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Practical routes to diacetylenic ketones and their application for the preparation of alkynyl substituted pyridines, pyrimidines and pyrazoles

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Abstract—Alkynyl substituted pyridines, pyrimidines and pyrazoles have been synthesised by cyclocondensations of diacetylenic ketones with enamines, amidines and hydrazines, respectively.

Heterocycles are widely utilised compounds in both pharmaceutical and agricultural fields.[1] Consequently, the development of methodologies useful for the assembly of molecules containing heterocyclic templates continues to attract the attention of both the academic and industrial communities. Due to the increasing demand for a large number of potentially biologically active compounds, we have been intrigued in pursuing the synthesis of heterocyclic containing molecules using a parallel synthesis approach. Our approach has been to synthesise either families of analogues or different series of compounds starting from a common synthon.[2–5] Such a strategy involves the synthesis of a reactive intermediate, which can subsequently be reacted with a number of polynucleophiles. Indeed in the recent years we have reported the synthesis of a number of reactive electrophilic chiral synthons derived from the natural chiral pool as starting materials and their subsequent application to make heterocycles.[2–5] By this route, families of pyrimidine and isoxazole containing amino acids,[2] C-nucleosides,[3] non-proteinogenic aminoacids[4]and kainic acid analogues[5] have been prepared (Fig. 1).

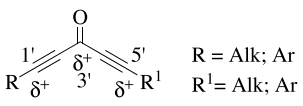

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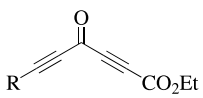
Figure 1.

With the need to synthesise diversely substituted heterocycles, we became interested in polyelectrophilic systems and their reactivity. Diacetylenic ketones such as **1** represent a class of polyelectrophiles bearing three electrophilic centres. We have reasoned that when compounds such as **1** were coupled with polynucleophiles, the similar electrophilic character of the centres $1'$ and $5'$ would lead to a mixture of regioisomeric products. To obviate this problem, the bis acetylenic ketone **2**–**4** bearing an ester group at one end of the acetylenic terminus were designed. We envisaged that the presence of a strongly electron withdrawing group would render the two alkynyl moieties inequivalent towards nucleophilic attack, leading to high regiochemical control when coupled with suitable nucleophiles. Symmetrical and asymmetrical diacetylenic ketones of type **1** have been reported in the literature[6,7] and we have recently described a synthesis of alkynylketones **2**–**5**.[8] The high shielding nature of the alkynyl moieties is illustrated in compounds **2**–**4** by the high field shift of the carbonyl carbons as seen in the ^{13}C NMR (typically 158–159 ppm). This finding is in line with data reported for similar compounds[6b] (Fig. 2).

In our previous route[8] the carbethoxyester functionality was introduced as an orthoester, which was subsequently transformed to the desired ester by treatment with mild acid. Thus, commercially available trimethylsilylacetylene



2 R = Ph
3 R = C_3H_7
4 R = C_4H_9

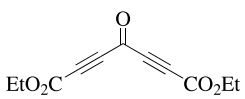


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Figure 2.

Keywords: heterocycle; pyrimidine; pyrazoles.

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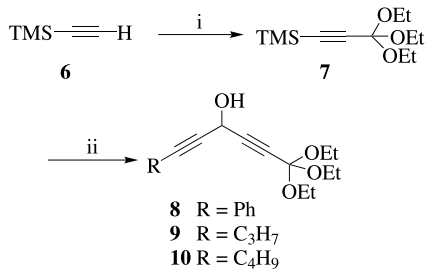
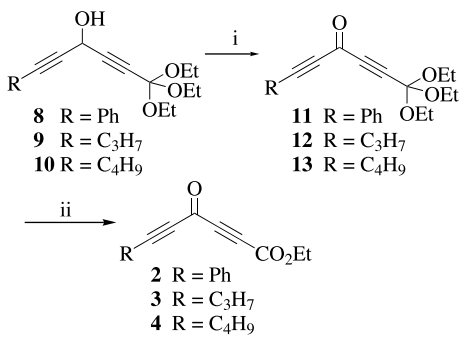


Scheme 1. *Reagents and conditions*: i, **6**, *n*-BuLi, Et_2O, −78°C, $(EtO)_3CBF_4$, 80%; ii, **7**, *n*-BuLi, THF, 0°C; RC≡CCHO, 74–80%.

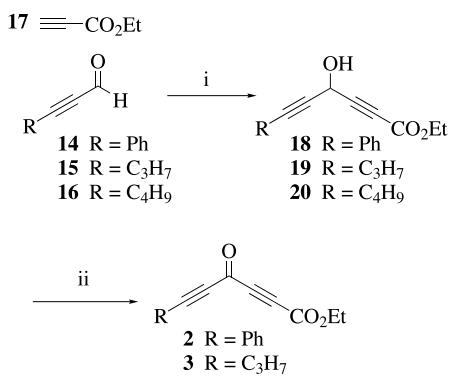
6 was firstly converted into the alkynyl orthoester **7**.[9] Subsequent treatment of **7** with *n*-butyllithium, in THF, generates an organolithium which could be reacted with a range of acetylenic aldehydes to give the diynols **8**–**10** in excellent yields (Scheme 1). Oxidation of the diynols **8**–**10** with freshly prepared manganese dioxide gave the acetylenic ketoorthoesters **11**–**13** in nearly quantitative yields (Scheme 2).



Scheme 2. *Reagents and conditions*: i, MnO_2, benzene, 99%; ii, Amberlyst 15®, benzene, RT, 98%.

The orthoesters could then be converted to the ethyl ester by stirring with Amberlyst 15® resin, to give the required ketones **2**–**4**. The facile deprotection reaction gave material that was essentially homogeneous. Further purification was unnecessary and, indeed, detrimental due to the highly reactive nature of the products **2**–**4**.

We now report a more direct route to desired products **2**–**4**. Thus, reaction of aryl or alkyl propargylic aldehydes **14**–**16**

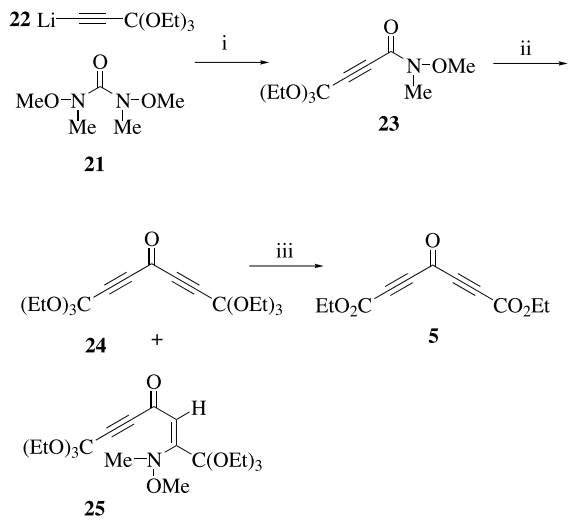


Scheme 3. *Reagents and conditions*: i, **17**, *n*-BuLi, THF, −78°C; **14**–**16**, THF; NH_4Cl, 40–45%; ii, **18**–**20**, Oxone® (2.2 equiv.), TEMPO (10 mol%), NBu_4Br (30 mol%), RT, 91–95%.

with the lithium salt of ethyl propinoate **17** furnished alcohols **18**–**20** in moderate yields (Scheme 3). We found that, in these reactions, the method of quenching was critical in order to isolate the product in reasonable yield. Indeed raising the temperature above −50°C prior to acid quenching caused the almost complete decomposition of the product. However, when the reaction mixture is quenched at −78°C, alcohols **18**–**20** can be isolated in 40–45% yield. Alcohols **18**–**20** were then oxidised using the TEMPO/Oxone® procedure developed by Bolm.[10]

Hence reacting **18**–**20** with 2.2 equiv. of Oxone® in the presence of 10 mol% of TEMPO and 30 mol% of tetrabutylammonium bromide, gave ketones **2**–**4** in high yield, uncontaminated by side products.

