A One-Pot Method for the Synthesis of Naphthyridines via Modified Friedländer Reaction

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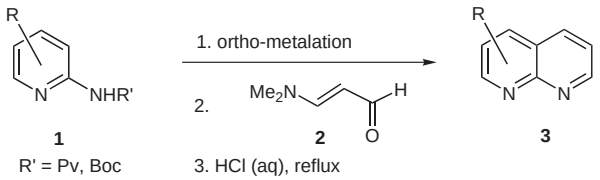
Abstract: A one-pot method for the preparation of 1,8-naphthyridine derivatives is reported. The method involves the dimetalation of an appropriate *N*-2-pyridylpivalamide or *tert*-butylcarbamate followed by reaction with a β-dimethylamino or β-alkoxyacrolein derivative. This method is also applicable to 1,6-naphthyridines.

Key words: pyridines, directed ortho-metalation, cyclization, naphthyridines

Recently there has been increased interest in the synthesis of 1,8-naphthyridines and their application in medicinal chemistry as quinoline bioisosteres.[1] Traditionally, the cyclocondensation of amino pyridines with diethyl methoxymethylenemalonate or similar derivatives (EMME synthesis) has provided entry into the naphthyridine core.[2] In order to prepare even the simplest mono- and disubstituted 1,8-naphthyridines, it was necessary to subject the products derived from EMME synthesis to a lengthy and low-yielding series of tranformations.[3] A more direct method of naphthyridine preparation is the reaction of amino pyridines with an α,β-unsaturated ketones or aldehydes (Skraup or Doebner–Miller syntheses). This cyclization is carried out in hot sulfuric acid and affords poor yields with all but strongly activated pyridines.[4] The most efficient method of construction of naphthyridine ring appears to be the extension of the Friedländer quinoline synthesis pioneered by Hawes.[5,6] In this method, an amino pyridine containing an *ortho*-carbonyl functionality is reacted with an enolizable carbonyl compound. However, a significant disadvantage of this approach is the limited commercial availability of *ortho*-carbonyl substituted amino pyridines. In most cases these starting materials have to be prepared from the corresponding amino pyridines in 3–4 steps with only a moderate yield in the crucial ortho-metalation–functionalization step.[6a,7]

As part of a recent research program, we required a general route to variously substituted 1,8-naphthyridines. Multiple attempts to reproduce yields obtained by Hamada[8] following his modified Skraup synthesis procedure were not successful in our hands.[9] The regular Friedländer condensation using *ortho*-formyl substituted amino pyridines was considered and rejected due to its lengthiness and mediocre yield (vide supra). At this point our attention was attracted by an earlier published synthesis of quinolines via a modification of the Friedländer reaction.[10] This synthesis employed a one-pot reaction of the ortho-metalated anilides with a masked malondialdehyde species followed by an acid-mediated cyclization. We expected that extension of this methodology to naphthyridines would allow an efficient two-step preparation of 1,8-naphthyridines from commercially available amino pyridines.

We were, therefore, pleased to find out that the unsubstituted 1,8-naphthyridine **3a** can be obtained in high yield from pivalamide **1a** derived in turn from 2-amino pyridine (R = H, R′ = Pv). The dianion of **1a** could be formed by treatment of a THF solution of the pivalamide with 2.2 equivalents of *n*-butyllithium.[7a] Subsequent reaction with β-dimethylaminoacrolein (**2**) followed by heating to reflux in aqueous acid effected smooth conversion to the required 1,8-naphthyridine in 80% overall yield (Scheme 1 and Table 1).



Scheme 1

Table 1 Synthesis of 1,8-Naphthyridine Using Various Procedures[a]

Pyridine	R	R′	Procedure	Product	Yield (%)
1a	H	Pv	A	**3a**	80
1b	4-Me	Pv	B	**3b**	77
1c	5-Me	Pv	A	**3c**	60
1d	5-Cl	Pv	A	**3d**	61
1e	4-Et	Pv	B	**3e**	82
1f	4-Cl	Boc	C	**3f**	30
1g	5-Cl	Boc	C	**3d**	50

[a] Procedure A: *n*-BuLi, THF, –70 °C to 0 °C. Procedure B: *t*-BuLi, Et_2O, –70 °C to –10 °C. Procedure C: *n*-BuLi, TMEDA, THF, –70 °C to –50 °C.

