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Nucleophilic addition to 2,3-pyridyne and synthesis of benzonaphthyridinones

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Abstract

A study of the nucleophilic addition of amines to 2,3-pyridyne has been carried out. 2-Aminopyridines have been generated exclusively. A series of benzonaphthyridinones have been synthesized by reacting 2,3-pyridyne and *o*-aminobenzoates.

Keywords

2,3-Pyridyne; Amination; Annulation; Benzonaphthyridinone; Heterocycle

1. Introduction

Heterocyclic compounds have attracted significant attention for decades, because of their considerable biological activity and potential medicinal applications. Among the various heterocycles, benzonaphthyridinones, and dibenzonaphthyridinones (Fig. 1) are known as antimicrobial alkaloids,¹ anticancer agents,² and compounds that can reverse multidrug resistance.³

However, synthetic approaches to these heterocycles remain limited. Quéguiner reported a process involving nucleophilic aromatic substitution to afford the benzonaphthyridinone core (Scheme 1).⁴ This ring system can also be prepared from 2-(phenylamino)nicotinic acid using either the strong acid PPA⁵ or microwave irradiation⁶ (Scheme 2). Dibenzonaphthyridinones have also been synthesized using PPA and a high temperature.⁷

Benzyne, a highly reactive intermediate, was first proposed by Wittig⁸ in 1942 and confirmed by Roberts⁹ in 1956. Kobayashi in 1983 reported a novel way to generate arynes from silylaryl triflates in the presence of fluoride.¹⁰ The Larock group has had an extensive ongoing research program in aryne chemistry in recent years.¹¹ We have reported nucleophilic addition reactions of arynes,¹² and later, a synthesis of xanthenes, thioxanthenes, and acridones from substituted benzoates involving nucleophilic attack on arynes, followed by ring closure.¹³ The exciting possibility of extending this methodology to hetarynes¹⁴ to generate polyheterocycles has now been examined.

2,3-Pyridyne has been the target of considerable research for decades.¹⁵ Classic approaches to this interesting intermediate include oxidation of an aminotriazolopyridine¹⁶ and a halogen-metal exchange-elimination sequence starting from 3-bromo-2-chloropyridine and employing a lithium reagent.¹⁷ 3-(Trimethylsilyl)pyridin-2-yl triflate (**1a**) has been prepared by Effenberger and its fluoride-induced desilylation-elimination process generating 2,3-

pyridyne has been reported.¹⁸ In a classic elimination–addition reaction of 3-halopyridine using KNH_2/NH_3 ,^{15a} both 2- and 3-adducts have been reported with the former predominating. Fleming reported one example of the addition of acetic acid to 2,3-pyridyne to form the 2-substituted product.¹⁹ One example of the amination of 2,3-pyridyne has been reported in 2009, but not fully investigated.²⁰ Herein, we report a study of the nucleophilic addition reactions of 2,3-pyridyne and amines, and a synthesis of benzonaphthyridinones from 2,3-pyridyne and *o*-aminobenzoates.

2. Results and discussion

Our initial work began with a study of the nucleophilic addition of *N*-methylaniline to 2,3-pyridyne. The 2,3-pyridyne precursor, 3-(trimethylsilyl)pyridin-2-yl triflate, was prepared using a literature procedure¹⁸ and the method was extended to the preparation of the 2,3-quinolyne precursor 3-(trimethylsilyl)quinolin-2-yl triflate (Scheme 3). We first allowed 3-(trimethylsilyl)pyridin-2-yl triflate to react with 2.0 equiv of CsF and 1.0 equiv of *N*-methylaniline in acetonitrile (MeCN) at room temperature for 24 h (Eq. 1). The tertiary amine *N*-methyl-*N*-phenylpyridin-2-amine was obtained in a 33% yield. Although two possible regioisomers could be formed in this reaction, we found that nucleophilic attack occurs exclusively at the 2-position of the 2,3-pyridyne, and the 2-pyridinylamine was the only observed product, albeit in only a relatively low yield.

Computational chemists have reported years ago that the cumulenenic structure (structure **B**, Fig. 2) is favored for 2,3-pyridyne,²¹ which makes the 2-position more susceptible to be attacked by nucleophiles. This cumulenenic structure also makes pyridyne extraordinarily reactive, which apparently results in unexpected side reactions leading to a low yield. We have actually stirred the pyridyne precursor with the fluoride source in the absence of any other reagents to check the reactivity and relative stability of pyridyne. It appears that the precursor disappears within an hour, and the pyridyne generated immediately turns into intractable tars, which we believe are the major by-products of the pyridyne chemistry.

