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

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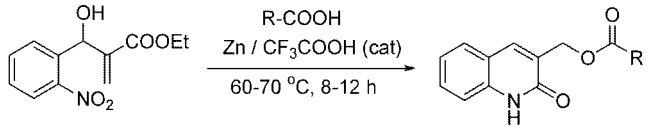
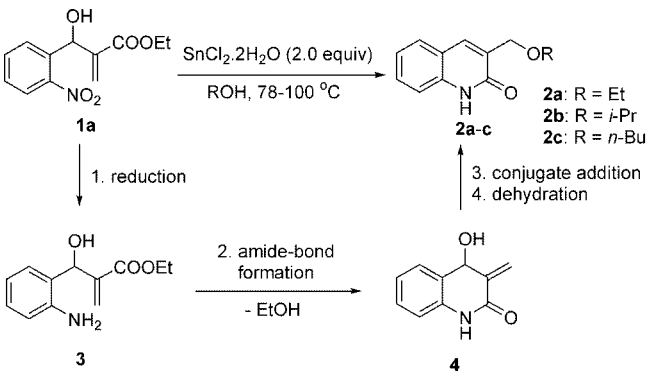
The Baylis-Hillman reaction is a useful carbon-carbon bond-forming method from activated vinyls and carbonyl compounds.[1] Chemical transformation of the Baylis-Hillman adducts or their derivatives into useful heterocyclic compounds have been studied recently by us and other groups.[2,3] Especially,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

Recently, we have reported on the synthesis of 3-substituted 2(1*H*)-quinolinone derivatives by the reduction of the Baylis-Hillman adducts with zinc and appropriate carboxylic acid in the presence of catalytic amounts of trifluoroacetic acid (Scheme 1).[5,6] The reaction proceeded by the tandem reduction, intramolecular amide bond formation, conjugate addition of the carboxylic acid and dehydration. Thus, the use of alcohol solvents under the appropriate reducing conditions might give the corresponding 3-alkoxymethyl-substituted 2(1*H*)-quinolinone derivatives.

Among the various examined reduction conditions, the use of tin(II) chloride in an alcohol solvent was found to meet our requirement. The reaction of the Baylis-Hillman adducts **1a** and tin(II) chloride dihydrate (2.0 equiv.) in ethanol at reflux temperature gave **2a** in 60% isolated yield (Scheme 2 and entry 1 in Table 1). The same reaction in 2-propanol afforded the corresponding isopropoxy derivative **2b** in a similar yield (entry 2, 58%). Similarly butoxy derivative **2c** was obtained in *n*-butanol (entry 3). The representative results are summarized in Table 1. When we used alkoxy-substituted starting materials such as **1d** and **1e**, somewhat

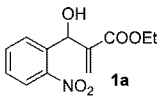
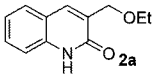
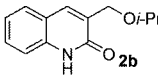
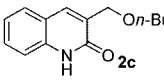
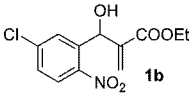
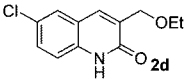
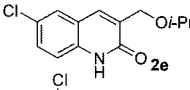
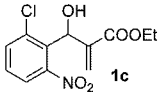
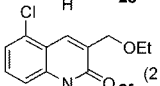
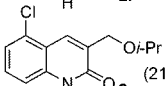
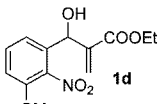
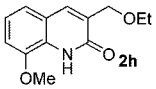
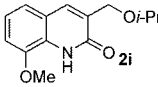
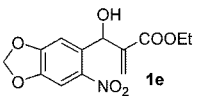
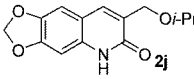