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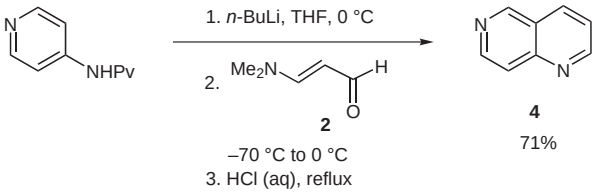
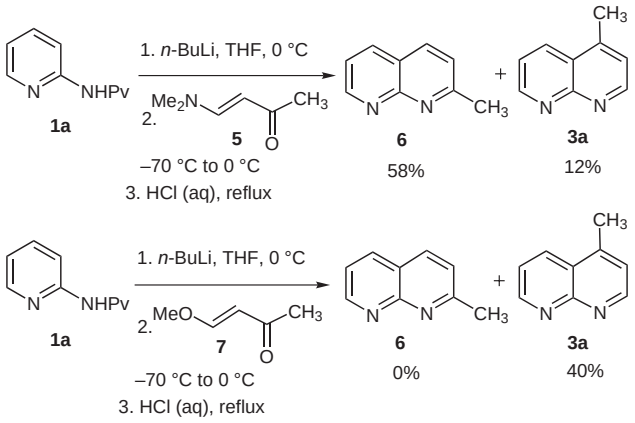
This procedure tolerates a variety of base-stable substituents. The pivaloyl group could also be substituted by the *tert*-butyloxycarbamoyl group, although the yields are somewhat lower (Table 1). In order to form the corresponding anions, the conditions recommended in the literature[11] (also see experimental part) were employed.

The above cyclization sequence was not limited to only 1,8-naphthyridine synthesis. 1,6-Naphthyridine (**4**) could also be readily obtained from *N*-4-pyridylpivalamide in 71% yield using similar conditions (Scheme 2).



Scheme 2

In an attempt to further explore the scope of this transformation, the dianion of **1a** was treated with methyl vinyl ketone derivative **5** then heated in the presence of aqueous hydrochloric acid. This afforded a mixture of 2-methyl-1,8-naphthyridine (**6**) and the 4-regioisomer **3a** in a 5:1 ratio, respectively. Furthermore, this regioselectivity could be readily reversed by utilizing alternate reagent **7**, in which the dimethylamino group has been replaced by a methoxy group. Repeating the same experiment but substituting **7** for **5** resulted in the formation of 4-methyl-1,8-naphthyridine (**3a**) in 40% yield with none of the 2-methyl isomer **6** observed, as shown in Scheme 3.

