Synthesis of Quinoline *N*-Oxides from the Baylis-Hillman Adducts of 2-Nitrobenzaldehydes: Conjugate Addition of Nitroso Intermediate

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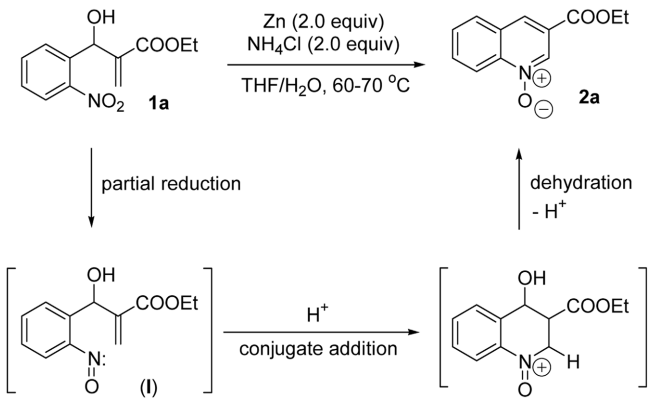
The Baylis-Hillman reaction is a useful carbon-carbon bond-forming method from activated vinyls and carbonyl compounds.[1] Chemical transformation of the Baylis-Hillman adducts or their derivatives into useful heterocyclic compounds has been studied recently by us and other groups.[1-3] Especially, conversion of the Baylis-Hillman adducts derived from 2-nitrobenzaldehydes into quinoline skeleton is a useful entry for the quinoline chemistry.[2o,3,4]

Kaye and co-workers have reported the synthesis of quinoline skeleton from the Baylis-Hillman adducts.[3b] We have also reported the synthesis of 4-hydroxyquinoline *N*-oxides from the Baylis-Hillman adducts of 2-nitrobenzaldehydes.[2o,3a] As a continuing study, we examined the synthesis of quinoline *N*-oxides **2** by reduction of the nitro functionality of the Baylis-Hillman adducts **1** into nitroso group followed by dehydrative cyclization strategy. Among the various examined reduction conditions,[4] the use of zinc and ammonium chloride system in aqueous THF was found to be effective.

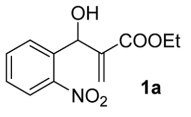
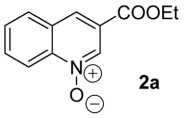
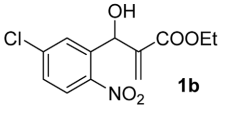
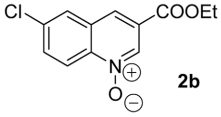
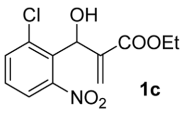
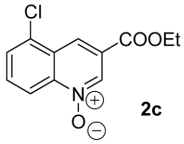
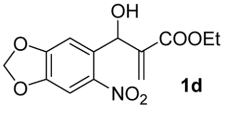
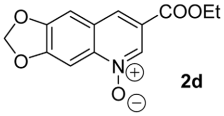
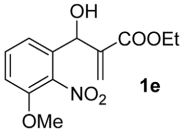
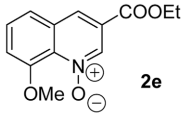
The nitro group is readily converted to a series of functions of various degrees of reduction: very exceptionally to a nitroso group, more often to a hydroxylamino group and most frequently to the amino group.[5] Nitroso compounds are usually not obtained directly but rather by reoxidation of hydroxylamino compounds,[5] which can be prepared from nitro compounds by zinc and aqueous ammonium chloride.[6] Moreover there have been few instances in which nitroso compounds have been isolated as intermediates in reductions of nitro compounds.[5,7] In some instances the nitroso nitrogen behaves as a nucleophile with formaldehyde, glyoxylic acid and pyruvic acid.[8] Only one example of the conjugate addition of arylnitroso compound to the conjugated azoalkene system was known to the best of our knowledge.[9]

The reaction of the Baylis-Hillman adduct **1a** and zinc (2.0 equiv) and ammonium chloride (2.0 equiv) in aqueous THF at 60-70 °C gave the quinoline *N*-oxide **2a** in 49% isolated yield (Scheme 1) together with many intractable side products. In the reaction, quenching of the unstable nitroso intermediate (**I**) occurred before further reduction to a hydroxylamine stage due to the facile intramolecular Michael addition process. This might be the first example of conjugate addition of the nitroso intermediate to the Michael acceptor in an intramolecular fashion as mentioned

