Synthesis of Novel 1,7-Naphthyridines by Friedländer Condensation of Pyridine Substrates

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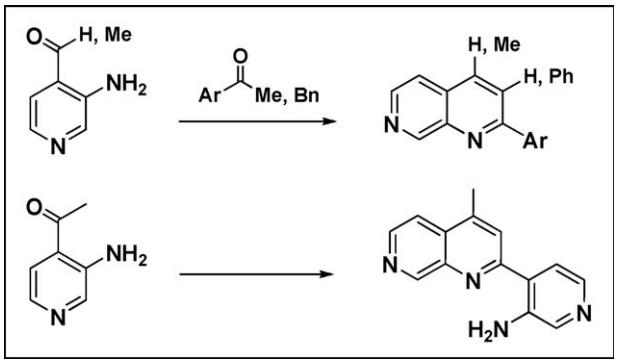

The general ability of appropriate pyridyl compounds (aldehyde or ketone) to undergo Friedländer condensation to give different 1,7-naphthyridines has been demonstrated. 2,4-Disubstituted 1,7-naphthyridine **8** was prepared from 3-amino-4-acetylpyridine (**6**) and ketone **4** (82%). The Friedländer self-condensation of pyridyl substrate **6** is reported, as well. The dimer product, 2-(3-aminopyridin-4-yl)-4-methyl-1,7-naphthyridine (**7**), was obtained in 97% yield. 2-Aryl- and 2,3-diaryl-1,7-naphthyridines (**16**–**18**) were prepared from 3-aminoisonicotinaldehyde (**13**) and arylketones **4**, **14**, and **15** (28–71%). The key substrates **6** and **13** are readily available via the improved pyridine nitration method.

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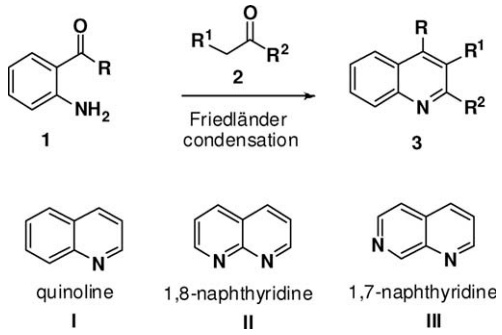
INTRODUCTION

The Friedländer reaction is a cyclisation method consisting of (i) a base- or acid-promoted aldol condensation of an aromatic 2-amino-substituted carbonyl compound **1**, with an appropriate ketone **2**, possessing a reactive α-CH_2 group and (ii) an amine-carbonyl cyclodehydration to form an imine moiety (Scheme 1). The Friedländer annulations are often carried out by refluxing an ethanolic solution of the reactants in the presence of NaOH. This cyclocondensation method is widely used in heterocyclic chemistry, in particular, for the preparation of substituted quinolines **3**. Recent advances in the Friedländer reaction [1], as well as the Friedländer approach for quinoline synthesis [2] have been reviewed. New protocols for the preparation of quinoline derivatives by Friedländer annulation reactions have lately been reported [3–7].

The classical Friedländer reaction conditions make use of 2-aminobenzaldehyde (**1**, R=H) to afford quinolines, **I**, **3** (Scheme 1). However, in recent years, the substrate has been replaced with 2-amino-nicotinaldehyde, allowing the preparation of some 1,8-naphthyridines, **II** [5,8–14]. Naphthyridines provide an important scaffold for a variety of compounds of unique biological activities. Their synthesis, properties, reactivity and biological activity are covered in several reviews [15–17]. The synthetic use of the Friedländer reaction for preparation of 1,7-naphthyridines (**III**) has, however, been limited by the inconvenient preparation methods for the necessary 2-amino carbonyl compounds, such as 3-aminoisonicotinaldehyde (**13**) [18]. Therefore, the Friedländer approach has nearly not been applied for the preparation of 1,7-naphthyridines [19] and the biological activity of 1,7-naphthyridines has been less studied. 1,7-Naphthyridines are, however, reported to be more active than the corresponding 1,8-isomers as potential new therapeutic antitumor agents [20]. Recently, 1,7-naphthyridine derivatives have been identified as selective Tpl2 kinase inhibitors. Tpl2 is an attractive target for the treatment of rheumatoid arthritis [21].

