



Green Chemistry

PAPER

A Greener Synthesis of Substituted 1,8-Naphthyridines

Edward C. Anderson,^a Helen F. Sneddon,^b and Christopher J. Hayes*^a

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x
www.rsc.org/greenchem

A greener method for the synthesis of substituted 1,8-naphthyridines has been developed, which is supported by reaction metric analysis. Using 2-aminonicotinaldehyde as a starting material with a variety of carbonyl reaction partners, the Friedländer reaction can be performed with high yield using water as the reaction solvent. Divergent reactivity was seen when using acrolein, and an alternative method was developed to give access to 2-vinyl-1,8-naphthyridine in high yield, and an assessment of addition reactions to 2-vinyl-1,8-naphthyridine was performed.

Introduction

Since Koller's first report in 1927,¹ 1,8-naphthyridines (**1**, Chart 1) have emerged as important heterocycles,^{2–5} and interest in them has grown rapidly.⁶ This recent growth of activity in 1,8-naphthyridine chemistry is due to their presence in a wide variety of functional molecules, with the first phase being stimulated by the discovery of novel antibacterial agents (e.g. gemifloxacin **2**).^{7–9} Partially reduced 1,8-naphthyridines also occur in a number of natural products (e.g. eucophylline **3**)¹⁰ and in drug candidates (e.g. **4**),¹¹ where they can act as arginine mimics. In addition to being a key structural element of biologically active molecules, 1,8-naphthyridines find use as ligands,^{12,13} as molecular sensors (e.g. **5**),¹⁴ as molecular tweezers,¹⁵ self-assembly/host-guest systems,¹⁶ and in optoelectronic devices such as dye-sensitized solar cells¹⁷ and light-emitting diodes.¹⁸ The wide utility of 1,8-naphthyridine derivatives has led to a number of key synthetic methods being developed for their preparation, with focus now being placed on cleaner, more sustainable routes. A recent review on quinolone synthesis highlighted opportunities to improve heterocycle synthesis (from a green chemistry perspective¹⁹) by adopting alternative solvents (e.g. water), catalytic transformations and less energy intensive processing, and stimulated by this report, we now present our own work in this area that has resulted in an improved (greener) synthesis of 1,8-naphthyridine derivatives.

At the inception of our studies, we chose 2-aminonicotinaldehyde (**11**) as a key synthetic intermediate as it provides one of the required pyridine rings, and it also incorporates adjacent amine and aldehyde

functional groups that allow for the second pyridine to be constructed via a Friedländer reaction with a suitable enolisable carbonyl (Scheme 1).³ From a green chemistry perspective, 2-aminonicotinaldehyde (**11**) is attractive as it can be synthesised directly from the natural product nicotinamide (vitamin B3) (**10**).²⁰

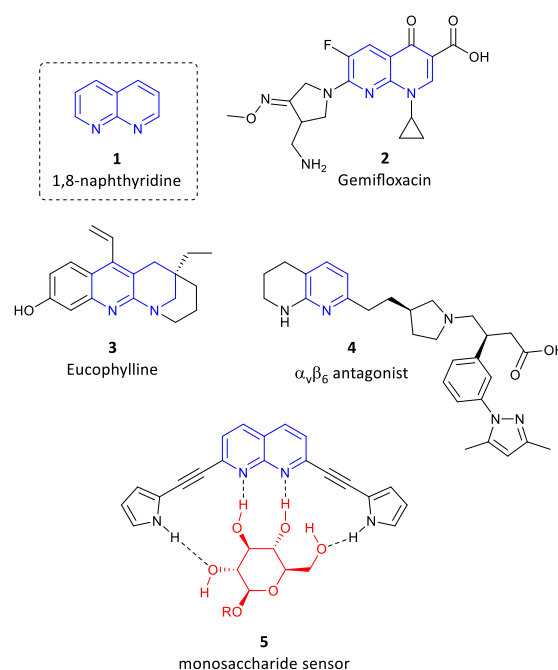


Chart 1. Examples of fully aromatic and partially reduced 1,8-naphthyridines.

Due to the commercial importance of the vitamin B3 complex, numerous methods have been developed for its production using biotransformations^{21,22} and catalytic ammoxidation of 3-picoline.^{23–25} These routes use non-petrochemical feedstocks (e.g. glycerol,²⁶

^aCentre for Sustainable Chemistry, School of Chemistry, University of Nottingham, Nottingham, NG7 2RD, UK

E-mail: chris.hayes@nottingham.ac.uk

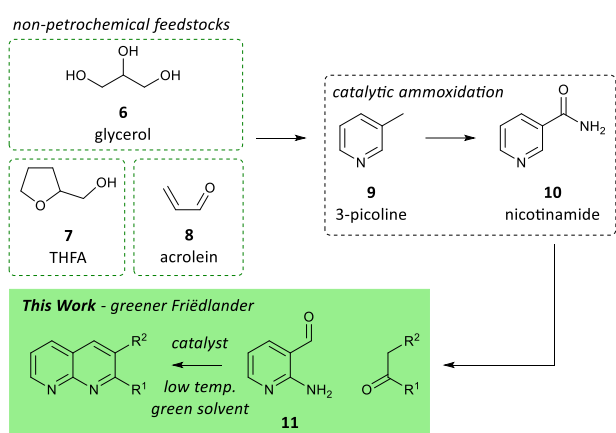
^bGSK, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts. SG1 2NY, UK.

E-mail: helen.f.sneddon@gsk.com

†Electronic Supplementary Information (ESI) available. See

DOI: 10.1039/x0xx00000x

acrolein,²⁷ tetrahydrofurfuryl alcohol (THFA)^{28,29} and they offer sustainable access to 2-aminonicotinaldehyde (**11**) (Scheme 1).



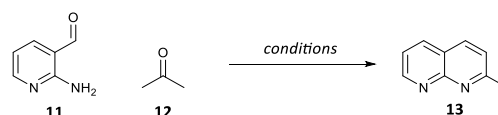
Scheme 1. Synthesis of 1,8-naphthyridines from non-petrochemical feedstocks.