We also have revisited our reported route to the symmetric bis-acetylenic ketone **5** bearing two ester functionalities (Scheme 4).[8]

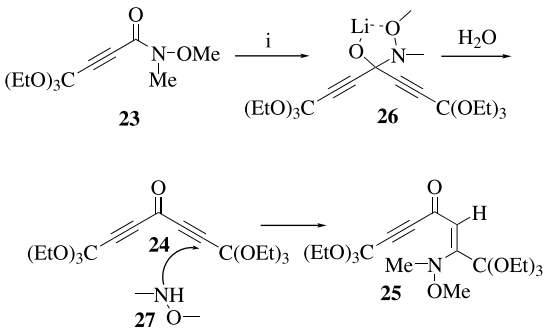


Scheme 4. *Reagents and conditions*: i, **7**, *n*-BuLi, THF, 0°C; **21**, THF, RT, 79%; ii, **7**, *n*-BuLi, THF, 0°C; **23**, THF, RT, 21%; iii, Amberlyst 15®, benzene, RT, 98%.

In the current study, compound **5** was prepared in three steps starting from the double Weinreb amide **21**[11] (Scheme 4). Addition of lithium alkynoate orthoester **22**, generated in situ from **7** and *n*-BuLi, to **21** proceeded smoothly to give the monoacetylenic amide **23** in good isolated yield.

Subsequent reaction of **23** with a second equivalent of **22** led to the formation of the desired symmetric bis acetylenic ketone orthoester **24** in low yield, which upon treatment with Amberlyst 15® resin in benzene was smoothly deprotected to give **5** in 98% yield. Along with **24**, product **25** was also formed in 71% yield.

We have spent some time trying to optimise this reaction. From the onset it was clear that the addition of *N*-methoxy-*N*-methylamine **27** onto the triple bond was taking place during the neutral work up procedure. Indeed, reaction of lithium alkynoate **22** with **23** proceeds via the stabilised lithium adduct **26**, which requires a protic aqueous work up to eliminate amine **27** in the course of liberating the



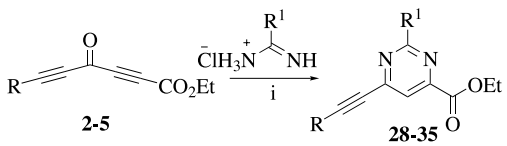
Scheme 5. *Reagents and conditions*: i, **7**, *n*-BuLi, THF, 0°C; **23**, THF, RT.

carbonyl functionality (Scheme 5). However acidic work up conditions are not compatible with the orthoester functionalities of **24**. Indeed, we have tried a number of quenching procedures including dilute hydrochloric acid in water, ammonium chloride in water, ammonium chloride powder, distilled water and found that none of these was efficient. The use of a strong acidic condition led to product decomposition whilst the use of ammonium chloride in water failed to prevent Michael addition of **27** onto the acetylenic moiety. We speculated that as the Michael addition was a bimolecular process, dilution prior to aqueous work up would slow the rate of formation of **25**. The optimised route was thus obtained by diluting the reaction mixture by a factor of 6.

Substitution of *N*,*N*′-dimethoxy-*N*,*N*′-dimethyl urea **21** by ethyl-*N*-methoxy-*N*-methyl-carbamate in the previously reported work[8] led to **24** in reasonable yield (20–25%).

With a range of diacetylenic ketoesters **2–5** in hand we examined their reactivity with a range of nitrogen nucleophiles. Our starting point was to apply the conditions we had developed for the synthesis of heterocyclic substituted non-proteinogenic α-amino acids.[2]

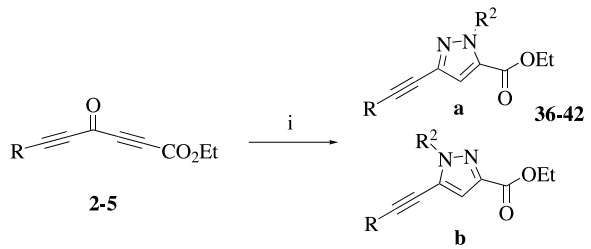
Thus **2–5** were found to react smoothly with amidines to yield a range of densely functionalised pyrimidines **28–35** in high yields (Scheme 6 and Table 1). It is worth noting that compounds **28–35** were obtained as single regioisomers, attributed to the acetylenic carbon bearing the ester group



Scheme 6. *Reagents and conditions*: i, MeCN–H_2O, K_2CO_3; **2–5**, MeCN–H_2O.

Table 1. Preparation of functionalised pyrimidines

Substrate	Compound	R	R^1	Yield (%)
2	**28**	Ph	Ph	90
2	**29**	Ph	SMe	85
3	**30**	C_3H_7	Ph	92
3	**31**	C_3H_7	SMe	90
4	**32**	C_4H_9	Ph	87
4	**33**	C_4H_9	SMe	90
5	**34**	CO_2Et	Ph	80
5	**35**	CO_2Et	SMe	75



Scheme 7. *Reagents and conditions*: i, EtOH, $NH_2NHR{\cdot}H_2O$; **2–5**, EtOH, 0°C, 10 min, then reflux 1 h.

Table 2. Preparation of functionalised pyrazoles

Substrate	Compound	R	R^2	Yield of **a** (%)	Yield of **b** (%)
2	**36**	Ph	Ph	48	24
2	**37**	Ph	H	49	–
3	**38**	C_3H_7	Ph	60	20
3	**39**	C_3H_7	H	51	–
4	**40**	C_4H_9	Ph	60	20
4	**41**	C_4H_9	H	52	–
5	**42**	CO_2Et	H	35	–

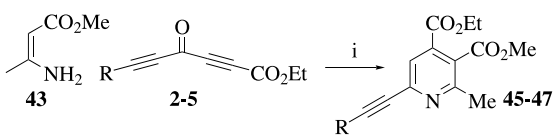
being the most electron deficient, making this the preferential site for nucleophilic attack of the amidine. Remarkably when the bis acetylenic ketoester **5** was used, pyrimidines **34** and **35** were obtained in good yields.

Miller has reported that for symmetrical ketones, after the initial attack of simple nitrogen nucleophiles, the second acetylene moiety becomes deactivated towards further nucleophilic attack, resulting in only mono-addition of the nucleophile.[12] The presence of two equivalent electrophilic centers in this moiety therefore is not detrimental.

We have also observed that diacetylenic ketoesters **2–5** react well with both substituted and unsubstituted hydrazines to give the corresponding pyrazoles **36–42** in good yield (Scheme 7 and Table 2).[13]

When phenylhydrazine was used a mixture of regioisomers **a/b** was generated in a 3:1 ratio for compounds **38–39**.[14] When hydrazine hydrate was used as the nucleophile only regioisomer **a** was observed, presumably resulting from intramolecular hydrogen bonding.

We have also explored the condensation of **2–4** and **5** with enamines **43** (Scheme 8 and Table 3). Bohlmann and Rahtz



Scheme 8. *Reagents and conditions*: i, EtOH, **43**, **2–5**, EtOH, reflux, 6 h.

