JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b01298 • Publication Date (Web): 22 Jun 2016

Just Accepted

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

A Route to 2-Substituted 3-Cyanopyrroles: Synthesis of Danaidal and Suffrutine A

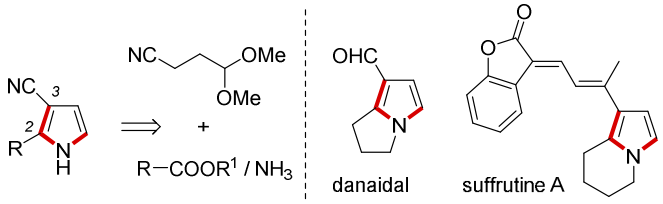
Johannes M. Wiest, Thorsten Bach*

Department Chemie and Catalysis Research Center (CRC), Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany

Corresponding Author

*Email: thorsten.bach@ch.tum.de

ABSTRACT

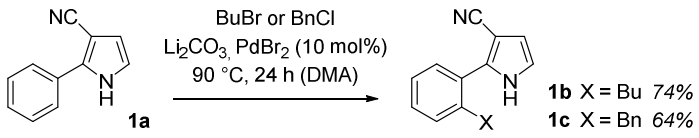


The title compounds were prepared in a two-step sequence from 4,4-dimethoxybutyronitrile and the respective esters by Claisen condensation and subsequent Paal-Knorr pyrrole synthesis. The sequence could be performed as one-pot procedure delivering the pyrroles in yields of 47-72% over two steps (13 examples). Intramolecular variants of the method were applied to the total synthesis of danaidal and suffrutine A from the respective trityl-protected ω-amino alkanoates.

In 1932, Strain reported the first synthesis of a mono-2-substituted 3-cyanopyrrole from cyanoacetone, ammonia, and 1,2-dichloroethyl methyl ether.[1] Like some previously synthesized

compounds of this class, which contained additional substituents in 4- and 5-position,[2] the compound was found to behave neither like a typical pyrrole nor like a typical nitrile. Indeed, the conjugation of the cyano group renders 3-cyanopyrroles remarkably stable towards oxidation and they have played an important role in pyrrole chemistry as testified by several reports on their synthesis.[3,4] We became interested in the compound class in connection with our work on the Pd-catalyzed alkylation of 2-phenylpyrroles.[5] It was found that the respective 3-cyanopyrroles such as **1a** can be selectively monoalkylated upon Pd catalysis delivering products such as **1b** and **1c** in good yields (Scheme 1). The pyrrole ring serves as directing group which allows for selective palladation in *ortho*-position of the benzene ring. The remarkable fact that a single but no double alkylation was observed is due to the substituent in 3-position, which avoids rotation around the phenyl-pyrrol bond after the first alkylation has occurred.

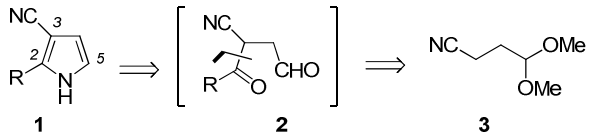
SCHEME 1. Pd-Catalyzed Alkylation of 3-Cyano-2-phenylpyrrole (**1a**).



Although the synthesis of compound **1a** was feasible by known procedures[3b-c,3h] we found the published procedures on the synthesis of 2-substituted 3-cyanopyrroles less concise and less general than desirable for the preparation of this compound class. We therefore searched for an alternative to their synthesis and found a convenient one-pot procedure, which allows the introduction of the pyrrole C2 carbon atom and the 2-substituent from the respective alkanoate. The results are disclosed in this manuscript and applications to the synthesis of danaidal[6,7] and to the first synthesis of suffrutine A[8] are described.

Inspired by a patent publication, according to which *N*-hydroxypyrroles were prepared from the Claisen condensation products of halogenated benzoates and 4,4-dimethoxybutyronitrile (three examples),[9] we considered a disconnection of pyrroles **1** in the spirit of a Paal-Knorr synthesis leading to γ-ketoaldehyde **2** or a derivative thereof (Scheme 2). Following a Claisen disconnection, 4,4-dimethoxybutyronitrile (**3**) emerged as a precursor for the cyano group at C3 and for carbon atoms C3-C5 within the pyrrole ring.

SCHEME 2. Retrosynthetic Analysis Leading via a Putative 1,4-Dicarbonyl Compound **2** to Nitrile **3** as Starting Material

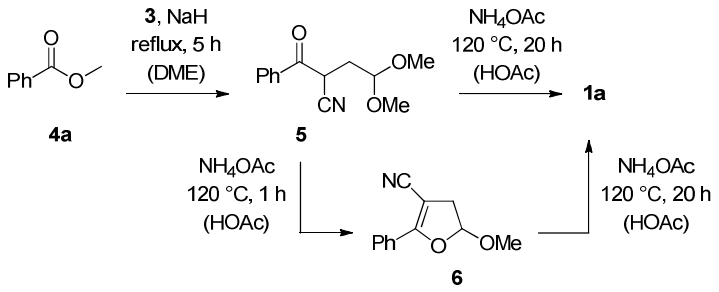


1 **2** **3**

Initial studies towards the Claisen condensation of nitrile **3** and an alkanoate were performed with methyl benzoate (**4a**) and revealed that sodium hydride (3 equiv.) is a suitable base for this transformation. The choice of solvent was crucial for the success of the reaction and 1,2-dimethoxyethane (DME) was found to be the superior choice. Apolar solvents such as toluene did not produce the desired condensation product while DME enabled the formation of product **5** within five hours at reflux employing an equimolar ratio of **3** and **4a** (Scheme 3). Gratifyingly, the desired Paal-Knorr condensation to product **1a** could be induced by heating intermediate **5** in a solution of ammonium acetate (20 equiv.) in acetic acid for 20 hours at 120 °C. Aldehyde **2** was not detected as an intermediate but its cyclic enol acetal **6** could be isolated if the reaction was stopped after one hour. The isolated acetal **6** underwent the conversion to pyrrole **1a** if subjected

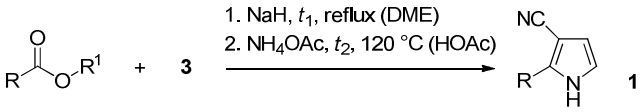
to the reaction conditions of the Paal-Knorr reaction and is thus a likely intermediate in the conversion **5** → **1a**.

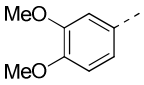
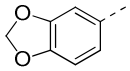
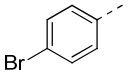
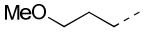
SCHEME 3. Optimization of the Two-step Protocol for the Synthesis of Pyrrole **1a** from Methyl Benzoate (**4a**) via Intermediates **5** and **6**.



It was found that the conversion of **4a** to **1a** could be performed in one reaction flask without purification of intermediate **5**. Once TLC analysis indicated full conversion in the first step, the solvent was removed under reduced pressure and the second set of reagents was added. The reaction mixture was kept at 120 °C until the formation of pyrrole **1a** was complete. Following this precedence several other pyrroles **1** were prepared from 4,4-dimethoxybutyronitrile (**3**) and the respective esters (Table 1). The choice of ester (methyl vs. ethyl) was determined by its commercial availability and volatility. All aryl esters which were tested (entries 2-6) gave moderate to good yields (54-70%) in the one-pot protocol. In the aliphatic series (entries 7-13), alkanoates with a primary or secondary alkyl group R reacted smoothly while the reaction of methyl pivaloate (entry 11) turned out to be sluggish. The conversion in the Claisen condensation could be improved if the reaction was performed in the higher boiling solvent diethoxyethane (DEE) but the overall yield remained moderate (47%).

TABLE 1. Formation of 2-Substituted 3-Cyanopyrroles **1** by Claisen Condensation and Subsequent Cyclization



entry	R	R^1	t_1 [h][a]	t_2 [h][a]	product	yield[b] [%]
1		Me	5	20	**1a**	64
2		Me	20	19	**1d**	66
3		Me	14	16	**1e**	64
4		Me	16	14	**1f**	70
5		Me	20	20	**1g**	69
6		Me	18	17	**1h**	54
7		Me	6	60	**1i**	65
8	Me	Me	12	16	**1j**	68
9	Et	Me	21	21	**1k**	65
10	^{i}Bu	Et	5	18	**1l**	54
11	^{t}Bu	Me	17[c]	120	**1m**	47
12		Et	14	20	**1n**	72
13		Me	17	13	**1o**	54

[a] Reaction time in the individual step until full conversion was reached. [b] Yield after two reaction steps. [c] The reaction was performed in 1,2-diethoxyethane (DEE) as the solvent.

