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Competitive intramolecular nucleophilic aromatic substitution: a new route to coumarins

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4-Hydroxy-3-(2′-pyridyl)coumarins (4) (R = 6-Cl, H, 6-NO_2, 8-NO_2) were prepared in moderate to good yields by the intramolecular nucleophilic aromatic substitution reaction of β-ketoesters (I) in refluxing xylenes; evidence for the reversible formation of benzo[*c*]quinolizinium III from I (X = 4-Cl), with eventual formation of 4 (R = 6-Cl), is also presented.

Cystic fibrosis (CF) results from defects in the gene encoding a cyclic adenosine monophosphate-dependent chloride ion channel known as the cystic fibrosis transmembrane conductance regulator[1] (CFTR) and is characterized by defective chloride transport across epithelia of the airways, exocrine ducts, and intestine as well as viscous epithelial mucous secretions.[2] Becq's recent report[3] that the benzo[*c*]quinolizinium derivative MPB-07 (**II**, Fig. 1) activates wild-type CFTR membrane protein[4] in a variety of cell systems, coupled with our interests[5] in developing small molecule drugs capable of modulating chloride-selective ion channels,[6] led us to explore the use of 3-oxo-2-(2′-pyridyl)(*o*-halophenyl)propanoates as precursors to CFTR-active compounds. The synthesis of benzo[*c*]quinolizinium salts *via* an intramolecular cyclization reported by Fozard and Bradsher[7] led us to consider cyclization of **I** to MPB-07 analog **III** by an intramolecular *ipso* substitution reaction. We report here a wider perspective on the intriguing and useful intramolecular nucleophilic aromatic substitution chemistry of these α-(2-pyridyl)-β-ketoesters.

Our work started with *C*-acylation of benzyl 2-(2-pyridyl)acetate (**1**, Scheme 1),† in turn generated by the transesterification of methyl 2-(2-pyridyl)acetate with lithium benzoxide.[8] Generation of the lithium salt of **1** and subsequent treatment with various *o*-halobenzoyl chlorides gave the corresponding 3-oxo-2-(2′-pyridyl)(*o*-halophenyl)propanoates (**2**). Yields for **1** → **2** are generally moderate (60–75%) for a variety of halobenzoyl chlorides.

Heating **2a** in xylenes at reflux for 2 h delivered a crystalline product which we initially assumed was benzo[*c*]quinolizinium salt **III** (82% yield, Scheme 2). However, single crystal X-ray crystallographic analysis‡ (Fig. 2) revealed that the product was in fact isolated as the neutral benzo[*c*]quinolizine **3a** replete with 1-carboalkoxy and 2-oxo substituents on the newly formed ring. The observation that **2a** → **3a** *via* **III**, which was consistent with the results reported by Fozard and Bradsher for cycloquaternization of *cis*-2′-chloro-2-stilbazole, suggested that *ipso* substitution in our 3-oxo-2-(2′-pyridyl)(*o*-halophenyl)propanoate series would provide a general route to the benzo[*c*]quinolizine ring system.