Table 3. Preparation of functionalised pyridines

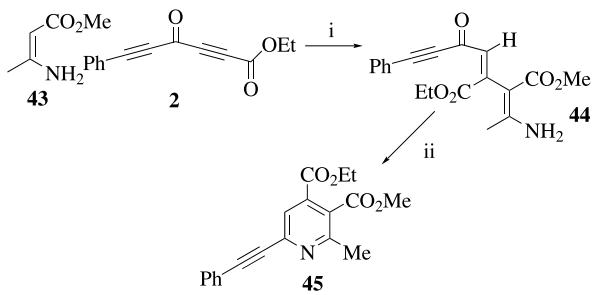
Substrate	Compound	R	Yield (%)
2	**45**	Ph	85
3	**46**	C_3H_7	75
4	**47**	C_4H_9	78
5	**48**	CO_2Et	–

have described the cyclocondensation of enamines with alkynyl ketones to give pyridines in good yields.[15]

Thus reacting ketones **2**–**4** with enaminones in refluxing ethanol afforded pyridines **45**–**47** in good isolated yield. When the symmetric bis acetylenic ester **5** was used, only a complex mixture of product was obtained.

We also have reported a route to pyridines employing the condensation between acetylenic ketones and enamines.[2] In our case it was proved that the enamine adds to the triple bond to give an isolable adduct, which was subsequently heated to give the desired pyridine.

Hence reacting the acetylenic ketone **2** with enamine **43** at room temperature led to isolation of adduct **44** in 74% yield (Scheme 9). Adduct **44** was then condensed to pyridine **45** by heating in refluxing ethanol. The isolation and characterisation of **44** was critical to the assignment of the correct regiochemistry for pyridines **45**–**47**.



Scheme 9. *Reagents and conditions*: i, EtOH, **2**, **43**, RT, 2 h, 74%; ii, EtOH, reflux, 6 h, 84%.

In summary we have shown that it is possible to prepare a range of highly functionalised pyrimidines **28**–**35**, pyrazoles **36**–**42** and pyridines **45**–**47** in good yields by reaction of highly reactive diacetylenic ketones with nitrogen nucleophiles. As ethyl esters and alkynes are versatile groups for synthetic manipulation, we believe these products will be of interest for further synthetic application.

1. Experimental

Anhydrous diethyl ether and tetrahydrofuran were freshly distilled from sodium benzophenone ketyl. Petrol refers to light petroleum (bp 30–40°C). All other solvents used in reactions were spectroscopic grade and used as received. Infrared (IR) spectra of thin films or KBr discs were recorded on a Perkin–Elmer 1750 Fourier transform spectrometer. Absorption maxima are recorded in wavenumbers (cm^{-1} s, m, w) relative to a polystyrene standard. ^1H NMR spectra were recorded on a Brüker AM20 (200 MHz). Chemical shifts (δ_H) are reported in parts per million (ppm) downfield from tetramethylsilane. Coupling constants (J) are reported in hertz (Hz). ^{13}C NMR spectra were recorded on a Brüker AM200 (50.3 MHz). Chemical shifts (δ_C) are reported in parts per million (ppm) downfield from tetramethylsilane. Mass spectra were run on a V. G. Micromass ZAB 1F, V. G. Masslab 20–250 and V.G. Bio-Q instruments as appropriate. Thin layer chromatography (tlc) was performed on Merck silica gel 60 F_{254} 0.25 mm aluminium plates. The plates were visualised using alkaline potassium permanganate and/or irradiation under low-frequency ultraviolet light. Flash chromatography was performed using silica gel 60 (35–75 μm, 200–400 mesh) as the stationary phase. Experimental details for the procedures described in Schemes 1 and 2 has been previously reported.[8]

1.1. General procedure for the preparation of bis acetylenic alcohols 18–20

To a stirred solution of ethyl propiolate (500 mg, 5.1 mmol) in dry THF (8 mL) at −78°C kept under an argon atmosphere, was added *n*-butyllithium (2.3 mL, 2.2 M in hexane, 1 equiv.) over 5 min. The reaction mixture was stirred (15 min) at −78°C before a solution of aldehyde **14**–**16** (5.1 mmol, 1 equiv.) in THF (10 mL) was added via slow addition syringe pump (60 mL/h). The red brown solution so obtained was stirred at −78°C (30 min) and then quenched by slow addition of saturated aqueous ammonium chloride (6 mL). The reaction mixture was then allowed to reach RT, diluted with diethyl ether (20 mL) and washed with $NaHCO_3$ sat. in water (10 mL), then twice with water (10 mL). The organic phase was dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash chromatography to give compounds **18**–**20**.

1.1.1. 4-Hydroxy-6-phenyl-hexa-2,5-diynoic acid ethyl ester 18. Yellow oil (513 mg, 2.25 mmol, 45% yield); R_f=0.25 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 3480s (OH), 2959m (CH), 2934m (CH), 2202m (C≡C), 1713s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 7.50–7.21 (5H, m, Ar), 5.50 (1H, s, CC*H*OHC), 4.50–4.40 (1H, broad, O*H*), 4.29 (2H, q, J=7 Hz, OCH_2CH_3), 1.32 (3H, t, J=7 Hz, OCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$): 153.34 (C=O), 132.09 (CH), 129.26 (CH), 128.43 (CH), 121.51 (C), 85.93 (C≡), 83.98 (C≡), 83.35 (C≡), 75.64 (C≡), 62.53 (CH_2), 52.48 (CH), 14.03 (CH_3); HRMS found: MNH_4^+ 246.1130, $C_{14}H_{16}NO_3$ requires 246.1130; *m/z* (APCI$^+$, NH_3) 246 (100%, MNH_4^+).

1.1.2. 4-Hydroxy-nona-2,5-diynoic acid ethyl ester 19. Yellow oil (397 mg, 2.04 mmol, 41% yield); R_f=0.2 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 3438s (OH), 2967m (CH), 2875m (CH), 2237m (C≡C), 1716s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 5.20 (1H, s, CC*H*OHC), 4.21 (2H, q, J=7 Hz, OCH_2CH_3), 3.70–3.50 (1H, broad, O*H*), 2.17–2.11 (2H, m, $CH_2C_2H_5$), 1.54– 1.32 (2H, m, CH_2CH_2 CH_3), 1.27 (3H, t, J=7 Hz, OCH_2CH_3), 0.94 (3H, t, J=7 Hz, $CH_2CH_2CH_3$); δ_C (50.3 MHz, $CDCl_3$): 153.35 (C=O), 86.93 (C≡), 84.18 (C≡), 73.61 (C≡), 74.84 (C≡), 64.41 (CH_2), 51.95 (CH), 21.62 (CH_2), 20.06 (CH_2), 14.03 (CH_3), 13.40 (CH_3); HMRS found: MNH_4^+ 212.1297, $C_{11}H_{18}NO_3$ requires 212.1287; *m/z* (APCI$^+$, NH_3) 212 (100%, MNH_4^+).

1.1.3. 4-Hydroxy-deca-2,5-diynoic acid ethyl ester 20. Yellow oil (447 mg, 2.15 mmol, 43% yield); R_f=0.2 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 3417s (OH), 2968m (CH), 2873m (CH), 2240m (C≡C), 1715s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 5.19 (1H, s, CC*H*OHC), 4.23 (2H, q, J=7 Hz, OCH_2CH_3), 3.40–3.20 (1H, broad, O*H*), 2.25–2.15 (2H, m, $C_3H_7CH_2$), 1.52– 1.31 (4H, m, $CH_3CH_2CH_2$), 1.26 (3H, t, J=7 Hz, OCH_2CH_3), 0.85 (3H, t, J=7 Hz,

$CH_2CH_2CH_3$); δ_C (50.3 MHz, $CDCl_3$): 153.35 (C═O), 87.10 (C≡), 84.18 (C≡), 75.41 (C≡), 74.81 (C≡), 62.41 (CH_2), 51.93 (CH), 30.20 (CH_2), 21.09 (CH_2), 18.31 (CH_2), 13.98 (CH_3), 13.49 (CH_3); HRMS found: MNH_4^+ 226.1441, $C_{12}H_{20}NO_3$ requires 226.1443; *m/z* (APCI$^+$, NH_3) 226 (100%, MNH_4^+).

