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Synthesis and reactivity of 2-thionoester pyrroles: a route to 2-formyl pyrroles†

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2-Functionalised pyrroles exhibit considerable synthetic utility. Herein, the synthesis and reactivity of 2-thionoester (–C(S)OR) pyrroles is reported. 2-Thionoester pyrroles were synthesised using a Knorr-type approach from aliphatic starting materials. 2-Thionoester pyrroles were reduced to the corresponding 2-formyl pyrroles, or the deuterated formyl variant, in one step using RANEY® nickel, thereby removing the need for the much-utilised hydrolysis/decarboxylation/formylation steps that are typically required to convert Knorr-type 2-carboxylate pyrroles into 2-formyl pyrroles. 2-Thionoester pyrroles proved tolerant of typical functional group interconversions for which the parent 2-carboxylate pyrroles have become known.

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2-Formyl pyrroles are critical to the synthesis of (poly)pyrroles such as porphyrins and BODIPYs courtesy of their availability from widely used Knorr-type syntheses, and their robust and reliable reactivity.¹ However, attempts to reduce the 2-carboxylate functionality of Knorr-type pyrroles with H-DIBAL are unfruitful, which is unsurprising considering the doubly-vinyllogous carbamate character of the ester (Fig. 1, top). Instead, transformation to 2-formyl pyrroles typically entails hydrolysis of the 2-carboxylate functionality,^{2,3} followed by decarboxylation and finally formylation.^{4–7} Alternatively, reduction of the 2-carboxylate functionality to the corresponding alcohol, followed by oxidation back to the desired aldehyde,⁸ also provides the requisite 2-formyl pyrrole. In addition to the inevitably poor atom economy that results from such circuitousness, these reactions can be low yielding and necessitate harsh conditions. The potential of utilising new reactivity at the 2-position of pyrroles opens new synthetic opportunities in pyrrole chemistry that build on traditional approaches.⁹ Herein, we report the one-step reduction of 2-thionoester pyrroles to provide 2-formyl pyrroles, and explore the stability of 2-thionoester pyrroles under conditions typically used for the synthetic manipulation of Knorr-type pyrroles.

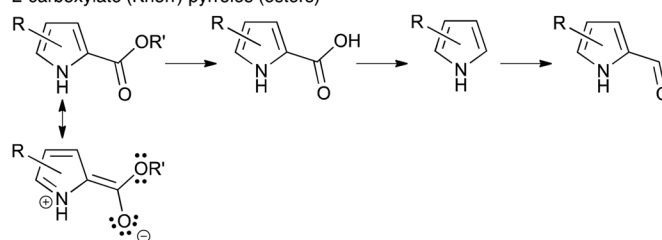
2-Thionoester pyrroles, which bear the –C(S)OR functional group at the 2-position, have not been studied in detail despite the fact that thionoesters are more electrophilic compared to the corresponding “all-oxygen ester” functional groups (–CO₂R).^{10,11} In contrast, 2-thioester pyrroles (–C(O)SR) have been thoroughly evaluated as such species are common

secondary metabolites in marine bacteria and plants.^{9,12,13} In particular, we noticed a role for thiophilic reagents in the reduction of 2-thioester pyrroles^{14–17} induced by RANEY® nickel.^{14,15,18}

We thus explored the reactivity of 2-thionoester pyrroles with RANEY® nickel, taking advantage of the availability of RANEY® nickel as a slurry in water. *O*-Ethyl 2-thionoester pyrrole **1a**, initially prepared *via* treatment of the corresponding 2-carboxylate pyrrole with Lawesson's reagent,⁹ was reacted with excess 2800 RANEY® nickel to provide the 2-formyl pyrrole **2a** in 67% isolated yield (Table 1, entry 1). To commence the reaction, a slurry of RANEY® nickel in water and acetone was activated *via* heating at reflux temperature for an hour before **1a** was added. Although the purpose of the activation step is unclear,

Literature

2-carboxylate (Knorr) pyrroles (esters)



This work

2-thionoester pyrroles

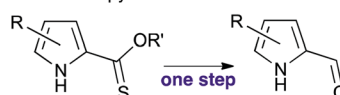


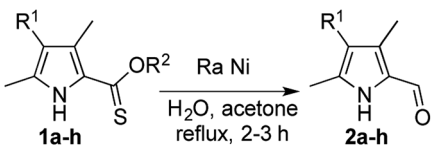
Fig. 1 Conversion of Knorr-type pyrroles to 2-formyl pyrroles.

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Table 1 Reduction of 2-carboxylate pyrroles to 2-formyl pyrroles using RANEY® nickel



Entry	Substrate	R ¹	R ²	Yield of 2 (%) ^a
1	1a	–H	Et	67
2	1b	–Me	Et	52
3	1c	–Et	Et	63
4	1d	–Ph	Et	45
5	1e	–C(O)CH ₃	Et	44 ^b (46 ^c)
6	1f	–Me	Bn	45 ^d
7	1g	–(CH ₂) ₄ CH ₃	Bn	70
8	1h	–(CH ₂) ₂ C(O)OCH ₃	Bn	12

^a Isolated yield. ^b 15% starting material recovered. ^c Deuterated **2e'** using RANEY® nickel in D₂O slurry. ^d Expected product is **2b**.

