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Applications of Baylis–Hillman adducts: a simple, convenient, and one-pot synthesis of 3-benzoylquinolines

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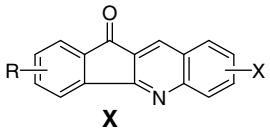
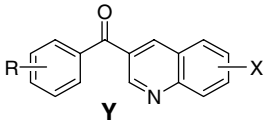
Abstract—A simple and convenient synthesis of 3-(2-hydroxybenzoyl)quinoline derivatives via the treatment of 3-[hydroxy(2-nitroaryl)methyl]-4*H*-chromen-4-ones, derived from chromones and various 2-nitrobenzaldehydes, with Fe/AcOH, in a one-pot operation, is described.

The Baylis–Hillman reaction is a useful carbon–carbon bond forming reaction because it provides a simple and convenient method for the synthesis of interesting classes of densely functionalized molecules in operationally simple, one-pot, and atom economical procedures.[1,2] The functionalized quinoline framework continues to occupy an important place in nitrogen heterocyclic chemistry due to the presence of this moiety in a variety of molecules possessing a wide spectrum of physiological activities and also has attractive pharmaceutical applications.[3] Hence, the development of simple and easy methodologies for the synthesis of quinoline derivatives represents an interesting and challenging endeavor.[4] There has been increasing interest in the synthesis of oxo-indeno[1,2-*b*]quinoline (fused 3-benzoylquinoline) derivatives **X** because these molecules have been found to bind DNA with high affinity, inhibit DNA topoisomerase 1, and possess cytotoxic, antitumor, and anti-cancer activities.[5] In the hope that 3-benzoylquinoline derivatives **Y**,[6] which are structurally close to oxo-indeno[1,2-*b*]quinoline derivatives **X**, might also be of some biological importance, and in continuation of our interest in the synthesis of heterocyclic molecules[7] we herein report an easy, convenient, and one-pot synthesis of 3-benzoylquinoline derivatives via treatment of the Baylis–Hillman alcohols, 3-[hydroxy(2-nitroaryl)methyl]-4*H*-chromen-4-ones, derived from chromones and various 2-nitrobenzaldehydes, with Fe/AcOH.



X



Y

Applications of Baylis–Hillman adducts in the synthesis of quinolines, 1,4-dihydroquinolines, tetrahydroindeno[1,2-*b*]quinolines, and quinoline *N*-oxides have been well demonstrated.[7i,8] Recently, we reported a simple synthesis of substituted quinolines, tetrahydroacridines, and cyclopenta[*b*]quinolines from the Baylis–Hillman adducts obtained from 2-nitrobenzaldehydes and acyclic/cyclic enones, via treatment with Fe/AcOH (Scheme 1).[7b,i] It occurred to us that the Baylis–Hillman adducts[9] **1a–i** derived from chromones and various 2-nitrobenzaldehydes, should in principle provide tetracyclic heterocyclic molecules **I** or **II** via similar treatment with Fe/AcOH in a one-pot operation (Scheme 2).

We first studied the reaction with Fe powder in AcOH of 3-[hydroxy(2-nitrophenyl)methyl]-4*H*-chromen-4-one **1a**, a Baylis–Hillman alcohol obtained from 1-benzopyran-4(4*H*)-one and 2-nitrobenzaldehyde. Unfortunately, we did not obtain the expected tetracyclic heterocyclic molecules **I** or **II** (Scheme 2). However, we obtained an equally interesting molecule, 3-(2-hydroxybenzoyl)quinoline **2**. Thus **1a** (1 mmol) on treatment with Fe powder (6 mmol) in acetic acid (5 mL) at reflux for 2 h, gave **2** in 61% isolated yield, after work-up and