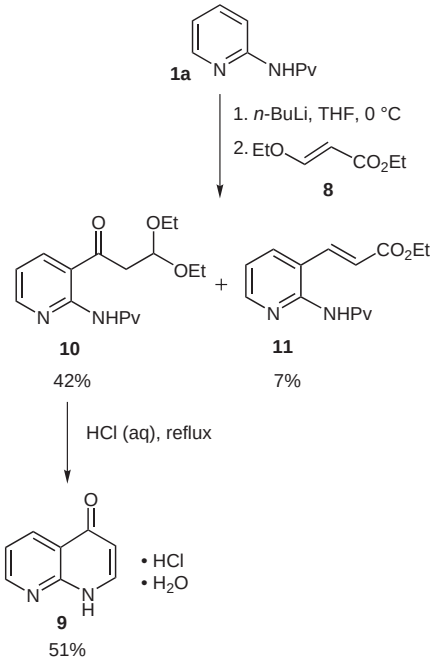


Scheme 3

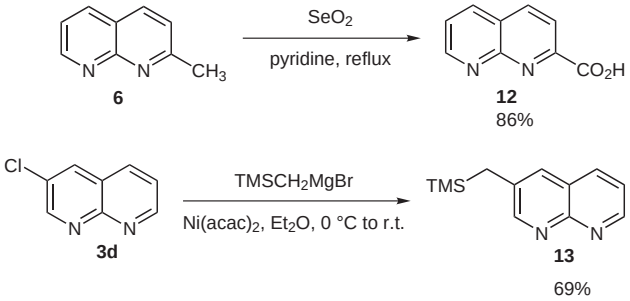
This result suggests that both 1,2- and 1,4-modes of addition to the enone are viable and the predominant mode depends on the relative reactivity of the β-carbon and carbonyl group. Furthermore, the reaction of acrylate ester **8** with the dianion derived from **1a** resulted in the ready construction of 1,8-naphthyridin-4-one (**9**). Interestingly, this reaction initially afforded two compounds (Scheme 4), one of which was determined to be acetal **10**, derived from 1,2-addition of the dianion followed by 1,4-addition of the resulting ethoxide to the α,β-unsaturated ketone intermediate. The second compound was determined to be acrylate **11** derived from a 1,4-addition–elimination sequence. The 1,2-mode of addition was greatly favored in this case, with a 6:1 ratio of **10**:**11** observed. Intermediate **11** could be readily converted to naphthyridinone **9** by heating in aqueous acid.

The naphthyridines obtained in the above reactions can be readily elaborated into a variety of functional groups (Scheme 5). For example, 2-methyl-1,8-naphthyridine (**6**) can be smoothly oxidized in 86% yield with selenium dioxide to 1,8-naphthyridine-2-carboxylic acid (**12**), an isostere of quinaldic acid whose amides constitute a part of many biologically active compounds including HIV protease inhibitor saquinavir. The active chlorine of 3-chloro- (**3d**) and 4-chloro- (**3f**) 1,8-naphthyridines is expected to readily participate in transition metal-catalyzed reactions. For example, **3d** can be reacted with trimethylsilylmethylmagnesium bromide under nickel catalysis to afford 3-trimethylsilylmethyl-1,8-naphthyridine (**13**) in 69% yield. Compound **13** may then serve as a convenient starting point for a further elaboration to the corresponding chloromethyl, bromomethyl[12a] or hydroxymethyl[12b] substituted naphthyridines and for other reactions of electrophiles[12c] at the methylene carbon in the presence of CsF.

In conclusion, a direct one-pot synthesis of 1,8- and 1,6-naphthyridine derivatives has been developed via the dimetalation of an appropriately substituted *N*-pyridylpivalamide or *tert*-butylcarbamate followed by reaction with a β-dimethylamino, or β-alkoxyacrolein, or acrylate. This method appears to be quite general for non-alkyllithium sensitive functionality allowing for potential access to a wide range of 1,6- and 1,8-naphthyridine derivatives.



Scheme 4



Scheme 5

1,8-Naphthyridine (3a)[4b] – General Procedure A

A solution of compound **1a** (3.65 g, 20.5 mmol) in THF (40 mL) was cooled to –70 °C and *n*-BuLi (2.5 M in hexane, 18 mL, 45.0 mmol) was added dropwise. The reaction was warmed to 0 °C, stirred at this temperature for 3 h, and then re-cooled to –70 °C. Compound **2** was then added dropwise, the reaction stirred at –70 °C for 1 h then slowly warmed to 0 °C over 2 h. The reaction was then quenched with 4 N HCl (30 mL); the aqueous layer was separated and heated to 80–90 °C, distilling off most of the organic solvent. After a further 45 minutes, the reaction was cooled, treated with solid K_2CO_3 (30 g) and the resulting solids extracted with EtOAc (4 × 50 mL), decanting the extracts. After concentration, the resulting crude material was purified by column chromatography to afford **3a** in 80% isolated yield (2.14 g). Appearance: brown solid; mp 84–86 °C; R_f = 0.33 (6% MeOH in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.15 (dd, *J* = 4.2, 1.9 Hz, 2 H), 8.22 (dd, *J* = 8.2, 1.9 Hz, 2 H), 7.51 (dd, *J* = 8.2, 4.2 Hz, 2 H). MS (ESI): *m/z* = 131 $[M + H]^+$.

