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Zinc mediated straightforward access to diacylpyrroles

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ABSTRACT

In this article, we report the preparation of various 2,4- and 2,5-diacylpyrroles via two zinc-mediated acylation reactions of non-protected pyrroles.

1. Introduction

2-Ketopyrroles and 2,5-ketopyrroles are two substructures underrepresented in the literature while these motives are well represented in biologically relevant molecules (for example, X-14547A [1], and calcimycin [2] in Fig. 1), in polymer chemistry (see in Fig. 1 for representative ligands) [3,4], or in hydroamination reactions [5].

Some procedures have been reported for the monoacylation of pyrroles (including the Vilsmeier–Haack reaction) [6–11]. The diacetylation reaction of pyrroles is less studied and can lead to two regioisomers: the 2,4- and the 2,5-disubstituted pyrroles. Only few syntheses have been reported, even if the corresponding 2,5-diiminopyrrole ligands (prepared by condensation of aromatic amines and mono- or diacylpyrroles) are emerging as suitable ligands [12] in polymerization reactions [4], or in hydroamination reactions catalyzed by organometallic complexes [5]. As an example, Gao et al. reported a sequential acylation reaction of a pyrrole (Scheme 1) [13]. The second acylation was carried out at room temperature for two weeks. The regioselectivity of this sequence was in favour of the 2,4-isomer (ratio: 3/1) and the 2,5-diacylated compound was isolated in a low 16% overall yield. A step wise diacylation of non protected pyrroles was initially reported by Olsson in 1981 [14]. This procedure allowed the synthesis of the sole 2,5-isomer in an overall yield of 34% but required a protection step before the introduction of the second carbonyl function (Scheme 1). To the best of our knowledge, the most efficient and general route to diketopyrroles was described by Fochi et al. [15] 2-Substituted 1,3-benzoxathiolium tetrafluoroborate was used as a masked acylating reagent in this protocol. In the presence of an excess of this derivative, the 2,5-disubstituted pyrroles were isolated regioselectively in high yields (Scheme 1). One of the advantages of this methodology is that identical or different acyl groups could be introduced at the 2- and 5-position. However, all these methodologies suffer from some drawbacks, such as harsh conditions, problem of selectivity, indirect methods of synthesis or long reaction times.

To date, no simple and direct procedure has yet been reported for the synthesis of diketopyrroles. In this work,

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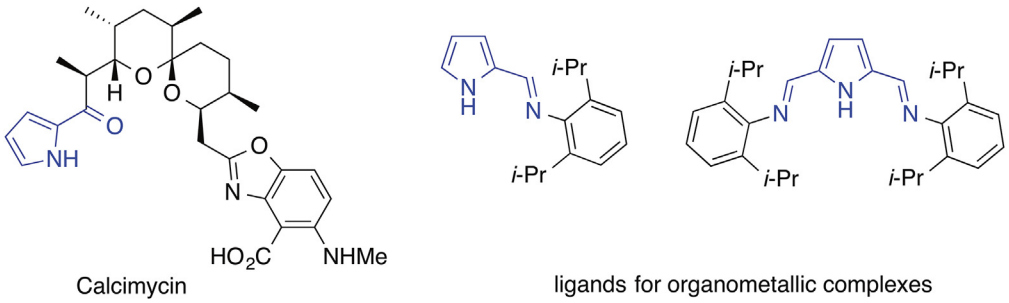
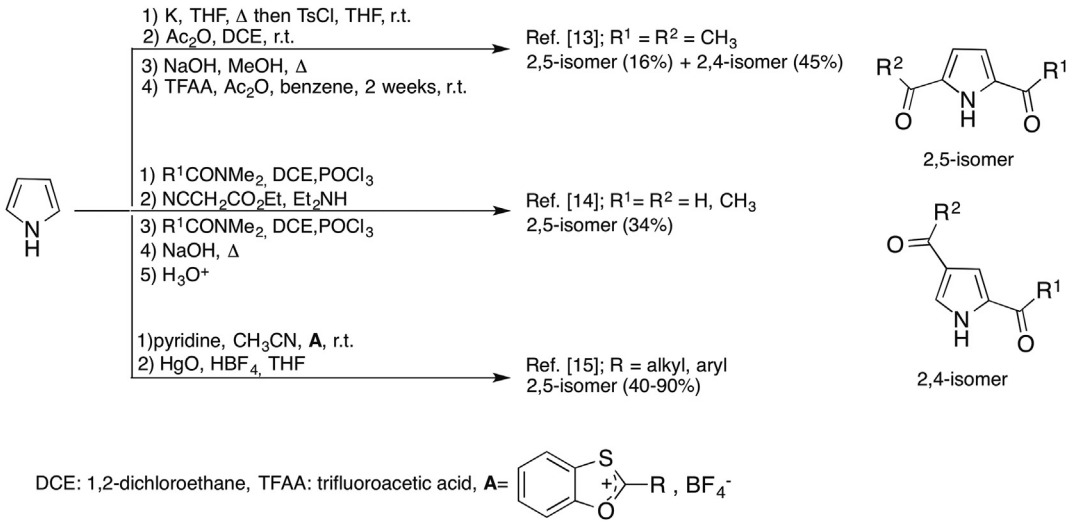


Fig. 1. Natural compounds and ligands for organometallic complexes containing acylpyrrole or diacylpyrrole subunits.



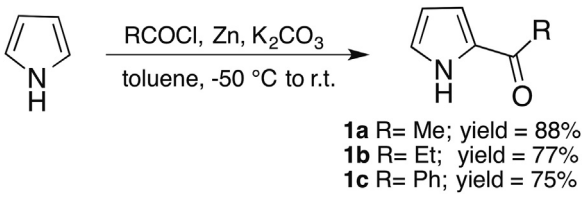
Scheme 1. Reported procedures for the synthesis of diacetyl pyrroles.

we report on a straightforward synthesis of diacetylated pyrroles from non-protected pyrroles and commercially or easily prepared acyl chloride derivatives.

