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Regioselective synthesis of β-iodo-enamides and β-yn-enamides

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ABSTRACT

Iodo-enamides were synthesised in a single step, in good yield and with complete selectivity from *N*-formyl imides. The β-iodo-enamides are stable and were converted efficiently into novel geometrically defined β-yn-enamides.

1. Introduction

Halo-enamides are extremely versatile and useful enamide derivatives, which could be used in the generation of highly functional intermediates in materials, synthetic, medicinal and materials chemistry. However, despite their great potential to play a key role in the synthesis of more elaborated enamide derivatives, there remains a lack of reliable approaches and methods available for their efficient and practical synthesis.[1]

Bal'on and Moskaleva reported one of the first and most direct routes for the synthesis of halo-enamides through the addition of hydrogen halide (HX) across an ynamide unit **1**. However, despite its efficiency, this method generates mixtures of halo-enamides with very poor regio- and stereo-chemical control. Furthermore, the separation of the halo-enamide isomers obtained is often impossible.[2,3]

Hsung later reported the unexpected halogenation of ynamides **1** with magnesium halide salts to generate the corresponding α-halo-enamides **2** in good yield and with excellent *E* selectivity.[4] Interestingly none of the β-halo-enamides could be detected through either Bal'on's or Hsung's methods (Fig. 1).

Two examples of the synthesis of β-halo-enamides have been reported recently (Scheme 1).[5,6] Smith's synthesis began with *cis*-2-iodomethylacrylate **3**, which was converted into enamide **4** through a copper mediated coupling. Ester hydrolysis followed by iodo-decarboxylation then afforded the β-iodo-enamide **5** in 14% yield over the three step sequence.

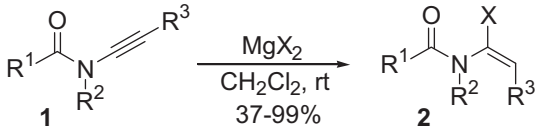

Fig. 1. α-Halo-enamide synthesis from ynamides.

Daoust, on the other hand, took advantage of copper promoted conditions to couple *trans*-1,2-diiodoethene **7** with three cyclic amides and an acyl protected acyclic amide derivative in good yield. Unfortunately, Daoust's method requires the use of 1,2-diiodoethene **7**, for which only the synthesis of the *trans*-isomer is known.

2. Results and discussion

We have previously reported the use of *N*-formyl imides **9** in olefination reactions to generate conjugated *E* enamides **10** and *Z*,*E*-dienamides **11** in a single step, good yield and most significantly without the need for nitrogen protection in the acyclic cases (Fig. 2).[7]

In all cases, the *N*-formyl group effectively behaves as an aldehyde surrogate, which opens the possibility of using *N*-formyl

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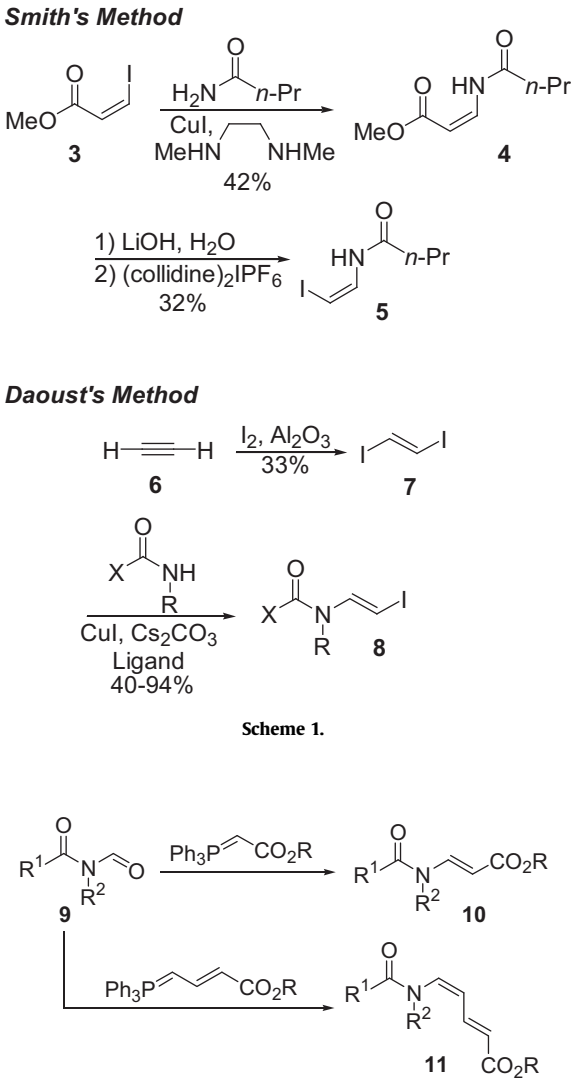


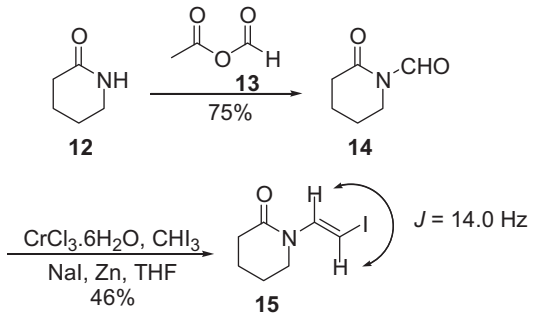
Scheme 1.

Fig. 2. *N*-Formyl imides **9** and their conversion into enamides **10** and dienamides **11**.

imides as key building blocks in the generation of substrates not readily available through any other means.

