Isoquinoline synthesis by C-H activation/annulation using vinyl acetate as an acetylene equivalent

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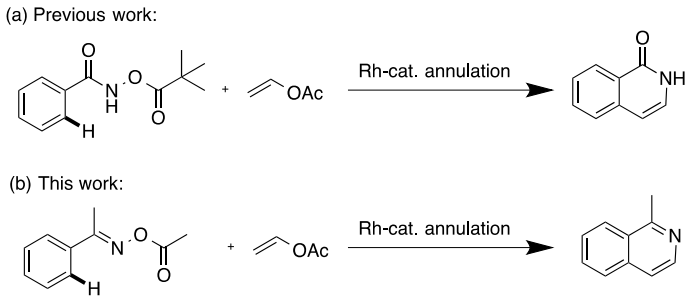
Abstract: Vinyl acetate is used as an acetylene equivalent in rhodium(III)-catalysed C-H activation/annulation with aryl ketoxime esters. Extension to an aldoxime ester allows for a concise formal synthesis of decumbenine B.

1. Introduction

Isoquinolines are prevalent scaffolds in pharmaceutical agents, natural products and other fine chemicals.[1-5] Traditional syntheses of isoquinolines include the well-established Bischler-Napieraski,[6] Pictet-Spengler,[7] Pictet-Gams,[8] and Pomeranz-Fritsch[9] reactions: in each case the precursors are monosubstituted aromatic compounds, but the key cyclisation step proceeds *via* an S_EAr mechanism, which inherently limits the substrate scope to relatively electron-rich aromatic substrates. Alternative approaches have been developed which circumvent this limitation e.g. condensation/cyclisation of 2-azidocinnamates with α-diazocarbonyl compounds,[10] reaction of benzynes with enamides,[11] or cyclisation of aryl imines bearing *ortho*-alkenyl or alkynyl functionality,[12] but at the expense of more complex or less readily available starting materials which may require multi-step syntheses.

The recent development of metal-catalysed C-H activation/annulation cascades[13] has enabled the synthesis of polysubstituted isoquinolines from simple aryl imine derivatives and alkynes.[14-19] The reactions can be carried out under rhodium,[14,15] ruthenium,[16] cobalt[17,18] or manganese[19] catalysis, and can be run either using N-H imines in the presence of external oxidants[14,17] or alternatively using derivatives (oximes, oxime ethers and esters, hydrazones or sulfinyl imines) wherein cleavage of an *N*-heteroatom bond serves as an internal oxidant.[15,16,18,19] The majority of these methods, however, are limited to the use of internal alkynes and so generate 3,4-disubstituted isoquinolines. Alternative strategies utilizing 1,3-dienes[20] or ketoximes[21] in place of alkynes have been introduced which allow access to 4-unsubstituted isoquinolines. However, many biologically-interesting molecules feature 3,4-unsubstituted isoquinolines,[1-5] which would require either the development of a method employing acetylene gas (with associated hazards) or the development of a synthetic equivalent.

We recently reported that rhodium-catalysed C-H activation/annulation of benzoyl hydroxamic esters[22] with vinyl acetate generated 3,4-unsubstituted isoquinolones,[23] wherein the vinyl acetate had acted as a convenient acetylene equivalent (Scheme 1a).[24-26]



Scheme 1. Vinyl acetate as an acetylene surrogate in C-H activation/annulation reactions.

Subsequently, Yu and Cheng reported that internally-substituted vinyl acetates react with acetophenone oxime esters under rhodium catalysis facilitating access to 3-substituted quinolines.[27] In this paper, they also disclosed that vinyl acetate itself could be used as a reagent, generating 3,4-unsubstituted isooquinolines, exemplified in a synthesis of the alkaloid papaverine. This prompts us to report our own work on the use of vinyl acetate as an acetylene equivalent in the synthesis of isquinolines (Scheme 1b). Specifically, under complementary conditions to those employed by Yu and Cheng, we probe the regiochemical preferences of the reaction of non-symmetrically substituted aroyl oxime esters. We also describe the first application of aldoxime esters in this transformation, demonstrated in a formal synthesis of decumbenine B.

2. Results/discussion

To commence our study, the ketoximes **1**-**4a** were examined using the reaction conditions we previously employed in the synthesis of isoquinolones, using 1 mol% $[Cp^*RhCl_2]_2$ with 0.3 equivalents of cesium acetate as base in MeOH at 45 °C for 24h (Table 1, entries 1-4).[23] After 24 hours the reactions still contained unreacted starting material, and so were left for 48h. Disappointingly, all four ketoximes produced <5% of the corresponding isoquinoline **5a**. In the case of substrates **3** and **4**, the remaining starting material had hydrolysed to give the ketoxime **1**.

