ORGANIC LETTERS

2000
Vol. 2, No. 3
343−345

Synthesis of 3-Ethoxycarbonyl-4-hydroxyquinoline *N*-Oxides from the Baylis–Hillman Adducts of *o*-Nitrobenzaldehydes

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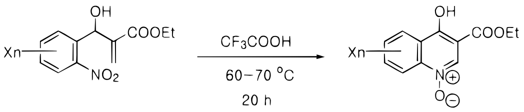
Received December 1, 1999

ABSTRACT

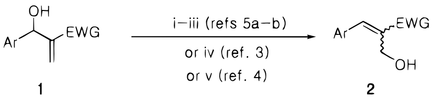


The reaction of the Baylis–Hillman adducts 1a–e of *o*-nitrobenzaldehydes and trifluoroacetic acid at 60–70 °C gave 3-ethoxycarbonyl-4-hydroxyquinoline *N*-oxide derivatives 3a–e in good to moderate yields.

The Baylis−Hillman reaction is one of the most powerful carbon−carbon bond-forming methods in organic synthesis.[1] The Baylis−Hillman adducts, which are allylic alcohol derivatives, can be formed most often by the reaction of activated vinyls and carbonyl compounds.[1] Besides the usefulness of these Baylis−Hillman adducts themselves, further derivatization with various nucleophilic reagents toward synthetically useful compounds has been studied in depth by us and other groups.[2]

The Baylis−Hillman adducts **1** have secondary allylic alcohol functionality, which can be rearranged to the thermodynamically more stable primary allylic alcohols **2** via direct[3,4] or more frequently indirect three-step methods.[5] In the course of our attempts for the one-pot preparation of rearranged allylic alcohols **2**, we were able to develop a facile method using trifluoroacetic acid (method v in Scheme 1).[4]

Scheme 1



(i) PBr_3, ether
(ii) HCO_2NHEt_3, CH_3CN, reflux
(iii) HCl, MeOH, rt
(iv) 20% aq. H_2SO_4, rt (*E* form of **2** when EWG = CN)
(v) CF_3COOH, 30−70 °C (*E* form of **2** when EWG = COOEt)

Our method works well for the Baylis−Hillman adducts derived from benzaldehyde, 2-chlorobenzaldehyde, 2-fluorobenzaldehyde, and 4-methylbenzaldehyde.[4]

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[1] (a) Ciganek, E. *Organic Reactions*; John Wiley & Sons: New York, 1997; Vol. 51, pp 201−350. (b) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653. (c) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (d) Brezezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 4317. (e) Rafel, S.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 1521.

[2] (a) Lee, H. J.; Seong, M. R.; Kim, J. N. *Tetrahedron Lett.* **1998**, *39*, 6223. (b) Lee, H. J.; Kim, H. S.; Kim, J. N. *Tetrahedron Lett.* **1999**, *40*, 4363. (c) Basavaiah, D.; Sarma, P. K. S. *J. Chem. Soc., Chem. Commun.* **1992**, 955. (d) Charette, A. B.; Cote, B.; Monroc, S.; Prescott, S. *J. Org. Chem.* **1995**, *60*, 6888. (e) Basavaiah, D.; Krishnamacharyulu, M.; Hyma, R. S.; Pandiaraju, S. *Tetrahedron Lett.* **1997**, *38*, 2141. (f) Chavan, S. P.; Ethiraj, K. S.; Kamat, S. K. *Tetrahedron Lett.* **1997**, *38*, 7415. (g) Perlmutter, P.; Tabone, M. *Tetrahedron Lett.* **1988**, *29*, 949. (h) Lawrence, R. M.; Perlmutter, P. *Chem. Lett.* **1992**, 305. (i) Foucaud, A.; El Guemmout, F. *Bull. Soc. Chim. Fr.* **1989**, 403.

[3] An aqueous sulfuric acid mediated one-pot conversion has been reported quite recently by Basavaiah et al.: Basavaiah, D.; Kumaragurubaran, N.; Padmaja, K. *Synlett* **1999**, 1630.

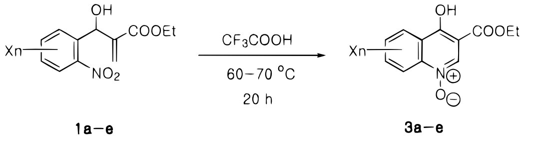
[4] The manuscript for the transformation of secondary allylic alcohols **1** to the corresponding primary allylic alcohols **2** was submitted: Kim, H. S.; Kim, T. Y.; Lee, K. Y.; Chung, Y. M.; Lee, H. J.; Kim, J. N. Facile Synthesis of Stereochemically Defined Allylic Alcohol Derivatives from the Easily Available Baylis-Hillman Adducts.

[5] (a) Hbaieb, S.; Ayed, T. B.; Amri, H. *Synth. Commun.* **1997**, *27*, 2825. (b) Beltaief, I.; Hbaieb, S.; Besbes, R.; Amri, H.; Villieras, M.; Villieras, J. *Synthesis* **1998**, 1765. (c) Charette, A. B.; Cote, B.; Monroc, S.; Prescott, S. *J. Org. Chem.* **1995**, *60*, 6888.