We now report our efforts towards the development of an efficient approach to the regioselective synthesis of β-halo-enamides as well as a demonstration of their practical synthetic potential.

Our initial studies began with valerolactam **12**, which was efficiently *N*-formylated using acetic formic anhydride **13** to generate the desired *N*-formyl imide **14** under our previously reported conditions (Scheme 2).[7]



Scheme 2.

Treatment of *N*-formyl imide **14** under standard Takai conditions[8] using commercially sourced chromium(II)chloride afforded the desired β-iodo-enamide **15** in variable yields, and as inseparable mixtures of *E* and *Z* isomers. The reaction proved to be highly dependent on the quality of the commercially sourced chromium(II)chloride employed. Indeed, in a number of cases, some batches of chromium(II)chloride failed to yield any of the desired β-iodo-enamide adduct.

Faced with such an unreliable procedure, a more reproducible method was sought. Pleasantly, using Auge's modification of the Takai reaction, using chromium(III)chloride hydrate, yielded the desired β-iodo-enamide **15** in reasonable yield from *N*-formyl imide **14**. Crucially, the product was obtained as a single *E* double bond isomer (Scheme 2).[9]

The assignment of the double bond geometry of the newly formed β-iodo-enamide **15** was confirmed by both ^{1}H NMR and crystallographic analysis (Fig. 3).[10]

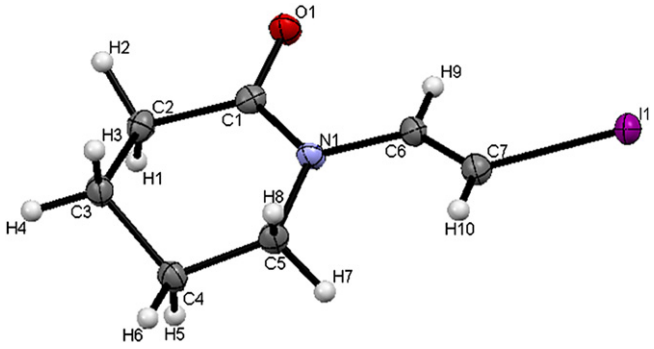


Fig. 3. Crystal structure of β-iodo-enamide **15**.

Using these optimised conditions, different lactams were formylated and the resulting *N*-formyl imides **14** and **22**–**24** were treated under Auge's modified Takai conditions to generate the desired β-iodo-enamides **15**, **28**–**30** in good yield (Table 1). In all cases, only the *E*-isomer was detected both in the ^{1}H NMR spectra of the crude reaction mixture, and after purification by column chromatography.

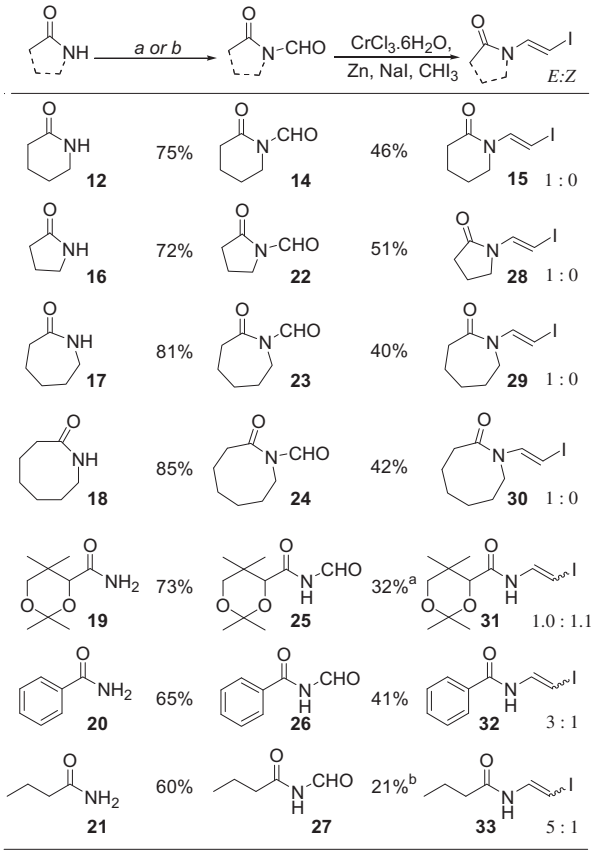
Having shown the ability of cyclic *N*-formyl imides to undergo iodoolefination, we were interested in exploring primary amide derived *N*-formyl imides as Takai substrates. The successful iodoolefination of an unprotected primary amide derived *N*-formyl imide is very appealing as this obviate the need to subject the sensitive enamide derivatives to the typically harsh conditions required for the removal of nitrogen protecting groups.

The acyclic amides **19**–**21**, were *N*-formylated using *N*-formylbenzotriazole/*n*-BuLi.[11] The quality and the purity of the *N*-formylbenzotriazole are key to obtaining pure *N*-formyl imides in reproducible yields.

Subsequent iodoolefination of acyclic imides **25**–**27** under Auge's conditions however, yielded some very interesting and intriguing results (Table 1). *N*-Formylbenzimide **26** and *N*-formylpropionimide **27** yielded mixtures of *E*/*Z* iodo enamides **32** and **33** in which the *E*-iodo olefin was the major isomer formed. On the other hand, in the case of the dioxolane substituted *N*-formyl imide **25**, a nearly equal mixture of *E*/*Z* iodoolefins **31** was obtained in which the *Z* isomer was slightly predominant by ^{1}H NMR analysis of the crude reaction mixture. Interestingly, the dioxolane derived *E*-iodoenamide **31***E* could not be isolated under different separation conditions.