4-Methyl-1,8-naphthyridine (3b)[4b] – General Procedure B

The dianion of **1b** was obtained as follows. A solution of compound **1b** (9.60 g, 50.0 mmol) in Et_2O (200 mL) was cooled to –70 °C and *t*-BuLi (1.7 M in pentane, 65 mL, 111 mmol) was added dropwise. After 1 h at –78 °C, the mixture was warmed to –10 °C over 30 min then re-cooled to –70 °C. Then procedure A was followed. Yield 77%. Appearance: brown solid; mp 25–27 °C; R_f = 0.32 (6% MeOH in CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.12 (dd, *J* = 4.2, 1.9 Hz, 1 H), 8.98 (d, *J* = 4.4 Hz, 1 H), 8.40 (dd, *J* = 8.3, 2.0 Hz, 1 H), 7.51 (dd, *J* = 8.4, 4.2 Hz, 1 H), 7.33 (d, *J* = 4.4 Hz, 1 H), 2.73 (s, 3 H). MS (APCI+): *m/z* = 146 $[M + H]^+$.

3-Methyl-1,8-naphthyridine (3c)[13]

Procedure A was used but the acid-mediated condensation reaction was heated at reflux overnight. Yield 60%. Appearance: tan solid; mp 109–110 °C; R_f = 0.46 (6% MeOH in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.07 (dd, *J* = 4.2, 1.8 Hz, 1 H), 9.00 (d, *J* = 2.4 Hz, 1 H), 8.13 (dd, *J* = 8.1, 1.8 Hz, 1 H), 7.95 (d, *J* = 0.9 Hz, 1 H), 7.47 (dd, *J* = 8.1, 4.2 Hz, 1 H), 2.57 (s, 3 H). MS (ESI): *m/z* = 145 $[M + H]^+$.

3-Chloro-1,8-naphthyridine (3d)[14]

Modified procedure A was used. The dianion of **1d** was obtained as follows. A solution of compound **1d** (4.40 g, 20.5 mmol) in THF (40 mL) was cooled to –70 °C. Then, *t*-BuLi (1.7 M in pentane, 27 mL, 45.1 mmol) was added dropwise and the mixture was stirred for 3 h at –78 °C. Then procedure A was followed. Yield 77%. Appearance: tan solid; mp 147–149 °C; R_f = 0.36 (EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.14 (dd, *J* = 4.0, 2.0 Hz, 1 H), 9.06 (d, *J* = 2.5 Hz, 1 H), 8.19 (d, *J* = 2.5 Hz, 1 H), 8.16 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.55 (dd, *J* = 8.0, 4.0 Hz, 1 H). MS (ESI): *m/z* = 165 $[M + H]^+$.

4-Ethyl-1,8-naphthyridine (3e)

Procedure B was used. Yield 82%. Appearance: dark oil; R_f = 0.37 (MeCN). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.12 (dd, *J* = 4.2, 1.9 Hz, 1 H), 9.04 (d, *J* = 4.5 Hz, 1 H), 8.44 (dd, *J* = 8.4, 1.9 Hz, 1 H), 7.51 (dd, *J* = 8.4, 4.2 Hz, 1 H), 7.34 (d, *J* = 4.5 Hz, 1 H), 3.14 (q, *J* = 7.6 Hz, 2 H), 1.41 (t, *J* = 7.6 Hz, 3 H). MS (APCI+): *m/z* = 159 $[M + H]^+$.

