The Baylis–Hillman approach to quinoline derivatives†

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Baylis–Hillman reactions of 2-nitrobenzaldehydes with various activated alkenes afford adducts that undergo reductive cyclisation to quinoline derivatives. The chemo- and regioselectivity of cyclisation appears to be influenced by the choice of both the substrate and the reagent system, and competing reactions have been observed.

The quinoline nucleus features prominently in compounds which exhibit medicinal properties.[1] Notable amongst these are synthetic antimalarials[2] such as chloroquine and primaquine, fungicides such as halacrinate,[3] antibacterial 4-quinolones such as ciprofloxacin and norfloxacin,[4] the HIV-1 protease inhibitor saquinavir,[5] and styrylquinolines as potential HIV-1 integrase inhibitors.[6] Not surprisingly, an array of synthetic methods has been developed to access quinoline derivatives, including the classic Skraup, Doebner–von Miller, Conrad–Limpach and Knorr syntheses.[2,7]

As part of our ongoing research into applications of the Baylis–Hillman reaction in the construction of benzannulated heterocycles,[8] we reported, in a preliminary communication,[9] the synthesis of quinoline, quinoline-*N*-oxide and 2-quinolone derivatives from 2-nitrobenzaldehyde—an approach which obviates use of the relatively inaccessible 2-aminobenzaldehydes required in the Friedlander synthesis. Numerous applications of Baylis–Hillman methodology in the preparation of quinoline derivatives have since been reported.[10–20] In this paper, we discuss: the results of our studies into the generality of the Baylis–Hillman approach to quinoline derivatives; competing reactions; and the interconversion of the quinoline and quinoline-*N*-oxide products.

An extensive range of 2-nitrophenyl Baylis–Hillman adducts **3a–r** (Scheme 1), required as potential precursors for the targeted quinoline derivatives, were prepared by reacting the nitrobenzaldehydes **1a–i** with the activated alkenes **2a–f** in the presence of the nucleophilic catalyst, DABCO. Electron-releasing substituents (*e.g.*, hydroxy or alkoxy, as in compounds **1c**, **d**, **f** and **g**) may be expected to decrease electrophilicity and, hence, reactivity at the aldehydic carbonyl carbon while (additional) electron-withdrawing substituents (*e.g.*, nitro, as in compounds **1h** and **1i**) should enhance reactivity. However, the disparate yields observed for the corresponding sets of products [**3c** (33%); **3d** (24%); **3f** (73%); **3g** (60%); **3j** (90%) and **3m** (14%)] and [**3k** (*ca.* 0%)[21] and **3o** (25%)] are hardly consistent with such expectations and may well reflect the importance of steric, kinetic and thermodynamic factors in a reaction that has been shown to be reversible.[22] The apparent failure[21] of the reaction with 2,5-dinitrobenzaldehyde **1i** is attributed to steric shielding by the nitro groups on either side of the carbonyl moiety effectively inhibiting nucleophilic attack by the zwitterionic Baylis–Hillman intermediate. Attention was given to optimising the reaction conditions by varying reactant concentrations, the catalyst and the reaction time. Under conditions found to be optimal, a solution of 2-nitrobenzaldehyde **1a** (1 eq.), ethyl acrylate **2d** (1.5 eq.) and DABCO (0.05 eq.) in a minimal volume of chloroform was stirred at room temperature for 6 days; the resulting yield of the chromatographed product **3p** was thus increased from 46% to 95%. While the yield of compound **3o** was also increased from 25% to 92%, these conditions were not equally effective across the limited range of substrates examined, and there is clearly room for improvement in certain cases.