Table 1

Optimisation of the C-H activation/annulation

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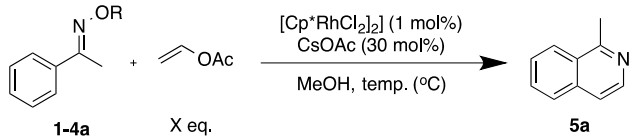


1-4a X eq. 5a

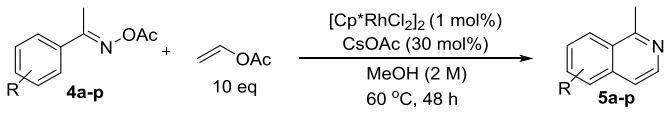
Entry[a]	Oxime	R	X(eq.)	Conc. (M)	Temp. (°C)	Yield (%)[b]
1	1	H	1.5	0.2	45	5
2	2	Me	1.5	0.2	45	0
3	3	Piv	1.5	0.2	45	5
4	4a	Ac	1.5	0.2	45	3
5	1	H	1.5	0.2	60	4
6	2	Me	1.5	0.2	60	0
7	3	Piv	1.5	0.2	60	4
8	4a	Ac	1.5	0.2	60	24
9	4a	Ac	1.5	0.2	60	2[c]
10	4a	Ac	1.5	0.2	60	0[d]
11	4a	Ac	1.5	2.0	60	19
12	4a	Ac	5	2.0	60	48
13	4a	Ac	10	2.0	60	79
14	4a	Ac	20	2.0	60	30
15	4a	Ac	10	1.0	60	56

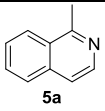
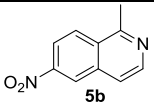
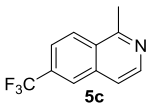
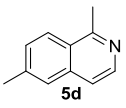
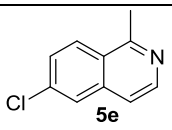
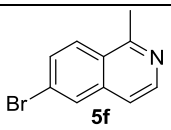
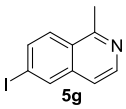
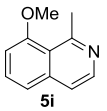
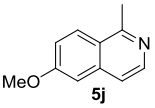
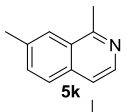
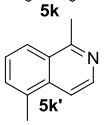
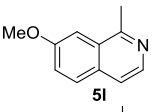
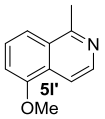
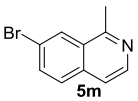
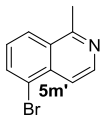
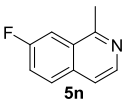
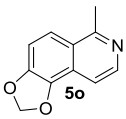
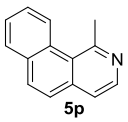
[a] Standard conditions: $[Cp^*RhCl_2]_2$ (1 mol%), CsOAc (0.3 eq.), MeOH, 48 h. [b] ^1H NMR yield using trimethoxybenzene as an internal standard. [c] using CsOAc (1 eq.) as base. [d] using K_2CO_3 (1 eq.) as base.

Increasing the temperature to 60 °C improved the yield of the reaction of the *O*-acetylated oxime **4a** from 3% to 24% (entry 8). Proceeding with *O*-acetylated ketoxime **4a**, increasing the equivalents of caesium acetate base to one equivalent had a detrimental effect on yield, as did use of potassium carbonate which had been successfully employed by Fagnou in related annulations (entries 9 and 10).[22a] Increasing the concentration of the reaction and equivalents of vinyl acetate resulted in an increase in yield, with the optimum yield of **5a** of 79% obtained with ten equivalents at 2M (entry 13). Further increasing the amount of vinyl acetate (entry 14) or lowering the reaction concentration (entry 15) were deleterious. Comparing our optimized conditions with those of Yu and Cheng,[27] significantly we are operating at a fourfold lower loading ot the precious metal catalyst, and also employing a more economic base (caesium versus silver(I) acetate) and operating at a lower temperature, albeit at a longer reaction time.

Table 2

Scope of the C-H activation/annulation



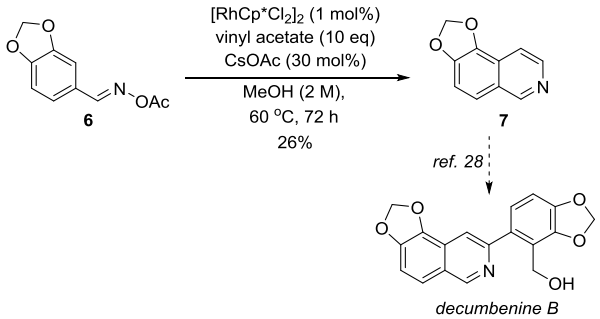
Entry	Product	Yield	Entry	Product	Yield
1	 5a	57	2	 5b	83
3	 5c	82	4	 5d	44
5	 5e	60	6	 5f	72
7	 5g	64	8	 5h	41
9	 5i	14	10	 5j	9[a]
11	 5k  5k'	52% (10:1)	12	 5l  5l'	58% (1:1.4)
13	 5m  5m'	50% (2.7:1)	14	 5n  5n'	47% (1:5)
15	 5o	36	16	 5p	24

[a] reaction run for 24h

With our optimized conditions in hand, we sought to establish the scope of the reaction utilizing a broad range of substrates, the results of which are summarized in Table 2. The isolated yield of the parent 2-methylisoquinoline **5a** was 57%. Electron-withdrawing substituents had a beneficial effect on yield, with the *p*-nitro- and *p*-trifluoromethyl substrates giving 83% and 82% yields of **5b**/**c** respectively. In contrast, the presence of an electron-donating *p*-methyl group returned a lower yield of 44%. Halogens were well tolerated, with 8-fluoro- and 6-chloro-, bromo-, and iodoisoquinolines **5e-h** being formed in reasonable to good yields (41-72%).