1.2. General procedure for the preparation of bis acetylenic ketones 2–4

To a stirred solution of bis acetylenic alcohols **18**–**20** (3 mmol) in toluene (5 mL) were added Oxone® (2.2 equiv.), tetrabutylammonium bromide (30 mol%) and TEMPO (10 mol%). The reaction mixture was stirred at RT for 5 h, then the solids filtered and the solvent removed in vacuo. The product was then purified by flash chromatography [light petroleum/EtOAc (10:1)] to give compounds **2**–**4**.

1.2.1. 4-Oxo-6-phenyl-hexa-2,5-diynoic acid ethyl ester 2. Colourless oil (644 mg, 2.84 mmol, 95% yield); R_f=0.5 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 2984m (CH), 2204m (C≡C), 1720s (CO_2Et), 1631s (C═O); δ_H (200 MHz, $CDCl_3$) 7.67–7.42 (5H, m, Ar), 4.32 (2H, q, *J*=7 Hz, OCH_2CH_3), 1.33 (3H, t, *J*=7 Hz, OCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$) 159.81 (C═O), 151.99 (C═O), 133.61 (CH), 131.92 (CH), 128.75 (CH), 118.65 (C), 99.93 (C≡), 88.69 (C≡),80.79 (C≡), 78.01 (C≡), 63.17 (CH_2), 13.79 (CH_3); HMRS found: MH^+ 227.0630, $C_{14}H_{11}O_3$ requires 227.0708); *m/z* (APCI$^+$, NH_3) 182 (100%, $MH^+-OC_2H_5$).

1.2.2. 4-Oxo-nona-2,5-diynoic acid ethyl ester 3. Colourless oil (524 mg, 2.72 mmol, 91% yield); R_f=0.5 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 2969m (CH), 2211m (C≡C), 1723s (CO_2Et), 1635s (C═O); δ_H (200 MHz, $CDCl_3$) 4.33 (2H, q, *J*=7 Hz, OCH_2CH_3), 2.42 (2H, t, *J*=7 Hz, CH_2C≡), 1.63 (2H, sextet, *J*=7 Hz, CH_3CH_2), 1.30 (3H, t, *J*=7 Hz OCH_2CH_3), 0.99 (3H, t, *J*=7 Hz, CH_3CH_2 CH_2); δ_C (50.3 MHz, $CDCl_3$) 158.89 (C═O), 151.98 (C═O), 99.41 (C≡), 81.57 (C≡), 80.90 (C≡), 76.98 (C≡), 63.15 (CH_2), 21.12 (CH_2), 20.87 (CH_2), 13.86 (CH_3), 13.86 (CH_3); HMRS found: MNH_4^+ 210.1137; $C_{11}H_{16}NO_3$ requires 210.1130; *m/z* (APCI$^+$, NH_3) 148 (100%, $MH^+-OC_2H_5$).

1.2.3. 4-Oxo-deca-2,5-diynoic acid ethyl ester 4. Colourless oil (574 mg, 2.78 mmol, 93% yield); R_f=0.5 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 2928m (CH), 2211m (C≡C), 1721s (CO_2Et), 1636s (C═O); δ_H (200 MHz, $CDCl_3$) 4.33 (2H, q, *J*=7 Hz, OCH_2CH_3), 2.42 (2H, t, *J*=7 Hz, CH_2C≡), 1.63–1.24 (7H, m, $CH_3CH_2CH_2$, OCH_2CH_3), 0.91 (3H, t, *J*=7 Hz, $CH_3CH_2CH_2$); δ_C (50.3 MHz, $CDCl_3$) 158.95 (C═O), 152.02 (C═O), 99.69 (C≡), 81.47 (C≡), 80.93 (C≡), 77.41 (C≡), 63.09 (CH_2), 29.28 (CH_2), 21.90 (CH_2), 18.32 (CH_2), 13.95 (CH_3), 13.42 (CH_3); HMRS found: MNH^+ 224.1292, $C_{12}H_{18}NO_3$ requires 224.1287; *m/z* (APCI$^+$, NH_3) 162 (100%, $MH^+-OC_2H_5$).

1.2.4. Synthesis of 4,4,4-triethoxy-but-2-ynoic acid methoxy-methyl-amide 23. To a stirred solution of trimethylsilyl orthopropiolate triethylester 7[9] (500 mg, 2.0 mmol) in dry THF (10 mL) and kept at 0°C, was added *n*-butyllithium (1.05 mL, of a 1.9 M solution in hexanes, 2.0 mmol, 1 equiv.). The resultant solution was allowed to warm to RT and stir for a further hour before being transferred *via* cannular into a solution of *N*,*N*′-dimethoxy-*N*,*N*′-dimethyl urea 21[11] (270 mg, 2 mmol, 1 equiv.) in dry THF (20 mL) at −78°C. The resultant solution was allowed to stir at this temperature for 30 min before being allowed to warm to RT and stirred for a further hour. The mixture was diluted with ether (20 mL) and washed with water (4×10 mL). The organic phase was dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash chromatography [30% ethyl acetate in petrol] to give **23** as a colourless liquid (410 mg, 79% yield). R_f=0.6 [30% ethyl acetate in petrol]; ν_{max} (film, cm^{-1}) 2978m (CH), 2873w (CH), 2239m (C≡C), 1655s (C═O); δ_H (200 MHz, $CDCl_3$) 3.74 (3H, s), 3.68 (6H, q, *J*=7 Hz, O–CH_2CH_3), 3.20 (3H, s), 1.21 (9H, t, *J*=7 Hz, O–CH_2CH_3); δ_C (50.3 MHz, $CDCl_3$) 153.12 (C═O), 108.72 [$C(OCH_2CH_3)_3$], 84.15 (C≡), 74.61 (C≡), 62.17 (CH_2), 59.28 (CH_3), 32.23 (CH_3), 14.75 (CH_3); HMRS found: MNa^+ 282.1314, $C_{12}H_{21}NO_5Na$ requires 282.1317; *m/z* (APCI$^+$, Na) 282 (100%, MNa^+).

1.2.5. Synthesis of 1,1,1,7,7,7-hexaethoxy-hepta-2,5-diyn-4-one 24. To a stirred solution of trimethylsilyl orthopropiolate triethylester 7[9] (250 mg, 1.0 mmol) in dry THF (5 mL) at 0°C, was added *n*-butyllithium (0.55 mL, of a 1.9 M solution in hexanes, 1.0 mmol, 1 equiv.). The resultant solution was allowed to warm to RT and stirred for a further hour before being transferred via cannular into a solution of 4,4,4-triethoxybut-2-ynoic acid methoxy-methyl-amide **23** (260 mg, 1.0 mmol, 1 equiv.) in dry THF (10 mL) at −78°C. The resultant solution was allowed to stir at this temperature for 30 min before being allowed to warm to RT and stirred for a further hour. The mixture was diluted with ether (100 mL) and washed with water (4×20 mL). The organic phase was dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash chromatography [3% diethyl ether in petrol] to give **24** as a colourless liquid (79 mg, 21% yield). R_f=0.2 [3% diethyl ether in petrol]; ν_{max} (film, cm^{-1}) 2928m (CH), 2211m (C≡C), 1747m (C═O); δ_H (200 MHz, $CDCl_3$) 3.67 (12H, q, *J*=7 Hz, OCH_2CH_3), 1.24 (18H, t, *J*=7 Hz, OCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$) 158.88 (C═O), 108.56 [$C(OCH_2CH_3)_3$], 85.77 (C≡), 81.03 (C≡), 59.42 (CH_2), 14.66 (CH_3); HMRS found: MH^+ 371.1991, $C_{19}H_{31}O_7$ requires 371.2069; *m/z* (APCI$^+$, NH_3) 194 (100%).