Results and discussion

An initial inspection of the literature highlighted three methods for the synthesis of 2-methyl-1,8-naphthyridine **13** as starting points for reaction development.^{12,30,31} All three methods used 2-aminonicotinaldehyde (**11**) and acetone as starting materials, with variation being seen in the choice of solvent and base/catalyst. Bera *et al.* used methanol and KOH at reflux,¹² Campbell *et al.* used ethanol and proline at reflux,³⁰ and Matveeva *et al.* used piperidine in acetone at 100 °C in a sealed tube.³¹ A reaction metric analysis was performed on these methods for later comparison (*vide infra*, Table 2), and our studies began by repeating Campbell's conditions using (S)-proline as catalyst as a benchmark (Table 1 entry 1). Thus, treating **11** with an excess of acetone (3 equiv.) and superstoichiometric proline (110 mol%) in refluxing ethanol gave the desired product **13** in good yield.³⁰ Whilst these reaction conditions contain some attractive features (i.e. use of proline as catalyst and use of ethanol as solvent), the process does require an excess of both the catalyst and starting ketone, along with heating at reflux for an extended period (19 h) to reach completion. In an attempt to reduce reaction time (and temperature), we next performed the reaction using acetone as the solvent (Table 1 entry 2), but unfortunately, an extended reaction time was still required and the overall yield was reduced. In an effort to use a more benign solvent, water was used instead of acetone and this gave a similar outcome (Table 1 entry 3), with the reaction failing to reach full conversion (by TLC). Returning to ethanol as the solvent, we sought to reduce the amount of acetone used in the reaction, and found that the reaction performed extremely well with only 1.2 equivalents of acetone (Table 1 entry 4). Attempts to lower the loading of (S)-proline to 10 mol%, resulted in very poor conversion, and we next explored alternative catalysts. We first investigated the use of lithium hydroxide monohydrate as a low

molecular weight alternative to proline, and this delivered much shortened reaction times (10 mins to 1 h) and provided excellent yields at 100 mol% loading, with either ethanol or water as the solvent (Table 1 entries 5-6). Furthermore, the reaction proceeded well without heating using lithium hydroxide monohydrate in water, and the reaction was high yielding at room temperature in only 45 mins. (Table 1 entry 7). Further to this, we found that the catalyst loading could be lowered to 10 mol% when using lithium hydroxide monohydrate, and the number of equivalents of acetone could also be reduced (1.05 equiv.), without affecting yield (Table 1 entry 9). An increase in concentration to 1 M afforded comparable yield and more expedient reaction time (Table 1 entry 10). Sodium hydroxide, potassium hydroxide, and pyrrolidine all perform in a comparable manner at 10 mol% using water as solvent (Table 1 entries 11-13). These optimised reaction conditions represent a distinct improvement over the original (Table 1 entry 1), and have delivered shortened reaction time, lower reaction temperature, lower catalyst loading, more efficient ketone usage in a benign reaction solvent.

Table 1. Optimisation of the synthesis of 2-methyl-1,8-naphthyridine (**13**).



Entry	Eq. Me ₂ CO	Catalyst (mol%)	Solvent ^a	T	t	Yield (%)
1	3	(S)-proline (110)	EtOH (0.3 M)	Reflux	19 h	86
2	22.7	(S)-proline (110)	Me ₂ CO (0.6 M)	Reflux	21 h	63
3	3	(S)-proline (110)	H ₂ O (0.5 M)	80 °C	19 h	60
4	1.2	(S)-proline (110)	EtOH (0.5 M)	Reflux	19 h	93
5	1.2	LiOH•H ₂ O (100)	EtOH (0.5 M)	Reflux	1 h	96
6	1.2	LiOH•H ₂ O (100)	H ₂ O (0.5 M)	80 °C	10 min	95
7	1.2	LiOH•H ₂ O (100)	H ₂ O (0.5 M)	rt	45 min	96
8	1.2	LiOH•H ₂ O (10)	EtOH (0.5 M)	rt	1 h	96
9	1.05	LiOH•H ₂ O (10)	H ₂ O (0.5 M)	rt	5 h	97
10	1.05	LiOH•H ₂ O (10)	H ₂ O (1 M)	rt	2 h	98
11	1.05	NaOH (10)	H ₂ O (0.5 M)	rt	5 h	92
12	1.05	KOH (10)	H ₂ O (0.5 M)	rt	5 h	99
13	1.05	Pyrrolidine (10)	H ₂ O (0.5 M)	rt	1.75 h	94
14	1.05	(S)-proline (10)	H ₂ O (0.5 M)	rt	24 h	0

^aConcentrations quoted with respect to **11**.

In order to objectively assess the improvements made (from a green chemistry perspective), we performed a reaction metric analysis on our optimised method for comparison to the three previously published routes^{12,30,31} to **13** (Table 2). As all four syntheses of **13** use the same starting materials (i.e. **11** and **12**) the atom economy is the same (80%) for all methods, and hence this metric is not well suited to highlighting improvements in the reaction methodology. However, if the catalyst is included in the calculations, then our method compares favourably, as lithium hydroxide has a lower molecular weight than the other catalysts used in the previous work.³²

In order to address the limitations associated with atom economy, we selected Process Mass Intensity (PMI),³³ effective mass yield (EMY),³⁴ and also the two less commonly-used metrics: EcoScale,³⁵ and GREEN MOTION™ (Table 2).³⁶ These latter two metrics are penalty point systems, where 100 is the ideal value, and points are subtracted for every penalty (e.g. safety concerns, high energy costs, origin & cost of starting materials/reagents, poor reaction efficiency). Whilst such metrics introduce an element of subjectivity, they do give a good indication of the criteria that should be discussed when designing reactions in a more green and sustainable manner. When designing a “green & sustainable reaction”, there is a risk that applying one metric in isolation can lead to a single reaction parameter being over emphasised, which can result in oversight of other important features such as whether the starting materials and reagents are available from renewable sources; whether the reagents are benign to the user and environment; or whether large amounts of energy (e.g. for prolonged heating) are required in the reaction process.

Table 2. Metric analysis of 2-methyl-1,8-naphthyridine (**13**) synthesis.


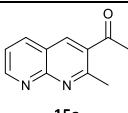
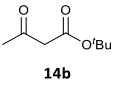
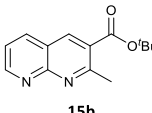

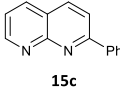

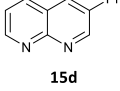

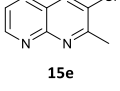

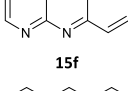

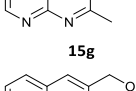

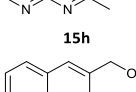

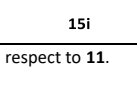
Entry	Method	PMI ^a	EMY ^b (%)	EcoScale	GREEN MOTION™
1	KOH/MeOH ¹³	8	106 (73)	56	58
2	(S)-Proline/EtOH ³⁰	10	117 (79) ^c	61	79
3	Piperidine/sealed tube ³¹	6	54 (43)	66	68
4	LiOH/H ₂ O (0.5 M) (This work)	16	111 (75)	84	82
5	LiOH/H ₂ O (1 M) (This work)	8	112 (75)	85	84

^aPMI values calculated using the reaction step only; ^bAcetone is used both as a solvent and a reagent in some examples, so the values in parentheses are EMY values that take into account the acetone consumed in the reaction, and give a better reflection of the EMY of the process when ‘non-benign’ ketones are used as reagents. The unedited EMY calculations can be found in the supporting information; ^c(S)-Proline was assumed benign due to lack of hazardous SDS information.