this procedure is documented alongside the success of W2 RANEY® nickel in the desulfurisation of a 2-thioester pyrrole.¹⁹ We found that this activation step was essential for success of our desired reduction using currently commercially available 2800 RANEY® nickel, which is different from W2 RANEY® nickel. After the starting material has been fully consumed, the reaction mixture was filtered through a short pad of silica to remove the spent RANEY® nickel and thus enable isolation of the desired aldehyde. Execution of the reaction under an atmosphere of hydrogen did not improve the yield,^{18,20–22} supporting the synergy of the thiophilicity and hydride content of the RANEY® nickel, and we were unable to reduce the stoichiometry without significant detriment to yield (see ESI†). Similarly, dissolution of the substrate in acetone was key to success, as the use of other water-miscible solvents (methanol, ethanol, tetrahydrofuran and isopropanol),²³ all previously reported as suitable for reactions involving RANEY® nickel, resulted only in isolation of starting material. Furthermore, treatment of **1a** with nickel boride returned only starting material.²⁴

Although yields were moderate (Table 1), the one-step desulfurative reduction of 2-thioester pyrroles to 2-formyl pyrroles is more streamlined than the common hydrolysis/decarboxylation/formylation route shown in Fig. 1. The one-step synthesis of 2-formyl pyrroles from *O*-ethyl 2-thioester pyrroles in reasonable yield was successful for substrates bearing unsubstituted positions (**1a**, Table 1, entry 1) as well as those with alkyl (entries 2 and 3) and aryl (entry 4) substituents. Similarly, the incorporation of a conjugated keto-substituent was tolerated (entry 5). The reduction of *O*-benzyl 2-thioester pyrroles was also successful (entries 6–9). Long-chain substituents were tolerated (entry 7), but incorporation of an alkyl ester functionality served to reduce the efficacy of the desired thioester reduction using RANEY® nickel (entry 8).

Although a complete mechanism for desulfurisation by RANEY® nickel remains unclear,^{25,26} we explored a number of

avenues to try to understand the atom efficiency of the reaction, as well as the source of the formyl hydrogen atom. First, although we did not attempt to dry the pyrophoric reductant, water from the commercially available RANEY® nickel slurry was manually removed by pipette. Acetone was then added, and the slurry shaken. After being allowed to settle, the liquid was removed once again. This process was repeated several times so as to produce a slurry of RANEY® nickel in wet acetone. The reaction of pyrrole **1e** with this acetone-based slurry resulted in only trace amounts of **2e** suggesting that the water within the slurry is critical to the formation of the aldehyde. To investigate whether deuterium^{27,28} could be introduced into the 2-formyl moiety, a slurry of RANEY® nickel in D₂O was prepared through removal/addition as above, with the added sonication step after each addition. The solvent removal/addition and sonicator wash cycle was repeated 10 times to ensure efficient exchange. Reaction of the deuterated slurry with pyrrole **1e**, in acetone, resulted in formation of the deuterated aldehyde *i.e.* R–C(O)D, **2e'** in moderate yield (Table 1, entry 6). Interestingly, without the use of sonication a 3 : 1 mixture of the deuterated and undeuterated aldehydes was recovered, again indicating the critical role of the slurry water to the reductive capability of the RANEY® nickel.

The manner by which RANEY® nickel effects desulfurative reduction has been long debated.^{25,26,29} Assuming a radical mechanism, we used two radical clocks/traps in the hopes of intercepting radical intermediate species (Fig. 2).^{30,31} However, in neither case was trapping observed with reduction of **1a** serving to return the 2-formyl pyrrole **2a** (50–60% yield) no matter whether large excess of a cyclopropane were present or not. However, in light of the large excess of RANEY® nickel used, we maintain that a radical mechanism is most likely for the reduction. In contrast, reaction of **1a** with RANEY® nickel in the presence of 50 eq. TEMPO resulted in the isolation of only 7% **2a**. However, no trapped products could be identified *via* either mass spectrometry or NMR spectroscopy.^{32,33}

With the one-step reduction to form 2-formyl pyrroles in hand, we sought a practical synthesis of 2-thioester pyrroles that did not entail thionation of 2-carboxylate pyrroles. We thus turned our attention to the preparation of 2-thioester pyrroles from aliphatic materials, modelling the Knorr synthesis by incorporation of thioester functionality. Reaction of potassium ethyl xanthogenate and chloroacetone, following modified literature methods,^{34,35} gave **3** (Scheme 1), and then extrusion of sulfur produced the desired acetothioacetate **4**. Treatment with sodium nitrite gave the oxime **5**, which could be isolated and characterised although the typical procedure entailed treating the crude material with 2,4-pentanedione and zinc powder to provide *O*-ethyl 2-thioester

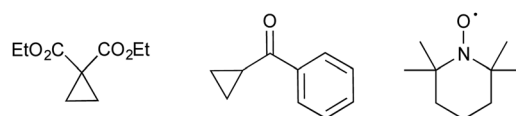
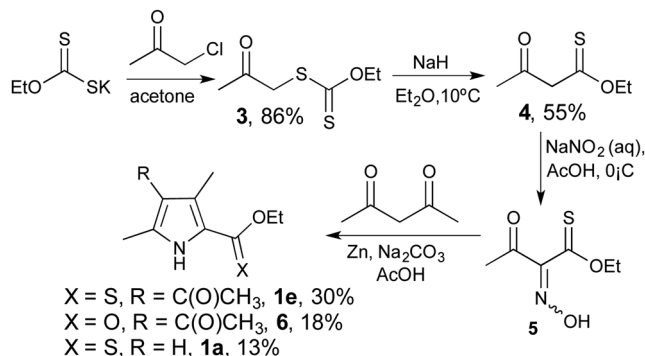


Fig. 2 Cyclopropane radical clocks and TEMPO.