1.2.6. 1,1,1,7,7,7-Hexaethoxy-2-(*N*-methoxy-*N*-methyl-amino)-hept-2-en-5-yn-4-one 25. Yellow oil (306 mg, 0.71 mmol, 71% yield); R_f=0.5 [50% ethyl acetate in petrol]; ν_{max} (film, cm^{-1}) 2970m (CH), 2897m (CH), 2221m (C≡C), 1710s (C═O); δ_H (200 MHz, $CDCl_3$) 5.72 (1H, s, C*H*═C), 3.68 (6H, q, *J*=7 Hz, OCH_2CH_3), 3.58 (3H, s, OCH_3), 3.49 (6H, q, *J*=7 Hz, OCH_2CH_3), 3.30 (3H, s, NCH_3), 1.18 (18H, t, *J*=7 Hz, OCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$): 172.31 (C═O), 151.05 (C═), 111.06 (CH═), 109.15 (C), 84.32 (C≡), 80.09 (C≡), 59.18 (CH_2), 58.41 (CH_2), 41.84 (OCH_3), 32.25 (NCH_3), 14.51 (CH_3), 14.26 (CH_3); HMRS found: MH^+ 432.2596, $C_{21}H_{38}NO_8$ requires 432.2597; *m/z* (APCI$^+$) 432 (MH^+, 100%).

1.2.7. Synthesis of 4-oxo-hepta-2,5-diynedioic acid diethyl ester 5. Amberlyst 15® (120 mg) was added in one portion to a stirred solution of **24** (75 mg) in benzene (10 mL). The resultant suspension was stirred at RT for 15 min before the solids were removed by filtration and the solvent removed in vacuo to yield a yellow oil (48 mg, 97%); R_f=0.3 [3% diethyl ether in petrol]; ν_{max} (film, cm^{-1}) 2928m (CH), 2223m (C≡C), 1725s (CO_2Et), 1655s (C=O); δ_H (200 MHz, $CDCl_3$) 4.32 (4H, q, J=7 Hz, OCH_2CH_3), 1.35 (6H, t, J=7 Hz, OCH_2CH_3); this compound gave unsatisfactory mass spectral data and rapidly decomposed after being generated.

1.3. General procedure for the preparation of pyrimidines 28–35

A solution of freshly prepared ketone **2**–**5** (1.0 equiv.) in MeCN–H_2O [10:1] (50 mg/3 cm^3) was added to a stirred solution of the amidine (1.5 equiv.) and K_2CO_3 (3.0 equiv.) in MeCN–H_2O [10:1] (100 mg/10 cm^3). The resultant deep red solutions were stirred at room temperature for 30 min before being absorbed onto silica gel and purified by flash chromatography [light petroleum/EtOAc (10:1)].

1.3.1. 2-Phenyl-6-phenylethynylpyrimidine-4-carboxylic acid ethyl ester 28. Yellow oil (56 mg, 0.170 mmol, 85% yield); R_f=0.5 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 2981m (CH), 2930m (CH), 2217m (C≡C), 1749s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 8.59–8.54 (2H, m, Ar), 7.56 (1H, s, C*H*), 7.70–7.66 (3H, m, Ar), 7.46–7.41 (5H, m, Ar), 4.41 (2H, q, J=7 Hz, O–CH_2CH_3), 1.49 (3H, t, J=7 Hz, OCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$) 165.59 (C=O), 164.15, 155.72, 153.13, 136.48, 132.45, 131.35, 130.02, 128.75, 128.58, 120.66, 97.77 (C≡), 87.09 (C≡), 62.55 (CH_2), 14.18 (CH_3); HMRS found: MH^+ 329.1221, $C_{21}H_{17}N_2O_2$ requires 329.1290; *m/z* (EI) 329 (100%, MH^+).

1.3.2. 2-Methylthio-6-phenylethynyl pyrimidine-4-carboxylic acid ethyl ester 29. Yellow oil (51 mg, 0.170 mmol, 85% yield); R_f=0.5 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 2984m (CH), 2928m (CH), 2215m (C≡C), 1727s (CO_2Et); δ_H 7.73 (1H, s, C*H*), 7.65–7.60 (2H, m, Ar), 7.44–7.39 (3H, m, Ar), 4.45 (2H, q, J=7 Hz, OCH_2CH_3), 2.64 (3H, s, SCH_3), 1.43 (3H, t, J=7 Hz, OCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$) 163.65 (C=O), 155.24, 152.76, 132.45, 130.14, 128.53, 121.1, 118.01, 94.66 (C≡), 89.44 (C≡), 62.59 (CH_2), 44.96 (SCH_3), 14.13 (CH_3); HMRS found: MH^+ 299.0790, $C_{16}H_{15}SN_2O_2$ requires 299.0854; *m/z* (EI) 299 (100%, MH^+).

1.3.3. 6-Pent-1-ynyl-2-phenyl-pyrimidine-4-carboxylic acid ethyl ester 30. Yellow oil (54 mg, 0.183 mmol, 92% yield); R_f=0.5 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 2964m (CH), 2930m (CH), 2231m (C≡C), 1747s (CO_2Et); δ_H 8.54–8.29 (2H, m, Ar), 7.56 (1H, s, C*H*), 7.52–7.27 (3H, m, Ar), 4.48 (2H, q, J=7 Hz, OCH_2CH_3), 2.50 (2H, t, J=7 Hz, CH_2–C≡), 1.70 (2H, m, CH_2–C≡), 1.47 (3H, t, J=7 Hz, O–CH_2CH_3), 1.09 (3H, t, J=7 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 165.39 (C=O), 164.24, 153.55, 136.51, 131.24, 128.68, 128.50, 120.64, 97.51 (C≡), 79.94 (C≡), 62.47 (CH_2), 44.96 (CH_2), 21.52 (CH_2), 14.15 (CH_3), 13.59 (CH_3); HMRS found: MH^+ 295.1638, $C_{18}H_{19}N_2O_2$ requires 295.1447; *m/z* (EI) 295 (100%, MH^+).

1.3.4. 2-Methylthio-6-pent-1-ynyl-pyrimidine-4-carboxylic acid ethyl ester 31. Yellow oil (47 mg, 0.178 mmol, 90% yield); R_f=0.5 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 2964m (CH), 2930m (CH), 2231m (C≡C), 1749s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 7.56 (1H, s, C*H*), 4.41 (2H, q, J=7 Hz, OCH_2CH_3), 2.59 (3H, s, SCH_3), 2.49 (2H, t, J=7 Hz, CH_2–C≡), 1.64 (2H, m, CH_2–CH_2–C≡), 1.40 (3H, t, J=7 Hz, OCH_2CH_3), 1.04 (3H, t, J=7 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 173.92 (C=O), 153.18 (C), 152.11 (C), 117.95 (CH), 98.07 (C≡), 83.00 (C≡), 62.49 (CH_2), 44.96 (CH_2), 21.44 (CH_2), 18.65 (CH_3), 14.24 (CH_2), 14.10 (CH_3), 13.58 (CH_3); HMRS found: MH^+ 265.0932, $C_{13}H_{17}SN_2O_2$ requires 265.1011; *m/z* (EI) 265 (100%, MH^+).

