Tuned methods for conjugate addition to a vinyl oxadiazole; synthesis of pharmaceutically important motifs†

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The addition of various nucleophiles to a vinyl 1,2,4-oxadiazole is described. Following optimisation, individual protocols tuned for the use of each specific class of reagent have been developed to allow the installation of nitrogen, sulfur, oxygen, and carbon nucleophiles, and leading to the preparation of a series of compounds containing the pharmaceutically important oxadiazole motif.

Introduction

The 1,2,4-oxadiazole motif is an important pharmacophore within medicinal chemistry and can be regarded as a bioisosteric, and metabolically stable, replacement for an ester unit.[1] Indeed, the 1,2,4-oxadiazole is present in several notable drug molecules, including antitussive drugs, such as Perebron, **1**,[2] and Libexin, **2**,[3] as well as the serotonin agonist **3**, for the treatment of migraine,[4] and L-690548, **4**, for the treatment of Alzheimer's disease (Fig. 1).[5]

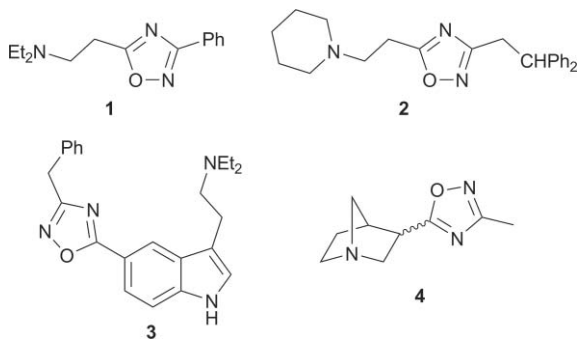
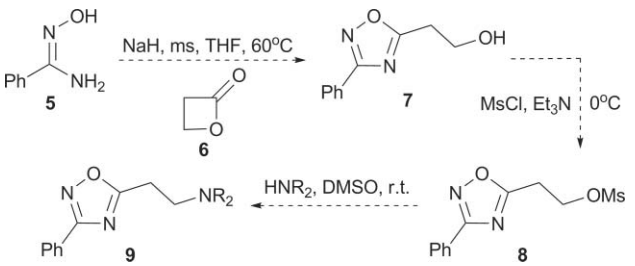


Fig. 1 Therapeutic compounds containing the 1,2,4-oxadiazole unit.

Additionally, compounds containing the oxadiazole motif have been the subject of interest as novel 5-HT_3 antagonists.[6] A number of such compounds have been shown to be effective in the control of cancer chemotherapy-induced emesis,[7] and evidence suggests therapeutic benefits towards migraine,[8] schizophrenia,[9] and anxiety.[10] Therefore, considering the range of potential biological applications, the formulation of more efficient synthetic strategies to access functionalised compounds containing the 1,2,4-oxadiazole motif has emerged as an attractive preparative goal.

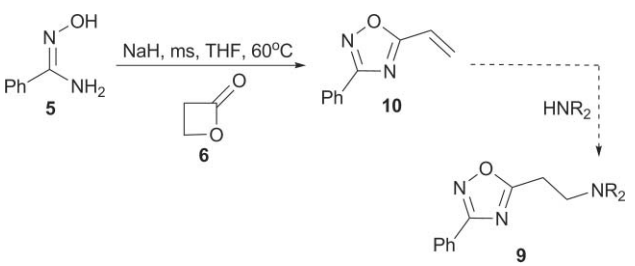
Accessing oxadiazolylethylamines

Recently, in efforts to access oxadiazolyl small molecules possessing an ethylamine motif, we envisaged a simple alkylation strategy, as described in Scheme 1.[11] To initiate this process, we anticipated the construction of the oxadiazole by condensation of benzamidoxime **5** with lactone **6**, to give the alcohol **7**. Conversion to mesylate **8** would then allow alkylation of a series of amines in a parallel synthesis fashion to produce a library of oxadiazolylethylamines.



Scheme 1 Proposed route to oxadiazolylethylamines.

In contrast to that proposed, it was observed that upon treatment of benzamidoxime **5** with β-lactone **6**, alcohol **7** was not isolated and instead vinyl oxadiazole **10** was obtained as the major product (Scheme 2).[11] Nevertheless, it was envisaged that by employing vinyl oxadiazole **10** as an acceptor unit, the desired products could still be obtained by exploiting a conjugate addition protocol. Moreover, it was considered that this emerging strategy would be more preparatively efficient overall, with access to **10** being achieved more concisely than synthesis of mesylate **8**.



Scheme 2 Preparation of vinyl oxadiazole **10** and proposed access to oxadiazolylethylamines.

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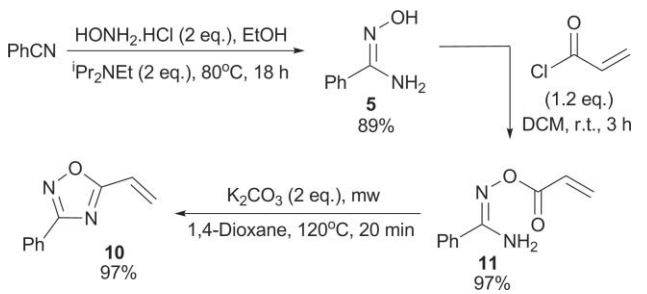
Moreover, the greater stability and easier handling of **10** rendered the conjugate addition protocol more amenable to future parallel synthesis programmes. To this end, the scope of the proposed conjugate addition sequence, to gain access to compounds of type **9**, was investigated.