We next probed regioselectivity with *meta*-substituted substrates. The *meta*-methyl substrate **4k** returned a 52% yield of a 10:1 mixture of the C7/C5-isomers **5k**/**5k'**, presumably driven by steric effects. However, the *meta*-methoxy substrate **4l** produced a 1.4:1 mixture in favour of the C5 isomer of **5l'** in 58% yield. In this case, it is likely that the acidifying effect of the methoxy group on the *ortho*-hydrogens compensates for the steric effects.[22a,23] In line with this observation, the *meta*-bromo substrate **4m** favoured production of the C7 isomer (2.7:1) with steric effects dominating, whereas the smaller, more strongly acidifying fluoride substituent in **4n** returned a 5:1 mixture in favour of the C5 product. We reasoned that reducing the steric influence of the oxygen substituent by constraining it as part of a methylenedioxy unit would allow the electronic influence to dominate, and were gratified to find that isoquinoline **5o** was formed as a single isomer in 36% yield. Finally, the presence of additional ring fusion was tolerated, with the naphthyl substrate **4p** generating benzoisoquinoline **5p**, albeit in modest yield.

Encouraged by the formation of a single regioisomer in the case of the methylenedioxy-substituted **5o**, we were interested to apply the methodology to the corresponding aldoxime **6** in the hope of preparing the isoquinoline intermediate **7**. Compound **7** has previously been prepared as an intermediate[28] in the synthesis of decumbenine B, a naturally occurring alkaloid used for the treatment of hypertension, rheumatoid arthritis and sciatic neuraligia.[29] The five step route developed by Orito *et al.*[28] involves a key Pictet-Gams cyclisation to afford the isoquinoline **7** in a yield of 25% over five steps. However, to our knowledge, aldoxime derivatives have not yet been employed in direct isoquinoline annulation reactions, and this provided an ideal opportunity to test their suitability. By application of our standard conditions, we were able to convert the aldoxime **6** to the corresponding isoquinoline as a single regioisomer, with a yield of 26% (21% over three steps from piperonal; Scheme 2).



Scheme 2. C-H activation/annulation reaction of aldoxime esters.

Attempts to optimize the conditions further by increasing the catalyst and base loading proved unsuccessful, with elimination of acetic acid to give the corresponding nitrile being a significant competing process. Employing the pivaloyl oxime ester (in the hope that the less acidic pivalic acid would prove a worse leaving group and slow elimination) was also unsuccessful. Nevertheless, the formation of **7** shows for the first time that aldoxime esters are capable directing groups for rhodium-catalysed C-H activation and that the electronic directing effect of the methylenedioxy group translates from the ketoxime series.

3. Conclusion

In conclusion, a C-H activation protocol has been developed for the synthesis of seventeen 3,4-unsubstituted isoquinolines. The synthetic utility of vinylic esters as acetylene synthons continues to find applicability in C-H activation chemistry. A three-step synthesis of a known intermediate **7** in the synthesis of decumbenine B has additionally demonstrated that aldoximes are viable substrates for such C-H activation/annulation processes.

4. Experimental

The ketoximes **4** were made according to the procedure outlined by Chiba *et al.*[15a] Chromatography: Column chromatography was peformed with Fischer Matrix silica gel (35-70 μm particles). SCX catridges: Biotage Isolute SPE Columns 5g SCX-2 25 mL columns were used. Chemical shifts (δ) and coupling constants (J) were expressed as parts per million and Hertz, respectively. Proton (^{1}H) and carbon (^{13}C{^{1}H}) nuclear magnetic resonance spectra were recorded using a Bruker DPX 300, a Bruker DRX 500 or a Bruker Avance 500 spectrometer using an internal deuterium lock. High resolution electrospray mass spectra (ESI-MS) were measured on a Bruker MicroTOF-Q or Bruker MaXis Impact spectrometer in positive mode.

General procedure for the synthesis of isoquinolines: Vinyl acetate (922 μL, 10.0 mmol) was added to a solution of the acetylated oxime (1 mmol) in MeOH (0.5 mL, 2 M) with CsOAc (58 mg, 0.3 mmol) and $[Cp^*RhCl_2]_2$ (6 mg, 0.01 mmol) in a septum-topped vial under nitrogen. The reaction vials were sealed and heated to 60 °C for 48 hours. The crude reaction mixture was loaded on to a 5 g SCX column that was subsequently washed with MeOH (2 × 25 mL). The product eluted with the secondary wash using 0.7 M NH_3 in MeOH (2 × 25 mL) to give the clean product (>90% purity). Products containing impurities were purified using flash silica chromatography.

1-Methylisoquinoline (5a) The desired compound was isolated as a brown oil (82 mg, 57%) from (*E*)-acetophenone *O*-acetyl oxime (177 mg, 1.00 mmol) following the general procedure. δ_H (300 MHz, $CDCl_3$) 8.37 (1H, d, *J* 5.7), 8.08 (1H, d, *J* 7.6), 7.77 (1H, d, *J* 7.8 Hz), 7.68-7.60 (1H, m), 7.60-7.52 (1H, m, H), 7.48 (1H, d, *J* 5.8), 2.94 (3H, s); δ_C (75 MHz, $CDCl_3$) 158.6 (C), 141.8 (CH), 135.8 (C), 129.9 (CH), 127.2 (2 signals, C and CH), 127.0 (CH), 125.6 (CH), 119.3 (CH), 22.4 (CH_3); LRMS (ESI$^+$): *m/z* 144.0 [MH$^+$]; IR (ν_{max}, film, cm^{-1}) 2968, 1623, 1563, 1391. Data consistent with the literature.[30]

