Oxidation of 2,5-Dialkylpyrrole Derivatives with Cerium(IV) Ammonium Nitrate

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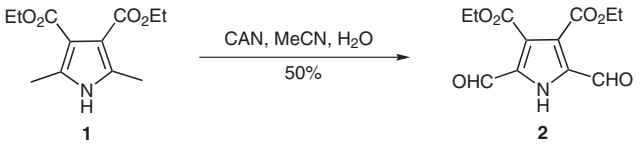
Abstract: A new four-step procedure for the synthesis of 2,5-diformylpyrrole from hexane-2,5-dione was developed. The oxidation reaction of substituted 2,5-dialkylpyrroles with cerium(IV) ammonium nitrate (CAN) has been studied in detail. It was found that the outcome of the reaction strongly depends on the substituents present on the pyrrole moiety and on the reaction conditions. *N*-Tosyl- and *N*-mesyl-protected 2,5-dimethylpyrroles and 3,4-diiodo-2,5-dimethylpyrrole were oxidized to the corresponding dialdehydes, whereas 2,5-dialkylpyrroles bearing electron-withdrawing groups at positions 3 and 4 were transformed into the corresponding keto ethers or monoaldehydes rather than into the expected diketones.

Key words: pyrroles, oxidation, aldehydes, ketones, sulfonamides

Pyrroles are abundant in natural products,[1] medicinal agents,[2] and are present in a number of intermediates in multistep syntheses.[3] They are also crucial building blocks in the synthesis of such cyclic π-conjugated oligopyrrolic systems as porphyrins,[4] corroles,[5] texaphyrins,[6] sapphyrins,[7] and chlorins,[8] amongst others.[9] As a consequence, many synthetic methods are known for the construction of the pyrrole ring.[10] Such methods range from classical Knorr[11] and Paal–Knorr[12] strategies to modern multicomponent protocols.[13]

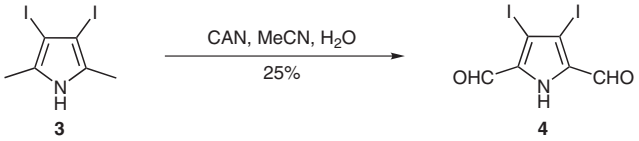
During the development of new methods for the synthesis of 'locked chlorins' we found that 2,5-dimethylpyrroles bearing ester groups at positions 3 and 4 can be selectively oxidized to the corresponding 2,5-diformylpyrroles (Scheme 1).[14] The model compound **1** was tested with a variety of reagents [PbO_2/$Pb(OAc)_4$,[15] $Pb(OAc)_4$,[16] 2-iodoxybenzoic acid (IBX) and PCC] and it was found that the only reagent capable of oxidizing **1** to dialdehyde **2** was cerium(IV) ammonium nitrate (CAN).[17] In this case, extensive modifications had to be made to the existing procedure in order to obtain an acceptable yield.



Scheme 1

The potentially broad application of 2,5-diformylpyrrole and its substituted derivatives prompted us to study the transformation of 2,5-dialkylpyrrole derivatives into formylpyrroles under various conditions in greater details. Here we report the results of this study.

We started our investigation by studying the oxidation of readily available 3,4-diiodo-2,5-dimethylpyrrole (**3**),[18] since its successful oxidation to the corresponding dialdehyde would lead to richly functionalized compounds, which are otherwise difficult to prepare.[19] We were pleased to find that subjecting **3** to optimized[14a] reaction conditions led to the expected aldehyde **4** in 25% yield (Scheme 2). The presence of iodine atoms in the starting pyrrole **3** did not interfere with the outcome of the studied reaction.