Conjugate additions to vinyl heterocycles

In a general sense, conjugate addition to vinyl heteroarenes represents an effective method for the direct preparation of pharmaceutically relevant architectures. These processes have been documented for several heterocyclic systems and success has been realised with a range of nucleophilic agents.[12] With regards to vinyl oxadiazoles, Swain *et al.*,[6] and later Macor *et al.*,[1a] described the addition of very specific nucleophiles to such substrates. However, these processes lacked both the scope of nucleophile and the preparative flexibility required for the generation of a diverse series of oxadiazole-derived adducts. We, therefore, targeted the development of simple and preparatively robust procedures for the conjugate addition of a range of nucleophiles, which have the potential to be used to develop libraries of substituted oxadiazoles *via* parallel synthesis strategies.

Results and discussion

To begin the study, the synthesis of the convenient and bench-stable model substrate, 3-phenyl-5-vinyl-1,2,4-oxadiazole **10**, was altered to a more efficient and practically accessible reaction sequence (Scheme 3).[13] Treatment of benzonitrile with hydroxylamine hydrochloride in the presence of base afforded benzamidoxime **5** in 89% yield, with this reaction also being readily amenable to scale-up. Acylation at ambient temperature delivered acrylic ester **11**, which cyclised to the desired vinyloxadiazole **10** upon treatment with K_2CO_3 under microwave irradiation and in near quantitative yield. Notably, the cyclisation step can also be performed on larger scales either by using a 50 mL microwave vessel (up to 25 mmol scale) or by conventional reflux for an extended reaction time (6 h) with equivalent preparative efficiency.



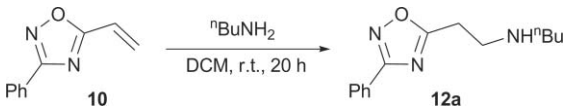
Scheme 3 Improved synthesis of vinyl oxadiazole **10**.

Turning to the targeted conjugate addition reactions, initially we treated **10** with $^nBuNH_2$ to ascertain whether the desired process would proceed in the absence of any additional base reagent (Table 1, Entry 1). Pleasingly, a good yield of addition product **12a** was obtained, highlighting that **10** is a suitable acceptor unit. Furthermore, a very brief optimisation of reaction concentration delivered the desired product **12a** in 98% isolated yield (Entry 2).

With these conditions operating efficiently, the reaction scope was probed by extension to a small range of primary and secondary amines (Table 2). Yields of addition products in this study were again very high, with the only transformation of more moderate efficiency involving the sterically encumbered $^tBuNH_2$ (Table 2, Entry 3), which provided the product **12c** in 62% yield. Only minimal purification was required for all other entries and, generally, concentration of the reaction mixture was adequate to produce products of >95% purity, which would allow ready adoption of such a preparative approach for the generation of compound libraries. Moreover, using diethylamine as the nucleophilic reaction component, we were able to prepare Perebron **1** (Fig. 1) in 99% yield (Entry 5). This establishes an expedient synthesis of this marketed pharmaceutical in a 93% overall isolated yield following three steps from benzamidoxime **5**; this compares favourably with the described literature method, which proceeds in 80% yield over two steps from the same starting compound **5**.[2]

While simple alkyl amines participated efficiently in the desired addition process, installation of aniline in a similar fashion proved to be more preparatively challenging. Initial reactions using the optimum conditions for the aliphatic amine substrates failed to deliver any of the desired product (Table 3, Entry 1) and increasing the temperature to reflux in DCM for a more extended reaction period led to no improvement (Entry 2). When moving to heating in a higher boiling solvent (PhMe) for 48 h, a low conversion to product was obtained (Entry 3), and a slight enhancement was noted when a protic solvent (^{n}PrOH) was employed at reflux (Entry 4). Despite this, the reaction yields obtained here were less than acceptable. Furthermore, addition of a series of base species (NaH, K_2CO_3, Cs_2CO_3), as potential reaction promoters, unfortunately, provided no improvements in the efficiency of the desired addition process.

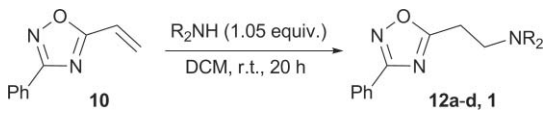
Table 1 Optimisation of the addition process with an alkylamine[a]



Entry	Equiv. Amine	Conc. of **10**/M	Conc. of amine/M	Yield (%)[b]
1	1.05	0.2	0.21	72
2	1.05	0.4	0.42	98
3	2.10	0.2	0.42	89

[a] See Experimental Section. [b] Yield refers to isolated pure products.