Selected Baylis–Hillman products **3** were then subjected to reduction under various conditions, in the expectation that the resulting 2-amino analogues would undergo cyclisation to the desired quinoline derivatives. The methods of choice, following examination of several reducing systems, were either catalytic hydrogenation using a 10% palladium-on-carbon catalyst or reduction using stannous chloride dihydrate. Use of the former reagent system is illustrated in Scheme 2, the latter in Scheme 3. Intramolecular cyclisation of the 2-amino derivatives **5** (Scheme 2) might be expected to proceed either *via* conjugate addition (Path **I**) or *via* nucleophilic attack at the carbonyl carbon (Path **II**). Under catalytic hydrogenation conditions, however, Path **II** appears to be favoured, affording initially, we suggest, the "tetrahedral intermediate" **7**. When the substituent 'R' is alkyl, nucleophilic attack followed by dehydration leads to the quinoline and quinoline-*N*-oxides **8** and **9**, respectively, whereas when 'R' is alkoxy, acyl substitution affords the quinolone derivatives **11**, **12** and **13**. Ketone precursors **3** (R^5 = CO.R) thus tend to yield quinoline derivatives, while ester precursors **3** ($R^5 = CO_2R$) afford quinolone derivatives. The formation of quinoline-*N*-oxides is attributed to early cyclisation of incompletely reduced, nucleophilic, *N*-oxygenated intermediates. In three cases, hydrogenation of the alkene moiety alone afforded compounds **10a**, **d** and **g**.

While product selectivity on reduction with stannous chloride dihydrate also appears to be substrate-dependent, the pattern is rather different. Under these conditions (Scheme 3), ketone precursors **3** (R^5 = CO.R) favour conjugate addition and dehydration or, more likely, concerted S_N' displacement of the hydroxyl group, to give the *N*-hydroxydihydroquinolines **14**; ester precursors

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† Electronic supplementary information (ESI) available: Analytical data for compounds **33**, **3d**, **17**, **3e**, **3g**, **3i**, **3j**, **3m**, **3q**, **3r**, **8b**, **9b**, **8c**, **9c**, **8d**, **10d**, **8e**, **9e**, **8g**, **10g**, **9h**, **8h**, **12l**, **13l**, **11l**, **12n**, **13n**, **19**, **18**, **14a**, **14h**, **15p**, **20q** and **20r**. See DOI: 10.1039/b608592j

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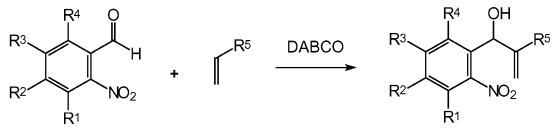
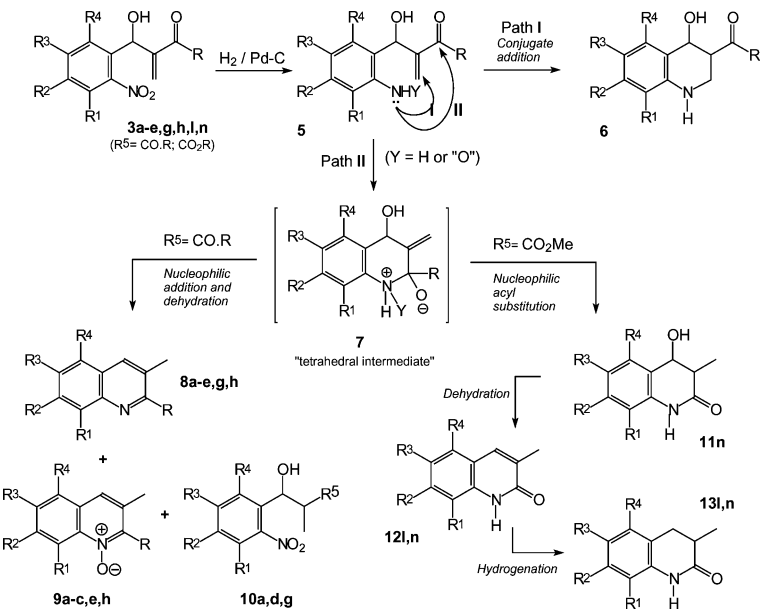