Scheme 1 Knorr-type synthesis of *o*-ethyl 2-thioester pyrrole.

pyrrole **1e**. As with traditional Knorr-type syntheses,³⁶ by-products accompanied the desired pyrrole: **6** is the ester ($-\text{CO}_2\text{R}$) variant of **1e**; and **1a** is produced as a consequence of deacylation. As such, the basic Knorr conditions were modified using various stoichiometries of sodium carbonate, tripotassium phosphate and sodium acetate salts to assert that the use of sodium carbonate resulted in the highest yield (33%) of the desired 2-thioester pyrrole **1e**. Cognisant that a Knorr-type synthesis of 2-carboxylate pyrroles yields 30–60% of the desired product on the same scale, this synthetic approach to 2-thioester pyrroles is in keeping with the most prevalent of the routes to functionalised pyrroles.^{37,38} The corresponding benzyl thioester pyrrole was synthesised following a similar approach, but originating with the reaction of CS_2 with benzyl alcohol in the presence of potassium hydroxide to produce the required potassium *O*-benzyl carbonodithioate starting material.

In order to probe the utility of 2-thioester pyrroles beyond their conversion to 2-formyl pyrroles, we explored the potential of **1e** as a substrate for the most common reactions that utilise 2-carboxylate pyrrole analogues. As shown in Scheme 2,

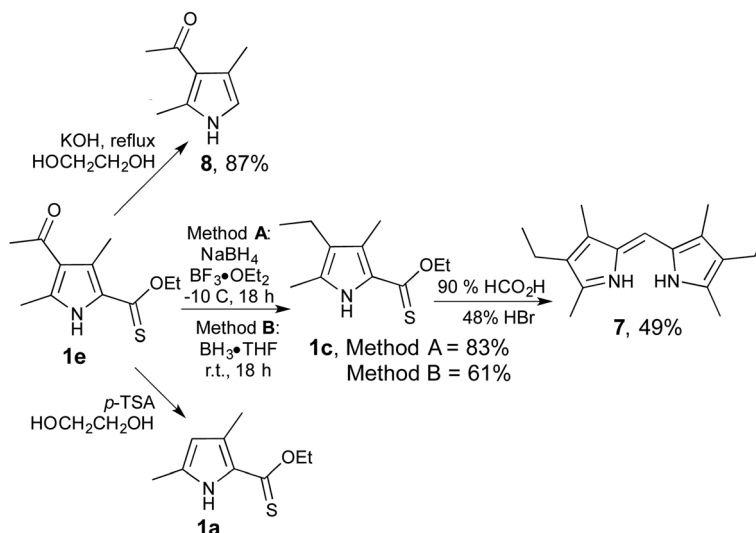
treatment of **1e** with borane cleanly reduced the acyl group to give the corresponding ethyl derivative **1c**, no matter whether borane were generated *in situ* (Method A) or used as reagent (Method B). 2-Thioester **1c** mirrored the reactivity of 2-carboxylate pyrroles in the preparation of dipyrins, thereby providing **7**. Similarly, treatment of **1e** with base effected hydrolysis and decarboxylation to give **8**, and treatment with acid resulted in deacylation to render **1a**. However, reaction of pyrrole **1e** with CAN or $\text{Pb}(\text{OAc})_4$ returned the corresponding ester ($-\text{CO}_2\text{R}$) with no sign of the desired oxidation of the 5-methyl group, clearly presenting a limitation as none of the desired 5-formyl species was produced.

In conclusion, an alternative route to 2-formyl pyrroles has been achieved *via* development of a modified Knorr procedure to produce 2-thioester pyrroles, followed by the use of RANEY® nickel to promote reduction of the thioester moiety to an aldehyde. The tolerance and utility of 2-thioester pyrroles in reactions that are in widespread use within dipyrin and porphyrin chemistry were investigated. Given the circuitousness nature of the synthesis of 2-formyl pyrroles of this genre and for these applications, the synthesis and use of 2-thioester pyrroles is presented as a viable alternative to the specialised manipulation of traditional Knorr-type 2-carboxylate pyrroles.

Experimental section

General information

Anhydrous solvents, silica 40–63 μm 60 Å and reagents were purchased and used as received. NMR spectra were obtained using 300 or 500 MHz instruments using CDCl_3 or DMSO as solvents and are reported in part per million (ppm). Internal solvents were referenced at 7.26 ppm for ^1H and at 77.16 ppm for ^{13}C when using CDCl_3 , and at 2.50 ppm for ^1H when using DMSO- d_6 . Coupling constants (J) are given in Hertz (Hz). Mass spectra were obtained using a time-of-flight ion trap instrument

Scheme 2 Reactions of 2-thioester pyrrole **1e**.

operating in ESI^{+/−} mode. Flash chromatography was performed using Silicycle ultra-pure silica (230–400 mm). Pyrroles **1a**, **1b**, **1e**, and **1f** were prepared according to literature procedure involving Lawesson's reagent.⁹ Compound **3** was prepared according to the literature method.³⁹ RANEY® nickel used was W. R. Grace Grade 2800 (CAS# 7440-02-0), purchased in the form of a slurry in water with the nickel composition stated as equal to or greater than 89%. Before each use, the bottle containing the RANEY® nickel slurry was thoroughly shaken before aliquots were drawn out quickly with a pipette in order to enable efficient transfer of the slurried material to a reaction flask.