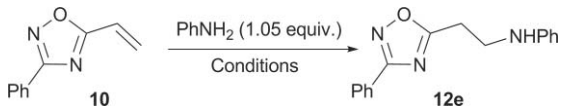
Table 2 Conjugate addition of aliphatic amines to vinyl oxadiazole **10**[a]



Entry	Amine	Product	Yield (%)[b]
1	$^nBuNH_2$	**12a**	98
2	$^iBuNH_2$	**12b**	99
3	$^tBuNH_2$	**12c**	62
4	$BnNH_2$	**12d**	98
5	Et_2NH	**1**	99

[a] See Experimental Section. [b] Yield refers to isolated pure products.

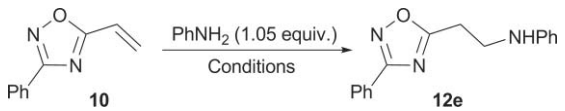
Table 3 Initial conjugate addition reactions using aniline



Entry	Conditions	Yield (%)[a]
1	DCM, r.t., 20 h	0
2	DCM, reflux, 48 h	0
3	PhMe, reflux, 48 h	5
4	^{n}PrOH, reflux, 48 h	14

[a] Yield refers to isolated pure products.

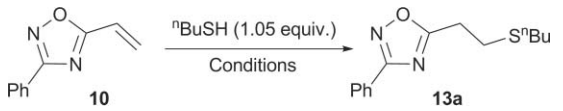
Table 4 Use of Brønsted and Lewis acids in the addition of $PhNH_2$ to **10**[a]



Entry	Additive[b]	Conditions	Yield (%)[c]
1	AcOH	MeOH, reflux, 20 h	34
2	AcOH	^{n}PrOH, reflux, 20 h	35
3	$EtCO_2H$	^{n}PrOH, reflux, 20 h	38
4	—	MeCN, mw, 188 °C, 1 h	0
5	AcOH	MeCN, mw, 188 °C, 1 h	26
6	—	^{n}PrOH, mw, 200 °C, 1 h	0
7	AcOH	^{n}PrOH, mw, 200 °C, 1 h	30
8	$LiClO_4$	MeOH, reflux, 20 h	25
9	$BF_3{\cdot}OEt_2$	THF, reflux, 20 h	55

[a] See Experimental Section. [b] 1.05 equiv. [c] Yield refers to isolated pure products.

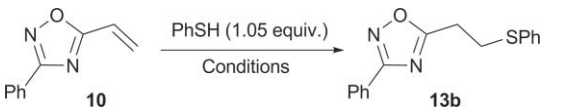
Table 5 Screening of conditions for the addition of ^{n}BuSH to **10**[a]



Entry	Additive	Conditions	Yield (%)[b]
1	—	DCM, r.t., 20 h	0
2	—	DCM, reflux, 20 h	0
3	NaH (1.2 equiv.)	THF, reflux, 20 h	2
4	K_2CO_3 (1.2 equiv.)	THF, reflux, 20 h	0
5	K_2CO_3 (1.2 equiv.)	DMF, 80 °C, 20 h	8
6	AcOH (1.05 equiv.)	MeOH, reflux, 20 h	6
7	HCl (1.05 equiv.)	MeOH, reflux, 20 h	88

[a] See Experimental Section. [b] Yield refers to isolated pure products.

Table 6 Screening of conditions for the addition of PhSH to **10**[a]



Entry	Additive	Conditions	Yield (%)[b]
1	—	DCM, r.t., 40 h	50
2	—	DCM, reflux, 20 h	94
3	NaH (1.2 equiv.)	THF, r.t., 24 h	79
4	K_2CO_3 (1.2 equiv.)	THF, r.t., 24 h	85
5	Cs_2CO_3 (1.2 equiv.)	THF, r.t., 24 h	58
6	AcOH (1.05 equiv.)	MeOH, reflux, 20 h	23
7	HCl (1.05 equiv.)	MeOH, reflux, 20 h	40

[a] See Experimental Section. [b] Yield refers to isolated pure products.

At this point, an alternative strategy was considered, whereby the electrophilicity of the vinyl oxadiazole would be augmented by the addition of a Brønsted or Lewis acid. As shown in Table 4, this approach clearly had the intended effect of enhancing the acceptor capabilities of the oxadiazole unit. Use of Brønsted acids delivered the desired addition product in modest yields, with the use of (the higher boiling) propionic acid in *n*-propanol being optimum (Table 4, Entry 3). Several reactions were also performed under microwave irradiation. Whilst moderate yields were also delivered in these cases, with a Brønsted acid additive (Entries 4–7), no improvement was observed over the results achievable using conventional heating methods. In contrast, specific Lewis acid promotion did, indeed, deliver further improvements to the targeted addition process with aryl amines. When using $BF_3{\cdot}OEt_2$ as an additive, the most efficient addition reaction with aniline in this series was obtained with a 55% isolated yield of **12e** (Entry 9).