4-Chloro-1,8-naphthyridine (3f)[14] – General Procedure C

A solution of compound **1f** (4.56 g, 20.0 mmol) and TMEDA (7.0 mL, 46.5 mmol) in THF (60 mL) was cooled to –70 °C and *n*-BuLi (2.5 M in hexane, 18 mL, 45.0 mmol) was added dropwise. The reaction was stirred at –50 °C for 1 h. Compound **2** was then added dropwise, and the reaction stirred at –70 °C for 1.5 h followed by quenching with 3 N HCl (30 mL). After warming to r.t., the aqueous layer (pH 8–9) was separated and the organic layer extracted with 3 N HCl (40 mL). The acidic aqueous extract was then heated to reflux for 3 h. After this time the reaction was cooled to r.t., treated with solid K_2CO_3 (40 g) and the resulting mixture immediately extracted with EtOAc (4 × 100 mL), decanting the extracts. The resulting crude material was purified by column chromatography to afford **3f** in 30% yield (0.97 g). Appearance: tan solid; mp 48–50 °C; R_f = 0.30 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.20 (dd, *J* = 4.2, 1.9 Hz, 1 H), 9.04 (d, *J* = 4.7 Hz, 1 H), 8.63 (dd, *J* = 8.4, 1.9 Hz, 1 H), 7.62 (dd, *J* = 8.4, 4.2 Hz, 1 H), 7.60 (d, *J* = 4.8 Hz, 1 H). MS (ESI): *m/z* = 165 $[M + H]^+$.

1,6-Naphthyridine (4)[15]

Procedure A was used but the reaction was heated at reflux for 3 h. Yield 71%. Appearance: brown solid; mp 25–26 °C; R_f = 0.42 (6% MeOH in CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.30 (d, *J* = 1.0 Hz, 1 H), 9.12 (dd, *J* = 4.5, 2.0 Hz, 1 H), 8.78 (d, *J* = 6.0 Hz, 1 H), 8.31 (ddd *J* = 8.0, 2.0, 1.0 Hz, 1 H), 7.94 (d, *J* = 6.0 Hz, 1 H), 7.56 (dd, *J* = 8.0, 4.5 Hz, 1 H). MS (ESI): *m/z* = 131 $[M + H]^+$.

2-Methyl-1,8-naphthyridine (6)[4b]

Compounds **1a** and **5** were reacted using procedure A but the reaction was heated at reflux for 4 h. 2-Methyl-1,8-naphthyridine (**6**) was separated from regioisomer **3a** using flash chromatography on silica gel and eluting with a gradient from 100% EtOAc to 90:10 EtOAc–MeOH. Compound **6** eluted first. Yield 58%. Appearance: tan solid; mp 95–96 °C; R_f = 0.34 (6% MeOH in CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.07 (dd, *J* = 4.5, 2.0 Hz, 1 H), 8.14 (dd, *J* = 8.0, 2.0 Hz, 1 H), 8.07 (d, *J* = 8.5 Hz, 1 H), 7.43 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 2.82 (s, 3 H). MS (ESI): *m/z* = 145 $[M + H]^+$.

1,8-Naphthyridin-4-one Hydrochloride Hydrate (9)

Acrylate **8** (7.0 mL, 48.4 mmol) was added dropwise at –70 °C to the dianion obtained from 3.56 g (20.0 mol) of **1a** (see procedure A). The mixture was stirred at –50 °C to –40 °C for 5.5 h and quenched with AcOH (3.0 mL, 50 mmol) followed by H_2O (30 mL). The organic layer was separated, washed with sat. $NaHCO_3$ and the components were isolated by flash chromatography. Yield of **10** 42% (2.71 g). Appearance: yellow solid; R_f = 0.40 (EtOAc). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.46 (s, 1 H), 8.51 (dd, *J* = 4.8, 1.8 Hz, 1 H), 8.05 (dd, *J* = 7.7, 1.8 Hz, 1 H), 7.30 (dd, *J* = 7.7, 4.8 Hz, 1 H), 4.84 (t, *J* = 5.5 Hz, 1 H), 3.55 (m, 2 H), 3.42 (m, 2 H), 3.08 (d, *J* = 5.6 Hz, 2 H), 1.21 (s, 9 H), 1.03 (t, *J* = 7.1 Hz, 6 H). MS (ESI): *m/z* = 323 $[M + H]^+$.

