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Room Temperature, Copper-Catalyzed Amination of Bromonaphthyridines with Aqueous Ammonia

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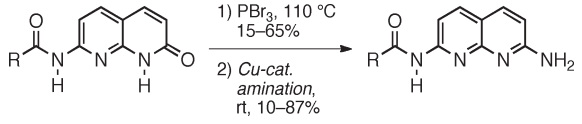

Room temperature, copper-catalyzed amination of amido-bromo-1,8-naphthyridines is reported. Use of Cu_2O and aqueous ammonia at ambient temperature affords amination products in 10−87% yield. Bromonaphthyridines are prepared in 15−65% yield via treatment of amidonaphthyridinones with phosphorus tribromide. This methodology provides an alternative route to functional, nonsymmetric 2,7-diamido-1,8-naphthyridines.

Within the area of hydrogen bond-mediated self-assembly,[1] quadruple hydrogen bonding modules (QHBMs) have proven particularly useful, especially those that strongly dimerize ($K_{dimer} > 10^5$ M^{-1} in $CDCl_3$).[2] Such systems are limited with respect to the complexity of the resulting architectures. Consequently, we[3] and others[4] have pursued heterocomplementary QHBM systems exhibiting high-affinity and high-fidelity.[5] The weak self-dimerization of the 2,7-diamido-1,8-naphthyridine (DAN) unit, i.e., $K_{dimer} > 10$ M^{-1}, and its high affinity for QHBMs, such as UG, DeUG, and UPy, makes this unit particularly valuable.[2b,3−6] Indeed, the DAN motif has been employed in molecular recognition and self-assembly studies,[7] and has found applications in supramolecular polymer chemistry.[8,9] These and future advances depend on the availability of preparations that allow access to functional derivatives of DAN. Such functional groups should allow the covalent attachment of DAN to other molecules, macromolecules, surfaces, and nanostructures.

Functional DAN units have typically incorporated the reactive functionality in one or both amide side chains. The naphthyridine ring system can also be functionalized;[10] however, these methods involve either lengthy syntheses or have not yet been shown to allow attachment to other materials. The syntheses of nonsymmetric diamidonaphthyridines **1** have typically involved selective hydrolysis of one amide of diamidonaphthyridine **2** (Figure 1a).[3,6a] Compound **2** is prepared via acylation of 2,7-diaminonaphthyridine, which is in turn obtained through high-pressure ammonolysis of a chloronaphthyridine precursor.[11] The hazardous ammonolysis conditions, or use of ammonia surrogates,[12] combined with the circuitous synthetic sequence have prompted investigations into alternative routes.[3,13] A straightforward approach has been reported by Sijbesma and Meijer[14] wherein chloronaphthyridines **3** undergo palladium-catalyzed amidation (Figure 1b). Multiple nonsymmetric diamidonaphthyridines were successfully obtained in 50−90% yield. Given recent advancements in C−N bond

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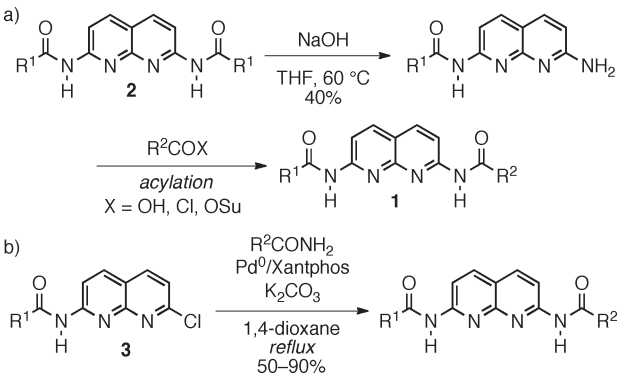
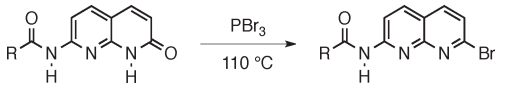


FIGURE 1. Conventional synthetic routes to nonsymmetric diamido-naphthyridines via (a) hydrolysis and acylation of symmetric diamidonaphthyridines or (b) Buchwald−Hartwig amidation.

forming reactions,[15] we explored a copper-catalyzed amination toward the synthesis of diamidonaphthyridines. Herein we describe methodology featuring mild amination of bromonaphthyridines followed by acylation. This approach may be useful in cases where palladium catalysis cannot be used or where the amide needed in Figure 1b is not readily available.

Syntheses of (hetero)aryl amines are often accomplished via the Ullmann reaction, wherein use of high temperatures and stoichiometric amounts of copper reagents are frequently required. Recent examples demonstrate that various secondary and tertiary (hetero)aryl amines can be prepared under milder conditions.[15] Obtaining primary (hetero)aryl amines, however, has proven difficult. Palladium-mediated syntheses are typically achieved via coupling of (hetero)aryl halides with ammonia surrogates.[16] Hartwig,[17] Buchwald,[18] and Beller[19] have recently demonstrated palladium-catalyzed coupling of (hetero)aryl halides with anhydrous ammonia. Elevated pressures and strong bases are often required to obtain these amines. Reports of copper-mediated syntheses have also been rare.[20] For example, Lang[20a] and Gaillard[20b] reported the preparation of aminopyridines by heating halopyridines, Cu_2O, and anhydrous ammonia. Bromides, iodides, and chlorides were successfully converted to the corresponding amines; however, yields appear to be quite substrate dependent. More recently, Wolf[20e] reported amination of activated and unactivated aryl iodides and bromides by heating the substrate, Cu_2O, and concentrated aqueous ammonia (NH_4OH_{aq}) in NMP. Conversion of aryl chlorides required activated substrates or microwave conditions. Syntheses of anilines via Cu^I salts and ammonium chloride or aqueous ammonia have been reported; however, supporting ligands and base additives are necessary.[20c,d] Mechanistic aspects of these and related copper-mediated transformations have yet to be resolved.[21]

TABLE 1. Bromination of Amidonaphthyridinones



entry[a]	substrate, R =	time (h)	product (yield, %)
1	**4**	12	**8** (65)
2[b]	**5**	24	**9** (49)
3	**6**	12	**10** (58)
4[c]	**7**	6	**11** (28)
5	**12**	72	**14** (28)
6[b]	**13**	48	**15** (15)

[a]20 equiv of PBr_3. [b]30 equiv of PBr_3. [c]65 equiv of PBr_3.