Based on the fact that a number of substituted 3-nitropyridines have become readily available through an improved nitration method [22,23], we have access to appropriate *o*-amino-4-carbonylpyridine substrates, such as 3-amino-4-acetylpyridine (**6**, Scheme 2) and 3-amino-4-pyridinecarboxaldehyde (**13**, Scheme 3), for the preparation of 1,7-naphthyridines. The present results on 1,7-naphthyridine syntheses are part of an investigation of

Scheme 1



the chemistry of nitropyridines, which is in progress in our laboratories.

RESULTS AND DISCUSSION

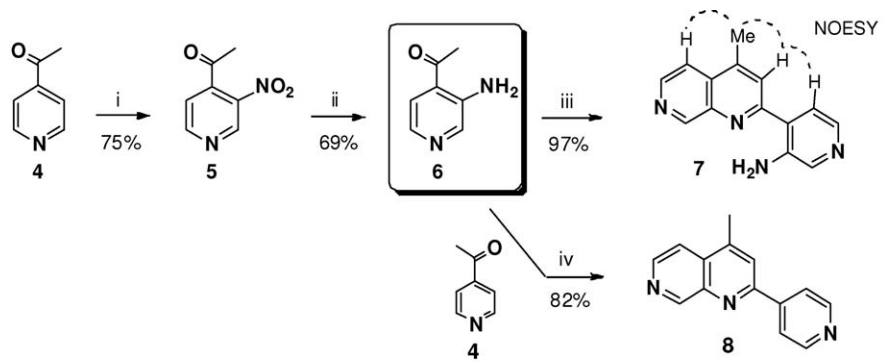
3-Amino-4-acetylpyridine (**6**) was prepared by nitration and reduction (Scheme 2) [24]. The dual functionality of aminopyridylketone **6** enables an internal Friedländer self-condensation. In fact, substrate **6** underwent a Friedländer dimerisation reaction by treatment of excess (1.5 equiv) NaH in dry THF at 0–20°C in 2 h. The 1,7-naphthyridine product **7** was obtained in quantitative yield, which is exceptional compared to the highest yields (80–90%) normally reported for the Friedländer reaction [1]. The structure was unambiguously confirmed by HMBC and HSQC experiments. NOESY experiments of product **7** showed a through-space proximity between H_3 and both C_4-$C\underline{H}_3$ and pyridine-H_5 as well as between C_4-$C\underline{H}_3$ and H_5.

Aminoketones are less frequently used in the Friedländer reactions than aminoaldehydes, since the self-condensation, as discussed above, may represent a problem and therefore limit the scope and generality of the reaction. Therefore, the capability of 3-amino-4-acetylpyridine (**6**) to undergo regular Friedländer condensation with other ketones and, thus, to exclude dimerisation, was studied. Indeed, treatment of methylpyridylketone **4** with NaH in THF and subsequent addition of substrate **6**, afforded the 2,4-disubstituted 1,7-naphthyridine **8**. The ratio between the desired product **8** and the dimer product **7** increased by reducing the amount of NaH from 2.5 to 1.1 equivalent. Rising the initial reaction temperature from 0 to 20°C to assure full deprotonation of ketone **4** before the addition of substrate **6**, increased the yield of the target product **8** twofold. As a result, the optimized reaction conditions allowed the isolation of 1,7-naphthyridine **8** in 82% yield.

3-Aminoisonicotinaldehyde (**13**) was also used as a substrate to demonstrate the general potential of pyridyl compounds for the preparation of 1,7-naphthyridines by the Friedländer condensation (Scheme 3). Methyl 3-aminoisonicotinate (**11**), readily accessible from methyl isonicotinate (**9**) by nitration and reduction [24], was transformed into the corresponding Weinreb amide (**12**, 73%), using the Me_2AlCl/MeONHMe·HCl reagent system [25]. Following reduction with $LiAlH_4$ afforded 3-aminoisonicotinaldehyde (**13**, 90%).