1a-i **2a-f** **3a-r**

	R^1	R^2	R^3	R^4		R^5
a	H	H	H	H	**a**	CO.Me
b	H	H	Cl	H	**b**	CO.Et
c	H	H	OH	H	**c**	CO_2Me
d	OMe	H	H	H	**d**	CO_2Et
e	H	H	H	Cl	**e**	CN
f	H	OMe	OMe	H	**f**	SO_2Ph
g	H	-OCH_2O-		H		
h	H	NO_2	H	H		
i	H	H	H	NO_2		

	R^1	R^2	R^3	R^4	R^5	Yield/%
a	H	H	H	H	CO.Me	75
b	H	H	Cl	H	CO.Me	100
c	H	H	OH	H	CO.Me	33
d	OMe	H	H	H	CO.Me	24
e	H	H	H	Cl	CO.Me	85
f	H	OMe	OMe	H	CO.Me	73
g	H	-OCH_2O-		H	CO.Me	60
h	H	H	H	H	CO.Et	62
i	H	H	H	Cl	CO.Et	25
j	OMe	H	H	H	CO.Et	90
k	H	H	H	NO_2	CO.Et	0
l	H	H	H	H	CO_2Me	54
m	H	OMe	OMe	H	CO_2Me	14
n	H	H	Cl	H	CO_2Me	51
o	H	NO_2	H	H	CO_2Me	92
p	H	H	H	H	CO_2Et	95
q	H	H	H	H	CN	38
r	H	H	H	H	SO_2Ph	32

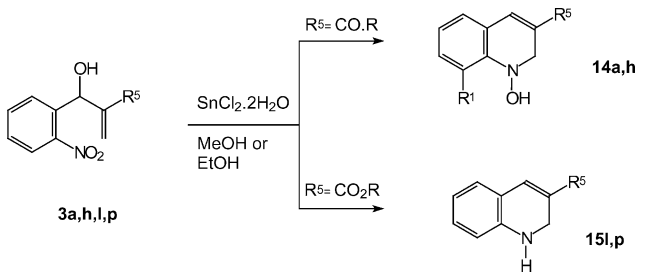
Scheme 1



Scheme 2

3 (R^5 = CO_2R) behave similarly but cyclisation affords the dihydroquinoline derivatives **15**. Stannous chloride presumably not only serves to reduce the nitro group but also to coordinate with the hydroxyl group, thus facilitating cyclisation *via* the S_N' pathway.

Given the formation of both quinolines and quinoline-*N*-oxides on catalytic hydrogenation of ketone precursors (Scheme 2), methods for interconverting these products were explored. Treatment of 2,3-dimethylquinoline **8a** with *m*-chloroperbenzoic acid (MCPBA) in chloroform[23] afforded the corresponding *N*-oxide