We have examined a number of different reaction conditions in an attempt to eliminate any undesired side reactions and improve the yield of the aminopyridine (Table 1). The yield was not improved when we changed the solvent (entries 2–6). The product was, in fact, totally different when we used tetrahydrofuran (THF) as the solvent. In THF, the THF acted as the nucleophile apparently attacking the pyridyne first to afford the final ring-opened, amine-containing product **3aa'** in up to a 58% yield (entries 7–9, Scheme 4). The yield was also not improved when we tried a different fluoride/base system (entry 10) or reaction temperature (entry 11). We did find that higher yields can be achieved when we changed the stoichiometry of the reactants **1a** and **2a**. A yield of 50% has been achieved when employing twice as much of the pyridyne precursor **1a** (entry 12). The yield also improved when we reversed the ratio of **1a** and **2a** (entry 13), although the improvement was not as large as in the previous case (44% vs 50% in entry 12). Since the pyridyne precursor is less readily available than the amine, we decided to employ an excess of the amine in all further studies. However, the yield did not increase further when we used 3 equiv and 4 equiv of **2a** (entries 14 and 15). The yield did, however, reach 49% when we diluted the reaction solution (entries 16 and 17). It appears that the pyridyne itself is so reactive that it causes side reactions. Thus, a lower concentration of pyridyne appears to reduce unwanted side reactions.

(1)

A second round of optimization has been carried out based on the idea that a lower concentration of pyridyne reduces side reactions (Table 2). We prepared a solution of **1a** in 4 mL of MeCN (solution A) and a solution of **2a** and CsF in 4 mL of MeCN (solution B). Solution A was slowly added to solution B by using a syringe pump over a long period of time. We found that the yield improved significantly (compare entry 1 and entry 2), because of the slow addition. The loading of **2a** was subsequently reduced to 1 equiv, which did not affect the yield very much (entry 3). A longer addition time also did not improve the yield (entry 4). Therefore, we decided to use this optimized slow addition approach (entry 3) in all further investigations of this process.

A number of 2-pyridinylamines have been synthesized by reacting 2,3-pyridyne with a number of simple amines (Table 3). As can be seen, both secondary and tertiary amines have been obtained. However, tertiary amine products have not been observed in the reaction of 2,3-pyridyne and primary amines (entries 2–8). Halogens, such as iodine, can be tolerated under our reaction conditions to afford the corresponding halogenated products (entries 3 and 4). Both an electron-rich (entry 5) and an electron-deficient aniline (entry 6) have reacted well with pyridyne, although the electron-deficient aniline led to a lower yield. The yield was somewhat lower when the amine bears a sterically bulky group next to the amino group (entry 7). Aliphatic amines react as well under our reaction conditions to afford the corresponding products (entries 8 and 9). The quinolyne precursor **1b** reacted in the same fashion, again tolerating a halogen (entry 10). Unfortunately, we failed to achieve ethers in a satisfactory yield by reacting 2,3-pyridyne and phenols due to the lower nucleophilicity of oxygen than nitrogen.

Next, a polycyclic system has been achieved by reacting 2,3-pyridyne and *o*-aminobenzoates. In this process, a plausible mechanism is proposed in Scheme 5. The deprotonated (Scheme 5, Route A) or neutral amino group (Scheme 5, Route B) attacks the 2-position of the pyridyne, generating a carbanion, which is then trapped intramolecularly by the ester group of the *o*-amino-benzoate to form the benzonaphthyridinone.

Using this basic process, a variety of benzonaphthyridinones and a dibenzonaphthyridinone have been synthesized from 2,3-pyridyne and 2,3-quinolyne using our slow addition reaction conditions (Table 4). It is worth noting that primary amines led to a complex mixture in this chemistry; therefore, only secondary amines have been employed for this synthesis. *N*-Methylbenzonaphthyridinone has been synthesized in a modest 56% yield by reacting 2,3-pyridyne and methyl 2-(methylamino)benzoate (entry 1). *N*-Allylbenzonaphthyridinone has been generated from the corresponding *N*-(allylamino)benzoate in a 48% yield (entry 2). Halides from chloride to iodide are tolerated under our reaction conditions (entries 2–6). The yields are moderate in these cases. It is interesting to compare entries 3–5 and entry 6, where we observe that the yield is higher when the halogen atom is *para* to the ester group of the benzoate. This trend is more obvious in entry 7, where an electron-withdrawing group is present *para* to the ester group, which makes the ester group more electrophilic, leading to a higher yield. A tertiary amine (entry 8) reacted as well as the secondary amines, affording the same product **5aa** as in entry 1. This example shows that the neutral amine itself is nucleophilic enough for this transformation to take place (Scheme 6), suggesting that Route

B in Scheme 5 is perhaps more favorable. 2,3-Quinolyne reacts the same way as 2,3-pyridyne, and the dibenzonaphthyridinone **5ba** has been formed by reacting the quinolyne with **4a** (entry 9).