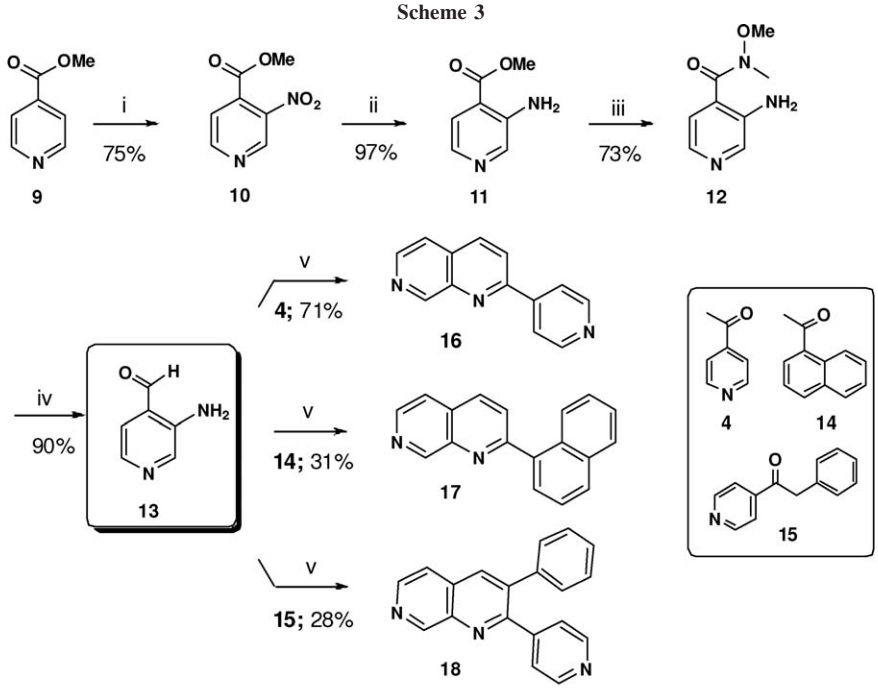
Friedländer reactions of pyridyl substrate **13** with the respective ketones **4**, **14**, and **15** and 2–2.5 equiv NaH in THF gave the 2-aryl and 2,3-diaryl-1,7-naphthyridines **16–18**. Ketone **15** was prepared from isonicotinaldehyde via 4-dimethoxymethylpyridine, BuLi proton abstraction, subsequent nucleophilic substitution of benzylchloride and hydrolysis [26]. Ketones **4** and **14** were commercially available. Product **16** has previously been prepared by standard Friedländer reaction conditions (NaOH/EtOH) in lower yield (60%) [19] than obtained by our alternative NaH/THF method (71%). The novel products **17** and **18** were obtained in 28–31% yield, due to the formation of unidentified by-products. The yields of products **16–18** were not influenced by the order of reactant addition. HMBC and HSQC data obtained by

Scheme 2



Reagents and conditions: (i) 1. N_2O_5 in $MeNO_2$, 0 °C, 2. $NaHSO_3$ in MeOH/H_2O; (ii) $Na_2S_2O_4$ in EtOH, reflux, 6 h; (iii) NaH, THF 0 °C → rt, 2 h; (iv) NaH, THF, rt, 2 h.

Scheme 3



Reagents and conditions: (i) 1. N_2O_5 in $MeNO_2$, 0 °C, 2. $NaHSO_3$ in $MeOH/H_2O$; (ii) $Na_2S_2O_4$ in EtOH, reflux, 6 h; (iii) MeONHMe·HCl/Me_2AlCl in DCM, rt, 20 h; (iv) $LiAlH_4$ in THF, -15 °C; (v) NaH in THF, 0 °C - rt, 2 h.

2D NMR experiments of products **16–18** confirmed the respective structures.

CONCLUSION

Optimized reaction conditions allowed Friedländer cyclocondensation of substrate **6** and methylpyridylketone **4** to afford 2,4-disubstituted 1,7-naphthyridine **8** (82%). 3-Amino-4-acetylpyridine (**6**) underwent a Friedländer self-condensation by treatment of excess NaH to afford the 1,7-naphthyridine product **7** in quantitative yield. 3-Aminoisonicotinaldehyde (**13**) reacted by Friedländer condensation with arylketones **4**, **14**, and **15** to give 2-aryl- and 2,3-diaryl-1,7-naphthyridines **16–18** (28–71%). Substrates **6** and **13** were readily obtained by pyridine nitration and reduction. Thus, the present results demonstrate that the pyridine nitration pathway followed by Friedländer condensation represent a convenient strategy for the preparation of 1,7-naphthyridines.

EXPERIMENTAL

General. Chemicals: NaH, $LiAlH_4$, MeONHMe·HCl, Me_2AlCl (Aldrich), 4-acetylpyridine (**4**, Fluka), 1-acetonaphthone (**14**, Aldrich). 3-Amino-4-acetylpyridine (**6**) [24], methyl 3-aminoisonicotinate (**11**) [24], and 2-phenyl-1-(pyridine-4-yl)ethanone (**15**) [26] were prepared as described in literature. Solvents: *pro analysi* quality. Dry THF and DCM were collected from a MB SPS-800 solvent purification system. All reactions were performed under argon atmosphere in predried glassware. NMR: Bruker Avance DPX 400 MHz. ^1H and ^{13}C chemical shifts are reported in ppm downfield from TMS. *J* values are given in Hz. ESI-MS accurate mass determination was performed on a Waters QTOF II instrument. IR: Nicolet 20SXC FT-IR spectrophotometer. IR spectra were recorded using a Smart Endurance reflexion cell, unless KBr are specified. All melting points are uncorrected and were recorded on a Stuart apparatus. Flash chromatography: SiO_2 (SDS, 60 Å, 40–63 μm).