Scheme 2

Oxidation of either 2,5-dimethylpyrrole itself or 2,5-dimethyl-1-benzylpyrrole (**12**) led to the formation of intractable black mixtures. We hypothesized that, for the oxidation to be successful, either at least one electron-withdrawing group has to be present in the structure of the substrate, or positions 3 and 4 have to be blocked. We decided to introduce electron-withdrawing N-protecting tosyl, mesyl and benzoyl groups. Interestingly, some of these simple compounds (i.e. **7** and **8**) are unknown. All attempts to obtain them via simple acylation of 2,5-dimethylpyrrole using general procedures[20] failed. Consequently, ring-closure with amides instead of ammonia was considered as an option. The reported reaction of benzamide with 2,5-dimethoxytetrahydrofuran leads to *N*-benzoylpyrrole,[21] however, the same approach with a combination of hexane-2,5-dione and sulfonamides, failed. When the reaction was conducted with acetal **6** instead of diketone **5** (hexane-2,5-dione was transformed into its bis-acetal **6** according to a modified literature procedure),[22] and $TosNH_2$ in the presence of P_2O_5,[23] compound **7** was obtained (Scheme 3). Following the same approach, *N*-Ms-pyrrole **8** and *N*-Bz-pyrrole **13** were also obtained. We were delighted to find that the reaction of pyrrole **7** with CAN in aqueous acetonitrile led to the for-

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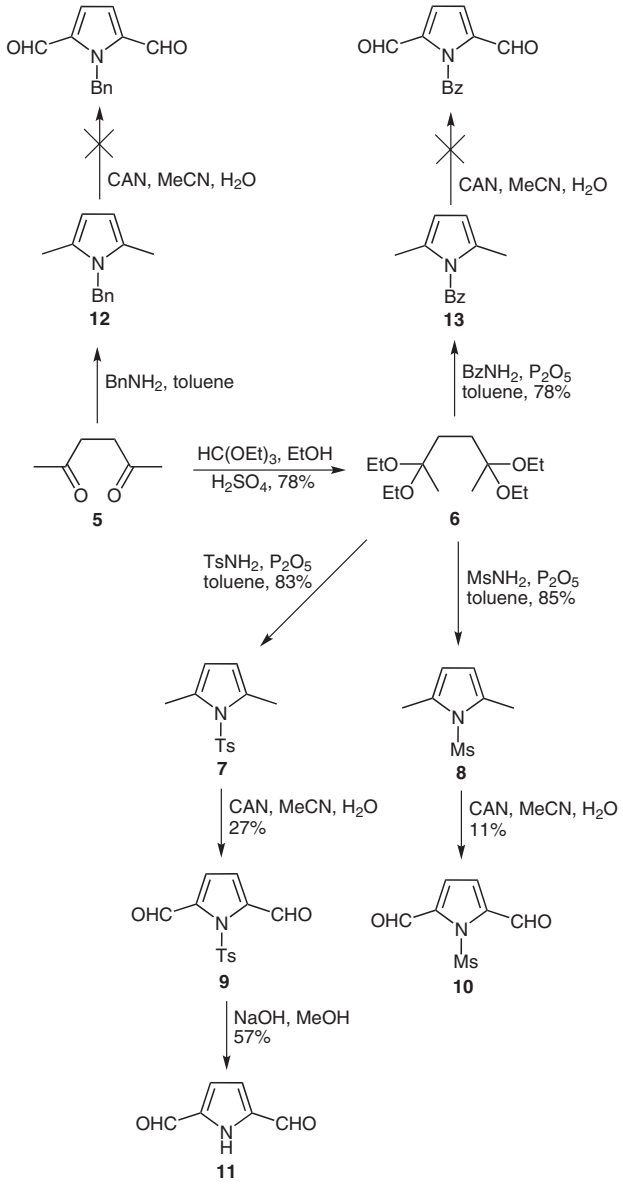
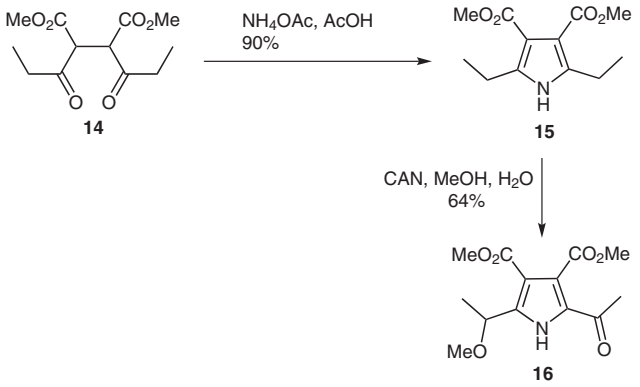
mation of the corresponding dialdehyde **9** in 27% yield (Scheme 3). Subsequently, according to a known procedure,[24] the tosyl group was removed from **9** to give 2,5-diformylpyrrole (**11**). Overall, this sequence of reactions constitutes an alternative[25] four-step route to this valuable building block. The oxidation of compound **8** also led to the desired product **10** in 11% yield, however, in the case of derivative **13**, the oxidation reaction led to a complex and intractable mixture of products.