Upon comparing the four processes that are run at similar concentrations (0.8 M (entry 1), 0.76 M (entry 2), 1.5 M, (entry 3) 1.0 M (entry 5), Table 2), the PMI values fall in a narrow range (6-10), which reflects the fact that solvent use is a dominant factor in this metric. However, PMI doesn't take into account the nature of the

solvent, and both toxic and innocuous solvents are treated exactly the same. To illustrate this point, entry 4, which uses our preferred reaction concentration of 0.5 M shows a significantly worse PMI value (i.e. 16) due to the extra use of water as solvent. In contrast, EMY does not show this same trend, and entries 4 and 5 (Table 2) give very similar (good) values, which reflects the fact that water (despite known problems when considering, for example, product isolation, and disposal of contaminated waste water) is classed as a benign solvent, and its use should be encouraged. Entry 3 (Table 2) gives the worse EMY value due to the fact that stoichiometric amounts of piperidine (non-benign) are used. Both EcoScale and GREEN MOTION™ score our new method well.

Table 3. Synthesis of substituted 1,8-naphthyridines.

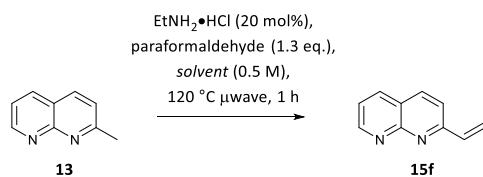
Entry	Active methylene	Product	Base	Solvent ^a	Yield (%)
1			LiOH•H ₂ O	H ₂ O (0.5 M)	69
2			LiOH•H ₂ O	H ₂ O (0.5 M)	70
3			LiOH•H ₂ O	H ₂ O (0.5 M)	96
4			LiOH•H ₂ O	H ₂ O (0.5 M)	83
5			LiOH•H ₂ O	H ₂ O (0.5 M)	18
6			LiOH•H ₂ O	H ₂ O (0.5 M)	40
7			KOH	MeOH (0.25 M)	86
8			KOH	EtOH (0.25 M)	79
9			KOH	ⁱ PrOH (0.125 M)	41

^aConcentrations quoted with respect to **11**.

Having developed excellent reaction conditions for the synthesis of **13**, we explored the synthesis of a wider range of substituted 1,8-naphthyridines (Table 3). Pleasingly, 1,3-dicarbonyls (Table 3 entries 1 and 2), aldehydes (entry 4) and a variety of ketones (entries 3, 5-6) all provided the desired 1,8-naphthyridine product in modest to excellent yield. The use of α -chloroacetone (entry 5) gave the lowest yield, and although the reason for this is yet to be established, a number of competitive decomposition pathways for the chloro ketone can be imagined under the basic aqueous conditions. As an extension to this study, we found that by reacting **11** and acrolein (**14f**) in simple alcohol solvents using KOH as base, a range of disubstituted 1,8-naphthyridines **15g-i** were obtained (Table 3 entries 7-9). The regioselective formation of **15g-i** can be rationalised by invoking conjugate addition of the alcohol to **14f**, resulting in a regiospecific enol/enolate. After addition of this to the carbonyl of **11**, subsequent condensation of the amine and resulting ketone, and elimination, the naphthyridines **15g-i** are afforded. It should be noted that when lithium hydroxide monohydrate was used as base under these alcoholic conditions, inseparable mixtures of the mono- and disubstituted 1,8-naphthyridine regioisomers were afforded.

Given the divergent reactivity displayed during the reactions of **11** with acrolein **14f**, we were keen to explore a complimentary route to 2-vinyl-1,8-naphthyridine **15f** as we could see the potential synthetic utility of this previously unknown heterocycle, and developing a high yielding (green) synthetic route is desirable. Having established a new, near quantitative yielding route to 2-methyl-1,8-naphthyridine **13** (Table 1 entry 9) we decided to explore the transformation of **13** into **15f** by adapting conditions reported by Feng and co-workers for the synthesis of 2-vinylquinolines from 2-methylquinolines.³⁷ Thus, condensation of **13** with paraformaldehyde under microwave irradiation using diethylamine hydrochloride (20 mol%) as catalyst in acetonitrile, gave the desired product **15f** in good yield (79%, Table 4 entry 1).

Table 4. Solvent screen for 2-vinyl-1,8-naphthyridine (**15f**) synthesis.



Entry	Solvent	Yield (%)
1	MeCN	79
2	DMSO	0
3	Heptane	8
4	Anisole	23
5	Methyl isobutyl ketone	32
6	Octyl acetate	33
7	Furfural	52
8	Dimethyl carbonate	74

In keeping with our goal to develop greener synthetic routes, we performed a solvent screen to find an alternative to acetonitrile.³⁸ Initial experiments with ethanol as the solvent showed that conjugate addition to the electrophilic vinyl group of **15f** was an issue, thus reducing the yield of desired product. A range of alternative solvents was screened (Table 4), and we were pleased to find that dimethylcarbonate was a more sustainable alternative to acetonitrile, giving a comparable yield (74% vs 79%) (Table 4 entry 8). This two-step route to **15f** from **11**, via **13** gives a significantly higher overall yield (>70%) than the 1 step alternative (Table 3 entry 6), and it avoids the divergent reactivity of acrolein described previously.

Having developed a reliable route to 2-vinyl-1,8-naphthyridine (**15f**),³⁹ we next performed a preliminary assessment of addition reactions to the vinyl moiety, analogous to the recently published study of additions to 2-vinylpyridine.⁴⁰ In Williams' work, a substoichiometric amount of the Lewis acid $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and elevated temperatures were required to facilitate addition to 2-vinylpyridine, but in our investigation (and with the exception of diethylamine (Table 5 entry 3)), we found that 2-vinyl-1,8-naphthyridine (**15f**) was a more reactive electrophile, generally needing no Lewis acid activation, nor elevated temperatures for addition to occur.

Table 5. Preliminary addition reactions of 2-vinyl-1,8-naphthyridine (**15f**).