We believe that the marked difference in behaviour during the iodoolefination between the lactam derived imides and the acylic cases can be attributed to the geometry of the *N*-formyl imide. In the

Table 1
Synthesis of β-iodo-enamides.



[a]Isolated yield of the *Z* isomer.
[b]Isolated yield of the *E* isomer.

lactam cases, the availability of the nitrogen's lone pairs severely restricts the conformational flexibility of the imide unit, which in turn translates into the generation of a single *E* iodoolefin isomer.

In the case of the acyclic *N*-formyl imides, the situation is more complicated as both *E* and *Z* halo enamides are formed in different ratios. Crystallographic data for the *N*-formyl imides **25** and **26** suggest that the *N*-formyl carbonyl adopts a similar conformation within the two imides (Fig. 4).[7]

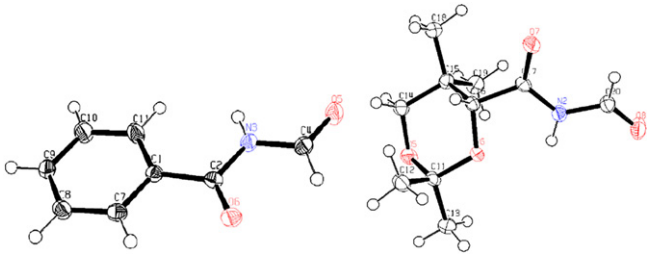


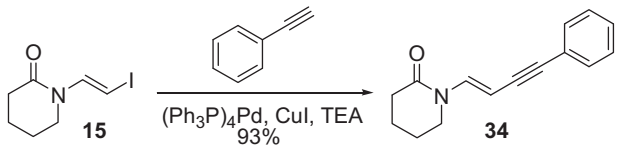
Fig. 4. *N*-Formylbenzimide **26** and dioxolane derived *N*-formyl imide **25**.

This would imply that it is the rotational freedom of the imide unit along the bond between the internal carbonyl and the acyclic unit that determines the selectivity of the reaction. This would be consistent with the results observed in which the alkyl group in imide **27** exerts a slightly greater steric influence on the imide conformation than the flat aromatic substituent in imide **26**. The geometry of *N*-formyl imide **25** on the other hand, is influenced by the conformation of the dioxolane ring as well as the potential electronic interaction of the imide unit with the proximal oxygen of the ketal unit.

Having generated the desired β-iodo-enamides, we were interested in using them in combination with other methodologies, (i.e., metal mediated couplings) to generate novel and diverse building blocks.

We decided to initially evaluate the utility of β-iodo-enamides in palladium mediated Sonogashira couplings with the aim of generating novel β-yn-enamide units.[12] It was reasoned that structurally constrained β-yn-enamides could have applications as reactive intermediates in both synthetic and medicinal organic chemistry. Furthermore, their defined molecular shape makes them prime candidates for the development of molecular tweezers and other structurally defined useful units in materials and supramolecular chemistry.[13]

Initial Sonogashira coupling of β-iodo-enamide **15** with phenyl acetylene afforded the desired β-yn-enamide **34** in excellent yield and as a single isomer (Scheme 3). The structural assignment of the β-yn-enamide **34** was confirmed by X-ray crystallography (Fig. 5).[9]



Scheme 3.

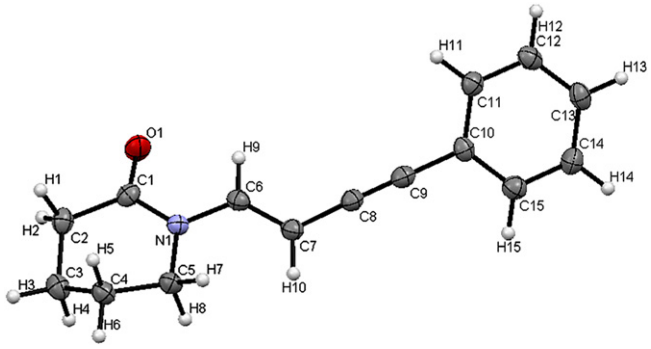


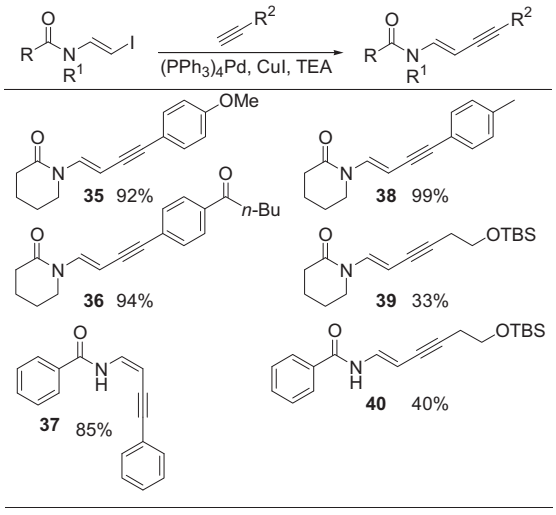
Fig. 5. Crystal structure of β-yn-enamide **34**.