Keywords: Baylis–Hillman reaction; Benzoylquinolines; Chromones; Reductive cyclization; Fe/AcOH.
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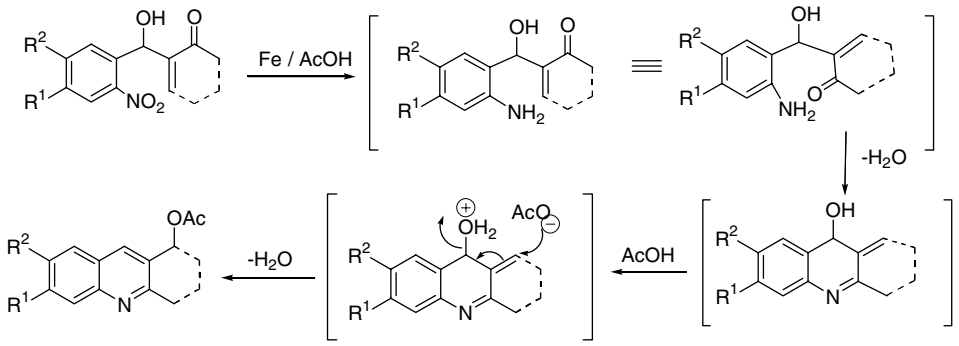
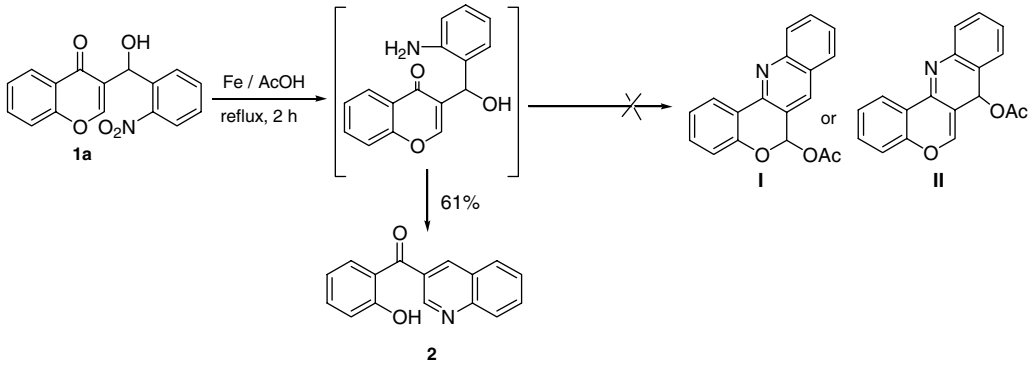


Scheme 1. Synthesis of quinoline derivatives: reductive cyclization of Baylis–Hillman alcohols.[7b,i]

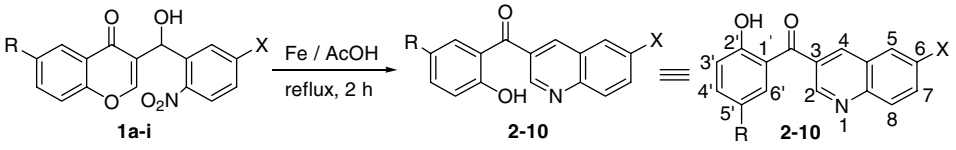


Scheme 2. An easy, one-pot synthesis of a 3-benzoylquinoline.

purification by column chromatography (Scheme 2, Table 1 and entry 1).[10]

This is indeed an interesting reaction in the sense that the chromone moiety is cleaved by the amino (anilino) group, generated in situ, thus leading to the easy formation of 3-(2-hydroxybenzoyl)quinoline (Scheme 2). With a view to mapping the generality of this reaction, we successfully transformed representative Baylis–Hillman alcohols (B–H alcohols) (**1b**,**c**) obtained from 1-benzopyran-4(4*H*)-one and various 2-nitrobenzaldehydes, via treatment with Fe/AcOH at reflux for 2 h, into the

Table 1. Reductive cyclization of Baylis–Hillman alcohols **1a–i** into 3-benzoylquinoline derivatives[a]