2-(3-Aminopyridin-4-yl)-4-methyl-1,7-naphthyridine (7). A solution of amine **6** (113 mg, 0.830 mmol) in dry THF (3 mL) was added dropwise over 10 min to a solution of NaH (30.0 mg, 1.25 mmol) in dry THF (2 mL) at 0°C and kept stirring for 15 min. The reaction was allowed to heat to room temperature and stirred for 2 h before quenching with water (15 mL). The mixture was extracted with EtOAc (4 × 20 mL) and the combined organic phases were dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by flash column chromatography (gradient; 5–10% $MeOH/CH_2Cl_2$) to give 95 mg (97%) of the title compound **7** as a yellow solid, mp 250–251°C, pure by NMR; R_f 0.35 (10% $MeOH/CH_2Cl_2$); IR (KBr): 3348, 3244, 3123, 1602, 1561, 1503, 1434, 1240, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.47 (d, $J = 0.8$ Hz, 1H, H8), 8.67 (d, $J = 5.6$ Hz, 1H, H6), 8.27 (s, 1H, py'-H2), 8.07 (d, $J = 5.2$ Hz, 1H, py'-H6), 7.93 (s, 1H, H3), 7.80 (dd, $J = 5.6$, 0.8 Hz, 1H, H5), 7.55 (d, $J = 5.2$ Hz, 1H, py'-H5), 6.31 (br s, 2H, $-NH_2$), 2.78 (s, 3H, C4-CH_3); ^{13}C NMR

(100 MHz, $CDCl_3$): δ_C 158.2 (C2), 153.9 (C8), 144.8 (C4), 144.2 (C6), 142.9 (py'-C3), 141.7 (C8a), 140.9 (py'-C2), 138.3 (py'-C6), 130.2 (C4a), 124.9 (py'-C4), 123.6 (C3), 121.9 (py'-C5), 116.3 (C5), 18.5 (C4-CH_3); NMR assignments are based on HMBC, HSQC, and NOESY experiments; ESI-HRMS: calcd for $[M + H]^+$ $C_{14}H_{13}N_4$: 237.1135; obsd 237.1151; calcd for $[M + Na]^+$ $C_{14}H_{12}N_4Na$: 259.0954; obsd 259.0962.

4-Methyl-2-(pyridin-4-yl)-1,7-naphthyridine (8). To a solution of NaH (18.0 mg, 0.750 mmol) in dry THF (2 mL) at 0°C was added ketone **4** (100 mg, 0.825 mmol). The reaction was stirred for 15 min at 0°C and then 15 min at room temperature. Amine **6** (94.0 mg, 0.690 mmol) in THF (1 mL) was added dropwise over 15 min and the reaction was stirred for 2 h at room temperature. The reaction mixture was diluted with THF (1 mL) before it was added to water (20 mL). After extraction with EtOAc (3 × 20 mL), drying over $NaSO_4$ and concentration under reduced pressure, the crude product was purified by flash chromatography (gradient: 5–10% MeOH/CH_2Cl_2) to give 126 mg (82%) of the title compound **8** as a white solid, mp 135–136°C, pure by NMR. Compound **7** was isolated as a by-product (8 mg, 10%). **8**: R_f 0.15 (5% MeOH/CH_2Cl_2); IR: 1595, 1417, 837, 829, 750, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.57 (s, 1H, H8), 8.81 (d, J = 5.6 Hz, 2H, py'-H2, -H6), 8.67 (d, J = 5.6 Hz, 1H, H6), 8.06 (d, J = 5.6 Hz, 2H, py'-H3, -H5), 7.92 (s, 1H, H3), 7.79 (d, J = 5.6 Hz, 1H, H5), 2.79 (s, 3H, C4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 155.9 (C2), 155.4 (C8), 150.8 (py'-C2, -C6), 146.0 (py'-C4), 145.2 (C4), 144.3 (C6), 143.2 (C8a), 131.2 (C4a), 122.7 (C3), 121.7 (py'-C3, -C5), 116.4 (C5), 18.6 (C4-CH_3); NMR assignments are based on HMBC and HSQC experiments; ESI-HRMS: calcd for $[M + H]^+$ $C_{14}H_{12}N_3$: 222.1026; obsd 222.1029.

