An efficient protocol for the production of pymetrozine *via* a new synthetic strategy

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A practical four-step synthesis of pymetrozine is reported, starting from a green chemical dimethyl carbonate and using the key intermediate methyl (*E*)-1-(2-oxopropyl)-2-(pyridin-3-ylmethylene)hydrazine-1-carboxylate. The main advantages of the route include inexpensive starting materials, environmental friendliness, short synthetic route, easy-to-use synthetic method and acceptable overall yield. A scale-up experiment was carried out to provide pymetrozine with 99.84% purity in 53.2% total yield.

Keywords: pymetrozine, methyl(*E*)-1-(2-oxopropyl)-2-(pyridin-3-ylmethylene) hydrazine-1-carboxylate, hydrazinolysis, condensation, alkylation, cyclisation

Pymetrozine (**1**, Fig. 1) is a novel insecticide containing a pyridine heterocycle that is used to control aphids and whitefly, and was developed by Syngenta.[1–4] It has been found that pymetrozine may take effect through the nervous system, with a unique mode of action that differs from other well-known insecticides.[5] The touching or ingestion of pymetrozine by pests with piercing and sucking mouths, such as aphids, whiteflies, leafhoppers and various fly hoppers, causes them to starve. Pymetrozine and its major metabolites are found only in the topsoil, which shows its weak leaching ability. Hence, pymetrozine is unlikely to contaminate groundwater at the recommended application dose.[6] Owing to its high efficiency, low toxicity, high selectivity and environmental friendliness, pymetrozine has attracted widespread interest as a pesticide.

Reports are available in the literature[7–11] related to the preparation of pymetrozine (as shown in Scheme 1).

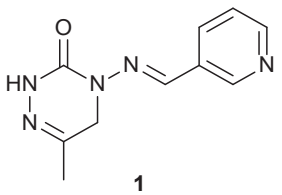

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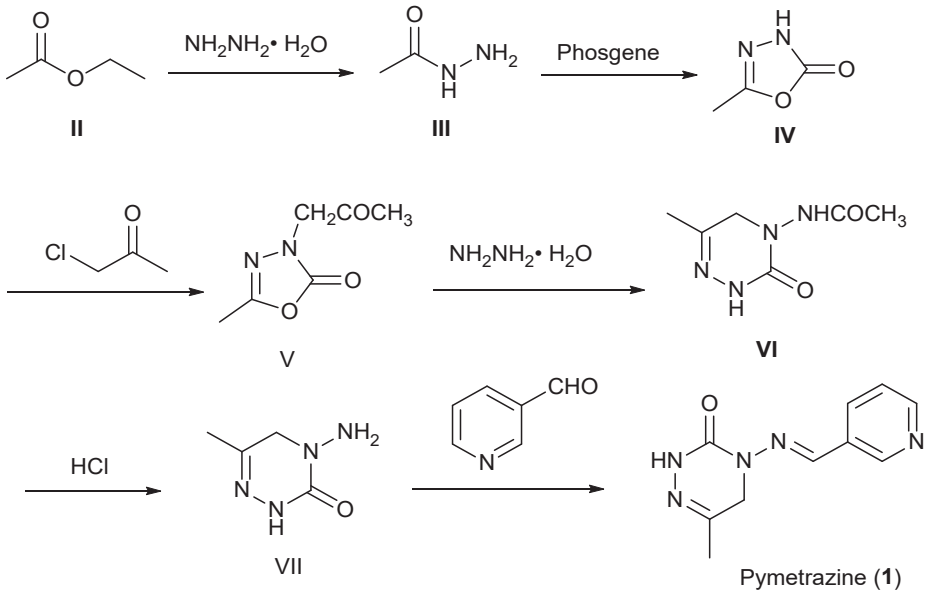
Fig. 1 Chemical structure of pymetrozine.