O-Ethyl 4-ethyl-3,5-dimethyl-1H-pyrrole-2-carbothioate (1c)

According to the literature method,⁴⁰ the title compound was obtained as a yellow solid (0.63 g, 60%). Mp 66–68 °C; ¹H-NMR (500 MHz, CDCl₃): δ 9.08 (broad s, 1H), 4.66 (q, 2H, *J* = 7.0 Hz), 2.36 (q, 2H, *J* = 7.5 Hz), 2.27 (s, 3H), 2.21 (s, 3H), 1.46 (t, 3H, *J* = 7.0 Hz), 1.04 (t, 3H, *J* = 7.5 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 199.5, 134.2, 128.7, 126.0, 66.5, 17.2, 15.4, 14.3, 12.0, 11.9, one carbon signal missing; HRMS-ESI (*m/z*): [M + Na]⁺ calculated for C₁₁H₁₇NNaOS, 234.0923; found 234.0931.

O-Ethyl 3,5-dimethyl-4-phenyl-1H-pyrrole-2-carbothioate (1d)

According to the literature method,⁴⁰ the title compound was obtained as a yellow solid (0.76 g, 39%). Mp 89–92 °C; ¹H-NMR (300 MHz, CDCl₃): δ 9.31 (broad s, 1H), 7.39–7.45 (m, 2H), 7.29–7.34 (m, 1H), 7.22–7.25 (m, 2H), 4.71 (q, 2H, *J* = 6.9 Hz), 2.30 (s, 3H), 2.26 (s, 3H), 1.49 (t, 3H, *J* = 6.9 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 200.0, 134.5, 134.3, 130.2, 129.0, 128.4, 126.6, 124.8, 66.8, 14.3, 12.9, 12.5, one carbon signal missing; HRMS-ESI (*m/z*): [M + Na]⁺ calculated for C₁₅H₁₇NNaOS, 282.0923; found 282.0923.

O-Benzyl 3,5-dimethyl-4-pentyl-1H-pyrrole-2-carbothioate (1g)

According to the literature method,⁴⁰ the title compound was obtained as a yellow oil (0.53 g, 50%). ¹H-NMR (300 MHz, CDCl₃): δ 9.13 (broad s, 1H), 7.35–7.49 (m, 5H), 5.70 (s, 2H), 2.34 (t, 2H, *J* = 7.2 Hz), 2.24 (s, 3H), 2.22 (s, 3H), 1.42 (quin., 2H, *J* = 7.2 Hz), 1.28–1.35 (m, 4H), 0.91 (t, 3H, *J* = 7.2 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 198.7, 136.2, 135.0, 129.1, 128.6, 128.4, 128.2, 127.0, 124.7, 72.0, 31.7, 30.5, 23.9, 22.7, 14.2, 12.4, 12.0; HRMS-ESI (*m/z*): [M + Na]⁺ calculated for C₁₉H₂₅NNaOS, 338.1549; found 338.1545.

O-Benzyl 3,5-dimethyl-4-methylpropionic-1H-pyrrole-2-carbothioate (1h)

According to the literature method,⁴⁰ the title compound was obtained as a yellow solid (0.45 g, 43%). Mp 98–100 °C; ¹H-NMR (500 MHz, CDCl₃): δ 9.11 (broad s, 1H), 7.33–7.45 (m, 5H), 5.67 (s, 2H), 3.65 (s, 3H), 2.69 (t, 2H, *J* = 7.5 Hz), 2.41 (t, 2H, *J* = 7.5 Hz), 2.23 (s, 3H), 2.23 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 198.9, 173.4, 136.1, 135.0, 128.6, 128.4, 128.3, 126.1, 122.2, 72.2, 51.7, 34.8, 19.5, 12.3, 11.9, one carbon signal missing; HRMS-ESI (*m/z*): [M + Na]⁺ calculated for C₁₈H₂₁NNaO₃S, 354.1134; found 354.1127.

General procedure for synthesising 2-formyl pyrroles from 2-thionoester pyrroles (GP1)

Slurried RANEY® nickel (2 mL containing water and RANEY® nickel) was suspended in acetone, and the mixture was heated at reflux temperature for 1 hour. 2-Thionoester pyrrole **1** (0.47 mmol) was dissolved in acetone (10 mL), and the resulting solution was added to the reaction mixture containing RANEY® nickel in acetone held at reflux temperature. The reaction mixture was heated at reflux temperature for 2 hours, with stirring under nitrogen gas. Analysis using thin layer chromatography showed the complete consumption of starting material and the appearance of the product at lower *R_f*. The reaction mixture was allowed to cool to room temperature and then filtered through a short pad of silica, washing with acetone (500 mL). The filtrate was concentrated under vacuum, diluted with ethyl acetate and washed with brine. The organic layer was then dried using anhydrous sodium sulfate, and the solvent was removed through use of a rotary evaporator to yield a dark greenish brown solid. The crude product was purified *via* column chromatography over silica, eluting with 40% ethyl acetate/hexanes.