We have also tested a 2-hydroxybenzoate and a 2-mercaptobenzoate in this annulation process (Scheme 7). Again, the phenol group did not react well with the pyridyne apparently due to its lower nucleophilicity, while the sulfur-containing polyheterocycle **5ai** has been formed from the 2-mercaptobenzoate, but in only a 34% yield.

3. Conclusions

Some nucleophilic amination reactions of 2,3-pyridyne and 2,3-quinolyne have been studied. We have found that nucleophilic attack of the amine occurs at the 2-position of 2,3-pyridyne/2,3-quinolyne exclusively, which is consistent with previous computational conclusions. 2,3-Pyridyne and 2,3-quinolyne appear to be so reactive that they cause unwanted side reactions. A slow addition procedure has thus been employed to reduce the side reactions. A variety of 2-pyridinylamines have thus been prepared using primary and secondary amines. When secondary and tertiary *o*-aminobenzoates are employed in this process, benzonaphthyridinones can be synthesized in reasonable yields.

4. Experimental section

4.1. General information

All reagents purchased from commercial sources were used as received. The solvent THF was distilled over Na/benzophenone. Anhydrous toluene and MeCN were used as received. The aryne precursors were prepared according to a literature procedure.¹⁸ Silica gel for column chromatography was supplied as 230–400 mesh from commercial source. Powdered CsF was used as received and stored in a desiccator.

All melting points were measured and are uncorrected. The ¹H and ¹³C NMR spectra were recorded and are referenced to the residual solvent signals (7.26 ppm for ¹H in CDCl₃ and 77.2 ppm for ¹³C in CDCl₃).

All aryne nucleophilic addition reactions and annulations were carried out in oven-dried glassware and were magnetically stirred. A nitrogen atmosphere was not used, except that a balloon of nitrogen was attached to the reaction flask to allow for the extra volume of added solution. A syringe pump was employed for the slow addition reaction conditions.

4.2. Preparation of pyridyne and quinolyne precursors

These aryne precursors were prepared following the literature procedure.¹⁸

4.2.1. 3-(Trimethylsilyl)pyridin-2-yl triflate (1a)—Colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 8.33 (dd, *J*=4.8, 2.1 Hz, 1H), 7.92 (dd, *J*=7.2, 2.1 Hz, 1H), 7.31 (dd, *J*=7.2, 5.1 Hz, 1H), 0.37 (s, 9H).

4.2.2. 3-(Trimethylsilyl)quinolin-2-yl triflate (1b)—Colorless oil: *R*_F=0.33 (20:1 petroleum ether/EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 8.36 (s, 1H), 7.98 (d, *J*=8.4 Hz, 1H), 7.85 (d, *J*=8.4 Hz, 1H), 7.76 (td, *J*=7.6, 0.8 Hz, 1H), 7.59 (t, *J*=7.2 Hz, 1H), 0.43 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 158.6, 148.8, 146.3, 131.4, 128.5, 127.7, 127.5, 127.4, 124.4, 118.8 (CF₃), 123.6, 120.4, 117.2, 114.1, −1.2; LRMS (EI) 349 (M); HRMS (EI) calcd for C₁₃H₁₄F₃NO₃SSi (M) 349.0416, found 349.0422; IR (KBr, cm^{−1}) 3064 (w), 2959 (m), 2904 (w), 1590 (m).

4.3. General procedure for the synthesis of 2-pyridinylamines

To an oven-dried 4 dram vial equipped with a stir bar were added 0.25 mmol of amine and 76 mg of CsF (0.5 mmol, 2.0 equiv). MeCN (4 mL) was added and the vial was sealed with a rubber septum equipped with a balloon of nitrogen. A solution of 0.25 mmol of aryne precursor in 4 mL of MeCN was prepared separately, and was added to the reaction vial slowly by using a syringe pump while stirring. After the addition was complete, the reaction mixture was allowed to stir for additional time and quenched with water, and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether/EtOAc) to afford the 2-pyridinylamine.

4.3.1. N-Methyl-N-phenylpyridin-2-amine (3aa)—Following the general procedure, this product was isolated as a yellow oil: *R*_f=0.24 (20:1 petroleum ether/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 8.23 (dd, *J*=4.8, 0.9 Hz, 1H), 7.40 (m, 2H), 7.30 (m, 2H), 7.21 (m, 2H), 6.60 (td, *J*=6.0, 0.9 Hz, 1H), 6.53 (d, *J*=8.4 Hz, 1H), 3.48 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 159.0, 148.0, 147.0, 136.7, 129.9, 126.5, 125.6, 113.3, 109.4, 38.6; LRMS (EI) 184 (M), 183 (M–H); HRMS (EI) calcd for C₁₂H₁₁N₂ (M–H) 183.0922, found 183.0928. The structure of this compound was assigned based on the ¹H NMR coupling pattern and was confirmed by comparison with the reported ¹H and ¹³C NMR spectral data.²²