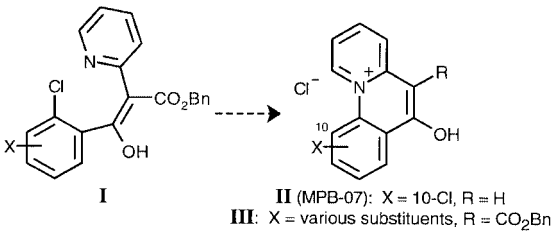
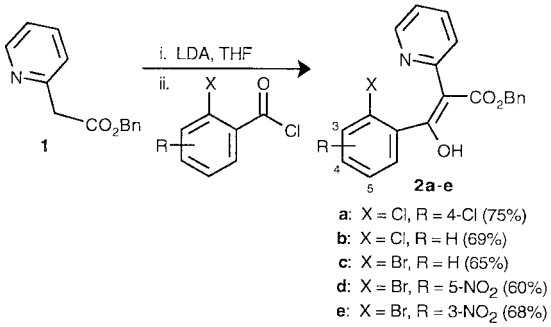
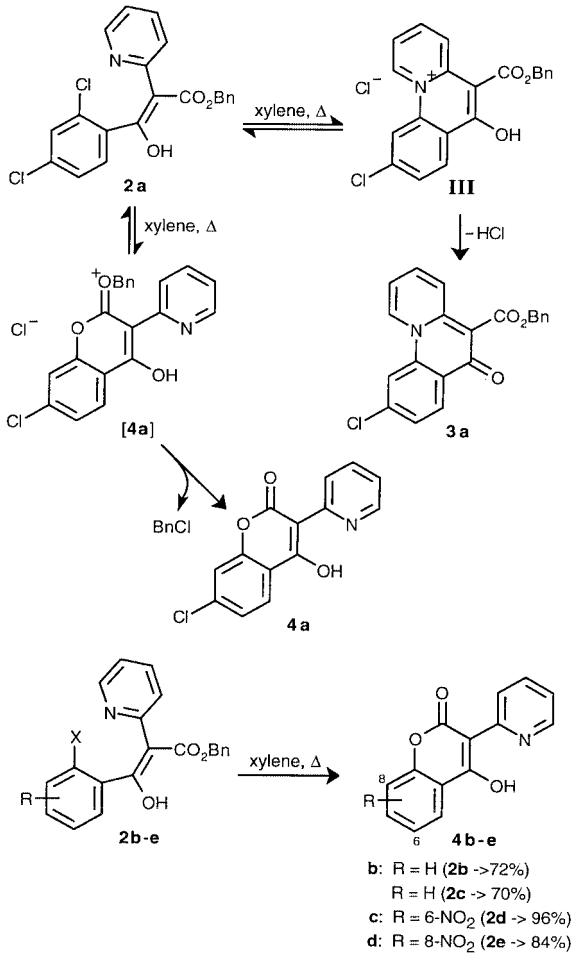


Fig. 1 3-Oxo-2-(2′-pyridyl)(*o*-halophenyl)propanoates as precursors to benzo[*c*]quinolizinium derivatives.



Scheme 1 Preparation of 3-oxo-2-(2′-pyridyl)(*o*-halophenyl)propanoates.



Scheme 2 Intramolecular *ipso* substitution in 3-oxo-2-(2′-pyridyl)(*o*-halophenyl)propanoates.

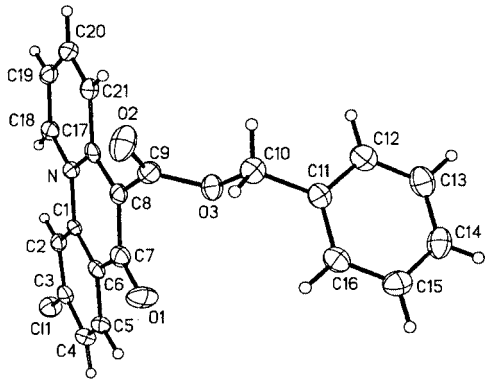


Fig. 2 X-Ray crystallographic structure of **3a**.

However, the next substrate investigated, **2b**, underwent ring-closing *ipso* substitution with loss of the benzyl ester moiety.† On closer inspection, it became apparent that *ipso* substitution of the *o*-chloro substituent in **2b** had occurred *via* nucleophilic attack of the carboalkoxy giving 4-hydroxycoumarin **4b** as the sole isolated product (72%). We speculate that **2** exists in a highly enolized, hydrogen-bonded (N···H–O) conformation[9] which biases the system to intramolecular carboalkoxy—rather than pyridyl—nucleophilic attack resulting in **2b** → **4b**. In the case of **2a**, the *p*-chloro substituent apparently deactivates the ring toward nucleophilic attack to the extent that only the 2-pyridyl moiety is nucleophilic enough to participate in *ipso* substitution, leading to formation of **3a**.