3-Amino-*N*-methoxy-*N*-methylisonicotinamide (12). To a solution of MeONHMe·HCl (2.00 g, 20.5 mmol) in dry CH_2Cl_2 (50 mL) at 0°C was added Me_2AlCl (1 *M* in hexanes, 20.5 mL, 20.5 mmol) dropwise over 30 min. The reaction was allowed to heat to room temperature over 2 h. A solution of amine **11** (1.265 g, 8.21 mmol) in dry CH_2Cl_2 (50 mL) was added and the reaction was stirred for 20 h. A solution of borate buffer (pH 8.0, 80 mL) was added and stirring was continued for 10 min. Extraction with CH_2Cl_2 (4 × 60 mL), drying over Na_2SO_4, concentration under reduced pressure and flash chromatography (gradient: 5–10% MeOH/CH_2Cl_2) afforded the title compound **12** as a white solid, 1.09 g (73%), mp 94–95°C, pure by NMR; R_f 0.17 (5% MeOH/CH_2Cl_2); IR: 3449, 3310, 3141, 1623, 1583, 1418, 1384, 983, 968, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.18 (s, 1H, py-H2), 7.98 (d, J = 4.8 Hz, 1H, py-H6), 7.25 (d, J = 4.8 Hz, 1H, py-H5), 4.64 (br s, 2H, NH_2), 3.57 (s, 3H, -OCH_3), 3.37 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.5 (C=O), 141.7 (py-C3), 139.8 (py-C2), 138.2 (py-C6), 123.0 (py-C4), 121.8 (py-C5), 61.5 (O-CH_3), 33.3 (N-CH_3); NMR assignments are based on HMBC and HSQC experiments; ESI-HRMS: calcd for $[M + H]^+$ $C_8H_{12}N_3O_2$: 182.0924; obsd 182.0931.

3-Aminoisonicotinaldehyde (13). A solution of Weinreb amide **12** (138 mg, 0.759 mmol) in dry THF (2 mL) was added dropwise over 15 min to a solution of $LiAlH_4$ (86.4 mg, 2.28 mmol) in dry THF (3 mL) at −15°C. The reaction was stirred for 1.5 h at −15°C and quenched by pouring the mixture into a phosphate buffer solution (1 *M*, pH 7.5, 30 mL) at 0°C. The aqueous solution was extracted with ether (3 × 20 mL), dried over Na_2SO_4 and concentrated to give the title compound **13** as a yellow solid, 83 mg (90%), pure by ^1H NMR; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.97 (s, 1H, -CHO), 8.24 (s, 1H, py-H2), 8.07 (d, J = 5.2 Hz, 1H, py-H6), 7.33 (d, J = 5.2 Hz, 1H, py-H5), 6.00 (br s, 2H, NH_2).

General procedure for the formation of the 1,7-naphthyridines 16–18. 3-Aminoisonicotinaldehyde (**13**) in dry THF (1 mL) was added to a solution NaH in dry THF (1 mL) at 0°C. The appropriate ketone **4**, **14**, or **15** in dry THF (2 mL) was added dropwise over 10 min. The reaction was stirred for 15 min at 0°C before it was allowed to heat to room temperature and stirred for 2 h. Water (15 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The products **16–18** were isolated after purification by flash column chromatography.

2-(Pyridin-4-yl)-1,7-naphthyridine (16). The title compound was prepared form aminoaldehyde **13** (34.0 mg, 0.278 mmol), ketone **4** (37.0 mg, 0.305 mmol) and NaH (15.0 mg, 0.625 mmol). After flash column chromatography (gradient: 5–10% MeOH/CH_2Cl_2), product **16** [19] was isolated as a white solid, 41 mg (71%), mp 157–158°C, pure by NMR; R_f 0.45 (10% MeOH/CH_2Cl_2); IR (KBr): 3039, 1596, 1489, 1420, 948, 828, 788, 705, 682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.61 (s, 1H, H8), 8.82 (dd, J = 4.8, 1.6 Hz, 2H, py'-H2, -H6), 8.66 (d, J = 5.6 Hz, 1H, H6), 8.30 (d, J = 8.4 Hz, 1H, H4), 8.11 (d, J = 8.4 Hz, 1H, H3), 8.08 (dd, J = 4.8, 1.6 Hz, 2H, py'-H3, -H5), 7.70 (d, J = 5.6 Hz, 1H, H5); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.3 (C2), 154.9 (C8), 150.9 (py'-C2, -C6), 145.7 (py'-C4), 144.4 (C6), 143.4 (C8a), 136.2 (C4), 130.7 (C4a), 122.6 (C3), 121.6 (py'-C3, -C5), 119.7 (C5); NMR assignments are based on HMBC and HSQC experiments; ESI-HRMS: calcd for $[M + H]^+$ $C_{13}H_{10}N_3$: 208.0869; obsd 208.0880; calcd for $[M + Na]^+$ $C_{13}H_9N_3Na$: 230.0689; obsd 230.0691.