4.3.2. N-Phenylpyridin-2-amine (3ab)—Yellow oil: *R*_f=0.11 (20:1 petroleum ether/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 8.21 (dt, *J*=5.1, 0.9 Hz, 1H), 7.49 (td, *J*=7.8, 1.2 Hz, 1H), 7.33 (d, *J*=4.5 Hz, 4H), 7.05 (m, 1H), 6.88 (d, *J*=8.4 Hz, 1H), 6.82 (s, 1H), 6.73 (td, *J*=3.6, 0.9 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 156.2, 148.6, 140.7, 137.9, 129.5, 123.0, 120.5, 115.2, 108.4; LRMS (EI) 170 (M), 169 (M–H); HRMS (EI) calcd for C₁₁H₁₀N₂ (M) 170.0844, found 170.0847.

4.3.3. N-(2-Iodophenyl)pyridin-2-amine (3ac)—Yellow solid: mp 65–67 °C; *R*_f=0.35 (5:1 petroleum ether/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 8.25 (dd, *J*=5.1, 1.2 Hz, 1H), 7.83 (td, *J*=7.2, 1.2 Hz, 2H), 7.52 (td, *J*=7.2, 1.8 Hz, 1H), 7.31 (td, *J*=7.8, 1.2 Hz, 1H), 6.80 (m, 3H), 6.65 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 155.4, 148.6, 141.3, 139.6, 138.0, 129.2, 124.4, 120.4, 116.1, 109.7, 91.6; LRMS (EI) 296 (M); HRMS (EI) calcd for C₁₁H₉IN₂ (M) 295.9810, found 295.9816; IR (KBr, cm^{–1}) 3380 (s), 3192 (w), 3012 (m), 2954 (m), 2925 (m), 2866 (m), 1599 (s), 1573 (m), 1515 (s).

4.3.4. N-(3-Iodophenyl)pyridin-2-amine (3ad)—Yellow oil: *R*_f=0.33 (5:1 petroleum ether/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 8.22 (d, *J*=4.5 Hz, 1H), 7.75 (s, 1H), 7.52 (td, *J*=7.8, 1.5 Hz, 1H), 7.33 (t, *J*=8.4 Hz, 2H), 7.02 (m, 2H), 6.85 (d, *J*=8.4 Hz, 1H), 6.77 (dd, *J*=6.9, 5.1 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 155.4, 148.5, 142.2, 138.0, 131.5, 130.8, 128.4, 119.0, 115.8, 109.1, 94.8; LRMS (EI) 296 (M); HRMS (EI) calcd for C₁₁H₉IN₂ (M) 295.9810, found 295.9816; IR (KBr, cm^{–1}) 3378 (s), 3190 (w), 3012 (m), 2929 (m), 2860 (m), 1595 (s), 1573 (m).

4.3.5. N-(2,4-Dimethylphenyl)pyridin-2-amine (3ae)—Yellow oil: *R*_f=0.22 (2:1 petroleum ether/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 8.15 (d, *J*=4.2 Hz, 1H), 7.41 (td, *J*=7.2, 1.8 Hz, 1H), 7.25 (t, *J*=3.6 Hz, 1H), 7.08 (s, 1H), 7.01 (d, *J*=7.8 Hz, 1H), 6.60 (m, 2H), 6.31 (s, 1H), 2.32 (s, 3H), 2.23 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 157.5, 148.6, 137.8, 135.8, 134.7, 131.9, 131.3, 127.6, 124.2, 114.4, 107.2, 21.1, 18.1; LRMS (EI) 198 (M); HRMS (EI) calcd for C₁₃H₁₄N₂ (M) 198.1157, found 198.1159.

4.3.6. N-(4-Nitrophenyl)pyridin-2-amine (3af)—Yellow solid: mp 167–168 °C (lit.²³ 174–176 °C); *R*_f=0.41 (1:1 petroleum ether/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 8.34 (d,

$J=4.2$ Hz, 1H), 8.20 (d, $J=9.3$ Hz, 2H), 7.64 (m, 3H), 6.94 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 153.9, 148.5, 147.1, 141.4, 138.3, 125.9, 117.6, 116.9, 111.5; LRMS (EI) 215 (M), 214 (M–H); HRMS (EI) calcd for $\text{C}_{11}\text{H}_9\text{N}_3\text{O}_2$ (M) 215.0695, found 215.0699.