1.3.5. 6-Hex-1-ynyl-2-phenyl-pyrimidine-4-carboxylic acid ethyl ester 32. Yellow oil (53 mg, 0.172 mmol, 87% yield); R_f=0.5 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 2959m (CH), 2934m (CH), 2234m (C≡C), 1749s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 8.54–8.49 (2H, m, Ar), 7.86 (1H, s, C*H*), 7.50–7.45 (3H, m, Ar), 4.49 (2H, q, J=7 Hz, OCH_2CH_3), 2.57 (2H, t, J=7 Hz, CH_2–C≡), 1.86–1.43 (7H, m, $CH_2CH_2CH_2$–C≡, OCH_2CH_3), 0.97 (3H, t, J=7 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 165.39 (C=O), 164.24, 155.49, 136.51, 131.21, 128.64, 128.47, 120.61, 97.68 (C≡), 79.78 (C≡), 62.45 (CH_2), 44.96 (CH_2), 30.00 (CH_2), 22.02 (CH_2), 14.15 (CH_3), 13.54 (CH_3); HMRS found: MH^+ 309.1542, $C_{19}H_{21}N_2O_2$ requires 309.1603; *m/z* (EI) 309 (100%, MH^+).

1.3.6. 6-Hex-1-ynyl-2-methylthio-pyrimidine-4-carboxylic acid ethyl ester 33. Yellow oil (47 mg, 0.169 mmol, 85% yield); R_f=0.5 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 2994m (CH), 2930m (CH), 2232m (C≡C), 1749s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 7.55 (1H, s, C*H*), 4.41 (2H, q, J=7 Hz, OCH_2CH_3), 2.58 (3H, s, SCH_3), 2.49 (2H, t, J=7 Hz, CH_2–C≡), 1.66–1.36 (7H, m, $CH_2CH_2CH_2$–C≡, OCH_2CH_3), 0.94 (3H, t, J=7 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 173.70 (C=O), 155.04, 153.18, 117.93, 98.25 (C≡), 77.02 (C≡), 62.47 (CH_2), 44.11 (CH_3), 29.93 (CH_2), 21.93 (CH_2), 19.18 (CH_2), 14.07 (CH_3), 13.48 (CH_3); HMRS found: MH^+ 279.0199, $C_{14}H_{19}SN_2O_2$ requires 279.01167; *m/z* EI) 279 (100%, MH^+).

1.3.7. 6-Ethoxycarbonylethynyl-2-phenyl-pyrimidine-4-carboxylic acid ethyl ester 34. Yellow oil (52 mg, 0.160 mmol, 80% yield); R_f=0.30 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 3019m (CH), 2938m (CH), 2234m (C≡C), 1719s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 8.56–8.51 (2H, m, Ar), 8.01 (1H, s, C*H*), 7.56–7.40 (3H, m, Ar), 4.53 (2H, q, J=7 Hz, OCH_2CH_3), 4.36 (2H, q, J=7 Hz, O–CH_2CH_3), 1.48 (3H, t, J=7 Hz, CH_3), 1.39 (3H, t, J=7 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 165.86 (C=O), 163.56 (C=O), 156.40, 152.69, 150.44, 135.86, 131.81, 128.79, 128.63, 121.25, 82.66 (C≡), 80.99 (C≡), 62.88 (CH_2), 62.81 (CH_2), 14.16 (CH_3), 13.99 (CH_3); HMRS found: MH^+ 325.1188, $C_{18}H_{17}N_2O_4$ requires 325.1188; m/z (EI) 325 (100%, MH^+).

1.3.8. 6-Ethoxycarbonylethynyl-2-methylsulfanyl-pyrimidine-4-carboxylic acid ethyl ester 35. Yellow oil (47 mg, 0.160 mmol, 80% yield); R_f=0.30 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 3018m (CH), 2933m (CH),

2235m (C≡C), 1719s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 7.75 (1H, s, C*H*), 4.43 (2H, q, *J*=7 Hz, OCH_2CH_3), 4.34 (2H, q, *J*=7 Hz, OCH_2CH_3), 2.61 (3H, s, SCH_3), 1.43 (3H, t, *J*=7 Hz, CH_3), 1.36 (3H, t, *J*=7 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 174.88 (C=O), 163.04 (C=O), 155.90, 152.54, 150.08, 118.49, 82.96 (C≡), 80.47 (C≡), 62.87 (CH_2), 62.81 (CH_2), 14.16 (CH_3), 13.94 (CH_3); HMRS found: MH^+ 295.0754, $C_{13}H_{15}N_2O_4S$ requires 295.0753; *m/z* (EI) 295 (100%, MH^+).

1.4. General procedure for the preparation of pyrazoles 36–42

Phenylhydrazine or hydrazine hydrate (1.5 equiv.) was slowly added to a cooled (0°C) solution of the respective freshly prepared ketone (1.0 equiv.) in EtOH (50 mg/10 cm^3). The resultant solutions were stirred at this temperature for 10 min, then heated at reflux for 1 h before being absorbed onto silica gel and each regioisomer **a** and **b** purified by flash chromatography [light petroleum/EtOAc (10:1) or light petroleum/EtOAc (1:1)].

1.4.1. 2-Phenyl-5-phenylethynyl-2*H*-pyrazole-3-carboxylic acid ethyl ester 36a. Yellow oil (30 mg, 0.09 mmol, 48% yield); R_f=0.6 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 2985m (CH), 2932m (CH), 2244m (C≡C), 1732s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 7.59–7.34 (11H, m, Ar and C*H*), 4.28 (2H, q, *J*=7 Hz, OCH_2CH_3), 1.22 (3H, t, *J*=7 Hz, OCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$) 159.51 (C=O), 148.6 (C), 139.71 (C), 132.71 (CH), 129.15 (CH), 128.22 (CH), 128.10 (CH), 126.11 (C), 126.00 (CH), 122.98 (C), 118.23 (CH), 110.00 (CH), 92.73 (C≡), 89.68 (C≡), 59.10 (CH_2), 13.61 (CH_3); HMRS found: MH^+ 317.1233, $C_{20}H_{17}N_2O_2$ requires 317.1290; *m/z* (EI) 317 (100%, MH^+).

1.4.2. 1-Phenyl-5-phenylethynyl-1*H*-pyrazole-3-carboxylic acid ethyl ester 36b. Yellow oil (15 mg, 0.05 mmol, 24% yield); R_f=0.4; ν_{max} (film, cm^{-1}) 2985m (CH), 2932m (CH), 2244m (C≡C), 1732s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 7.59–7.34 (11H, m, Ar and C*H*), 4.48 (2H, q, *J*=7 Hz, OCH_2CH_3), 1.43 (3H, t, *J*=7 Hz, OCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$) 165.49 (C=O), 140.92 (C), 139.18 (C), 134.87 (C), 132.70 (CH), 129.30 (CH), 128.25 (CH), 127.03 (CH), 126.22 (CH), 122.76 (C), 118.30 (CH), 110.73 (CH), 84.96 (C≡), 78.12 (C≡), 59.16 (CH_2), 13.48 (CH_3); HMRS found: MH^+ 317.1233, $C_{20}H_{17}N_2O_2$ requires 317.1229; *m/z*(EI) 317 (100%, MH^+).

1.4.3. 5-Phenylethynyl-2*H*-pyrazole-3-carboxylic acid ethyl ester 37. Yellow oil (23 mg, 0.09 mmol, 49% yield); R_f=0.5 [light petroleum/EtOAc (1:1)]; ν_{max} (film, cm^{-1}) 3343m (NH), 2985m (CH), 2932m (CH), 2234m (C≡C), 1725s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 7.61–7.41 (5H, m, Ar), 7.34 (1H, s, C*H*), 4.41 (2H, q, *J*=7 Hz, OCH_2CH_3), 1.49 (3H, t, *J*=7 Hz, OCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$) 165.85 (C=O), 141.33 (C), 133.95 (C), 132.09 (CH), 128.11 (CH), 128.01 (CH), 122.92 (C), 105.39 (CH), 84.36 (C≡), 78.11 (C≡), 61.28 (CH_2), 13.59 (CH_3); HMRS found: MH^+ 241.0899, $C_{14}H_{13}N_2O_2$ requires 241.0977; *m/z* (EI) 241 (100%, MH^+).