2. Results and discussion

In 2002, Yadav et al. described an efficient method for the regioselective preparation of 2-acylpyrroles from pyrroles and various acyl chlorides in the presence of zinc powder at room temperature in toluene [10]. Due to our interest for the synthesis of functionalized pyrroles, we envisioned to develop a rapid and simple access to disubstituted pyrroles. For this purpose, we synthesized three 2-ketopyrroles (**1a**–**c**) in toluene, from −50 °C to room temperature, in 75–88% yield, according to a modified procedure (Scheme 2). It is worth mentioning that, in our hands, the yields were lower due to the polymerization of pyrroles if no base was added and if the addition of the acyl chloride was carried out at room temperature.

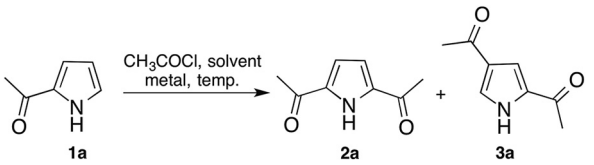
Having the monoacylated pyrroles, we next defined the optimized reaction conditions. The second acylation step was initially carried out with **1a** and acetyl chloride, as acylating reagent, in the presence of different metals (Zn, Fe, Al, Mn, and Mg) at various temperatures and in various



Scheme 2. Synthesis of ketopyrrole **1a**–**c**.

solvents (Table 1). An initial attempt at 80 °C in toluene led to a complete decomposition of the starting material (entry 1, Table 1). However, a decrease of the temperature to room temperature overnight led gratifyingly to a mixture of diacetylpyrroles in 75% conversion and a ratio **2a**:**3a** of 1:2.33, without any N-acylation (entry 2, Table 1). The two regioisomers can easily be separated by chromatography on silica gel (see Experimental section). Variation of the solvent was also examined. In polar solvents, such as acetonitrile and THF, no or almost no reactivity was noticed (entries 5–6, Table 1), while in dichloroethane (DCE) complete conversion and moderate regioselectivity in favour of the 2,4-isomer were obtained (ratio **2a**:**3a** of 1:1.5, entry 4, Table 1). Surprisingly, dichloromethane (DCM) led

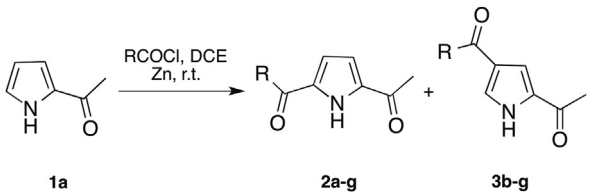
Table 1
Acylation reaction of 2-acetylpyrrole.[a]



Entry	Solvent	Temp. (°C)	Metal	Conv. (%)[b]	Selectivity[c] **2a**:**3a**
1	Toluene	80	Zn	Decomp.	N.D.
2	Toluene	rt	Zn	75	1:2.33
3	DCM	rt	Zn	50	1:1.63
4	DCE	rt	Zn	100	1:1.5
5	CH_3CN	rt	Zn	Traces	N.D.
6	THF	rt	Zn	N.R	N.D.
7	Toluene	rt	Al	N.R	N.R
8	Toluene	rt	Fe	N.R	N.R
9[d]	DCE	rt	Mn	N.R	N.R
10[d]	DCE	rt	Mg	N.R	N.R
11	DCE	rt	Fe	25	1:1.5
12	DCM	rt	Fe	100	1:1.70

[a] Acetylpyrrole (1 equiv), acetyl chloride (1.5 equiv), Zn (2 equiv), solvent (2 mL/mmol) for 16 h.
[b] Conversion was determined by ^{1}H NMR analysis.
[c] Selectivity was determined by ^{1}H NMR analysis.
[d] In toluene, no reaction was observed.

Table 2
Zinc-mediated acylation of 2-ketopyrrole.[a]



Entry	R	Yield (%)[b]	Ratio **2**:**3**[c]
1	Me	51 (**2a**, **3a**)	1:1.5
2	Ph	45 (**2b**, **3b**)	1:1.38
3	*t*-Bu	54 (**2c**, **3c**)	1:1.5
4	*i*-Pr	42 (**2d**, **3d**)	1:1.7
5	Et	60 (**2e**, **3e**)	1:1.5
6	Cyclopropyl	24 (**2f**, **3f**)	1:1.67[d]
7	Adamantyl	15 (**2g**, **3g**)	0:1[e]

[a] Acetylpyrrole (1 equiv), acyl chloride (1.5 equiv), Zn (2 equiv), dichloroethane (2 mL/mmol) for 16–24 h.
[b] Isolated yield.
[c] Selectivity was determined by ^{1}H NMR analysis of the crude mixture.
[d] **3f** contained also the corresponding ring-opened adduct, see the Experimental section.
[e] No 2,5-isomer was observed, even in the crude product, by ^{1}H NMR analysis.

to lower reactivity (50% conversion, entry 3, Table 1). The screening of metals showed that aluminium, manganese and magnesium did not provide any product whatever the solvent (entries 7, 9–10, Table 1). However, iron metal led to diacetylated pyrroles in low to good conversions and moderate regioselectivity (entries 8, 11–12, Table 1). It is noteworthy that with iron, the conversion was higher in DCM compared to DCE (100% and 25%, respectively, entries 11–12, Table 1). Finally, due to higher yield in DCE with zinc, this solvent and metal have been used all along the study. The reactions were followed by TLC analysis and showed no evolution after 16–24 h.

Having these reaction conditions in hand, we delineated the scope of this reaction with various acyl chlorides (Table 2).