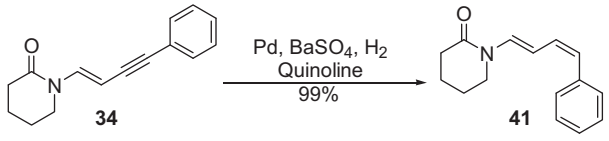
The excellent yield observed in the Sonogashira cross-coupling of β-iodo enamide **15** and phenyl acetylene was then extended using a number of phenyl substituted acetylenes, using both cyclic and acyclic β-iodo-enamides to generate the β-yn-enamides **35**–**38**. When alkyl substituted alkynes were used in the cross-coupling, lower yields of the β-yn-enamides **39** and **40** obtained was observed. We believe that this difference in yield between the alkyl substituted and phenyl substituted alkyne β-yn-enamide products is due to the greater stability of the phenyl β-yn-enamide adducts obtained rather than due to the Sonogashira coupling itself (Table 2).

Recent preliminary experiments, have shown that it is possible to selectively reduce the β-yn-enamides **34** to generate *E*,*Z*-dienamides **41** in excellent yield through catalytic hydrogenation (Scheme 4).

In conclusion, we have developed a fast and efficient method, which takes advantage of the pseudo-aldehyde behaviour of *N*-formyl imides to access β-iodo-enamides in a single step, in synthetically useful yields and without the need for nitrogen protecting groups. The β-iodo-enamides can be easily functionalised into β-yn-enamides and dienamides in excellent yields and with complete selectivity. We believe that this route complements and

Table 2
Synthesis of yn-enamides from iodo-enamides.





Scheme 4.

expands the methodologies available currently for the synthesis of β-halo-enamides, β-yn-enamides and dienamides, and can be easily modified for the generation of novel structural motifs with potential applications in synthetic, biological, medicinal, supramolecular and materials chemistry.

3. Experimental

3.1. General

All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. Tetrahydrofuran (THF), diethyl ether and dichloromethane (DCM) were purified through a Pure Solv 400-5MD solvent purification system (Innovative Technology, Inc). All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at 40 °C.

IR spectra were recorded using a JASCO FT/IR410 Fourier Transform spectrometer using a diamond gate. Only significant absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}). Melting points were recorded using a Bibby Stuart Scientific Melting Point SMP1 and are uncorrected.

Proton magnetic resonance spectra (^1H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were, respectively, recorded at 400 MHz and 100 MHz using a Bruker DPX Avance400 instrument. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad, dm=double multiplet), and (3) coupling constant (J) quoted in Hertz to the nearest 0.5 Hz. High resolution mass spectra were recorded on a JEOL JMS-700 spectrometer by electrospray and chemical ionisation mass spectrometer operating at a resolution of 15,000 full widths at half height. Flash chromatography was performed using silica gel (Flourochem Scientific Silica Gel 60, 40–63 micron) as the stationary phase. TLC was performed on aluminium sheets pre-coated with silica (Merck Silica Gel 60 F_{254}). The plates were visualised by the quenching of UV fluorescence (λ_{max} 254 nm) and/or by staining with either anisaldehyde, potassium permanganate, iodine or cerium ammonium molybdate followed by heating.

3.2. General procedure for the synthesis of β-iodo-enamides

Chromium(III)chloride hexahydrate (18.0 mmol) was placed in a two neck round bottom flask and was heated using a bunsen burner until the colour of the chromium(III)chloride changed from dark green to light green and then to purple. The purple chromium(III)chloride was then treated with zinc (9.0 mmol) and NaI (15.0 mmol), and the resulting mixture was stirred and heated under vacuum and for 15 min.

The reaction was then allowed to cool down to room temperature whilst still under vacuum and then placed under argon. The dry mixture was then suspended in anhydrous THF (30 mL) and the reaction mixture was stirred at room temperature for 10 min. A solution of *N*-formyl imide (1.3 mmol) and iodoform (2.6 mmol) in THF (15 mL) was then cannulated into the chromium mixture and the resulting brown suspension was stirred overnight at room temperature.

The reaction was then quenched with satd aq NaCl (30 mL), followed by satd aq IDRANAL III (30 mL) and the solution was allowed to stir at room temperature for 30 min before being extracted with diethyl ether (3×20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was then purified by flash column chromatography on silica gel eluting with 10% ethyl acetate in petroleum ether to afford the desired *E*-iodo-enamides.

3.2.1. (E)-1-(2-Iodovinyl)piperidin-2-one, ***15****.* Chromium(III)chloride hexahydrate (2.90 g, 10.8 mmol), zinc (352 mg, 5.4 mmol), sodium iodide (1.34 g, 8.9 mmol) and iodoform (614 mg, 1. 6 mmol) reacted with *N*-formyl imide **14** (100 mg, 0. 8 mmol) to afford 90 mg (46%) of *E*-iodo-enamide **15** as a yellow solid. Mp 33 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.11 (1H, d, J=14.0 Hz), 5.44 (1H, d, J=14.0 Hz), 3.41 (2H, t, J=6.0 Hz), 2.48 (2H, t, J=6.4 Hz), 1.88–1.81 (2H, m), 1.79–1.70 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.8, 137.7, 55.0, 45.0, 32.8, 22.4, 20.6; ν_{max} (neat)/cm^{-1}; 2924, 2854, 1651, 1599, 1458, 1404, 1296, 1257; HRMS (CI/ISO) found $(M+H)^+$ 251.9885, $C_7H_{11}INO$ requires 251.9886.