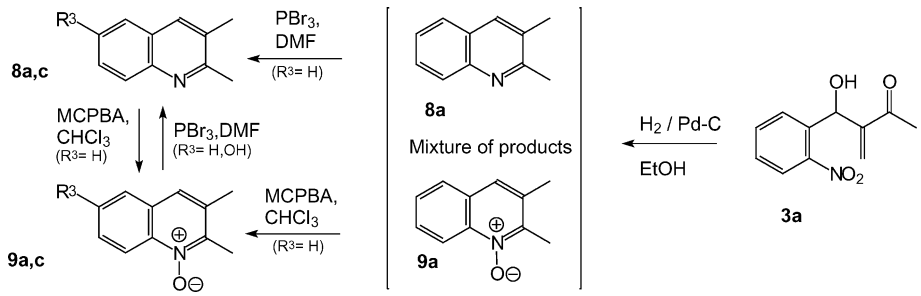


Scheme 3

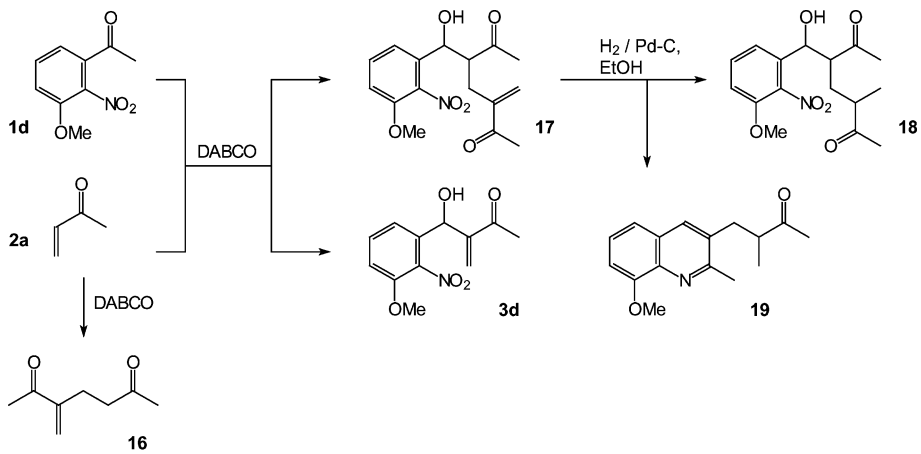
9a in 78% yield, while the *N*-oxide **9a** was readily converted to the quinoline **8a** in 79% yield on treatment with phosphorus tribromide in *N*,*N*-dimethylformamide (DMF).[24] In order to demonstrate "direct" syntheses of *either* the quinoline *or* the quinoline-*N*-oxide derivatives from the Baylis–Hillman precursor **3a**, crude mixtures of both products were treated (i) with PBr_3 to afford the quinoline **8a** in 86% yield; and (ii) with MCPBA to afford the quinoline-*N*-oxide **9a** in 85% yield (Scheme 4).

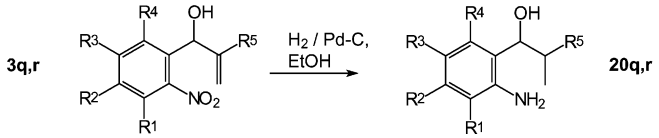
A number of unexpected side reactions have also been observed. Thus, reaction of 8-methoxy-2-nitrobenzaldehyde **1d** with MVK **2a** afforded the Baylis–Hillman product **3d** in only 24% yield, the major product (60%) being the bis-MVK adduct **17** (Scheme 5). Shi *et al.*[25] have reported the formation of similar adducts in DABCO- or 4-(dimethylamino)pyridine (DMAP)-catalysed reactions of certain arylaldehydes with MVK, and noted that the yields of the adducts could be enhanced by increasing the concentration of MVK. Interestingly, however, Shi *et al.*[25] found (in line with our own observations) that 2-nitrobenzaldehyde **1a** failed to afford the bis-MVK adduct, the sole product being the normal Baylis–Hillman adduct **3a**. It seems that the presence of the 3-methoxy group is a critical factor in the formation of the bis-MVK adduct **17**, and detailed mechanistic and theoretical studies are now being undertaken to explore substituent effects on these transformations. The formation of the MVK dimer **16** in Baylis–Hillman reactions involving MVK is well known.[26]

Catalytic hydrogenation of the bis-MVK adduct **17** gave a mixture of the acyclic diketone **18** (43%) and the quinoline derivative **19** (7%). The latter product arises from tandem (in uncertain order!) reduction of the nitro group, cyclisation *via* condensation of the resulting amino group with the unconjugated ketone, hydrogenation of the conjugated alkene and dehydration to afford the aromatic quinoline. Simple catalytic hydrogenation of the conjugated alkene moiety in the substrate **17** would account for the formation of the dominant, acyclic product **18**; similar



Scheme 4





Scheme 5

hydrogenation of the alkene moiety in the Baylis–Hillman adducts **3a**, **d** and **g** has already been noted (Scheme 2). However, catalytic hydrogenation of the cyano- and phenylsulfonyl derivatives, **3q** and **3r** respectively, results in reduction of *both* the alkene *and* the nitro moieties (presumably in that order) to afford the corresponding acyclic systems **20** as the sole products.