1-Methyl-6-nitroisoquinoline (5b) The desired compound was isolated as a brown oil (156 mg, 83%) from (*E*)-1-(4-nitrophenyl)ethanone *O*-acetyl oxime (222 mg, 1.00 mmol) following the general procedure. δ_H (300 MHz, $CDCl_3$) 8.72 (1H, d, *J* 2.0), 8.56 (1H, d, *J* 5.8), 8.36-8.24 (2H, m), 7.69 (1H, d, *J* 5.8), 3.02 (3H, s); δ_C (75 MHz, $CDCl_3$) 159.3 (C), 148.0 (C), 143.9 (CH), 135.2 (C), 129.1 (C), 127.8 (CH), 123.5 (CH), 120.4 (2 signals, 2 x CH), 22.7 (CH_3); HRMS (ESI$^+$): *m/z* calculated for formula $C_{10}H_9N_2O_2$ [MH$^+$] 189.0659; found 189.0660; IR (ν_{max}, solid, cm^{-1}) 3074, 1535, 1344, 906.

1-Methyl-6-(trifluoromethyl)isoquinoline (5c) The desired compound was isolated as a brown oil (174 mg, 82%) from (*E*)-1-(4-(trifluoromethyl)-phenyl)ethanone *O*-acetyl oxime (245 mg, 1.00 mmol) following the general procedure. δ_H (300 MHz, $CDCl_3$) 8.49 (1H, d, *J* 5.8), 8.22 (1H, d, *J* 8.8), 8.09 (1H, dt, *J* 1.9, 1.0), 7.75 (1H, dd, *J* 8.8, 1.8), 7.57 (1H, d, *J* 5.8), 2.99 (3H, s); δ_C (75 MHz, $CDCl_3$) δ 158.9 (C), 143.2 (CH), 135.0 (C), 131.6 (q, *J* 32.6, C), 128.3 (C), 126.9 (CH), 124.9 (q, *J* 4.4, CH), 123.9 (q, *J* 271.0, C), 122.7 (q, *J* 3.1, CH), 119.6 (CH), 22.4 (CH_3); HRMS (ESI$^+$): *m/z* calculated for formula $C_{11}H_9F_3N$ [MH$^+$] 212.0682; found 212.0690; IR (ν_{max}, solid, cm^{-1}) 3060, 1590, 1574, 1340, 1237, 1127.

1,6-Dimethylisoquinoline (5d) The desired compound was isolated as a brown oil (69 mg, 44%) from (*E*)-1-(*p*-tolyl)ethanone *O*-acetyl oxime (191 mg, 1.00 mmol) following the general procedure. δ_H (300 MHz, $CDCl_3$) 8.32 (1H, d, *J* 5.9), 8.00 (1H, d, *J* 8.6), 7.56 (1H, s), 7.47-7.39 (2H, m), 2.95 (3H, s), 2.53 (3H, s); δ_C (75 MHz, $CDCl_3$) 158.0 (C), 141.0 (CH), 140.6 (C), 136.4 (CH), 129.6 (C), 126.2 (CH), 125.8 (C), 125.6 (CH), 119.2 (CH), 21.9 (CH_3), 21.7 (CH_3); HRMS (ESI$^+$): *m/z* calculated for formula $C_{11}H_{12}N$ [MH$^+$] 158.0964; found 158.0962; IR (ν_{max}, solid, cm^{-1}) 1643, 1631, 1403, 1258, 1037.

6-Chloro-1-methylisoquinoline (5e) The desired compound was isolated as a brown oil (106 mg, 60%) from (*E*)-1-(4-chlorophenyl)ethanone *O*-acetyl oxime (211 mg, 1.00 mmol) following the general procedure. δ_H (300 MHz, $CDCl_3$) 8.40 (1H, d, *J* 5.8), 8.04 (1H, d, *J* 9.0), 7.77 (1H, d, *J* 2.1), 7.52 (1H, dd, *J* 9.0, 2.1), 7.41 (1H, d, *J* 5.8), 2.93 (3H, s); δ_C (75 MHz, $CDCl_3$) 158.7 (C), 143.0 (CH), 136.8 (C), 136.1 (C), 128.0 (CH), 127.4 (CH), 125.9 (CH), 125.7 (C), 118.4 (CH), 22.4 (CH_3); HRMS (ESI$^+$): *m/z* calculated for formula $C_{10}H_9{}^{35}ClN$ [MH$^+$] 178.0418;

found 178.0421; IR (ν_{max}, solid, cm^{-1}) 3390, 3056, 1616, 1562, 1089.

6-Bromo-1-methylisoquinoline (5f) The desired compound was isolated as a brown oil (159 mg, 72%) from (*E*)-1-(4-bromophenyl)ethanone *O*-acetyl oxime (256 mg, 1.00 mmol) following the general procedure. δ_H (300 MHz, $CDCl_3$) 8.38 (1H, d, *J* 5.8), 7.96-7.90 (2H, m), 7.63 (1H, dd, *J* 9.0, 1.9), 7.38 (1H, d, *J* 5.8), 2.91 (3H, s); δ_C (75 MHz, $CDCl_3$) 158.8 (C), 142.7 (CH), 137.1 (C), 130.6 (CH), 129.3 (CH), 127.4 (CH), 125.9 (C), 124.7 (C), 118.3 (CH), 22.3 (CH_3); HRMS (ESI^+): *m/z* calculated for formula $C_{10}H_9{}^{79}BrN$ [MH^+] 221.9913; found 221.9915; IR (ν_{max}, solid, cm^{-1}) 1611, 1560, 1393, 1077.