Scheme 1

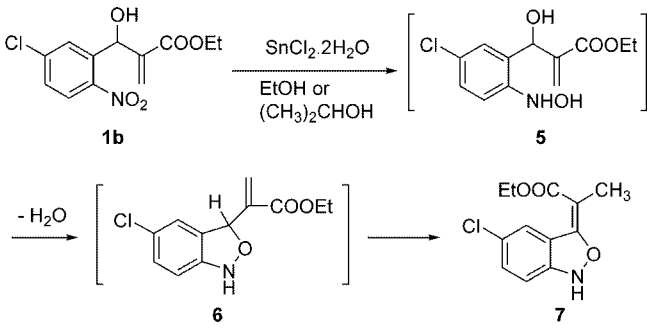


Scheme 2

Table 1. Synthesis of 3-alkoxymethyl 2(1*H*)-quinolinones **2**

Entry	B-H adduct **1**	Conditions	Product **2**	Yield (%)[a]
1	 **1a**	EtOH reflux, 12 h	 **2a**	60[b] (156-158)
2	**1a**	$(CH_3)_2CHOH$ reflux, 14 h	 **2b**	58[b] (160-161)
3	**1a**	*n*-BuOH 100 °C, 2 h	 **2c**	55 (125-127)
4	 **1b**	EtOH reflux, 12 h	 **2d**	52[b] (194-195)
5	**1b**	$(CH_3)_2CHOH$ reflux, 14 h	 **2e**	43[b] (195-197)
6	 **1c**	EtOH reflux, 12 h	 **2f**	48[b] (214-219, dec.)
7	**1c**	$(CH_3)_2CHOH$ reflux, 14 h	 **2g**	52 (215-218, dec.)
8	 **1d**	EtOH reflux, 12 h	 **2h**	40 (116-118)
9	**1d**	$(CH_3)_2CHOH$ reflux, 14 h	 **2i**	53 (97-98)
10	 **1e**	$(CH_3)_2CHOH$ reflux, 14 h	 **2j**	29 (184-185)

[a]Mp was written in parenthesis. [b]The corresponding benzisoxazoline derivatives were obtained in 5-10% yields.



Scheme 3

lower yields of products were obtained.

The reaction mechanism is thought to be as follows as shown in Scheme 2: (1) Reduction of the nitro functionality of **1** to the amino group, (2) intramolecular amide-bond formation and finally (3) conjugate addition of the alcohol followed by dehydration.

As a side reaction benzisoxazoline derivatives were isolated in some cases. As an example, in the reaction of **1b** (entry 4) we could isolate benzisoxazoline **7** in about 10% yield.[7] This compound might be obtained from the hydroxylamine derivative **5**, which was generated by partial reduction of **1b** as shown in Scheme 3. The same compound **7** was isolated when the reaction was performed in 2-propanol. The stereochemistry of the double bond of **7** was assigned as *E* from the NOE experiment (no NOE increment of the proton at the benzene ring was observed when we irradiated the methyl peak at δ = 2.74 ppm).

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

Experimental Section

All materials and solvents were of reagent grade as received from commercial sources. Baylis-Hillman adducts were prepared as reported.[1-3]

Typical procedure for the synthesis of 2a: A stirred solution of **1a** (251 mg, 1.0 mmol) and tin chloride dihydrate (450 mg, 2.0 mmol) in ethanol (5 mL) was heated to reflux for 12 h. After appropriate workup process and column chromatographic purification (hexane/ethyl acetate = 1 : 1) **2a** was obtained as a white solid, 122 mg (60%); mp 156-158 °C; IR (KBr) 3446, 1663 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, *J* = 6.9 Hz, 3H), 3.72 (q, *J* = 6.9 Hz, 2H), 4.61 (s, 2H), 7.19-7.61 (m, 4H), 7.91 (s, 1H), 11.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.27, 66.70, 67.18, 115.48, 120.08, 122.63, 127.75, 129.83, 130.60, 135.99, 137.40, 162.76; Mass (70 eV) *m/z* (rel. intensity) 77 (18), 128 (29), 130 (26), 159 (100), 172 (19), 174 (48), 203 (M^+, 2). The following compounds were synthesized analogously.

3-(Isopropoxymethyl)-(1*H*)-quinol-2-one (2b): 58%; mp 160-161 °C; IR (KBr) 2968, 1661, 1575 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (d, *J* = 6.0 Hz, 6H), 3.84 (heptet, *J* = 6.0 Hz, 1H), 4.62 (s, 2H), 7.18-7.60 (m, 4H), 7.94 (s, 1H), 12.27 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.25, 64.83, 72.16, 115.73, 120.13, 122.53, 127.62, 129.67, 131.01, 135.84, 137.45, 163.22; MS (70 eV) *m/z* (rel. intensity) 128 (19), 146 (9), 159 (100), 174 (64), 217 (M^+, 1).

3-(Butoxymethyl)-(1*H*)-quinol-2-one (2c): 55%; mp 125-127 °C; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, *J* = 7.2 Hz, 3H), 1.41-1.54 (m, 2H), 1.65-1.75 (m, 2H), 3.66 (t, *J* = 7.2 Hz, 2H), 4.61 (s, 2H), 7.16-7.58 (m, 4H), 7.90 (s, 1H), 12.74 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.00, 19.43, 31.87, 67.40, 71.15, 115.96, 120.05, 122.54, 127.57, 129.76, 130.38, 136.02, 137.59, 163.44.