Intermediate **III** is obtained *via* hydrazinolysis using ethyl acetate and hydrazine hydrate as starting materials, and then cyclised with phosgene to give 5-methyl-1,3,4-oxadiazol-2(3*H*)-one (**IV**). 5-Methyl-3-(2-oxopropyl)-1,3,4-oxadiazol-2(3*H*)-one (**V**) is obtained *via* alkylation with 1-chloropropan-2-one and intermediate **IV**, and then treated with hydrazine hydrate to obtain triazinone **VI**. Subsequently, hydrolysis using hydrochloric acid is carried out to afford 4-amino-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (**VII**). The desired product pymetrozine is obtained *via* the condensation of nicotinaldehyde with compound **VII**. These processes have limited industrial application due to the stringent reaction requirements needed to meet the quality of a finished drug substance. The traditional pathway by which pymetrozine is obtained has many drawbacks. The reported approaches to obtain the oxadiazolone mainly include cyclisation of acetohydrazide with phosgene,[4,12] triphosgene[10] and diphosgene.[13] Although phosgene can provide a suitable conversion, it is not suitable for large-scale production due to its high toxicity and environmental pollution. Although propylene oxide[14] or dimethyl carbonate[15] have been used instead for the cyclisation in a recently reported synthetic route, they are still at the laboratory stage. This route is long, raising large-scale concerns for long-term production. The processes of acetylation and deacetylation are incompatible with ease of operation and atom economy.



Scheme 1 Traditional synthetic route for pymetrozine.

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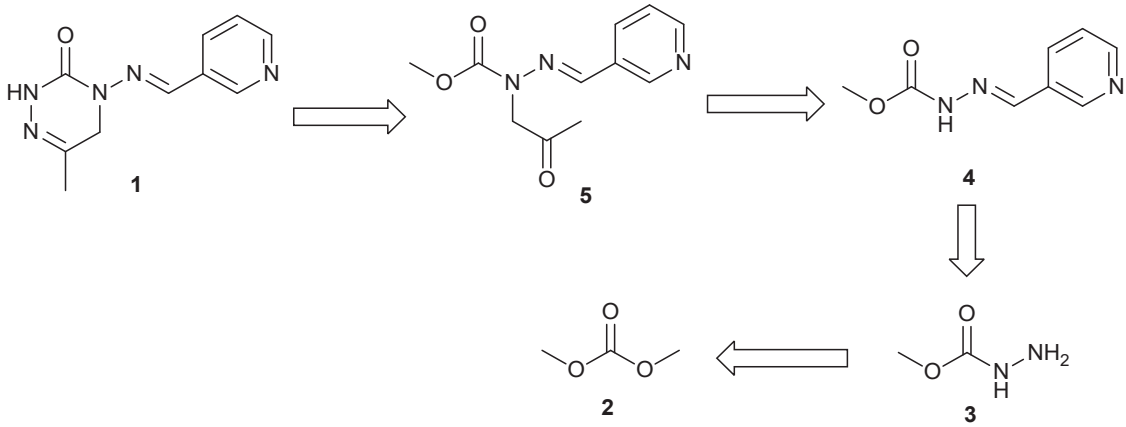
Results and discussion

In view of the problems that were identified as concerns in the route outlined in Scheme 1, a potential pathway for preparation of **1** was designed by a retrosynthetic analysis (Scheme 2). In light of the tedious protection and deprotection process, we tried to utilise niacinaldehyde, a fragment of pymetrozine, to protect hydrazine by condensation. The triazinone ring was established by the reaction of hydrazine hydrate and **5**. The latter can be easily obtained *via* two steps including condensation and alkylation from commercially accessible methyl hydrazinecarboxylate (**3**) and nicotinaldehyde. Compound **3** could be obtained *via* hydrazinolysis with dimethyl carbonate. Accordingly, an alternative procedure for the construction of pymetrozine was established by using a novel chemical entity methyl (*E*)-1-(2-oxopropyl)-2-(pyridin-3-ylmethylene)hydrazine-1-carboxylate (**5**) that has not been reported previously (Scheme 3). As a result, the desired product **1** can be obtained *via* hydrazinolysis, condensation, alkylation and cyclisation in four steps with a green chemical dimethyl carbonate as starting material. In the following work, processes for the preparation of mainly **3**, **5** and **1** are investigated.