In summary, it is apparent that, while competing reactions have been observed, cyclisation of the initial Baylis–Hillman adducts **3** provides convenient access to a range of quinoline derivatives and that significant chemoselectivity can be achieved by judicious choice of the reactants and reagent systems. Thus, catalytic hydrogenation of ketone precursors **3** (R^5 = CO.R; Scheme 6) yields quinolines **8** and quinoline-*N*-oxides **9** *via* nucleophilic carbonyl addition and dehydration, whereas ester precursors **3** (R^5 = CO_2R) afford quinolone derivatives **11–13** *via* acyl substitution. Reduction with $SnCl_2{\cdot}2H_2O$, on the other hand, favours cyclisation *via* conjugate addition to give 1,2-dihydropyridine derivatives **14** or **15**. However, it should be noted that, in most cases, reaction conditions have not been optimised and it is likely that product yields, in general, could be improved.

Experimental

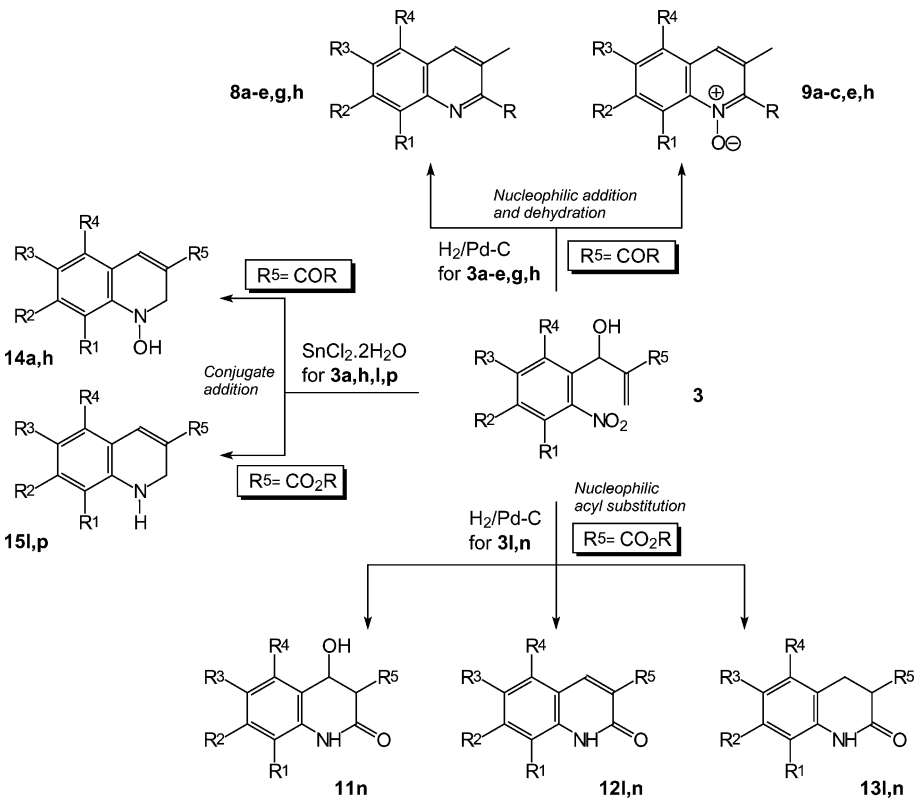
Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. 400 MHz ^{1}H and 100 MHz ^{13}C NMR spectra were recorded on Bruker AMX400 or AVANCE 400 MHz spectrometers at 303 K in $CDCl_3$ (or, where specified, in DMSO-d_6), and calibrated using solvent signals. Infrared spectra were recorded on a Perkin Elmer FT-IR spectrum 2000 spectrometer. Low-resolution (EI) mass spectra were obtained on a Finnigan-Mat GCQ mass spectrometer and high-resolution (EI) mass spectra on a VG70-SEQ double-focusing magnetic sector spectrometer (Cape Technikon Mass Spectrometry unit or Department of Chemistry, University of the Witwatersrand). The general synthetic procedures are illustrated by the following examples.