4.3.7. N-(2-*tert*-Butylphenyl)pyridin-2-amine (3ag)—White solid: mp 122–123 °C; $R_f=0.18$ (5:1 petroleum ether/EtOAc); ^1H NMR (300 MHz, CDCl_3) δ 8.16 (d, $J=4.2$ Hz, 1H), 7.46 (d, $J=7.5$ Hz, 1H), 7.40 (t, $J=7.2$ Hz, 1H), 7.32 (d, $J=7.5$ Hz, 1H), 7.20 (m, 2H), 6.66 (t, $J=6.0$ Hz, 1H), 6.45 (d, $J=8.4$ Hz, 1H), 6.30 (s, 1H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 158.3, 148.7, 145.9, 138.8, 137.8, 128.8, 127.4, 127.3, 126.1, 114.3, 107.2, 35.2, 30.8; LRMS (EI) 226 (M); HRMS (EI) calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2$ (M) 226.1470, found 226.1475.

4.3.8. N-[2-(Cyclohex-1-en-1-yl)ethyl]pyridin-2-amine (3ah)—Yellow oil: $R_f=0.13$ (5:1 petroleum ether/EtOAc); ^1H NMR (300 MHz, CDCl_3) δ 8.08 (dd, $J=4.5, 1.2$ Hz, 1H), 7.42 (td, $J=7.2, 1.8$ Hz, 1H), 6.55 (t, $J=5.7$ Hz, 1H), 6.37 (d, $J=8.4$ Hz, 1H), 5.53 (s, 1H), 4.50 (s, 1H), 3.30 (dd, $J=12.3, 6.9$ Hz, 2H), 2.27 (t, $J=6.6$ Hz, 2H), 1.98 (m, 4H), 1.60 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.0, 148.4, 137.6, 134.8, 124.0, 112.8, 106.6, 39.9, 37.8, 28.0, 25.4, 23.0, 22.6; LRMS (EI) 202 (M); HRMS (EI) calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2$ (M) 202.1470, found 202.1474.

4.3.9. N,N-Dibenzylpyridin-2-amine (3ai)—Yellow oil: $R_f=0.27$ (20:1 petroleum ether/EtOAc); ^1H NMR (300 MHz, CDCl_3) δ 8.20 (dt, $J=5.1, 0.9$ Hz, 1H), 7.31 (m, 11H), 6.58 (td, $J=5.1, 0.9$ Hz, 1H), 6.45 (d, $J=8.7$ Hz, 1H), 4.79 (s, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 158.8, 148.2, 138.6, 137.6, 128.8, 127.2, 127.1, 112.4, 106.1, 51.0; LRMS (EI) 274 (M); HRMS (EI) calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2$ (M) 274.1470, found 274.1473.

4.3.10. N-(4-Bromophenyl)quinolin-2-amine (3bj)—Brown solid: mp 143–145 °C; $R_f=0.56$ (2:1 petroleum ether/EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 7.94 (d, $J=8.8$ Hz, 1H), 7.80 (d, $J=8.0$ Hz, 1H), 7.61 (m, 4H), 7.46 (d, $J=8.8$ Hz, 2H), 7.32 (t, $J=7.2$ Hz, 1H), 6.90 (d, $J=8.8$ Hz, 1H), 6.75 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.8, 147.6, 139.6, 138.0, 132.2, 130.1, 127.6, 127.1, 124.4, 123.7, 121.6, 115.2, 112.2; LRMS (EI) 299 (M); HRMS (EI) calcd for $\text{C}_{15}\text{H}_{11}\text{BrN}_2$ (M) 298.0106, found 298.0111.

4.3.11. N-Methyl-N-[4-(pyridin-2-yloxy)butyl]aniline (3aa')—Yellow oil: $R_f=0.49$ (20:1 petroleum ether/EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 8.14 (d, $J=4.0$ Hz, 1H), 7.54 (td, $J=10.0, 4.0$ Hz, 1H), 7.20 (m, 2H), 6.84 (m, 1H), 6.69 (m, 4H), 4.31 (t, $J=6.0$ Hz, 2H), 3.38 (t, $J=8.0$ Hz, 2H), 2.93 (s, 3H), 1.77 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.1, 149.5, 147.0, 138.7, 129.3, 116.7, 116.2, 112.4, 111.3, 65.7, 52.7, 38.5, 26.9, 23.7; LRMS (ESI) 257 (M+H); HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}$ (M+H) 257.1648, found 257.1654; IR (KBr, cm^{-1}) 3091 (w), 2945 (m), 2884 (m), 2867 (m), 1596 (s), 1569 (m).

4.4. General procedure for the synthesis of benzonaphthyridinones

The benzonaphthyridinones were prepared from the corresponding *o*-aminobenzoates and aryne precursors following the same procedure used for the synthesis of 2-pyridinylamines. The residue was purified by column chromatography (petroleum ether/EtOAc+1% TEA) to afford the benzonaphthyridinones.

