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Extending the Scope of the Aza-Fischer Synthesis of 4- and 6-Azaindoles

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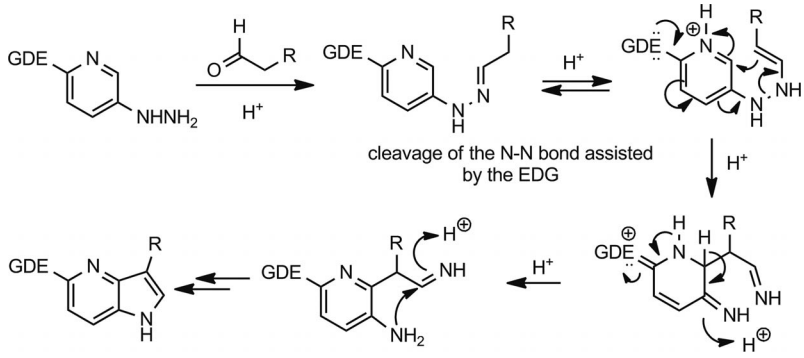
Fischer indole cyclization has recently been described as an efficient approach to the synthesis of azaindoles bearing electron-donating groups. We now show that this cascade reaction can be very efficient for the formation of a wider range of 4- and 6-azaindoles by using microwave irradiation.

Introduction

The azaindole scaffold is found in many natural products and pharmaceuticals.[1] The construction of the azaindole ring is often among the first steps or the key steps in the synthesis of a more complex molecule. The development of simple, general, and efficient synthetic methods to prepare this building block continues to be an essential area of research.[2] Most azaindole syntheses in the past few years have been inspired by the different synthetic strategies developed for the indole ring formation. These methods include Madelung-type cyclization,[3] the Reissert-type procedure,[4] the Leimgruber–Batcho reaction,[5] Lorenz-type cyclization,[6] palladium-catalyzed heteroannulation,[7] and the Bartoli sequence.[8] Although the Fischer reaction[9] presents considerable advantages in the indole series, this method has seldom been applied to the synthesis of azaindoles, due to the unfavorable electron-poor character of the hydrazinopyridine precursor.[10] A few examples of azaindole synthesis by a Fischer reaction have been described, but they suffer from low to moderate yields and/or moderate functional group tolerance due to the harsh reaction conditions required.[11]

In the context of the synthesis of azaindoles with potential biological activity,[12] we described, in a previous letter, the efficient synthesis of 4-aza- and 6-azaindoles bearing an electron-donating group using the Fischer reaction (Scheme 1).[13] This sequence has since been extended to the formation of alternative hydrazine intermediates and to other pyrrole-fused heterocycles.[14] In this paper, we present the results of our investigations into extending the scope of the Fischer reaction to allow the synthesis of 4- and 6-azaindoles.



Scheme 1. Suggested mechanism for Fischer azaindole synthesis from ref.[13] (EDG = electron-donating group).

Results and Discussion

Bearing in mind that Fischer indole synthesis is often more efficient for arylhydrazines bearing electron-donating

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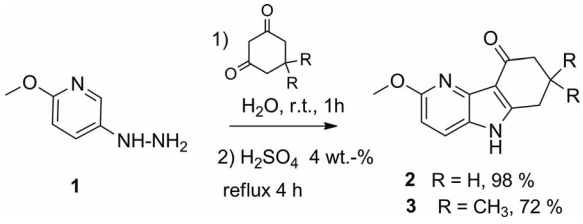
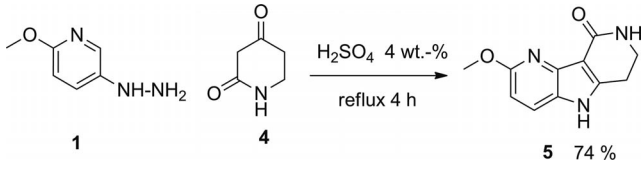
groups, we started our investigation into the aza-Fischer cyclization with an electron-donating group on the starting pyridylhydrazine, and studied the reactivity of several carbonyl partners.

This strategy for the synthesis of azaindoles was previously evaluated with cyclic ketones.[13] We were interested in using cyclic 1,3-diones, as this could give an efficient synthesis of azacarbazolone derivatives. When hydrazine **1** was treated with 1,3-cyclohexanedione in sulfuric acid (4% w/w) at reflux, only 12% of the desired product (i.e., **2**) was isolated. To avoid the autocondensation side-reaction of the 1,3-cyclohexanedione, we slightly changed the procedure, and hydrazine **1** was first mixed with the 1,3-cyclohexanedione for 1 h at room temperature. After the formation of the hydrazone/enehydrazine intermediate, cyclization occurred when this intermediate was heated in the presence of sulfuric acid at reflux for 4 h. The expected product (i.e., **2**) was thus isolated in high yield (98%; Scheme 2). The same procedure was used to prepare **3** in good yield (72%, R = CH_3; Scheme 2) starting from **1** and dimedone.



Scheme 2. Synthesis of azacarbazolones by Fischer reaction.

In this context, piperidinones appeared to be interesting substrates for the preparation of aza analogues of tetrahydro-γ-carbolines. 2,4-Piperidinedione (**4**) was first prepared as described in the literature.[15] Compound **4** was stirred with hydrazine **1** for 1 h at room temperature in water, and then for 4 h at reflux in H_2SO_4 (4% aq. w/w) to give tricycle **5** in good yield (74%; Scheme 3).

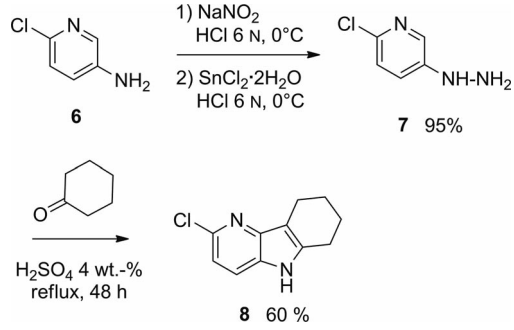


Scheme 3. Synthesis of **5** by Fischer reaction.

In all cases, only the 4-azaindoles were isolated, without any traces of the 6-azaindole isomers. Furthermore, complete regioselectivity with respect to the position of the carbonyl group was observed in the cyclization reactions to form compounds **2**, **3**, and **5**, thanks to the selective formation of the conjugated enehydrazine.

To further extend the potential of the aza-Fischer reaction, we replaced the methoxy or methylsulfonyl group[13] on the pyridine ring by a halogen, to allow further metal-catalyzed cross-coupling reactions, aromatic nucleophilic substitutions, metalation reactions,[16] etc. on the desired azaindole products. The synthesis of such 5-halo-4-azaindoles has already been reported in the literature from appropriate aminochloropyridines and aldehydes or ketones by palladium-catalyzed cyclization.[17]

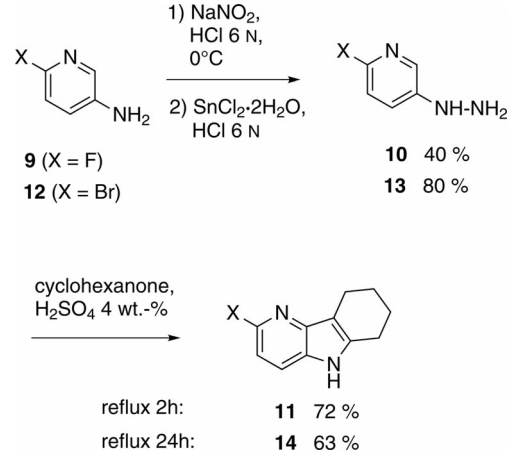
Using Fischer indole synthesis to obtain the 5-halo-4-azaindoles did not appear to be straightforward at first sight. This approach was investigated in a patent in 1928 using Lewis acid activation ($ZnCl_2$) under very harsh reaction conditions (200 °C) to give the 5-chloro-2-methyl-4-azaindole in 50% yield.[18] The preparation of 2-chloro-5-hydrazinopyridine (**7**) was achieved by diazotization and reduction of 5-amino-2-chloropyridine (95%, Scheme 4).[19]



Scheme 4. Synthesis of 5-chloro-4-azaindole **8**.