Entry	B–H alcohol	R	X	Product[b]	Yield[c] (%)	Mp (°C)
1	**1a**	H	H	**2**[d]	61	70–72
2	**1b**	H	Cl	**3**	67	116–118
3	**1c**	H	Br	**4**[d]	46	125–127
4	**1d**	Me	H	**5**[d]	55	79–81
5	**1e**	Me	Cl	**6**[d]	53	118–120
6	**1f**	Me	Br	**7**[e]	51	123–125
7	**1g**	Cl	H	**8**[d]	52	166–168
8	**1h**	Br	H	**9**[d]	56	155–157
9	**1i**	Cl	Cl	**10**[d,e]	54	129–131

[a] All reactions[10] were carried out on a 1 mmol scale of Baylis–Hillman alcohols[9] **1a–i** with Fe powder (6 mmol)/AcOH (5 mL) at reflux for 2 h.
[b] Compounds **2–10** were obtained as pale yellow solids and were characterized by IR, ^{1}H NMR (400 MHz), ^{13}C NMR (50/100 MHz) spectroscopy, and elemental analyses.
[c] Yields are of the pure products (based on alcohols) after purification by silica gel column chromatography (silica gel, 6% EtOAc in hexanes).
[d] Structures of these molecules were further confirmed by mass spectral analyses.
[e] The structures of these molecules were also established from the single crystal X-ray data (Figs. 1 and 2).

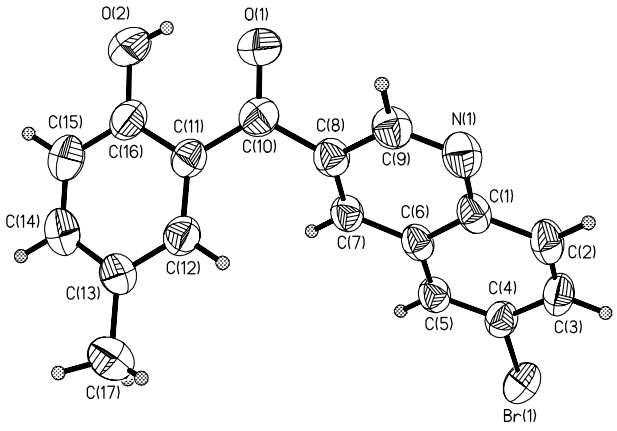


Figure 1. ORTEP diagram of compound **7**.