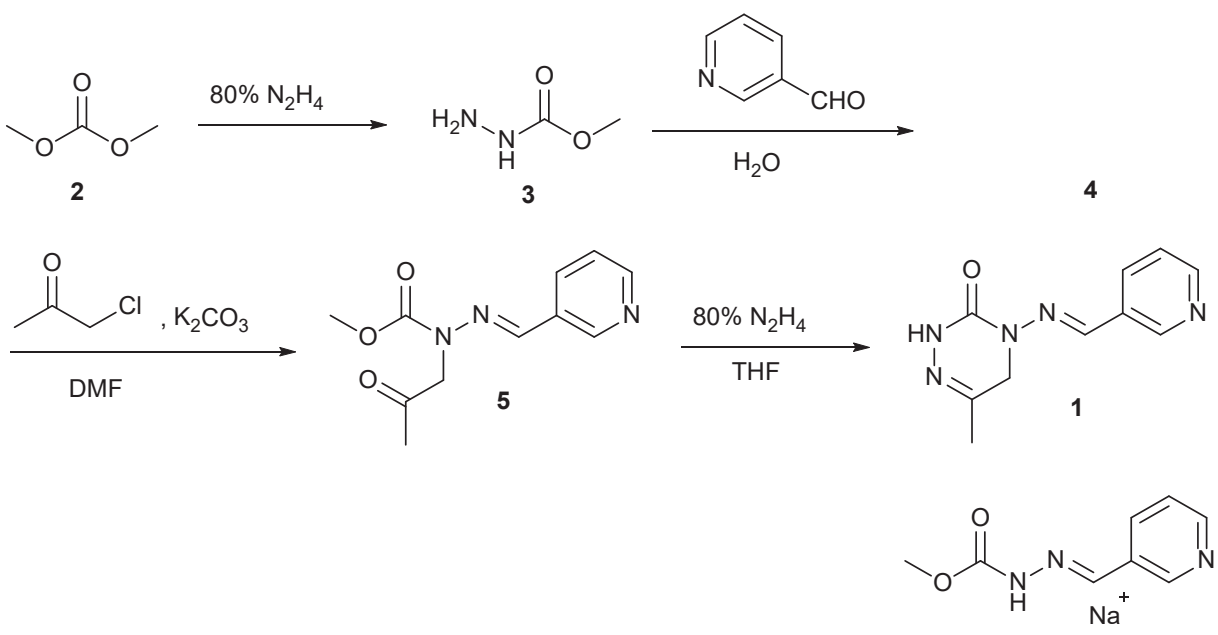
In the process to prepare **3**, following the literature[16–18], dimethyl carbonate (1.05 equiv.) and 80% hydrazine hydrate (1 equiv.) were reacted at 50 °C. However, the conversation to **3** was low with a yield of 67% (Table 1, entry 1). Increasing the temperature or increasing the amount of **3** equally led to a significant increasing conversion (Table 1, entries 2–4). As we suspected, the main by-product, purified by column chromatography, was carbohydrazide **6**. The synthesis of **6** was generally required to go through the intermediate **3**, which was subsequently reacted with hydrazine after separation.[19] Accordingly, hydrazine hydrate was added dropwise to a molar excess of **2** (1.1 equiv.) at 50 °C. It was found that this procedure had a significant effect on increasing conversion, which reached 88% yield without carbohydrazide being detected (Table 1, entry 5). Attempts to improve the yield *via* increasing the amount of **2** proved unsuccessful (Table 1, entry 6). Therefore, the amount of **2** was finally chosen to be 1.1 equiv., which was advisable in view of minimising industrial production costs.

After optimisation of this step, it was observed that the most suitable method to carry out the reaction was to add hydrazine hydrate dropwise to **2** without any solvent at 50 °C, and then increase the temperature to 70 °C for 4 h. On completion of the reaction, the mixture was cooled to crystallise **3** in 91% yield on a scale of 300 g (Table 1, entry 7).

According to the literature[20–22], hydrazine and benzaldehyde can be condensed in ethanol, with added glacial acetic acid as a catalyst. Considering the good water solubility of **3** and the

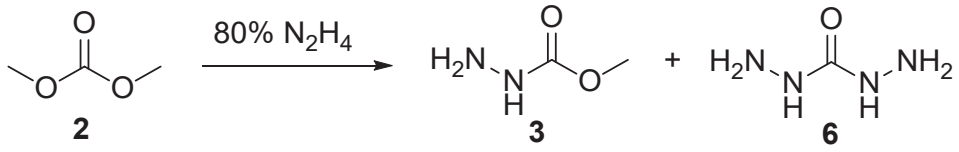


Scheme 2 Retrosynthetic analysis of pymetrozine.



Scheme 3 A new synthetic route for pymetrozine.

