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Tetrahedron 64 (2008) 874–882
Tetrahedron
www.elsevier.com/locate/tet

Intramolecular Diels–Alder reactions of α,β-unsaturated oxime ethers as 1-azadienes: synthesis of [*c*]-fused pyridines

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Received 24 July 2007; accepted 7 September 2007
Available online 25 October 2007

Abstract

The intramolecular hetero-Diels–Alder reaction of α,β-unsaturated oxime ethers as the diene with acetylenic dienophiles, readily prepared from salicylaldehyde derivatives, is described as a rapid and versatile route to [*c*]-annelated pyridines in modest to good yields.

1. Introduction

The hetero-Diels–Alder reaction is a useful route to a range of six-membered heterocyclic compounds,[1,2] and the use of both 1-aza and 2-aza-dienes as 4π-components in such reactions is well known.[3–6] Since the discovery by Ghosez and co-workers that α,β-unsaturated *N*,*N*-dimethylhydrazones participate readily in [4+2]-cycloadditions,[7] their high reactivity towards electron-deficient dienophiles, presumably being due to the strong electron-donating effect of the dimethylamino substituent, the hetero-Diels–Alder reaction of 1-azabutadienes has proved to be a versatile method for the preparation of a range of pyridines and dihydropyridines. Intramolecular Diels–Alder (IMDA) reactions of α,β-unsaturated *N*,*N*-dimethylhydrazones with alkynes have also been reported,[8,9] and this is an attractive route to annelated pyridines since the initial Diels–Alder adducts readily aromatise by loss of dimethylamine.[10–12] In contrast, analogous α,β-unsaturated oxime ethers are often thought of as poorer 1-azadienes, and consequently there are fewer examples of both intermolecular and intramolecular hetero-Diels–Alder routes to pyridines involving vinyl oximes as dienes.[13–18] In continuation of our recent work on the synthesis of highly functionalised pyridines via hetero-Diels–Alder reaction of 3-siloxy-1-aza-1,3-butadienes with electron-deficient acetylenes,[19] subsequently extended by others,[20] we now report an intramolecular variant using α,β-unsaturated oxime ethers as 1-azadienes in a route to [*c*]-annelated pyridines.

2. Results and discussion

2.1. Preparation of hetero-Diels–Alder substrates

The required substrates for hetero-Diels–Alder reaction were prepared in three steps from commercially available starting materials. First, alkylation of salicylaldehyde **1a** and 3-methylsalicylaldehyde **1b** with propargyl chloride proceeded in excellent yield to provide the aryl propargyl ethers (Scheme 1). Next, the Wadsworth–Emmons reaction was examined. Treatment of the required β-ketophosphonate, either obtained from commercial sources or prepared by acylation of phosphonate-derived carbanions by known or modified methods,[21] with sodium hydride or potassium *tert*-butoxide in dimethoxyethane (DME) or toluene, followed by slow addition of the aldehyde gave the desired α,β-unsaturated ketones **2a–d** as single (*E*)-geometric isomers in good to excellent yields. Further functionalisation to the 1-aza-1,3-butadiene moiety was readily achieved by conversion of **2a–d** into the *O*-methyl oximes **3a–d** on heating with methoxylamine hydrochloride and sodium acetate trihydrate in aqueous ethanol in almost quantitative yield, without the need for further purification by column chromatography.

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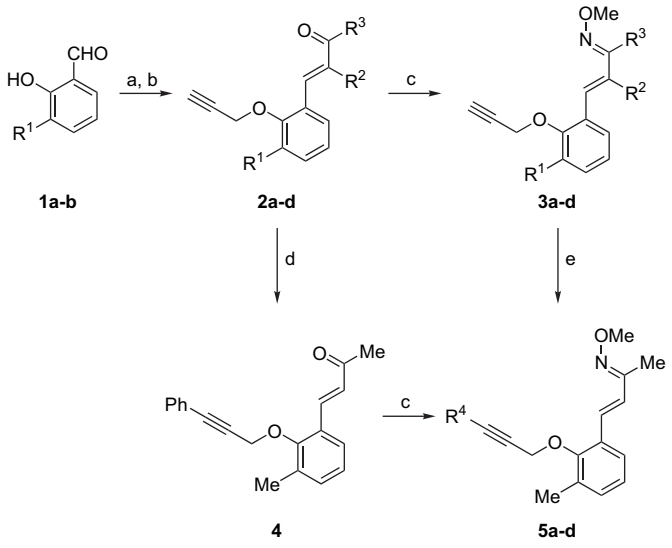
0040-4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.09.090



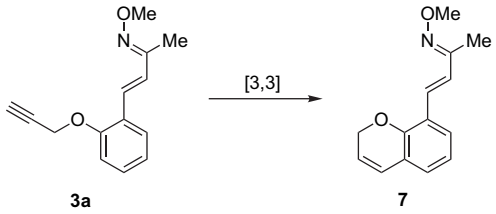
	R^1	R^2	R^3		R^4
2a, 3a	H	H	Me	**5a**	CO_2Me
2b, 3b	Me	H	Me	**5b**	Ph
2c, 3c	Me	Me	Me	**5c**	Cl
2d, 3d	Me	Me	CH_2OMe	**5d**	$SiMe_3$

Scheme 1. Reagents and conditions: (a) $HC{\equiv}CCH_2Cl$, K_2CO_3, EtOH, reflux, 16 h, 86–100%; (b) $(RO)_2P(O)CHR^2COR^3$, NaH or KO^{t}Bu, DME or toluene, rt, 16 h, 75–96%; (c) $MeONH_2{\cdot}HCl$, $NaOAc{\cdot}3H_2O$, EtOH, H_2O, 60 °C, 16 h, 94–98%; (d) PhI, $Pd(PPh_3)_2Cl_2$ (7 mol %), CuI (30 mol %), Et_3N, THF, 60 °C, 16 h, 66%; (e) LiHMDS, electrophile, THF, −78 °C to rt, 16 h, 41–53%.

A range of substrates bearing a substituent at the terminus of the acetylenic dienophile were also prepared in order to examine their effect on the intramolecular hetero-Diels–Alder reaction. The IMDA substrates **5a**, **c**, or **d** bearing a methyl ester, chloro or trimethylsilyl group at the alkyne terminus were prepared directly from oxime **3b** via deprotonation of the alkyne with lithium hexamethyldisilazide (LiHMDS) and trapping with the appropriate electrophile. IMDA substrate **5b** was obtained by Sonogashira reaction between acetylene **2b** and iodobenzene under standard conditions to give **4**, followed by formation of the corresponding oxime as detailed above.