Scheme 3

Since further advances in the methodology of chlorin synthesis relies strongly on the availability of specifically functionalized pyrrole building blocks, an extension of this study to the synthesis of more complex 2,5-diacylpyrroles was attempted. We thus focused on the synthesis of pyrrole derivative **15**, bearing two ethyl groups in positions 2 and 5 (Scheme 4). The classical Paal–Knorr method was chosen as a means to form the pyrrole ring since it worked well for the synthesis of analogous compound **1**. 1,4-Diketone **14** (readily available from ethyl propionylacetate)[26] was reacted with ammonium acetate, which led to the formation of pyrrole **15**. The CAN-mediated oxidation of **15** in either acetonitrile or acetic acid gave intractable mixtures of compounds, whereas, changing the solvent to methanol led to the clean formation of keto ether **16** (64% yield) rather than the expected diketone. The use of other oxidants [PCC, IBX, $Pb(OAc)_4$ and CrO_3] also failed to give the desired diketone.

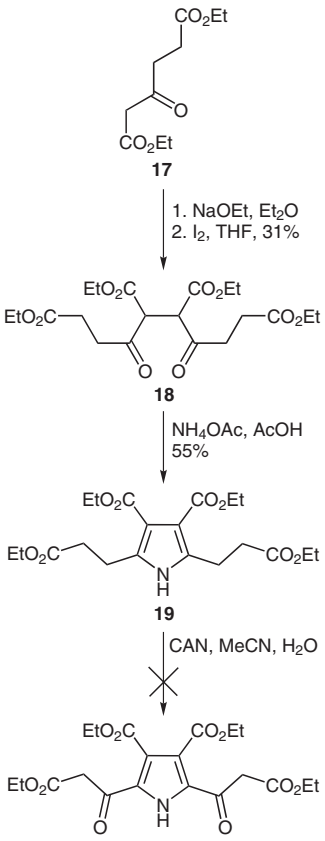


Scheme 4

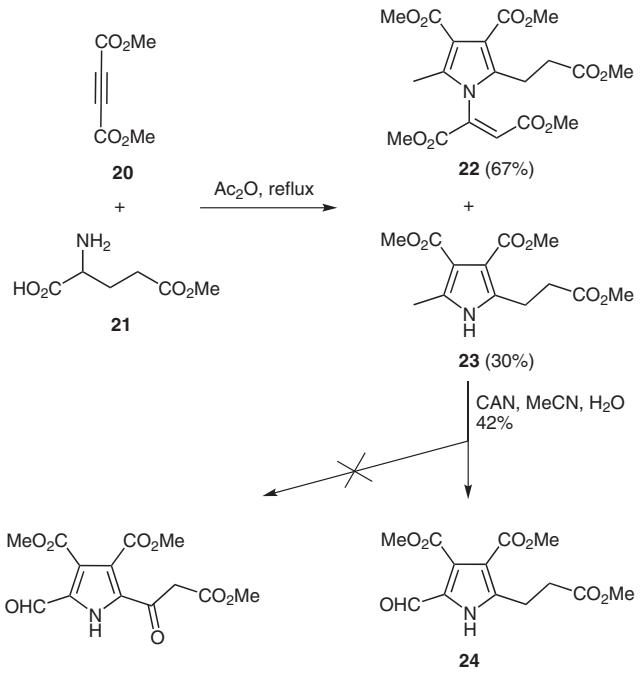
Although we failed to obtain the diacyl pyrrole, we decided to prepare the more elaborated derivative **19**, which would potentially allow access to an interesting building block relevant to chlorin chemistry (Scheme 5). The starting diester **17** was prepared via acylation of Meldrum acid with the respective acid chloride.[27] Oxidative dimerization followed by reaction with ammonium acetate afforded tetraester **19**. Surprisingly, all attempts at oxidizing this compound to the corresponding diketone or keto ether under a wide range of reaction conditions, failed.