Table 1 Optimisation of reaction conditions for preparing intermediate **3**[a]



Entry	**2** (equiv.)	Temperature (°C)	Addition method	Yield (%)[b]	
				3	**6**
1	1.05	50	One portion	67	20
2	1.05	80	One portion	53	35
3	1.1	50	One portion	69	18
4	1.1	70	One portion	71	17
5	1.1	50→70	Dropwise	88	ND[d]
6	1.5	50→70	Dropwise	90	ND
7[c]	1.1	50→70	Dropwise	91	ND

[a]Standard conditions: 80% N_2H_4 (53 mmol), no solvent.
[b]Isolated yield after chromatography.
[c]The load of **2** was 300 g.
[d]Not detected by the TLC analysis.

Table 2 Effects of chloroacetone, base, solvent and temperature on alkylation reaction[a]

Entry	Chloroacetone (equiv.)	Base (equiv.)	Solvent	Temperature (°C)	Yield (%)[b]
1	1.5	KOH (3)	Ethanol	25→50	ND[c]
2	1.5	*t*-BuOK (3)	Acetone	25→60	ND
3	1.2	NaH (1.5)	DMF	0→50	ND
4	1.5	K_2CO_3 (3)	Acetone	25	ND
5	1.5	K_2CO_3 (3)	Acetone	60	C[d]
6	1.5	K_2CO_3 (3)	Butanone	80	C
7	1.2	K_2CO_3 (3)	Ethanol	25→80	C
8	1.2	K_2CO_3 (3)	Acetonitrile	25→82	C
9	1.2	K_2CO_3 (3)	Methanol	25→60	C
10	1.2	K_2CO_3 (3)	DMF	25	70
11	2.0	$NaHCO_3$ (2)	DMF	25	ND
12	1.2	K_2CO_3 (3)	DMF	50	72
13	1.2	K_2CO_3 (3)	DMF	80	20
14	1.2	K_2CO_3 (3)	DMF[e]	25	88
15[f]	1.2	K_2CO_3 (3)	DMF	25	87

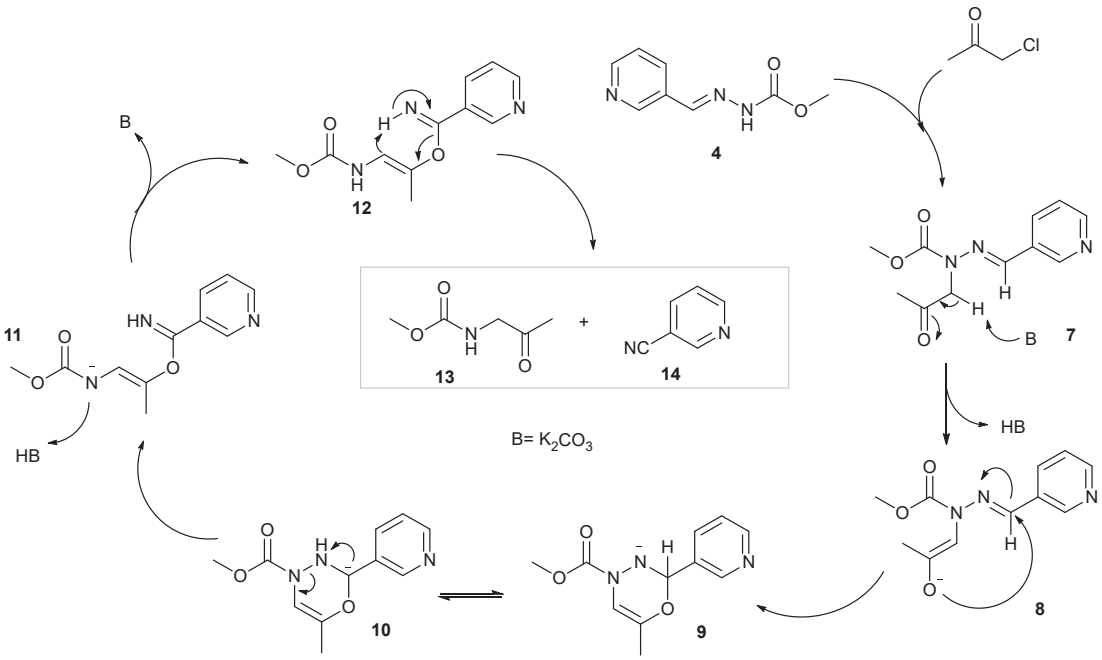
[a]Standard conditions: **4** (10 mmol), solvent (15 mL).
[b]Isolated yield after chromatography.
[c]Not detected by the TLC analysis.
[d]TLC result was complex.
[e]The amount of DMF was 8 mL.
[f]The load of **4** was 300 g.