As we had presumed, 2-chloro-5-hydrazinopyridine was less reactive in the Fischer cyclization than were pyridohydrazines bearing more strongly donating groups, such as those in **1**. Nevertheless, with longer reaction times (2 d reflux), we were able to isolate **8** in 60% yield (Scheme 4).

This reactivity in an aza-Fischer synthesis starting from a chloro-substituted hydrazinopyridine prompted us to check the reactivity of 2-fluoro-5-hydrazinopyridine **10**, which bears a better π-donating group. Diazotation and reduction of 5-amino-2-fluoropyridine (**9**) gave hydrazine **10** in an unexpectedly low yield (40%; Scheme 5). Intermediate **10** was subjected to the Fischer reaction with cyclohexanone, and 5-fluoro-4-azaindole **11** was isolated in a very good yield after only 2 h at reflux (X = F, 72%; Scheme 5).

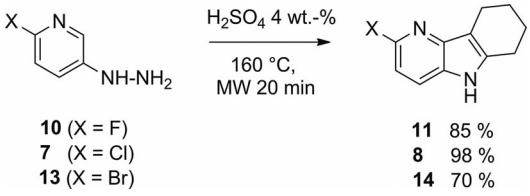


Scheme 5. Synthesis of 5-halo-4-azaindoles under reflux.

These results are consistent with the proposed mechanism (Scheme 1), which explains the beneficial effect of π-donating substituents. This observation was confirmed

firstly with bromopyridylhydrazine **13**, which enabled the isolation of the corresponding 5-bromo-4-azaindole (i.e., **14**) after 24 h reflux in 63% yield (X = Br; Scheme 5), and secondly by the lack of reactivity with methylpyridylhydrazine **15**,[20] which bears only a σ-donating methyl substituent.

To reduce the reaction time for this thermal process, we investigated the effect of microwave irradiation.[21] 2-Fluoro, 2-chloro, and 2-bromo-5-hydrazinopyridines **10**, **7**, and **13** were treated with cyclohexanone, and 5-halo-4-azaindoles **11**, **8**, and **14** were formed in very good yields after only 20 min at 160 °C in H_2SO_4 (4% aq. w/w; Scheme 6).



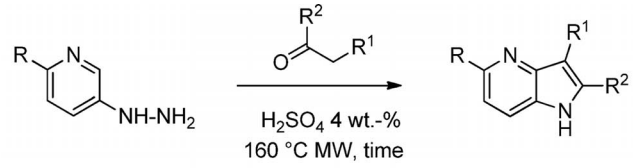
Scheme 6. Synthesis of 5-halo-4-azaindoles under microwave irradiation.

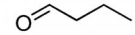
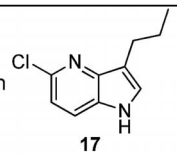
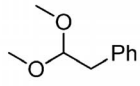
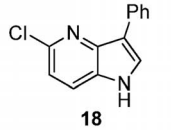
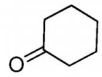
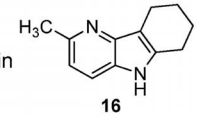
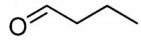
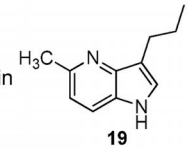
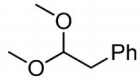
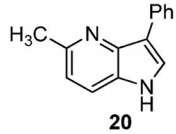
The versatility of the chlorine atom in terms of S_NAr or cross-coupling reactions prompted us to extend the scope of the reaction with this substrate. 2-Chloro-5-hydrazinopyridine (**7**) was treated with valeraldehyde in aqueous H_2SO_4 (4% aq. w/w) for 20 min under microwave irradiation to give azaindole **17** in 77% yield [Table 1, entry 1; compared to 34% yield after 3 d at reflux with H_2SO_4 (4% aq. w/w)]. In the case of 2,2-dimethoxyethylbenzene, the reaction time should not exceed 5 min under microwave irradiation to avoid the degradation of product **18**, which could be isolated in 66% yield [Table 1, entry 2; compared to 56% yield after 2 d at reflux with H_2SO_4 (4% aq. w/w)].

Given the huge improvement achieved by using microwave irradiation, we returned to the reactivity of substrates with weakly σ-donating substituents such as the methyl group (with high synthetic potential for use in reactions such as oxidation, metalation, etc.). When hydrazine **15** was treated with cyclohexanone for 20 min under microwave irradiation, 5-methyl-4-azaindole **16** was isolated in 70% yield (Table 1, entry 3). This excellent yield can be explained by the reduced amount of degradation product. (i.e., 5-amino-2-methoxypyridine) in comparison to the reaction with classical heating. 5-Methyl-4-azaindoles **19** and **20** were also synthesized using microwave irradiation at 160 °C for 5 and 20 min, respectively. The crude products consisted of a mixture of the degradation product 5-amino-2-methoxypyridine and the expected 5-methyl-4-azaindoles, which were isolated in 25 and 46% yields after column chromatography (Table 1, entries 4 and 5). At the extreme limit, we investigated these reaction conditions on a pyridine ring without any electron-donating substituent, but unfortunately, 3-hydrazinopyridine was not reactive.

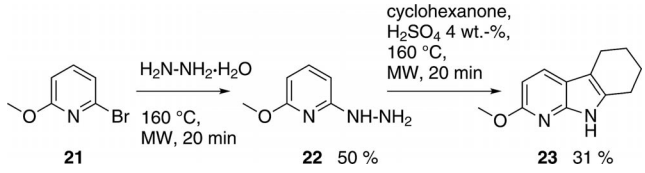
We then focused our attention on 2-hydrazino-6-methoxypyridine (**22**), which was not reactive under conventional heating.[13] Starting from 2-bromo-6-methoxypyridine (**21**) and an excess of hydrazine monohydrate, and heating at 160 °C for 20 min under microwave irradiation,

Table 1. Synthesis of 5-chloro-4-azaindoles and 5-methyl-4-azaindoles under microwave irradiation.



Entry	R	R^1, R^2	Time	Product	Yields
1	Cl (**7**)		20 min	 **17**	77%
2	Cl (**7**)		5 min	 **18**	66%
3	Me (**15**)		20 min	 **16**	70%
4	Me (**15**)		20 min	 **19**	25%
5	Me (**15**)		5 min	 **20**	46%

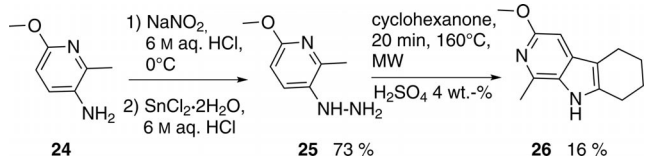
we obtained the expected pyridylhydrazine (i.e., **22** 50%; Scheme 7). We then performed the Fischer reaction with cyclohexanone at 160 °C for 20 min under microwave irradiation, and isolated the 7-azaindole product (i.e., **23**) in 31% yield (Scheme 7). This low yield, consistent with similar syntheses of 7-azaindoles described in the literature,[22] matches the proposed mechanism (Scheme 1), as the π-donating group is not in the *ortho* or *para* position with respect to the hydrazine.



Scheme 7. Synthesis of 7-azaindole **23**.