Preliminary studies revealed that the method could also be applied to the synthesis of *N*-substituted pyrroles. When the primary Claisen product **5** (Scheme 2) was treated with benzyl amine instead of ammonium acetate, product **7** was obtained in 40% yield (Figure 1). Based on this observation, an easy access to the heterocyclic core of danaidal (**8**) and suffrutine A [(*E*,*E*)-**9**] seemed feasible if the Paal-Knorr reaction step was performed intramolecularly.[10]

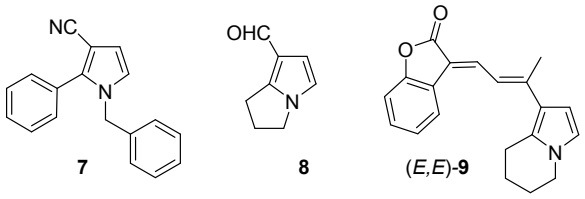
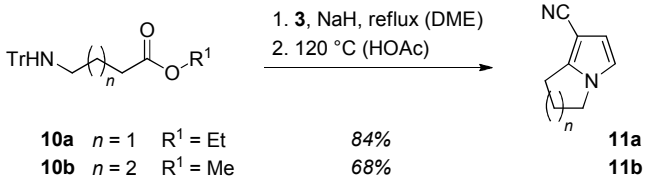


FIGURE 1. Structures of pyrrole **7**, of danaidal (**9**), and of suffrutine A [(*E*,*E*)-**9**]

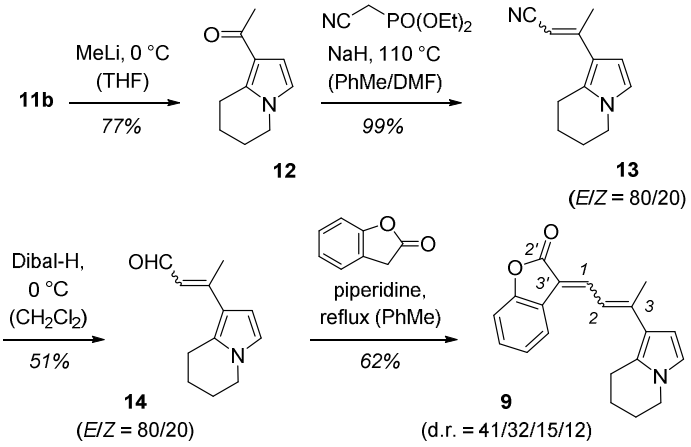
The required ω-amino alkanoates **10** for the synthesis of the indolizine and pyrrolizine ring were chosen to be protected as *N*-trityl (Tr) derivatives and were readily available from the respective amino acids.[11] As in the synthesis of pyrroles **1**, the reaction could be performed as a one-pot process. Trityl removal was facilitated under the acidic conditions of the second reaction step and delivered the free ammonium salts, which readily cyclized to products **11** (Scheme 4). The pheromone danaidal (**8**) was easily available from 3-cyano-2,3-dihydro-1*H*-pyrrolizine (**11a**) upon reduction with diisobutylaluminium hydride (Dibal-H) at 0 °C in CH_2Cl_2 (87%).

SCHEME 4. Synthesis of the Pyrrole Fragments of Danaidal and Suffrutine A



While danaidal has been a frequent synthetic target[7] the indolizidine alkaloids suffrutine A and suffrutine B have just recently been described and their total synthesis has not yet been reported. The compounds were isolated from the roots of *Flueggea suffruticosa* and were shown to promote Neuro-2a cell differentiation.[8] The compounds were found to be interconvertible upon irradiation with light. In our synthetic approach to the suffrutines, nitrile **11b** was treated with methyl lithium to generate methyl ketone **12** in a yield of 77% (Scheme 5).[12] Horner-Wadsworth-Emmons reaction with diethyl cyanomethylphosphonate delivered quantitatively nitrile **13**, which was obtained as a mixture of (*E*)- and (*Z*)-isomers. The compounds were separable at this stage but were prone to rapid *E*/*Z*-isomerization upon storage. The diastereomeric mixture was reduced with Dibal-H to aldehyde **14**, which was obtained as an *E*/*Z*-mixture with similar composition (*E*/*Z* = 80/20) as the nitrile. In this instance, a separation by column chromatography could not be achieved, which is why aldehyde **14** was taken as an *E*/*Z*-mixture into the Knoevenagel condensation with 2-coumaranone.

SCHEME 5. Synthesis of Suffrutine A and its Diastereoisomers (**9**) from 5,6,7,8-Tetrahydroindolizine **11b**.



Product **9** was obtained as a mixture of four diastereoisomers in a ratio of 41/32/15/12. The major components could be separated in the dark and suffrutine A could be obtained cleanly as the respective isomer (*E*,*E*)-**9**. All analytical data of this compound were identical to the reported data of the natural product.[8] The second isolated major component exhibits a different configuration at the double bond between the benzofuran-2(3*H*)-one carbon atom C3' and carbon atom C1 of the butenylidene bridge and it could be identified as (*Z*,*E*)-**9**, suffrutine B, although its spectra were not a clean as the spectra of suffrutine A. The minor components could not be separated but there is evidence (same molecular mass, similar UV/vis spectra) for them to be isomers of suffrutines A and B and they are tentatively assigned the structure (*E*,*Z*)-**9** and (*Z*,*Z*)-**9**. Upon standing at day light, isomerization of suffrutines A and B was observed, which was not only a mutual interconversion but indicated also the formation of compounds (*E*,*Z*)-**9** and (*Z*,*Z*)-**9** (see Supporting Information for further details).

CONCLUSION

In summary, a concise route to 2-substituted 3-cyanopyrroles was developed, which can potentially be expanded to the synthesis of *N*-substituted pyrroles. The cyano group can be further elaborated as shown in the total syntheses of danaidal and suffrutine A. The method employs 4,4-dimethoxybutyronitrile as a C_4-building block and leaves consequently the 4- and the 5-position of the pyrrole unsubstituted and it is therefore envisaged to serve as a useful entry to 2,3-disubstituted pyrroles.

EXPERIMENTAL SECTION

General Methods:

Air and moisture sensitive reactions were carried out in oven-dried glassware sealed with rubber septa under a positive pressure of dry argon. Dry tetrahydrofuran (THF), dichloromethane (CH_2Cl_2) and diethyl ether (Et_2O) were obtained from a solvent purification system. Other dry solvents, e.g. methanol (MeOH), were obtained in the highest purity available stored over molecular sieves and were used without further purification. Analytical thin layer chromatography (TLC) was performed on silica gel 60 (F_{254}) glass plates. The TLC plates were visualized by either ultraviolet (UV) light (λ = 254 nm) or treatment with cerium ammonium molybdate (CAM) stain followed by gentle heating. Purification of products was accomplished by flash chromatography on silica gel 60 (230-400 mesh). All solvents for chromatography, e.g. ethyl acetate (EtOAc), were distilled prior to use. NMR spectra were measured on either a 300, or a 400 or a 500 MHz nuclear magnetic resonance spectrometer. The ^{1}H NMR spectra were calibrated against the residual solvent peak of chloroform (7.26 ppm), and the $^{13}C\{^{1}H\}$ NMR spectra were calibrated against the central peak of $CDCl_3$ (77.16 ppm). Data for ^{1}H NMR spectra were reported as follows: chemical shift in parts per million (ppm), peak shape, coupling constant in Hertz (Hz), and integration. Apparent multiplicity which occurs as a result of accidental equality of coupling constants to those of magnetically non-equivalent protons are marked as virtual (*virt.*); broad signals are marked as broad (*br.*). Infrared spectra were recorded by attenuated total reflection (ATR) technique and are reported as wave numbers $\tilde{\nu}$ (cm^{-1}). Mass spectra were measured with a mass selective quadrupole detector (EI, 70 eV) or with an ion trap mass spectrometer (ESI). HRMS data were determined at a double-focussing magnetic sector instrument (EI, 70 eV) or at a linear ion trap with a Fourier transform ion cyclotron resonance detector (ESI). All measured melting points (mp) are uncorrected.