3.2.2. (E)-1-(2-Iodovinyl)pirrolidin-2-one, ***28****.* Chromium(III)chloride hexahydrate (4.80 g, 18.0 mmol), zinc (588 mg, 9.0 mmol), sodium iodide (2.25 g, 15.0 mmol) and iodoform (1.02 g, 2.6 mmol) reacted with *N*-formyl imide **22** (147 mg, 1.3 mmol) to afford 156 mg (51%) of *E*-iodo-enamide **28** as a yellow solid. Mp 28 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.60 (1H, d, J=13.9 Hz), 5.37 (1H, d, J=13.9 Hz), 3.52 (2H, t, J=7.3 Hz), 2.48 (2H, t, J=7.9 Hz), 2.13 (2H, app qn, J=7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.3, 134.6, 54.9, 44.5, 30.5, 17.3; ν_{max} (neat)/cm^{-1}; 3057, 2957, 2917, 2889, 1685, 1607, 1480, 1457, 1263, 1174; HRMS (EI) found $(M)^+$ 236.9651, C_6H_8INO requires 236.9655.

3.2.3. (E)-1-(2-Iodovinyl)azepan-2-one, ***29****.* Chromium(III)chloride hexahydrate (4.80 g, 18.0 mmol), zinc (588 mg, 9.0 mmol), sodium iodide (2.25 g, 15.0 mmol) and iodoform (1.02 g, 2.6 mmol) reacted with *N*-formyl imide **23** (183.5 mg, 1.3 mmol) to afford 137 mg (40%) of *E*-iodo-enamide **29** as a yellow solid. Mp 36 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.85 (1H, d, J=14.0 Hz), 5.51 (1H, d, J=14.0 Hz), 3.59–3.49 (2H, m), 2.64–2.57 (2H, m), 1.79–1.64 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.5, 137.4, 54.9, 45.2, 36.9, 29.5, 27.5, 23.5;

ν_{max} (neat)/cm^{-1}; 2930, 1658, 1602, 1476, 1389, 1325, 1191; HRMS (CI/ISO) found (M+H)$^+$ 266.0042, $C_8H_{13}INO$ requires 266.0041.

3.2.4. (E)-1-(2-Iodovinyl)azocan-2-one, ***30****.* Chromium(III)chloride hexahydrate (4.80 g, 18.0 mmol), zinc (588, 9.0 mmol), sodium iodide (2.25 g, 15.0 mmol) and iodoform (1.02 g, 2.6 mmol) reacted with *N*-formyl imide **24** (201.5 mg, 1.3 mmol) to afford 150 mg (42%) of *E*-iodo-enamide **30** as a yellow solid. Mp 54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (1H, d, *J*=14.1 Hz), 5.51 (1H, d, *J*=14.1 Hz), 3.72 (2H, dd, *J*=5.9, 5.8 Hz), 2.63–2,56 (2H, m), 1.88–1.78 (2H, m), 1.73–1.68 (2H, m), 1.62–1.58 (2H, m), 1.50–1.42 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.1, 136.2, 55.5, 43.6, 34.3, 29.1, 27.9, 26.4, 24.2; ν_{max} (neat)/cm^{-1}; 3083, 2938, 2929, 2915, 1647, 1603, 1484, 1453, 1388, 1312; HRMS (CI/ISO) found (M+H)$^+$ 280.0198, $C_9H_{15}INO$ requires 280.0203.

3.2.5. (Z)-N-(2-Iodovinyl)-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide, ***31****Z.* Chromium(III)chloride hexahydrate (4.80 g, 18.0 mmol), zinc (588 mg, 9.0 mmol), sodium iodide (2.25 g, 15.0 mmol) and iodoform (1.02 g, 2.6 mmol) reacted with *N*-formyl imide **25** (280 mg, 1.3 mmol) to afford a crude 1.0/1.1 mixture of *E*/*Z* isomers. After column purification, 140 mg (32%) of *Z*-iodo-enamide **31***Z* was obtained as a light yellow solid. Mp 110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63–8.42 (1H, m), 7.28 (1H, dd, *J*=11.2, 6.4 Hz), 5.42 (1H, d, *J*=6.4 Hz), 4.17 (1H, s), 3.72 (1H, d, *J*=11.8 Hz), 3.32 (1H, d, *J*=11.8 Hz), 1.54 (3H, s), 1.47 (3H, s), 1.05 (3H, s), 1.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.6, 129.4, 99.4, 77.2, 71.4, 61.4, 33.3, 29.5, 21.9, 19.1, 18.8; ν_{max} (neat)/cm^{-1}; 2988, 2956, 2872, 1699, 1626, 1464, 1375, 1285, 1235; HRMS (EI) found (M)$^+$ 339.0332, $C_{11}H_{18}INO_3$ requires 339.0331.

3.2.6. (E)-N-(2-Iodovinyl)benzamide, ***32****E and (Z)-N-(2-Iodovinyl) benzamide,* ***32****Z.* Chromium(III)chloride hexahydrate (3.70 g, 13.8 mmol), zinc (452.3 mg, 6.9 mmol), sodium iodide (1.73 g, 11.5 mmol) and iodoform (0.78 g, 2.0 mmol) reacted with *N*-formyl imide **26** (149 mg, 1.0 mmol) to afford 113 mg (41%) of a 3.0/1.0 mixture of *E*/*Z* isomers from which an analytical clean fraction of the *E* isomer could be obtained. Mp 115–130 °C.