3-(Ethoxymethyl)-6-chloro-(1*H*)-quinol-2-one (2d): 52%; mp 194-195 °C; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, *J* = 7.2 Hz, 3H), 3.72 (q, *J* = 7.2 Hz, 2H), 4.59 (s, 2H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.57 (s, 1H), 7.84 (s, 1H), 12.43 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.27, 66.81, 67.07, 117.23, 121.00, 126.78, 127.89, 130.03, 131.80, 134.85, 135.89, 163.03.

3-(Isopropoxymethyl)-6-chloro-(1*H*)-quinol-2-one (2e): 43%; mp 195-197 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (d, *J* = 6.0 Hz, 6H), 3.82 (heptet, *J* = 6.0 Hz, 1H), 4.59 (s, 2H), 7.25-7.58 (m, 3H), 7.87 (s, 1H), 12.40 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.21, 64.38, 71.41, 116.85, 120.48, 125.79, 126.84, 129.60, 132.68, 133.62, 136.62, 160.86.

3-(Ethoxymethyl)-5-chloro-(1*H*)-quinol-2-one (2f): 48%; mp 214-219 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 1.35 (t, *J* = 7.2 Hz, 3H), 3.73 (q, *J* = 7.2 Hz, 2H), 4.62 (s, 2H), 7.26-7.42 (m, 3H), 8.32 (s, 1H), 12.28 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.28, 66.78, 67.19, 114.72, 118.00, 123.25, 130.09, 131.57, 132.31, 132.63, 138.64, 163.00.

3-(Isopropoxymethyl)-5-chloro-(1*H*)-quinol-2-one (2g): 52%; mp 215-218 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 1.31 (d, *J* = 6.0 Hz, 6H), 3.83 (heptet, *J* = 6.0 Hz, 1H), 4.62 (s, 2H), 7.25-7.43 (m, 3H), 8.34 (s, 1H), 11.71 (s, 1H).

3-(Ethoxymethyl)-8-methoxy-(1*H*)-quinol-2-one (2h): 40%; mp 116-118 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, *J* = 7.2 Hz, 3H), 3.69 (q, *J* = 7.2 Hz, 2H), 3.97 (s, 3H), 4.56 (s, 2H), 6.95-7.20 (m, 3H), 7.85 (s, 1H) 9.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.17, 55.91, 66.65, 67.13, 109.34, 119.51, 120.14, 122.08, 127.43, 131.52, 135.28, 145.31, 160.87.

3-(Isopropoxymethyl)-8-methoxy-(1*H*)-quinol-2-one (2i): 53%; mp 97-98 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (d, *J* = 6.0 Hz, 6H), 3.80 (heptet, *J* = 6.0 Hz, 1H), 3.97 (s, 3H), 4.56 (s, 2H), 6.92-7.27 (m, 3H), 7.87 (s, 1H), 9.27 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.22, 55.95, 64.83, 72.23, 109.26, 119.56, 120.26, 122.13, 127.33, 132.12, 135.08, 145.35, 160.97.

3-(Isopropoxymethyl)-6,7-methylenedioxy-(1*H*)-quinol-2-one (2j): 29%; mp 184-185 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (d, *J* = 6.0, 6H), 3.82 (heptet, *J* = 6.0 Hz, 1H), 4.57 (s, 2H), 6.04 (s, 2H), 6.88 (s, 1H), 6.95 (s, 1H), 7.80 (s, 1H), 12.14 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.23, 64.37, 71.17, 95.02, 101.69, 105.41, 113.48, 128.01, 134.71, 135.00, 143.25, 149.54, 160.85.

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References and Notes

1. (a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (b) Ciganek, E. *Organic Reactions*; John Wiley & Sons: New York, 1997; Vol. 51, pp 201-350. (c) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653. (d) Langer, P. *Angew. Chem., Int. Ed*. **2000**, *39*, 3049.
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5. Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc*. **2002**, *23*, 939.
6. During the preparation of this manuscript, Basavaiah *et al*. have reported the similar results (Basavaiah, D.; Reddy, R. M.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron* **2002**, *58*, 3693). They used iron and acetic acid for the synthesis of 3-acetoxymethyl-2(1*H*)-quinolinones.
7. Benzisoxazoline **7**: mp 168-169 °C; IR (KBr) 3277, 1666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (t, J = 7.1 Hz, 3H), 2.74 (s, 3H), 4.40 (q, J = 7.1 Hz, 2H), 7.14 (dd, J = 8.5 and 2.0 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 8.07 (d, J = 2.0 Hz, 1H), 8.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.12, 14.62, 59.32, 103.50, 111.95, 120.40, 121.81, 126.70, 128.43, 133.41, 145.99, 165.75.