We were especially keen to obtain the keto aldehyde presented in Scheme 6. According to our strategy, the required substrate would be triester **23**. In order to install this necessary pyrrole building block in an concise fashion, we took advantage of the Huisgen 1,3-dipolar cycloaddition of azlactones to esters of acetylenedicarboxylic acid.[28] Using this cascade reaction, pyrrole **23** could, in principle, be synthesized from the commercially available monoester of glutamic acid and acetic anhydride. To our delight, and in analogy to previous results,[14b] the exposure of amino acid **21** to acetic anhydride in the presence of two equivalents of dimethyl acetylenedicarboxylate, furnished the expected pyrrole **23** together with Michael adduct **22** (Scheme 6). Unfortunately, subsequent oxidation of **23** in acetonitrile gave only mono-aldehyde **24**, which could not be oxidized further to the corresponding keto aldehyde.

In conclusion, we have performed a comprehensive study of the oxidation of variously substituted pyrrole derivatives with cerium(IV) ammonium nitrate. The most notable synthetic findings are as follows: (1) hexane-2,5-dione can be easily transformed into 2,5-diformylpyrrole with



Scheme 5



Scheme 6

CAN-mediated oxidation as the crucial step; (2) 2,5-dimethylpyrrole derivatives, protected on the nitrogen atom with sulfonyl groups, are oxidized to the corresponding dialdehydes in moderate yields; (3) the presence of electron-withdrawing group(s) is a prerequisite for obtaining high yields of carbonyl compounds in CAN-mediated oxidations of alkyl pyrroles; (4) oxidation of pyrrole derivatives bearing alkyl groups other than methyl in positions 2 and 5 does not lead to the corresponding diketone but rather to keto ethers; (5) the outcome of this oxidation strongly depend both on the functional groups present and the details of the reaction conditions. This study opens the way to a variety of complex pyrrole-derived aldehydes and ketones that can be used in materials or medicinal chemistry.

All chemicals were used as received unless otherwise noted. Reagent grade solvents (MeCN, CH_2Cl_2, hexanes, toluene) were distilled prior to use. All reported NMR spectra were recorded on 400 MHz or 500 MHz spectrometers unless otherwise noted. Chemical shifts (δ, ppm) were determined with TMS as the internal reference; *J* values are given in Hz. UV/Vis absorption spectra were recorded in THF. Chromatography was performed on silica (Kieselgel 60, 200–400 mesh). Mass spectra were obtained via EI MS (70 eV) using an AMD-604 Intectra instrument. The following compounds were prepared as described in the literature: **3**,[18] **12**,[29] **14**,[26] and **17**.[27]

2,2,5,5-Tetraethoxyhexane (6)

To the stirred mixture of hexane-2,5-dione (30 mL, 0.25 mol) and $HC(OEt)_3$ (100 mL, 0.6 mol) in EtOH (70 mL), concd H_2SO_4 (2 drops) was added. Initially the temperature was kept below 30 °C by intermittent cooling in ice water. After 5 d stirring at r.t., the reaction mixture was stirred with Na_2CO_3 (2 g) for 0.5 h and then heated to reflux and filtered. The resulting mixture was boiled with activated carbon to remove color impurities. The solvent was removed under reduced pressure and the residue was recrystallized from hexanes. Spectral and physical properties concurred with published data.[22]

Yield: 50.87 g (78%); crystalline; mp 63 °C.