2.2. Intramolecular hetero-Diels–Alder reactions

The key IMDA reactions were investigated under simple thermal conditions. Heating oxime **3a** to 180 °C in xylene in a sealed tube gave the desired [*c*]-annelated pyridine **6a** in 30% yield after 16 h (Table 1, entry 1). On one occasion a minor byproduct (8%) was isolated, which was identified as (3*E*)-4-(2*H*-chromen-8-yl)but-3-en-2-one *O*-methyl oxime **7** (Scheme 2) that presumably arises through a [3,3]-sigmatropic rearrangement and [1,5]-hydrogen shift in analogous fashion to that previously reported for vinyl hydrazone dienes.[12] A blocking substituent in the form of a methyl group *ortho* to the propargylic ether moiety eliminates this competing rearrangement, and the desired pyridine **6b** was isolated in 37% yield (Table 1, entry 2). Variations in the diene component were also tolerated. Indeed, IMDA reaction of substrates **3c** and **d** (Table 1, entries 3 and 4) proceeded smoothly, albeit in modest yield, to provide the tetra-substituted pyridines **6c** and **d**.



Scheme 2. Chromene byproduct resulting from competing [3,3]-sigmatropic rearrangement of **3a**.

Introduction of an electron-withdrawing group at the terminus of the acetylene would be expected to facilitate the IMDA reaction on the basis of lowering the relevant LUMO of the dienophile, assuming that the α,β-unsaturated oximes participate in a 'normal' electron-demand hetero-Diels–Alder reaction ($HOMO_{diene}/LUMO_{dienophile}$). This indeed proved to be the case; heating oxime **5a** in xylene in a sealed tube at 180 °C gave the desired tetra-substituted pyridine **8a** in 50% yield (Table 1, entry 5). The reaction still proceeds at 140 °C, unlike the terminal acetylenes, although a slight drop in yield is noticed (Table 1, entry 6). IMDA reaction of oxime **5b** also proceeded smoothly, with the expected product **8b** isolated in 62% and 42% yields after 16 h at 180 °C and 140 °C, respectively (Table 1, entries 7 and 8). However, IMDA reaction of oxime **5c** gave only small amounts of the expected 2-chloropyridine **8c** (Table 1, entry 9), with the main isolated product being pyridine **6b** that arises through formal loss of the chlorine atom, although it is not yet clear at which stage this loss occurs. As may be expected, introduction of a bulky TMS group into the dienophile greatly retarded the IMDA reaction (Table 1, entry 10), such that even after prolonged heating 69% of the unreacted starting material was recovered, with 12% of the desilylated pyridine **6b** as the only other isolable product.

We also envisaged that direct conversion of the α,β-unsaturated ketones to the aromatic products should be possible through a one-pot oxime formation/hetero-Diels–Alder reaction. Pleasingly, treatment of ketones **2b** and **4** with methoxylamine hydrochloride and triethylamine in xylene in a sealed tube and heating to 180 °C for 16 h gave the desired pyridines in 29% and 37% yields, respectively (Table 1, entries 11 and 12).

3. Conclusions

We have successfully demonstrated that the intramolecular hetero-Diels–Alder reaction of vinyl oxime ethers with acetylenes represents a rapid and versatile route to a range of [*c*]-annelated pyridines, best results being obtained with electron-deficient acetylenes in accordance with the likely frontier orbital interactions ($HOMO_{diene}/LUMO_{dienophile}$). The results

Table 1
Intramolecular hetero-Diels–Alder reactions

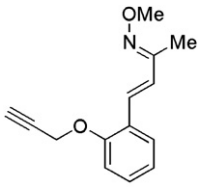
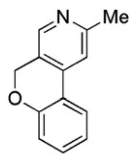
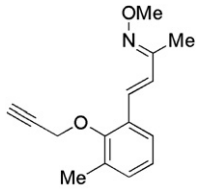
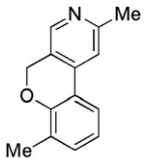
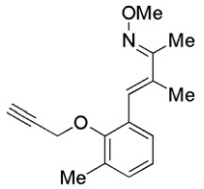
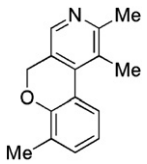
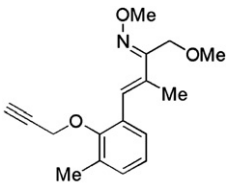
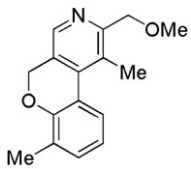
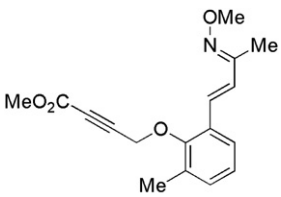
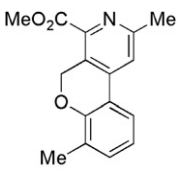
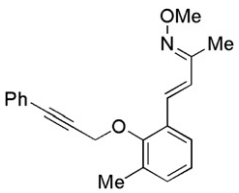
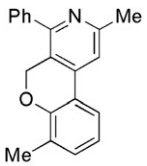
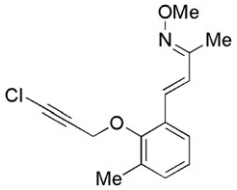
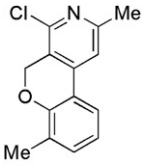
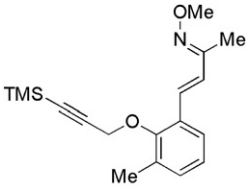
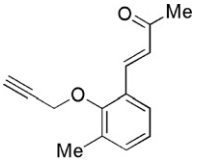
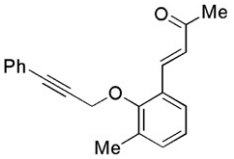
Entry	IMDA substrate	Product	Temp/°C	Time/h	Yield/%
1	 **3a**	 **6a**	180	16	30
2	 **3b**	 **6b**	180	16	37
3	 **3c**	 **6c**	180	16	26
4	 **3d**	 **6d**	180	16	27
5	 **5a**	 **8a**	180	16	50
6	**5a**	**8a**	140	16	41
7	 **5b**	 **8b**	180	16	62
8	**5b**	**8b**	140	16	42

Table 1 (*continued*)

Entry	IMDA substrate	Product	Temp/°C	Time/h	Yield/%
9	 **5c**	 **8c (+ 6b)**	180	16	16 (**8c**) 30 (**6b**)
10	 **5d**	**6b**	180–200	120	12[a]
11[b]	 **2b**	**6b**	180	16	29
12[b]	 **4**	**8b**	180	16	37

[a] Unreacted **5d** recovered: 69%.

[b] The hetero-Diels–Alder substrates (**3b** and **5a**) were formed in situ by heating the α,β-unsaturated ketone with methoxylamine hydrochloride and triethylamine in xylene.

exemplify further the utility of α,β-unsaturated oximes as 1-azadienes in the hetero-Diels–Alder route to pyridines, as they exhibit comparable reactivity to that previously described for analogous α,β-unsaturated hydrazone systems.