4.4.1. 10-Methylbenzo[b][1,8]naphthyridin-5(10H)-one (5aa)—Yellow solid: mp 214–215 °C; $R_f=0.24$ (3:1 petroleum ether/EtOAc+1% TEA); ^1H NMR (300 MHz, CDCl_3) δ 8.79 (m, 2H), 8.55 (dd, $J=8.1, 1.5$ Hz, 1H), 7.79 (td, $J=7.2, 1.5$ Hz, 1H), 7.63 (d, $J=8.4$ Hz, 1H), 7.35 (t, $J=7.5$ Hz, 1H), 7.25 (m, 1H), 4.15 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 178.6, 153.5, 151.3, 142.6, 137.0, 134.6, 127.8, 122.8, 122.1, 117.6, 117.4, 115.6, 31.0;

LRMS (EI) 210 (M), 209 (M–H); HRMS (EI) calcd for C₁₃H₁₀N₂O (M) 210.0793, found 210.0796.

4.4.2. 10-Allyl-8-bromobenzo[b][1,8]naphthyridin-5(10H)-one (5ab)—Yellow solid: mp 145–146 °C; *R*_f=0.25 (5:1 petroleum ether/EtOAc+1% TEA); ¹H NMR (400 MHz, CDCl₃) δ 8.78 (d, *J*=6.4 Hz, 2H), 8.38 (d, *J*=8.4 Hz, 1H), 7.71 (s, 1H), 7.43 (d, *J*=8.4 Hz, 1H), 7.29 (m, 1H), 6.08 (m, 1H), 5.41 (s, 2H), 5.26 (d, *J*=10.0 Hz, 1H), 5.07 (d, *J*=17.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 178.0, 154.0, 150.9, 142.6, 137.0, 131.7, 129.7, 129.4, 125.6, 121.5, 119.1, 118.5, 117.34, 117.32, 46.0; LRMS (EI) 314 (M); HRMS (EI) calcd for C₁₅H₁₁BrN₂O (M) 314.0055, found 314.0053; IR (KBr, cm^{–1}) 3084 (w), 2954 (m), 2924 (m), 2870 (w), 1639 (m), 1587 (s).

4.4.3. 7-Iodo-10-methylbenzo[b][1,8]naphthyridin-5(10H)-one (5ac)—Yellow solid: mp 198–199 °C; *R*_f=0.13 (8:1 petroleum ether/EtOAc+1% TEA); ¹H NMR (400 MHz, CDCl₃) δ 8.78 (m, 3H), 7.99 (d, *J*=9.2 Hz, 1H), 7.38 (d, *J*=9.2 Hz, 1H), 7.25 (m, 1H), 4.11 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 177.2, 153.8, 151.1, 142.8, 141.9, 137.0, 136.4, 124.4, 118.0, 117.8, 117.4, 85.5, 31.1; LRMS (EI) 335 (M); HRMS (EI) calcd for C₁₃H₉IN₂O (M) 335.9760, found 335.9765; IR (KBr, cm^{–1}) 3083 (w), 2954 (m), 2915 (m), 2869 (w), 1635 (m), 1585 (s).

4.4.4. 7-Bromo-10-methylbenzo[b][1,8]naphthyridin-5(10H)-one (5ad)—Yellow solid: mp 202–203 °C; *R*_f=0.18 (5:1 petroleum ether/EtOAc+1% TEA); ¹H NMR (400 MHz, CDCl₃) δ 8.73 (m, 2H), 8.55 (s, 1H), 7.78 (d, *J*=8.8 Hz, 1H), 7.46 (d, *J*=8.8 Hz, 1H), 7.26 (m, 1H), 4.09 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 177.3, 153.8, 151.1, 141.3, 137.2, 136.9, 130.1, 123.9, 118.0, 117.6, 117.2, 115.6, 31.1; LRMS (EI) 288 (M); HRMS (EI) calcd for C₁₃H₉BrN₂O (M) 287.9898, found 287.9904.

4.4.5. 7-Chloro-10-methylbenzo[b][1,8]naphthyridin-5(10H)-one (5ae)—Yellow solid: mp 210–212 °C; *R*_f=0.5 (2:1 petroleum ether/EtOAc+1% TEA); ¹H NMR (400 MHz, CDCl₃) δ 8.76 (m, 2H), 8.45 (s, 1H), 7.68 (d, *J*=9.2 Hz, 1H), 7.57 (d, *J*=9.2 Hz, 1H), 7.25 (m, 1H), 4.13 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 177.5, 153.8, 151.1, 141.0, 137.0, 134.6, 128.2, 126.9, 123.6, 118.0, 117.4, 117.2, 31.2; LRMS (EI) 244 (M); HRMS (EI) calcd for C₁₃H₉ClN₂O (M) 244.0403, found 244.0408.