General procedure for radical studies (GP2)

Following GP1, the radical clock or TEMPO was added along with 2-thionoester pyrrole **1a**. Each reaction was run in parallel with a reference reaction prepared by GP1 using the same batch of RANEY® nickel. Cyclopropyl phenyl ketone: 500 equivalencies of the radical clock were added with **1a**, and the product **2a** was isolated in 55% (in absence of a radical clock: 53%). Diethyl cyclopropane-1,1-dicarboxylate: 200 equivalencies of the radical clock were added with **1a**, and the product **2a** was isolated in 64% (in absence of a radical clock: 58%). TEMPO: 500 equivalencies of TEMPO were added with **1a**, and the product **2a** was isolated in 7% (in absence of a radical trap: 37%).

2-Formyl-3,5-dimethylpyrrole (2a)

Following GP1, the title compound was obtained as a beige solid (67%). Mp 87–88 °C; ¹H-NMR (300 MHz, CDCl₃): δ 10.16 (broad s, 1H), 9.43 (s, 1H), 5.82 (m, 1H), 2.29 (s, 3H), 2.27 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 176.0, 138.7, 134.9, 128.9, 112.1, 13.3, 10.7; HRMS-ESI (*m/z*): [M + Na]⁺ calculated for C₇H₉NNaO, 146.0576; found 146.0576.

2-Formyl-3,4,5-trimethylpyrrole (2b) from 1b

Following GP1, the title compound was obtained as a beige solid (52%). Mp 142–145 °C; ¹H-NMR (300 MHz, CDCl₃): δ 9.99 (broad s, 1H), 9.44 (s, 1H), 2.24 (s, 6H), 1.91 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 175.6, 136.2, 132.9, 127.9, 118.3, 11.7, 9.0, 8.5; HRMS-ESI (*m/z*): [M + Na]⁺ calculated for C₈H₁₁NNaO, 160.0733; found 160.0731.

4-Ethyl-2-formyl-3,5-dimethylpyrrole (2c)

Following GP1, the title compound was obtained as a beige solid (63%). Mp 98–100 °C; ¹H-NMR (300 MHz, CDCl₃): δ 10.03 (broad s, 1H), 9.45 (s, 1H), 2.38 (q, 2H, *J* = 7.5 Hz), 2.27 (s, 3H),



2.26 (s, 3H), 1.06 (t, 3H, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3): δ 175.8, 136.0, 132.4, 128.1, 125.1, 17.2, 15.3, 11.7, 9.0; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_9\text{H}_{13}\text{NNaO}$, 174.0889; found 174.0889.

2-Formyl-3,5-dimethyl-4-pyrrolole (2d)

Following GP1, the title compound was obtained as a beige solid (45%). Mp 148–150 °C; ^1H -NMR (300 MHz, DMSO-d_6): δ 11.77 (br s, 1H), 9.56 (s, 1H), 7.39–7.44 (t, 2H), 7.25–7.31 (m, 3H), 2.25 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 176.6, 135.6, 134.3, 131.7, 130.0, 128.5, 128.4, 126.7, 125.6, 12.4, 9.6; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{13}\text{H}_{13}\text{NNaO}$, 222.0889; found 222.0887.

4-Acetyl-2-formyl-3,5-dimethylpyrrole (2e)

Following GP1, the title was compound was prepared as a beige solid (44%). Mp 168–170 °C; ^1H -NMR (300 MHz, CDCl_3): δ 9.89 (br s, 1H), 9.65 (s, 1H), 2.58 (s, 3H), 2.57 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 195.0, 177.7, 142.6, 134.2, 128.4, 123.9, 31.4, 15.4, 11.5; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_9\text{H}_{11}\text{NNaO}_2$, 188.0682; found 188.0681.

4-Acetyl-2-formyl-d-3,5-dimethylpyrrole (2e')

To a slurry of RANEY® nickel (2 mL containing water and RANEY® nickel), deuterium oxide (5 mL portion) was added. The reaction vessel was stirred and sonicated at room temperature for 30 seconds, and the solvent was decanted. The exchange/wash cycle was repeated 10 times. After a final wash, deuterium oxide (2 mL) and acetone (10 mL) were added. GP1 was followed to obtain the title compound as a beige solid (46%). Mp ^1H -NMR (300 MHz, CDCl_3): δ 9.69 (br s, 1H), 2.58 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 195.0, 177.4 (t), 142.6, 134.2, 128.3, 123.9, 31.4, 15.5, 11.6; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_9\text{H}_{10}\text{DNNaO}_2$, 189.0745; found 189.0736.

2-Formyl-3,5-dimethylpyrrole (2b) from 1f

Following GP1, the title compound was prepared (45%). ^1H -NMR (300 MHz, CDCl_3): δ 9.86 (broad s, 1H), 9.42 (s, 1H), 2.23 (s, 6H), 1.91 (s, 3H) matching the data given above for this compound.