higher reactivity of the nicotinaldehyde carbonyl, we added nicotinaldehyde dropwise to **3** with water as the solvent at room temperature. External cooling is normally required due to the mild exothermic nature of the reaction. When **3** had disappeared, monitored by TLC, the precipitate was collected by filtration and washed with water to give the condensation product **4** with suitable purity and yield at 96%.

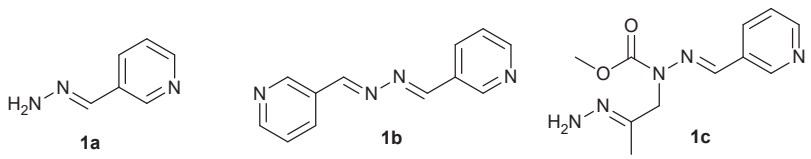
As the synthetic method of intermediate **5** has not been reported before in the literature,[23,24] we speculated that a strong alkali such as sodium hydride, potassium *tert*-butoxide or potassium hydroxide were necessary for the alkylation of **4** (Table 2, entries 1–3). Unfortunately, the desired compound was not observed by TLC when the reaction was conducted at room temperature or higher. We reasoned that chloroacetone was readily destroyed by the strong alkalis. Unexpectedly, the desired product still could not be obtained with a weak alkali, potassium carbonate, using acetone or butanone as solvent (Table 2, entry 4). However, a complicated result was obtained when the temperature was increased (Table 2, entries 5 and 6).[25] Inspired by entry 5, we screened methanol, ethanol, acetonitrile, *N*,*N*-dimethylformamide and dimethyl sulfoxide to optimise the solvent (Table 2, entries 7–10). No product was observed with methanol, ethanol or acetonitrile at room temperature, while increasing the temperature to reflux led to complex products. Fortunately, the product was obtained with a yield of 70% with *N*,*N*-dimethylformamide as the solvent at room temperature. Efforts to catalyse the reaction with the weaker base sodium bicarbonate and *N*,*N*-dimethylformamide as solvent at room temperature were unsuccessful, and no product was identified by TLC (Table 2, entry 11). Frustratingly, the literature[26] confirmed that this kind of Schiff base can yield amides and nitriles in the presence of potassium carbonate or cesium carbonate at high temperature. Accordingly, we suggest that the reason for the complex results in entries 7–9 may be accounted for in Scheme 4.

In this mechanism, hydrazone **4** reacts with chloroacetone under the basic conditions to yield nucleophilic substitution product **7**. Then, compound **7** undergoes an enolisation reaction/intramolecular cyclisation process to generate a six-membered ring intermediate **9** through transition state **8**. The unstable six-membered ring **9** then undergoes a 1,2-hydrogen shift/N–N bond cleavage/protonation step to yield intermediate **12**, which is finally transformed into **13** and **14** through a rapid retro-ene-type fragmentation. As a result (Table 2, entries 12 and 13), we found that the side reaction did not occur below 50 °C. To improve the yield, we reduced the amount of *N*,*N*-dimethylformamide (Table 2, entry 14), and a large increase in yield was obtained. Therefore, we increased the scale to 300 g (Table 2, entry 14) using 1.2 L of *N*,*N*-dimethylformamide as solvent, and potassium carbonate was added in batches in an ice-water bath, and compound **5** was obtained in 87% yield (Table 2, entry 15).

In the cyclisation reaction reported in the literature[27,28], **5** (1 equiv.) was reacted with 80% hydrazine hydrate (8 equiv.) under reflux in ethanol. However, a complex mixture was observed by TLC, as shown in Fig. S1A in the Electronic Supplementary Information (ESI). The desired product **1**, isolated by column chromatography, was obtained in a yield of only 16% (Table 3, entry 1), and the structures of the other three main separated impurities (**1a**–**c**) were identified (Scheme 5) by ^{1}H NMR and ESI MS. On the basis of entry 1, reducing the amount of



Scheme 4 A plausible mechanism in entries 5–9 of Table 2.