4. Experimental

4.1. General

Commercially available reagents were used throughout without further purification unless otherwise stated; solvents were dried by standard procedures. Light petroleum refers to the fraction with bp 40–60 °C and ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen atmosphere. Fully characterised compounds were chromatographically homogeneous. IR spectra were recorded in the range 4000–600 cm^{-1} using a Bruker Tensor 27 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AV400 spectrometer operating at 400 MHz (^{1}H frequency, corresponding ^{13}C frequency is 100 MHz). In the ^{13}C NMR spectra, signals corresponding to CH, CH_2, or CH_3 groups are assigned from DEPT. High- and low-resolution mass spectra were recorded on a Bruker MicroTOF spectrometer using electrospray ionisation (ESI).

4.1.1. General procedure 1—alkylation of salicylaldehydes

To a solution of the salicylaldehyde **1** (10.0 mmol) in ethanol (60 mL) were added potassium carbonate (15.0 mmol, 1.5 equiv) and propargyl chloride (50.0 mmol, 5.0 equiv). The reaction mixture was heated under reflux for 16 h, cooled to room temperature and the solvent removed in vacuo. The residue was partitioned between sodium hydroxide solution (2 M; 150 mL) and ether (3×150 mL). The combined organic extracts were washed with water (150 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate–light petroleum (1:19) to afford the title compound.

4.1.2. General procedure 2—Wadsworth–Emmons reaction

To a solution of sodium hydride (9.00 mmol, 1.5 equiv) or potassium *tert*-butoxide (9.00 mmol, 1.5 equiv) in 1,2-dimethoxyethane (10 mL) was added the phosphonate (9.00 mmol, 1.5 equiv) in 1,2-dimethoxyethane (5 mL) dropwise over 30 min. The reaction mixture was stirred for 30 min, followed by dropwise addition of the aldehyde (6.00 mmol) in 1,2-dimethoxyethane (5 mL) over 30 min. The resulting mixture was stirred at room temperature for 16 h and partitioned between saturated ammonium chloride (75 mL) and ethyl acetate (3×75 mL). The combined organic extracts were washed with water (75 mL) and saturated brine (75 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate–light petroleum (1:9), to afford the title compound.

4.1.3. General procedure 3—preparation of O-methyl oximes

A solution of the ketone **2** (4.00 mmol), methoxylamine hydrochloride (5.00 mmol, 1.25 equiv) and sodium acetate trihydrate (4.20 mmol, 1.05 equiv) in ethanol (28 mL) and water (3.5 mL) was heated to 60 °C for 16 h. The reaction mixture was cooled to room temperature and the solvent removed in vacuo. The resulting residue was partitioned between water (65 mL) and ethyl acetate (3×65 mL). The combined organic extracts were washed with water (2×65 mL) and saturated brine (65 mL), dried over $MgSO_4$ and concentrated in vacuo to afford the title compound that was used without further purification.

4.1.4. General procedure 4—functionalisation of terminal alkynes

To a solution of *O*-methyl oxime **3b** (0.973 g, 4.00 mmol) in THF (10 mL) at −78 °C was added lithium hexamethyldisilazide (1 M in THF; 4.20 mL, 4.20 mmol) dropwise over 20 min. The reaction mixture was stirred at −78 °C for 1 h, then the electrophile (6.00 mmol) added dropwise over 15 min. The resulting mixture was then stirred for a further 1 h at −78 °C, allowed to warm to room temperature and stirred for 16 h. The reaction was quenched by addition of saturated ammonium chloride (75 mL), and the aqueous phase extracted with ethyl acetate (3×75 mL). The combined organic extracts were washed with water (75 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford the title compound.

4.1.5. General procedure 5—intramolecular hetero-Diels–Alder reaction

A solution of the α,β-unsaturated oxime **3/5** (0.50 mmol) in dry xylene (10 mL) was placed in a sealed tube and heated to the required temperature for the time shown in Table 1. The reaction mixture was then cooled to room temperature, concentrated in vacuo and the crude product purified by flash chromatography on silica gel to afford the title compound.

4.2. Preparation of IMDA substrates

4.2.1. 2-(Prop-2-ynyloxy)benzaldehyde

Prepared as previously described.[12]

4.2.2. 3-Methyl-2-(prop-2-ynyloxy)benzaldehyde

Following general procedure 1, the title compound was obtained from 3-methylsalicylaldehyde **1b** (0.340 g, 2.50 mmol), potassium carbonate (0.518 g, 3.75 mmol) and propargyl chloride (0.90 mL, 12.5 mmol) as a pale oil (0.375 g, 86%) (found: MH^+, 175.0758; $C_{11}H_{10}O_2$+H requires 175.0754); ν_{max} ($CHCl_3$)/cm^{-1} 3306 (alkyne C–H), 2126 (C≡C), 1693 (C=O), 1588 (C=C), 1469 (C=C), 1249 (C–O), 1086 (C–O); δ_H (400 MHz; $CDCl_3$) 10.42 (1H, s, CHO), 7.71 (1H, d, J=7.6 Hz, H-6), 7.45 (1H, d, J=7.6 Hz, H-4), 7.17 (1H, t, J=7.6 Hz, H-5), 4.68 (2H, d, J=2.0 Hz, CH_2), 2.54 (1H, t, J=2.0 Hz, C≡CH), 2.36 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 190.6 (CH), 158.9 (C), 137.5 (CH), 132.4 (C), 130.2 (C), 126.5 (CH), 125.0 (CH), 77.9 (C), 76.8 (CH), 62.1 (CH_2), 15.9 (Me); *m/z* (ESI) 197 (MNa^+, 100%), 175 (MH^+, 37), 147 (66).

4.2.3. (*E*)-4-(2-(Prop-2-ynyloxy)phenyl)but-3-en-2-one ***2a***

Following general procedure 2, the title compound was obtained from 2-(prop-2-ynyloxy)benzaldehyde (0.288 g, 1.80 mmol), sodium hydride (0.108 g, 2.70 mmol) and dimethyl-2-oxopropylphosphonate (0.448 g, 2.70 mmol) as a pale oil (0.329 g, 91%) (lit.,[12] oil); δ_H (400 MHz; $CDCl_3$) 7.88 (1H, d, J=16.4 Hz, C=CH), 7.56 (1H, d, J=7.6 Hz, H-6), 7.37 (1H, t, J=7.6 Hz, H-5), 7.05 (1H, d, J=7.6 Hz, H-3), 7.02 (1H, t, J=7.6 Hz, H-4), 6.73 (1H, d, J=16.4 Hz, C=CH), 4.78 (2H, d, J=1.2 Hz, CH_2), 2.55 (1H, t, J=1.2 Hz, C≡CH), 2.38 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 199.0 (C), 156.1 (C), 138.4 (CH), 131.6 (CH), 128.3 (CH), 128.1 (CH), 124.0 (C), 121.8 (CH), 112.8 (CH), 78.1 (C), 76.1 (CH), 56.2 (CH_2), 27.2 (Me).