General Procedure for the Synthesis of Pyrroles 1: NaH (300 mg, 7.50 mmol, 60% suspension in mineral oil, 3.0 equiv) was suspended in 1,2-dimethoxyethane (10 mL). 4,4-Dimethoxybutyronitrile (323 mg, 330 µL, 2.50 mmol, 1.0 equiv) was added and the reaction mixture heated to 90 °C. The appropriate ester (2.50 mmol, 1.0 equiv) was added *via* syringe and the heterogeneous solution refluxed under argon atmosphere until all starting material was consumed. The reaction mixture was cooled to room temperature, quenched with methanol, and all volatiles were removed under reduced pressure. NH_4OAc (3.86 g, 50.0 mmol, 20 equiv) and HOAc (10 mL) were added to the crude material and the mixture heated to 120 °C until full conversion was reached. The reaction mixture was diluted with EtOAc (150 mL) and neutralized with 2 M aqueous NaOH solution. The organic layer was washed with brine (50 mL), separated, dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Purification by flash chromatography (SiO_2, solvent, detection mode) gave the respective 3-cyanopyrroles.

2-Benzoyl-4,4-dimethoxybutanenitrile (5)

NaH (400 mg, 10.0 mmol, 60% suspension in mineral oil, 2.0 equiv) was suspended in 1,2-dimethoxyethane (20 mL). 4,4-Dimethoxybutyronitrile (776 mg, 782 µL, 6.00 mmol, 1.2 equiv) was added and the reaction mixture heated to 90 °C. Methyl benzoate (681 mg, 625 µL, 5.00 mmol, 1.0 equiv) was added *via* syringe and the heterogeneous solution refluxed under argon atmosphere for 5 h. The reaction mixture was cooled to room temperature, quenched with methanol, and all volatiles were removed under reduced pressure. The crude material was taken up in CH_2Cl_2 (150 mL) and washed with 0.01 M aq. HCl solution (150 mL) and brine (50 mL). The organic layer was separated, dried over Na_2SO_4, filtered and all volatiles were removed *in vacuo*. Purification by flash chromatography (SiO_2, pentane/Et_2O 4:1 to 3:1, UV) gave the product as a colorless liquid (980 mg, 4.20 mmol, 84%). TLC (pentane/Et_2O 3:1): R_f = 0.18

[UV]. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ = 2.25 (ddd, ^{2}J = 14.1 Hz, ^{3}J = 8.5, 4.3 Hz, 1H), 2.38 (ddd, ^{2}J = 14.1 Hz, ^{3}J = 6.5, 5.9 Hz, 1H), 3.34 (s, 3H), 3.43 (s, 3H), 4.54 (dd, ^{3}J = 8.5, 5.9 Hz, 1H), 4.57 (dd, ^{3}J = 6.5, 4.3 Hz, 1H), 7.50-7.57 (m, 2H), 7.62-7.69 (m, 1H), 7.96-8.02 (m, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 298 K) δ = 32.9 (t), 35.2 (d), 54.1 (q), 54.9 (q), 102.3 (d), 117.3 (s), 129.0 (d), 129.2 (d), 134.0 (s), 134.7 (d), 190.3 (s). IR (ATR): $\tilde{\nu}$ = 2940, 2835, 2249, 1696, 1449, 1231, 1126, 1074, 978, 697. MS (EI, 70 eV): *m/z* (%) = 201 (19), 170 (11), 105 (100), 77 (38). HRMS (EI, 70 eV): calcd for $C_{13}H_{14}O_3N^+$ $[(M–H)^+]$ = 232.0968; found = 232.0962.

5-Methoxy-2-phenyl-4,5-dihydrofuran-3-carbonitrile (6)

2-Benzoyl-4,4-dimethoxybutanenitrile (300 mg, 1.28 mmol, 1.0 equiv) was dissolved in acetic acid (2.0 mL) and stirred at 120 °C for 1 h. Acetic acid was removed under reduced pressure and the crude was taken up in CH_2Cl_2 (100 mL) and washed with saturated, aqueous Na_2CO_3 solution (100 mL) and brine (50 mL). The organic layer was separated, dried over Na_2SO_4, filtered and all volatiles removed under reduced pressure. Purification by flash chromatography (SiO_2, pentane/Et_2O 4:1, UV) gave the product (230 mg, 1.14 mmol, 89%) as a colorless liquid. TLC (pentane/Et_2O 3:1): R_f = 0.44 [UV]. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ = 2.90 (dd, ^{2}J = 16.1 Hz, ^{3}J = 2.6 Hz, 1H), 3.26 (dd, ^{2}J = 16.1 Hz, ^{3}J = 7.2 Hz, 1H), 3.56 (s, 3H), 5.66 (dd, ^{3}J = 7.2, 2.6 Hz, 1H), 7.40-7.55 (m, 3H), 7.91-8.02 (m, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 298 K) δ = 38.5 (t), 56.2 (q), 79.3 (s), 106.5 (d), 117.3 (s), 127.2 (d), 128.1 (s), 128.8 (d), 131.5 (d), 165.3 (s). IR (ATR): $\tilde{\nu}$ = 2937, 2207, 1623, 1355, 1219, 1091, 1072, 1009, 973, 890, 769, 689. MS (EI, 70 eV): *m/z* (%) = 201 (100), 170 (23), 140 (23), 105 (58), 77 (36). HRMS (EI, 70 eV): calcd for $C_{12}H_{11}NO_2^+$ $[M^+]$ = 201.0784; found = 201.0782.

2-Phenyl-1*H*-pyrrole-3-carbonitrile (1a)

Route A. 5-Methoxy-2-phenyl-4,5-dihydrofuran-3-carbonitrile (70.0 mg, 340 µmol, 1.0 equiv) was dissolved in acetic acid (1 mL). NH_4OAc (536 mg, 6.95 mmol, 20.0 equiv) was added and the solution stirred at 120 °C for 20 h. The reaction mixture was diluted with EtOAc (20 mL) and neutralized with 2 M aqueous NaOH solution (20 mL). The organic layer was washed with brine (10 mL), separated, dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. Purification by flash chromatography (SiO_2, pentane/Et_2O 2:1, UV) gave the product (49.0 mg, 291 µmol, 86%) as a colorless solid. **Route B.** Synthesized from methyl benzoate (341 mg, 316 µL, 2.50 mmol) according to the general procedure (Reaction times: 5 h and 20 h). Purification by flash chromatography (SiO_2, pentane/Et_2O 3:1 to 2:1, UV) gave the product as a colorless solid (271 mg, 1.61 mmol, 64%). TLC (pentane/Et_2O 2:1): R_f = 0.22 [UV]. mp: 145-147 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ = 6.56 (*virt.* t, $^3J \approx {}^4J$ = 2.8 Hz, 1H), 6.83 (dd, ^3J = 2.9, 2.7 Hz, 1H), 7.35-7.42 (m, 1H), 7.43-7.52 (m, 2H), 7.65-7.75 (m, 2H), 8.73 (*br.* s, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, 298 K) δ = 90.5 (s), 114.0 (d), 117.6 (s), 119.1 (d), 125.9 (d), 128.9 (d), 129.4 (d), 129.9 (s), 139.1 (s). The spectral data matched those reported in the literature.[3b]

2-(3,4-Dimethoxyphenyl)-1*H*-pyrrole-3-carbonitrile (1d)

Synthesized from methyl 3,4-dimethoxybenzoate (341 mg, 2.50 mmol) according to the general procedure (Reaction times: 20 h and 19 h). Purification by flash chromatography (SiO_2, 3% Et_2O in CH_2Cl_2, UV) gave the product as a colorless solid (377 mg, 1.65 mmol, 66%). TLC (SiO_2): R_f = 0.24 (3% Et_2O in CH_2Cl_2) [UV]. mp: 135-137 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 3.92 (s, 3H), 3.95 (s, 3H), 6.54 (dd, ^3J = 3.1 Hz, ^4J = 2.6 Hz, 1H), 6.78 (dd, ^3J = 3.1, 2.6 Hz, 1H), 6.94 (d, ^3J = 8.4 Hz, 1H), 7.17 (dd, ^3J = 8.4 Hz, ^4J = 2.2 Hz, 1H), 7.30 (d, ^4J = 2.2 Hz, 1H), 8.61

(*br*. s, 1H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$, 298 K): δ = 56.2 (q), 56.2 (q), 89.7 (s), 109.5 (d), 111.8 (d), 113.7 (d), 117.9 (s), 118.4 (d), 118.6 (d), 122.9 (s), 139.4 (s), 149.6 (s), 149.7 (s). IR (ATR): $\tilde{\nu}$ = 3322, 2215, 1516, 1468, 1255, 1229, 1146, 1023, 694. MS (EI, 70 eV): *m/z* (%) = 228 (100), 213 (48), 185 (55), 142 (22). HRMS (EI): calcd for $C_{13}H_{12}N_2O_2^+$ [M^+] = 228.0893; found = 228.0896.