2-Formyl-3,5-dimethyl-4-pentylpyrrole (2g)

Following GP1, the title compound was obtained as a beige solid (70%). Mp 70–71 °C; ^1H -NMR (300 MHz, CDCl_3): δ 9.87 (br s, 1H), 9.47 (s, 1H), 2.37 (t, 2H, $J = 7.5$ Hz), 2.28 (s, 3H), 2.27 (s, 3H), 1.45 (quin., 2H, $J = 7.5$ Hz), 1.28–1.38 (m, 4H), 0.92 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3): δ 175.8, 135.6, 132.3, 128.0, 123.6, 31.8, 30.4, 23.9, 22.7, 14.2, 11.8, 9.0; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{12}\text{H}_{19}\text{NNaO}$, 216.1359; found 216.1362.

2-Formyl-3,5-dimethyl-4-methylpropionic pyrrole (2h)

Following GP1, the title was compound was obtained as a beige solid (12%). Mp 128–129 °C; ^1H -NMR (500 MHz, CDCl_3): δ 9.82

(br s, 1H), 9.45 (s, 1H), 3.66 (s, 3H), 2.72 (t, 2H, $J = 7.0$ Hz), 2.44 (t, 2H, $J = 7.5$ Hz), 2.27 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 176.0, 173.4, 135.9, 132.3, 128.1, 121.1, 51.8, 34.7, 19.4, 11.7, 8.9; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{11}\text{H}_{15}\text{NNaO}_3$, 232.0944; found 232.0946.

O-Ethyl acetothioacetate (4)

The title compound was synthesised following a modified literature procedure.³⁴ A solution of *S*-acetyl *O*-ethyl dithiocarbonate 3³⁹ (31.4 g, 176 mmol) in anhydrous Et_2O (70 mL) was added drop-wise over 20 minutes to a suspension of NaH (60% in oil, 10.7 g, 268 mmol) in anhydrous Et_2O (350 mL) at 10 °C, with stirring under nitrogen. After 10 minutes, the mixture was poured into aqueous K_2HPO_4 solution (0.91 M, 390 mL) and stirred. The ethereal layer was separated and the aqueous layer was extracted with Et_2O (3×200 mL). The combined organic extracts were washed with brine (300 mL), dried over anhydrous MgSO_4 and concentrated *in vacuo*. The crude product was purified *via* fractional vacuum distillation (heated at 140–150 °C), using a water-fed aspirator (~ 25 –60 mmHg), and the desired product was collected at 84 °C as a yellow liquid (14.1 g, 55%). The product was present in both enol and keto forms with an approximate 3 : 1 enol–keto ratio, according to the ^1H NMR spectrum. ^1H -NMR (300 MHz, CDCl_3): δ 13.75 (s, 1H), 5.67 (s, 1H), 4.54 (q, $J = 7.1$ Hz, 0.7H), 4.47 (q, $J = 7.1$ Hz, 2H), 3.89 (s, 0.7H), 2.26 (s, 1H), 2.03 (s, 3H), 1.41 (t, $J = 7.1$ Hz, 1H), 1.38 (t, $J = 7.1$ Hz, 3H), in accordance with literature.³⁴ However, the literature³⁴ reports a 4 : 1 enol–keto ratio.

O-Ethyl 2-oximinoacetothioacetate (5)

The title compound was synthesised following a modified literature procedure.⁴¹ The resulting product mixture was poured into distilled water (25 mL) and extracted into CH_2Cl_2 (3×10 mL). The combined organic fractions were washed with saturated NaHCO_3 , dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield the product as a bright yellow solid (277 mg, 23%). Mp 75–77 °C; ^1H -NMR (300 MHz, CDCl_3): δ 8.13 (s, 1H), 4.66 (q, $J = 7.1$ Hz, 2H), 2.42 (s, 3H), 1.45 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 204.6, 193.5, 155.0, 68.5, 26.0, 13.6; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_6\text{H}_9\text{NO}_3\text{SNa}$, 198.0195; found 198.0189.

O-Ethyl 4-acetyl-3,5-dimethyl-1H-pyrrole-2-carbothioate (1e)

The title compound was synthesised following a modified literature procedure typically used for Knorr-type synthesis of 2-carboxylate pyrroles.⁴¹ A solution of sodium nitrite (530 mg, 7.67 mmol) in distilled water (1.9 mL) was added drop-wise to a solution of *O*-ethyl acetothioacetate (4) (1.02 g, 6.98 mmol) in AcOH (1.6 mL) at 0 °C. The reaction mixture was stirred at room temperature and monitored *via* thin layer chromatography until the starting material was consumed. After 45 minutes, the resulting mixture containing crude *O*-ethyl 2-oximinoacetothioacetate (5) was transferred to a dropping funnel and added drop-wise to a slurry of 2,4-pentanedione (0.71 mL, 6.98 mmol), Na_2CO_3 (1.63 g, 15.3 mmol) and AcOH (10 mL). At the same time, Zn dust (0.958 g, 14.6 mmol) was slowly added to the



slurry. The rate of addition and an ice-bath were used to keep the temperature below 30 °C. After the addition was complete, the reaction mixture was stirred at room temperature and monitored *via* thin layer chromatography. After 30 minutes the resulting mixture was poured into distilled water (150 mL) and then filtered through Celite, washing with CH₂Cl₂ until the washings were colorless.⁴⁰ The filtrate was extracted with CH₂Cl₂ (3 × 100 mL). The combined organic fractions were washed with saturated NaHCO₃ (150 mL) and brine (150 mL), then dried over anhydrous Na₂SO₄ and the solvent evaporated *in vacuo*. The resulting residue was purified *via* column chromatography on silica, eluting with a gradient of 5–20% EtOAc/hexanes, yielding the desired product as a yellow solid (0.53 g, 33%). Mp 109–111 °C; ¹H-NMR (500 MHz, CDCl₃): δ 9.41 (br s, 1H), 4.68 (q, *J* = 7.1 Hz, 2H), 2.58 (s, 3H), 2.52 (s, 3H), 2.45 (s, 3H), 1.49 (t, *J* = 7.1 Hz, 3H), in accordance with literature.⁹