4.4.6. 8-Bromo-10-methylbenzo[b][1,8]naphthyridin-5(10H)-one (5af)—Yellow solid: mp 234–235 °C; *R*_f=0.4 (3:1 petroleum ether/EtOAc+1% TEA); ¹H NMR (400 MHz, CDCl₃) δ 8.77 (m, 2H), 8.37 (d, *J*=8.8 Hz, 1H), 7.80 (s, 1H), 7.44 (d, *J*=8.4 Hz, 1H), 7.28 (t, *J*=6.0 Hz, 1H), 4.12 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 178.0, 153.7, 151.2, 143.3, 136.9, 129.8, 129.3, 125.5, 121.4, 118.5, 118.1, 117.5, 31.1; LRMS (EI) 288 (M); HRMS (EI) calcd for C₁₃H₉BrN₂O (M) 287.9898, found 287.9901; IR (KBr, cm^{–1}) 3084 (w), 2951 (w), 2917 (m), 2870 (m), 2849 (w), 1637 (m), 1587 (m).

4.4.7. Methyl 10-methyl-5-oxo-5,10-dihydrobenzo[b][1,8]naphthyridine-8-carboxylate (5ag)—Yellow solid: mp 225–226 °C; *R*_f=0.12 (5:1 petroleum ether/EtOAc+1% TEA); ¹H NMR (400 MHz, CDCl₃) δ 8.78 (m, 2H), 8.56 (d, *J*=8.0 Hz, 1H), 8.34 (s, 1H), 7.92 (d, *J*=8.4 Hz, 1H), 7.27 (m, 1H), 4.20 (s, 3H), 4.02 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 178.2, 166.4, 153.9, 151.4, 142.1, 136.9, 135.0, 128.1, 125.0, 122.0, 118.0, 117.6, 117.5, 52.9, 31.2; LRMS (EI) 268 (M); HRMS (EI) calcd for C₁₅H₁₂N₂O₃ (M) 268.0848, found 268.0854; IR (KBr, cm^{–1}) 3082 (w), 2954 (m), 2923 (m), 2871 (w), 1730 (s), 1638 (s), 1614 (m), 1593 (s).

4.4.8. 6-Methyldibenzo[b,g][1,8]naphthyridin-11(6H)-one (5ba)—Yellow solid: mp 229–231 °C; R_f 0.27 (5:1 petroleum ether/EtOAc+1% TEA); ^1H NMR (400 MHz, CDCl_3) δ 9.32 (s, 1H), 8.53 (d, J =7.6 Hz, 1H), 8.00 (m, 2H), 7.80 (m, 2H), 7.60 (d, J =8.4 Hz, 1H), 7.47 (t, J =7.6 Hz, 1H), 7.31 (t, J =7.6 Hz, 1H), 4.22 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 179.7, 157.1, 150.1, 143.7, 139.2, 135.2, 132.8, 129.7, 128.1, 127.8, 124.8, 122.4, 121.6, 121.5, 117.8, 115.4, 31.0; LRMS (EI) 260 (M); HRMS (EI) calcd for $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}$ (M) 260.0950, found 260.0955; IR (KBr, cm^{-1}) 3064 (w), 2954 (w), 2917 (m), 2871 (m), 2850 (w), 1608 (s).

4.4.9. 5H-Thiochromeno[2,3-b]pyridin-5-one (5ai)—White solid: mp 236–238 °C (lit.²⁴ 233–234 °C); R_f 0.24 (5:1 petroleum ether/EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 8.83 (m, 2H), 8.60 (d, J =8.0 Hz, 1H), 7.70 (m, 2H), 7.53 (td, J =8.0, 1.6 Hz, 1H), 7.46 (dd, J =8.0, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.8, 158.9, 153.5, 138.0, 137.7, 133.2, 130.1, 129.0, 127.0, 126.65, 126.62, 121.8; LRMS (EI) 213 (M); HRMS (EI) calcd for $\text{C}_{12}\text{H}_7\text{NOS}$ (M) 213.0248, found 213.0253.

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10-methylbenzo[*b*][1,8]naphthyridin-5(10*H*)-one 6-methyldibenzo[*b,g*][1,8]naphthyridin-11(6*H*)-one**Fig. 1.**

A representative benzonaphthyridinone and a dibenzonaphthyridinone.

Fig. 2.
The cumulenenic structure of 2,3-pyridyne.

Scheme 1.

Synthesis of benzonaphthyridinone involving nucleophilic aromatic substitution.

Scheme 2.
Synthesis of benzonaphthyridinone under harsh conditions.

Scheme 3.

Preparation of the 2,3-pyridyne and 2,3-quinolyne precursors.

Scheme 4.
Nucleophilic attack of THF and the formation of compound **3aa'**.

Scheme 5.
Proposed mechanism for the formation of benzonaphthyridinone.

Scheme 6.