Except with 1-adamantane carbonyl chloride, the yields and the regioselectivities were moderate, whatever the acyl chloride. The major isomer was always the 2,4-isomer. With 1-adamantane carbonyl chloride, the 2,4-isomer **3g** was isolated in 15% yield as a sole isomer within 24 h. To unambiguously establish the atom connectivity in this compound, single crystals were grown by slow diffusion of pentane in chloroform. Suitable single crystals were obtained and subjected to X-ray diffraction (XRD). A thermal ellipsoid representation is showed in Fig. 2.

Acylation with cyclopropanecarbonyl chloride led to the expected isomers **2f** and **3f** in a moderate yield (19%) and a low 1:1 selectivity. Moreover, **3f** was accompanied by a ring-opening adduct as a side-product in 5% yield [16,17]. Indeed, as showed in Scheme 3, the zinc chloride formed during this process could activate the carbonyl function, and allow the addition of a chloride to the cyclopropyl moiety and the cleavage of one C–C bond. This $ZnCl_2$-mediated ring opening sequence could lead to an enol intermediate and then to the corresponding ketone after

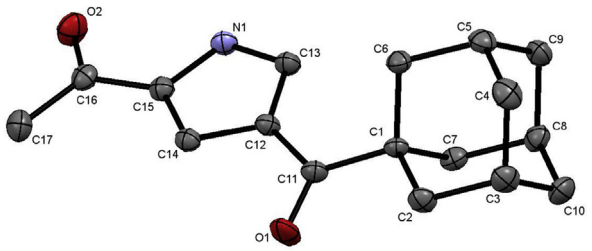


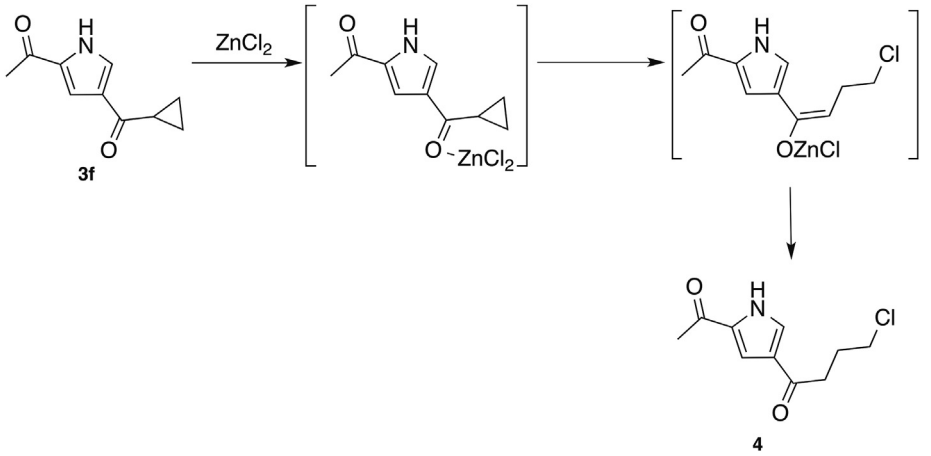
Fig. 2. Thermal ellipsoid representation (50% probability) of **3g**. Hydrogen atoms were removed for clarity.

hydrolysis. It is worth noting that such ring opening was not observed with the 2,5-isomer **2f**.

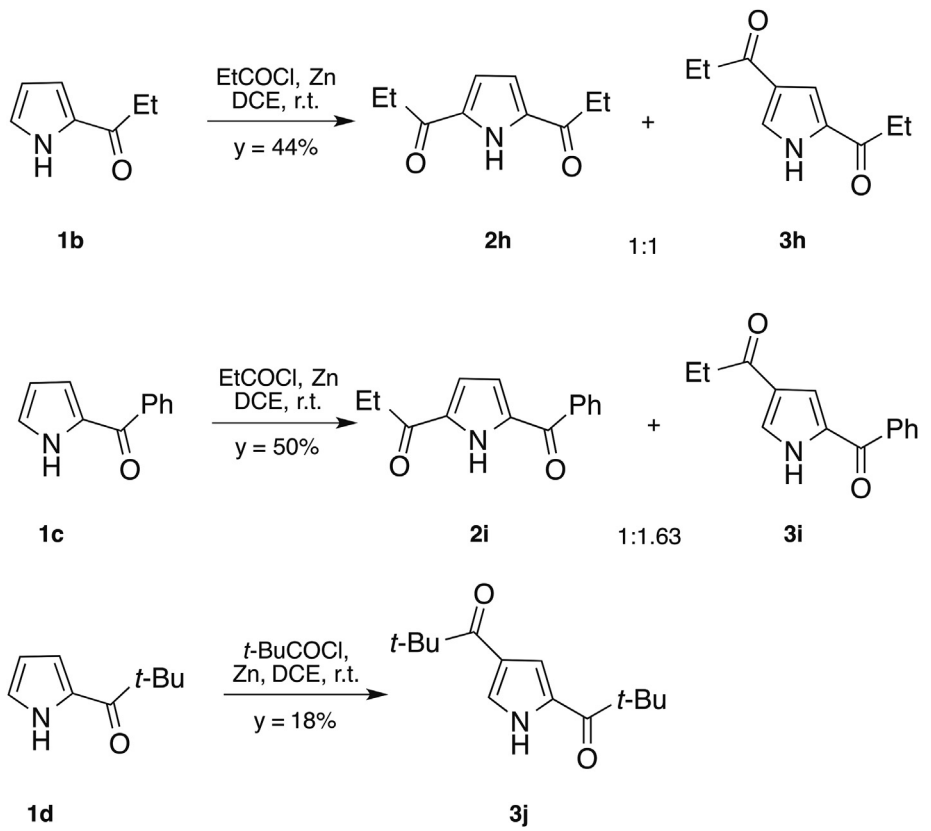
Acylation reactions were also performed with pyrroles **1b** and **1d**. The corresponding diacylpyrroles were again obtained in moderate yields (44–50%) and in selectivities ranging from 1:1 to 1:1.63 in favour of the 2,4-isomer (Scheme 4). Regioselective acylation was observed starting from pivaloylpyrrole. The 2,4-isomer **3j** was isolated in 18% yield as a sole isomer. Based on this result and the synthesis of **3g**, the regioselectivity might be tuned and controlled by the steric hindrance of the second acyl group.