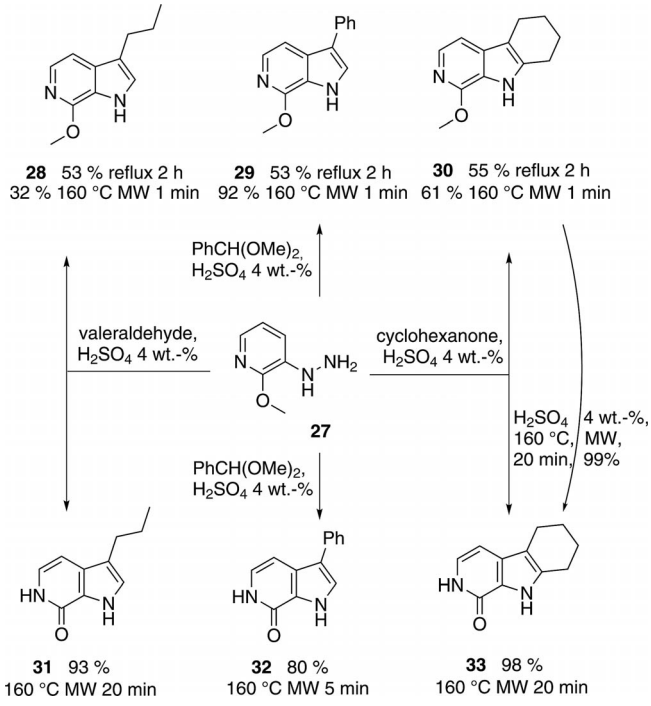
The incorporation of an amino substituent as an electron-donating group was studied. Unfortunately, 4-(5-hydrazino-2-pyridinyl)morpholine was not a good substrate for this Fischer reaction. In acidic media, the amino group is protonated and loses its π-donating ability. Only the degradation product, 4-(5-amino-2-pyridinyl)morpholine, was recovered from the reaction.

Finally, we wondered what the impact on the [3,3]-sigmatropic rearrangement in the Fischer reaction would be if the C-2 position of the starting pyridine ring was blocked. Commercially available 3-amino-6-methoxy-2-methylpyridine (**24**) was transformed into the corresponding hydrazine (i.e., **25**). Under our optimized conditions (i.e., microwave irradiation at 160 °C for 20 min with cyclohexanone), 7-methyl-5-methoxy-6-azaindole **26** was isolated in a low yield and low purity (Scheme 8). However, this example is very informative, as the presence of the methyl group at C-2 of pyridylhydrazine **25** prevents any cyclization at C-2, and moreover, at the same time, does not efficiently direct to position C-4. Such behavior is completely consistent with the proposed mechanism (Scheme 1), with a crucial pull effect being the origin of the observed regioselectivity of the cyclization.



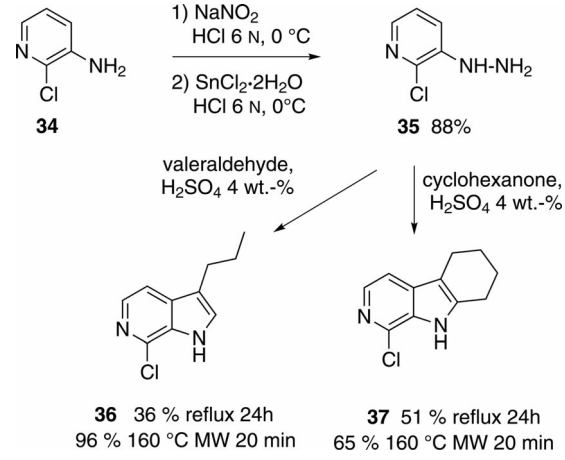
Scheme 8. Synthesis of **26** by Fischer reaction.

Microwave irradiation was also used for the Fischer synthesis of 6-azaindoles. Starting from 3-hydrazino-2-methoxypyridine (**27**),[13] 6-azaindoles **28**, **29**, and **30** were obtained in reasonable yields after 2 h reflux (53–60%; Scheme 9). Under microwave irradiation, the reaction times had to be reduced to 1 min to give acceptable yields of compounds **28**, **29**, and **30** (32, 61, and 92% yields; Scheme 9). Interestingly, longer reaction times allowed the rapid demethoxylation of 7-methoxy-6-azaindoles.[23] Thus, from pyridylhydrazine **27** with valeraldehyde, cyclohexanone, or (2,2-dimethoxyethane)benzene, we directly obtained the corresponding pyrrolo[2,3-*c*]pyridin-7-ones (i.e., **31**, **32**, and **33**) in high yields (80–98%; Scheme 9) after 5 or 20 min under microwave irradiation. Compound **33** could be isolated in quantitative yield from 7-methoxy-6-azaindole **30** after 20 min under microwave irradiation in sulfuric acid (Scheme 9).



Scheme 9. Synthesis of 6-azaindoles **30**–**32** and azaindolinones **33**–**35**.

Following on from our previous observations (see above), we investigated the reactivity of 2-chloro-3-hydrazinopyridine **35** synthesized from 3-amino-2-chloropyridine **34**. The aza-Fischer reaction was performed in refluxing H_2SO_4 (4% aq.) for 24 h to give 7-chloro-6-azaindoles **36** and **37** in 36 and 51% yields (Scheme 10). With microwave irradiation, the same compounds were synthesized much more quickly (20 min) in good to high yields (65–96%; Scheme 10).



Scheme 10. Synthesis of 7-chloro-6-azaindoles **36** and **37**.

Conclusions

We have shown that Fischer synthesis can be a very efficient, selective, and straightforward method for the synthesis of 4- and 6-azaindoles. All the reactions were performed in aqueous sulfuric acid (4% w/w) with aldehydes, ketones, or ketals. The method can be extended to many other derivatives, and the reaction was successfully scaled up. The use of microwave irradiation makes it possible to increase the scope of the substituents on the pyridylhydrazine substrates from strongly to weakly electron-donating groups. These substituents can be of interest as they can enable the 4-aza- and 6-azaindole products to undergo further reactions. All of our results are consistent with the proposed mechanism for this aza-Fischer reaction.

Experimental Section

General Methods: The solvents used were ACS grade, except for THF, which was freshly distilled from Na/benzophenone. Microwave irradiation was carried out in sealed 2–5 mL vessels in a Bio-

tage Initiator system using a standard absorbance level (300 W maximum power). The temperatures were measured externally by an IR probe that determined the temperature on the surface of the vial and could be read directly from the instrument screen. The reaction time was measured from when the reaction mixture reached the stated temperature for temperature-controlled experiments. Nuclear Magnetic Resonance (^{1}H and ^{13}C) spectra were recorded with 250 or 400 MHz Bruker spectrometers. Chemical shifts are reported in parts per million (δ) downfield from the reference tetramethylsilane. Coupling constants (J) are reported in Hertz (Hz). The following symbols have been used to indicate multiplicities: s (singlet), br. s (broad singlet), d (doublet), t (triplet), q (quartet), sext (sextet), m (multiplet). IR spectra were recorded with an ATR Nicolet iS10 spectrometer. Low-resolution mass spectra (MS) were recorded with a Perkin–Elmer SCIEX AOI 300 spectrometer; IS^+ = positive ion spray ionisation. HRMS (ESI-TOF) was performed with a Micromass LC TOF spectrometer. Analytical TLC was performed on silica gel (on aluminium foil) 60F-254 plates. Visualization was carried out with UV light (254 nm) or using potassium permanganate solution. Flash chromatography was carried out using 40–70 μM (230–400 mesh) silica gel. Reagent grade ethyl acetate, diethyl ether, and petroleum ether were used for chromatography. All starting materials were commercially available, and sodium 3-(methoxycarbonyl)-4-oxo-1,4,5,6-tetrahydropyridin-2-olate was supplied by the Evonik–Degussa company. Compounds **1**, **22**, **27**, **29**, **30** have already been described.[13]