Entry	Nucleophile	Time	Product	Yield (%) ^a
1		2.5 h		99
2		4 h		95
3 ^b		22 h		87
4		10 min		87
5		26.5 h		99 (4:1 dr)

^aIsolated yield; ^b $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (2.5 mol%) added

Experimental

All reagents and solvents were obtained from commercial suppliers, and were used without further purification unless otherwise stated. All reactions were carried out using conventional glassware, or Reacti-Vials™, at ambient temperature under an air atmosphere, and with no special attention given to the exclusion of moisture, unless otherwise stated. Thin layer chromatography was carried out using Merck TLC silica gel 60 F₂₅₄ aluminium sheets. These were analysed under 254 nm UV light or developed using potassium permanganate solution. Column chromatography was carried out using Fluorochem Silicagel 60A 40–63 μm. Fourier-transformed infrared (FTIR) spectra were obtained using a Bruker ALPHA FTIR spectrometer with a single reflection attenuated total reflectance (ATR) module. ¹H and ¹³C NMR spectra were obtained on a Bruker AV 400 at 400 MHz and 100 MHz respectively. Chemical shifts are reported in ppm, and coupling constants are reported in Hz, with CDCl₃ referenced at 7.2600 (¹H) and 77.160 (¹³C). High resolution mass spectra were obtained using a Bruker MicroTOF machine using electrospray ionisation.

2-Methyl-1,8-naphthyridine (13)

To a stirred mixture of 2-aminonicotinaldehyde (**11**) (122 mg, 1.00 mmol) and LiOH•H₂O (4.20 mg, 100 μmol) in H₂O (1 mL) was added acetone (77.1 μL, 61.0 mg, 1.05 mmol) and the reaction mixture allowed to stir at ambient temperature for 2 h. The reaction mixture was diluted with sat. aq. Na₂CO₃ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried (Na₂SO₄) and concentrated under reduced pressure to give **13** as a cream solid (141 mg, 98%). mp 99–100 °C (lit.,⁴¹ 99–100 °C), $\nu_{\max}/\text{cm}^{-1}$ 3043, 2998, 1601, 1544, 1496; ¹H NMR (400 MHz, CDCl₃) δ 8.99 (dd, *J* = 4.3, 2.0 Hz, 1H), 8.06 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.35 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 2.74 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 163.0 (C), 155.9 (C), 153.3 (CH), 136.8 (CH), 136.6 (CH), 123.0 (CH), 121.3 (CH), 120.7 (C), 25.7 (CH₃); *m/z* (ESI) 145.0762 (M + H⁺ C₉H₉N₂⁺ requires 145.0760).

1-(2-Methyl-1,8-naphthyridin-3-yl)ethan-1-one (15a)

To a stirred mixture of 2-aminonicotinaldehyde (**11**) (122 mg, 1.00 mmol) and LiOH•H₂O (4.20 mg, 100 μmol) in H₂O (2 mL) was added acetylacetone (108 μL, 105 mg, 1.05 mmol) and the reaction mixture allowed to stir at ambient temperature for 1.5 h. The reaction mixture was diluted with sat. aq. Na₂CO₃ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc) to give **15a** as a colourless solid (129 mg, 69%). mp 144–145 °C (lit.,³ 146–147 °C), $\nu_{\max}/\text{cm}^{-1}$ 3246, 3033, 2999, 2947, 1680, 1608, 1599, 1552; ¹H NMR (400 MHz, CDCl₃) δ 9.13 (dd, *J* = 4.3, 2.0 Hz, 1H), 8.46 (s, 1H), 8.22 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.49 (dd, *J* = 8.1, 4.3 Hz, 1H), 2.94 (s, 3H), 2.70 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 199.4 (C), 161.7 (C), 156.0 (C), 155.5 (CH), 138.8 (CH), 137.5 (CH), 132.3 (C), 122.4 (CH), 120.1 (C), 29.6 (CH₃), 26.0 (CH₃); *m/z* (ESI) 187.0865 (M + H⁺ C₁₁H₁₁N₂O⁺ requires 187.0866).

tert-Butyl 2-methyl-1,8-naphthyridine-3-carboxylate (15b)

To a stirred mixture of 2-aminonicotinaldehyde (**11**) (122 mg, 1.00 mmol) and LiOH•H₂O (4.20 mg, 100 μmol) in H₂O (2 mL) was added *tert*-butyl acetoacetate (174 μL, 166 mg, 1.05 mmol) and the reaction mixture allowed to stir at ambient temperature for 23 h. The reaction mixture was diluted with sat. aq. Na₂CO₃ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc) to give **15b** as a pale orange crystalline solid (157 mg, 70%). $\nu_{\max}/\text{cm}^{-1}$ 3048, 2923, 2937, 1721, 1609, 1554; ¹H NMR (400 MHz, CDCl₃) δ 9.12 (dd, *J* = 4.3, 2.0 Hz, 1H), 8.63 (s, 1H), 8.22 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.47 (dd, *J* = 8.1, 4.3 Hz, 1H), 3.02 (s, 3H), 1.64 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 165.4 (C), 162.2 (C), 156.1 (C), 155.2 (CH), 140.3 (CH), 137.5 (CH), 127.0 (C), 122.1 (CH), 120.3 (C), 82.7 (C), 28.3 (CH₃), 26.2 (CH₃); *m/z* (ESI) 245.1283 (M + H⁺ C₁₄H₁₇N₂O₂⁺ requires 245.1285).

2-Phenyl-1,8-naphthyridine (15c)

To a stirred mixture of 2-aminonicotinaldehyde (**11**) (122 mg, 1.00 mmol) and LiOH•H₂O (4.20 mg, 100 μmol) in H₂O (2 mL) was added acetophenone (122 μL, 126 mg, 1.05 mmol) and the reaction mixture allowed to stir at ambient temperature for 20.5 h. The reaction mixture was diluted with sat. aq. Na₂CO₃ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc) to give **15c** as a colourless solid (197 mg, 96%). mp 114–115 °C (lit.,⁴² 115–116 °C), $\nu_{\max}/\text{cm}^{-1}$ 3045, 3003, 1602, 1537, 1483; ¹H NMR (400 MHz, CDCl₃) δ 9.11 (dd, *J* = 4.3, 2.0 Hz, 1H), 8.33–8.28 (m, 2H), 8.21 (d, *J* = 8.5 Hz, 1H), 8.16 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.54–7.46 (m, 3H), 7.44 (dd, *J* = 8.1, 4.3 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 160.3 (C), 156.2 (C), 153.9 (CH), 138.6 (C), 137.8 (CH), 136.8 (CH), 130.2 (CH), 128.9 (CH), 128.0 (CH), 121.8 (CH), 121.8 (C), 119.8 (CH); *m/z* (ESI) 207.0917 (M + H⁺ C₁₄H₁₁N₂⁺ requires 207.0917).