6-Iodo-1-methylisoquinoline (5g) The desired compound was isolated as a tan crystalline solid (172 mg, 64%) from (*E*)-1-(4-iodophenyl)ethanone *O*-acetyl oxime (303 mg, 1.00 mmol) following the general procedure. The product was crystallized from EtOAc–hexane. M.p. 132-134 °C (EtOAc–hexane); δ_H (300 MHz, $CDCl_3$) 8.41 (1H, d, *J* 5.9), 8.24 (1H, d, *J* 1.1), 7.88-7.84 (2H, m), 7.42 (1H, d, *J* 5.8), 2.96 (3H, s); δ_C (75 MHz, $CDCl_3$) 158.8 (C), 142.7 (CH), 137.5 (C), 136.1 (CH), 136.0 (CH), 127.2 (CH), 126.3 (C), 118.2 (CH), 97.1 (C), 21.6 (CH_3); HRMS (ESI^+): *m/z* calculated for formula $C_{10}H_9IN$ [MH^+] 269.9774; found 269.9774; IR (ν_{max}, solid, cm^{-1}) 1607, 1558, 1392, 1072.

8-Fluoro-1-methylisoquinoline (5h) The desired product was isolated as a brown oil (66 mg, 41%) from (*E*)-1-(2-fluorophenyl)ethanone *O*-acetyl oxime (195 mg, 1.00 mmol) following the general procedure. The material was purified by column chromatography using 0-100% EtOAc in hexane without the use of an SCX column. R_F 0.73 (50% EtOAc in pentane); δ_H (300 MHz, $CDCl_3$) 8.37 (1H, d, *J* 5.8), 7.56-7.52 (2H, m), 7.45 (1H, dd, *J* 5.8, 2.7), 7.22-7.14 (1H, m), 3.05 (3H, d, *J* 7.0); δ_C (75 MHz, $CDCl_3$) 160.0 (d, *J* 256.8, C), 156.8 (d, *J* 5.9, C), 142.3 (d, *J* 1.8, CH), 138.5 (d, *J* 3.5, C), 130.4 (d, *J* 9.3, CH), 123.3 (d, *J* 4.5, CH), 118.7 (d, *J* 3.7, CH), 118.4 (d, *J* 14.1, C), 112.4 (d, *J* 23.2, CH), 26.8 (d, *J* 10.7, CH_3); HRMS (ESI^+): *m/z* calculated for formula $C_{10}H_9FN$ [MH^+] 162.0714; found 162.0709; IR (ν_{max}, film, cm^{-1}): 2932, 1629, 1565, 1385, 1346, 1325, 1260, 1223, 1118, 1017.

8-Methoxy-1-methylisoquinoline (5i) The desired product was isolated as a brown oil (23 mg, 14%) from (*E*)-1-(2-methoxyphenyl)ethanone *O*-acetyl oxime (207 mg, 1.00 mmol) following general procedure E. The material was purified by column chromatography using 0-100% EtOAc in hexane without the use of an SCX column. R_F 0.65 (50% EtOAc in pentane); δ_H (300 MHz, $CDCl_3$) 8.31 (1H, d, *J* 5.7), 7.53 (1H, t, *J* 8.0), 7.40 (1H, d, *J* 5.7), 7.32 (1H, d, *J* 7.6), 6.88 (1H, d, *J* 7.8), 3.97 (3H, s), 3.10 (3H, s); δ_C (75 MHz, $CDCl_3$) 158.6 (C), 158.2 (C), 142.1 (CH), 138.9 (C), 130.3 (CH), 120.6 (C), 119.5 (CH), 119.1 (CH), 106.4 (CH), 55.6 (CH_3), 28.9 (CH_3); HRMS (ESI^+): *m/z* calculated for formula $C_{11}H_{12}NO$ [MH^+] 174.0913; found 174.0910; IR (ν_{max}, film, cm^{-1}): 2970, 2934, 1619, 1561, 1457, 1359, 1344, 1327, 1272, 1231, 1067.

6-Methoxy-1-methylisoquinoline (5j) The desired compound was isolated as a brown oil (16 mg, 9%) from (*E*)-1-(4-methoxyphenyl)ethanone *O*-acetyl oxime (207 mg, 1.00 mmol) following the general procedure. δ_H (300 MHz, $CDCl_3$) 8.32 (1H, d, *J* 5.8), 8.02 (1H, d, *J* 9.2), 7.44 (1H, d, *J* 5.9), 7.23 (1H, dd, *J* 9.2, 2.6), 7.06 (1H, d, *J* 2.5), 3.95 (3H, s), 2.92 (3H, s); δ_C (75 MHz, $CDCl_3$) 160.9 (C), 157.7 (C), 141.4 (CH), 138.2 (C), 127.6 (CH), 120.0 (CH), 119.0 (CH), 104.9 (CH), 55.5 (CH_3), 21.6 (CH_3) (one C_q not observed); HRMS (ESI^+): *m/z* calculated for formula $C_{11}H_{12}NO$ [MH^+] 174.0913; found 174.0919; IR (ν_{max}, solid, cm^{-1}) 3249, 1619, 1514, 1251, 1179, 1029.