10.1021/ol9903741 CCC: $19.00

However, to our surprise the expected allylic alcohol **2a** was not obtained from the *o*-nitro derivative **1a** as in Scheme 2. Instead we obtained a very polar compound which was identified as 3-ethoxycarbonyl-4-hydroxyquinoline *N*-oxide (**3a**, 82%). The structure of **3a** was confirmed unequivocally by various spectroscopic data including NOE experiments (Figure 1)[6] and chemical transformation (Scheme 3). Deoxygenation of **3a** with triphenylphosphine in refluxing THF gave **4**, which was identical in all respects with the authentic sample prepared by the well-known Gould–Jacobs reaction[7] as shown in Scheme 3.

Scheme 2



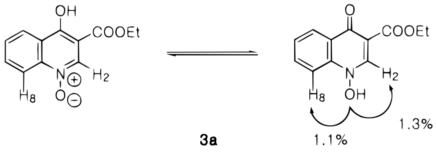
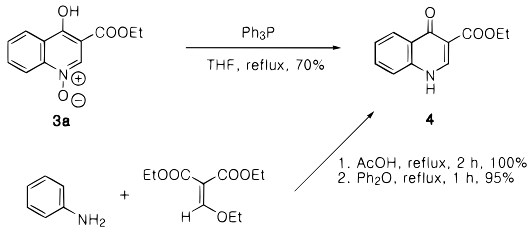


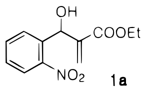
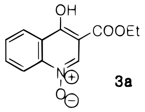
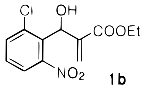
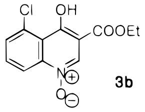
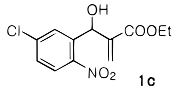
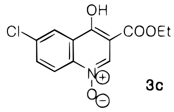
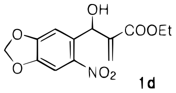
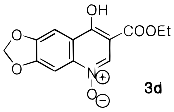
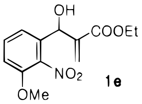
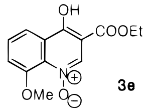
Figure 1. NOE results of **3a**.

Scheme 3



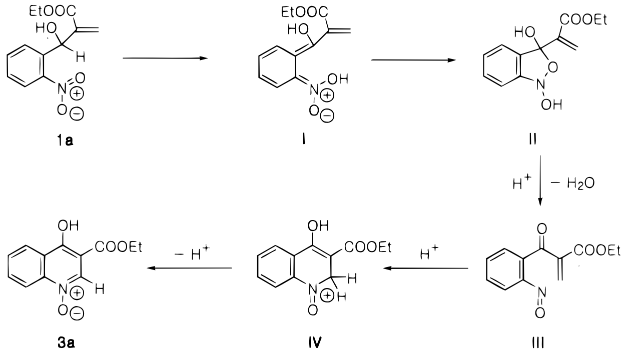
Representative examples including electron-withdrawing chloro substituents (entries 2 and 3) or electron-donating alkoxy substituents (entries 4 and 5) are shown in Table 1. Starting materials **1a**–**e** were prepared from the corresponding *o*-nitrobenzaldehydes and ethyl acrylate in the presence of 1,4-diazabicyclo[2.2.2]octane in 83–97% yields.[8]

Table 1

entry	B–H adducts	products	yield (%)	mp (°C)
1	 1a	 3a	82	182–183
2	 1b	 3b	48	192–193
3	 1c	 3c	59	248–249
4	 1d	 3d	83	172–173
5	 1e	 3e	59	160–161

The reaction mechanism could be proposed as shown in Scheme 4 as Woodrell et al. have reported recently in mechanistically similar systems.[9a] Proton abstraction at the benzylic position by nitro group generates unstable *aci*-nitro intermediate **I**. Cyclization followed by rearomatization gave *N*-hydroxy oxazolidine derivative **II**. Trifluoroacetic acid-catalyzed dehydration of **II** produced nitroso intermediate

Scheme 4



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[6] A stirred solution of **1a** (251 mg, 1 mmol) in trifluoroacetic acid (2 mL) was heated to 60–70 °C during 20 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with chloroform (2 × 30 mL). The organic layers were dried ($MgSO_4$) and evaporated to give crude **3a**. Column chromatography on silica gel (CH_2Cl_2/MeOH, 14:1) afforded analytically pure **3a** as a white solid, 192 mg (82%): mp 182–183 °C; IR (KBr) 3463, 2547, 1716, 1617, 1552, 1487, 1349, 1231, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$ + few drops of DMSO-d_6) δ 1.39 (t, $J = 7.2$ Hz, 3H), 4.5 (br s, 1H), 4.36 (q, $J = 7.2$ Hz, 2H), 7.47 (t, $J = 8.1$ Hz, 1H), 7.74 (t, $J = 8.1$ Hz, 1H), 7.95 (d, $J = 8.1$ Hz, 1H), 8.38 (d, $J = 8.1$ Hz, 1H), 8.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.78, 60.13, 106.74, 115.02, 125.16, 125.91, 126.68, 132.23, 139.05, 143.52, 164.44, 171.58; irradiation of the peak of H-2 (s, $\delta = 8.73$ ppm) produced no NOE of any protons. Irradiation of the hydroxyl proton (br s, $\delta = 4.5$ ppm) showed 1.3% enhancement of the intensity of H-2 (s, $\delta = 8.73$ ppm) and 1.1% of H-8 (d, $\delta = 7.95$ ppm); CIMS *m/z* (rel intensity) 89 (12), 114 (16), 115 (12), 143 (14), 170 (89), 171 (73), 200 (12), 216 (55), 218 (100), 233 (7), 234 (MH^+, 1). Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.65; H, 4.91; N, 6.00.