2-(Thiophen-3-yl)-1*H*-pyrrole-3-carbonitrile (1e)

Synthesized from methyl thiophene-3-carboxylate (586 mg, 0.50 mL 4.12 mmol) according to the general procedure (Reaction times: 14 h in 15 mL DME and 16 h in 15 mL HOAc). Purification by flash chromatography (SiO_2, CH_2Cl_2, UV) gave the product as a red solid (456 mg, 1.65 mmol, 64%). TLC (pentane/Et_2O 1:1): R_f = 0.30 [UV]. mp: 124-126 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 6.51 (*virt.* t, $^{3}J \approx {}^{4}J$ = 2.8 Hz, 1H), 6.77 (*virt.* t, $^{3}J \approx$ 2.8 Hz, 1H), 7.44 (dd, ^{3}J = 5.1 Hz, ^{4}J = 2.8 Hz, 1H), 7.46 (dd, ^{3}J = 5.1 Hz, ^{4}J = 1.5 Hz, 1H), 7.69 (dd, ^{4}J = 2.8, 1.5 Hz, 1H), 8.65 (s, 1H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 298 K): δ = 90.0 (s), 113.3 (d), 117.7 (s), 118.5 (d), 121.9 (d), 124.9 (d), 127.4 (d), 130.8 (s), 135.2 (s). IR (ATR): $\tilde{\nu}$ = 3289, 3116, 2212, 860, 785, 684. MS (EI, 70 eV): *m/z* (%) = 174 (100), 147 (14). HRMS (EI): calcd for $C_9H_6N_2S^+$ [M^+] = 174.0246; found = 174.0246.

2-(Furan-2-yl)-1*H*-pyrrole-3-carbonitrile (1f)

Synthesized from methyl 2-furoate (315 mg, 267 µL, 2.50 mmol) according to the general procedure (Reaction times: 16 h and 14 h). Purification by flash chromatography (SiO_2, dry-loaded, pentane/Et_2O 3:1 to 2:1, UV) gave the product as a colorless solid (275 mg, 1.74 mmol, 70%). TLC (pentane/Et_2O 3:1): R_f = 0.17 [UV]. mp: 86-88 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 6.49 (*virt.* t, $^{3}J \approx {}^{4}J$ = 2.9 Hz, 1H), 6.53 (dd, ^{3}J = 3.5, 1.8 Hz, 1H), 6.77 (*virt.* t, ^{3}J =

2.8 Hz, 1H), 6.97 (dd, ^3J = 3.5 Hz, ^4J = 0.7 Hz, 1H), 7.43 (dd, ^3J = 1.8 Hz, ^4J = 0.7 Hz, 1H), 8.88 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, 298 K): δ = 88.6 (s), 107.6 (d), 112.4 (d), 113.0 (d), 116.8 (s), 118.7 (d), 130.8 (s), 142.0 (d), 144.6 (s). IR (ATR): $\tilde{\nu}$ = 3261, 3166, 2221, 1434, 995, 733. MS (EI, 70 eV): *m/z* (%) = 158 (100), 129 (65), 103 (18). HRMS (EI): calcd for $C_9H_6N_2O^+$ [M^+] = 158.0475; found = 158.0465.

2-(Pyridin-3-yl)-1*H*-pyrrole-3-carbonitrile (1g)

Synthesized from methyl nicotinate (378 mg, 341 µL, 2.50 mmol) according to the general procedure (Reaction times: 20 h and 20 h). Purification by flash chromatography (SiO_2, EtOAc, UV) gave the product as a colorless solid (292 mg, 1.74 mmol, 69%). TLC (EtOAc): R_f = 0.31 [UV]. mp: 163-165 °C. ^1H NMR (500 MHz, $CDCl_3$, 298 K): δ = 6.62 (*virt*. t, $^3J \approx {}^4J$ = 2.8 Hz, 1H), 6.92 (*virt*. t, ^3J = 2.8 Hz, 1H), 7.43 (ddd, ^3J = 8.1, 4.8 Hz, ^5J = 0.9 Hz, 1H), 8.15 (ddd, ^3J = 8.0 Hz, ^4J = 2.4, 1.6 Hz, 1H), 8.61 (dd, ^3J = 4.8 Hz, ^4J = 1.6 Hz, 1H), 8.87 (dd, ^4J = 2.4, 0.8 Hz, 1H), 9.37 (*br*. s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, 298 K): δ = 91.9 (s), 114.4 (d), 117.0 (s), 120.4 (d), 124.3 (d), 126.4 (s), 133.9 (d), 135.4 (s), 146.4 (d), 149.5 (d). IR (ATR): $\tilde{\nu}$ = 3106, 2216, 1496, 1471, 808, 733, 685. MS (EI, 70 eV): *m/z* (%) = 169 (100), 142 (18), 129 (10). HRMS (EI): calcd for $C_{10}H_7N_3^+$ [M^+] = 169.0634; found = 169.0635.

2-(Benzo[*d*][1,3]dioxol-5-yl)-1*H*-pyrrole-3-carbonitrile (1h)

Synthesized from methyl benzo[*d*][1,3]dioxole-5-carboxylate (2.00 g, 11.1 mmol) according to the general procedure (Reaction times: 18 h in 60 mL DME and 17 h in 10 mL HOAc). Purification by flash chromatography (SiO_2, pentane/Et_2O 1:1, UV) gave the product as a pale orange solid (1.27 g, 5.98 mmol, 54%). TLC (pentane/Et_2O 1:1): R_f = 0.18 [UV]. mp: 166-168 °C. ^1H NMR (500 MHz, $CDCl_3$, 298 K): δ = 6.03 (s, 2H), 6.53 (*virt*. t, $^3J \approx {}^4J$ = 2.8 Hz, 1H), 6.78

(dd, ^3J = 3.1, 2.6 Hz, 1H), 6.88-6.92 (m, 1H), 7.11-7.17 (m, 2H), 8.51 (*br.* s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, 298 K): δ = 89.9 (s), 101.6 (t), 106.5 (d), 109.1 (d), 113.6 (d), 117.5 (s), 118.5 (d), 120.1 (d), 123.8 (s), 139.0 (s), 148.2 (s), 148.5 (s). IR (ATR): $\tilde{\nu}$ = 3282, 2213, 1506, 1465, 1240, 1040, 807, 681. MS (EI, 70 eV): *m/z* (%) = 212 (100), 154 (15), 127 (15). HRMS (EI): calcd for $C_{12}H_8N_2O_2^+$ [M^+] = 212.0580; found = 212.0571.

2-(4-Bromophenyl)-1*H*-pyrrole-3-carbonitrile (1i)

Synthesized from methyl 4-bromobenzoate (538 mg, 2.50 mmol) according to the general procedure (Reaction times: 6 h and 60 h). Purification by flash chromatography (SiO_2, dry-loaded, pentane/Et_2O 2:1 to 1:1, UV) gave the product as a pale red solid (398 mg, 1.62 mmol, 65%). TLC (pentane/Et_2O 3:2): R_f = 0.16 [UV]. mp: 177-179 °C. ^1H NMR (500 MHz, $CDCl_3$, 298 K): δ = 6.57 (*virt*. t, $^3J \approx {}^4J$ = 2.8 Hz, 1H), 6.85 (*virt*. t, ^3J = 2.9 Hz, 1H), 7.54-7.58 (m, 2H), 7.58-7.63 (m, 2H), 8.67 (*br.* s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, 298 K): δ = 91.0 (s), 114.2 (d), 117.3 (s), 119.5 (d), 123.1 (s), 127.4 (d), 128.7 (s), 132.7 (d), 137.8 (s). IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3262, 2220, 1495, 1448, 897, 821, 707, 681. MS (EI, 70 eV): *m/z* (%) = 248 (99), 246 (100), 167 (32), 140 (41). HRMS (EI): calcd for $C_{11}H_7{}^{79}BrN_2^+$ [M^+] = 245.9787; found = 245.9789.