4.2.4. (*E*)-4-(3-Methyl-2-(prop-2-ynyloxy)phenyl)but-3-en-2-one ***2b***

Following general procedure 2, the title compound was obtained from 3-methyl-2-(prop-2-ynyloxy)benzaldehyde (0.314 g, 1.80 mmol), sodium hydride (0.108 g, 2.70 mmol) and dimethyl-2-oxopropylphosphonate (0.448 g, 2.70 mmol) as a pale oil (0.340 g, 88%) (found: MH^+, 215.1077; $C_{14}H_{14}O_2$+H requires 215.1066); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C–H), 2127 (C≡C), 1669 (C=O), 1644 (C=C), 1623 (C=C), 1607 (C=C), 1462 (C=C), 1259 (C–O), 1090 (C–O); δ_H (400 MHz; $CDCl_3$) 7.94 (1H, d, J=16.4 Hz, C=CH), 7.44 (1H, d, J=7.6 Hz, H-6), 7.24 (1H, d, J=7.6 Hz, H-4), 7.08 (1H, t, J=7.6 Hz, H-5), 6.69 (1H, d, J=16.4 Hz, C=CH), 4.55 (2H, d, J=1.2 Hz, CH_2), 2.55 (1H, t, J=1.2 Hz, C≡CH), 2.41 (3H, s, Me), 2.34 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 198.9 (C), 156.0 (C), 139.0 (CH), 133.6 (CH), 132.1 (C), 128.5 (CH), 128.4 (C), 125.2 (CH), 125.0 (CH), 78.6 (C), 76.1 (CH), 61.4 (CH_2), 27.0 (Me), 16.4 (Me); *m/z* (ESI) 237 (MNa^+, 61%), 215 (MH^+, 100).

*4.2.5. (E)-3-Methyl-4-(3-methyl-2-(prop-2-ynyloxy)phenyl)-but-3-en-2-one **2c***

Following general procedure 2, the title compound was obtained from 3-methyl-2-(prop-2-ynyloxy)benzaldehyde (0.401 g, 2.30 mmol), potassium *tert*-butoxide (0.387 g, 3.45 mmol) and diethyl 1-methyl-2-oxopropylphosphonate[21] (0.718 g, 3.45 mmol) as a pale oil (0.420 g, 82%) (found: MH^+, 229.1227; $C_{15}H_{16}O_2$+H requires 229.1223); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C–H), 2128 (C≡C), 1665 (C=O), 1623 (C=C), 1586 (C=C), 1461 (C=C), 1263 (C–O), 1089 (C–O); δ_H (400 MHz; $CDCl_3$) 7.78 (1H, s, C=CH), 7.23–7.20 (2H, m, ArH), 7.10 (1H, t, J=7.6 Hz, H-5), 4.50 (2H, d, J=1.3 Hz, CH_2), 2.52 (1H, t, J=1.3 Hz, C≡CH), 2.51 (3H, s, Me), 2.37 (3H, s, Me), 2.01 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 200.5 (C), 155.2 (C), 138.6 (C), 136.0 (CH), 131.8 (CH), 131.7 (C), 129.5 (C), 128.2 (CH), 124.3 (CH), 78.9 (C), 75.6 (CH), 61.0 (CH_{2*}), 26.0 (Me), 16.4 (Me), 13.0 (Me); *m/z* (ESI) 251 (MNa^+, 75%), 229 (MH^+, 100).

*4.2.6. (E)-1-Methoxy-3-methyl-4-(3-methyl-2-(prop-2-ynyloxy)phenyl)but-3-en-2-one **2d***

To a solution of potassium *tert*-butoxide (0.421 g, 3.75 mmol) in toluene (4 mL) was added diethyl 4-methoxy-3-oxobutan-2-ylphosphonate (prepared from diethyl ethylphosphonate and methyl-2-methoxyacetate using the method described in Ref. 21) (0.893 g, 3.75 mmol) in toluene (3 mL) dropwise over 15 min. The reaction mixture was stirred for 30 min, followed by dropwise addition of 3-methyl-2-(prop-2-ynyloxy)benzaldehyde (0.436 g, 2.50 mmol) in toluene (3 mL) over 15 min. The resulting mixture was stirred at room temperature for 16 h and partitioned between saturated ammonium chloride (45 mL) and ethyl acetate (3×45 mL). The combined organic extracts were washed with water (45 mL) and saturated brine (45 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate–light petroleum (1:9), to afford the title compound as a pale oil (0.487 g, 75%) (found: MH^+, 259.1336; $C_{16}H_{18}O_3$+H requires 259.1329); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C–H), 2127 (C≡C), 1683 (C=O), 1627 (C=C), 1586 (C=C), 1461 (C=C), 1261 (C–O), 1090 (C–O), 1056 (C–O); δ_H (400 MHz; $CDCl_3$) 7.70 (1H, s, C=CH), 7.23–7.20 (2H, m, ArH), 7.09 (1H, t, J=7.6 Hz, H-5), 4.61 (2H, s, CH_2), 4.49 (2H, d, J=1.2 Hz, CH_2), 3.49 (3H, s, OMe), 2.53 (1H, t, J=1.2 Hz, C≡CH), 2.35 (3H, s, Me), 2.03 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 197.9 (C), 155.2 (C), 136.1 (C), 135.2 (CH), 132.1 (CH), 131.8 (C), 129.1 (C), 128.1 (CH), 124.4 (CH), 78.9 (C), 75.7 (CH), 74.8 (CH_2), 61.1 (CH_2), 59.4 (Me), 16.4 (Me), 13.1 (Me); *m/z* (ESI) 281 (MNa^+, 100%), 259 (MH^+, 42), 241 (72).

*4.2.7. (E)-4-(2-(3-Phenylprop-2-ynyloxy)-3-methylphenyl)-but-3-en-2-one **4***

To a solution of iodobenzene (0.67 mL, 6.00 mmol), bis(triphenylphosphine)palladium(II) chloride (0.201 g, 0.286 mmol) and copper(I) iodide (0.229 g, 1.20 mmol) in THF (15 mL) was added triethylamine (0.84 mL, 6.00 mmol) followed by alkyne **2b** (0.857 g, 4.00 mmol) in THF (5 mL). The reaction mixture was heated to 60 °C for 16 h, cooled to room temperature and partitioned between saturated ammonium chloride solution (150 mL) and ethyl acetate (3×150 mL). The combined organic extracts were washed with saturated ammonium chloride solution (150 mL) and saturated brine (150 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate–light petroleum (1:9) to afford the title compound as a colourless oil (0.768 g, 66%) (found: MH^+, 291.1382; $C_{20}H_{18}O_2$+H requires 291.1380); ν_{max} ($CHCl_3$)/cm^{-1} 2233 (C≡C), 1669 (C=C), 1644 (C=C), 1622 (C=C), 1606 (C=C), 1588 (C=C), 1491 (C=C), 1461 (C=C), 1443 (C=C), 1260 (C–O), 1090 (C–O); δ_H (400 MHz; $CDCl_3$) 8.05 (1H, d, J=16.5 Hz, C=CH), 7.49 (1H, d, J=7.6 Hz, H-6), 7.40–7.38 (2H, m, ArH), 7.35–7.32 (3H, m, ArH), 7.28 (1H, d, J=7.2 Hz, H-4), 7.12 (1H, t, J=7.6 Hz, H-5), 6.72 (1H, d, J=16.5 Hz, C=CH), 4.81 (2H, s, CH_2), 2.41 (3H, s, Me), 2.34 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 199.0 (C), 156.0 (C), 139.2 (CH), 133.6 (CH), 132.3 (C), 131.6 (CH), 128.8 (CH), 128.7 (C), 128.4 (CH), 128.1 (CH), 125.1 (CH), 125.0 (CH), 122.1 (C), 87.9 (C), 84.0 (C), 62.3 (CH_2), 26.9 (Me), 16.5 (Me); *m/z* (ESI) 313 (MNa^+, 51%), 291 (MH^+, 100).

