2) **2a** was obtained as a white solid, 161 mg (74%); mp 183-185 °C; IR (KBr) 3433, 1727, 1663 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19 (s, 3H), 5.24 (s, 2H), 7.21-7.60 (m, 4H), 7.89 (s, 1H), 12.44 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.71, 61.96, 115.97, 119.75, 122.97, 128.70, 128.94, 131.31, 137.99, 139.27, 161.85, 171.22; Mass (70 eV) *m/z* (rel. intensity) 128 (14), 146 (8), 158 (9), 174 (100), 175 (22), 217 (M^+, 10). **2b**: 68%; mp 187-189 °C; ^1H NMR ($CDCl_3$ + few drops of DMSO-d_6) δ 5.24 (s, 2H), 7.19 (t, J = 7.5 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.47 (t, J = 8.1 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.84 (s, 1H), 8.23 (s, 1H), 11.84 (s, 1H); ^{13}C NMR ($CDCl_3$ + few drops of DMSO-d_6) δ 60.30, 114.82, 118.38, 121.42, 126.42, 126.99, 129.60, 137.19, 137.92, 159.91, 160.92. **2c**: 52%; mp 169-170 °C; ^1H NMR (DMSO-d_6) δ 1.07 (t, J = 7.5 Hz, 3H), 2.45 (q, J = 7.5 Hz, 2H), 4.99 (s, 2H), 7.18 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.88 (s, 1H), 11.93 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 8.90, 26.73, 60.82, 114.92, 118.72, 121.89, 127.78, 127.88, 130.22, 136.84, 138.23, 160.79, 173.39. **2d**: 70%; mp 229-230 °C; ^1H NMR ($CDCl_3$ + few drops of DMSO-d_6) δ 2.20 (s, 3H), 5.22 (s, 2H), 7.35-7.59 (m, 3H), 7.79 (s, 1H), 12.31 (s, 1H); ^{13}C NMR ($CDCl_3$ + few drops of DMSO-d_6) δ 20.86, 61.13, 117.05, 120.09, 126.64, 126.78, 129.18, 130.04, 135.74, 136.95, 161.36, 170.25. **2e**: 64%; mp 181-183 °C; ^1H NMR ($CDCl_3$) δ 2.21 (s, 3H), 5.24 (s, 2H), 7.26-7.44 (m, 3H), 8.24 (s, 1H), 12.79 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.97, 61.32, 114.99, 117.53, 123.36, 128.66, 130.78, 132.36, 134.34, 139.17, 162.95, 170.66. **2f**: 58%; mp 227-228 °C; ^1H NMR ($CDCl_3$ + few drops of DMSO-d_6) δ 2.14 (s, 3H), 5.08 (s, 2H), 6.03 (s, 2H), 6.88 (s, 1H), 6.92 (s, 1H), 7.67 (s, 1H), 11.87 (s, 1H); ^{13}C NMR ($CDCl_3$ + few drops of DMSO-d_6) δ 21.01, 61.57, 95.78, 101.60, 104.95, 113.53, 124.51, 135.71, 137.96, 143.82, 150.49, 161.86, 170.63. **2g**: 51%; mp 170-172 °C; ^1H NMR ($CDCl_3$ + few drops of DMSO-d_6) δ 2.17 (s, 3H), 3.98 (s, 3H), 5.17 (s, 2H), 6.96-7.19 (m, 3H), 7.79 (s, 1H), 9.40 (s, 1H); ^{13}C NMR ($CDCl_3$ + few drops of DMSO-d_6) δ 21.02, 56.03, 61.44, 110.11, 119.60, 119.65, 122.36, 128.09, 128.51, 137.88, 145.40, 160.88, 170.69.