3.2.6.1. (E)-N-(2-Iodovinyl)benzamide, ***32****E.* ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01–7.92 (1H, m), 7.79 (2H, app dd, *J*=7.3, 1.4 Hz), 7.65 (1H, dd, *J*=13.7, 10.1 Hz), 7.55 (1H, appt, *J*=7.3 Hz), 7.46 (1H, appt, *J*=8.1 Hz), 5.84 (1H, d, *J*=13.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.3, 132.8, 132.7, 130.7, 129.1, 127.4, 61.2; ν_{max} (neat)/cm^{-1}; 3299, 2929, 1687, 1652, 1620, 1508, 1464, 1283; HRMS (EI) found (M)$^+$ 272.9654, C_9H_8INO requires 272.9651.

3.2.6.2. (E)-N-(2-Iodovinyl)benzamide, ***32****Z.* ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06 (1H, br s), 7.89–7.84 (2H, m), 7.62–7.48 (3H, m), 5.49 (1H, d, *J*=6.70 Hz).

3.2.7. (E)-N-(2-Iodovinyl)butyramide, ***33****E.* Chromium(III)chloride hexahydrate (4.80 g, 18.0 mmol), zinc (588 mg, 9.0 mmol), sodium iodide (2.2.5g, 15.0 mmol) and iodoform (1.02 g, 2.6 mmol) reacted with *N*-formyl imide **27** (149 mg, 1.3 mmol) to afford a crude 5.0/1.0 mixture of *E*/*Z* isomers. After column purification, 65 mg (21%) of *E*-iodo-enamide **33***E* was obtained as a yellow solid. Mp 85–90 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.45 (1H, dd, *J*=13.9, 10.6 Hz), 7.38–7.18 (1H, br s), 5.64 (1H, d, *J*=13.9 Hz), 2.20 (2H, t, *J*=7.3 Hz), 1.68 (2H, sext, *J*=7.5 Hz), 0.96 (3H, t, *J*=7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.8, 133.7, 56.6, 38.3, 18.9, 13.8; ν_{max} (neat)/cm^{-1}; 3265, 2960, 1664, 1624, 1492, 1462, 1222; HRMS (CI) found (M+H)$^+$ 239.9880, $C_6H_{11}INO$ requires 239.9885.

3.3. General procedure for the Sonogashira coupling of β-iodo-enamides

A 0.3 M solution of β-iodo-enamide (1.0 equiv) in DMF was treated with $Pd(PPh_3)_4$ (0.1 equiv) and the suspension was stirred at room temperature for 10 min. Then the alkyne (5.0 equiv), CuI (0.2 equiv) and TEA (2.0 equiv) were sequentially added, and the resulting mixture was stirred at room temperature for 72 h.

The reaction mixture was quenched with distilled water (20 mL) and extracted with diethyl ether (3×20 mL). The combined organic extracts were then washed with water (10×20 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a brown residue. The crude product was purified by flash column chromatography on silica gel eluting with 50/50 petroleum ether/dichloromethane+5% diethyl ether to afford the pure β-yn-enamide products.

3.3.1. (E)-1-(4-Phenylbut-1-en-3-ynyl)piperidin-2-one, ***34****.* β-Iodo-enamide **15** (60 mg, 0.24 mmol) was coupled with phenyl acetylene (132 μL, 1.2 mmol) in the presence of $Pd(PPh_3)_4$ (28 mg, 24 μmol), CuI (10 mg, 48 μmol) and triethylamine (72 μL, 0.48 mmol) to afford 50 mg (93%) of β-yn-enamide **34** as a yellow-brown solid. Mp 92 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.02 (1H, d, *J*=14.8 Hz), 7.37–7.32 (2H, m), 7.26–7.17 (3H, m), 5.21 (1H, d, *J*=14.8 Hz), 3.43 (2H, t, *J*=6.0 Hz), 2.54 (2H, t, *J*=6.5 Hz), 1.90–1.82 (2H, m), 1.79–1.73 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.2, 137.3, 131.3, 128.4, 127.7, 123.7, 89.8, 88.9, 87.4, 45.0, 32.9, 22.4, 20.3; ν_{max} (neat)/cm^{-1}; 3086, 2939, 2877, 2198, 1728, 1658, 1612, 1458; HRMS (CI/ISO) found (M+H)$^+$ 226.1232, $C_{15}H_{16}NO$ requires 226.1233.

3.3.2. (E)-1-(4-(4-Methoxyphenyl)but-1-en-3-ynyl)piperidin-2-one, ***35****.* β-Iodo-enamide **15** (50 mg,199 μmol) was coupled with 4-ethynylanisole (132 mg, 995 μmol) in the presence of $Pd(PPh_3)_4$ (23 mg, 19 μmol), CuI (7 mg, 38 μmol) and triethylamine (60 μL, 39.8 μmol) to afford 47 mg (92%) of β-yn-enamide **35** as a yellow-brown solid. Mp 132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.99 (1H, d, *J*=14.8 Hz), 7.35 (2H, dm, *J*=8.7 Hz), 6.83 (2H, dm, *J*=8.8 Hz), 5.20 (1H, d, *J*=14.8 Hz), 3.81 (3H, s), 3.43 (2H, t, *J*=6.0 Hz), 2.54 (2H, t, *J*=6.5 Hz), 1.96–1.88 (2H, m), 1.84–1.77 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.1, 159.2, 136.7, 132.7, 115.9, 114.0, 90.2, 88.8, 85.9, 55.3, 45.0, 33.0, 22.5, 20.4; ν_{max} (neat)/cm^{-1}; 3080, 2949, 2837, 2191, 1660, 1616, 1565, 1506, 1473; HRMS (EI) found (M)$^+$ 255.1259, $C_{16}H_{17}NO_2$ requires 255.1260.