*4.2.8. (E)-4-(2-(Prop-2-ynyloxy)phenyl)but-3-en-2-one O-methyl oxime **3a***

Following general procedure 3, the title compound was obtained from ketone **2a** (0.280 g, 1.40 mmol), methoxylamine hydrochloride (0.146 g, 1.75 mmol) and sodium acetate trihydrate (0.200 g, 1.47 mmol) as a pale oil (0.314 g, 98%) (found: MH^+, 230.1192; $C_{14}H_{15}NO_2$+H requires 230.1181); ν_{max} ($CHCl_3$)/cm^{-1} 3308 (alkyne C–H), 2125 (C≡C), 1600 (C=C), 1487 (C=C), 1457 (C=C), 1240 (C–O), 1055 (C–O); δ_H (400 MHz; $CDCl_3$) 7.57 (1H, d, J=7.6 Hz, H-6), 7.35–7.24 (2H, m, ArH+C=CH), 7.04–6.86 (2H, m, ArH), 6.85 (1H, d, J=16.4 Hz, C=CH), 4.77 (2H, d, J=1.2 Hz, CH_2), 3.96 (3H, s, OMe), 2.54 (1H, t, J=1.2 Hz, C≡CH), 2.10 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.3 (C), 154.9 (C), 145.8 (C), 129.2 (CH), 127.3 (CH), 126.6 (CH), 126.4 (CH), 121.8 (CH), 112.8 (CH), 78.5 (C), 75.8 (CH), 61.8 (Me), 56.3 (CH_2), 10.2 (Me); *m/z* (ESI) 252 (MNa^+, 11%), 230 (MH^+, 100).

*4.2.9. (E)-4-(3-Methyl-2-(prop-2-ynyloxy)phenyl)but-3-en-2-one O-methyl oxime **3b***

Following general procedure 3, the title compound was obtained from ketone **2b** (0.300 g, 1.40 mmol), methoxylamine hydrochloride (0.146 g, 1.75 mmol) and sodium acetate trihydrate (0.200 g, 1.47 mmol) as a pale oil (0.333 g, 98%) (found: MH^+, 244.1346; $C_{15}H_{17}NO_2$+H requires 244.1332); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C–H), 2127 (C≡C), 1619 (C=C), 1586 (C=C), 1462 (C=C), 1240 (C–O), 1056 (C–O); δ_H (400 MHz; $CDCl_3$) 7.43 (1H, d, J=6.8 Hz, H-6), 7.29 (1H, d, J=16.8 Hz, C=CH), 7.13 (1H, d, J=7.2 Hz, H-4), 7.05 (1H, t, J=7.2 Hz, H-5), 6.81 (1H, d, J=16.8 Hz, C=CH), 4.51 (2H, d, J=1.2 Hz, CH_2), 3.96 (3H, s, OMe),

2.54 (1H, t, J=1.2 Hz, C≡CH), 2.34 (3H, s, Me), 2.12 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.1 (C), 154.8 (C), 131.9 (C), 131.2 (CH), 130.2 (C), 127.9 (CH), 126.9 (CH), 124.9 (CH), 124.0 (CH), 79.0 (C), 75.6 (CH), 61.9 (Me), 61.1 (CH_2), 16.4 (Me), 10.2 (Me); *m/z* (ESI) 266 (MNa^+, 22%), 244 (MH^+, 100).

4.2.10. (E)-3-Methyl-4-(3-methyl-2-(prop-2-ynyloxy)-phenyl)but-3-en-2-one O-methyl oxime ***3c***

Following general procedure 3, the title compound was obtained from ketone **2c** (0.297 g, 1.30 mmol), methoxylamine hydrochloride (0.136 g, 1.63 mmol) and sodium acetate trihydrate (0.186 g, 1.37 mmol) as a pale oil (0.242 g, 72%) (found: MH^+, 258.1497; $C_{16}H_{19}NO_2$+H requires 258.1489); ν_{max} ($CHCl_3$)/cm^{-1} 3308 (alkyne C–H), 2128 (C≡C), 1586 (C=C), 1461 (C=C), 1253 (C–O), 1055 (C–O); δ_H (400 MHz; $CDCl_3$) 7.14–7.13 (2H, m, ArH), 7.06 (1H, d, J=7.6 Hz, H-4), 7.01 (1H, s, C=CH), 4.47 (2H, d, J=1.2 Hz, CH_2), 3.97 (3H, s, OMe), 2.48 (1H, t, J=1.2 Hz, C≡CH), 2.36 (3H, s, Me), 2.15 (3H, s, Me), 2.06 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.9 (C), 155.0 (C), 135.7 (C), 131.5 (C), 130.7 (C), 130.3 (CH), 128.6 (CH), 126.5 (CH), 124.0 (CH), 79.3 (C), 75.0 (CH), 61.8 (Me), 60.5 (CH_2), 16.5 (Me), 14.4 (Me), 10.8 (Me); *m/z* (ESI) 280 (MNa^+, 32%), 258 (MH^+, 100).

4.2.11. (E)-1-Methoxy-3-methyl-4-(3-methyl-2-(prop-2-ynyloxy)phenyl)but-3-en-2-one O-methyl oxime ***3d***

Following general procedure 3, the title compound was obtained from ketone **2d** (0.387 g, 1.50 mmol), methoxylamine hydrochloride (0.157 g, 1.88 mmol) and sodium acetate trihydrate (0.214 g, 1.58 mmol) as a pale oil (0.410 g, 95%) (found: MH^+, 288.1603; $C_{17}H_{21}NO_3$+H requires 288.1594); ν_{max} ($CHCl_3$)/cm^{-1} 3308 (alkyne C–H), 2127 (C≡C), 1596 (C=C), 1461 (C=C), 1254 (C–O), 1051 (C–O); δ_H (400 MHz; $CDCl_3$) 7.18–7.13 (3H, m, ArH), 7.06 (1H, d, J=7.4 Hz, H-4), 4.52 (2H, d, J=1.2 Hz, CH_2), 4.51 (2H, s, CH_2), 3.99 (3H, s, OMe), 3.43 (3H, s, OMe), 2.50 (1H, t, J=1.2 Hz, C≡CH), 2.49 (3H, s, Me), 2.03 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.7 (C), 154.8 (C), 133.3 (C), 131.6 (C), 130.6 (C), 130.5 (CH), 128.6 (CH), 127.8 (CH), 123.9 (CH), 79.4 (C), 75.0 (CH), 62.3 (CH_2), 62.0 (Me), 60.4 (CH_2), 58.6 (Me), 16.6 (Me), 14.6 (Me); *m/z* (ESI) 310 (MNa^+, 67%), 288 (MH^+, 100).