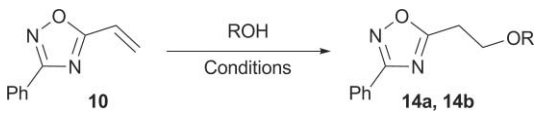
Having formulated conditions for the use of both alkyl and aryl amines with good to excellent levels of efficiency, attention turned to the delivery of alternative nucleophilic species. Firstly, sulfur-based nucleophiles are known to participate effectively in conjugate addition processes and, as such, we attempted the addition of a simple alkyl thiol to the vinyloxadiazole **10** (Table 5). Under the standard conditions used with alkyl amines at either room temperature or at reflux in DCM, no product was obtained (Table 5, Entries 1 and 2). Moving to an additive study, a similar reactivity profile was observed as with aniline, in which added base reagents provided only very low conversions to product (Entries 3–5). On the other hand, the addition of HCl was found to deliver a very good yield of the desired sulfide **13a** (Entry 7).

A similar study was subsequently conducted with thiophenol. In this case, it was found that an excellent yield of the intended product could be obtained simply by heating in DCM (Table 6, Entry 2). For completeness, an additive study was performed which demonstrated that the presence of acid was detrimental to the reaction (Entries 6 and 7). In contrast, the presence of base provided a moderate preparative advantage by allowing good yields of the aryl thiol addition product to be obtained at lower (ambient) temperatures (Entries 3–5).

To build on the success of the emerging nucleophile-specific addition methods which had been developed to this stage for vinyloxadiazole, we next sought to install oxygen-based nucleophiles in a conjugate fashion. As shown in Table 7, successful addition of alcohols was achievable in acceptable yields either in the presence of basic (Entry 1) or acidic additives (Entry 2). Unfortunately, regardless of the conditions applied (with acid/base additives and over various temperature/time studies), phenol did not successfully participate in the desired addition reaction.

Finally, we turned briefly to the use of carbon-based nucleophiles with vinyloxadiazole **10** (Table 8). Pleasingly, addition of diethyl malonate proceeded to deliver **15a** in 51% yield, using NaH as the base reagent (Entry 1). Additionally, use of the more

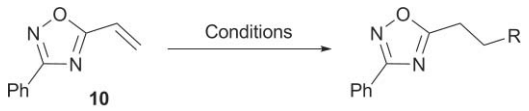
Table 7 Addition of alcohols to **10**[a]



Entry	R	Additive	Conditions	Yield (%)[b]
1	Et	NaH (1.2 equiv.)	EtOH, r.t., 20 h	78
2	^{n}Pr	HCl (1.05 equiv.)	^{n}PrOH, reflux, 20 h	63

[a] See Experimental Section. [b] Yield refers to isolated pure products.

Table 8 Addition of carbon-based nucleophiles to **10**[a]



Entry	Nucleophile	Product	Conditions	Yield (%)[b]
1	$H_2C(CO_2Et)_2$ (1.05 equiv.)	**15a**	NaH (1.2 equiv.), THF, r.t., 5 h	51
2	$^{n}Bu_2CuLi$ (1.2 equiv.)	**15b**	Et_2O, −78 °C, 2 h	40

[a] See Experimental Section. [b] Yield refers to isolated pure products.

challenging butyl cuprate delivered the desired product **15b** in a moderate 40% yield (Entry 2). Further endeavours, employing a range of additives and conditions, did not improve upon the result shown for this latter process.

Conclusions

In conclusion, after a broad screening process, we have developed a series of practically-convenient conditions which allow for the effective conjugate addition of a range of nucleophiles to a vinyl 1,2,4-oxadiazole. In particular, the individual protocols are tuned for the use of each specific class of nucleophile and enable the efficient introduction of alkylamines and alkyl and aryl thiols without the requirement for any appreciable purification protocols and which will be readily applicable within parallel synthesis programmes. Additionally, further specific conditions for the introduction of aryl amines, aliphatic alcohols, and carbon-based nucleophiles have also been established which, despite being somewhat less efficient, have the potential for ready adoption within medicinal chemistry or agrochemical environments. Overall, by employment of a common heterocyclic core and a spectrum of suitable nucleophiles, these procedures will allow the flexible and effective production of arrays of compounds containing the biologically significant oxadiazole motif.

Experimental

All reactions were carried out using conventional glassware and procedures. Starting materials and solvents were used as obtained from commercial suppliers without further purification. For air sensitive reactions, standard protocols were employed using dry solvents and under a N_2 atmosphere. Solutions, solvents and liquid reagents were added *via* syringe. Microwave reactions were performed in a CEM Discover dedicated microwave reactor in sealed tubes. Light petroleum refers to the fraction of b.p. 30–40 °C. Thin layer chromatography was carried out using Camlab silica plates coated with indicator UV_{254}. These were analysed using a Mineralight UVGL-25 lamp or developed using vanillin or potassium permanganate solutions. Flash column chromatography was carried out using Prolabo silica gel (230–400 mesh). IR spectra were obtained on a Perkin Elmer Spectrum One machine. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz and 100 MHz, respectively, or a Bruker DRX 500 spectrometer at 500 MHz and 125 MHz, respectively. Chemical shifts are reported in ppm. Coupling constants are reported in Hz.