III. Conjugate addition of nitroso to the unsaturated carbonyl group would form **IV**. Finally deprotonation of **IV** afforded *N*-oxide derivative **3a**. However, we could not exclude the mechanisms involving radical species or involving electrocyclization of the intermediate **I** entirely at this point.

The reaction of **1a** in acetic acid (60−70 °C, 36 h) did not produce **3a** at all. In formic acid (60−70 °C, 36 h) **3a** was also not obtained; instead the formate of **1a** was isolated in low yield (10%). It is interesting to note that the corresponding B−H adduct prepared from *o*-nitrobenzaldehyde and acrylonitrile did not form the quinoline ring. Instead, trace amounts of rearranged allylic alcohol derivative of type **2** were isolated in low yield (10%).

Further studies on the reaction mechanism are currently underway. Most of all, we are interested in finding the photochemical conditions for the same transformation. Photochemically labile protecting groups are very important in medicinal chemistry and bioorganic chemistry,[9] and our final aims will also be focused on developing a photolabile connector for the two biologically active moieties.

Acknowledgment. We wish to thank Dr. Hyoung Rae Kim (Korea Research Institute of Chemical Technology) for his help with NOE experiments. Financial support from the Ministry of Education of Korea is greatly acknowledged.

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(7) (a) Carretero, J. C.; Garcia Ruano, J. L.; Vicioso, M. *Tetrahedron* **1992**, *48*, 7373. (b) Anderson, G. L. *J. Heterocycl. Chem*. **1985**, *22*, 1469. (c) Kaminsky, D. Fr. Demande 2,002,888 (*Chem. Abstr*. **1970**, *72*, 90322v). Characterization of **4**: mp 265−267 °C (lit. 269−270 °C, see ref 7c); IR (KBr) 3434, 3169, 2982, 2904, 1706, 1623, 1529, 1476, 1380, 1292, 1202, 1141, 766 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.29 (t, $J = 7.1$ Hz, 3H), 4.23 (q, $J = 7.1$ Hz, 2H), 7.42 (t, $J = 8.1$ Hz, 1H), 7.63 (d, $J = 8.1$ Hz, 1H), 7.71 (t, $J = 8.1$ Hz, 1H), 8.17 (d, $J = 8.1$ Hz, 1H), 8.56 (s, 1H), 12.41 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 14.52, 59.77, 109.94, 118.98, 124.90, 125.82, 127.44, 132.61, 139.15, 145.11, 165.00, 173.68.

(8) To a stirred solution of the corresponding *o*-nitrobenzaldehydes (2 mmol) and ethyl acrylate (0.6 mL) was added DABCO (225 mg, 0.2 mmol), and the solution was stirred at room temperature for 3 days. After the usual workup, pure products **1a**−**e** were obtained by column chromatography on silica gel (hexane/ether, 7:3).

(9) (a) Woodrell, C. D.; Kehayova, P. D.; Jain, A. *Org. Lett*. **1999**, *1*, 619. (b) Pirrung, M. C.; Lee, Y. R.; Park, K.; Springer, J. B. *J. Org. Chem.* **1999**, *64*, 5042. (c) Pirrung, M. C.; Shuey, S. W. *J. Org. Chem*. **1994**, *59*, 3890. (d) Walker, J. W.; Reid, G. P.; McCray, J. A.; Trentham, D. R. *J. Am. Chem. Soc*. **1998**, *110*, 7170. (e) Givens, R. S.; Matuszewski, B. *J. Am. Chem. Soc*. **1984**, *106*, 6860. (f) Amit, B.; Zehavi, U.; Patchornik, A. *J. Org. Chem*. **1974**, *39*, 192. (g) Givens, R. S.; Athey, P. S.; Kueper, L. W., III.; Matuszewski, B.; Xue, J.-y. *J. Am. Chem. Soc.* **1992**, *114*, 8708. (h) Givens, R. S.; Athey, P. S.; Matuszewski, B.; Kueper, L. W.; Xue, J.-y.; Fister, T. *J. Am. Chem. Soc.* **1993**, *115*, 6001. (i) Pillai, V. N. R. *Synthesis* **1980**, 1. (j) Givens, R. S.; Kueper, L. W., III. *Chem. Rev*. **1993**, *93*, 55.