N-Substituted 2,5-Dimethylpyrroles from Sulfonamides; General Procedure (GP1)

To a stirred suspension of P_2O_2 (10 mmol, 1.42 g) and sulfonamide (10 mmol) in anhydrous toluene (40 mL), kept at r.t. under argon, 2,2,5,5-tetraethoxyhexane (**6**; 12 mmol, 3.15 g) was added. The reaction mixture was subsequently stirred at 110 °C in a preheated bath for 20 min and then quenched with aq KOH (2 N, 10 mL). The reaction mixture was cooled to r.t., diluted with H_2O (50 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O (2 × 20 mL) and brine (1 × 10 mL), and dried over $MgSO_4$. The solvent was removed under reeduced pressure. The purification details are described for each case below.

N-Tosyl-2,5-dimethylpyrrole (7)

The residue from GP1 was purified by chromatography on a short silica column (CH_2Cl_2–hexanes, 1:4).

Yield: 2.06 g (83%); colorless crystals; mp 79–80 °C (CH_2Cl_2–hexanes); R_f = 0.4 (CH_2Cl_2–hexanes, 1:3).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.38 (s, 6 H, CH_3), 2.40 (s, 3 H, CH_3), 5.83 (s, 2 H, CH), 7.27 (m, 2 H, ArH), 7.55 (m, 2 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.5, 21.5, 111.6, 126.1, 130.0, 132.3, 137.6, 144.3.

HRMS-EI: *m*/*z* calcd for $C_{13}H_{15}NO_2S^+$: 249.0824; found: 249.0832.

Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06; N, 5.62. Found: C, 62.81; H, 6.09; N, 5.59.

N-Mesyl-2,5-dimethylpyrrole (8)

The residue from GP1 was subjected to column chromatography using a short silica column (7 cm; CH_2Cl_2–hexanes, 2:3). The collected product was recrystallized (CH_2Cl_2–hexanes).

Yield: 1.472 g (85%); pale-yellow crystals; mp 76.5–77 °C (CH_2Cl_2–hexanes); R_f = 0.3 (CH_2Cl_2–hexanes, 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.40 (s, 6 H, CH_3), 3.04 (s, 3 H, CH_3), 5.88 (s, 2 H, CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.4, 42.3, 111.7, 131.6.

HRMS-EI: *m/z* calcd for $C_7H_{11}NO_2S^+$: 173.0511; found: 173.0507.

Anal. Calcd for $C_7H_{11}NO_2S$: C, 48.53; H, 6.40; N, 8.09. Found: C, 48.53; H, 6.34; N, 8.06.

N-Benzoyl-2,5-dimethylpyrrole (13)

The residue mixture from GP1 was purified by chromatography on a short silica column (CH_2Cl_2–hexanes, 1:3) to give the title compound. Spectral and physical properties concurred with published data.[30]

Yield: 2.06 g (83%).

2,5-Diformylpyrroles via CAN-Mediated Oxidation; General Procedure (GP2)

2,5-Dimethylpyrrole derivative (3 mmol) was dissolved in MeCN (90 mL) and H_2O (15 mL) was added. After addition of CAN (22.2 mmol, 12.2 g), the reaction was gently refluxed for 3 h (reaction monitored by TLC). The purification details are described for each case below.

3,4-Diiodo-2,5-diformylpyrrole (4)

After cooling the reaction mixture from GP2 to r.t., two layers formed, along with a yellow precipitate. The solid was filtered off (virtually pure product) and the supernatant was concentrated under vacuum, washed with H_2O (50 mL), extracted with EtOAc (3 × 30 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was combined with the first portion of product and recrystallized (acetone–hexanes) to afford the title compound. Spectral and physical properties concurred with published data.[19]

Yield: 776 mg (25%); pale-yellow crystals; mp 270 °C (dec.).

MS-EI: *m/z* calcd for $C_6H_3I_2NO_2^+$: 374.8; found: 375.0.

N-Tosyl-2,5-diformylpyrrole (9)

The reaction mixture from GP2 was cooled to r.t., concentrated under vacuum, washed with H_2O (50 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with H_2O (2 × 20 mL), brine (10 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to chromatography on a short silica column (CH_2Cl_2–hexanes, 2:1).