4-Hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one 3a

A solution of 2-nitrobenzaldehyde **1a** (10.0 g, 66.0 mmol), methyl vinyl ketone **2a** (6.99 g, 99.0 mmol), DABCO (0.37 g, 3.3 mmol) in $CHCl_3$ (2 mL) was stirred in a stoppered flask at room temperature for 7 days. The solvent was evaporated from the resulting mixture *in vacuo*, and the crude product was purified by flash chromatography on silica [using EtOAc–hexane (1 : 3)] to afford, as yellow-brown crystals, 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **3a** (11.2 g, 75%), mp 79.5–82.5 °C (lit.[17] 94–95 °C)[27] (Found, M^+: 221.06672. Calc. for $C_{11}H_{11}NO_4$: M, 221.06881); ν_{max}(KBr)/cm^{-1} 3361 (OH) and 1665 (C=O); δ_H 2.34 (3H, s, CH_3), 3.29 (1H, br s, OH), 5.77 and 6.15 (2H, 2 × s, CH_2) and 6.20 (1H, s, CH), 7.43 (1H, t, *J* 7.2 Hz, 4′-H), 7.62 (1H, t, *J* 7.2 Hz, 5′-H), 7.74 (1H, d, *J* 8.0 Hz, 6′-H) and 7.92 (1H, d, *J* 8.0 Hz, 3′-H); δ_C 26.4 (C-1), 67.9 (C-4), 124.6, 126.8, 128.9, 129.3, 133.8, 136.4, 148.1 and 148.9 (C=CH_2 and Ar–C) and 199.8 (C=O); *m*/*z* 221 (M^+, 0.2%) and 43 (100).

Catalytic hydrogenation of 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one 3a

4-Hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **3a** (1.00 g, 4.50 mmol) was dissolved in ethanol (50 mL), 10% Pd–C catalyst (0.16 g) was added, and the reaction mixture was stirred vigorously



Scheme 6

under hydrogen at atmospheric pressure for 1.5 hours. The solvent was evaporated *in vacuo*, and the crude product was dissolved in CH_2Cl_2, dried (anhyd. $MgSO_4$) and finally purified by flash chromatography on silica [elution with hexane–EtOAc (3 : 1)] to afford three fractions.

Fraction 1. As light yellow crystals, 2,3-dimethylquinoline **8a**[31] (0.13 g, 14%), mp 69–70 °C (Found, M^+: 157.08826. Calc. for $C_{11}H_{11}N$: M, 157.08915); ν_{max}(KBr)/cm^{-1} 1663 (N=C); δ_H 2.42 and 2.67 (6H, 2 × s, 2 × CH_3), 7.43 (1H, t, *J* 7.6 Hz, 6-H), 7.58 (1H, t, *J* 7.6 Hz, 7-H), 7.68 (1H, d, *J* 8.0 Hz, 5-H), 7.80 (1H, s, 4-H) and 7.99 (1H, d, *J* 8.0 Hz, 8-H); δ_C 19.7 and 24.2 (2 × CH_3), 124.9, 125.8, 126.8, 128.4, 128.5, 130.4, 135.8, 146.2 and 159.1 (Ar–C); *m*/*z* 157 (M^+, 100%).

Fraction 2. As reddish-brown oil, 4-hydroxy-3-methyl-4-(2-nitrophenyl)butan-2-one **10a** (0.108 g, 8%) (lit.[26] not detailed); ν_{max}(KBr)/cm^{-1} 3390 (OH) and 1715 (C=O); δ_H 1.18 (3H, d, *J* 7.2 Hz, C*H*$_3$CH), 2.12 (3H, s, CH_3CO), 3.09 (1H, m, 3-H), 3.83 (1H, br s, OH), 5.39 (1H, d, *J* 6.0 Hz, 4-H), 7.43 (1H, t, *J* 7.2 Hz, 5′-H), 7.61 (1H, t, *J* 7.6 Hz, 4′-H), 7.67 (1H, d, *J* 6.8 Hz, 3′-H) and 7.91 (1H, d, *J* 8.4 Hz, 6′-H); δ_C 14.6 (*C*H$_3$CH), 30.3 (*C*H$_3$CO), 51.9 (C-3), 71.4 (C-4), 124.5, 128.5, 128.7, 133.3, 137.4 and 139.9 (Ar–C) and 213.5 (C=O).