Synthesis of Vinyloxadiazole, 10

(a) Preparation of 5. A solution of benzonitrile (1 equiv., 25 mmol, 2.55 mL), hydroxylamine hydrochloride (2 equiv., 50 mmol, 3.475 g) and $^{i}Pr_2NEt$ (2 equiv., 50 mmol, 8.76 mL) in EtOH (250 mL) was heated at 80 °C for 18 h. The solution was cooled to room temperature and the solvent removed *in vacuo*. The residue was partitioned between DCM (100 mL) and H_2O (100 mL) and the organic phase separated. The aqueous phase was further extracted with DCM (3 × 100 mL) and the organic extracts were combined. After drying ($MgSO_4$) and filtering, the organic solution was concentrated to afford **5** as a viscous oil (3.04 g, 89%).

(b) Preparation of 11. To a solution of **5** (1 equiv., 20.9 mmol, 2.84 g) in DCM (230 mL) was added acryloyl chloride (1.2 equiv., 25 mmol, 2.03 mL). The mixture was stirred for 3 h at room temperature before quenching with an aq. solution of $NaHCO_3$ (100 mL). The organic layer was separated and the aqueous layer was further extracted with DCM (2 × 50 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated to afford **11** as an off-white solid (3.856 g, 97%).

(c) Preparation of 10.

(i) Microwave conditions. A microwave tube charged with **11** (1 equiv., 2.63 mmol, 0.5 g), 1,4-dioxane (5 mL) and K_2CO_3 (2 equiv., 5.26 mmol, 0.726 g) was heated at 120 °C for 20 min in a microwave reactor. The mixture was allowed to cool before being filtered and concentrated to a residue which was purified by column chromatography eluting with 10% Et_2O/light petroleum to afford **10** as a colourless oil (0.439 g, 97%).

(ii) Reflux conditions. A solution of **11** (1 equiv., 2.63 mmol, 0.5 g), 1,4-dioxane (5 mL) and K_2CO_3 (2 equiv., 5.26 mmol, 0.726 g) was heated at 120 °C for 6 h. The mixture was allowed to cool before being filtered and concentrated to a residue which was purified by column chromatography eluting with 10% Et_2O/light petroleum to afford **10** as a colourless oil (0.453 g, 100%).

Conjugate addition of alkylamines to 10

To a solution of **10** (1 equiv., 1 mmol, 172 mg) in DCM (2.5 mL) was added the amine (1.05 equiv., 1.05 mmol). The reaction mixture was then stirred at room temperature for 20 h before concentrating *in vacuo* to a residue which was purified by column chromatography eluting with 10% Et_2O/light petroleum

to afford the desired addition product. For example, using $^{n}BuNH_2$ (1.05 mmol, 0.101 mL) gave **12a** as a pale yellow oil (240 mg, 98%).

Conjugate addition of $PhNH_2$ to 10

To a solution of **10** (1 equiv., 1 mmol, 172 mg) in THF (2.5 mL) was added aniline (1.05 equiv., 1.05 mmol, 0.096 mL) and $BF_3{\cdot}OEt_2$ (1.05 equiv., 1.05 mmol, 0.133 mL). The reaction mixture was then refluxed for 20 h before cooling to room temperature and quenching with $NaHCO_3$ aq. solution (5 mL). The mixture was then extracted with DCM (4 × 15 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to a residue which was purified by column chromatography eluting with 10–50% Et_2O/light petroleum to afford **12e** as a yellow/brown solid (145 mg, 55%).

Conjugate addition of $^{n}BuSH$ to 10

To a solution of **10** (1 equiv., 1 mmol, 172 mg) in MeOH (2.5 mL) was added $^{n}BuSH$ (1.05 equiv., 1.05 mmol, 0.113 mL) and HCl (1 M solution in Et_2O, 1.05 equiv., 1.05 mmol, 1.05 mL). The reaction mixture was then refluxed for 20 h before cooling to room temperature and quenching with $NaHCO_3$ aq. solution (5 mL). The mixture was then extracted with DCM (4 × 15 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to a residue which was purified by column chromatography eluting with 10% Et_2O/light petroleum to afford **13a** as a yellow oil (232 mg, 88%).

Conjugate addition of PhSH to 10

To a solution of **10** (1 equiv., 1 mmol, 172 mg) in DCM (2.5 mL) was added PhSH (1.05 equiv., 1.05 mmol, 0.108 mL). The reaction mixture was then refluxed for 24 h before concentrating *in vacuo* to a residue which was purified by column chromatography eluting with 10% Et_2O/light petroleum to afford **13b** as a yellow oil (265 mg, 94%).

Conjugate addition of alcohols to 10

(i) Using NaH. To a solution of **10** (1 equiv., 1 mmol, 172 mg) in EtOH (2.5 mL) was added NaH (60% dispersion in mineral oil, 1.2 equiv., 1.2 mmol, 48 mg). The reaction mixture was then stirred under N_2 for 20 h before quenching with $NaHCO_3$ aq. solution (5 mL). The mixture was then extracted with DCM (4 × 15 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to a residue which was purified by column chromatography eluting with 10% Et_2O/light petroleum to afford **14a** as a colourless oil (170 mg, 78%).