Yield: 225 mg (27%); colorless crystals; mp 125–128 °C (CH_2Cl_2–hexanes); R_f = 0.4 (CH_2Cl_2–hexanes, 2:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 7.12 (s, 2 H, CH), 7.36 (d, *J* = 8.4 Hz, 2 H, ArH), 7.76 (d, *J* = 8.4 Hz, 2 H, ArH), 10.38 (s, 2 H, CHO).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7, 120.7, 127.0, 130.6, 135.0, 138.0, 146.8, 181.2.

HRMS-EI: *m/z* calcd for $C_{13}H_{11}NO_4S^+$: 277.0409; found: 277.0412.

Anal. Calcd for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05. Found: C, 56.55; H, 4.21; N, 5.06.

2,5-Diformylpyrrole (11)

N-Tosyl-2,5-diformylpyrrole (**9**; 1 mmol, 277 mg) was dissolved in a solution of KOH in MeOH (2 M, 13 mL) and H_2O (0.5 mL) was added. The reaction mixture was stirred for 2 h, diluted with H_2O (40 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with H_2O (2 × 20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to chromatography on a short silica column (CH_2Cl_2–hexanes, 2:1) to afford the pure product. Spectral and physical properties concurred with published data.[25]

Yield: 70 mg (57%); colorless crystals.

N-Mesyl-2,5-diformylpyrrole (10)

After cooling to r.t., the reaction mixture from GP2 was concentrated under vacuum, diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with H_2O (2 × 20 mL), brine (10 mL), and dried over $MgSO_4$. The solution was concentrated under vacuum and purified by chromatography on silica (CH_2Cl_2).

Yield: 66 mg (11%); mp 105–106 °C (CH_2Cl_2–hexanes); R_f = 0.4 (CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.79 (s, 3 H, CH_3), 7.16 (s, 2 H, CH), 10.05 (s, 2 H, CHO).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 44.2, 122.3, 139.0, 180.5.

HRMS-EI: *m/z* calcd for $C_7H_7NO_4S^+$: 201.0096; found: 201.0102.

Anal. Calcd for $C_7H_7NO_4S$: C, 41.79; H, 3.51; N, 6.96. Found: C, 41.62; H, 3.43; N, 6.86.

Dimethyl 2,5-Diethylpyrrole-3,4-dicarboxylate (15)

Dimethyl 2,3-dipropionylsuccinate (**14**; 15.9 mmol, 3.8 g) and NH_4OAc (318 mmol, 22.7 g) were dissolved in AcOH (100 mL) and stirred at 25 °C for 20 h. Subsequently, AcOH was evaporated and H_2O (50 mL) was added to the residue. The suspension was extracted with CH_2Cl_2 (2 × 30 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed to afford the pure product.

Yield: 3.17 g (90%); mp 78–80 °C.

IR (KBr): 110, 1224, 1443, 1441, 1675, 1705, 2968, 3296 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.2 (t, *J* = 7.6 Hz, 6 H, 2 × CH_3CH_2), 2.78 (q, *J* = 7.6 Hz, 4 H, 2 × CH_3CH_2), 3.80 (s, 6 H, 2 × CH_3), 8.50 (br s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8, 20.0, 51.3, 111.3, 138.0, 165.9.

HRMS (EI): *m/z* [M^+] calcd for $C_{12}H_7NO_4$: 239.1158; found: 239.1150.

Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.10; N, 5.85. Found: C, 60.08; H, 7.18; N, 5.73.

Dimethyl 2-Acetyl-5-(1-methoxyethyl)pyrrole-3,4-dicarboxylate (16)

Dimethyl 2,5-diethylpyrrole-3,4-dicarboxylate (**15**; 1 mmol, 239 mg) was dissolved in a mixture of MeOH (5 mL) and H_2O (13 mL). CAN (10 mmol, 5.48 g) was added and the resulting mixture was stirred at r.t. for 3 h. H_2O (200 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed with H_2O (10 mL), dried (Na_2SO_4), concentrated and purified by column chromatography (hexanes–EtOAc, 3:2) to afford the pure product.