3. Conclusion

In summary we have developed the first simple and straightforward method for the preparation of diketopyrroles, which can be versatile synthons for the synthesis of polydentate ligands. The key advantages of this procedure are the small number of chemical steps, the short reaction times (16–24 h) and the absence of protection-deprotection steps. We are currently working on the



Scheme 3. Proposed mechanism for the ring opening of the cyclopropyl derivative **3f**.



Scheme 4. Zinc-mediated acylation of 2-propanoxypyrrole **1b**, 2-benzyloxypyrrole **1c** and 2-pivaloylpyrrole **1d**.

development of families of pyrrole ligands and their application in catalysis.

4. Experimental section

All reactions were carried out under an atmosphere of dry Argon. Solvents were purchased from Carlo Erba and degassed prior to use by bubbling argon gas directly in the solvent. Solvents for NMR spectroscopy were dried over molecular sieves. NMR spectra were recorded on a 400 MHz and 500 MHz Bruker spectrometer. Proton (^{1}H) NMR information is given in the following format: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sept, septet; and m, multiplet), coupling constant(s) (*J*) in Hertz (Hz), and number of protons. The prefix app is occasionally applied when the true signal

multiplicity was unresolved and br indicates that the signal in question broadened. Carbon (^{13}C) NMR spectra are reported in ppm (δ) relative to residual $CHCl_3$ (δ 77.0) unless noted otherwise. HRMS analyses were performed by LCMT analytical services. NMR solvents were passed through a pad of basic alumina before use.

CCDC 1496559 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

4.1. General procedure for the synthesis of 2-acyl-pyrrole

To a mixture of pyrrole (1 equiv), potassium carbonate (1.5 equiv) and zinc powder (2 equiv) in toluene (2 mL/mmol) at −50 °C, acyl chloride (1.5 equiv) was added slowly. The mixture was warmed slowly to room temperature. After completion by TLC analysis, the reaction mixture was quenched with saturated sodium bicarbonate solution (3 mL/mmol) and extracted with ethyl acetate (2 × 3 mL/mmol). Evaporation of the solvent followed by purification on a short plug of silica gel (Merck, 100–200 mesh, ethyl acetate/hexane, 0.5–9.5) afforded the pure 2-acyl pyrrole derivative.

4.2. 1-(1H-Pyrrol-2-yl)ethanone (**1a**) [18a]

Following the general procedure from pyrrole (1 g, 15 mmol), **1a** was isolated in 88% yield.

^1H NMR ($CDCl_3$, 400 MHz): δ = 9.43 (s, 1H, NH), 7.03 (d, J = 1.2 Hz, 1H), 6.92 (d, J = 1.1 Hz, 1H), 6.29–6.26 (m, 1H), 2.44 (s, 3H) ppm.

4.3. 1-(1H-Pyrrol-2-yl) propanone (**1b**) [18a]

Following the general procedure from pyrrole (1 g, 15 mmol), **1b** was isolated in 77% yield.

^1H NMR ($CDCl_3$, 400 MHz): δ = 9.43 (s, 1H, NH), 7.03 (d, J = 1.2 Hz, 1H), 6.92 (d, J = 1.1 Hz, 1H), 6.28–6.26 (m, 1H), 2.82 (q, J = 7.3 Hz, 2H), 1.22 (t, J = 7.3 Hz, 3H) ppm.

4.4. 1-(1H-Pyrrol-2-yl)-phenylethanone (**1c**) [18a,b]

Following the general procedure from pyrrole (1 g, 15 mmol), **1c** was isolated in 75% yield.

^1H NMR ($CDCl_3$, 400 MHz): δ = 10.45 (s, 1H, NH), 7.94 (d, J = 7.1 Hz, 2H), 7.71 (m, 2H), 7.42–7.34 (m, 1H), 7.01 (d, J = 1.2 Hz, 1H), 6.72 (d, J = 1.1 Hz, 1H), 6.15–6.13 (m, 1H) ppm.

4.5. General procedure for the synthesis of 2,4- and 2,5-diacyl-pyrrole

To a mixture of 2-acylpyrrole 1 (1 equiv) and zinc powder (2 equiv, 59 mg, 0.917 mmol) in dichloroethane (2 mL/mmol) acyl chloride (1.5 equiv) was added. The mixture was stirred at room temperature and, after completion by TLC analysis (16–24 h), the reaction mixture was quenched with saturated sodium bicarbonate solution (15 mL/mmol) and extracted with ethyl acetate (3 × 15 mL/mmol). Evaporation of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate/hexane) afforded the pure 2,4-diacylpyrrole (**2**) and 2,5-diacylpyrrole (**3**).

4.6. 1,1′-(1H-Pyrrole-2,5-diyl)bis(ethan-1-one) (**2a**)

Following the general procedure from 2-acetylpyrrole (50 mg, 0.46 mmol), **2a** was isolated as a yellow foam (15 mg, 21% yield).

^1H NMR ($CDCl_3$, 400 MHz): δ 9.85 (s, 1H, NH), 6.85 (d, J = 2.5 Hz, 2H) 2.48 (s, 6H, Me) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.0, 133.8, 115.1, 25.0 ppm.

IR (neat): ν 3438, 3116, 2963, 1652, 1535, 1425, 1357, 1259, 1245, 1082, 1020, 991, 921, 798, 687 cm^{-1}.

HRMS (ESI): m/z calculated for $C_8H_{10}NO_2$ $[M+H]^+$: 152.0712; found: 152.0704.

4.7. 1,1′-(1H-Pyrrole-2,4-diyl)bis(ethan-1-one) (**3a**)

Following the general procedure, **3a** was isolated as a yellow foam (21 mg, 30% isolated yield).