2-(Naphthalen-1-yl)-1,7-naphthyridine (17). The title compound was prepared form aminoaldehyde **13** (29.0 mg, 0.237 mmol), ketone **14** (42.0 mg, 0.247 mmol), and NaH (15.0 mg, 0.625 mmol). After flash column chromatography [EtOAc/pentane (1:1)], product **17** was isolated as a white solid, 19 mg (31%), mp 116–117°C, pure by NMR; R_f 0.27 [EtOAc/pentane (1:1)]; IR: 3045, 1598, 1496, 1409, 1241, 942, 855, 803, 789, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.64 (s, 1H, H8), 8.69 (d, J = 5.6 Hz, 1H, H6), 8.28 (d, J = 8.4 Hz, 1H, H4), 8.12 (m, 1H, Np'-H), 7.97 (m, 2H, Np'-H), 7.92 (d, J = 8.4 Hz, 1H, H3), 7.74 (d, J = 5.6 Hz, 1H, H5), 7.72 (m, 1H, Np'-H), 7.62 (m, 1H, Np'-H) 7.52 (m, 2H, Np'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 161.4 (C2), 154.7 (C8), 144.1 (C6), 143.4 (C8a), 138.0 (Np'-C_q), 135.1 (C4), 134.2 (Np'-C_q), 131.2 (Np'-C_q), 130.1 (C4a), 129.9 (Np'-C), 128.8 (Np'-C), 128.3 (Np'-C), 127.5 (C3), 127.1 (Np'-C), 126.4 (Np'-C), 125.6 (Np'-C), 125.5 (Np'-C), 119.9 (C5); NMR assignments are based on HMBC and HSQC experiments; ESI-HRMS: calcd for $[M + H]^+$ $C_{18}H_{13}N_2$: 257.1073; obsd 257.1082.

3-Phenyl-2-(pyridin-4-yl)-1,7-naphthyridine (18). The title compound was prepared form aminoaldehyde **13** (47.0 mg, 0.385 mmol), ketone **15** (82 mg, 0.416 mmol) and NaH (19.0 mg, 0.792 mmol). After flash column chromatography (gradient: 5–10% MeOH/CH_2Cl_2), product **18** was isolated as an orange solid, 30 mg (28%), mp 131-132°C, pure by NMR; R_f 0.16 (5%

MeOH/CH_2Cl_2); IR (KBr): 3030, 1598, 1586, 1408, 970, 909, 831, 819, 767, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.61 (s, 1H, H8), 8.68 (d, $J = 5.6$ Hz, 1H, H6), 8.57 (d, $J = 6.0$ Hz, 2H, py'-H2, -H6), 8.21 (s, 1H, H4), 7.72 (d, $J = 5.6$ Hz, 1H, H5), 7.36 (m, 5H, py'-H3, -H5, Ph-H3, -H4, -H5), 7.25 (m, 2H, Ph-H2, -H6); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.6 (C2), 154.6 (C8), 149.9 (py'-C2, -C6), 147.3 (py'-C4), 144.7 (C6), 142.4 (C8a), 138.7 (C3), 138.3 (Ph—C1), 136.6 (C4), 130.5 (C4a), 129.7 (Ph-C2, -C6), 128.9 (Ph-C3, -C5), 128.6 (Ph-C4) 124.5 (py'-C3, -C5), 119.7 (C5); NMR assignments are based on HMBC and HSQC experiments; ESI-HRMS: calcd for $[M + H]^+$ $C_{19}H_{14}N_3$: 284.1182; obsd 284.1185; calcd for $[M + Na]^+$ $C_{19}H_{13}N_3Na$: 307.1032; obsd 307.1032.

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