3-Phenyl-1,8-naphthyridine (15d)

To a stirred mixture of 2-aminonicotinaldehyde (**11**) (122 mg, 1.00 mmol) and LiOH•H₂O (4.20 mg, 100 μmol) in H₂O (2 mL) was added phenylacetaldehyde (122 μL, 126 mg, 1.05 mmol) and the reaction mixture allowed to stir at ambient temperature for 26 h. The reaction mixture was diluted with sat. aq. Na₂CO₃ (10 mL) and extracted with a mixture of EtOAc (10 mL) and CHCl₃ (20 mL), then further extracted with CHCl₃ (2 x 10 mL). The combined organic phases were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc) to give **15d** as a colourless solid (172 mg, 83%). mp 125–127 °C (lit.,³ 126–127 °C), $\nu_{\max}/\text{cm}^{-1}$ 3046, 3001, 1595, 1561, 1478; ¹H NMR (400 MHz, CDCl₃) δ 9.38 (d, *J* = 2.6 Hz, 1H), 9.11 (dd, *J* = 4.2, 2.0 Hz, 1H), 8.29 (d, *J* = 2.6 Hz, 1H), 8.23 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.72–7.68 (m, 2H), 7.55–7.48 (m, 3H), 7.47–7.41 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 155.6 (C), 153.5 (CH), 153.2 (CH), 137.3 (CH), 137.1 (C),

135.0 (C), 134.0 (CH), 129.4 (CH), 128.6 (CH), 127.6 (CH), 122.6 (CH); m/z (ESI) 207.0918 ($M + H^+ C_{14}H_{11}N_2^+$ requires 207.0917).

3-Chloro-2-methyl-1,8-naphthyridine (15e)

To a stirred mixture of 2-aminonicotinaldehyde (**11**) (122 mg, 1.00 mmol) and LiOH·H₂O (4.20 mg, 100 μmol) in H₂O (2 mL) was added chloroacetone (83.6 μL, 97.1 mg, 1.05 mmol), and the reaction mixture allowed to stir at ambient temperature for 20.5 h. The reaction mixture was diluted with sat. aq. Na₂CO₃ (10 mL), and the aqueous phase extracted with EtOAc (3 x 10 mL). The combined organic phases were dried (Na₂SO₄) and concentrated under reduced pressure to give a brown oil. The residue was purified by column chromatography (silica gel, EtOAc) to give **15e** (32.2 mg, 18%) as a tan-coloured solid. $\nu_{\max}/\text{cm}^{-1}$ 3036, 2988, 2922, 1595, 1544; ¹H NMR (400 MHz, CDCl₃) δ 9.06 (dd, $J = 4.2, 2.0$ Hz, 1H), 8.12 (s, 1H), 8.09 (dd, $J = 8.2, 2.0$ Hz, 1H), 7.46 (dd, $J = 8.2, 4.2$ Hz, 1H), 2.87 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.8 (C), 154.2 (C), 153.6 (CH), 135.9 (CH), 135.4 (CH), 130.0 (C), 122.3 (CH), 122.1 (C), 24.2 (CH₃); m/z (ESI) 179.0369 ($M + H^+ C_9H_8ClN_2^+$ requires 179.0371).

2-Vinyl-1,8-naphthyridine (15f)

Method A: To a stirred mixture of 2-aminonicotinaldehyde (122 mg, 1.00 mmol) in H₂O (2 mL) was added LiOH·H₂O (4.20 mg, 100 μmol), then methyl vinyl ketone (85.0 μL, 73.6 mg, 1.05 mmol), and the reaction mixture allowed to stir at room temperature for 4.5 h. The reaction mixture was diluted with sat. aq. Na₂CO₃ (10 mL), and the aqueous extracted with EtOAc (3 x 10 mL). The combined organic phases were dried (Na₂SO₄) and concentrated under reduced pressure to give a dark yellow oil. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc 1:1) – 5% *iso*-propyl alcohol in EtOAc) to give **15f** (62.8 mg, 40%) as a yellow-brown oil.

Method B: A mixture of 2-methyl-1,8-naphthyridine (**13**) (144 mg, 1.00 mmol), Et₂NH·HCl (21.9 mg, 200 μmol), and paraformaldehyde (39.0 mg, 1.30 mmol) in dimethyl carbonate (2 mL) was heated to 120 °C (μwave) for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue purified by column chromatography (silica gel, EtOAc) to give **15f** as a light brown solid (115 mg, 74%). $\nu_{\max}/\text{cm}^{-1}$ 3043, 2995, 1596, 1539, 1494; ¹H NMR (400 MHz, CDCl₃) δ 9.07 (dd, $J = 4.2, 2.0$ Hz, 1H), 8.12 (d, $J = 8.1$ Hz, 1H), 8.11 (d, $J = 8.3$ Hz, 1H), 7.61 (d, $J = 8.3$ Hz, 1H), 7.41 (dd, $J = 8.1, 4.2$ Hz, 1H), 7.06 (dd, $J = 17.6, 10.8$ Hz, 1H), 6.46 (dd, $J = 17.6, 1.0$ Hz, 1H), 5.71 (dd, $J = 10.8, 1.0$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 159.2 (C), 156.2 (C), 153.9 (CH), 137.5 (CH), 137.4 (CH), 136.7 (CH), 121.8 (C), 121.8 (CH), 120.0 (CH); m/z (ESI) 157.0759 ($M + H^+ C_{10}H_9N_2^+$ requires 157.0760).

3-(Methoxymethyl)-2-methyl-1,8-naphthyridine (15g)

To a stirred mixture of 2-aminonicotinaldehyde (**11**) (122 mg, 1.00 mmol) and KOH (112 mg, 2.00 mmol) in MeOH (4 mL) was added MVK (**14f**) (109 μL, 94.6 mg, 1.05 mmol) and the reaction mixture

allowed to stir at ambient temperature for 2.5 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with sat. aq. Na₂CO₃ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, EtOAc/EtOH (4:1)) to give **15g** as a yellow solid (162 mg, 86%). $\nu_{\max}/\text{cm}^{-1}$ 3031, 2981, 2925, 2866, 2826; ¹H NMR (400 MHz, CDCl₃) δ 9.00 (dd, $J = 4.3, 2.0$ Hz, 1H), 8.10 (dd, $J = 8.0, 2.0$ Hz, 1H), 8.06 (d, $J = 1.1$ Hz, 1H), 7.38 (dd, $J = 8.0, 4.3$ Hz, 1H), 4.58 (d, $J = 1.1$ Hz, 2H), 3.48 (s, 3H), 2.72 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 161.4 (C), 155.4 (C), 153.1 (CH), 136.6 (CH), 134.9 (CH), 131.5 (C), 121.6 (CH), 121.2 (C), 71.7 (CH₂), 58.8 (CH₃), 23.0 (CH₃); m/z (ESI) 189.1026 ($M + H^+ C_{11}H_{13}N_2O^+$ requires 189.1022).