4.2.12. (E)-4-(2-(3-Methoxycarbonylprop-2-ynyloxy)-3-methylphenyl)but-3-en-2-one O-methyl oxime ***5a***

Following general procedure 4, the title compound was obtained from *O*-methyl oxime **3b** (0.973 g, 4.00 mmol) and methyl chloroformate (0.46 mL, 6.00 mmol) as a colourless oil (0.495 g, 41%) (found: MH^+, 302.1388; $C_{17}H_{19}NO_4$+H requires 302.1387); ν_{max} ($CHCl_3$)/cm^{-1} 2245 (C≡C), 1717 (C=O), 1585 (C=C), 1462 (C=C), 1436 (C=C), 1266 (C–O), 1056 (C–O); δ_H (400 MHz; $CDCl_3$) 7.43 (1H, d, J=7.6 Hz, H-6), 7.23 (1H, d, J=16.5 Hz, C=CH), 7.14 (1H, d, J=7.6 Hz, H-4), 7.07 (1H, t, J=7.6 Hz, H-5), 6.82 (1H, d, J=16.5 Hz, C=CH), 4.65 (2H, s, CH_2), 3.86 (3H, s, OMe), 3.77 (3H, s, OMe), 2.34 (3H, s, Me), 2.11 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.1 (C), 154.5 (C), 153.3 (C), 131.6 (C), 131.3 (CH), 130.2 (C), 127.5 (CH), 127.4 (CH), 125.2 (CH), 124.3 (CH), 82.6 (C), 78.6 (C), 61.9 (Me), 60.6 (CH_2), 52.8 (Me), 16.4 (Me), 10.2 (Me); *m/z* (ESI) 324 (MNa^+, 100%), 302 (MH^+, 17).

4.2.13. (E)-4-(2-(3-Phenylprop-2-ynyloxy)-3-methylphenyl)-but-3-en-2-one O-methyl oxime ***5b***

Following general procedure 3, the title compound was obtained from ketone **4** (0.667 g, 2.30 mmol), methoxylamine hydrochloride (0.240 g, 2.88 mmol) and sodium acetate trihydrate (0.329 g, 2.42 mmol) as a pale oil (0.690 g, 94%) (found: MH^+, 320.1661; $C_{21}H_{21}NO_2$+H requires 320.1645); ν_{max} ($CHCl_3$)/cm^{-1} 2235 (C≡C), 1599 (C=C), 1491 (C=C), 1462 (C=C), 1443 (C=C), 1244 (C–O), 1056 (C–O); δ_H (400 MHz; $CDCl_3$) 7.49–7.31 (7H, m, 6×ArH+C=CH), 7.17 (1H, d, J=7.4 Hz, H-4), 7.08 (1H, t, J=7.4 Hz, H-5), 6.86 (1H, d, J=16.6 Hz, C=CH), 4.77 (2H, s, CH_2), 3.97 (3H, s, OMe), 2.41 (3H, s, Me), 2.08 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.2 (C), 155.0 (C), 131.9 (CH), 131.8 (C), 131.2 (CH), 130.3 (C), 128.6 (CH), 128.3 (CH), 128.1 (CH), 126.7 (CH), 124.8 (CH), 124.0 (CH), 122.3 (C), 87.4 (*C*≡CPh), 84.3 (C≡*C*Ph), 62.0 (CH_2), 61.9 (Me), 16.5 (Me), 10.2 (Me); *m/z* (ESI) 342 (MNa^+, 42%), 320 (MH^+, 100), 288 (30).

4.2.14. (E)-4-(2-(3-Chloroprop-2-ynyloxy)-3-methylphenyl)but-3-en-2-one O-methyl oxime ***5c***

Following general procedure 4, the title compound was obtained from *O*-methyl oxime **3b** (0.973 g, 4.00 mmol) and *N*-chlorosuccinimide (0.801 g, 6.00 mmol) as a colourless oil (0.546 g, 49%) (found: MH^+, 278.0947; $C_{15}H_{16}^{35}ClNO_2$+H requires 278.0942); ν_{max} ($CHCl_3$)/cm^{-1} 2245 (C≡C), 1627 (C=C), 1586 (C=C), 1463 (C=C), 1056 (C–O); δ_H (400 MHz; $CDCl_3$) 7.44 (1H, d, J=7.6 Hz, H-4), 7.28 (1H, d, J=16.6 Hz, C=CH), 7.13 (1H, d, J=7.6 Hz, H-6), 7.06 (1H, t, J=7.6 Hz, H-5), 6.82 (1H, d, J=16.6 Hz, C=CH), 4.52 (2H, s, CH_2), 3.97 (3H, s, OMe), 2.33 (3H, s, Me), 2.13 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.1 (C), 154.7 (C), 131.7 (C), 131.3 (CH), 130.3 (C), 127.8 (CH), 126.8 (CH), 125.0 (CH), 124.0 (CH), 66.0 (C), 64.9 (C), 61.9 (Me), 61.5 (CH_2), 16.3 (Me), 10.2 (Me); *m/z* (ESI) *m/z* (ESI) 280/278 (MH^+, 36/100%), 246 (30).

4.2.15. (E)-4-(2-(3-Trimethylsilylprop-2-ynyloxy)-3-methylphenyl)but-3-en-2-one O-methyl oxime ***5d***

Following general procedure 4, the title compound was obtained from *O*-methyl oxime **3b** (0.973 g, 4.00 mmol) and chlorotrimethylsilane (0.77 mL, 6.00 mmol) as a colourless oil (0.664 g, 53%) (found: MH^+, 316.1724; $C_{18}H_{25}NO_2Si$+H requires 316.1727); ν_{max} ($CHCl_3$)/cm^{-1} 2181 (C≡C), 1625 (C=C), 1586 (C=C), 1462 (C=C), 1056 (C–O), 848 (C–Si); δ_H (400 MHz; $CDCl_3$) 7.44 (1H, d, J=7.6 Hz, H-6), 7.30 (1H, d, J=16.5 Hz, C=CH), 7.13 (1H, d, J=7.6 Hz, H-4), 7.05 (1H, t, J=7.6 Hz, H-5), 6.82 (1H, d, J=16.5 Hz, C=CH), 4.53 (2H, s, CH_2), 3.98 (3H, s, OMe), 2.35 (3H, s, Me), 2.14 (3H, s, Me), 0.18 (9H, s, $SiMe_3$); δ_C (100 MHz;

$CDCl_3$) 156.5 (C), 155.2 (C), 132.1 (C), 131.5 (CH), 130.5 (C), 128.4 (CH), 127.0 (CH), 125.1 (CH), 124.2 (CH), 100.8 (C), 93.0 (C), 62.2 (CH_2), 61.9 (Me), 16.8 (Me), 10.6 (Me), 0.0 ($SiMe_3$); *m/z* (ESI) 338 (MNa^+, 18%), 316 (MH^+, 100).