2-Ethyl-1*H*-pyrrole-3-carbonitrile (1j)

Synthesized from methyl propionate (220 mg, 240 µL, 2.50 mmol) according to the general procedure (Reaction times: 12 h and 16 h). Purification by flash chromatography (SiO_2, pentane/Et_2O 3:1 to 1:1, UV) gave the product as a colorless solid (205 mg, 1.71 mmol, 68%). TLC (pentane/Et_2O 4:1): R_f = 0.16 [UV]. mp: 47-49 °C. ^1H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.30 (t, ^3J = 7.6 Hz, 3H), 2.81 (q, ^3J = 7.6 Hz, 2H), 6.36 (*virt.* t, $^3J \approx {}^4J$ =2.8 Hz, 1H), 6.62 (dd, ^3J = 3.1, 2.5 Hz, 1H), 8.39 (*br.* s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, 298 K): δ = 13.7 (q), 20.3

(t), 90.2 (s), 111.6 (d), 117.3 (d), 117.3 (s), 143.2 (s). IR (ATR): $\tilde{\nu}$ = 3287, 2974, 2216, 1463, 731. MS (EI, 70 eV): *m/z* (%) = 120 (41), 105 (100), 78 (12). HRMS (EI): calcd for $C_7H_8N_2^+$ [M^+] = 120.0682; found = 120.0683.

2-Methyl-1*H*-pyrrole-3-carbonitrile (1k)

Synthesized from methyl acetate (240 mg, 258 µL, 3.25 mmol, 1.5 equiv) according to the general procedure (Reaction times: 7 h, then another 3 equiv of ester were added and the reaction mixture refluxed for another 14 h; 21 h for the cyclization). Purification by flash chromatography (SiO_2, pentane/Et_2O 2:1 to 1:1, UV) gave the product as a colorless solid (173 mg, 1.63 mmol, 65%). TLC (pentane/Et_2O 3:1): R_f = 0.10 [UV]. mp: 128-130 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 2.42 (s, 3H), 6.35 (*virt.* t, $^3J \approx {}^4J$ = 2.9 Hz, 1H), 6.62 (*virt.* t, ^3J = 2.8 Hz, 1H), 8.43 (*br.* s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 298 K): δ = 12.3 (q), 91.4 (s), 111.5 (d), 117.3 (s), 117.5 (d), 137.4 (s). IR (ATR): $\tilde{\nu}$ = 3262, 2219, 1459, 1375, 1097, 899, 740. MS (EI, 70 eV): *m/z* (%) = 106 (58), 105 (100). HRMS (EI): calcd for $C_6H_6N_2^+$ [M^+] = 106.0525; found = 106.0532. The spectral data matched those reported in the literature.[3d]

2-Isobutyl-1*H*-pyrrole-3-carbonitrile (1l)

Synthesized from ethyl isovalerate (326 mg, 377 µL, 2.50 mmol) according to the general procedure (Reaction times: 5 h and 18 h). Purification by flash chromatography (SiO_2, pentane/Et_2O 3:1, UV) gave the product as a colorless oil (200 mg, 1.36 mmol, 54%). TLC (pentane/Et_2O 3:1): R_f = 0.25 [UV]. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 0.95 (d, ^3J = 6.7 Hz, 6H), 1.98 (*virt.* nonet, ^3J = 6.7 Hz, 1H), 2.63 (d, ^3J = 7.3 Hz, 2H), 6.37 (*virt.* t, $^3J \approx {}^4J$ = 2.9 Hz, 1H), 6.63 (dd, ^3J = 2.5 Hz, 1H), 8.29 (*br.* s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 298 K): δ = 22.3 (q), 29.5 (d), 36.0 (t), 91.6 (s), 111.5 (d), 117.4 (d), 117.5 (s), 141.1 (s). IR (ATR): $\tilde{\nu}$ = 3284,

2959, 2218, 1459, 724. MS (EI, 70 eV): *m/z* (%) = 148 (26), 106 (60), 105 (100). HRMS (EI): calcd for $C_9H_{12}N_2^+$ [M^+] = 148.0995; found = 148.0998.

2-(*tert*-Butyl)-1*H*-pyrrole-3-carbonitrile (1m)

Synthesized from methyl pivalate (445 mg, 509 µL, 3.00 mmol, 1.20 equiv) according to the general procedure (Reaction times: 17 h in diethoxyethane and 119 h). Purification by flash chromatography (SiO_2, pentane/Et_2O 4:1 to 3:1, UV) gave the product as a pale red solid (174 mg, 1.18 mmol, 47%). TLC (pentane/Et_2O 3:1): R_f = 0.18 [UV]. mp: 63-65 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.45 (s, 9H), 6.40 (*virt.* t, $^3J \approx {}^4J$ = 2.9 Hz, 1H), 6.58 (*virt.* t, ^3J = 2.9 Hz, 1H), 8.42 (*br.* s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, 298 K): δ = 29.8 (q), 32.9 (s), 88.2 (s), 113.3 (d), 116.0 (d), 118.2 (s), 149.1 (s). IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3270, 2966, 2220, 1452, 1085, 897, 698. MS (EI, 70 eV): *m/z* (%) = 148 (27), 133 (100), 105 (19). HRMS (EI): calcd for $C_9H_{12}N_2^+$ [M^+] = 148.0995; found = 148.0996.

2-Cyclopropyl-1*H*-pyrrole-3-carbonitrile (1n)

Synthesized from ethyl cyclopropanecarboxylate (428 mg, 446 µL, 3.75 mmol, 1.5 equiv) according to the general procedure (Reaction times: 14 h and 20 h). Purification by flash chromatography (SiO_2, pentane/Et_2O 2:1 to 1:1, UV) gave the product as an almost colorless solid (237 mg, 1.79 mmol, 72%). TLC (pentane/Et_2O 4:1): R_f = 0.08 [UV]. mp: 71-73 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 0.83-0-94 (m, 2H), 0.96-1.09 (m, 2H), 1.99 (tt, ^3J = 8.5, 5.2 Hz, 1H), 6.33 (*virt.* t, $^3J \approx {}^4J$ = 2.9 Hz, 1H), 6.57 (*virt.* t, ^3J = 2.7 Hz, 1H), 8.25 (*br.* s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, 298 K): δ = 6.9 (t), 8.0 (d), 90.7 (s), 111.9 (d), 117.0 (d), 117.3 (s), 142.5 (s). IR (ATR): $\tilde{\nu}$ = 3261, 2223, 1577, 1464, 1339, 1046, 876, 732. MS (EI, 70 eV): *m/z*

(%) = 132 (100), 131 (79), 105 (79). HRMS (EI): calcd for $C_8H_8N_2^+$ [M^+] = 132.0682; found = 132.0680.

2-(3-Methoxypropyl)-1*H*-pyrrole-3-carbonitrile (1o)

Synthesized from methyl 4-methoxybutyrate (341 µL, 331 mg, 2.50 mmol) according to the general procedure (Reaction times: 17 h and 14 h). Purification by flash chromatography (SiO_2, pentane/Et_2O 1:1, UV) gave the product as a colorless oil (223 mg, 1.36 mmol, 54%). TLC (pentane/Et_2O 1:1): R_f = 0.16 [UV]. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.93 (m, 2H), 2.90 (m, 2H), 3.41 (s, 3H), 3.47 (t, ^3J = 5.6 Hz, 2H), 6.33 (t, $^3J \approx {}^4J$ = 2.8 Hz, 1H), 6.61 (dd, ^3J = 3.1, 2.4 Hz, 1H), 9.34 (*br*. s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, 298 K): δ = 24.4 (t), 28.4 (t), 58.9 (q), 72.5 (t), 90.6 (s), 111.2 (d), 117.5 (s), 117.5 (d), 141.4 (s). IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3280, 2928, 2873, 2217, 1458, 1116, 731. MS (EI, 70 eV): *m/z* (%) = 164 (24), 132 (100), 131 (56), 105 (89). HRMS (EI): calcd for $C_9H_{12}N_2O^+$ [M^+] = 164.0944; found = 164.0944.