1,7-Dimethylisoquinoline (5k) and 1,5-dimethylisoquinoline (5k') The regioisomeric compounds were isolated as an inseparable 1:10 mixture of 1,5-dimethylisoquinoline (X) and 1,7-dimethylisoquinoline (X) in the form of a brown oil (82 mg, 52%) from (*E*)-1-(3-methylphenyl)ethanone *O*-acetyl oxime (193 mg, 1.00 mmol) following the general procedure. The material was purified by column chromatography using 0-100% EtOAc in hexane without the use of an SCX column. R_F 0.56 (50% EtOAc in pentane); δ_H (300 MHz, $CDCl_3$) 8.40 (0.09H, d, *J* 6.0, *H_3 minor*), 8.31 (0.91H, d, *J* 5.8, H_3), 7.96-7.91 (0.09H, m, *H_8 minor*), 7.84 (0.91H, d, *J* 1.5, H_8), 7.67 (0.91H, d, *J* 8.3, H_5), 7.60 (0.09H, d, *J* 6.1, *H_4 minor*), 7.47 (1H, dd, J 8.4, 1.5, H_6 and *H_6 or H_7 minor*), 7.44 (1H, d, *J* 5.7, H_4 and *H_6 or H_7 minor*), 2.94 (0.27H, s, *1-Me minor*), 2.91 (2.73H, s, 1-Me), 2.63 (0.27H, s, *5-Me minor*), 2.54 (2.73H, s, 7-Me); δ_C (75 MHz, $CDCl_3$) Signals for major isomer only: 157.8 (C), 140.8 (CH), 137.0 (C), 134.2 (C), 132.3 (CH), 127.7 (C), 127.1 (CH), 124.6 (CH), 119.2 (CH), 22.2 (CH_3), 22.1 (CH_3); HRMS (ESI^+): *m/z* calculated for formula $C_{11}H_{12}N$ [MH^+] 158.0964; found 158.0961; IR (ν_{max}, film, cm^{-1}): 2919, 1589, 1561, 1434, 1411, 1366, 1309, 1239.

7-Methoxy-1-methylisoquinoline (5l) and 5-methoxy-1-methylisoquinoline (5l') The ^1H NMR spectrum of the crude reaction indicated a 1:1.2 mixture of the 7-:5-methoxy-1-methylisoquinolines. Mixed fractions of 5-methoxy-1-methylisoquinoline **5l** and 7-methoxy-1-methylisoquinoline **5l'** (51 mg, 29%, 1:5) and pure fractions of 5-methoxy-1-methylisoquinoline **5l** (49 mg, 29%) were isolated in the form of brown oils (combined yield: 100 mg, 58%, 1:1.4 ratio of 7-:5-) from (*E*)-1-(3-methoxyphenyl)ethanone *O*-acetyl oxime (207 mg, 1.00 mmol) following the general procedure. The material was purified by column chromatography using 0-100% EtOAc in hexane without the use of an SCX column. **7-Methoxy-1-methylisoquinoline (5l):** R_F 0.5 (50% EtOAc in pentane); δ_H (300 MHz, $CDCl_3$) 8.27 (1H, d, *J* 5.7), 7.68 (1H, d, *J* 8.9), 7.41 (1H, d, *J* 5.7), 7.30 (1H, dd, *J* 8.9, 2.5), 7.25 (1H, d, *J* 2.5), 3.93 (3H, s), 2.89 (3H, s); δ_C (75 MHz, $CDCl_3$) 158.2 (C), 156.9 (C), 134.0 (CH), 131.4 (C), 128.8 (CH), 128.6 (C), 122.7 (CH), 119.1 (CH), 103.5 (CH), 55.5 (CH_3), 22.4 (CH_3); IR (ν_{max}, film, cm^{-1}): 2957, 2935, 2836, 1621, 1585, 1495, 1446, 1412, 1389, 1353, 1261, 1248, 1181, 1041. **5-Methoxy-1-methylisoquinoline (5l'):** R_F 0.3 (50% EtOAc in pentane); δ_H (300 MHz, $CDCl_3$) 8.38 (1H, d, *J* 5.9), 7.88 (1H, d, *J* 5.9), 7.65 (1H, d, *J* 8.5, 0.7), 7.47 (1H, t, *J* 8.1), 6.97 (1H, dd, *J* 7.7, 0.7), 3.98 (3H, s), 2.93 (3H, s); δ_C (75 MHz, $CDCl_3$) 158.0 (C), 155.0 (C), 141.5 (CH), 128.7 (C), 128.3 (C), 127.0 (CH), 117.5 (CH), 113.6 (CH), 107.4 (CH), 55.8 (CH_3), 22.8 (CH_3); HRMS (ESI^+): *m/z* calculated for formula $C_{11}H_{12}N$ [MH^+] 174.0913; found 174.0908; IR (ν_{max}, film, cm^{-1}): 2936, 2837, 1625, 1588, 1563, 1506, 1411, 1273, 1262, 1241, 1222, 1183, 1055, 1027.