^1H NMR ($CDCl_3$, 400 MHz): δ 9.93 (s, 1H, NH), 7.60 (s, 1H, py), 7.31 (s, 1H, py), 2.48 (s, 3H, Me), 2.46 (s, 3H, Me) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.2, 189.2, 132.9, 127.9, 127.5, 116.0, 27.2, 25.5 ppm.

IR (neat): ν 3264, 3089, 3923, 2853, 2112, 1640, 1556, 1491, 1436, 1369, 1279, 1208, 1155, 1129, 1062, 1021, 975, 943, 932, 843, 780 cm^{-1}.

HRMS (ESI): m/z calculated for $C_8H_{10}NO_2$ $[M+H]^+$: 152.0712; found: 152.0714.

4.8. 1-(5-Benzoyl-1H-pyrrol-2-yl)ethan-1-one (**2b**)

Following the general procedure from 2-acetylpyrrole (50 mg, 0.46 mmol), **2b** was isolated as a yellow foam (19 mg, 19% yield).

^1H NMR ($CDCl_3$, 400 MHz): δ 10.14 (s, 1H, NH), 7.90 (d, J = 7.8 Hz, 2H), 7.63–7.58 (m, 1H), 7.53–7.49 (m, 2H), 6.90 (d, J = 4.0 Hz, 1H), 6.85 (d, J = 4.0 Hz, 1H), 2.52 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 187.9, 184.5, 136.4, 134.0, 132.7, 131.6, 128.0 (2C), 127.5 (2C), 117.4, 114.9, 25.1 ppm.

IR (neat): ν 3440, 3125, 3063, 2925, 1720, 1656, 1627, 1601, 1577, 1533, 1495, 1444, 1421, 1359, 1336, 1312, 1272, 1179, 1154, 1093, 1075, 1012, 937, 882, 803, 783, 725, 689, 679 cm^{-1}.

HRMS (ESI): m/z calculated for $C_{13}H_{12}NO_2$ $[M+H]^+$: 214.0868; found: 214.0869.

4.9. 1-(4-Benzoyl-1H-pyrrol-2-yl)ethan-1-one (**3b**)

Following the general procedure from 2-acetylpyrrole (50 mg, 0.46 mmol), **3b** was isolated as a brownish foam (26 mg, 26% yield).

^1H NMR ($CDCl_3$, 400 MHz): δ 10.55 (s, 1H, NH), 8.13 (dd, J = 8.0, 4.0 Hz, 1H), 7.85–7.83 (m, 2H), 7.61–7.56 (m, 2H), 7.52–7.45 (m, 1H), 7.44 (s, 1H), 2.52 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.4, 188.3, 138.0, 132.6, 131.7, 131.0, 127.9 (2C), 127.4 (2C), 125.0, 117.1, 24.6 ppm.

IR (neat): ν 3335, 2963, 2924, 2554, 1920, 1688, 1652, 1621, 1597, 1577, 1544, 1497, 1453, 1428, 1379, 1325, 1268,

1231, 1168, 1117, 1025, 943, 880, 845, 799, 728, 705, 681 cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{13}H_{12}NO_2$ $[M+H]^+$: 214.0868; found: 214.0876.

4.10. 1-(5-Acetyl-1H-pyrrol-2-yl)-2,2-dimethylpropan-1-one (**2c**)

Following the general procedure from 2-acetylpyrrole (50 mg, 0.46 mmol), **2c** was isolated as a yellow foam (17 mg, 19% yield).

^1H NMR ($CDCl_3$, 400 MHz): δ 9.94 (s, 1H, NH) 6.88 (br s, 1H), 6.85 (br s, 1H), 2.47 (s, 3H), 1.36 (s, 9H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.7, 189.1, 133.7, 132.4, 116.3, 115.9, 42.2, 28.3, 26.5 ppm.

IR (neat): ν 3386, 2965, 2929, 2872, 2119, 1660, 1643, 1533, 1478, 1460, 1395, 1359, 1276, 1199, 1156, 1101, 1074, 1011, 935, 904, 797, 766, 678 cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{11}H_{16}NO_2$ $[M+H]^+$: 194.1181; found: 194.1178.

4.11. 1-(5-Acetyl-1H-pyrrol-3-yl)-2,2-dimethylpropan-1-one (**3c**)

Following the general procedure from 2-acetylpyrrole (50 mg, 0.46 mmol), **3c** was isolated as a brownish foam (26 mg, 24% yield).

^1H NMR ($CDCl_3$, 400 MHz): δ 10.09 (s, 1H, NH), 7.66 (br s, 1H), 7.37 (br s, 1H), 2.48 (s, 3H), 1.35 (s, 9H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.1, 188.6, 132.8, 128.2, 124.1, 117.4, 42.7, 27.8, 25.3 ppm.

IR (neat): ν 3182, 2966, 2930, 2871, 1658, 1626, 1554, 1474, 1441, 1387, 1354, 1282, 1261, 1188, 1157, 1104, 1018, 981, 942, 905, 891, 792, 760, 732 cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{11}H_{16}NO_2$ $[M+H]^+$: 194.1181; found: 194.1184.

4.12. 1-(5-Acetyl-1H-pyrrol-2-yl)-2-methylpropan-1-one (**2d**)

Following the general procedure from 2-acetylpyrrole (50 mg, 0.46 mmol), **2d** was isolated as a yellow foam (10 mg, 11% yield).

^1H NMR ($CDCl_3$, 400 MHz): δ 9.90 (s, 1H), 6.86 (s, 1H), 6.85 (s, 1H), 3.33–3.23 (m, 1H), 2.48 (s, 3H), 1.22 (d, $J = 6.9$ Hz, 6H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.9, 188.8, 134.6, 133.7, 116.0, 115.1, 36.5, 29.7, 26.0, 19.2 ppm.