Compound **10** (2.71 g, 9.78 mmol) was heated with 3 N HCl in H_2O for 2 h. Upon cooling to 10 °C, **9** precipitated and was filtered off and dried. Yield 51% (1.00 g). Appearance: light yellow solid; mp 243–245 °C; R_f = 0.21 (6% MeOH in CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 15.00–11.70 (br s, 1 H), 9.00 (dd, *J* = 4.4, 1.9 Hz, 1 H, H-7), 8.65 (dd, *J* = 8.2, 1.9 Hz, 1 H, H-5), 8.49 (d, *J* = 7.2 Hz, 1 H, H-2), 7.66 (dd, *J* = 8.2, 4.4 Hz, 1 H, H-6), 6.85 (d, *J* = 7.2 Hz,

1 H, H-5), 7.50–5.90 (br s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.8 (C-4), 155.3 (C-7), 149.9 (C-8a), 144.2 (C-2), 134.7 (C-5), 122.2 (C-6), 118.4 (C-4a), 108.3 (C-3). MS (ESI): *m/z* = 147 [M + H]$^+$. Anal. Calcd for $C_8H_9ClN_2O_2$: C, 47.89; H, 4.52; N, 13.96. Found: C, 48.01; H, 4.56; N, 13.71. The NMR peaks assignment and the structure of **9** are consistent with ^{13}C DEPT, HMBC, HSQC, COSY and NOESY spectra.

1,8-Naphthyridin-2-carboxylic Acid Hydrochloride Hydrate (12)

Naphthyridine **6** (200 mg, 1.38 mmol) and SeO_2 (308 mg, 2.77 mmol) were refluxed in pyridine (1 mL) for 30 min. The solids were filtered off and the solvent evaporated. The residue was purified by preparative HPLC, and the resulting solid was treated with 2 M HCl in Et_2O to afford **12** in 79% yield (190 mg). Appearance: off-white solid; mp 229–230 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.33 (dd, *J* = 4.5, 2.0 Hz, 1 H), 8.85 (dd, *J* = 8.5, 2.0 Hz, 1 H), 8.81 (d, *J* = 8.0 Hz, 1 H), 8.31 (d, *J* = 8.0 Hz, 1 H), 7.93 (dd, *J* = 8.0, 4.5 Hz, 1 H). ^{13}C (125 MHz, DMSO-d_6): δ = 164.7, 152.3, 151.2, 150.1, 139.6, 138.9, 123.2, 123.0, 121.5. Anal. Calcd for $C_9H_9ClN_2O_3$: C, 47.28; H, 3.97; N, 12.25. Found: C, 47.39; H, 3.74; N, 12.16. MS (ESI): *m/z* 175 [M + H]$^+$.

3-(Trimethylsilyl)methyl-1,8-naphthyridine (13)

To a suspension of **3d** (500 mg, 3.04 mmol) and $Ni(acac)_2$ (39 mg, 0.15 mmol) in toluene (3.0 mL) was added $TMSCH_2MgBr$ (1 M in Et_2O, 4.6 mL) dropwise at 0 °C. The reaction was stirred overnight at r.t. then partitioned between EtOAc (25 mL) and H_2O (10 mL). After filtering the mixture through Celite 521, the organic layer was separated, dried over Na_2SO_4 and evaporated to afford **13** in 69% yield (443 mg). Appearance: light brown solid; mp 93–95 °C; R_f = 0.30 (EtOAc). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.94 (d, *J* = 2.5 Hz, 1 H), 8.80 (d, *J* = 2.5 Hz, 1 H), 8.34 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.99 (d, *J* = 2.5 Hz, 1 H), 7.56 (dd, *J* = 8.0, 4.0 Hz, 1 H), 1.97 (s, 2 H), 0.00 (s, 9 H). MS (ESI): *m/z* = 217 [M + H]$^+$.

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