3.3.3. (E)-1-(4-(4-Pentanoylphenyl)but-1-en-3-ynyl)piperidin-2-one, ***36****.* β-Iodo-enamide **15** (35 mg, 139 μmol) was coupled with 1-(4-ethynylphenyl)pentan-1-one (130 mg, 0.7 mmol) in the presence of $Pd(PPh_3)_4$ (16 mg, 14 μmol), CuI (5 mg, 28 μmol) and triethylamine (40 μL, 0.3 mmol) to afford 40 mg (94%) of enynamide **36** as a yellow-brown solid. Mp 170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (1H, d, *J*=14.9 Hz), 7.89 (2H, d, *J*=8.7 Hz), 7.47 (2H, t, *J*=8.7 Hz), 5.22 (1H, d, *J*=14.8 Hz), 3.45 (2H, t, *J*=6.0 Hz), 2.95 (2H, t, *J*=7.4 Hz), 2.57 (2H, t, *J*=6.4 Hz), 1.99–1.91 (2H, m), 1.89–1.82 (2H, m), 1.71 (2H, app qn, *J*=7.1 Hz), 1.41 (2H, appsextet, *J*=7.5 Hz), 0.88 (3H, t, *J*=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.5, 168.5, 138.3, 134.7, 131.2, 128.6, 128.0, 100.0, 95.4, 89.3, 45.1, 38.4, 33.0, 26.5, 22.5, 22.4, 20.4, 14.0; ν_{max} (neat)/cm^{-1}; 3078, 3045, 2955, 2193, 1680, 1664, 1616, 1593, 1552, 1500; HRMS (EI) found (M)$^+$ 309.1729, $C_{20}H_{23}NO_2$ requires 309.1727.

3.3.4. N-((E)-4-Phenyl-but-1-en-3-ynyl)-benzamide, ***37****E and N-((Z)-4-phenyl-but-1-en-3-ynyl)-benzamide,* ***37****Z.* A 2/1 mixture of *E*/*Z* β-iodo-enamides **32** (55 mg, 201 μmol) was coupled with phenyl acetylene (120 μL, 1.00 mmol) in the presence of $Pd(PPh_3)_4$ (23 mg, 21 μmol), CuI (8 mg, 40.2 μmol) and triethylamine (60 μL,

0.40 mmol) to afford 42 mg (85%) of enynamides **37***E*/**37***Z* as a 2/1 mixture of double bond isomers.

3.3.4.1. N-((E)-4-Phenyl-but-1-en-3-ynyl)-benzamide, ***37E.*** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (1H, br d, J=9.8 Hz), 7.86–7.80 (1H, m), 7.65–7.28 (10H, m), 5.56 (1H, d, J=14.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.8, 133.1, 132.5, 132.2, 131.3, 128.8, 128.5, 128.3, 127.2, 122.9, 97.5, 89.9, 83.5; ν_{max} (neat)/cm^{-1}; 3302, 2930, 2854, 2360, 1699, 1657, 1626, 1597, 1518, 1491; HRMS (CI/ISO) found $(M+H)^+$ 248.1074, $C_{17}H_{14}NO$ requires 248.1075.

3.3.4.2. N-((Z)-4-Phenyl-but-1-en-3-ynyl)-benzamide, ***37Z.*** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (1H, br d, J=9.8 Hz), 7.82 (1H, m), 7.65–7.28 (10H, m), 5.11 (1H, d, J=8.8 Hz).

3.3.5. (E)-1-(4-p-Tolylbut-1-en-3-ynyl)piperidin-2-one, ***38.*** β-Iodo-enamide **15** (50 mg, 0.2 mmol) was coupled with *p*-tolyl acetylene (116 mg, 1.0 mmol) in the presence of $Pd(PPh_3)_4$ (23 mg, 20 μmol), CuI (8 mg, 40 μmol) and triethylamine (60 μL, 0.4 mmol) to afford 48 mg (99%) of β-yn-enamide **38** as a yellow-brown solid. Mp 148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.00 (1H, d, J=14.8 Hz), 7.30 (2H, d, J=8.0 Hz), 7.10 (2H, d, J=7.6 Hz), 5.20 (1H, d, J=14.8 Hz), 3.43 (2H, t, J=6.2 Hz), 2.54 (2H, t, J=6.6 Hz), 2.34 (3H, s), 1.97–1.91 (2H, m), 1.86–1.81 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.2, 137.8, 137.0, 131.1, 129.1, 120.7, 90.1, 89.1, 86.7, 45.0, 33.0, 22.4, 21.5, 20.4; ν_{max} (neat)/cm^{-1}; 3086, 2955, 2924, 2877, 2191, 1666, 1620, 1504, 1458; HRMS (EI) found $(M)^+$ 239.1310, $C_{16}H_{17}NO$ requires 239.1311.

3.3.6. (E)-1-(6-(tert-Butyldimethylsilyloxy)hex-1-en-3-ynyl)piperidin-2-one, ***39.*** β-Iodo-enamide **15** (25 mg, 100 μmol) was coupled with 1-(*tert*-butyldimethylsilyloxy)-3-butyne (92 mg, 0.5 mmol) in the presence $Pd(PPh_3)_4$ (12 mg, 10 μmol), CuI (4.0 mg, 20 μmol) and triethylamine (30 μL, 0.2 mmol) to afford 10.2 mg (33%) of enynamide **39** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.78 (1H, d, J=14.8 Hz), 4.88 (1H, dm, J=14.8Hz), 3.64 (2H, t, J=7.3 Hz), 3.28 (2H, t, J=6.3 Hz), 2.43 (4H, m), 1.85–1.78 (2H, m), 1.77–1.69 (2H, m), 1.46 (6H, s), 0.81 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.5, 136.7, 90.21, 77.6, 62.1, 44.9, 32.9, 25.9, 23.9, 22.5, 20.4, 18.4, −5.2 (one unresolved carbon); ν_{max} (neat)/cm^{-1}; 2931, 2854, 2337, 1736, 1666, 1620; HRMS (CI/ISO) found $(M+H)^+$ 308.2051, $C_{17}H_{30}NO_2Si$ requires 308.2046.