(ii) Using HCl. To a solution of **10** (1 equiv., 1 mmol, 172 mg) in $^{n}PrOH$ (2.5 mL) was added HCl (1 M solution in Et_2O, 1.05 equiv., 1.05 mmol, 1.05 mL). The reaction mixture was then refluxed for 20 h before cooling to room temperature and quenching with $NaHCO_3$ aq. solution (5 mL). The mixture was then extracted with DCM (4 × 15 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to a residue which was purified by column chromatography eluting with 10% Et_2O/light petroleum to afford **14b** as a yellow oil (146 mg, 63%).

Conjugate addition of carbon-based nucleophiles to 10

(i) Using diethyl malonate and NaH. To a solution of **10** (1 equiv., 1 mmol, 172 mg) in THF (2.5 mL) was added NaH (60% dispersion in mineral oil, 1.2 equiv., 1.2 mmol, 48 mg). The mixture was then stirred for 5 h under N_2 before quenching with $NaHCO_3$ aq. solution (5 mL). The mixture was then extracted with DCM (4 × 15 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to a residue which was purified by column chromatography eluting with 10% Et_2O/light petroleum to afford **15a** as a colourless oil (170 mg, 51%).

(ii) Using $^{n}Bu_2CuLi$. To a solution of CuI (1.2 equiv., 1.2 mmol, 229 mg) in dry Et_2O (10 mL) at −78 °C was added $^{n}BuLi$ (2.38 M in hexane, 2.4 equiv., 2.4 mmol, 1.01 mL) drop-wise over 5 min. The mixture was stirred at −78 °C for 1 h before the addition of a solution of **10** (1 equiv., 1 mmol, 172 mg) in Et_2O (2 mL) over 5 min. The mixture was then stirred at −78 °C for 2 h before quenching with H_2O (10 mL). The mixture was allowed to warm to room temperature before extraction with Et_2O (3 × 15 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to a residue which was purified by column chromatography eluting with 10% Et_2O/light petroleum to afford **15b** as a colourless oil (93 mg, 40%).

Compound data

Compound 5. Viscous colourless oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3598, 3519, 3410, 2924, 1647, 1581; δ_H (400 MHz, $CDCl_3$) 8.52 (1H, s), 7.65 (2H, dd, *J* 9.8, 2.8), 7.45-7.38 (3H, m), 4.90 (2H, s); δ_C (100 MHz, $CDCl_3$) 152.6, 132.5, 130.0, 128.7, 125.9; Anal. Calcd. for $C_7H_8N_2O$ requires C, 61.75%; H, 5.92%; N, 20.58%. Found: C, 62.65%; H, 5.85%; N, 20.58%; HRMS (ES) Found $[M + H]^+$ 137.0708, $C_7H_9N_2O$ requires 137.0709.

Compound 10. Colourless oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3074, 2960, 1648, 1593, 1563, 1542; δ_H (400 MHz, $CDCl_3$) 8.11 (2H, dd, *J* 9.8, 2.7), 7.55-7.47 (3H, m), 6.78 (1H, dd, *J* 17.7, 11.0), 6.61 (1H, dd, *J* 17.7, 0.9), 6.01 (1H, dd, *J* 11.0, 0.9); δ_C (100 MHz, $CDCl_3$) 174.5, 168.7, 131.2, 128.9, 128.7, 127.5, 126.8, 120.6; Anal. Calcd. for $C_{10}H_8N_2O$ requires C, 69.76%; H, 4.68%; N, 16.27%. Found: C, 69.78%; H, 4.41%; N, 16.42%; HRMS (ES) Found $[M + H]^+$ 173.0709, $C_{10}H_9N_2O$ requires 173.0709.

Compound 11. Off-white solid; Mp 69–70 °C; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3528, 3421, 1701, 1634; δ_H (400 MHz, $CDCl_3$) 7.73 (2H, dd, *J* 7.9, 1.5), 7.52-7.41 (3H, m), 6.56 (1H, dd, *J* 17.3, 1.0), 6.32 (1H, dd, *J* 17.3, 10.5), 5.92 (1H, dd, *J* 10.5, 1.0), 5.11 (2H, s); δ_C (100 MHz, $CDCl_3$) 163.9, 156.8, 131.4, 131.1, 131.0, 128.7, 126.8, 126.7; Anal. Calcd. for $C_{10}H_{10}N_2O_2$ requires C, 63.15%; H, 5.30%; N, 14.73%. Found: C, 63.11%; H, 5.22%; N, 14.75%; HRMS (ES) Found $[M + H]^+$ 191.0814, $C_{10}H_{11}N_2O_2$ requires 191.0815.