1-Benzyl-2-phenyl-1*H*-pyrrole-3-carbonitrile (7)

Synthesized from methyl benzoate (340 mg, 2.50 mmol) according to the general procedure (Reaction times: 14 h and 20 h) using benzyl amine (5.46 mL, 5.36 g, 50.0 mmol, 20.0 equiv) instead of NH_4OAc. Purification by flash chromatography (SiO_2, pentane/Et_2O 10:1 to 6:1, UV) gave the product as an almost colorless solid (269 mg, 1.04 mmol, 42%). TLC (pentane/Et_2O 3:1): R_f = 0.33 [UV]. mp: 89-91 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 5.09 (s, 2H), 6.55 (d, ^3J = 3.1 Hz, 1H), 6.68 (d, ^3J = 3.1 Hz, 1H), 6.98 (m, 2H), 7.27-7.34 (m, 3H), 7.37-7.41 (m, 2H), 7.41-7.48 (m, 3H).$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, 298 K): δ = 51.3 (t), 92.8 (s), 112.4 (d), 117.4 (s), 122.9 (d), 126.7 (d), 128.1 (d), 129.0 (d), 129.1 (d), 129.2 (s, C-1'), 129.3 (d, C-4'),

129.7 (d), 136.9 (s), 141.8 (s). IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3031, 2219, 1497, 1482, 1454, 1429, 766, 730, 697. MS (EI, 70 eV): *m/z* (%) = 258 (50) [M^+], 91 (100). HRMS (EI): calculated for $C_{18}H_{14}N_2^+$ [M^+] = 258.1152; found = 258.1152.

Ethyl 4-(tritylamino)butanoate (10a)

Ethyl-4-aminobutyrate hydrochloride (1.68 g, 10.0 mmol, 1.02 equiv) was dissolved in dry $CHCl_3$ (30.0 mL) and neutralized with NEt_3 (2.02 g, 2.77 mL, 20.0 mmol, 2.04 equiv). Trityl chloride (2.73 g, 9.80 mmol, 1.00 equiv) was added and the reaction mixture stirred at 70 °C for 5 h. The solution was diluted with CH_2Cl_2 and washed with H_2O and brine. The organic layer was separated, dried over Na_2SO_4, filtered and all volatiles were removed under reduced pressure. Purification by flash chromatography (SiO_2, dry-loaded, pentane Et_2O 15:1 to 9:1, UV) gave the product as a colorless oil (3.24 g, 8.67 mmol, 87%). TLC (pentane/Et_2O 9:1): R_f = 0.26 [UV]. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.23 (t, ^3J = 7.1 Hz, 3H), 1.48 (*br.* s), 1.81 (*virt.* quintet, $^3J \approx {}^3J$ = 7.1 Hz, 2H), 2.15 (t, ^3J = 6.8 Hz, 2H), 2.43 (t, ^3J = 7.4 Hz, 2H), 4.12 (q, ^3J = 7.1 Hz, 2H), 7.15-7.20 (m, 3H), 7.25-7.28 (m, 6H), 7.41-7.51 (m, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, 298 K): δ = 14.4 (q), 26.2 (t), 32.6 (t), 43.1 (t), 60.5 (t), 70.9 (s), 126.3 (d), 127.9 (d), 128.7 (d), 146.2 (s), 173.9 (s). IR (ATR): $\tilde{\nu}$ = 3059, 2979, 1731, 1447, 1183, 1157, 769, 746, 706. MS (EI, 70 eV): *m/z* (%) = 373 (1), 296 (100), 258 (57), 243 (91), 165 (48). HRMS (EI): calcd for $C_{25}H_{27}NO_2^+$ [M^+] = 373.2036; found = 373.2027.

2,3-Dihydro-1*H*-pyrrolizine-7-carbonitrile (11a)

NaH (300 mg, 7.50 mmol, 60% suspension in mineral oil, 3.0 equiv) was suspended in 1,2-dimethoxyethane (10 mL). 4,4-dimethoxybutyronitrile (323 mg, 330 µL, 2.50 mmol, 1.0 equiv) was added and the reaction mixture heated to 90°C. Ethyl 4-(tritylamino)butanoate (3.75 mmol,

1.5 equiv) in dimethoxyethane (5 mL) was added *via* syringe and the heterogeneous solution refluxed under argon atmosphere for 40 h. The reaction mixture was cooled to room temperature, quenched with methanol, and all volatiles were removed under reduced pressure. HOAc (10 mL) was added to the crude material and the solution heated to 120 °C for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and neutralized with 2 M aqueous NaOH solution (150 mL). The organic layer was washed with brine (50 mL), separated, dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. Purification by flash chromatography (SiO_2, pentane/Et_2O 3:1, UV) gave the product as a colorless solid (295 mg, 2.23 mmol, 84%). TLC (pentane/Et_2O 3:1): R_f = 0.14 [UV]. mp: 58-60 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 2.57 (*virt.* quintet, ^3J = 7.3 Hz, 2H), 2.98 (t, ^3J = 7.4 Hz, 2H), 3.99 (t, ^3J = 7.2 Hz, 2H), 6.42 (d, ^3J = 2.9 Hz, 1H), 6.55 (d, ^3J = 2.9 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 298 K): δ = 24.5 (t), 27.3 (t), 47.5 (t), 84.3 (s), 115.3 (d), 115.8 (d), 117.5 (s), 145.4 (s). IR (ATR): $\tilde{\nu}$ = 3132, 3112, 2962, 2216, 1507, 1299, 744. MS (EI, 70 eV): *m/z* (%) = 132 (65), 131 (100), 105 (19). HRMS (EI): calcd for $C_8H_8N_2^+$ [M^+] = 132.0682; found = 132.0678. The spectral data matched those reported in the literature.[12]

Danaidal (2,3-Dihydro-1*H*-pyrrolizine-7-carbaldehyde) (8)

2,3-Dihydro-1*H*-pyrrolizine-7-carbonitrile (53 mg, 400 µmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (6.0 mL) under an argon atmosphere. Dibal-H (1 M in CH_2Cl_2, 600 µL, 600µmol, 1.5 equiv) was added dropwise at 0 °C and the reaction mixture stirred at 0 °C for 1 h. Saturated aqueous Rochelle salt solution (5 mL) was added at 0 °C and the solution vigorously stirred at room temperature for 2 h. H_2O was added and the aqueous layer extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, separated, dired over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. Purification by flash chromatography (SiO_2,

pentane/Et_2O 1:1 to 1:2 UV) gave Danaidal as a colorless solid (47 mg, 348 µmol, 87%). TLC (pentane/Et_2O 1:1): R_f = 0.16 [UV]. mp: 59-61 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 2.59 (*virt.* quintet, ^3J = 7.3 Hz, 2H), 3.09 (t, ^3J = 7.4 Hz, 2H), 3.98 (t, ^3J = 7.2 Hz, 2H), 6.60 (d, ^3J = 3.0 Hz, 1H), 6.63 (d, ^3J = 3.0 Hz, 1H), 9.72 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, 298 K): δ = 24.6 (t), 27.3 (t), 46.8 (t), 112.9 (d), 116.4 (d), 117.7 (s), 146.0 (s), 185.1 (d). IR (ATR): $\tilde{\nu}$ = 1660, 1543, 1506, 1435, 1292, 1125. MS (EI, 70 eV): *m/z* (%) = 135 (100), 134 (96), 106 (44). HRMS (EI): calculated for $C_8H_9NO^+$ [M^+] = 135.0679; found = 135.0673. CHN: Anal. calcd for C_8H_9NO = C 71.09, H 6.71, N 10.36; found = C 70.77, H 6.72, N 10.10.