1.4.4. 5-Pent-1-ynyl-2-phenyl-2*H*-pyrazole-3-carboxylic acid ethyl ester 38a. Yellow oil (34 mg, 0.120 mmol, 60% yield); R_f=0.6 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 2985m (CH), 2932m (CH), 2244m (C≡C), 1732s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 7.43 (5H, m, Ar), 7.04 (1H, s, C*H*), 4.21 (2H, q, *J*=7 Hz, OCH_2CH_3), 2.43 (2H, t, *J*=7 Hz, CH_2–C≡), 1.71–1.24 (5H, m, CH_2CH_2–C≡, OCH_2CH_3), 0.94 (3H, t, *J*=7 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 158.46 (C=O), 139.84 (C), 135.82 (C), 133.48 (C), 128.54 (CH), 128.26 (CH), 125.83 (CH), 115.22 (CH), 92.08 (C≡), 72.16 (C≡), 61.04 (CH_2), 21.65 (CH_2), 21.12 (CH_2), 13.73 (CH_3), 13.31 (CH_3); HMRS found: MH^+ 283.1572, $C_{17}H_{19}N_2O_2$ requires 283.1447; *m/z* (EI) 283 (100%, MH^+).

1.4.5. 5-Pent-1-ynyl-1-phenyl-1*H*-pyrazole-3-carboxylic acid ethyl ester 38b. Yellow oil (11 mg, 0.04 mmol, 20% yield); R_f=0.4 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 2985m (CH), 2932m (CH), 2244m (C≡C), 1732s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 7.78–7.74 (2H, m, Ar), 7.47–7.42 (3H, m, Ar), 7.03 (1H, s, C*H*), 4.41 (2H, q, *J*=7 Hz, OCH_2CH_3), 2.39 (2H, t, *J*=7 Hz, CH_2–C≡), 1.59–1.24 (5H, m, CH_2CH_2–C≡, OCH_2CH_3), 0.94 (3H, t, *J*=7 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 161.75 (C=O), 143.87 (C), 139.17 (C), 129.34 (C), 128.50 (CH), 128.09 (CH), 126.89 (CH), 113.75 (CH), 98.88 (C≡), 69.12 (C≡), 60.92 (CH_2), 21.31 (CH_2), 21.25 (CH_2), 14.12 (CH_3), 13.80 (CH_3); HMRS found: MH^+ 283.1572, $C_{17}H_{19}N_2O_2$ requires 283.1447; *m/z* (EI) 283 (100%, MH^+).

1.4.6. 5-Pent-1-ynyl-2*H*-pyrazole-3-carboxylic acid ethyl ester 39. Yellow oil (21 mg, 0.102 mmol, 51% yield); R_f=0.5 [light petroleum/EtOAc (1:1)]; ν_{max} (film, cm^{-1}) 3343m (NH), 2985m (CH), 2932m (CH), 2234m (C≡C), 1725s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 6.87 (1H, s, C*H*), 4.36 (2H, q, *J*=7 Hz, OCH_2CH_3), 2.41 (2H, t, *J*=7 Hz, CH_2C≡), 1.58–1.24 (5H, m, CH_2CH_2C≡, OCH_2CH_3), 0.91 (3H, t, *J*=7 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 158.65 (C=O), 139.92 (C), 135.95 (C), 115.39 (CH), 92.48 (C≡), 72.11 (C≡), 61.28 (CH_2), 30.39 (CH_2), 19.01 (CH_2), 13.95 (CH_3), 13.59 (CH_3); HMRS found: MH^+ 207.1055, $C_{11}H_{15}N_2O_2$ requires 207.1134; *m/z* (EI) 207 (100%, MH^+).

1.4.7. 5-Hex-1-ynyl-2-phenyl-2*H*-pyrazole-3-carboxylic acid ethyl ester 40a. Yellow oil (35 mg, 0.120 mmol, 60% yield); R_f=0.6 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 2985m (CH), 2932m (CH), 2244m (C≡C), 1732s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 7.43 (5H, m, Ar), 7.04 (1H, s, C*H*), 4.21 (2H, q, *J*=7 Hz, OCH_2CH_3), 2.43 (2H, t, *J*=7 Hz, CH_2C≡), 1.71–1.24 (7H, m, $CH_2CH_2CH_2C$≡, OCH_2CH_3), 0.94 (3H, t, *J*=7 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 158.52 (C=O), 139.81 (C), 135.84 (C), 133.46 (C), 128.67 (CH), 128.37 (CH), 125.88 (CH), 115.29 (CH), 92.35 (C≡), 72.03 (C≡), 61.18 (CH_2), 30.28 (CH_2), 21.87 (CH_2), 18.90 (CH_2), 13.85 (CH_3), 13.50 (CH_3); HMRS found: MH^+ 297.1542, $C_{18}H_{21}N_2O_2$ requires 297.1603; *m/z* (EI) 297 (100%, MH^+).

1.4.8. 5-Hex-1-ynyl-2-phenyl-1*H*-pyrazole-3-carboxylic acid ethyl ester 40b. Yellow oil (12 mg, 0.04 mmol, 20% yield); R_f=0.4 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 2985m (CH), 2932m (CH), 2244m (C≡C), 1732s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 7.78–7.74 (2H, m, Ar), 7.47–7.42 (3H, m, Ar), 7.03 (1H, s, C*H*), 4.41 (2H, q, *J*=7 Hz, OCH_2CH_3), 2.39 (2H, t, *J*=7 Hz, CH_2C≡),

1.59–1.24 (7H, m, $CH_2CH_2CH_2C\equiv$, OCH_2CH_3), 0.94 (3H, t, J=7 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 161.90 (C=O), 143.84 (C), 139.20 (C), 128.65 (C), 128.26 (CH), 127.03 (CH), 124.15 (CH), 113.85 (CH), 99.18 (C≡), 69.06 (C≡), 61.11 (CH_2), 29.97 (CH_2), 21.78 (CH_2), 19.07 (CH_2), 14.29 (CH_3), 13.44 (CH_3); HMRS found: MH^+ 297.1542, $C_{18}H_{21}N_2O_2$ requires 297.1603; *m/z* (EI) 297 (100%, MH^+).

1.4.9. 5-Hex-1-ynyl-2*H*-pyrazole-3-carboxylic acid ethyl ester 41. Yellow oil (23 mg, 0.104 mmol, 52% yield); R_f=0.5 [light petroleum/EtOAc (1:1)]; ν_{max} (film, cm^{-1}) 3343m (NH), 2985m (CH), 2932m (CH), 2234m (C≡C), 1725s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 6.87 (1H, s, C*H*), 4.36 (2H, q, J=7 Hz, OCH_2CH_3), 2.41 (2H, t, J=7 Hz, CH_2–C≡), 1.58–1.24 (7H, m, $CH_2CH_2CH_2$–C≡, OCH_2CH_3), 0.91 (3H, t, J=7 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 158.65 (C=O), 139.92 (C), 135.95 (C), 115.39 (CH), 92.48 (C≡), 72.11 (C≡), 61.28 (CH_2), 30.39 (CH_2), 21.97 (CH_2), 19.01 (CH_2), 13.95 (CH_3), 13.59 (CH_3); HMRS found: MH^+ 221.1232, $C_{12}H_{17}N_2O_2$ requires 221.1290; *m/z* (EI) 221 (100%, MH^+).