The reaction of 2,3-pyridyne and methyl 2-(dimethylamino)benzoate.

Scheme 7.

The reaction of 2,3-pyridyne and 2-hydroxy- and 2-mercaptobenzoate.

Table 1

Optimization of the nucleophilic amination of 2,3-pyridyne^a

Entry	1a (equiv)	2a (equiv)	Fluoride source (equiv)	Solvent (mL)	T (°C)/time (h)	Yield ^b (%)
1	1	1	CsF (2)	MeCN (4)	rt, 24	33
2	1	1	CsF (2)	DME (4)	rt, 24	18
3	1	1	CsF (2)	DMF (4)	rt, 24	Trace
4	1	1	CsF (2)	MeCN (3)/Tol (1)	rt, 24	32
5	1	1	CsF (2)	MeCN (2)/Tol (2)	rt, 24	30
6	1	1	CsF (2)	MeCN (1)/Tol (3)	rt, 24	29
7	1	1	CsF (2)	THF (4)	rt, 48 ^c	36 ^d
8	1	1	CsF (2)	THF (4)	50, 24	58 ^d
9	1	1	TBAF (2)	THF (4)	rt, 24	Trace
10	1	1	CsF (2)/Cs ₂ CO ₃ (2)	MeCN (4)	rt, 24	35
11	1	1	CsF (2)	MeCN (4)	0→rt, 24	31
12	2	1	CsF (4)	MeCN (4)	rt, 24	50
13	1	2	CsF (2)	MeCN (4)	rt, 24	44
14	1	3	CsF (2)	MeCN (4)	rt, 24	43
15	1	4	CsF (2)	MeCN (4)	rt, 24	43
16	1	2	CsF (2)	MeCN (8)	rt, 24	49
17	1	4	CsF (2)	MeCN (8)	rt, 24	49

^a All reactions were carried out on a 0.25 mmol scale.^b Isolated yield.^c The pyridyne precursor remained unreacted.

$d_{\text{Product } 3aa'}$

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Table 2

Further optimization of the nucleophilic amination of 2,3-pyridyne^a

Entry	1a (equiv)	2a (equiv)	Solvent (mL)	Time (h)	Yield ^b (%)
1	1	2	MeCN (8)	24	49
2	1	2	MeCN (4+4) ^c	8+16 ^d	66
3	1	1	MeCN (4+4) ^c	8+16 ^d	65
4	1	1	MeCN (4+4) ^c	12+12 ^d	65

^a All reactions were carried out on a 0.25 mmol scale with 2 equiv of CsF at room temperature.

^b Isolated yield.

^c A solution of **1a** in 4 mL of MeCN (solution A) and a solution of **2a** and CsF in 4 mL of MeCN (solution B) were prepared separately.

^d Solution A was slowly added to solution B with a syringe pump over a period of time; the resulting solution was stirred for an additional period of time.

Table 3Synthesis of 2-aminopyridines from 2,3-pyridyne and various amines^a

Entry	Aryne precursor	Amine	Product	Yield ^b (%)
1	 1a	PhMeNH 2a	 3aa	65
2		PhNH ₂ 2b	 3ab	58
3		 2c	 3ac	57
4		 2d	 3ad	64
5		 2e	 3ae	61
6		 2f	 3af	47
7		 2g	 3ag	46
8		 2h	 3ah	60

Entry	Aryne precursor	Amine	Product	Yield ^b (%)
9		Bn ₂ NH 2i	 3ai	57
10	 1b	 2j	 3bj	36

^a All reactions were carried out on a 0.25 mmol scale with 2 equiv of CsF at room temperature. A solution of **1** in 4 mL of MeCN (solution A) and a solution of **2** and CsF in 4 mL of MeCN (solution B) were prepared separately. Solution A was slowly added to solution B with a syringe pump over 8 h, the resulting solution was stirred for an additional 16 h.

^b Isolated yield.

Table 4Synthesis of benzonaphthyridinones and a dibenzonaphthyridinone^a

Entry	Aryne precursor	Amine	Product	Yield ^b (%)
1	 1a	 4a	 5aa	56
2		 4b	 5ab	48
3		 4c	 5ac	53
4		 4d	 5ad	52
5		 4e	 5ae	48
6		 4f	 5af	66

Entry	Aryne precursor	Amine	Product	Yield ^b (%)
7		 4g	 5ag	72
8		 4h	 5aa	50
9	 1b	 4a	 5ba	32

^a All reactions were carried out on a 0.25 mmol scale with 2 equiv of CsF at room temperature. A solution of **1** in 4 mL of MeCN (solution A) and a solution of **4** and sF in 4 mL of MeCN (solution B) were prepared separately. Solution A was slowly added to solution B with a syringe pump over 8 h, the resulting solution was stirred for an additional 16 h.

^b Isolated yield.