7-Bromo-1-methylisoquinoline (5m) and 5-bromo-1-methylisoquinoline (5m') The regioisomeric compounds were isolated as an inseparable 1:2.7 mixture of 5-bromo-1-methylisoquinoline **5m** and 7-bromo-1-methylisoquinoline **5m'** in the form of a brown oil (131 mg, 50%) from (*E*)-1-(3-bromophenyl)ethanone *O*-acetyl oxime (256 mg, 1.00 mmol) following the general procedure. The material was purified by column chromatography using 0-100% EtOAc in hexane without the use of an SCX column. R_F 0.58 (50% EtOAc in pentane); δ_H (300 MHz, $CDCl_3$) 8.38 (1H, d, *J* 5.8), 8.20 (0.73H, d *J* 1.7), 8.03 (0.27H, dd, *J* 8.4, 0.9), 7.89 (0.27H, dd, *J* 7.5, 0.9), 7.81 (0.27H, d, *J* 6.0, H_4), 7.69 (0.73H, dd, *J* 8.7, 1.8), 7.61 (0.73H, d, *J* 8.7), 7.42 (0.73H, d, *J* 5.8), 7.37 (0.27H, t, *J* 8.0), 2.93 (0.81H, s), 2.88 (2.19H, s); δ_C (75 MHz, $CDCl_3$) 159.0 (C, *minor*), 157.8 (C, *major*), 143.0 (CH, *minor*), 142.1 (CH, *major*), 135.1 (C, *minor*), 134.4 (C, *major*), 133.8 (CH, *minor*), 133.5 (CH, *major*), 129.0 (CH, *major*), 128.6 (C, *minor*), 128.5 (C, *major*), 128.1 (CH, *major*), 127.4 (CH, *minor*), 125.4 (CH, *minor*), 122.3 (C, *minor*), 120.8 (C, *major*), 119.0 (CH, *major*), 118.2 (CH, *minor*), 22.5

(CH_3, *minor*), 22.3 (CH_3, *major*); HRMS (ESI^+): *m/z* calculated for formula $C_{10}H_9{}^{79}BrN$ [MH^+] 221.9913; found 221.9912; IR (ν_{max}, film, cm^{-1}): 2919, 1579, 1557, 1488, 1400, 1365, 1346, 1299, 1070.

7-Fluoro-1-methylisoquinoline (5n) and 5-fluoro-1-methylisoquinoline (5n') The regioisomeric compounds were isolated as an inseparable 5:1 mixture of 5-fluoro-1-methylisoquinoline **5n** and 7-fluoro-1-methylisoquinoline **5n'** in the form of a brown oil (76 mg, 47%) from (*E*)-1-(3-fluorophenyl)ethanone *O*-acetyl oxime (195 mg, 1.00 mmol) following the general procedure. The material was purified by column chromatography using 0-100% EtOAc in hexane without the use of an SCX column. R_F 0.56 (50% EtOAc in pentane); δ_H (300 MHz, $CDCl_3$) 8.42 (0.83H, d, *J* 5.9), 8.35 (0.17H, d, *J* 5.8, H), 7.85 (0.83H, d, *J* 8.5), 7.80-7.74 (0.34H, m), 7.71 (0.83H, d, *J* 5.9), 7.66 (0.17H, dd, *J* 9.9, 2.4), 7.52-7.44 (0.83H, m), 7.43-7.37 (0.17H, m), 7.30 (0.83H, dd, *J* 9.8, 7.8), 2.93 (2.49H, s), 2.88 (0.51H, s); δ_C (75 MHz, $CDCl_3$) 160.8 (d, *J* 248.8, C, *minor*), 158.4 (d, *J* 2.7, C, *major*), 158.0 (d, *J* 5.7, C, *minor*), 158.0 (d, *J* 253.3, C, *major*), 141.9 (d, *J* 1.7, CH, *major*), 141.0 (d, *J* 2.6, CH, *minor*), 133.0 (C, CH, *minor*), 129.8 (d, *J* 8.5, CH< *minor*), 128.3 (d, *J* 7.9, C, *minor*), 128.6 (d, *J* 4.6, C, *major*), 126.8 (d, *J* 7.9, CH, *major*), 126.6 (d, *J* 17.5, C, *major*), 121.4 (d, *J* 4.4, CH, *major*), 120.5 (d, *J* 25.3, CH, *minor*), 119.0 (CH, *minor*), 113.5 (d, *J* 19.2, CH, *major*), 111.9 (d, *J* 4.6, CH, *major*), 109.2 (d, *J* 21.1, CH, *minor*), 22.5 (CH_3, *major*), 22.1 (CH_3, *minor*); HRMS (ESI^+): *m/z* calculated for formula $C_{10}H_9FN$ [MH^+] 162.0714; found 162.0718; IR (ν_{max}, film, cm^{-1}): 2970, 2926, 1632, 1591, 1498, 1414, 1389, 1356, 1237, 1156.