2-Methoxy-5,6,7,8-tetrahydropyrido[3,2-*b*]indol-9-one (2): 1,3-Cyclohexanedione (1.56 g, 13.96 mmol) was added to a solution of 5-hydrazino-2-methoxypyridine (**1**; 1.85 g, 13.3 mmol) in water (28 mL), and the resulting solution was stirred at room temperature for 1 h. H_2SO_4 (concd.; 0.66 mL) was added dropwise, and the reaction mixture was heated at reflux for 4 h. After cooling to room temperature, the reaction mixture was poured into potassium hydroxide (saturated aq.; 50 mL). The resulting precipitate was filtered and washed with diethyl ether and acetonitrile, and recrystallized from a CH_2Cl_2/pentane mixture to give **2** (2.68 g, 98%) as a pale brown solid, m.p. >260 °C. IR: $\tilde{\nu}$ = 3167 (NH), 1656 (C=O) cm^{-1}. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 11.88 (br. s, 1 H, NH), 7.69 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, CH), 6.58 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, CH), 3.87 (s, 3 H, OCH_3), 2.95 (t, $^3J_{H,H}$ = 6.2 Hz, 2 H, CH_2), 2.40 (t, $^3J_{H,H}$ = 6.2 Hz, 2 H, CH_2), 2.08 (m, 2 H, 7-H) ppm. ^{13}C NMR (62.9 MHz, [D$_6$]DMSO): δ = 191.3 (CO), 152.7 (C_{IV}), 160.2 (C_{IV}), 139.6 (C_{IV}), 124.4 (C_{IV}), 122.3 (CH), 111.1 (C_{IV}), 105.0 (CH), 52.8 (OCH_3), 38.6 (CH_2), 23.3 (CH_2), 23.1 (CH_2) ppm. HRMS (ESI): calcd. for $C_{12}H_{13}N_2O_2$ [M + H]$^+$ 217.0977; found 217.0982.

2-Methoxy-7,7-dimethyl-5,6,7,8-tetrahydro-9*H*-pyrido[3,2-*b*]indol-9-one (3): Dimedone (0.588 g, 4.2 mmol) was added to a solution of 5-hydrazino-2-methoxypyridine (**1**; 0.556 g, 4 mmol) in water (8.5 mL), and the resulting solution was stirred at room temperature for 1 h. H_2SO_4 (concd.; 0.2 mL) was added dropwise, and the reaction mixture was heated at reflux for 4 h. After cooling to room temperature, the reaction mixture was poured into potassium hydroxide (saturated aq.; 30 mL). The resulting precipitate was filtered and washed with diethyl ether and acetonitrile, and recrystallized from a CH_2Cl_2/pentane mixture to give **3** (0.72 g, 74%) as a brown solid, m.p. 266 °C. IR: $\tilde{\nu}$ = 3046, 2954, 2918, 1632, 1410 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.84 (s, 1 H, NH), 7.69 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, 4-H), 6.58 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, 3-H), 3.87 (s, 3 H, CH_3), 2.85 (s, 2 H, 8-H), 2.31 (s, 2 H, 6-H), 1.08 (s, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 191.20 (CO), 160.72 (C_{IV}), 152.00 (C_{IV}), 139.85 (C_{IV}), 125.18 (C_{IV}), 122.81 (CH), 110.44 (C_{IV}), 105.36 (CH), 53.24 (OCH_3), 53.06 (C_{IV}), 37.24 (CH_2), 35.27 (CH_2), 28.47 (CH_3) ppm. HRMS (ESI): calcd. for $C_{14}H_{17}N_2O_2$ [M + H]$^+$ 245.1290; found 245.1297.

2,4-Piperidinedione (4): Sodium 3-(methoxycarbonyl)-4-oxo-1,4,5,6-tetrahydropyridin-2-olate (Evonik–Degussa company; 50 g, 259 mmol) was partitioned between HCl (2 N aq.) and dichloromethane. The aqueous phase was extracted two more times with dichloromethane. The combined organic extracts were dried with sodium sulfate and filtered, and the solvents were evaporated. The residue was suspended in acetonitrile (500 mL) and water (100 mL) and heated to reflux for 3 h. The reaction mixture was cooled and the solvents were evaporated to give crude **4** (27.07 g, 85%) as a yellow solid, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.71 (br. s, 1 H, NH), 3.58 (m, 2 H, 6-CH_2), 3.34 (s, 2 H, 3-CH_2), 2.64 (t, J = 8 Hz, 2 H, 5-CH_2) ppm.

6-Methoxy-1,2,3,9-tetrahydro-3,5,9-triazafluoren-4-one (5): 2,4-Piperidinedione (**4**; 0.42 g, 3.75 mmol) was added to a solution of 5-hydrazino-2-methoxypyridine **1** (0.5125 g, 3.68 mmol) in water (12 mL), and the resulting solution was stirred at room temperature for 1 h. H_2SO_4 (concd.; 0.17 mL) was added dropwise, and the reaction mixture was heated at reflux for 4 h. After cooling down to room temperature, the reaction mixture was poured into potassium hydroxide (saturated aq.; 50 mL). The resulting precipitate was filtered and washed with diethyl ether and acetonitrile to give **5** (0.591 g, 74%) as a brown solid., m.p. >260 °C IR: $\tilde{\nu}$ = 3193 (NH), 1674 (C=O) cm^{-1}. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 11.02 (br. s, 1 H, NH), 8.01 (br. s, 1 H, NH), 7.63 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, 7-H), 6.52 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, 8-H), 4.43 (m, 2 H, 2-H), 3.84 (s, 3 H, CH_3O), 3.57 (m, 2 H, 1-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 167.58 (C=O), 158.79 (C_{IV}), 139.00 (C_{IV}), 132.66 (C_{IV}), 125.03 (C_{IV}), 121.90 (CH), 103.72 (CH), 102.41 (C_{IV}), 52.52 (CH_3O), 30.68 (CH_2), 30.42 (CH_2) ppm. MS (IS^+): m/z = 273.5 [M + H]$^+$. HRMS (ESI): calcd. for $C_{11}H_{12}N_3O_2$ [M + H]$^+$ 218.0930; found 218.0928.

2-Chloro-5-hydrazinopyridine (7): A solution of sodium nitrite (107 mg, 1.55 mmol) in water (4 mL) was added dropwise to a solution of 5-amino-2-chloropyridine (**6**; 200 mg, 1.55 mmol) in HCl (6 M aq.; 3 mL) at 0 °C. After 30 min at 0 °C, a solution of $SnCl_2{\cdot}2H_2O$ (878 mg, 3.9 mmol) in HCl (6 M aq.; 3 mL) was slowly added at 0 °C. This mixture was stirred for 1 h at 0 °C, then the reaction was quenched by the addition of KOH (40% w/w aq.; until the pH turned basic). The crude material was extracted with ethyl acetate (4× 10 mL). The organic extracts were combined, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure to give **7** (532 mg, 95%) as a slightly brown solid. The stability of this product was quite low. It was preferable to use it straight away, m.p. 126 °C. IR: $\tilde{\nu}$ = 3245, 3080, 1578, 1461, 1292, 1101 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, $^3J_{H,H}$ = 2.9 Hz, 6-H), 7.20 (dd, $^3J_{H,H}$ = 8.6, $^4J_{H,H}$ = 2.9 Hz, 1 H, 4-H), 7.13 (d, $^3J_{H,H}$ = 8.6 Hz, 3-H), 5.42 (br. s, 1 H, NH), 3.61 (br. s, 2 H, NH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.2 (CH), 140.7 (CH), 134.1 (C_{IV}), 124.1 (C_{IV}), 122.6 (C_{IV}) ppm. MS: m/z = 144/146 [M + H]$^+$.