3-Acetyl-2,4-dimethyl-1H-pyrrole (8) from 1e

To a solution of ground KOH (252 mg, 4.50 mmol) in ethylene glycol (1.6 mL) was added **1e** (507 mg, 2.25 mmol). The reaction mixture was heated at 160 °C, with stirring, for 1 hour, monitoring *via* thin layer chromatography (40% EtOAc/hexanes). Water (5 mL) was then added and the mixture was extracted into CH₂Cl₂ (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to yield the desired product as an off-white solid (269 mg, 87%). ¹H-NMR (500 MHz, CDCl₃): δ 7.93 (br s, 1H), 6.36 (s, 1H), 2.50 (s, 3H), 2.42 (s, 3H), 2.27 (s, 3H), in accordance with literature.⁴¹

O-Ethyl 4-ethyl-3,5-dimethyl-1H-pyrrole-2-carbothioate (1c) from 1e

Method 1. To a cooled solution (−10 °C ice per salt) of **1e** (496 mg, 2.20 mmol) in THF (4 mL) was added NaBH₄ (184 mg, 4.40 mmol), and then BF₃·OEt₂ (750 μL). The resulting mixture was stirred for 50 minutes at −10 °C, monitoring using TLC (20% EtOAc/hexanes). 0.5 M HCl (5 mL) was added at 0 °C to quench the reaction. Water (10 mL) was added and the mixture was extracted into Et₂O (3 × 10 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude mixture was purified *via* column chromatography on silica, eluting with 5% EtOAc/hexanes to yield the desired product as a crystalline yellow solid (388 mg, 83%). Mp 63–64 °C; ¹H-NMR (500 MHz, CDCl₃): δ 9.07 (br s, 1H), 4.66 (q, *J* = 7.1 Hz, 2H), 2.37 (q, *J* = 7.6 Hz, 2H), 2.26 (s, 3H), 2.21 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.6 Hz, 3H); ¹³C-NMR{¹H} (125 MHz, CDCl₃): δ 199.5, 134.2, 128.7, 125.9, 122.1, 66.5, 17.2, 15.3, 14.3, 12.0, 11.8; HRMS-ESI (*m/z*): [M + Na]⁺ calculated for C₁₁H₁₇NOSNa, 234.0923; found 234.0914.

Method 2. 1 M BH₃·THF (1.9 mL, 1.9 mmol) was added dropwise to a solution of **1e** (569 mg, 2.52 mmol) in THF (18 mL) at 0 °C, under nitrogen. The reaction mixture was stirred for 18 hours, then quenched by slowly adding distilled water (2 mL), 5% aq. HCl (10 mL), and stirring for a further 30 minutes at room temperature. Saturated NaCl (10 mL) was added, and the resulting mixture was extracted into EtOAc (3 × 10 mL). The

combined organic fractions were washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude mixture was purified *via* column chromatography on silica, eluting with 3% EtOAc/hexanes to afford the desired product as a crystalline yellow solid (325 mg, 61%). Characterisation data matched that provided above.

1,3,7,9-Tetramethyl-2,8-diethyl-5-H-4,6-dipyrin hydrobromide (7)

Pyrrole **1c** (64 mg, 0.3 mmol) was added to formic acid (0.29 mL) and the resulting mixture heated to reflux temperature before HBr (0.096 mL, 0.84 mmol) was added. The reaction mixture was stirred for an hour at reflux temperature. Then, the mixture was allowed to cool down to room temperature and was kept in the fridge for 2 days. The precipitate was collected and washed with ether to obtain a red-orange solid (49 mg, 49%). ¹H-NMR (300 MHz, CDCl₃): δ 12.92 (br s, 2H), 7.02 (s, 1H), 2.66 (s, 6H), 2.42 (q, *J* = 7.6 Hz, 4H), 2.26 (s, 6H), 1.07 (t, *J* = 7.6 Hz, 6H), in accordance with literature.⁴²

O-Ethyl 3,5-dimethyl-1H-pyrrole-2-carbothioate (1a) from 1e

The title compound was synthesised following a modified literature procedure.⁴³ Ethylene glycol (1.5 mL), *para*-toluene sulfonic acid (16 mg, 0.08 mmol) and **1e** (174 mg, 0.77 mmol) were added to a 2 mL microwave vial equipped with a stir bar. The vial was sealed and the mixture was pre-stirred for 1 minute then heated for 2 minutes at 100 °C in a laboratory microwave. Once allowed to cool to room temperature, the vial was unsealed. Water (5 mL) was added and the mixture was extracted into CH₂Cl₂ (3 × 5 mL). The combined organic fractions were dried over anhydrous Na₂SO₄ and then concentrated *in vacuo*. The crude mixture was purified *via* column chromatography on silica, eluting with 5% EtOAc/hexanes to yield the desired product as a yellow solid (95 mg, 67%). ¹H-NMR (300 MHz, CDCl₃): δ 9.09 (br s, 1H), 5.85 (s, 1H), 4.65 (q, *J* = 7.1 Hz, 2H), 2.30 (s, 3H), 2.25 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H), in accordance with literature.⁹