Compound 12a. Pale yellow oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3692, 2960, 2931, 2861, 1595, 1571, 1476, 1447; δ_H (400 MHz, $CDCl_3$) 8.08 (2H, dd, *J* 7.5, 2.3), 7.51-7.46 (3H, m), 3.51 (4H, s), 2.68 (2H, t, *J* 7.2), 1.50 (2H, quintet, *J* 7.3), 1.46 (3H, sextet, *J* 7.3), 0.93 (3H, t, *J* 7.3); δ_C (100 MHz, $CDCl_3$) 178.8, 168.5, 131.1, 129.0, 127.6, 127.1, 49.4, 46.4, 32.4, 27.6, 20.6, 14.2; Anal. Calcd. for $C_{14}H_{19}N_3O$ requires C, 68.54%; H, 7.81%; N, 17.30%. Found:

C, 68.25%; H, 7.75%; N, 17.34%; HRMS (ES) Found $[M + H]^+$ 246.1599, $C_{14}H_{20}N_3O$ requires 246.1601.

Compound 12b. Pale yellow oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3692, 2958, 2842, 1595, 1571, 1476, 1447; δ_H (400 MHz, $CDCl_3$) 8.08 (2H, dd, *J* 5.6, 2.3), 7.53-7.45 (3H, m), 3.14 (4H, s), 2.49 (2H, d, *J* 6.8), 1.76 (1H, septet, *J* 6.7), 1.44 (1H, s), 0.92 (6H, d, *J* 6.7); δ_C (100 MHz, $CDCl_3$) 178.8, 168.4, 131.3, 129.0, 127.6, 127.1, 57.7, 46.5, 28.5, 27.6, 20.8; Anal. Calcd. for $C_{14}H_{19}N_3O$ requires C, 68.54%; H, 7.81%; N, 17.30%. Found: C, 68.18%; H, 7.61%; N, 17.50%; HRMS (ES) Found $[M + H]^+$ 246.1600, $C_{14}H_{20}N_3O$ requires 246.1601.

Compound 12c.[14] Pale yellow oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3692, 2969, 2867, 1595, 1571, 1477, 1447; δ_H (400 MHz, $CDCl_3$) 8.08 (2H, dd, *J* 7.3, 2.0), 7.51-7.46 (3H, m), 3.10 (4H, s), 1.14 (9H, s); δ_C (125 MHz, $CDCl_3$) 178.8, 168.2, 131.1, 128.8, 127.4, 126.9, 50.6, 39.5, 29.0, 28.6.

Compound 12d. Pale yellow oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3693, 3029, 2926, 2850, 1595, 1571, 1477, 1447; δ_H (400 MHz, $CDCl_3$) 8.08 (2H, dd, *J* 7.6, 1.9), 7.53-7.47 (3H, m), 7.34 (4H, d, *J* 4.3), 7.27 (1H, m), 3.87 (2H, s), 3.17 (4H, s); δ_C (100 MHz, $CDCl_3$) 178.7, 168.5, 140.1, 131.3, 129.0, 128.6, 128.2, 127.6, 127.2, 127.0, 53.6, 45.7, 27.6; Anal. Calcd. for $C_{17}H_{17}N_3O$ requires C, 73.10%; H, 6.13%; N, 15.04%. Found: C, 72.86%; H, 6.06%; N, 15.16%; HRMS (ES) Found $[M + H]^+$ 280.1443, $C_{17}H_{18}N_3O$ requires 280.1444.

Compound 1.[2] Pale yellow oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2937, 2974, 2876, 2821, 1595, 1571, 1476, 1447; δ_H (500 MHz, $CDCl_3$) 8.08 (2H, dd, *J* 7.3, 2.1), 7.50-7.46 (3H, m), 3.11-3.07 (2H, m), 3.04-3.01 (2H, m), 2.59 (4H, q, *J* 7.2), 1.06 (6H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 178.9, 168.3, 131.0, 128.8, 127.4, 127.0, 49.6, 46.9, 25.0, 12.0.

Compound 12e. Yellow-brown solid; Mp 83-84 °C; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3437, 3044, 2982, 2830, 1603, 1571, 1551, 1508, 1439; δ_H (400 MHz, $CDCl_3$) 8.10 (2H, dd, *J* 7.6, 1.9), 7.53-7.48 (3H, m), 7.22 (2H, t, *J* 7.9), 6.77 (1H, t, *J* 7.3), 6.69 (2H, d, *J* 7.7), 4.17 (1H, s), 3.74 (2H, t, *J* 6.5), 3.26 (2H, t, *J* 6.5); δ_C (100 MHz, $CDCl_3$) 178.5, 168.9, 147.6, 131.8, 130.0, 129.4, 128.0, 127.3, 118.8, 113.8, 41.2, 27.2; HRMS (ES) Found $[M + H]^+$ 266.1286, $C_{16}H_{16}N_3O$ requires 266.1288.

Compound 13a. Yellow oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3056, 2981, 2874, 2831, 1594, 1571, 1551, 1443; δ_H (500 MHz, $CDCl_3$) 8.08 (2H, dd, *J* 7.7, 1.9), 7.53-7.46 (3H, m), 3.24 (2H, t, *J* 7.7), 3.03 (2H, t, *J* 7.6), 2.59 (2H, t, *J* 7.4), 1.60 (2H, quintet, *J* 7.4), 1.42 (2H, sextet, *J* 7.4), 0.93 (3H, t, *J* 7.3); δ_C (125 MHz, $CDCl_3$) 178.1, 168.4, 131.2, 128.8, 127.4, 126.8, 31.9, 31.6, 28.5, 27.7, 21.9, 13.6; HRMS (ES) Found $[M + H]^+$ 263.1214, $C_{14}H_{19}N_2OS$ requires 263.1213.