6-Methyl-[1,3]dioxolo[4,5-*f*]isoquinoline (5o) The desired compound was isolated as a brown oil (58 mg, 36%) after column chromatography using 10-30% EtOAc in hexane, from (*E*)-1-(benzo[*d*][1,3]dioxol-5-yl)ethanone *O*-acetyl oxime (221 mg, 1.00 mmol) following the general procedure. δ_H (300 MHz, $CDCl_3$) 8.31 (1H, d, *J* 5.9), 7.74 (1H, d, *J* 8.7), 7.47 (1H, d, *J* 5.9), 7.26 (1H, d, *J* 8.7), 6.22 (2H, s), 2.92 (3H, s); δ_C (75 MHz, $CDCl_3$) 158.9 (C), 146.5 (C), 141.6 (CH), 140.8 (C), 123.9 (C), 122.0 (C), 120.6 (CH), 111.4 (CH), 110.9 (CH), 102.3 (CH_2), 23.0 (CH_3); HRMS (ESI^+): *m/z* calculated for formula $C_{11}H_{10}NO_2$ [MH^+] 188.0706; found 188.0700; IR (ν_{max}, solid, cm^{-1}) 1646, 1594, 1471, 1428, 1284, 1052.

1-Methylbenzo[*h*]isoquinoline (5p) The desired product was isolated as a brown amorphous solid (46 mg, 24%) from (*E*)- and (Z)-1-(naphthalene-1-yl)ethanone *O*-acetyl oxime (229 mg, 1.00 mmol) (*E:Z*, 3:1) following the general procedure. The material was purified by column chromatography using 0-100% EtOAc in hexane without the use of an SCX column. R_F 0.61 (50% EtOAc in pentane); δ_H (500 MHz, $CDCl_3$) 8.89 (1H, d, *J* 8.5), 8.59 (1H, d, *J* 5.3), 7.96 (1H, dd, *J* 7.8, 1.5), 7.91 (1H, d, *J* 8.7), 7.74 (1H, ddd, *J* 8.6, 7.0, 1.6), 7.67 (1H, d, *J* 8.7), 7.67 (1H, ddd, *J* 8.0, 7.1, 1.1), 7.60 (1H, d, *J* 5.3), 3.35 (3H, s); δ_C (75 MHz, $CDCl_3$) 157.0 (C), 143.1 (CH), 138.0 (C), 133.6 (C), 131.9 (CH), 130.5 (C), 129.3 (CH), 127.2 (CH), 126.8 (CH), 126.0 (CH), 125.5 (C), 120.4 (CH), 30.3 (CH_3); HRMS (ESI^+): *m/z* calculated for formula $C_{14}H_{12}N$ [MH^+] 194.0964; found 194.0961; IR (ν_{max}, film, cm^{-1}): 2969, 2929, 1675, 1588, 1448, 1416, 1382, 1248.

(*E*)-Benzo[*d*][1,3]dioxole-5-carbaldehyde *O*-acetyl oxime (6) Acetyl chloride (1.85 mL, 15.0 mmol) was added to a solution of (*E*)-benzo[*d*][1,3]dioxole-5-carbaldehyde oxime[31] (1.65 g, 10.0 mmol) in pyridine (10 mL, 2.0 M) with catalytic DMAP (5 mg). After 4 hours, water (30 mL) was added to quench the reaction and the product was extracted with EtOAc (2 × 50 mL). The organic layers were combined and washed with 1 N HCl (50 mL), brine (50 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was crystallised from Et_2O–pentane to afford a colourless crystalline solid (1.94 g, 73%). M.p. 107-109 °C (EtOAc–pentane); δ_H (300 MHz, $CDCl_3$) 8.24 (1H, s), 7.35 (1H, d, *J* 1.6), 7.08 (1H, dd, *J* 8.0, 1.6), 6.83 (1H, d, *J* 8.0), 6.03 (2H, s), 2.22 (3H, s); δ_C (75 MHz, $CDCl_3$) 168.9 (C), 155.6 (CH), 151.0 (C), 148.6 (C), 125.3 (CH), 124.4 (C), 108.6 (CH), 106.7 (CH), 101.9 (CH_2), 19.8 (CH_3); HRMS (ESI^+): *m/z* calculated for formula $C_{10}H_{10}NO_4$ [MH^+] 208.0604; found 208.0601; IR (ν_{max}, solid, cm^{-1}): 2914, 2855, 1757, 1596, 1508, 1493, 1439, 1359, 1338, 1253, 1209, 1100, 1035, 1001.

[1,3]Dioxolo[4,5-*f*]isoquinoline (7) The desired compound was isolated as a brown amorphous solid (45 mg, 26%) from (*E*)-benzo[*d*][1,3]dioxole-5-carbaldehyde *O*-acetyl oxime (207 mg, 1.00 mmol) following the general procedure. The remaining material contained benzo[*d*][1,3]dioxole-5-carbonitrile. δ_H (300 MHz, $CDCl_3$) 9.16 (1H, s), 8.43 (1H, d, *J* 5.8), 7.60-7.57 (2H, m), 7.29 (1H, d, *J* 8.7), 6.23 (2H, s); δ_C (75 MHz, $CDCl_3$) 152.9 (CH), 147.1 (C), 142.8 (C), 140.3 (CH), 125.3 (C), 122.9 (CH), 121.8 (C), 112.7 (CH), 111.8 (CH), 102.5 (CH_2); LRMS (ESI^+): *m/z* 174.1 [MH^+]; IR (ν_{max}, solid, cm^{-1}): 2897, 1648, 1549, 1466, 1431, 1369, 1287, 1261, 1070, 1050, 1020. Spectral data consistent with the literature.[28]

Acknowledgments

We thank AstraZeneca and the EPSRC for financial support (CASE award to NJW).

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