Potassium O-benzyl carbonodithioate

The title compound was synthesised following a modified literature procedure.²⁵ Carbon disulfide (17.4 mL, 289 mmol) and benzyl alcohol (25 mL, 242 mmol) were added to a suspension of KOH (13.5 g, 242 mmol) in diethyl ether (375 mL). The suspension was stirred at room temperature for 3 hours. The product was collected *via* suction filtration and washed with Et₂O to yield the desired product as a pale yellow solid (34.3 g, 64%). ¹H-NMR (300 MHz, DMSO-*d*₆): δ 7.35–7.27 (m, 5H), 5.33 (s, 2H), in accordance with literature.³⁵

O-Benzyl acetothioacetate

The title compound was synthesised following a modified literature procedure.³⁹ A solution of chloroacetone (5.4 mL, 67.4 mmol) in acetone (34 mL) was added dropwise to a solution of potassium O-benzyl carbonodithioate in acetone (84 mL) at 0 °C over a period



of 10 minutes with stirring. After 1 hour, the solvent was removed *in vacuo*. The resulting mixture containing *S*-acetyl *O*-benzyl dithiocarbonate was dissolved in dry Et₂O (27 mL) and was added drop-wise over 20 minutes to a suspension of NaH (60% in oil, 3.2 g, 81.0 mmol) in dry Et₂O (135 mL) under nitrogen at 10 °C. After 10 minutes, the reaction mixture was poured into aqueous KH₂PO₄ solution (1.2 M, 200 mL) and stirred at room temperature. The ethereal layer was separated and the aqueous layer was extracted with ether (3 × 100 mL). The combined organic fractions were washed with brine (150 mL), dried with anhydrous MgSO₄ and concentrated *in vacuo*. The resulting residue was purified *via* column chromatography on silica, eluting with 2% ethyl acetate/hexanes to isolate the desired product as a yellow liquid (1.9 g, 13%). The product was isolated as a mixture containing enol and keto forms with an approximate 3 : 1 enol-keto ratio according to the ¹H NMR spectrum. ¹H-NMR (500 MHz, CDCl₃): δ 13.70 (s, 1H), 7.40–7.35 (m, 6.9H), 5.76 (s, 1H), 5.51 (s, 0.7H), 5.46 (s, 2H), 3.95 (s, 0.7H), 2.24 (s, 1H), 2.04 (s, 3H); ¹³C-NMR{¹H} (125 MHz, CDCl₃): δ 213.1, 208.1, 177.8, 135.4, 134.7, 128.9, 128.8, 128.75, 128.72, 128.6, 128.5, 103.3, 74.7, 70.9, 61.7, 31.1, 29.9, 23.3; HRMS-ESI (*m/z*): [M + Na]⁺ calculated for C₁₁H₁₂O₂SNa, 231.0450; found 231.0460.

O-Benzyl 4-acetyl-3,5-dimethyl-1H-pyrrole-2-carbothioate

The title compound was synthesised following a modified literature procedure.⁴¹ A solution of NaNO₂ (235 mg, 3.41 mmol) in distilled water (852 μL) was added drop-wise to a solution of *O*-benzyl acetothioacetate (645 mg, 3.10 mmol) in AcOH (774 μL) at 0 °C. The reaction mixture was stirred at room temperature and monitored *via* thin layer chromatography until the starting material was consumed. The reaction mixture was then transferred to a dropping funnel and added drop-wise to a slurry of 2,4-pentanedione (316 μL, 3.10 mmol), Na₂CO₃ (361 mg, 3.41 mmol) and AcOH (2 mL). At the same time, Zn dust (11.4 g, 173.9 mmol) was slowly added to the slurry with the rate of addition and an ice-bath was used to keep the temperature below 30 °C. After full addition, the reaction mixture was stirred at room temperature. The resulting mixture was poured into distilled water (25 mL) and then filtered through Celite, washing with CH₂Cl₂. The filtrate was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic fractions were washed with saturated NaHCO₃ (10 mL) and brine (10 mL), then dried over anhydrous Na₂SO₄ and evaporated *in vacuo*. The resulting residue was purified *via* column chromatography on silica, eluting with a gradient of 5–20% ethyl acetate/hexanes, then washed with pentane (3 × 25 mL), yielding the desired product as a yellow solid (168 mg, 19%). Mp 122–124 °C; ¹H-NMR (500 MHz, CDCl₃): δ 9.43 (br s, 1H), 7.45–7.36 (m, 5H), 5.68 (s, 2H), 2.54 (s, 3H), 2.51 (s, 3H), 2.43 (s, 3H); ¹³C-NMR{¹H} NMR (125 MHz, CDCl₃): δ 200.7, 195.9, 141.0, 135.4, 128.8, 128.62, 128.58, 128.56, 127.1, 125.0, 73.1, 31.6, 15.5, 14.0; HRMS-ESI (*m/z*): [M + Na]⁺ calculated for C₁₆H₁₇NO₂SNa, 310.0872; found 310.0869.

Conflicts of interest

The authors declare no competing financial interest.

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