2-Fluoro-5-hydrazinopyridine (10): A solution of sodium nitrite (62 mg, 0.893 mmol) in water (2.4 mL) was added dropwise to a solution of 5-amino-2-fluoropyridine (**9**; 100 mg, 0.893 mmol) in HCl (6 M aq.; 1.8 mL) at 0 °C. After 30 min at 0 °C, a solution of $SnCl_2{\cdot}2H_2O$ (504 mg, 2.23 mmol) in HCl (6 M aq.; 1.8 mL) was added slowly. This mixture was stirred for 1 h 30 min at 0 °C, then the reaction was quenched by the addition of KOH (40% w/w aq.; until the pH turned basic). The crude material was extracted with ethyl acetate (3× 20 mL). The organic extracts were combined, washed with brine (10 mL), dried with anhydrous $MgSO_4$, and concentrated under reduced pressure to give **10** (40 mg, 40%) as a violet solid. The stability of this product is quite low, it must be used

straight away. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.74 (m, 1 H, 6-H), 7.33 (ddd, $^3J_{H,H}$ = 8.8, $^4J_{H,H}$ = 6.8, $^3J_{H,F}$ = 3.0 Hz, 1 H, 4-H), 6.80 (dd, $^3J_{H,H}$ = 8.8, $^3J_{H,F}$ = 3.3 Hz, 1 H, 3-H), 5.19 (s, 1 H, NH), 3.65 (s, 2 H, NH_2) ppm.

2-Bromo-5-hydrazinopyridine (13): A solution of sodium nitrite (62 mg, 0.893 mmol) in water (2.4 mL), was added dropwise to a solution of 5-amino-2-bromopyridine (**12**; 154.5 mg, 0.893 mmol) in HCl (6 M aq.; 1.8 mL) at 0 °C. After 30 min at 0 °C, a solution of $SnCl_2{\cdot}2H_2O$ (504 mg, 2.23 mmol) in HCl (6 M aq.; 1.8 mL) was added slowly. This mixture was stirred for 1 h 30 min at 0 °C, then the reaction was quenched by the addition of KOH (40% w/w aq.; until the pH turned basic). The crude material was extracted with ethyl acetate (3× 20 mL). The organic extracts were combined, washed with brine (10 mL), dried with anhydrous $MgSO_4$, and concentrated under reduced pressure to give **13** (0.091 g, 80%) as a beige solid. The stability of this product is quite low, it must be used straight away. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 2.25 Hz, 1 H), 7.30 (d, J = 8.00 Hz, 1 H), 7.12 (dd, J = 8.00, J = 2.25 Hz, 1 H), 5.33 (br. s, 1 H, NH), 3.66 (br. s, 2 H, NH_2) ppm.

5-Hydrazino-2-methylpyridine (15): A solution of sodium nitrite (64 mg, 0.925 mmol) in water (1 mL) was added dropwise to a solution of 5-amino-2-methylpyridine (100 mg, 0.925 mmol) in HCl (6 M aq.; 1.14 mL) at 0 °C. After 60 min at 0 °C, a solution of $SnCl_2{\cdot}2H_2O$ (521 mg, 2.2 mmol) in HCl (6 M aq.; 1.14 mL) was added slowly. This mixture was stirred for 45 min at 0 °C, then the reaction was quenched by the addition of KOH (40% w/w aq.; until the pH turned basic). The crude material was extracted with ethyl acetate (3× 20 mL). The organic extracts were combined, washed with brine (10 mL), dried with anhydrous $MgSO_4$, and concentrated under reduced pressure to give **15** (101 mg, 88%) as a yellow solid. The stability of this product is quite low, it must be used straight away. IR: $\tilde{\nu}$ = 3273, 1627, 1576, 1492 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, $^3J_{H,H}$ = 1 Hz, 1 H, 6-H), 7.13 (dd, $^3J_{H,H}$ = 8.4 Hz, 1 H, 4-H), 7.02 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H, 3-H), 5.22 (br. s, 1 H, NH), 3.37 (br. s, 2 H, NH_2), 2.45 (s, 3 H, CH_3) ppm.

3-Hydrazino-6-methoxy-2-methylpyridine (25): A solution of sodium nitrite (50 mg, 0.72 mmol) in water (1 mL) was added dropwise to a solution of 3-amino-6-methoxy-2-methylpyridine (**24**; 100 mg, 0.72 mmol) HCl (6 M aq.; 2 mL) at 0 °C. After 90 min at 0 °C, a solution of $SnCl_2{\cdot}2H_2O$ (2.5 g, 11.07 mmol) in HCl (6 M aq.; 10 mL) was added slowly. This mixture was stirred for 2 h at 0 °C, then the reaction was quenched by the addition of KOH (40% w/w aq.; until the pH turned basic). The crude material was extracted with ethyl acetate (3× 20 mL). The organic extracts were combined, washed with brine (10 mL), dried with anhydrous $MgSO_4$, and concentrated under reduced pressure to give **25** (100 mg, 90%) as a pale brown solid. This product is quite unstable, it has to be used straight away. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.39 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 6.62 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 3.90 (s, 3 H, OCH_3), 2.34 (s, 3 H, CH_3) ppm.

2-Chloro-3-hydrazinopyridine (35): A solution of sodium nitrite (306 mg, 4.43 mmol) in water (1 mL) was added dropwise to a solution of 3-amino-2-chloropyridine (**34**; 569 mg, 4.43 mmol) in HCl (6 M aq.; 10 mL) at 0 °C. After 60 min at 0 °C, a solution of $SnCl_2{\cdot}2H_2O$ (2.5 g, 11.07 mmol) in HCl (6 M aq.; 10 mL) was added slowly. This mixture was stirred for 30 min at 0 °C, then the reaction was quenched by the addition of KOH (40% w/w aq.; until the pH turned basic). The crude material was extracted with ethyl acetate (3× 20 mL). The organic extracts were combined, washed with brine (10 mL), dried with anhydrous $MgSO_4$, and concentrated under reduced pressure to give **35** (510 mg, 88%) as a pale brown solid. The stability of this product is quite low, it must be used straight away. IR: $\tilde{\nu}$ = 2956, 1681, 1095 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.78–7.80 (m, 1 H, 6-H), 7.57–7.37 (m, 1 H, 5-H), 7.23–7.11 (m, 1 H, 4-H), 5.77 (s, 1 H, NH), 3.66 (s, 2 H, NH_2) ppm.

General Methods for the Fischer Reaction

Classical Heating: The reactant [valeraldehyde, cyclohexanone, or (2,2-dimethoxyethyl)benzene; 1.05 mmol] was added to a solution of the corresponding hydrazine (1 mmol) in H_2SO_4 (4% w/w aq.; 7 mL). This mixture was stirred at reflux until the reaction was complete. The reaction mixture was poured slowly into KOH (40% w/w aq.; 10 mL). If a precipitate appeared, it was filtered off and washed with water (5 mL). In other cases, the crude material was extracted with ethyl acetate (3× 20 mL). The combined organic extracts were then washed with brine (10 mL), dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography or recrystallized from a mixture of CH_2Cl_2 and pentane.

Microwave Irradiation: The reactant [valeraldehyde, cyclohexanone or (2,2-dimethoxyethyl)benzene; 1.05 mmol] was added to a solution of the corresponding hydrazine (1 mmol) in H_2SO_4 (4% w/w aq.; 10 mL). This mixture was for stirred 1 min at room temperature and then heated at 160 °C until the reaction was complete (required time indicated in tables and below). The reaction mixture was poured slowly into KOH (40% w/w aq.; 10 mL). If a precipitate appeared, it was filtered off and washed with water (5 mL). In other cases, the crude material was extracted with ethyl acetate (3× 20 mL). The combined organic extracts were then washed with brine (10 mL), dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography or recrystallized from CH_2Cl_2 and pentane.