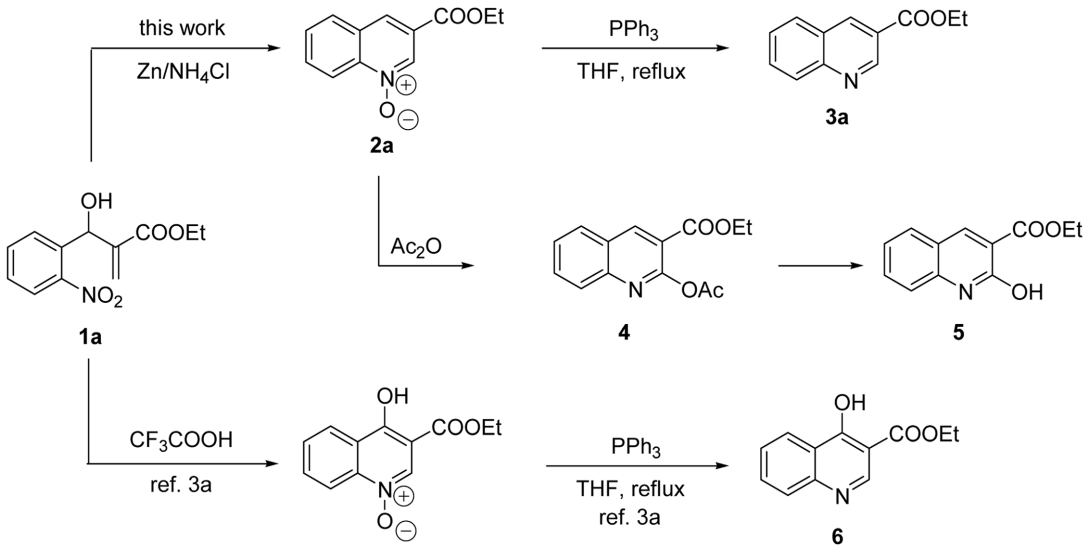


Scheme 1

Table 1. Synthesis of quinoline N-oxidex **2a-e**

Entry	B-H adduct	Time (h)[a]	Product	Yield (%)[b]
1	 **1a**	12	 **2a**	49 (101-102)
2	 **1b**	6	 **2b**	47 (170-172)
3	 **1c**	5	 **2c**	53 (101-102)
4	 **1d**	3	 **2d**	45 (113-114)
5	 **1e**	12	 **2e**	47 (91-92)

[a]Reaction conditions: Zn (2.0 equiv), NH_4Cl (2.0 equiv), THF-H_2O, 60-70 °C. [b]Mp was written in parenthesis.



Scheme 2

before.[2o,3a] The representative results are summarized in Table 1.

The reaction mechanism is thought to be as follows as shown in Scheme 1: (1) Reduction of the nitro functionality of **1** to the nitroso group to give (**I**), (2) acid catalyzed intramolecular conjugate addition, and finally (3) dehydration gave the products **2**. The structure of **2a** can be easily confirmed as shown in Scheme 2. Deoxygenation of **2a** with triphenylphosphine afforded the corresponding quinoline **3a** (THF, PPh_3, 48 h, 70%), which was identical with the authentic sample prepared according to our previous method from the Baylis-Hillman adduct of 2-fluorobenzaldehyde *N*-tosylimine.[2p] The reaction of **2a** with acetic anhydride gave 2-acetoxy derivative **4** in 58% yield as reported in a similar system.[10] It is interesting to note that the acetoxy compound **4** was unstable and converted spontaneously to the 2-hydroxyquinoline derivative **5**[11] slowly. As exemplified in Scheme 2, regioselective synthesis of 2-hydroxyquinoline **5** (*via* successive treatment of **1a** with Zn/NH_4Cl and Ac_2O) and 4-hydroxyquinoline **6** (*via* successive treatment of **1a** with CF_3COOH and PPh_3)[3a] could be carried out.[12] Partial deoxygenation of quinoline *N*-oxide to quinoline was observed after long reaction time under the reduction conditions in electron-rich system such as **2d**.[13]

In summary, we disclosed on the facile one-pot preparation method of quinoline *N*-oxides from the Baylis-Hillman adducts of 2-nitrobenzaldehydes via the conjugate addition of the nitroso functionality in an intramolecular fashion as the key step for the first time.