Scheme 5 Three major impurities produced in the process of cyclisation.

Table 3 Effects of amount of 80% hydrazine hydrate, solvent and temperature on cyclisation reaction[a]

Entry	Hydrazine hydrate (equiv.)	Solvent	Temperature (°C)	Yield (%)[b]				
				5	1	1a	1b	1c
1	8.0	Ethanol	80	ND[c]	16	21	18	36
2	1.5	Ethanol	80	ND	15	17	19	35
3	1.5	Ethanol	0→25	50	23	ND	ND	20
4	1.5	Ethanol	50	30	21	8	10	24
5	3.0	Ethanol	25	25	37	14	15	28
6	1.5	THF	25	23	59	ND	ND	D
7	1.5	DMF	25	15	12	19	18	26
8	3.0	THF	0→25	ND	76	ND	ND	D[d]
9[e]	3.0	THF	0→25	D	70	ND	ND	D

[a]Standard conditions: **5** (8.5 mmol), solvent (15 mL).

[b]Isolated yield after chromatography.

[c]Not detected by the TLC analysis.

[d]Detected by the TLC analysis, but not isolated as the little amount.

[e]The load of **5** was 100 g.

hydrazine hydrate to 1.5 equiv. also led to a thorough conversion (Table 3, entry 2). Owing to the complexity of TLC result, we reduced the temperature (Table 3, entries 3 and 4), which only resulted in much unchanged materials, although **1a** and **1b** were not detected by TLC analysis (Fig. S1B in the ESI). Attempts to improve the yield by increasing the amount of hydrazine hydrate were unsuccessful. This might be caused by the poor solubility of **5** in ethanol at room temperature (Table 3, entry 5). Meanwhile, tetrahydrofuran and *N*,*N*-dimethylformamide, in which **5** had a better solubility, were screened. When using tetrahydrofuran as solvent at room temperature (Table 3, entry 6), **1a** and **1b** were not observed by TLC, and only a small amount of **1c** was observed (Fig. S1C in the ESI). As a result, the material almost completely converted by increasing the amount of hydrazine hydrate into 3 equiv. (Table 3, entry 8). Product of suitable purity was obtained by recrystallisation from ethanol. On the basis of the optimised conditions, it was found that pymetrozine could be obtained by adding 80% hydrazine hydrate into a solution of **5** in tetrahydrofuran at room temperature. External cooling was required to maintain a temperature of 25 °C when large-scale production was carried out. The target product could be easily obtained with a suitable yield of 70% with a purity >95% after recrystallisation from ethanol (Table 3, entry 9).

Conclusion

We provide an alternative method for the production of pymetrozine, utilising a cheap green chemical dimethyl carbonate as starting material *via* four steps, including hydrazinolysis, condensation, alkylation and cyclisation, with an overall yield of 53.2%. The key to this optimisation was the preparation of intermediate **5** from **4** through *N*-alkylation reactions, followed by further cyclisation reaction to obtain pymetrozine with better quality and yield. In conclusion, the simple operation in every step, the environmentally friendly reaction and the easily obtained cheap material make this process suitable for industrial production.

Experimental

All of the starting materials, reagents and solvents are commercially available and were used without further purification. Analytical samples were obtained by column chromatography on silica gel. Melting points were determined with a X-4 apparatus and are uncorrected. The nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 (Billerica, MA, USA) using

tetramethylsilane (TMS) as an internal standard. Electrospray ionisation mass spectrometry (ESI-MS) analyses were recorded in an Agilent 1100 Series MSD Trap SL (Santa Clara, CA, USA). The reactions were monitored by thin-layer chromatography (TLC; HG/T2354-92, GF254), and compounds were visualised on TLC with UV light. HPLC analyses were performed on a Schimadzu LC-20, column, Shimadzu Inertsil-SP C18 (5 μm; 250 mm × 4.6 mm).

Synthesis of methyl hydrazinecarboxylate (**3**)

Hydrazine hydrate (80%, 188 mL, 3 mol) was added dropwise to a solution of dimethyl carbonate (281 mL, 3.3 mol) over 1 h at 50 °C. On the completion of addition, the mixture was stirred at 70 °C for 4 h. Then the mixture was cooled to 0 °C. The precipitate was collected by filtration, washed with petroleum ether and dried to give compound **3** as a white solid; yield 246 g (91%); m.p. 68–69 °C (lit.[29] 69–70 °C); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.10 (br, 1H), 3.77–3.73 (m, 5H).