3-(Ethoxymethyl)-2-methyl-1,8-naphthyridine (15h)

To a stirred mixture of 2-aminonicotinaldehyde (**11**) (122 mg, 1.00 mmol) and KOH (112 mg, 2.00 mmol) in EtOH (4 mL) was added MVK (**14f**) (μL, mg, 1.05 mmol) and the reaction mixture allowed to stir at ambient temperature for 45 min. The reaction mixture was concentrated under reduced pressure. The residue was diluted with sat. aq. Na₂CO₃ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, EtOAc) to give **15h** as a light brown oil (159 mg, 79%). $\nu_{\max}/\text{cm}^{-1}$ 2984, 2972, 2873, 1618, 1600; ¹H NMR (400 MHz, CDCl₃) δ 9.02 (dd, $J = 4.3, 2.0$ Hz, 1H), 8.13 (dd, $J = 8.1, 2.0$ Hz, 1H), 8.10 (s, 1H), 7.40 (dd, $J = 8.1, 4.3$ Hz, 1H), 4.64 (d, $J = 1.0$ Hz, 2H), 3.66 (q, $J = 7.0$ Hz, 2H), 2.75 (s, 3H), 1.30 (t, $J = 7.0$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) 161.5 (C), 155.4 (C), 153.1 (CH), 136.7 (CH), 134.9 (CH), 131.9 (C), 121.6 (CH), 121.3 (C), 69.8 (CH₂), 66.7 (CH₂), 23.1 (CH₃), 15.3 (CH₃); m/z (ESI) 203.1179 ($M + H^+ C_{12}H_{15}N_2O^+$ requires 203.1179).

3-(*iso*-Propoxymethyl)-2-methyl-1,8-naphthyridine (15i)

To a stirred mixture of 2-aminonicotinaldehyde (**11**) (122 mg, 1.00 mmol) and KOH (112 mg, 2.00 mmol) in *i*PrOH (8 mL) was added MVK (**14f**) (109 μL, 94.6 mg, 1.05 mmol) and the reaction mixture allowed to stir at ambient temperature for 17 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with sat. aq. Na₂CO₃ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, EtOAc/EtOH (4:1)) to give **15i** as an orange oil (87.7 mg, 41%). $\nu_{\max}/\text{cm}^{-1}$ 2970, 2929, 2870, 1619, 1560, 1555; ¹H NMR (400 MHz, CDCl₃) δ 9.00 (dd, $J = 4.3, 2.0$ Hz, 1H), 8.12 (d, $J = 8.1, 2.0$ Hz, 1H), 8.11 (d, $J = 1.1$ Hz, 1H), 7.39 (dd, $J = 8.1, 4.3$ Hz, 1H), 4.63 (d, $J = 1.1$ Hz, 2H), 3.77 (hept, $J = 6.1$ Hz, 1H), 2.74 (s, 3H), 1.27 (d, $J = 6.1$ Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 161.5 (C), 155.3 (C), 153.0 (CH), 136.7 (CH), 134.9 (CH), 132.4 (C), 121.6 (CH), 121.3 (C), 72.2 (CH), 67.3 (CH₂), 23.1 (CH₃), 22.2 (CH₃); m/z (ESI) 217.1335 ($M + H^+ C_{13}H_{17}N_2O^+$ requires 217.1335).

2-(2-(Piperidin-1-yl)ethyl)-1,8-naphthyridine (17a)

To a stirred mixture of 2-vinyl-1,8-naphthyridine (**15f**) (50.0 mg, 320 μmol) in MeCN (320 μL) was added piperidine (31.6 μL , 27.2 mg, 320 μmol), and the reaction mixture allowed to stir at ambient temperature for 2.5 h. The reaction mixture was concentrated under reduced pressure to give **17a** as a pale orange solid (76.7 mg, 99%). $\nu_{\text{max}}/\text{cm}^{-1}$ 3045, 3003, 2928, 2855, 2805, 1602, 1548, 1498, 1446, 1434; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.05 (dd, $J = 4.5, 2.0$ Hz, 1H), 8.12 (dd, $J = 8.0, 2.0$ Hz, 1H), 8.06 (d, $J = 8.5$ Hz, 1H), 7.41 (d, $J = 8.0$ Hz, 1H), 7.40 (d, $J = 8.5$ Hz, 1H), 3.28-3.19 (m, 2H), 2.94-2.85 (m, 2H), 2.57-2.39 (m, 4H), 1.58 (tt, $J = 5.5, 5.5$ Hz, 4H), 1.47-1.38 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 165.4 (C), 156.0 (C), 153.4 (CH), 137.0 (CH), 136.8 (CH), 123.0 (CH), 121.5 (CH), 121.1 (CH), 58.6 (CH_2), 54.6 (CH_2), 36.7 (CH_2), 26.2 (CH_2), 24.5 (CH_2); m/z (ESI) 242.1660 ($\text{M} + \text{H}^+$ $\text{C}_{15}\text{H}_{20}\text{N}_3^+$ requires 242.1652).

4-(2-(1,8-Naphthyridin-2-yl)ethyl)morpholine (17b)

To a stirred mixture of 2-vinyl-1,8-naphthyridine (**15f**) (50.0 mg, 320 μmol) in MeCN (320 μL) was added morpholine (27.6 μL , 320 μmol), and the reaction mixture allowed to stir at ambient temperature for 21 h. The reaction mixture was concentrated under reduced pressure to give **17b** as a pale orange solid (73.9 mg, 95%). $\nu_{\text{max}}/\text{cm}^{-1}$ 2974, 2959, 2854, 2790, 2759, 1600; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.05 (dd, $J = 4.5, 2.0$ Hz, 1H), 8.13 (dd, $J = 8.0, 2.0$ Hz, 1H), 8.08 (d, $J = 8.5$ Hz, 1H), 7.42 (dd, $J = 8.0, 4.5$ Hz, 1H), 7.41 (d, $J = 8.5$ Hz, 1H), 3.75-3.65 (m, 4H), 3.27-3.19 (m, 2H), 2.98-2.90 (m, 2H), 2.61-2.47 (m, 4H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 164.8 (C), 156.0 (C), 153.4 (CH), 137.1 (CH), 136.8 (CH), 122.9 (CH), 121.6 (CH), 121.2 (C), 67.1 (CH_2), 58.1 (CH_2), 53.7 (CH_2), 36.4 (CH_2); m/z (ESI) 244.1451 ($\text{M} + \text{H}^+$ $\text{C}_{14}\text{H}_{18}\text{N}_3\text{O}^+$ requires 244.1444).