Fraction 3. As brown crystals, 2,3-dimethylquinoline-*N*-oxide **9a**[9] (0.59 g, 66%), mp 123–125 °C (Found, M^+: 173.08338. Calc. for $C_{11}H_{11}NO$: M, 173.08406); ν_{max}(KBr)/cm^{-1} 1650 (N=C) and 1318 (N–O); δ_H 2.45 and 2.68 (6H, 2 × s, 2 × CH_3), 7.45 (1H, s, 4-H), 7.51 (1H, t, *J* 7.6 Hz, 6-H), 7.63 (1H, t, *J* 7.6 Hz, 7-H), 7.68 (1H, d, *J* 8.0 Hz, 5-H) and 8.68 (1H, d, *J* 8.8 Hz, 8-H); δ_C 14.7 and 20.2 (2 × CH_3), 119.6, 125.1, 127.1, 127.7, 128.1, 129.2, 130.8, 139.9 and 146.4 (Ar–C); *m*/*z* 173 (M^+, 70%) and 156 (100).

Stannous chloride reduction of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate 3l

To a solution of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **3l** (1.19 g, 5.0 mmol) was added a solution of $SnCl_2 \cdot 2H_2O$ (5.64 g, 25 mmol) in MeOH (10 mL). The resulting mixture was stirred at 70 °C for 5 h and then, after cooling, poured into ice, basified (pH 7–8) using aq. $NaHCO_3$, and extracted repeatedly with EtOAc. The combined organic extracts were washed (satd. aq. NaCl) and dried (anhyd. Na_2SO_4). Evaporation of the solvent *in vacuo* afforded the crude product, which was purified by flash chromatography on silica [elution with hexane–EtOAc (1 : 3)] to give methyl 1,2-dihydroquinoline-3-carboxylate **15l**, as an off-white powder (0.47 g, 50%), mp 175–177 °C (Found M^+: 189.07852. $C_{11}H_{11}NO_2$ requires M, 189.07898); δ_H 3.55 (3H, s, CH_3), 4.56 (2H, s, CH_2), 7.21 (1H, m, Ar–H), 7.45 (1H, m, Ar–H), 7.47 (1H, m, Ar–H), 7.55 (1H, d, Ar–H), 7.87 (1H, s, 4-H) and 12.27 (1H, br s, NH); δ_C 59.0 (CH_3), 69.3 (C-2), 115.8, 120.0, 122.6, 127.6, 129.9, 130.0, 136.3 and 137.6 (C=CH and Ar–C) and 163.2 (C=O); *m*/*z* 189 (M^+, 18%) and 159 (100).

Compounds **3b**,[28] **3d**,[29] **3f**,[17] **3h**,[17] **3l**,[17] **3n**,[15] **3o**,[30] **3p**,[17] **8b**,[31] **8d**,[32] **8g**,[33] **8h**,[34] **9a**,[35] **9h**,[36] **12l**,[37] **12n**,[38] **13l**[39] and **13n**[40] have also been reported by other researchers; data for compound **9a** were also reported in our preliminary communication.[9] Analytical data for other products are provided as Electronic Supplementary Information (ESI)†.

Interconversion of quinolines and quinoline-*N*-oxides

2,3-Dimethylquinoline 8a. To a stirred solution of the quinoline-*N*-oxide **9a** (0.27 g, 1.6 mmol) and DMF (8 mL) at room temperature under nitrogen was added PBr_3 (0.69 mL, 2.4 mmol), and the stirring was continued for 1 hour. The reaction mixture was poured into a mixture of satd. aq. $NaHCO_3$ (40 mL) and ice (10 g) and the resulting mixture extracted with EtOAc (3 × 20 mL). The extracts were combined, washed with satd. aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* to give the quinoline **8a** in 79% yield.