Experimental Section

Typical procedure for the synthesis of 2a. To a stirred suspension of **1a** (251 mg, 1.0 mmol), zinc (130 mg, 2.0 mmol) and ammonium chloride (110 mg, 2.0 mmol) in aqueous THF (4 mL, THF/H_2O = 3 : 1) was heated to 60-70 °C for 12 h. After filtration through a Celite pad, appropriate workup process and column chromatographic purification (hexanes/ethyl acetate = 1 : 1) **2a** was obtained as a white solid, 107 mg (49%). Compounds **2b-e** was prepared similarly and their spectroscopic data are as follows.

Compound **2a**: white solid, mp 101-102 °C; IR (KBr) 1724, 1374, 1364, 1276, 1247, 1207, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (t, J = 7.2 Hz, 3H), 4.47 (q, J = 7.2 Hz, 2H), 7.43 (t, J = 8.1 Hz, 1H), 7.89 (t, J = 8.4 Hz, 1H), 8.01 (d, J = 8.1 Hz, 1H), 8.43 (s, 1H), 8.79 (d, J = 8.4 Hz, 1H), 9.09 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.16, 62.13, 119.91, 124.61, 127.82, 129.11, 129.35, 129.49, 132.48, 135.13, 142.91, 163.31; Mass (CI) *m/z* (rel. intensity) 116 (14), 128 (16), 156 (30), 173 (17), 189 (19), 202 (68), 217 (M^+, 90), 218 (MH^+, 100).

Compound **2b**: white solid, mp 170-172 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (t, J = 7.2 Hz, 3H), 4.48 (q, J = 7.2 Hz, 2H), 7.79 (dd, J = 9.3 and 2.1 Hz, 1H), 7.98 (d, J = 2.1 Hz, 1H), 8.31 (s, 1H), 8.72 (d, J = 9.3 Hz, 1H), 9.02 (d, J = 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.20, 62.37, 121.92, 126.00, 126.26, 128.13, 130.02, 133.07, 135.24, 135.91, 141.60, 163.01.

Compound **2c**: white solid, mp 101-102 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (t, J = 7.2 Hz, 3H), 4.50 (q, J = 7.2 Hz, 2H), 7.77-7.80 (m, 2H), 8.71 (dd, J = 7.5 and 2.1 Hz, 1H), 8.76 (s, 1H), 9.08 (d, J = 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.21, 62.40, 119.12, 124.13, 125.33, 127.79, 129.73, 131.86, 133.85, 135.57, 144.14, 163.06.

Compound **2d**: white solid, mp 113-114 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (t, J = 7.2 Hz, 3H), 4.44 (q, J = 7.2 Hz, 2H), 6.23 (s, 2H), 7.20 (s, 1H), 8.12 (s, 1H), 8.23 (s, 1H), 8.95 (d, J = 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.22, 61.98, 97.91, 102.90, 104.35, 123.23, 126.58, 126.69, 134.57, 141.28, 150.15, 153.60, 163.55.

Compound **2e**: white solid, mp 91-92 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (t, J = 7.2 Hz, 3H), 4.12 (s, 3H), 4,49 (q, J = 7.2 Hz, 2H), 7.18 (dd, J = 7.2 and 1.8 Hz, 1H), 7.51-7.56 (m, 2H), 8.82 (d, J = 2.1 Hz, 1H), 9.45 (d, J = 2.1 Hz,

1H).

Conversion of 2a into 5. A solution of **2a** (217 mg, 1 mmol) in acetic anhydride (1 mL) was heated to reflux for 4 h. After usual workup and column chromatographic purification (hexanes/ether, 1 : 1) process we obtained **4** as a white solid, 150 mg (58%). However, the compound **4** was unstable and converted into spontaneously to **5**. After 7 days at room temperature we found quantitative formation of **5**. Analytically pure sample **5** was obtained by flash column chromatography (hexanes/ether, 1 : 1) in 82% yield (178 mg). The spectroscopic data of **4** and **5** are as follows.

Compound **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (t, J = 7.2 Hz, 3H), 2.45 (s, 3H), 4.42 (q, J = 7.2 Hz, 2H), 7.62 (t, J = 8.1 Hz, 1H), 7.84 (t, J = 8.1 Hz, 1H), 7.95 (d, J = 8.1 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 8.96 (s, 1H).

Compound **5**: white solid, mp 162-163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (t, J = 7.2 Hz, 3H), 4.46 (q, J = 7.2 Hz, 2H), 7.26 (t, J = 8.4 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.62 (t, J = 8.4 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 8.57 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.31, 61.45, 116.20, 118.61, 122.18, 123.19, 129.19, 133.08, 139.98, 145.67, 161.14, 164.39.

The spectroscopic data of **3a**[2p] and **6**[3a] can be found in our previous papers.

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