4.3. IMDA reactions

4.3.1. 2-Methyl-5H-chromeno[3,4-c]pyridine *6a*

Following general procedure 5, the title compound was obtained from *O*-methyl oxime **3a** (0.115 g, 0.50 mmol) after 16 h at 180 °C as a yellow oil (0.030 g, 30%) (lit.,[12] oil); δ_H (400 MHz; $CDCl_3$) 8.30 (1H, s, H-4), 7.73 (1H, d, *J*=8.0 Hz, H-10), 7.41 (1H, s, H-1), 7.33 (1H, t, *J*=8.0 Hz, H-9), 7.08 (1H, t, *J*=8.0 Hz, H-8), 7.01 (1H, d, *J*=8.0 Hz, H-7), 5.13 (2H, s, CH_2), 2.61 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 158.7 (C), 155.8 (C), 145.0 (CH), 137.9 (C), 131.6 (CH), 123.9 (CH), 123.2 (C), 122.3 (CH), 120.6 (C), 117.8 (CH), 115.4 (CH), 65.8 (CH_2), 24.5 (Me).

On one occasion, also isolated was (3*E*)-4-(2*H*-chromen-8-yl)but-3-en-2-one *O*-methyl oxime **7** as a colourless oil (8%) (found: MH^+, 230.1175; $C_{14}H_{15}NO_2$+H requires 230.1176); ν_{max} ($CHCl_3$)/cm^{-1} 1585 (C=C), 1488 (C=C), 1463 (C=C), 1239 (C–O), 1037 (C–O); δ_H (400 MHz; $CDCl_3$) 7.37 (1H, dd, *J*=1.8 and 7.6 Hz, H-5/H-7), 7.16 (1H, d, *J*=16.7 Hz, C=CH), 6.87 (1H, dd, *J*=1.8 and 7.6 Hz, H-5/H-7), 6.85 (1H, t, *J*=7.6 Hz, H-6), 6.84 (1H, d, *J*=16.7 Hz, C=CH), 6.42 (1H, dt, *J*=1.8 and 9.8 Hz, H-4), 5.81 (1H, dt, *J*=3.5 and 9.8 Hz, H-3), 4.89 (2H, dd, *J*=1.8 and 3.5 Hz, CH_2), 3.96 (3H, s, OMe), 2.08 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.3 (C), 151.6 (C), 127.1 (CH), 126.6 (CH), 126.2 (CH), 126.1 (CH), 124.7 (CH), 124.1 (C), 122.7 (C), 122.0 (CH), 121.2 (CH), 65.7 (CH_2), 61.8 (Me), 10.2 (Me); *m/z* (ESI) 230 (MH^+, 100%).

4.3.2. 2,7-Dimethyl-5H-chromeno[3,4-c]pyridine *6b*

(a) Following general procedure 5, the title compound was obtained from *O*-methyl oxime **3b** (0.122 g, 0.50 mmol) after 16 h at 180 °C as a colourless solid (0.039 g, 37%); mp 107–109 °C (from ethyl acetate–hexane) (found: MH^+, 212.1079; $C_{14}H_{13}NO$+H requires 212.1070); ν_{max} ($CHCl_3$)/cm^{-1} 1610 (C=C), 1599 (C=C), 1561 (C=C), 1465 (C=C), 1021 (C–O); δ_H (400 MHz; $CDCl_3$) 8.30 (1H, s, H-4), 7.57 (1H, d, *J*=7.7 Hz, H-10), 7.38 (1H, s, H-1), 7.21 (1H, d, *J*=7.4 Hz, H-8), 6.97 (1H, dd, *J*=7.7 and 7.4 Hz, H-9), 5.13 (2H, s, CH_2), 2.60 (3H, s, Me), 2.27 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 158.6 (C), 153.9 (C), 144.9 (CH), 138.3 (C), 132.8 (CH), 127.2 (C), 123.2 (C), 121.6 (CH), 121.5 (CH), 120.1 (C), 115.5 (CH), 65.8 (CH_2), 24.6 (Me), 15.9 (Me); *m/z* (ESI) 212 (MH^+, 100%).

(b) Following general procedure 5, the title compound was obtained from *O*-methyl oxime **5d** (0.158 g, 0.50 mmol) after 120 h at 180–200 °C as a colourless solid (0.013 g, 12%); data as above.

(c) A solution of ketone **2b** (0.107 g, 0.50 mmol), methoxylamine hydrochloride (0.084 g, 1.00 mmol) and triethylamine (0.101 g, 1.00 mmol) in xylene (10 mL) in a sealed tube was heated at 180 °C for 16 h. The reaction mixture was cooled to room temperature and the solvent removed in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate–light petroleum (1:9) to afford the title compound as a colourless solid (0.031 g, 29%); data as above.

4.3.3. 1,2,7-Trimethyl-5H-chromeno[3,4-c]pyridine *6c*

Following general procedure 5, the title compound was obtained from *O*-methyl oxime **3c** (0.129 g, 0.50 mmol) after 16 h at 180 °C as a colourless solid (0.026 g, 26%); mp 74–76 °C (from ethyl acetate–hexane) (found: MH^+, 226.1232; $C_{15}H_{15}NO$+H requires 226.1226); ν_{max} ($CHCl_3$)/cm^{-1} 1590 (C=C), 1556 (C=C), 1464 (C=C), 1066 (C–O); δ_H (400 MHz; $CDCl_3$) 8.18 (1H, s, H-4), 7.59 (1H, d, *J*=8.0 Hz, H-10), 7.20 (1H, d, *J*=7.2 H-8), 7.02 (1H, t, *J*=7.2 Hz, H-9), 4.95 (2H, s, CH_2), 2.60 (3H, s, Me), 2.53 (3H, s, Me), 2.31 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 158.6 (C), 155.7 (C), 141.7 (CH), 137.2 (C), 131.8 (CH), 127.2 (C), 126.9 (C), 126.6 (C), 126.4 (CH), 122.1 (C), 120.8 (CH), 66.9 (CH_2), 23.9 (Me), 17.7 (Me), 16.0 (Me); *m/z* (ESI) 226 (MH^+, 100%).