Methyl 5-(tritylamino)valerate (10a)

5-Aminovaleric acid (3.34 g, 28.5 mmol, 1.0 equiv) was dissolved in dry MeOH (25.0 mL). $SOCl_2$ (8.48 g, 5.18 mL, 71.2 mmol, 2.5 equiv) was added at 0 °C and the reaction mixture was allowed to warm to room temperature overnight. All volatiles were carefully removed under reduced pressure and the crude solid was taken up in dry CH_2Cl_2 (25 mL) and neutralized with NEt_3 (6.92 g, 9.47 mL, 68.4 mmol, 2.4 equiv). Trityl chloride (8.74 g, 31.4 mmol, 1.1 equiv) was added and the reaction mixture was stirred at room temperature for 3 h. H_2O (100 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic layer was dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. Purification by flash chromatography (SiO_2, pentane/Et_2O 19:1 to 9:1, UV) gave the product as a colorless solid (9.71 g, 26.0 mmol, 91%). TLC (pentane/Et_2O 19:1): R_f = 0.10 [UV]. mp: 88-90 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.50 (*br.* s, 1H), 1.51 (*virt.* quintet, ^3J = 7.3 Hz, 2H), 1.67 (*virt.* quintet, ^3J = 7.5 Hz, 2H), 2.12 (t, ^3J = 7.0 Hz, 2H), 2.28 (t, ^3J = 7.5 Hz, 2H), 3.65 (s, 3H), 7.14-7.22 (m, 3H), 7.23-7.30 (m, 6H), 7.43-7.50 (m, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, 298 K): δ = 22.9 (t), 30.5 (t), 34.2 (t), 43.3 (t), 51.7 (q), 71.0

(s), 126.3 (d), 127.9 (d), 128.7 (d), 146.3 (s), 174.3 (s). IR (ATR): $\tilde{\nu}$ = 2948, 1737, 1448, 1203, 706. MS (EI, 70 eV): *m/z* (%) = 373 (1), 296 (100), 258 (50), 243 (90), 165 (59). HRMS (EI): calcd for $C_{25}H_{27}NO_2^+$ [M^+] = 373.2036; found = 373.2027.

5,6,7,8-Tetrahydroindolizine-1-carbonitrile (11b)

NaH (850 mg, 21.3 mmol, 60% suspension in mineral oil, 3.0 equiv) was suspended in 1,2-dimethoxyethane (30 mL). 4,4-Dimethoxybutyronitrile (1.19 g, 1.20 mL, 8.50 mmol, 1.2 equiv) was added and the reaction mixture heated to 90°C. Methyl 5-(tritylamino)valerate (7.08 mmol, 1.0 equiv) in dimethoxyethane (10 mL) was added *via* syringe and the heterogeneous solution refluxed under argon atmosphere for 9 h. The reaction mixture was cooled to room temperature, quenched with methanol, and all volatiles were removed under reduced pressure. HOAc (40 mL) was added to the crude material and the solution heated to 120 °C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and neutralized with 4 M aqueous NaOH solution (200 mL). The organic layer was washed with brine (50 mL), separated, dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. Purification by flash chromatography (SiO_2, pentane/Et_2O 5:1 to 1:1, UV) gave the product as a pale yellow liquid (701 mg, 4.79 mmol, 68%). TLC (pentane/Et_2O 5:1): R_f = 0.18 [UV]. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.83-1.91 (m, 2H), 1.93-2.02 (m, 2H), 2.88 (t, ^3J = 6.4 Hz, 2H), 3.92 (t, ^3J = 6.0 Hz, 2H), 6.35 (d, ^3J = 3.0 Hz, 1H), 6.55 (d, ^3J = 3.0 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 298 K): δ = 20.2 (t), 22.4 (t), 23.1 (t), 45.7 (t), 88.8 (s), 111.0 (d), 117.4 (s), 120.0, (d), 138.4 (s). IR (ATR): $\tilde{\nu}$ = 2952, 2211, 1505, 1347, 1205, 718. MS (EI, 70 eV): *m/z* (%) = 146 (66), 145 (100), 118 (48). HRMS (EI): calcd for $C_9H_{10}N_2^+$ [M^+] = 146.0838; found = 146.0835. The spectral data matched those reported in the literature.[3b]

1-(5,6,7,8-Tetrahydroindolizin-1-yl)ethan-1-one (12)

5,6,7,8-Tetrahydroindolizine-1-carbonitrile (219 mg, 1.50 mmol, 1.0 equiv) was dissolved in dry THF (20 mL) and the solution was cooled to 0 °C. Under argon atmosphere MeLi (1.73 mL, 1.3 M in Et_2O, 2.25 mmol, 1.5 equiv) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h. The reaction was stopped by the addition of 2 M aqueous HCl solution (3 mL) and allowed to warm to room temperature overnight (vigorous stirring). The solution was neutralized with aqueous, saturated $NaHCO_3$ solution and the aqueous layer was extracted with EtOAc (100 mL). The organic layer was washed with brine (20 mL), separated, dried over Na_2SO_4, filtered and all volatiles were removed under reduced pressure. Purification by flash chromatography (SiO_2, pentane/Et_2O 2:1 to 1:1, UV) gave the product as a pale yellow liquid (189 mg, 1.16 mmol, 77%). TLC (pentane/Et_2O 1:1): R_f = 0.39 [UV]. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.80-1.87 (m, 2H), 1.91-1.98 (m, 2H), 2.37 (s, 3H), 3.10 (t, ^3J = 6.5 Hz, 2H), 3.93 (t, ^3J = 6.0 Hz, 2H), 6.44 (d, ^3J = 3.1 Hz, 1H), 6.55 (d, ^3J = 3.1 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 298 K): δ = 20.2 (t), 23.0 (t), 24.5 (t), 28.3 (q), 45.8 (t), 110.2 (d), 119.3 (d), 120.1 (s), 136.5 (s), 194.5 (s). IR (ATR): $\tilde{\nu}$ = 2946, 1647, 1535, 1502, 1318, 1227, 1154, 924. MS (EI, 70 eV): *m/z* (%) = 163 (47), 148 (100), 120 (25). HRMS (EI): calcd for $C_{10}H_{13}NO^+$ [M^+] = 163.0992; found = 163.0990. The spectral data matched those reported in the literature.[13]

3-(5,6,7,8-Tetrahydroindolizin-1-yl)but-2-enenitrile (13)

Diethyl cyanomethylphosphonate (886 mg, 809 µL, 5.00 mmol, 10 equiv) was added to a stirred suspension of NaH (200 mg, 60% in mineral oil, 5.00 mmol, 10 equiv) in dry toluene (10 mL) under argon atmosphere. The gel-like solution was heated to 110 °C and dry DMF (1 mL) was added to obtain a clear solution. 1-(5,6,7,8-Tetrahydroindolizin-1-yl)ethan-1-one (82.0 mg, 500 µmol, 1.0 equiv) in dry toluene (2 mL) was added dropwise and the reaction mixture stirred

at 110 °C for 15 h. The reaction mixture was cooled to room temperature and H_2O (50 mL) was added. The aqueous layer was extracted with EtOAc (50 mL) and the organic layer was separated, washed with brine, dried over Na_2SO_4, filtered and all volatiles removed under reduced pressure. Purification by flash chromatography (SiO_2, pentane/Et_2O 2:1 to 1:1, UV) gave the product as a colorless oil (93.0 mg, 500 µmol, 99%), which was obtained as a mixture of *E/Z* isomers (ratio *E/Z* ≈ 4:1). The isomers can be separated by careful flash chromatography (SiO_2, pentane/Et_2O 3:1 to 2:1, UV) to get pure samples (isomerization occurs within a day at room temperature/daylight). ***E*-isomer**: TLC (pentane/Et_2O 2:1): R_f = 0.41 [UV]. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.84-1.91 (m, 2H), 1.92-2.00 (m, 2H), 2.23 (d, ^4J = 0.9 Hz, 3H), 2.84 (t, ^3J = 6.4 Hz, 2H), 3.95 (t, ^3J = 6.0 Hz, 2H), 5.12 (q, ^4J = 0.9 Hz, 1H), 6.27 (d, ^3J = 3.0 Hz, 1H), 6.53 (d, ^3J = 3.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, 298 K): δ = 21.0 (t), 21.5 (q), 22.9 (t), 24.9 (t), 46.0 (t), 88.0 (d), 107.8 (d), 118.5 (s), 119.6 (s), 120.2 (d), 129.8 (s), 155.7 (s). IR (ATR): $\tilde{\nu}$ = 2949, 2200, 1584, 1498, 1322, 1157, 717. MS (EI, 70 eV): *m/z* (%) = 186 (100), 185 (85), 171 (67), 158 (28), 120 (19). HRMS (EI): calcd for $C_{12}H_{14}N_2^+$ [M^+] = 186.1152; found = 186.1146. ***Z*-isomer**: TLC (pentane/Et_2O 2:1): R_f = 0.50 [UV]. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.84-1.91 (m, 2H), 1.92-2.00 (m, 2H), 2.18 (d, ^4J = 1.4 Hz, 3H), 2.82 (t, ^3J = 6.4 Hz, 2H), 3.96 (t, ^3J = 6.2 Hz, 2H), 5.08 (q, ^4J = 1.4 Hz, 1H), 6.44 (d, ^3J = 3.0 Hz, 1H), 6.54 (d, ^3J = 3.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, 298 K): δ = 21.2 (t), 23.2 (t), 25.7 (t), 29.8 (q), 45.9 (t), 90.5 (d), 108.2 (d), 118.0 (s), 119.5 (s), 120.0 (d), 129.9 (s), 156.7 (s).