2-Chloro-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]indole (8): Compound **8** was obtained from the Fischer reaction of 2-chloro-5-hydrazinopyridine (**7**) and cyclohexanone, and was purified by recrystallization (CH_2Cl_2/pentane), yield 60% (0.124 g) after reflux, 2 d; 98% (0.202 g) after MW 160 °C, 20 min. Pale brown solid, m.p. 204 °C. IR: $\tilde{\nu}$ = 3150, 2935, 1570, 1542 cm^{-1}. ^{1}H NMR (250 MHz, DMSO): δ = 11.16 (br. s, 1 H, NH), 7.64 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H, 7-H), 6.99 (d, $^3J_{H,H}$ = 8 Hz, 1 H, 6-H), 2.74 (m, 2 H, CH_2), 2.63 (m, 2 H, CH_2), 1.82 (m, 4 H, 7-H, 8-H) ppm. ^{13}C NMR (62.5 MHz, DMSO): δ = 145.08 (C_{IV}), 141.83 (C_{IV}), 141.29 (C_{IV}), 127.61 (C_{IV}), 120.77 (C-3), 114.90 (C-4), 109.04 (C_{IV}), 23.49 (CH_2), 23.03 (CH_2), 22.91 (CH_2), 20.18 (CH_2) ppm. MS (IS$^+$): m/z = 207/209 [M + H]$^+$. HRMS (ESI): calcd. for $C_{11}H_{12}ClN_2$ [M + H]$^+$ 207.0689; found 207.0687.

2-Fluoro-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]indole (11): Compound **11** was obtained from the Fischer reaction of 2-fluoro-5-hydrazinopyridine (**10**) and cyclohexanone, and was purified by recrystallization (CH_2Cl_2/pentane), yield 72% (0.137 g) after reflux, 2 h. Pale yellow solid, m.p. 182 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (s, 1 H, NH), 7.58 (dd, $^3J_{H,H}$ = 8.3, $^3J_{H,F}$ 7.1 Hz, 1 H, 6-H), 6.63 (dd, $^3J_{H,H}$ = 8.3, $^4J_{H,F}$ = 1.3 Hz, 1 H, 7-H), 2.77 (t, $^3J_{H,H}$ = 5.8 Hz, 4 H, H_9, 6-H), 1.96–1.82 (m, 4 H, 7-H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.01 (C_{IV}), 126.59 (C_{IV}), 121.54 (C_{IV}), 121.44 (C_{IV}), 110.80 (CH), 101.02 (C_{IV}), 100.60 (CH), 23.67 (CH_2), 22.91 (CH_2), 22.86 (CH_2), 19.82 (CH_2) ppm. MS (IS$^+$): m/z = 191 [M + H]$^+$. HRMS (ESI): calcd. for $C_{11}H_{12}FN_2$ [M + H]$^+$ 191.0985; found 191.0978.

2-Bromo-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]indole (14): Compound **14** was obtained from the Fischer reaction of 2-bromo-5-hydrazinopyridine (**13**) and cyclohexanone, and was purified by column chromatography, yield 70% (0.176 g). Brown solid, m.p. 227 °C

(dec). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (br. s, 1 H, NH), 7.41 (d, $J_{6,7}$ = 8.50 Hz, 1 H), 7.15 (d, $J_{7,6}$ = 8.50 Hz, 1 H), 2.67–2.84 (m, 4 H), 1.85–1.99 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.49 (C_{IV}), 126.59 (C_{IV}), 139.95 (C_{IV}), 133.67 (C_{IV}), 127.66 (C_{IV}), 119.59 (CH), 119.08 (CH), 111.19 (C_{IV}), 23.78 (CH_2), 23.02 (CH_2), 22.94 (CH_2), 20.11 (CH_2) ppm. MS (IS$^+$): *m*/*z* = 251/253 [M + H]$^+$. HRMS (ESI): calcd. for $C_{11}H_{12}{}^{79}BrN_2$ [M + H]$^+$ 251.0178; found 251.0182.

2-Methyl-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]indole (16): Compound **16** was obtained from the Fischer reaction of 5-hydrazino-2-methylpyridine (**15**) and cyclohexanone, and was purified by recrystallization (CH_2Cl_2/pentane), yield 60% (0.112 g) after reflux, 2 d; 98% (0.182 g) after MW 160 °C, 20 min. Pale brown solid, m.p. >260 °C. IR: $\tilde{\nu}$ = 2920, 2843, 2722, 1572, 14250 1096 cm^{-1}. ^{1}H NMR (250 MHz, DMSO): δ = 10.75 (br. s, 1 H, NH), 7.46 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, 6-H), 6.83 (d, $^3J_{H,H}$ = 8 Hz, 1 H, 7-H), 2.72 (m, 2 H, CH_2), 2.66 (m, 2 H, CH_2), 2.50 (s, 3 H, CH_3), 1.82 (m, 4 H, 7-H, 8-H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 148.92 (C_{IV}), 145.21 (C_{IV}), 138.88 (C_{IV}), 127.03 (C_{IV}), 117.69 (CH), 115.28 (CH), 108.76 (C_{IV}), 26.89 (CH_3), 24.51 (CH_2), 23.52 (CH_2), 23.31 (CH_2), 23.17 (CH_2) ppm. MS (IS$^+$): *m*/*z* = 187.5 [M + H]$^+$. HRMS (ESI): calcd. for $C_{12}H_{15}N_2$ [M + H]$^+$ 187.1223; found 187.1235.

5-Chloro-3-propyl-1*H*-pyrrolo[3,2-*b*]pyridine (17): Compound **17** was obtained from the Fischer reaction of 2-chloro-5-hydrazinopyridine (**7**) and valeraldehyde, and was purified by recrystallization (CH_2Cl_2/pentane), yield 34% (0.066 g) after reflux, 3 d; 77% (0.150 g) after MW 160 °C, 20 min. Pale brown solid, m.p. 140 °C. IR: $\tilde{\nu}$ = 3152, 3067, 2962, 2922, 1547, 1464, 1400 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (br. s, 1 H, NH), 7.56 (d, $^3J_{H,H}$ = 8 Hz, 1 H, 7-H), 7.25 (s, 1 H, 2-H), 7.09 (d, $^3J_{H,H}$ = 8 Hz, 1 H, 6-H), 2.80 (t, $^3J_{H,H}$ = 6 Hz, 2 H, CH_2-CH_2), 1.75 (sext, $^3J_{H,H}$ = 6 Hz, 2 H, CH_2-CH_3), 0.97 (t, $^3J_{H,H}$ = 6 Hz, 2 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.13 (C_{IV}), 143.63 (C_{IV}), 127.64 (C_{IV}), 125.92 (CH), 120.64 (CH), 117.61 (C_{IV}), 116.66 (CH), 25.77 (CH_2), 23.04 (CH_2), 14.02 (CH_3) ppm. MS (IS$^+$): *m*/*z* = 195/197 [M + H]$^+$, 168/166. HRMS (ESI): calcd. for $C_{10}H_{12}{}^{35}ClN_2$ [M + H]$^+$ 195.0689; found 195.0681.

5-Chloro-3-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine (18): Compound **18** was obtained from the Fischer reaction of 2-chloro-5-hydrazinopyridine (**7**) and (2,2-dimethoxyethyl)benzene, and was purified by column chromatography (petroleum ether/EtOAc: 8:2), yield 56% (0.128 g) after reflux, 24 h; 66% (0.151 g) after MW 160 °C, 5 min, m.p. 204 °C. IR: $\tilde{\nu}$ = 3395, 3128, 1602, 1544, 1498 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.72 (br. s, 1 H, NH), 8.05 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, 2′-H), 7.66 (d, $^3J_{H,H}$ = 2.9 Hz, 1 H, 2-H), 7.61 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, 6-H), 7.42 (t, $^3J_{H,H}$ = 8.3 Hz, 2 H, 3′-H), 7.26 (m, 1 H, 4′-H), 7.14 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, 7-H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 144.53 (C_{IV}), 143.29 (C_{IV}), 133.21 (C_{IV}), 128.70 (CH_{Ph}), 128.21 (C_{IV}), 126.80 (CH_{Ph}), 126.40 (CH), 125.71 (CH_{Ph}), 121.14 (CH), 117.32 (CH), 117.09 (C_{IV}) ppm. MS (IS$^+$): *m*/*z* = 229/231 [M + H]$^+$. HRMS (ESI): calcd. for $C_{13}H_{10}ClN_2$ [M + H]$^+$ 229.0533; found 229.0537.