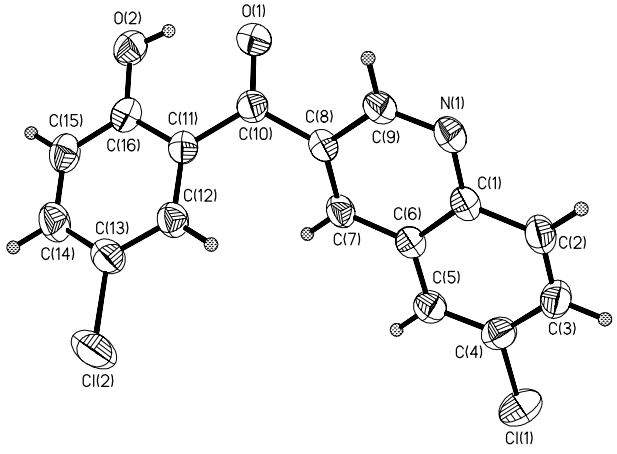


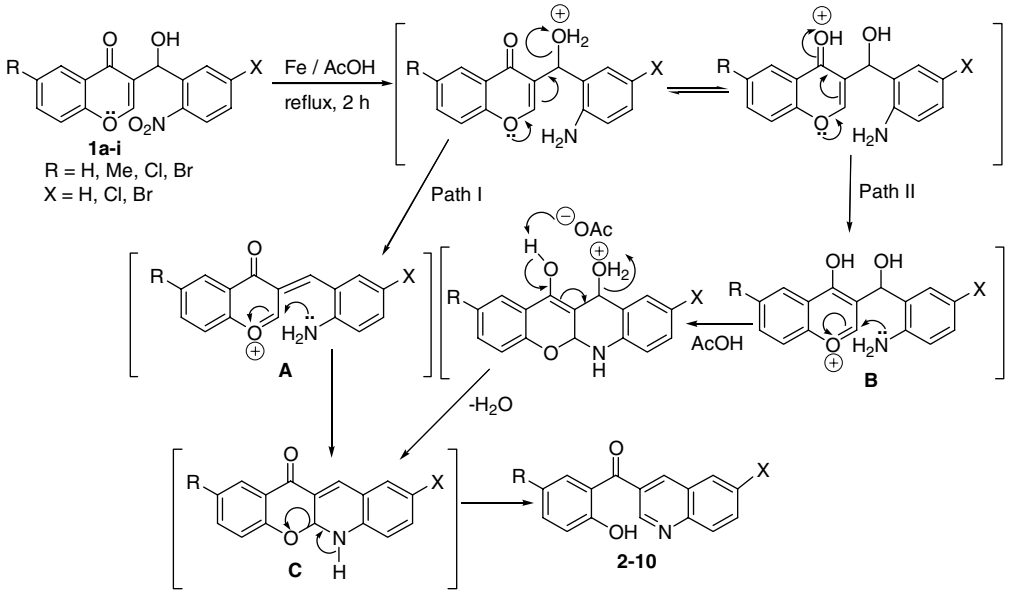
Figure 2. ORTEP diagram of compound **10**.

substituted 3-(2-hydroxybenzoyl)quinolines **3**–**4** in 67% and 46% yields, respectively (Table 1, entries 2 and 3).

We also successfully transformed compounds **1d**–**f**, obtained from 6-methyl-1-benzopyran-4(4*H*)-one and various 2-nitrobenzaldehydes into the corresponding 3-benzoylquinoline derivatives **5**–**7**, in 51–55% isolated yields (Table 1, entries 4–6). We also extended the strategy to Baylis–Hillman alcohols **1g**–**i**, obtained from 6-chloro-1-benzopyran-4(4*H*)-one/6-bromo-1-benzopyran-4(4*H*)-one and representative 2-nitrobenzaldehydes, leading to the formation of corresponding 3-benzoylquinoline derivatives **8**–**10** in 52–56% isolated yields (Table 1, entries 7–9). We obtained single crystals of 6-bromo-3-(2-hydroxy-5-methylbenzoyl)quinoline **7** and 6-chloro-3-(5-chloro-2-hydroxybenzoyl)quinoline **10** and further confirmed the structures of these molecules from single crystal X-ray data (see Figs. 1 and 2).[11,12]

A plausible mechanism for the formation of 3-benzoylquinolines **2**–**10** is presented in Scheme 3. The reaction is believed to proceed through the formation of tetracyclic system **C**, which might form through oxonium ions **A** or **B**, via the nucleophilic attack of amine (aniline) onto the oxonium ion. Finally, the hemiaminal in **C**, would cleave to provide the 3-benzoylquinoline derivatives **2**–**10**. Schiff's base formation (as indicated in Scheme 2) is probably prevented by the easy formation of an oxonium ion (**A** or **B**).

In conclusion, we have successfully developed an easy, convenient, and operationally simple one-pot procedure for the synthesis of 3-benzoylquinoline derivatives from Baylis–Hillman alcohols, thus demonstrating a further application of Baylis–Hillman chemistry. The reaction is interesting due to its mechanistic pathway involving an easy transformation of the moiety, containing acyclic nitrogen and cyclic oxygen, into another important framework having cyclic nitrogen and acyclic oxygen.



Scheme 3. A plausible mechanism for the formation of 3-benzoylquinoline derivatives.