1.4.10. 5-Ethoxycarbonylethynyl-2*H*-pyrazole-3-carboxylic acid ethyl ester 42. Yellow oil (16 mg, 0.067 mmol, 35% yield); R_f=0.51 [light petroleum/EtOAc (1:1)]; ν_{max} (film, cm^{-1}) 3264m (NH), 2981m (CH), 2934m (CH), 2235m (C≡C), 1712s (CO_2Et); δ_H (200 MHz, $CDCl_3$) 7.11 (1H, s, C*H*), 4.43 (2H, q, J=7 Hz, OCH_2CH_3), 4.32 (2H, q, J=7 Hz, OCH_2CH_3), 1.7–1.6 (1H, broad, N*H*), 1.42 (3H, t, J=7 Hz, CH_3), 1.37 (3H, t, J=7 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 159.15 (C=O), 153.30 (C=O), 131.02 (C), 128.22 (C), 114.19 (CH), 97.03 (C≡), 82.95 (C≡), 62.36 (CH_2), 61.79 (CH_2), 14.10 (CH_3), 13.91 (CH_3); HMRS found: MH^+ 237.0870, $C_{11}H_{13}N_2O_4$ requires 237.0875; m/z (EI) 237 (100%, MH^+).

1.4.11. Synthesis of 2-(1-amino-ethylidene)-3-(2-oxo-4-phenyl-but-3-ynylidene)-succinic acid 4-ethyl ester 1-methyl ester 44. 3-Amino-but-2-enoic acid methyl ester **43** (27 mg, 0.24 mmol, 1.2 equiv.) was added to a stirred solution freshly prepared ketone **2** (45 mg, 0.20 mmol, 1.0 equiv.) in EtOH (5 cm^3). The resultant solution was stirred for 2 h at RT before being absorbed onto silica gel and purified by flash chromatography [light petroleum/EtOAc (10:1)]. Yellow oil (53 mg, 0.170 mmol, 85% yield); R_f=0.6 [light petroleum/EtOAc (1:1)]; ν_{max} (film, cm^{-1}) 3090s (NH), 2975m (CH), 2901m (CH), 2215m (C≡C), 1730s (CO_2R); δ_H (200 MHz, $CDCl_3$) 8.85 (1H, s, N*H*), 7.60–7.50 (2H, m, Ar), 7.40–7.20 (3H, m), 6.95 (1H, s, C*H*), 5.45 (1H, s, N*H*), 4.27 (2H, q, J=7 Hz, OCH_2CH_3), 3.62 (3H, s, CH_3O), 1.83 (3H, s, CH_3C=), 1.25 (3H, t, J=7 Hz, OCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$) 177.90 (C=O), 168.54 (C=O), 168.10 (C=O), 142.39 (C), 135.37 (CH), 133.61 (CH), 130.82 (CH), 128.63 (CH), 120.03 (C), 93.20 (C), 90.90 (C≡), 88.52 (C≡), 61.84 (CH_2), 50.95 (OCH_3), 20.80 (CH_3C=), 14.21 (CH_3); HMRS found: MH^+ 342.1342, $C_{19}H_{20}NO_5$ requires 342.1341; *m/z* (EI) 342 (MH^+).

1.5. General preparation of pyridines 45–47

3-Amino-but-2-enoic acid methyl ester **43** (1.2 equiv.) was added to a stirred solution of the respective freshly prepared ketone (1.0 equiv.) in EtOH (50 mg/5 cm^3). The resultant solutions were heated at reflux for 6 h before being absorbed onto silica gel and purified by flash chromatography [light petroleum/EtOAc (10:1)].

1.5.1. 2-Methyl-6-phenylethynyl-pyridine-3,4-dicarboxylic acid 4-ethyl ester 3-methyl ester 45. Colourless oil (55 mg, 0.170 mmol, 85% yield); R_f=0.8 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 3020m (CH), 2968m (CH), 2230m (C≡C), 1730s (CO_2R); δ_H (200 MHz, $CDCl_3$) 7.85 (1H, s, C*H*), 7.70–7.55 (2H, m, Ar), 7.50–7.30 (3H, m, Ar), 4.43 (2H, q, J=7 Hz, OCH_2CH_3), 3.95 (3H, s, OCH_3), 2.61 (3H, s, CH_3C=), 1.43 (3H, t, J=7 Hz, OCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$) 168.48 (C=O), 164.44 (C=O), 157.02 (C), 144.39, 136.67, 132.41, 129.62, 128.63, 127.43, 124.01, 121.82, 91.36 (C≡), 87.82 (C≡), 62.44 (CH_2), 52.85 (OCH_3), 22.50 (CH_3C=), 13.91 (CH_3); HMRS found: MH^+ 324.1230, $C_{19}H_{18}NO_4$ requires 324.1236; *m/z* (EI) 324 (100%, MH^+).

1.5.2. 2-Methyl-6-pent-1-ynyl-pyridine-3,4-dicarboxylic acid 4-ethyl ester 3-methyl ester 46. Colourless oil (43 mg, 0.148 mmol, 75% yield); R_f=0.5 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 3020m (CH), 2968m (CH), 2233m (C≡C), 1731s (CO_2R); δ_H (200 MHz, $CDCl_3$) 7.68 (1H, s, C*H*), 4.36 (2H, q, J=7 Hz, OCH_2CH_3), 3.91 (3H, s, OCH_3), 2.57 (3H, s, CH_3C=), 2.43 (2H, t, J=7 Hz, $CH_2C\equiv$), 1.65 (2H, sextet, J=7 Hz, J=7 Hz, $CH_3CH_2CH_2C\equiv$), 1.37 (3H, t, J=7 Hz, CH_3CH_2O), 1.08–1.01 (3H, t, J=7 Hz, CH_3CH_2 CH_2); δ_C (50.3 MHz, $CDCl_3$) 168.37 (C=O), 164.34 (C=O), 156.74 (C), 144.78 (C), 136.41 (C), 126.86 (C), 123.41 (CH), 93.54 (C≡), 79.83 (C≡), 62.49 (CH_2), 52.94 (OCH_3), 22.62 (CH_3C=), 21.72 (CH_2), 21.47 (CH_2), 14.13 (CH_3), 13.71 (CH_3); HMRS found: MH^+ 290.1391, $C_{16}H_{20}NO_4$ requires 290.1392; *m/z* (EI) 290 (100%, MH^+).

1.5.3. 6-Hex-1-ynyl-2-methyl-pyridine-3,4-dicarboxylic acid 4-ethyl ester 3-methyl ester 47. Colourless oil (47 mg, 0.155 mmol, 78% yield); R_f=0.5 [light petroleum/EtOAc (10:1)]; ν_{max} (film, cm^{-1}) 3020m (CH), 2968m (CH), 2233m (C≡C), 1731s (CO_2R); δ_H (200 MHz, $CDCl_3$) 7.68 (1H, s, C*H*), 4.35 (2H, q, J=7 Hz, OCH_2CH_3), 3.93 (3H, s, OCH_3), 2.61 (3H, s, CH_3C=), 2.46 (2H, t, J=Hz, $CH_2C\equiv$), 1.73–1.44 (4H, m, $CH_3CH_2CH_2$), 1.37 (3H, t, J=7 Hz, CH_3CH_2O), 0.95 (3H, t, J=7 Hz, $CH_3CH_2CH_2$); δ_C (50.3 MHz, $CDCl_3$) 168.3 (C=O), 164.3 (C=O), 156.6 (C), 144.7 (C), 136.4 (C), 126.8 (C), 123.4 (CH), 93.7 (C≡), 79.7 (C≡), 62.4 (CH_2), 52.8 (OCH_3), 30.3 (CH_2), 22.6 (CH_3), 22.1 (CH_2), 19.2 (CH_2), 14.1 (CH_3), 13.6 (CH_3). HMRS found: MH^+ 304.1549, $C_{17}H_{22}NO_4$ requires 304.1549; *m/z* (EI) 304 (100%, MH^+).

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