Compound 13b. Yellow oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3045, 2989, 2831, 1594, 1571, 1551, 1443; δ_H (400 MHz, $CDCl_3$) 8.06 (2H, dd, *J* 6.9, 1.4), 7.53-7.47 (3H, m), 7.44 (2H, dd, *J* 6.9, 1.4), 7.33 (2H, t, *J* 7.4), 7.26 (1H, t, *J* 7.3), 3.42 (2H, t, *J* 7.5), 3.25 (2H, t, *J* 7.4); δ_C (100 MHz, $CDCl_3$) 178.3, 168.9, 134.8, 131.7, 131.4, 129.8, 129.4, 128.0, 127.7, 127.3, 31.4, 27.8; Anal. Calcd. for $C_{16}H_{14}N_2OS$ requires C, 68.06%; H, 5.00%; N, 9.92%. Found: C, 67.81%; H, 5.00%; N, 9.81%; HRMS (ES) Found $[M + H]^+$ 283.0901, $C_{16}H_{15}N_2OS$ requires 283.0900.

Compound 14a. Colourless oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3055, 2980, 2875, 2831, 1595, 1572, 1551, 1477, 1443; δ_H (400 MHz, $CDCl_3$) 8.06 (2H, dd, *J* 7.5, 2.2), 7.51-7.43 (3H, m), 3.91 (2H, t, *J* 6.7), 3.54 (2H, q, *J* 7.0), 3.22 (2H, t, *J* 6.7), 1.19 (3H, t, *J* 7.0); δ_C (100 MHz, $CDCl_3$) 177.8, 168.5, 131.2, 129.0, 127.6, 127.1, 66.7, 66.6, 28.0, 15.2; Anal. Calcd. for $C_{12}H_{14}N_2O_2$ requires C, 66.04%; H, 6.47%; N, 12.84%. Found: C, 65.86%; H, 6.31%; N, 12.86%; HRMS (ES) Found $[M + H]^+$ 219.1129, $C_{12}H_{15}N_2O_2$ requires 219.1128.

Compound 14b. Yellow oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3076, 2981, 2877, 2831, 1596, 1572, 1551, 1528, 1443; δ_H (500 MHz, $CDCl_3$) 8.09 (2H, dd, *J* 6.8, 1.7), 7.52-7.46 (3H, m), 3.92 (2H, t, *J* 6.6), 3.46 (2H, t, *J* 6.6), 3.23 (2H, t, *J* 6.6), 1.59 (2H, sextet, *J* 7.1), 0.90 (3H, t, *J* 7.4); δ_C (125 MHz, $CDCl_3$) 177.7, 168.3, 131.1, 128.8, 127.4, 126.9, 72.9, 66.7, 27.8, 22.7, 10.5; HRMS (ES) Found $[M + H]^+$ 233.1285, $C_{13}H_{17}N_2O_2$ requires 233.1285.

Compound 15a. Colourless oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3055, 2980, 2874, 2831, 1752, 1595, 1572, 1477, 1443; δ_H (400 MHz, $CDCl_3$) 8.08 (2H, dd, *J* 7.7, 1.9), 7.53-7.45 (3H, m), 4.26-4.20 (4H, q, *J* 7.2), 3.57 (1H, t, *J* 7.3), 3.07 (2H, t, *J* 7.6), 2.49 (2H, q, *J* 7.5), 1.29 (6H, t, *J* 7.1); δ_C (100 MHz, $CDCl_3$) 178.8, 170.3, 168.8, 131.4, 129.0, 127.6, 127.0, 61.9, 50.9, 25.4, 24.4, 14.3; Anal. Calcd. for $C_{17}H_{20}N_2O_5$ requires C, 61.44%; H, 6.07%; N, 8.43%. Found: C, 61.56%; H, 5.88%; N, 8.58%; HRMS (ES) Found $[M + H]^+$ 333.1443, $C_{17}H_{21}N_2O_5$ requires 333.1445.

Compound 15b. Colourless oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3065, 2982, 2860, 2831, 1594, 1570, 1528, 1425; δ_H (400 MHz, $CDCl_3$) 8.08 (2H, dd, *J* 7.4, 2.1), 7.53-7.46 (3H, m), 2.95 (2H, t, *J* 7.6), 1.88 (2H, quintet, *J* 7.6), 1.46-1.40 (2H, m), 1.36-1.32 (4H, m), 0.89 (3H, t, *J* 7.3); δ_C (100 MHz, $CDCl_3$) 180.3, 168.5, 131.2, 129.0, 127.6, 127.2, 31.5, 28.9, 26.9(2), 22.6, 14.2; HRMS (ES) Found $[M + H]^+$ 231.1491, $C_{14}H_{19}N_2O$ requires 231.1492.

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