Acknowledgements

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9. The Baylis–Hillman alcohols, 3-[hydroxy(2-nitroaryl)methyl]-4*H*-chromen-4-ones **1a**–**i** were prepared via the treatment of the chromones [1-benzopyran-4(4*H*)-one, 6-methyl-1-benzopyran-4(4*H*)-one, 6-chloro-1-benzopyran-4(4*H*)-one, and 6-bromo-1-benzopyran-4(4*H*)-one] with various 2-nitrobenzaldehydes [2-nitrobenzaldehyde, 5-chloro-2-nitrobenzaldehyde, and 5-bromo-2-nitrobenzaldehyde] under the influence of methanolic trimethyl-

amine following the procedure developed in our laboratory.[7g]

10. Typical experimental procedure: 3-(2-Hydroxybenzoyl)-quinoline **2**: To a stirred solution of 3-[hydroxy(2-nitrophenyl)methyl]-4*H*-chromen-4-one **1a** (1 mmol, 0.297 g) in acetic acid (5 mL) was added Fe powder (6 mmol, 0.335 g) and the reaction mixture was refluxed for 2 h. The mixture was cooled to room temperature and acetic acid was removed under reduced pressure, EtOAc (10 mL) was added, then the mixture was stirred for 2 min and filtered to remove any iron impurities. The insoluble iron residue was washed with EtOAc (10 mL). The filtrate and washings were combined and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product thus obtained was purified by column chromatography (silica gel) using 6% EtOAc in hexanes to afford 3-(2-hydroxybenzoyl)quinoline **2** as a pale yellow solid (0.152 g, 61%); mp: 70–72 °C; IR (KBr): 3042, 1628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.90–7.00 (m, 1H), 7.13 (d, 1H, $J = 8.4$ Hz), 7.55–7.78 (m, 3H), 7.85–7.93 (m, 1H), 7.95 (d, 1H, $J = 8.4$ Hz), 8.21 (d, 1H, $J = 8.4$ Hz), 8.50 (d, 1H, $J = 2.0$ Hz), 9.21 (d, 1H, $J = 2.0$ Hz), 11.91 (s, 1H, D_2O exchangeable); ^{13}C NMR (50 MHz, $CDCl_3$): δ 118.67, 119.04, 126.43, 127.72, 128.91, 129.44, 130.51, 131.75, 133.06, 136.84, 137.81, 149.16, 149.31, 163.21, 199.11; LCMS (*m*/*z*): 250 $(M+H)^+$. Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 77.38; H, 4.48; N, 5.63.

11. Crystal data for 6-bromo-3-(2-hydroxy-5-methylbenzoyl)quinoline **7**: The single crystal X-ray structure revealed the presence of two molecules in the asymmetric unit. For clarity we have shown one molecule in the ORTEP diagram (Fig. 1). Empirical formula, $C_{17}H_{12}BrNO_2$; formula weight, 342.19; pale yellow, rectangular crystals; crystal dimensions, $0.52 \times 0.48 \times 0.42$ mm^3; triclinic; lattice type, primitive; $a = 8.8737(12)$ Å, $b = 11.4541(15)$ Å, $c = 15.187(2)$ Å; $\alpha = 82.070(2)$; $\beta = 79.169(2)$; $\gamma = 72.976(2)$; $V = 1444.0(3)$ $Å^3$; space group, $P-1$ (International Table No. 2); $Z = 4$; $D_{calcd} = 1.574$ g/cm^3; $F_{000} = 688$; $\lambda(Mo\ K_\alpha) = 0.71073$ Å; $R(I \geqslant 2\sigma_1) = 0.0389$; $wR^2 = 0.0995$. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC No. 279098).

12. Crystal data for 6-chloro-3-(5-chloro-2-hydroxybenzoyl)quinoline **10**: Empirical formula, $C_{16}H_9NO_2Cl_2$; formula weight, 318.14; pale yellow, rectangular crystals; crystal dimensions, $0.42 \times 0.33 \times 0.18$ mm^3; orthorhombic; lattice type, primitive; $a = 7.3536(4)$ Å, $b = 18.2185(9)$ Å, $c = 20.7724(10)$ Å; $\alpha = \beta = \gamma = 90.00$; $V = 2782.9(2)$ $Å^3$; space group, *Pbca* (International Table No. 61); $Z = 8$; $D_{calcd} = 1.519$ g/cm^3; $F_{000} = 1296$; $\lambda(Mo\ K_\alpha) = 0.71073$ Å; $R(I \geqslant 2\sigma_1) = 0.0476$, $wR^2 = 0.1126$. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC No. 279099).