5-Methyl-3-propyl-1*H*-pyrrolo[3,2-*b*]pyridine (19): Compound **19** was obtained from the Fischer reaction of 5-hydrazino-2-methylpyridine (**15**) and valeraldehyde, and was purified by column chromatography (petroleum ether/EtOAc, 8:2), yield 25% (0.043 g) after MW 160 °C, 20 min. Pale brown solid, m.p. 142 °C. IR: $\tilde{\nu}$ = 3128, 3040, 2956, 2925, 2869, 1569, 1413 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.16 (br. s, 1 H, NH), 7.48 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, 7-H), 7.25 (s, 1 H, 2-H), 6.94 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, 6-H), 2.82 (t, $^3J_{H,H}$ = 8.0 Hz, 2 H, CH_2-CH_2), 2.62 (s, 3 H, CH_3), 1.73 (sext, *J* = 8.0 Hz, 2 H, CH_2-CH_3), 0.97 (t, *J* = 8 Hz, 2 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.72 (C_{IV}), 144.96 (C_{IV}), 127.53 (C_{IV}), 124.79 (CH), 118.55 (CH), 116.78 (C_{IV}), 116.73 (CH), 26.09 (CH_3), 24.39 (CH_2), 23.10 (CH_2), 14.09 (CH_2-*C*H_3) ppm. MS (IS$^+$): *m*/*z* = 175.5 [M + H]$^+$. HRMS (ESI): calcd. for $C_{11}H_{15}N_2$ [M + H]$^+$ 175.1235; found 175.1222.

5-Methyl-3-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine (20): Compound **20** was obtained from the Fischer reaction of 5-hydrazino-2-methylpyridine (**15**) and (2,2-dimethoxyethyl)benzene, and was purified by column chromatography (petroleum ether/EtOAc, 8:2), yield 46% (0.096 g) after MW 160 °C, 5 min. Yellow solid, m.p. 148 °C; IR: $\tilde{\nu}$ = 3025, 2895, 1602, 1402 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.31 (s, 1 H, NH), 8.14 (dd, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 1.5 Hz, 2 H, 2′-H), 7.61 (d, $^3J_{H,H}$ = 2.6 Hz, 1 H, 2-H), 7.56 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H, 6-H), 7.43 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H, 3′-H), 7.22 (m, 1 H, 4′-H), 7.03 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H, 7-H), 2.71 (s, 4 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 152.01 (C_{IV}), 143.18 (C_{IV}), 134.15 (C_{IV}), 128.57 (CH_{Ph}), 127.87 (C_{IV}), 126.94 (CH_{Ph}), 125.97 (CH), 124.63 (CH), 118.97 (CH), 117.25 (CH), 116.75 (C_{IV}), 24.67 (CH_3) ppm. MS (IS$^+$): *m*/*z* = 209 [M + H]$^+$. HRMS (ESI): calcd. for $C_{14}H_{13}N_2$ [M + H]$^+$ 209.1079; found 209.1075.

2-Methoxy-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indole (23): Compound **23** was obtained from the Fischer reaction of 2-hydrazino-6-methoxypyridine (**22**) and cyclohexanone, and was purified by column chromatography (petroleum ether/EtOAc, 8:2), yield 31% (0.019 g) after MW 160 °C, 20 min. Pale yellow solid, m.p. 116 °C. IR: $\tilde{\nu}$ = 2928, 1618, 1563, 1461, 1415, 1206, 1025 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (s, 1 H, NH), 7.63 (d, $^3J_{H,H}$ = 8.3 Hz, 1 H, 4-H), 6.51 (d, *J* = 8.3 Hz, 1 H, 3-H), 3.94 (s, 3 H, CH_3O), 2.68 (t, $^3J_{H,H}$ = 5.6 Hz, 2 H, 8-H), 2.68 (t, $^3J_{H,H}$ = 5.6 Hz, 2 H, 5-H), 1.92–1.82 (m, 4 H, 6-H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.34 (C_{IV}), 145.96 (C_{IV}), 130.89 (C_{IV}), 128.70 (CH), 114.13 (C_{IV}), 108.85 (C_{IV}), 102.46 (CH), 53.42 (CH_3O), 23.14 (CH_2), 23.02 (CH_2), 22.98 (CH_2), 20.80 (CH_2) ppm. MS (IS$^+$): *m*/*z* = 203.5 [M + H]$^+$. HRMS (ES$^+$): calcd. for $C_{12}H_{15}N_2O$ [M + H]$^+$ 203.1184; found 203.1191.

3-Methoxy-1-methyl-6,7,8,9-tetrahydro-5*H*-pyrido[3,4-*b*]indole (26): Compound **26** was obtained from the Fischer reaction of 3-hydrazino-6-methoxy-2-methylpyridine (**25**) and cyclohexanone. Compound **26** was not isolated as a pure product after column chromatography, yield 16% (0.034 g). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.57 (s, 1 H, Ar), 3.94 (s, 3 H, OCH_3), 2.8–2.5 (m, 4 H), 2.55 (s, 3 H, CH_3), 1.9–1.7 (m, 4 H) ppm.

7-Methoxy-3-propyl-1*H*-pyrrolo[2,3-*c*]pyridine (28): Compound **28** was obtained from the Fischer reaction of 3-hydrazino-2-methoxypyridine (**27**) and valeraldehyde, and was purified by recrystallization (CH_2Cl_2/pentane), yield 53% (0.100 g) after reflux, 2 h; 32% (0.060 g) after MW 160 °C, 1 min. Pale brown solid, m.p. >250 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (s, 1 H, NH), 7.75 (d, $^3J_{H,H}$ = 5.7 Hz, 1 H, 5-H), 7.13 (d, $^3J_{H,H}$ = 5.7 Hz, 1 H, 4-H), 7.03 (d, $^3J_{H,H}$ = 2.2 Hz, 1 H, 2-H), 4.09 (s, 3 H, CH_3O), 2.69 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H, CH_2-CH_2), 1.70 (sext, $^3J_{H,H}$ = 7.5 Hz, 2 H, CH_2-CH_3), 0.97 (t, $^3J_{H,H}$ = 7.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.18 (C_{IV}), 134.71 (CH), 133.51 (C_{IV}), 123.19 (CH), 121.12 (C_{IV}), 117.44 (C_{IV}), 108.83 (CH), 52.96 (CH_3-O), 27.22 (CH_2), 23.44 (CH_2), 13.99 (CH_3) ppm. MS (IS$^+$): 191 [M + H]$^+$. HRMS (ESI): calcd. for $C_{11}H_{15}N_2O$ [M + H]$^+$ 191.1184; found 191.1181.