*Synthesis of methyl(*E*)-2-(pyridin-3-ylmethylene)hydrazine-1-carboxylate* (**4**)

A stirred, cooled solution of methyl hydrazinecarboxylate (200 g, 2.2 mol) and water (800 mL) was treated with nicotinaldehyde (257 g, 2.4 mol) dropwise at room temperature. After stirring for 5 h, the precipitate was collected by filtration, washed with water and dried to give compound **4** as a white solid; yield 378 g (96%); m.p. 170–171 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.77 (s, 1H), 8.61–8.60 (q, J = 1.6, 4.8 Hz, 1H), 8.14 (d, J = 7.4 Hz, 1H), 7.96 (br, 1H), 7.34–7.32 (q, J = 4.8, 8.0 Hz, 1H), 3.87 (s, 3H); MS (ESI) m/z: 180.1 $[M + H]^+$. HRMS (ESI) calcd for $C_8H_9N_3O_2$ $[M + Na]^+$: 202.0587; found: 202.0470.

*Synthesis of methyl(*E*)-1-(2-oxopropyl)-2-(pyridin-3-ylmethylene) hydrazine-1-carboxylate* (**5**)

A mixture of methyl(*E*)-2-(pyridin-3-ylmethylene) hydrazine-1-carboxylate (300 g, 1.7 mol), 1-chloropropan-2-one (185 g, 2.0 mol) and *N*,*N*-dimethylformamide (1 L) was cooled in an ice-water bath. Powdered potassium carbonate (704 g, 5.1 mol) was added in batches, maintaining the temperature below 30 °C. After the addition, the mixture was stirred at room temperature for 5 h. Then the reaction mixture was poured into water (1 L), extracted with dichloromethane (3 × 1.2 L), the combined organic phase was washed with water (2 × 1 L) and brine (800 mL), then concentrated *in vacuo* to afford the crude product. The precipitate was then suspended in diethyl ether (1 L) and stirred for 1 h. Then, the mixture was filtered and dried to give compound **5** as a white solid; yield 348 g (87%); m.p. 125–127 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.79 (d, J = 1.5 Hz, 1H), 8.57–8.56 (dd, J = 1.5, 4.7 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.56 (br, 1H), 7.47–7.44 (q, J = 4.8, 7.9 Hz, 1H), 4.92 (s, 2H), 3.78 (s, 3H), 2.24 (s, 3H). HRMS (ESI) calcd for $C_{11}H_{13}N_3O_3$ $[M + Na]^+$: 258.0849; found: 258.0837.

Synthesis of pymetrozine (**1**)

A stirred and cooled solution of methyl (*E*)-1-(2-oxopropyl)-2-(pyridin-3-ylmethylene)hydrazine-1-carboxylate (100 g, 0.4 mol) and tetrahydrofuran (800 mL) was treated dropwise with 80% hydrazine hydrate (73 mL, 1.2 mol). The reaction was monitored by TLC until completion, and the crude solid was collected *in vacuo* and recrystallised from ethanol (2.2 L) to give compound **1** as a white solid; yield 87 g (70%); HPLC purity 99.84% (eluent, methanol/water = 25/75; flow rate 1 mL min^{-1}; temperature 30 °C; wavelength 260 nm; HPLC analysis data are reported in relative area % and were not adjusted to weight %); m.p. 214–216 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.15 (s, 1H), 8.86 (d, J = 1.4 Hz, 1H), 8.58–8.57 (dd, J = 1.2, 4.6 Hz, 1H), 8.11 (d, J = 7.9 Hz, 1H), 7.91 (s, 1H), 7.48–7.46 (q, J = 4.8, 7.9 Hz, 1H), 4.39 (s, 2H), 1.96 (s, 3H); MS (ESI) m/z: 218.1 $[M + H]^+$, 240.1 $[M + Na]^+$, 457.1 $[2M + Na]^+$. HRMS (ESI) calcd for $C_{10}H_{11}N_5O$ $[M + Na]^+$: 240.0856; found: 258.0837.

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Electronic Supplementary Information

The ESI associated with this paper can be found at:
http://ingentaconnect.com/content/stl/jcr/2018/00000042/00000008/art00010

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