3-(5,6,7,8-Tetrahydroindolizin-1-yl)but-2-enal (14)

3-(5,6,7,8-Tetrahydroindolizin-1-yl)but-2-enenitrile (93.0 mg, 500 µmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (7.5 mL) and cooled to 0 °C. Dibal-H (800 µL, 1 M in CH_2Cl_2, 800 µmol, 1.6 equiv) was added and the reaction mixture stirred at 0 °C for 2 h. The solution was

quenched with aqueous, saturated Rochelle salt (Na/K tartrate) solution (6 mL) and vigorously stirred at room temperature overnight. H_2O was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Purification by flash chromatography (SiO_2, pentane/Et_2O 2:1, UV) gave the product as a pale yellow oil (48.0 mg, 254 µmol, 51%), which was obtained as a mixture of *E/Z* isomers (ratio *E/Z* ≈ 4:1). A separation of the isomers could not be achieved. ***E*-isomer**: TLC (pentane/Et_2O 2:1): R_f = 0.18 [CAM]. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.82-1.90 (m, 2H), 1.93-1.99 (m), 2.48 (d, ^4J = 1.2 Hz), 2.91 (t, ^3J = 6.4 Hz), 3.96 (t, ^3J = 6.1 Hz), 6.10 (dq, ^3J = 8.3 Hz, ^4J = 1.2 Hz), 6.38 (d, ^3J = 3.0 Hz), 6.56 (d, ^3J = 3.0 Hz), 10.07 (d, ^3J = 8.3 Hz). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 298 K): δ = 17.4 (q), 21.0 (t), 22.9 (t), 25.5 (t), 46.1 (t), 108.2 (d), 120.1 (s), 120.4 (d), 123.4 (d), 131.2 (s), 155.3 (s), 191.2 (d). IR (ATR): $\tilde{\nu}$ = 2946, 1642, 1590, 1495, 1321, 1152. MS (EI, 70 eV): *m/z* (%) = 189 (100), 172 (56), 160 (79), 146 (37), 120 (89). HRMS (EI): calcd for $C_{12}H_{15}NO^+$ [M^+] = 189.1148; found = 189.1149. ***Z*-isomer**: TLC (pentane/Et_2O 2:1): R_f = 0.18 [CAM]. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.76-1.82 (m, 2H), 1.94-1.99 (m, 2H), 2.21 (d, ^4J = 1.3 Hz, 3H), 2.65 (t, ^3J = 6.3 Hz, 2H), 3.97 (t, ^3J = 6.3 Hz, 2H), 5.95 (dq, ^3J = 8.1 Hz, ^4J = 1.3 Hz), 6.18 (d, ^3J = 2.9 Hz, 1H), 6.57 (d, ^3J = 2.9 Hz, 2H), 9.47 (d, ^3J = 8.1 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 298 K): δ = 21.3 (t), 23.4 (t), 23.8 (t), 26.5 (q), 45.8 (t), 109.4 (d), 118.1 (s), 120.2 (d), 126.3 (d), 130.1 (s), 158.0 (s), 194.2 (d).

Suffrutine A ((*E*)-3-((*E*)-3-(5,6,7,8-tetrahydroindolizin-1-yl)but-2-en-1-ylidene)benzofuran-2(3*H*)-one) ((*E*,*E*)-9) and B ((*Z*)-3-((*E*)-3-(5,6,7,8-tetrahydroindolizin-1-yl)but-2-en-1-ylidene)benzofuran-2(3*H*)-one) ((*Z*,*E*)-9)

3-(5,6,7,8-Tetrahydroindolizin-1-yl)but-2-enal (18.9 mg, 100 µmol, 1.0 equiv), 2-courmaranone (20.1 mg, 150 µmol, 1.5 equiv) and piperidine (1.70 mg, 2.00 µL, 20.0 mmol, 0.2 equiv) were dissolved in dry toluene (2.0 mL) under an argon atmosphere. The yellow solution was heated to 110 °C for 1 h. The solvent was removed under reduced pressure and the crude purified by flash chromatography (SiO_2, pentane/Et_2O 4:1 to 3:1, Vis) gave the product as a red semisolid (19.0 mg, 62.2 mmol, 62%), which consists of 4 isomers (*E/E* : *Z/E* : *E/Z* : *Z/Z* 41:32:15:12). The isomers can be separated by flash chromatography in the dark (SiO_2, pentane/Et_2O, Vis) to give analytically pure samples (Suffrutine A and B are very sensitive towards visible light; isomerization occurs readily). ***E,E*-isomer** (Suffrutine A): TLC (pentane/Et_2O 2:1): R_f = 0.36 [Vis]. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.91-1.97 (m, 2H), 1.99-2.06 (m, 2H), 2.41 (d, ^4J = 1.2 Hz, 3H), 3.07 (t, ^3J = 6.3 Hz, 2H), 4.01 (t, ^3J = 6.0 Hz, 2H), 6.42 (d, ^3J = 3.1 Hz, 1H), 6.59 (d, ^3J = 3.1 Hz, 1H), 7.01 (dq, ^3J = 13.0 Hz, ^4J = 1.2 Hz, 1H), 7.12 (d, ^3J = 7.9 Hz, 1H), 7.15 (*virt*. td, $^3J \approx {}^3J$ =7.6 Hz, ^4J = 1.1 Hz, 1H), 7.26 (*virt*. td, $^3J \approx {}^3J$ =7.8 Hz, ^4J = 1.3 Hz, 1H), 7.60 (dd, ^3J = 7.5 Hz, ^4J = 1.4 Hz, 1H), 7.89 (d, ^3J = 13.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, 298 K): δ = 17.8 (q), 21.2 (t), 23.0 (t), 25.7 (t), 46.2 (t), 108.5 (d), 110.8 (d), 115.2 (s), 118.3 (d), 120.6 (d), 122.2 (d), 123.7 (d), 124.6 (s), 128.2 (d), 130.5 (s), 137.5 (d), 150.6 (s), 153.1 (s), 170.4 (s). UV-Vis (MeCN): λ_{max} = 458 nm. ***Z,E*-isomer** (Suffrutine B): TLC (pentane/Et_2O 2:1): R_f = 0.56 [Vis]. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.90-1.96 (m, 2H), 1.96-2.02 (m, 2H), 2.39 (d, ^4J = 1.0 Hz, 3H), 3.11 (t, ^3J = 6.2 Hz, 2H), 3.98 (t, ^3J = 6.0 Hz, 2H), 6.41 (d, ^3J = 3.1 Hz, 1H), 6.57 (d, ^3J = 3.1 Hz, 1H), 7.07 (d, ^3J = 8.0 Hz, 1H), 7.11 (*virt.* td, $^3J \approx {}^3J$ = 7.6 Hz, ^4J = 1.0 Hz), 7.21 (*virt.* td, $^3J \approx {}^3J$ = 7.8 Hz, ^4J = 1.3 Hz, 1H), 7.46 (dd, ^3J = 7.6 Hz, ^4J = 1.3 Hz, 1H), 7.79 (d, ^3J = 12.7 Hz, 1H), 7.86 (dq, ^3J = 12.7 Hz, ^4J = 1.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, 298 K): δ = 17.1 (q), 21.2 (t), 22.9 (t), 25.7 (t), 46.3 (t), 108.5 (d), 110.5 (d), 113.9 (s), 118.6 (d), 119.0

(d), 120.2 (d), 122.0 (s), 123.4 (d), 126.1 (s), 127.8 (d), 131.3 (s), 136.7 (d), 148.7 (s), 152.2 (s), 168.0 (s). UV-Vis (MeCN): λ_{max} = 467 nm.

ACKNOWLEDGEMENT

This work was supported by the *Fonds der Chemischen Industrie* (Kekulé scholarship to J.M.W.) and the Deutsche Forschungsgemeinschaft (DFG, Ba 1372/19-1).

SUPPORTING INFORMATION

^{1}H and ^{13}C{^{1}H} NMR spectra for all compounds, NMR comparison of danaidal and suffrutines A and B with literature data, UV/vis spectra of compounds **9**

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