3-Propyl-1,6-dihydro-7*H*-pyrrolo[2,3-*c*]pyridin-7-one (31): Compound **31** was obtained from the Fischer reaction of 3-hydrazino-2-methoxypyridine (**27**) and valeraldehyde, and was purified by recrystallization (CH_2Cl_2/pentane), yield 93% (0.163 g) after MW 160 °C, 20 min. Pale brown solid, m.p. 216 °C (dec). IR: $\tilde{\nu}$ = 3152,

2956, 2927, 2868, 1646 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ = 11.61 (s, 1 H, NH), 10.80 (s, 1 H, NH), 7.05 (s, 1 H, 2-H), 6.83 (m, 1 H, 5-H), 6.41 (d, $^3J_{H,H}$ = 6.9 Hz, 1 H, 4-H), 2.54–2.51 (m, 2 H, CH_2-CH_2), 1.68–1.48 (sext, $^3J_{H,H}$ = 8.0 Hz, 2 H, CH_2-CH_3) 0.88 (t, $^3J_{H,H}$ = 8.0 Hz, 2 H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 155.54 (C=O), 129.86 (C_{IV}), 124.44 (CH), 124.25 (C_{IV}), 124.19 (CH), 117.15 (C_{IV}), 99.78 (CH), 27.05 (CH_2), 23.94 (CH_2), 14.28 (CH_3) ppm. MS (IS^+): 177 $[M + H]^+$. HRMS (ESI): calcd. for $C_{10}H_{12}NaN_2O$ $[M + Na]^+$ 199.0847; found 199.0845.

3-Phenyl-1,6-dihydro-7*H*-pyrrolo[2,3-*c*]pyridin-7-one (32): Compound **32** was obtained from the Fischer reaction of 3-hydrazino-2-methoxypyridine (**27**) and (2,2-dimethoxyethyl)benzene, and was purified by recrystallization (CH_2Cl_2/pentane), yield 80% (0.168 g) after MW 160 °C, 5 min. Yellow solid, m.p. 264 °C (dec). IR: $\tilde{\nu}$ = 3133, 1637, 1575 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ = 12.18 (br. s, 1 H, NH), 11.02 (br. s, 1 H, NH), 7.65–7.53 (m, 3 H, 2-H, 2′-H), 7.40 (t, $^3J_{H,H}$ = 7.7 Hz, 2 H, 3′-H), 7.23 (t, $^3J_{H,H}$ = 7.7 Hz, 1 H, 4′-H), 6.95 (m, 1 H, 5-H), 6.70 (d, $^3J_{H,H}$ = 7.0 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 155.55 (C=O), 135.45 (C_{IV}), 129.27 (CH_{Ph}), 127.89 (C_{IV}), 126.98 (CH_{Ph}), 126.14 (CH), 125.63 (CH), 125.29 (C_{IV}), 124.89 (CH), 118.25 (C_{IV}), 99.95 (CH) ppm. MS (IS^+): *m*/*z* = 211 $[M + H]^+$. HRMS (ESI^+): calcd. for $C_{13}H_{10}NaN_2O$ $[M + Na]^+$ 233.0691; found 233.0691.

2,5,6,7,8,9-Hexahydro-1*H*-β-carbolin-1-one (33): Compound **33** was obtained from the Fischer reaction of 3-hydrazino-2-methoxypyridine (**27**) and cyclohexanone, and was purified by recrystallization (CH_2Cl_2/pentane), yield 98% (0.184 g) after MW 160 °C, 20 min. Pale brown solid, m.p. 174 °C (dec). IR: $\tilde{\nu}$ = 2112, 2948, 2920, 2833, 1651 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ = 11.40 (br. s, 1 H, NH), 10.70 (br. s, 1 H, NH), 6.80 (m, 1 H, 3-H), 7.00 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, 4-H), 2.61–2.51 (m, 4 H, 5-H, 8-H), 1.74 (m, 4 H, 6-H, 7-H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 151.13 (C=O), 136.64 (C_{IV}), 129.51 (C_{IV}), 124.32 (CH), 122.78 (C_{IV}), 110.80 (C_{IV}), 99.32 (CH), 23.34 (CH_2), 23.22 (CH_2), 23.11 (CH_2), 21.12 (CH_2) ppm. MS (IS^+): *m*/*z* = 189 $[M + H]^+$. HRMS (ESI^+): calcd. for $C_{11}H_{12}NaN_2O$ $[M + Na]^+$ 211.0847; found 211.0857.

7-Chloro-3-propyl-1*H*-pyrrolo[2,3-*c*]pyridine (36): Compound **36** was obtained from the Fischer reaction of 2-chloro-3-hydrazinopyridine (**35**) and valeraldehyde, and was purified by column chromatography (petroleum ether/EtOAc, 8:2), yield 36% (0.070 g) after reflux, 24 h; 96% (0.187 g) after MW 160 °C, 20 min. Pale brown solid, m.p. 186 °C (dec). IR: $\tilde{\nu}$ = 3133, 2961, 1615, 1096 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.46 (s, 1 H, NH), 8.02 (d, $^3J_{H,H}$ = 5.5 Hz, 1 H, 5-H), 7.45 (d, $^3J_{H,H}$ = 5.5 Hz, 1 H, 4-H), 7.19 (s, 1 H, 2-H), 2.71 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H, CH_2-CH_2), 1.72 (sext, $^3J_{H,H}$ = 7.5 Hz, 2 H, CH_2-CH_3), 0.98 (t, $^3J_{H,H}$ = 7.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.59 (CH), 134.23 (C_{IV}), 134.18 (C_{IV}), 130.09 (C_{IV}), 125.38 (CH), 118.19 (C_{IV}), 113.61 (CH), 27.07 (CH_2), 23.29 (CH_2), 13.95 (CH_3) ppm. MS (IS^+): *m*/*z* = 195/197 $[M + H]^+$. HRMS (ESI): calcd. for $C_{10}H_{12}ClN_2$ $[M + H]^+$ 195.0689; found 195.0688.

1-Chloro-6,7,8,9-tetrahydro-5*H*-β-carboline (37): Compound **37** was obtained from the Fischer reaction of 2-chloro-3-hydrazinopyridine (**35**) and cyclohexanone, and was purified by recrystallization (CH_2Cl_2/pentane), yield 51% (0.105 g) after reflux, 48 h; 65% (0.134 g) after MW 160 °C, 1 min. Pale brown solid, m.p. 146 °C (dec). IR: $\tilde{\nu}$ = 3171, 2929, 2847, 1620, 1562 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 11.51 (br. s, 1 H, NH), 7.82 (d, $^3J_{H,H}$ = 5.4 Hz, 1 H, 3-H), 7.36 (d, $^3J_{H,H}$ = 5.4 Hz, 1 H, 4-H), 2.76 (m, $^3J_{H,H}$ = 5.4 Hz, 2 H, 8-H), 2.62 (m, $^3J_{H,H}$ = 5.4 Hz, 2 H, 5-H), 1.88–1.76 (m, 4 H, 6-H, 7-H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 141.07 (C_{IV}), 137.09 (CH), 134.14 (C_{IV}), 132.93 (C_{IV}), 129.20 (C_{IV}), 112.84 (CH), 110.20 (C_{IV}), 23.29 (CH_2), 22.97 (CH_2), 22.82 (CH_2), 20.91 (CH_2) ppm. MS (IS^+): *m*/*z* = 207/209 $[M + H]^+$. HRMS (ESI^+): calcd. for $C_{11}H_{12}ClN_2O$ $[M + H]^+$ 207.0689; found 207.0680.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra.

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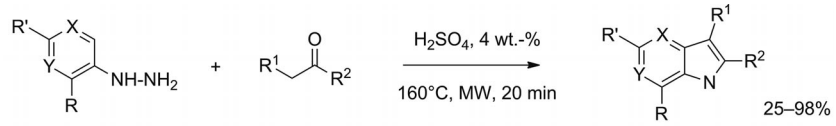

R, R' = Hal or poor EDG R^1, R^2 = alkyl and/or Ph X = N, Y = CH or X = CH, Y = N

Fischer indole cyclization starting from aminopyridines is a very efficient cascade sequence leading to 4- and 6-azaindoles. The scope of the substituents on the pyridine ring was extended to include halogens and to weakly electron-donating substituents by using microwave irradiation.

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Extending the Scope of the Aza-Fischer Synthesis of 4- and 6-Azaindoles

Keywords: Synthetic methods / Microwave chemistry / Cyclization / Rearrangement / Nitrogen heterocycles