IR (neat): ν 3291, 2929, 2384, 2359, 2342, 2326, 2299, 1674, 1658, 1541, 1360, 1231, 1091, 920, 806, 758 cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{10}H_{13}NO_2$ $[M+H]^+$: 180.1025; found: 180.1023.

4.13. 1-(5-Acetyl-1H-pyrrol-3-yl)-2-methylpropan-1-one (**3d**)

Following the general procedure from 2-acetylpyrrole (50 mg, 0.46 mmol), **3d** was isolated as a yellow foam (28 mg, 31% yield).

^1H NMR ($CDCl_3$, 400 MHz): δ 10.54 (s, 1H), 7.65 (d, $J = 1.8$ Hz, 1H), 7.34 (s, 1H), 3.26–3.16 (m, 1H), 2.49 (s, 3H), 1.20 (d, $J = 6.9$ Hz, 6H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.0, 189.2, 132.8, 128.1, 126.1, 116.4, 37.2, 25.6, 19.2 (×2) ppm.

IR (neat): ν 3165, 2967, 2929, 2871, 2300, 1640, 1541, 1439, 1276, 1199, 1169, 1144, 1096, 941, 929, 861, 803, 761 cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{10}H_{13}NO_2$ $[M+H]^+$: 180.1025; found: 180.1026.

4.14. 1-(5-Acetyl-1H-pyrrol-2-yl)propan-1-one (**2e**)

Following the general procedure from 2-acetylpyrrole (50 mg, 0.46 mmol), **2e** was isolated as a yellow-brown foam (18 mg, 24% yield).

^1H NMR ($CDCl_3$, 400 MHz): δ 9.89 (br s, 1H, NH), 6.84 (s, 2H), 2.85 (q, $J = 7.3$ Hz, 4H), 1.21 (t, $J = 7.3$ Hz, 6H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.3, 188.9, 134.4, 134.3, 116.0, 115.1, 31.8, 26.0, 8.3 ppm.

IR (neat): ν 3239, 2981, 2923, 1660, 1637, 1554, 1443, 1278, 1260, 1199, 1016, 872, 796, 763 cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_9H_{12}NO_2$ $[M+H]^+$: 166.0868; found: 166.0866.

4.15. 1-(5-Acetyl-1H-pyrrol-3-yl)propan-1-one (**3e**)

Following the general procedure from 2-acetylpyrrole (50 mg, 0.46 mmol), **3e** was isolated as a brown foam (28 mg, 36% yield).

^1H NMR ($CDCl_3$, 400 MHz): δ 10.1 (br s, 1H, NH), 7.61 (s, 1H), 7.31 (s, 1H), 2.84–2.79 (m, 2H), 2.48 (s, 3H), 1.22–1.19 (m, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.1, 188.7, 132.6, 127.3, 126.8, 115.6, 32.6, 25.3, 8.2 ppm.

IR (neat): ν 3442, 2937, 1652, 1538, 1423, 1358, 1229, 1078, 1023, 793 cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_9H_{12}NO_2$ $[M+H]^+$: 166.0868; found: 166.0869.

4.16. 1-(5-(Cyclopropanecarbonyl)-1H-pyrrol-2-yl)ethan-1-one (**2f**)

Following the general procedure from 2-acetylpyrrole (55 mg, 0.50 mmol), **2f** was isolated as a brown foam (8 mg, 9% yield).

^1H NMR ($CDCl_3$, 400 MHz): δ = 9.75–10.05 (br s, 1H, NH), 6.98 (dd, $J = 4.1$, 2.5 Hz, 1H), 6.88 (dd, $J = 4.1$, 2.6 Hz, 1H), 2.39–2.52 (m, 4H), 1.21–1.27 (m, 2H), 1.01–1.08 (m, 2H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): (partial description C=O and Cq of pyrrole are missing): δ 116.1, 115.2, 26.1, 17.7, 11.6 (2C) ppm.

IR (neat): ν 3284, 2923, 1665, 1640, 1383, 1229 cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{10}H_{12}NO_2$ $[M+H]^+$: 178.0868; found: 178.0868.

4.17. 1-(4-(Cyclopropanecarbonyl)-1H-pyrrol-2-yl)ethan-1-one (**3h**) and 1-(5-acetyl-1H-pyrrol-3-yl)-4-chlorobutan-1-one (**4**)

Following the general procedure from 2-acetylpyrrole (55 mg, 0.50 mmol), **3f** and **4** were isolated as a 2:1 inseparable mixture and a brown foam (14 mg, 15% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.15–10.43 (br s, 1H, NH), 7.48 (dd, J = 3.2, 1.4 Hz, 1H), 7.26 (dd, J = 2.4, 1.4 Hz, 1H), 2.38 (s, 3H), 2.25 (app. tt, J = 8.2, 3.9 Hz, 1H), 1.09 (app. dt, J = 6.8, 3.4 Hz, 2H), 0.81 (app. dq, J = 7.3, 3.7 Hz, 2H) ppm.

4: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.15–10.43 (br s, 1H, NH), 7.53 (dd, J = 2.4, 1.4 Hz, 1H), 7.21 (dd, J = 2.4, 1.4 Hz, 1H), 3.53 (t, J = 6.2 Hz, 2H, CH_2Cl), 2.87 (t, J = 7.0 Hz, 2H), 2.07 (quint, J = 6.7 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): (mixture of the **3g** and **4**) δ = 195.5, 194.3, 189.0, 189.1, 132.8, 127.9, 127.8, 127.6, 127.0, 115.8, 44.8, 36.2, 26.8, 25.6, 18.1, 10.9 ppm.

IR (neat): ν 3284, 3094, 1638, 1554, 1382, 1271 cm^{-1}.

HRMS (ESI): m/z calculated for $C_{10}H_{12}NO_2$ $[M+H]^+$: 178.0868; found: 178.0869.

HRMS (ESI): m/z calculated for $C_{10}H_{13}ClNO_2$ $[M+H]^+$: 214.0635; found: 214.0637.