Yield: 180 mg (64%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 6.3 Hz, 3 H, CH_3CH), 2.40 (s, 3 H, CH_3O), 3.35 (s, 3 H, CH_3CO), 3.83 (s, 3 H, CH_3CO_2), 3.97 (s, 3 H, CH_3CO_2), 4.96 (q, *J* = 6.3 Hz, 1 H, CH_3CH), 9.67 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.5, 26.4, 51.7, 53.0, 57.6, 72.7, 111.3, 127.3, 144.7, 163.2, 166.6, 187.2.

HRMS (EI): *m/z* [M^+] calcd for $C_{13}H_{17}NO_6$: 283.1056; found: 283.1138.

Diethyl 5,6-Bis-ethoxycarbonyl-4,7-dioxodecanedioate (18)
Sodium metal (61 mmol, 1.4 g) was reacted with EtOH (20 mL) and diethyl 3-oxoadipate (**17**; 61 mmol, 13.2 mL) was added. The reaction mixture was stirred for 1 h, then EtOH was removed in vacuum, the residue was suspended in anhydrous Et_2O (70 mL) and a solution of I_2 (30.5 mol, 7.78 g) in anhydrous THF (30 mL) was added dropwise with vigorous stirring until the reaction mixture started to become purple. The reaction mixture was filtered and solvent was evaporated. Crystallization of the residue (EtOAc–hexanes) afforded pure product.

Yield: 5.35 g (31%); white crystals.

IR (KBr): 1185, 1295, 1267, 1379, 1713, 1723, 1736, 2992, 3449 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.1 Hz, 6 H, 2 × C*H*$_3$CH$_2$), 1.26 (t, *J* = 7.1 Hz, 6 H, 2 × C*H*$_3$CH$_2$), 2.50–2.56 (m, 2 H, 2 × CHHCH$_2$), 2.59–2.65 (m, 2 H, 2 × CHHCH$_2$), 2.95–3.01 (m, 2 H, 2 × CH$_2$CHH), 3.25–3.31 (m, 2 H, 2 × CH$_2$CHH), 4.12 (q, *J* = 7.1 Hz, 4 H, 2 × CH$_3$C*H*$_2$CO$_2$), 4.16 (q, *J* = 7.1 Hz, 4 H, 2 × CH$_3$C*H*$_2$CO$_2$), 4.51 (s, 2 H, 2 × CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 14.1, 27.9, 38.2, 57.1, 60.6, 62.2, 166.8, 172.1, 201.8.

HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{20}H_{30}O_{10}Na$: 453.1731; found: 453.1750.

Anal. Calcd for $C_{20}H_{30}O_{10}$: C, 55.81; H, 7.02. Found: C, 55.13; H, 6.98.

Diethyl 2,5-Bis(2-ethoxycarbonylethyl)pyrrole-3,4-dicarboxylate (19)
Diethyl 5,6-bis-ethoxycarbonyl-4,7-dioxodecanedioate (**18**; 6.65 mmol, 2.86 g) and NH_4OAc (133 mmol, 10 g) were dissolved in AcOH (50 mL) and stirred at 25 °C for 20 h. Subsequently, AcOH was evaporated and H_2O (50 mL) was added to the residue. The suspension was extracted with CH_2Cl_2 (2 × 30 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated to directly obtain the pure product.

Yield: 1.5 g (55%).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.0 Hz, 6 H, 2 × C*H*$_3$CH$_2$), 1.32 (t, *J* = 7.2 Hz, 6 H, 2 × C*H*$_3$CH$_2$), 2.65 (t, *J* = 6.2 Hz, 4 H, 2 × CH$_2$CH$_2$), 3.04 (t, *J* = 6.2 Hz, 4 H, 2 × CH$_2$CH$_2$), 4.12 (q, *J* = 7.2 Hz, 4 H, 2 × CH$_3$C*H*$_2$CO$_2$), 4.16 (q, *J* = 7.0 Hz, 4 H, 2 × CH$_3$C*H*$_2$CO$_2$), 9.41 (br s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.5, 14.2, 21.2, 33.8, 60.1, 60.8, 112.4, 135.1, 165.2, 173.8.