***N,N*-Diethyl-2-(1,8-naphthyridin-2-yl)ethan-1-amine (17c)**

To a stirred solution of 2-vinyl-1,8-naphthyridine (**15f**) (50.0 mg, 320 μmol) in MeCN (320 μL) was added diethylamine (33.1 μL , 23.4 mg, 320 μmol), then $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (2.3 mg, 8.00 μmol) and the reaction mixture allowed to stir at ambient temperature for 22 h. The reaction mixture was concentrated under reduced pressure, the residue diluted with sat. aq. Na_2CO_3 solution (1 mL) and the aqueous phase extracted with EtOAc (3 x 1 mL). The combined organic phases were dried (Na_2SO_4), concentrated under reduced pressure to give **17c** as a brown oil (63.8 mg, 87%). $\nu_{\text{max}}/\text{cm}^{-1}$ 3377, 3053, 2971, 2933, 1603, 1553, 1497; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.02 (dd, $J = 4.5, 2.0$ Hz, 1H), 8.10 (dd, $J = 8.0, 2.0$ Hz, 1H), 8.04 (d, $J = 8.5$ Hz, 1H), 7.41-7.35 (m, 2H), 3.18-3.11 (m, 2H), 3.03-2.97 (m, 2H), 2.59 (q, $J = 7.0$ Hz, 4H), 1.02 (t, $J = 7.0$ Hz, 6H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 165.4 (C), 156.0 (C), 153.2 (CH), 136.8 (CH), 122.9 (CH), 121.4 (CH), 121.0 (C), 52.3 (CH_2), 46.9 (CH_2), 36 (CH_2), 12.0 (CH_3); m/z (ESI) 230.1660 ($\text{M} + \text{H}^+$ $\text{C}_{14}\text{H}_{20}\text{N}_3^+$ requires 230.1652).

2-(2-(Phenylthio)ethyl)-1,8-naphthyridine (17d)

To a stirred mixture of 2-vinyl-1,8-naphthyridine (**15f**) (50.0 mg, 320 μmol) in MeCN (320 μL) was added thiophenol (32.9 μL , 35.3 mg, 320 μmol) and the reaction mixture allowed to stir at ambient temperature for 10 min. The resulting solution was concentrated under reduced pressure and purified by column chromatography to give **17d** as a cloudy pale yellow oil with BHT present (73.8 mg, 87%). $\nu_{\text{max}}/\text{cm}^{-1}$ 3051, 2923, 1604, 1582, 1554; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.08 (dd, $J = 4.5, 2.0$ Hz, 1H), 8.14 (dd, $J = 8.0, 2.0$ Hz, 1H), 8.08 (d, $J = 8.5$ Hz, 1H), 7.44 (dd, $J = 8.0, 4.5$ Hz, 1H), 7.41-7.36 (m, 2H), 7.35 (d, $J = 8.5$ Hz, 1H), 7.29-7.23 (m, 2H), 7.18-7.13 (m, 1H), 3.57-3.51 (m, 2H), 3.38-3.32 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 164.2 (C), 156.0 (C), 153.5 (CH), 137.2 (CH), 136.9 (CH), 136.1 (C), 129.5 (CH), 129.0 (CH), 126.1 (CH), 123.0 (CH), 121.8 (CH), 121.4 (C), 38.6 (CH_2), 32.5 (CH_2); m/z (ESI) 267.0957 ($\text{M} + \text{H}^+$ $\text{C}_{16}\text{H}_{15}\text{N}_2\text{S}^+$ requires 267.0950).

2-(1,4,5,6,7-Pentamethylbicyclo[2.2.1]hept-5-en-2-yl)-1,8-naphthyridine (17e)

To a stirred mixture of 2-vinyl-1,8-naphthyridine (**15f**) (50.0 mg, 320 μmol) in MeCN (320 μL) was added 1,2,3,4,5-pentamethylcyclopentadiene (50.1 μL , 43.6 mg, 320 μmol) and the reaction mixture allowed to stir at ambient temperature for 26.5 h. The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography (silica gel, Et_2O) to give a mixture of diastereoisomers (4:1 dr) of **17e** as a colourless oil (92.3 mg, 99%). (Major isomer) $\nu_{\text{max}}/\text{cm}^{-1}$ 2951, 2926, 2868, 1604, 1546, 1496, 1444, 1423, 1376; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.06 (dd, $J = 4.5, 2.0$ Hz, 1H), 8.11 (dd, $J = 8.0$ Hz, 2.0 Hz, 1H), 7.96 (d, $J = 8.5$ Hz, 1H), 7.40 (dd, $J = 8.0$ Hz, 4.5 Hz, 1H), 7.06 (d, $J = 8.5$ Hz, 1H), 3.56 (dd, $J = 9.0, 4.5$ Hz, 1H), 1.99 (dd, $J = 12.0$ Hz, 9.0 Hz, 1H), 1.76 (dd, $J = 12.0, 4.5$ Hz, 1H), 1.69 (d, $J = 1.0$ Hz, 3H), 1.57 (q, $J = 6.5$ Hz, 1H), 1.14 (s, 3H), 1.10 (s, 3H), 0.96 (d, $J = 1.0$ Hz, 3H), 0.61 (d, $J = 6.5$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 168.2 (C), 153.1 (CH), 136.6 (CH), 135.7 (CH), 121.5 (CH), 121.2 (CH), 62.8 (CH), 61.1 (CH), 57.0 (C), 53.5 (C), 41.4 (CH_2), 15.5 (CH_3), 14.4 (CH_3), 12.2 (CH_3), 10.1 (CH_3), 8.2 (CH_3); m/z (ESI) 293.2011 ($\text{M} + \text{H}^+$ $\text{C}_{20}\text{H}_{25}\text{N}_2^+$ requires 293.2012).

Conclusions

We have reported conditions for a mild, greener synthesis of substituted 1,8-naphthyridines from 2-aminonicotinaldehyde (**11**), which can be ultimately sourced from sustainable starting materials, with accompanying analysis using green chemistry metrics. Furthermore, we have shown two routes to 2-vinyl-1,8-naphthyridine (**15f**), a previously unreported heterocycle. In addition, we have shown that 2-vinyl-1,8-naphthyridine (**15f**) displays good electrophilic character with various nucleophiles, and proves to be more reactive than the analogous pyridine species when used in this manner.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank the EPSRC Centre for Doctoral Training in Sustainable Chemistry (EP/L015633/1), and GlaxoSmithKline for funding.