4.18. 1-(4-(Adamantane-1-carbonyl)-1H-pyrrol-2-yl)ethan-1-one (**3g**)

Following the general procedure from 2-acetylpyrrole (50 mg, 0.46 mmol), **3g** was isolated as a yellow solid (20 mg, 15% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.73–10.0 (br s, 1H, NH), 7.69 (dd, J = 3.2, 1.5 Hz, 1H), 7.39 (dd, J = 2.4, 1.4 Hz, 1H), 2.48 (s, 3H), 2.08–2.13 (m, 3H), 2.00–2.07 (m, 3*2H), 1.75 –1.83 (m, 3*2H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.2 (C=O), 189.0 (C=O), 131.8 (C, pyrrole), 128.6 (CH pyrrole), 124.4 (C, pyrrole), 118.0 (CH, Pyrrole), 46.4 (C, adamantyl), 39.6 (3 CH_2, adamantyl), 36.8 (3 CH_2, adamantyl), 28.3 (3 CH, adamantyl), 25.6 (CH_3, acetyl) ppm.

IR (neat): ν 3314, 2901, 1655, 1637, 1548, 1388, 1360, 1277, 1209 cm^{-1}.

HRMS (ESI): m/z calculated for $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1651; found: 272.1653.

Mp = 197–198 °C.

Single crystals of compound **3g** suitable for X-ray crystallographic analysis were obtained by slow evaporation of chloroform solution. X-ray diffraction experiments for monocrystals of **3g** were performed at 150 K with graphite-monochromatized Mo Ka radiation (λ = 0.71073 Å) on a Bruker–Nonius Kappa CCD area detector diffractometer. Formula $C_{17}H_{21}NO_2$, formula weight 271.35, crystal system monoclinic, space group C2/c, a = 21.8308(6) Å, b = 6.4996(2) Å, c = 20.3968(6) Å, β = 108.2176(15)°, V = 2749.07(14) Å^3, Z = 8, calculated density = 1.311 g/cm^3, m = 0.09 mm^{-1}, 29,790 measured reflections, 4235 independent reflections, R_{int} = 0.029, $R[F^2 > 2\sigma(F^2)]$ = 0.0428, $wR(F^2)$ = 0.1176, GOF = 1.042, 2θmax = 60.92°, 186 parameters, final difference map between 0.387 and −0.217 eÅ^{-3}. Program(s) used to solve structure: SHELXS-97. Program(s) used to refine structure: SHELXL-2014.

4.19. 1,1′-(1H-Pyrrole-2,4-diyl)bis(propan-1-one) (**2h**)

Following the general procedure from 2-propanoylpyrrole (57 mg, 0.46 mmol), **2h** was isolated as a yellow foam (18 mg, 22% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.89 (br s, 1H, NH), 6.84 (s, 2H), 2.85 (q, J = 7.3 Hz, 4H), 1.21 (t, J = 7.3 Hz, 6H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.4, 134.2, 115.2, 31.9, 8.5 ppm.

IR (neat): ν 3440, 3281, 1652, 1539, 1202, 900, 790, 735 cm^{-1}.

HRMS (ESI): m/z calculated for $C_{10}H_{14}NO_2$ $[M+H]^+$: 180.10295; found: 180.1021.

4.20. 1,1′-(1H-Pyrrole-2,5-diyl)bis(propan-1-one) (**3h**)

Following the general procedure from 2-propanoylpyrrole (57 mg, 0.46 mmol), **3h** was isolated as a yellow foam (18 mg, 22% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.96 (br s, 1H, NH), 7.59 (s, 1H), 7.31 (s, 1H), 2.87–2.78 (m, 4H), 1.24–1.18 (m, 6H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.5, 192.5, 132.4, 127.2 (2C), 114.8, 32.9, 31.3, 8.7, 8.5 ppm.

IR (neat): ν 3264, 2976, 2937, 1644, 1552, 1378, 1182, 918, 904, 800 cm^{-1}.

HRMS (m/z): $[M+H]^+$ calculated for $C_{10}H_{14}NO_2$: 180.10295; found: 180.1021.

4.21. 1-(5-Benzoyl-1H-pyrrol-2-yl)propan-1-one (**2i**)

Following the general procedure from 2-benzoylpyrrole (79 mg, 0.46 mmol), **2i** was isolated as a yellow foam (20 mg, 19% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.14 (s, 1H, NH), 7.90 (d, J = 7.8 Hz, 2H), 7.63–7.58 (m, 1H), 7.53–7.49 (m, 2H), 6.90 (d, J = 4.0 Hz, 1H), 6.85 (d, J = 4.0 Hz, 1H), 2.85 (q, J = 7.3 Hz, 4H), 1.21 (t, J = 7.3 Hz, 6H) ppm.

IR (neat): ν 3266, 1663, 1626, 1547, 1375, 1279, 1209, 906, 891, 728 cm^{-1}.

4.22. 1-(4-Benzoyl-1H-pyrrol-2-yl)propan-1-one (**3i**)

Following the general procedure from 2-benzoylpyrrole (79 mg, 0.46 mmol), **3i** was isolated as a yellow foam (32 mg, 31% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.95 (br s, 1H, NH), 7.98 –7.83 (d, J = 7.1 Hz, 2H), 7.71 (m, 1H), 7.62 (t, J = 7.1 Hz, 1H), 7.52 (t, J = 7.1 Hz, 2H), 7.29 (m, 1H), 2.83 (q, J = 7.4 Hz, 2H), 1.21 (t, J = 7.4 Hz, 3H) ppm.

DEPTQ NMR ($CDCl_3$, 100 MHz): δ 196.3, 185.2, 137.3, 132.6, 131.7, 128.9 (2C), 128.6 (2C), 127.5 (2C), 117.8, 32.9, 8.4 ppm.

IR (neat): ν 3266, 1663, 1626, 1547, 1375, 1279, 1209, 906, 891, 728 cm^{-1}.