HRMS (EI): *m/z* [M^+] calcd for $C_{20}H_{29}NO_8$: 411.1893; found: 411.1878.

Dimethyl 2-(2-Methoxycarbonylethyl)-5-methylpyrrole-3,4-dicarboxylate (23)
L-Glutamic acid 5-monomethyl ester (**21**; 4.83 g, 30 mmol) was suspended in Ac_2O (30 mL), and dimethyl acetylenedicarboxylate (**20**; 60 mmol, 7.3 mL) was added. The reaction mixture was stirred at 140 °C for 1 h, then concentrated and purified by column chromatography (silica; CH_2Cl_2–MeOH, 100:0→99:1→98:2) to afford the pure desired product **23** and the by-product **22**.

Yield: 2.58 g (30%); yellowish oil.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.36 (s, 3 H, CH_3), 2.68 (t, *J* = 6.6 Hz, 2 H, CH_2CH_2), 3.03 (t, *J* = 6.6 Hz, 2 H, CH_2CH_2), 3.69 (s, 3 H, CH_3CO_2), 3.80 (s, 6 H, 2 × CH_3CO_2), 9.08 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.4, 20.9, 33.5, 51.7, 52.8, 53.5, 113.3, 131.6, 134.3, 135.1, 136.5, 165.5, 165.7, 175.1.

HRMS (EI): *m/z* [M^+] calcd for $C_{13}H_{17}NO_6$: 283.1056; found: 283.1049.

22
Yield: 8.48 g (67%); yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, CH_3), 2.52 (t, *J* = 7.8 Hz, 2 H, CH_2CH_2), 2.87 (t, *J* = 7.8 Hz, 2 H, CH_2CH_2), 3.64 (s, 3 H, CH_3CO_2), 3.68 (s, 3 H, CH_3CO_2), 3.81 (s, 3 H, CH_3CO_2), 3.82 (s, 3 H, CH_3CO_2), 3.86 (s, 3 H, CH_3CO_2), 7.39 (s, 1 H, C=CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.1, 21.0, 33.3, 51.5, 51.7, 52.8, 53.4, 53.7, 113.6, 129.0, 131.5, 134.2, 135.3, 136.8, 162.4, 162.7, 165.1, 165.5, 172.8.

HRMS (EI): *m/z* [M^+] calcd for $C_{19}H_{23}NO_{10}$: 425.1322; found: 425.1328.

Dimethyl 2-Formyl-5-(2-methoxycarbonylethyl)pyrrole-3,4-dicarboxylate (24)
Dimethyl 2-(2-methoxycarbonylethyl)-5-methylpyrrole-3,4-dicarboxylate (**23**; 1 mmol, 283 mg) was dissolved in a mixture of MeOH (20 mL) and H_2O (10 mL). CAN (8.2 mmol, 4.5 g) was added and the resulting mixture was stirred at r.t. for 3 h. Subsequently, H_2O (200 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed with H_2O (10 mL), dried (Na_2SO_4) and concentrated. Column chromatography (silica; CH_2Cl_2–EtOAc, 9:1) afforded the pure product.

Yield: 125 mg (42%); yellowish oil.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.74 (t, *J* = 6.3 Hz, 2 H, CH_2CH_2), 3.21 (t, *J* = 6.3 Hz, 2 H, CH_2CH_2), 3.70 (s, 3 H, CH_3CO_2), 3.84 (s, 3 H, CH_3CO_2), 3.92 (s, 3 H, CH_3CO_2), 9.78 (s, 1 H, CHO), 9.08 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6, 32.8, 51.8, 52.2, 52.5, 114.5, 124.4, 130.3, 142.2, 163.9, 173.8, 179.8, 200.1.

HRMS (EI): *m/z* [M^+] calcd for $C_{13}H_{15}NO_7$: 297.0849; found: 297.0831.

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