3.3.7. N-[(E)-6-(tert-Butyl-dimethyl-silanyloxy)-hex-1-en-3-ynyl]-benzamide, ***40.*** A 3/1 mixture of *E*/*Z* β-iodo-enamides **32** (55 mg, 201 μmol) was coupled with 1-(*tert*-butyldimethylsilyloxy)-3-butyne (153 mg, 0.33 mmol) in the presence of $Pd(PPh_3)_4$ (20 mg, 17 μmol), CuI (7 mg, 33 μmol) and triethylamine (50 μL, 0.33 mmol) to afford 153 mg (40%) of enynamide **40***E* as a single isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95–7.85 (1H, m), 7.79 (2H, d, J=6.8 Hz), 7.58–7.39 (3H, m), 5.33 (1H, app dt, J=14.4, 2.2 Hz), 3.75 (2H, t, J=6.9 Hz), 2.54 (2H, app td, J=7.1, 2.2 Hz), 0.91 (9H, s), 0.09 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.9, 133.4, 132.4, 131.2, 128.9, 127.3, 93.2, 88.2, 78.1, 62.6, 26.8, 24.2, 18.4, −4.8; ν_{max} (neat)/cm^{-1}; 3292, 2929, 2855, 2359, 1707, 1627, 1519, 1488, 1252, 1090. HRMS (CI/ISO) found $(M+H)^+$ 330.1893, $C_{19}H_{28}NO_2Si$ requires 330.1889.

3.3.8. 1-((1E,3Z)-4-Phenylbuta-1,3-dieny)piperidin-2-one, ***41.*** A solution of en-yne **34** (10 mg, 44.4 μmol) in anhydrous EtOAc (1 mL) containing 2% quinoline (v/v) was treated with Lindlar's catalyst (10 mg) and the resulting mixture was placed under a hydrogen atmosphere. The reaction was then stirred at room temperature until completion by TLC analysis (1.5 h). The solution was then filtered through Celite, and washed several times with brine (10×10 mL) followed by and 10% aq HCl (1 N, 10 mL). The aqueous layer was extracted with diethyl ether (3×10 mL) and the combined organic layers were dried over Na_2SO_4. The solution was filtered and concentrated under vacuum to afford 10 mg (99%) of the desired *E*,*Z*-dienamide as a yellow oil, which required no further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (1H, d, J=13.6 Hz), 7.37–7.30 (5H, m), 6.36–6.22 (3H, m), 3.44 (2H, t, J=6.1 Hz), 2.53 (2H, t, J=6.6 Hz), 1.93–1.87 (2H, m), 1.85–1.78 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.7, 132.2, 128.7, 128.6, 128.5, 128.3, 127.4, 126.6, 107.8, 45.5, 33.1, 22.9, 20.7; ν_{max} (neat)/cm^{-1}; 2950, 2929, 1726, 1665, 1629, 1595, 1402; HRMS (EI) found $(M)^+$ observed 227.1306, $C_{15}H_{17}NO$ requires 227.1310.

3.4. Crystallographic data collection and refinement details

X-ray data for **15** were collected at 100 K on a Bruker Nonius Kappa CCD diffractometer equipped with an Oxford Cryosystems Cryostream low-temperature device and using graphite monochromated Mo Kα radiation (λ=0.71073 Å) radiation. Data reduction was carried out using DENZO[14] and a semi-empirical absorption correction applied using SADABS (BrukerAXS Inc, Madison, Wisconsin, USA). X-ray data for **34** were collected at 100 K on a Rigaku R-Axis RAPID Image Plate diffractometer equipped with an Oxford Cryosystems Cryostream low-temperature device and using graphite monochromated Mo Kα radiation (λ=0.71075 Å) radiation. Data reduction and an empirical absorption correction was carried out using CrystalClear[15]. The structures were both solved by direct methods using the program SHELXS97[16] and refined using full-matrix least-squares refinement on F^2 using SHELXL97[16] within the WinGX program suite[17]. All non-hydrogen atoms were refined anisotropically. The H atom positions were located on a difference Fourier map and their positions and isotropic thermal parameters were allowed to freely refine.

3.4.1. Crystal data for ***15.*** $C_7H_{10}INO$, M_r=251.06, monoclinic, $C2/c$, a=10.2578(9), b=15.9675(16), c=9.9684(10) Å, β=93.715(3)°, T=100(2) K, Z=8, R=0.0277 for 1635 data with $F_0>2\sigma(F)$, $wR2$=0.058 for 1873 unique data (all data 8841), GOF=1.231.

3.4.2. Crystal data for ***34.*** $C_{15}H_{15}NO$, M_r=225.28, monoclinic, $P2_1/c$, a=11.5713(3), b=8.1426(2), c=12.6750(3) Å, β=92.5340(10)°, T=100 K, Z=4, R=0.0416 for 1590 data with $F_0>2\sigma(F)$, $wR2$=0.0809 for 2735 unique data (all data 9810), GOF=0.917.

CCDC 804820–804821 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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