These observations led us to speculate that benzo[*c*]quinolizine **3a** might represent the kinetic product in this reaction and raised the question whether further heating of the **2a** → **3a** reaction mixture might lead to formation of the corresponding 4-hydroxycoumarin derivative. This would presumably occur by reversion of **III** to **2a** by intermolecular *ipso* attack by chloride followed by slow intramolecular ring-closing by carboalkoxy *ipso* attack to [**4a**]. Once formed, irreversible loss of BnCl from [**4a**] would deliver **4a**. To test this idea, the **2a** → **3a** reaction was performed in toluene-d_8 (110 °C) and intermittently monitored by ^{1}H-NMR. As anticipated, we observed the fairly rapid formation of **3a** (**2a** consumed in 72 h) followed by its slow disappearance and matched by the slow appearance of both benzyl chloride and 4-hydroxycoumarin **4a** (intermittent monitoring over 12 d). Moreover, when the laboratory scale reaction of compound **2a** was performed in refluxing xylene, formation of benzo[*c*]quinolizine **3a** was detected early on (monitored by TLC). Continued heating for 10 d afforded 4-hydroxycoumarin **4a** in 65% yield.

Three additional 3-oxo-2-(2′-pyridyl)(*o*-halophenyl)propanoates were also investigated (**2c**–**e**). In each of these, the *o*-halo substituent was a bromine and, in two of these, a strongly activating nitro group was incorporated at C5 (**2d**) or C3 (**2e**). In each of these cases, only carboalkoxy nucleophilic attack was observed. The yields for **2** → **4** are generally quite good (70–96%), with the more electron deficient C-ring systems affording higher yields.

The method reported here provides a general and useful route for the production of 4-hydroxy-3-(2′-pyridyl)coumarin derivatives. While both pyridyl and carboalkoxy moieties can participate in this reaction, reversible formation of the benzo-[*c*]quinolizinium coupled with irreversible loss of benzyl chloride during coumarin formation leads to the exclusive formation of the 4-hydroxy-3-(2′-pyridyl)coumarin derivative.

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Notes and references

† *General procedure for C-acylation of benzyl 2-(2′-pyridyl)acetate* (**1**): to a cold (0 °C) solution of diisopropyl amine (0.33 mL, 2.4 mmol) in dry ethyl ether (6.0 mL) under inert atmosphere was added dropwise n-BuLi (1.63 M in hexane, 1.47 mL, 2.4 mmol). The mixture was cooled to −78 °C and a solution of phenylmethyl 2-(2′-pyridyl)acetate (0.456 g, 2.0 mmol) in dry ethyl ether (2.0 mL) was added dropwise. This mixture was stirred at −78 °C for 60 min at which time a solution of the appropriate benzoyl chloride (2.0 mmol) in dry ethyl ether (1.0 mL) was added dropwise. Stirring was continued at 0 °C for an additional 30 min at which time the reaction was treated with 1 M aq. HCl and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), concentrated, and the oily residue was recrystallized from hexane.

General procedure for 4-hydroxycoumarin formation (**2** → **4**): a solution of phenylmethyl 3-aryl-3-oxo-2-(2′-pyridyl)propanoate **2** (0.2 mmol) in xylenes (2.0 mL) was stirred at reflux under N_2 for 2 h. After removal of the solvent in vacuum, the 4-hydroxycoumarin product was purified by silica gel chromatography (hexanes : EtOAc).

‡ *Crystallographic data*: **3a** (R = −C_6H_5) $C_{21}H_{14}ClNO_3$, M = 363.78, triclinic, space group $P\bar{1}$, a = 7,1272(9), b = 9.5407(12), c = 13.1738(10) Å, α = 77.273(8), β = 79.502(9), γ = 68.701(10)°, U = 808.95(16) Å^3, Z = 2, μ = 2.280 mm^{-1}, T = 133(2) K, a unique data set of 2105 independent reflections was collected, $R1$ = 0.0355 for all data. CCDC 152984. See http://www.rsc.org/suppdata/cc/b0/b009172n/ for crystallographic data in .cif or other electronic format.

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9 Remarkably, the enolic proton in **2a** appears as a singlet at 18.4 ppm ($CDCl_3$) which we believe is indicative of a pyridine H-bonded conformation.