6-Hydroxy-2,3-dimethylquinoline 8c. The general procedure described for the conversion of the quinoline-*N*-oxide **9a** to 2,3-dimethylquinoline **8a** was followed, using 6-hydroxy-2,3-dimethylquinoline-*N*-oxide **9c** (0.22 g, 1.13 mmol), DMF (8 mL) and PBr_3 (0.49 mL, 1.72 mmol) to give the quinoline **8c** in 70% yield.

2,3-Dimethylquinoline-*N*-oxide 9a. To a stirred solution of 2,3-dimethylquinoline **8a** (0.1 g, 0.6 mmol) in $CHCl_3$ (0.6 mL) was added MCPBA (0.11 g, 0.64 mmol) portionwise during 3 min at room temperature. The mixture was stirred for 24 hours, following which, excess MCPBA was destroyed (as indicated by wet starch-iodide paper) by the addition of solid $Na_2S_2O_5$. *m*-Chlorobenzoic acid was precipitated from the solution as the potassium salt by the addition, with stirring, of solid K_2CO_3. The solids were removed by filtration, and the solvent was removed from the filtrate *in vacuo* to give a yellow solid. ^{1}H NMR analysis revealed the presence of some unreacted starting material, and further MCPBA (0.1 g) was added and the mixture stirred for another 24 hours. After work-up, 2,3-dimethylquinoline-*N*-oxide **9a** was obtained as a yellow powder (0.09 g, 78%).

Selective *in situ* oxygenation and deoxygenation reactions

A mixture of 3-hydroxy-2-methylene-3-(2-nitrophenyl)butan-2-one **3a** (0.50 g, 2.3 mmol) and 10% Pd–C catalyst (40 mg) in methanol (40 mL) was subjected to hydrogenation (following the general method) for 3 h. The catalyst was filtered off and the solvent evaporated from the filtrate *in vacuo.* The residue was dissolved in CH_2Cl_2, dried (anhydrous $MgSO_4$), and the solvent evaporated *in vacuo* to afford, as a brown oil, a mixture of 2,3-dimethylquinoline **8a** and 2,3-dimethylquinoline-*N*-oxide **9a** (0.41 g).

Formation of 2,3-dimethylquinoline-*N*-oxide 9a from the mixture of 8a and 9a. To a stirred solution of the foregoing mixture (0.135 g) of 2,3-dimethylquinoline **8a** and 2,3-dimethylquinoline-*N*-oxide **9a** in $CHCl_3$ (0.5 mL) was added MCPBA (0.107 g), portionwise, over 15 minutes at room temperature. The mixture was stirred for 24 hours, before excess MCPBA was destroyed by the addition of solid $Na_2S_2O_5$. *m*-Chlorobenzoic acid was precipitated from solution as the potassium salt by the addition of solid K_2CO_3. The solids were removed by filtration and the filtrate dried ($MgSO_4$); the solvent was removed *in vacuo* to give, as yellow crystals, 2,3-dimethylquinoline-*N*-oxide **9a** (0.116 g, 85%)

Formation of 2,3-dimethylquinoline 8a from the mixture of 8a and 9a. A mixture (0.125 g) of 2,3-dimethylquinoline **8a** and 2,3-dimethylquinoline-*N*-oxide **9a** in DMF (3 mL) was stirred at room temperature. PBr_3 (0.2 mL, 0.7 mmol) was added and

stirring continued for 1 hour. The mixture was poured into satd. aq. $NaHCO_3$, and the resulting mixture extracted with EtOAc (3 × 20 mL). The extracts were combined, washed with satd. aq. $NaHCO_3$ and brine, dried (anhyd. $MgSO_4$) and filtered. The solvent was removed from the filtrate *in vacuo* to give, as yellow crystals, 2,3-dimethylquinoline **8a** (0.107 g, 86%).

Acknowledgements

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