4.3.4. 2-Methoxymethyl-1,7-dimethyl-5H-chromeno[3,4-c]-pyridine *6d*

Following general procedure 5, the title compound was obtained from *O*-methyl oxime **3d** (0.144 g, 0.50 mmol) after 16 h at 180 °C as a colourless solid (0.035 g, 27%); mp 50–52 °C (from ethyl acetate–hexane) (found: MH^+, 256.1346; $C_{16}H_{17}NO_2$+H requires 256.1332); ν_{max} ($CHCl_3$)/cm^{-1} 1588 (C=C), 1556 (C=C), 1464 (C=C), 1094 (C–O); δ_H (400 MHz; $CDCl_3$) 8.30 (1H, s, H-4), 7.65 (1H, d, *J*=7.9 Hz, H-10), 7.23 (1H, d, *J*=7.6 Hz, H-8), 7.04 (1H, dd, *J*=7.6 and 7.9 Hz, H-9), 5.00 (2H, s, CH_2), 4.72 (2H, s, CH_2), 3.48 (3H, s, OMe), 2.64 (3H, s, Me), 2.33 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 157.1 (C), 155.6 (C), 142.0 (CH), 138.1 (C), 132.1 (CH), 128.4 (C), 128.0 (C), 127.2 (C), 126.5 (CH), 121.9 (C), 120.9 (CH), 75.6 (CH_2), 66.8 (CH_2), 58.5 (Me), 16.8 (Me), 16.0 (Me); *m/z* (ESI) 270 (32%), 256 (MH^+, 100%).

4.3.5. Methyl-2,7-dimethyl-5H-chromeno[3,4-c]pyridine-4-carboxylate *8a*

(a) Following general procedure 5, the title compound was obtained from *O*-methyl oxime **5a** (0.090 g, 0.30 mmol) after 16 h at 180 °C as a colourless solid (0.040 g, 50%); mp 47–49 °C (from ethyl acetate–hexane) (found: MH^+, 270.1129; $C_{16}H_{15}NO_3$+H requires 270.1125); ν_{max} ($CHCl_3$)/cm^{-1} 1719 (C=O), 1597 (C=C), 1556 (C=C), 1472 (C=C), 1438 (C=C) 1087 (C–O); δ_H (400 MHz; $CDCl_3$) 7.56–7.55 (2H, m, ArH), 7.21 (1H, d, *J*=7.3 Hz, H-8), 6.97 (1H, dd, *J*=7.3 and 8.1 Hz, H-9), 5.52 (2H, s, CH_2), 4.01 (3H, s, OMe), 2.67 (3H, s, Me), 2.28 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 165.0 (C), 156.7 (C), 152.9 (C), 142.4 (C), 139.1 (C), 132.1 (CH), 126.1 (C), 125.7 (C), 120.6 (CH), 120.5 (CH), 118.4 (C), 117.8 (CH), 63.9 (CH_2), 51.9 (Me), 23.6 (Me), 14.6 (Me); *m/z* (ESI) 292 (MNa^+, 28%), 284 (41), 270 (MH^+, 100).

(b) Following general procedure 5, the title compound was obtained from *O*-methyl oxime **5a** (0.151 g, 0.50 mmol) after 16 h at 140 °C as a colourless solid (0.055 g, 41%); data as above.

*4.3.6. 2,7-Dimethyl-4-phenyl-5H-chromeno[3,4-c]-pyridine **8b***

(a) Following general procedure 5, the title compound was obtained from *O*-methyl oxime **5b** (0.160 g, 0.50 mmol) after 16 h at 180 °C as a colourless solid (0.089 g, 62%); mp 148–150 °C (from ethyl acetate–hexane) (found: MH^+, 288.1396; $C_{20}H_{17}NO+H$ requires 288.1383); ν_{max} ($CHCl_3$)/cm^{-1} 1595 (C=C), 1579 (C=C), 1560 (C=C), 1498 (C=C), 1471 (C=C), 1450 (C=C), 1420 (C=C), 1021 (C–O); δ_H (400 MHz; $CDCl_3$) 7.64 (1H, d, *J*=7.6 Hz, H-10), 7.51–7.44 (5H, m, ArH), 7.42 (1H, s, H-1), 7.22 (1H, d, *J*=7.5 Hz, H-8), 7.02 (1H, dd, *J*=7.5 and 7.6 Hz, H-9), 5.18 (2H, s, CH_2), 2.69 (3H, s, Me), 2.27 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 157.7 (C), 155.2 (C), 153.9 (C), 139.2 (C), 139.0 (C), 132.6 (CH), 129.1 (CH), 128.9 (CH), 128.5 (CH), 127.0 (C), 121.8 (CH), 121.7(CH), 121.3 (C), 120.8 (C), 114.9 (CH), 65.5 (CH_2), 24.8 (Me), 15.8 (Me); *m/z* (ESI) 288 (MH^+, 100%).

(b) Following general procedure 5, the title compound was obtained from *O*-methyl oxime **5b** (0.151 g, 0.50 mmol) after 16 h at 140 °C as a colourless solid (0.055 g, 41%); data as above.

(c) A solution of ketone **4** (0.145 g, 0.50 mmol), methoxylamine hydrochloride (0.084 g, 1.00 mmol) and triethylamine (0.101 g, 1.00 mmol) in xylene (10 mL) in a sealed tube was heated at 180 °C for 16 h. The reaction mixture was cooled to room temperature and the solvent removed in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate–light petroleum (1:9) to afford the title compound as a colourless solid (0.053 g, 37%); data as above.

*4.3.7. 4-Chloro-2,7-dimethyl-5H-chromeno[3,4-c]pyridine **8c***

Following general procedure 5, the title compound was obtained from *O*-methyl oxime **5c** (0.139 g, 0.50 mmol) after 16 h at 180 °C as a colourless solid (0.020 g, 16%); mp 110–112 °C (from ethyl acetate–hexane) (found: MH^+, 246.0683; $C_{14}H_{12}^{35}ClNO+H$ requires 246.0680); ν_{max} ($CHCl_3$)/cm^{-1} 1600 (C=C), 1548 (C=C), 1448 (C=C), 1056 (C–O); δ_H (400 MHz; $CDCl_3$) 7.54 (1H, d, *J*=7.7 Hz, H-10), 7.35 (1H, s, H-1), 7.23 (1H, d, *J*=7.7 Hz, H-8), 6.99 (1H, t, *J*=7.7 Hz, H-9), 5.26 (2H, s, CH_2), 2.59 (3H, s, Me), 2.28 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 158.6 (C), 153.7 (C), 146.5 (C), 141.4 (C), 133.4 (CH), 127.3 (C), 121.8 (CH), 121.7 (CH), 121.4 (C), 119.2 (C), 115.0 (CH), 64.7 (CH_2), 24.3 (Me), 15.8 (Me); *m/z* (ESI) 248/246 (MH^+, 30/100%). Also obtained was 2,7-dimethyl-5*H*-chromeno[3,4-*c*]-pyridine **6b** (30%).

Acknowledgements

We thank the EPSRC for funding, and GlaxoSmithKline for a CASE award (T.E.H.).

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