4.23. 1-(4-(2,2-Dimethylpropane-1-one-1H-pyrrol-2-yl)-2,2-dimethylpropan-1-one (**3j**)

Following the general procedure from 2-pivaloylpyrrole (76 mg, 0.5 mmol), **3j** was isolated as a yellow foam (21 mg, 18% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.80 (s, 1H, NH) 7.57 (s, 1H), 7.41 (s, 1H), 1.34 (s, 18H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.4, 197.4, 128.9, 126.5, 124.2, 116.8, 43.7, 43, 28.1 ppm.

IR (neat): ν 3278, 3123, 2969, 2932, 2871, 2114, 1704, 1629, 1547, 1475, 1458, 1436, 1393, 1354, 1289, 1239, 1151, 1054, 999, 917, 902, 862, 792, 769 cm^{-1}.

HRMS (m/z): $[M+H]^+$ calculated $C_{14}H_{22}O_2N$ 236.1651; found: 236.1655.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.crci.2017.01.003.

References

[1] (a) J.M. Westley, R.H. Evans Jr., C.M. Liu, T.E. Hermann, J.F. Blount, J. Am. Chem. Soc. 100 (1978) 6784;
(b) C.M. Liu, T.E. Hermann, M. Liu, D.N. Bull, N.J. Palleroni, B.L.T. Prosser, J.M. Westley, P.A.J. Miller, Antibiotics 32 (1979) 95;
(c) K.C. Nicolaou, D.P. Papahatjis, D.A. Claremon, R.E. Dolle III, J. Am. Chem. Soc. 103 (1981) 6967;
(d) K.C. Nicolaou, D.A. Claremon, D.P. Papahatjis, R.L. Magolda, J. Am. Chem. Soc. 103 (1981) 6969.

[2] (a) M.O. Chaney, P.V. Demarco, N.D. Jones, J.L. Orrolowitz, J. Am. Chem. Soc. 96 (1974) 1932;
(b) R.K. Boeckmann Jr., A.B. Charette, T. Asberom, B.H. Johnston, J. Am. Chem. Soc. 109 (1987) 7553.

[3] For the use of acylpyrroles in polymerization, see: (a) I. Alia, G.F. Smith, J. Chem. Soc. (1954) 3842;
(b) R.M. Silverstein, E.E. Ryskiewiez, C. Willard, R.C. Koehler, J. Org. Chem. 20 (1955) 668;
(c) W.C. Anthony, J. Org. Chem. 25 (1960) 2048;
(d) G.H. Cooper, J. Org. Chem. 36 (1971) 2897;
(e) A.C. Pinheiro, T. Roisnel, E. Kirillov, J.-F. Carpentier, O.L. Casagrande Jr., Dalton Trans. 44 (2015) 16073.

[4] For the use of diacylpyrroles in polymerization, see: (a) D.M. Dawson, D.A. Walker, M. Thornton-Pett, M. Bochmann, Dalton Trans. (2000) 459;
(b) Y. Matsuo, K. Mashima, K. Tani, Organometallics 20 (2001) 3510.

[5] For the use of diacylpyrroles in hydroamination, see: J. Jenter, R. Köppe, P.W. Roesky Organometallics 30 (2011) 1404.

[6] J.M. Patterson, S. Soedigdo, J. Org. Chem. 33 (1968) 2057.

[7] G.P. Beon, J. Heterocycl. Chem. 2 (1965) 473.

[8] (a) K.C. Nicolaou, D.A. Claremon, D.P. Papahatjis, Tetrahedron Lett. 22 (1981) 4647;
(b) E. Baltazzi, L.I. Krimen, Chem. Rev. 63 (1963) 511.

[9] A.P. Kozikowski, A. Ames, J. Am. Chem. Soc. 102 (1980) 860.

[10] J.S. Yadav, B.V.S. Reddy, G. Kondaji, R. Srinivasa Rao, S. Praveen Kumar, Tetrahedron Lett. 43 (2002) 8133.

[11] F. Jafarpour, H. Hazrati, M. Darishmolla, Adv. Synth. Catal. 356 (2014) 3784.

[12] (a) H.A. Taym, Inorg. Chim. Acta 139 (1987) 69;
(b) N.E. Borisova, M.D. Reshetova, M.V. Kuznetcov, Y.A. Ustynyuk, Synthesis (2007) 1169.

[13] S. Hou, M. Ding, L. Gao, Macromolecules 36 (2003) 3826.

[14] For the use of dimethylformamide, see (a) R. Miller, K. Olsson, Acta Chem. Scand., Ser. B 35 (1981) 303;
(b) K.P. Olsson, Å. Pernemalm, Acta Chem. Scand., Ser. B 33 (1979) 125;
(c) V.A. Knizhnikov, N.E. Borisova, N.Y. Yurashevich, L.A. Popova, A.Y. Chernyad'ev, Z.P. Zubreichuk, M.D. Reshetova, Russ. J. Org. Chem. 43 (2007) 855;
(d) For other acetamides, see: Y. Kuroda, H. Murase, Y. Suzuki, H. Ogoshi Tetrahedron Lett. 30 (1989) 2411.

[15] M. Barbero, S. Cadamuro, I. Degani, R. Fochi, A. Gatti, V. Regondi, J. Org. Chem. 53 (1988) 2245.

[16] For a review on the reactivity of cyclopropyl carbonyl derivatives, see: F. De Simone, J. Waser Synthesis (2009) 3353.

[17] For one example of Lewis-acid mediated ring opening of cyclopropyl carbonyl compounds, see: X.-Y. Tang, M. Shi Tetrahedron 65 (2009) 9336.

[18] (a) R.G. Giles, H. Heaney, M.J. Plater, Tetrahedron 71 (2015) 7367;
(b) M. Milen, P. Ábrányi-Balogh, A. Dancsó, G. Simig, B. Volk, Tetrahedron 70 (2014) 465.