Notes and references

- G. Koller, *Berichte der Dtsch. Chem. Gesellschaft (A B Ser.)*, 1927, **60**, 407–410.
- C. F. H. Allen, *Chem. Rev.*, 1950, **47**, 275–305.
- E. M. Hawes and D. G. Wibberley, *J. Chem. Soc. C Org.*, 1966, **86**, 315.
- A. A. Fadda, S. A. El-Hadidy and K. M. Elattar, *Synth. Commun.*, 2015, **45**, 2765–2801.
- V. P. Litvinov, *Adv. Heterocycl. Chem.*, 2006, **91**, 189–300.
- For example, 1255 citations in 2018 compared to 224 citations in 2000 (using '1-8-naphthyridine' as the topic search term in 'Web of Science' (<http://wok.mimas.ac.uk>))
- G. Y. Leshner, E. J. Froelich, M. D. Gruett, J. H. Bailey and R. P. Brundage, *J. Med. Pharm. Chem.*, 1962, **5**, 1063–1065.
- J. I. Oh, K. S. Paek, M. J. Ahn, M. Y. Kim, C. Y. Hong, I. C. Kim and J. H. Kwak, *Antimicrob. Agents Chemother.*, 1996, **40**, 1564–1568.
- A. Madaan, R. Verma, V. Kumar, A. T. Singh, S. K. Jain and M. Jaggi, *Arch. Pharm. (Weinheim)*, 2015, **348**, 837–860.
- J. Deguchi, T. Shoji, A. E. Nugroho, Y. Hirasawa, T. Hosoya, O. Shiota, K. Awang, A. H. A. Hadi and H. Morita, *J. Nat. Prod.*, 2010, **73**, 1727–1729.
- J. Adams, E. C. Anderson, E. E. Blackham, Y. W. R. Chiu, T. Clarke, N. Eccles, L. A. Gill, J. J. Haye, H. T. Haywood, C. R. Hoenig, M. Kausas, J. Le, H. L. Russell, C. Smedley, W. J. Tipping, T. Tongue, C. C. Wood, J. Yeung, J. E. Rowedder, M. J. Fray, T. McNally and S. J. F. Macdonald, *ACS Med. Chem. Lett.*, 2014, **5**, 1207–1212.
- J. K. Bera, N. Sadhukhan and M. Majumdar, *Eur. J. Inorg. Chem.*, 2009, 4023–4038.
- T. Ghatak, M. Sarkar, S. Dinda, I. Dutta, S. M. W. Rahaman and J. K. Bera, *J. Am. Chem. Soc.*, 2015, **137**, 6168–6171.
- J.-M. Fang, S. Selvi, J.-H. Liao, Z. Slanina, C.-T. Chen and P.-T. Chou, *J. Am. Chem. Soc.*, 2004, **126**, 3559–3566.
- J. L. Katz, B. J. Geller and P. D. Foster, *Chem. Commun.*, 2007, 1026.
- G. B. W. L. Ligthart, H. Ohkawa, R. P. Sijbesma and E. W. Meijer, *J. Am. Chem. Soc.*, 2005, **127**, 810–811.
- T. J. Whittemore, A. Millet, H. J. Sayre, C. Xue, B. S. Dolinar, E. G. White, K. R. Dunbar and C. Turro, *J. Am. Chem. Soc.*, 2018, **140**, 5161–5170.
- A. Fernández-Mato, J. M. Quintela and C. Peinador, *New J. Chem.*, 2012, **36**, 1634.
- V. F. Batista, D. C. G. A. Pinto and A. M. S. Silva, *ACS Sustainable Chem. Eng.* 2016, **4**, 4064–4078.
- T. G. Majewicz and P. Caluwe, *J. Org. Chem.*, 1974, **39**, 720–721.
- B. Li, J. Su and J. Tao, *Org. Process Res. Dev.*, 2011, **15**, 291–293.
- Z. Wang, Z. Liu, W. Cui and Z. Zhou, *Appl Biochem Biotechnol*, 2010, **182**, 1458–1466.
- E. Treszcza, B. Lipka, B. Buszynski, J. Musierow, A. Teichert, L. Stefania, M. Grzybowski, A. Wawer, N. Bellen, S. Porada, L. Szoza, J. Iwinski and W. Ratajczka, *Przem. Chem.*, 1973, **52**, 167–169.
- B. M. Reddy and M. Subrahmanyam, *J. Chem. Soc., Chem. Commun.*, 1988, **0**, 940–941.
- R. Chuck, *Appl. Catal. A Gen.*, 2005, **280**, 75–82.
- A. Martin, U. Armbruster and H. Atia, *Eur. J. Lipid Sci. Technol.*, 2012, **114**, 10–23.
- X. Zhang, Z. Wu, W. Liu and Z.-S. Chao, *CATCOM*, 2016, **80**, 10–14.
- J. D. Butler, J. H. Dodsworth and A. T. Groom, *Chem. Commun.*, 1966, **0**, 54.
- J. Byun and J. Han, *Green Chem.*, 2017, **19**, 5214.
- J. E. Campbell, P. Jones, Sunovion Pharmaceuticals Inc., US Pat., US201261731404P, 2012
- A. G. Matveeva, P. S. Lempert, L. A. Leites, R. R. Aysin, A. V. Vologzhanina, Z. A. Starikova, M. P. Passechnik and E. E. Nifant'ev, *Inorganica Chim. Acta*, 2009, **362**, 3187–3195.
- This information can be found in the Electronic Supplementary Information (ESI).
- C. Jimenez-Gonzalez, C. S. Ponder, Q. B. Broxterman and J. B. Manley, *Org. Process Res. Dev.*, 2011, **15**, 912–917.
- T. Hudlicky, D. A. Frey, L. Koroniak, C. D. Claeboe and L. E. Brammer Jr., *Green Chem.*, 1999, **1**, 57–59.
- K. Van Aken, L. Strekowski and L. Patiny, *Beilstein J. Org. Chem.*, 2006, **2**, 3.
- T. V. T. Phan, C. Gallardo and J. Mane, *Green Chem.*, 2015, **17**, 2846–2852.
- J. Xiao, Y. Huang, Z. Song and W. Feng, *RSC Adv.*, 2015, **5**, 99095–99098.
- C. M. Alder, J. D. Hayler, R. K. Henderson, A. M. Redman, L. Shukla, L. E. Shuster and H. F. Sneddon, *Green Chem.*, 2016, **18**, 3879–3890.
- We recommend that 2-vinyl-1,8-naphthyridine (**15f**) be stored at lower than ambient temperature, or significant conversion to undesired species can be observed.
- S. Abou-Shehada, M. C. Teasdale, S. D. Bull, C. E. Wade and J. M. J. Williams, *ChemSusChem*, 2015, **8**, 1083–1087.
- W. W. Paudler and T. J. Kress, *J. Org. Chem.*, 1967, **32**, 832–833.
- D. K. J. Gorecki and E. M. Hawes, *J. Med. Chem.* 1977, **20**, 124–128.