Initial attempts to aminate **3** (R^1 = Me)[11] with 10 mol % of Cu_2O and 10 equiv of NH_4OH_{aq} at 90 °C in ethylene glycol were unsuccessful, giving exclusively the product of amide hydrolysis. Attention was thus turned to the study of bromonaphthyridines. Heating 7-amino-1,8-naphthyridin-2(1*H*)-one[22] in $POBr_3/PBr_5$ resulted in low conversion and decomposition of the starting material. PBr_3 was similarly ineffective; use of cosolvents such as pyridine or chloroform gave no improvement. Fortunately, heating alkyl amidonaphthyridinones **4**−**7** to 110 °C in PBr_3 gave acceptable yields of the corresponding bromides **8**−**11** after 6−24 h (Table 1). Reactions performed at lower temperatures or for shorter duration gave incomplete conversion. Substrates **12** and **13** gave incomplete conversion to bromides **14** and **15**, respectively, upon prolonged heating and were hard to purify.

With bromides **8**−**11** in hand, the copper-mediated amination was evaluated (Table 2). The method of Lang[20a] was used with the modification that NH_4OH_{aq} was used in place of anhydrous ammonia. The HPLC analysis of reaction mixtures obtained from heating bromide **8**, 10 mol % Cu_2O, and 10 equiv of NH_4OH_{aq} in ethylene glycol at 90 °C for 12 h indicated a 3:2 mixture of product **16** and 2,7-diaminonaphthyridine.[11] The latter resulted from amide cleavage of **16**. Some solvolysis products were detected by LC/MS. Conditions were sought to suppress the side reactions. Increasing catalyst loading to 30 mol % and heating to 90 °C allowed consumption of **8** within 1 h. HPLC analysis

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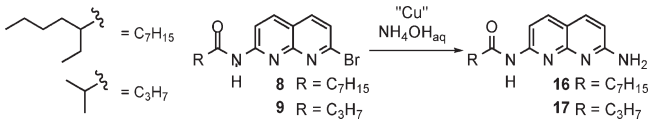
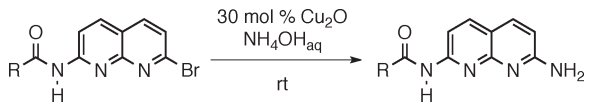
TABLE 2. Copper-Catalyzed Amination of Bromonaphthyridines

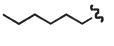
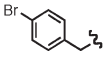


entry[a]	Cu source	mol % cat.[b]	time (h)	temp[c] (°C)	solvent[d]	yield (%)
1	Cu_2O	10	12	90	EG	34
2	Cu_2O	30	1	90	EG	74
3	Cu_2O	30	24	45	EG	73
4	Cu^0	10	24	45	EG	7
5	CuO	10	24	45	EG	0
6	$CuCl_2$	10	24	45	EG	0
7	$Cu(OAc)_2$	10	24	45	EG	0
8	CuI	10	24	45	EG	0
9	CuBr	10	24	45	EG	2
10	Cu_2O	5	24	45	EG	7
11			24	45	EG	0
12	Cu_2O	30	24	rt	EG	10
13[e]	Cu_2O	30	24	rt	EG	65
14	Cu_2O	30	24	rt	THF	5
15	Cu_2O	30	24	rt	glyme	8
16	Cu_2O	30	24	rt	*i*-PrOH	17
17	Cu_2O	30	24	rt	EtOH	37
18	Cu_2O	30	24	rt	1:1 (v:v) glyme:EG	87

[a]570 μmol of **8**, 10 equiv of NH_4OH_{aq}. [b]vs bromide. [c]rt = 25 ± 3 °C. [d]EG = ethylene glycol. [e]570 μmol of **9**.

TABLE 3. Room Temperature, Copper-Catalyzed Amination of Bromonaphthyridines with Aqueous Ammonia



entry[a]	substrate, R =	solvent[b]	product (yield, %)
1	**8** 	1:1 (v:v) EG/glyme	**16** (87)
2	**9** 	EG	**17** (65)
3	**10** 	1:1 (v:v) EG/glyme	**18** (53)
4	**11** 	1:1 (v:v) EG/glyme	**19** (0)
5	**14** 	EG	**20** (23)
6	**15** 	1:1 (v:v) EG/glyme	**21** (10)

[a]1 mmol of bromide, 10 equiv of NH_4OH_{aq}, 25 ± 3 °C, 24 h. [b]EG = ethylene glycol.

indicated a 19:1 ratio of **16** and its hydrolysis product, with **16** isolated in 73% yield. Changing the conditions to 45 °C for 24 h gave an improved ratio without a loss in yield.

A brief survey of other copper reagents indicated that Cu^0 and other Cu^I-based salts were competent, although Cu_2O was the most effective. Reactions performed with 30 mol % catalyst at room temperature (25 °C) gave incomplete conversion after 24 h; however, reaction of **9** under otherwise identical conditions (Table 2, entry 13) gave the corresponding product **17** in 65% yield, suggesting that solubility of the substrate is important to the outcome. A short survey of solvents revealed that reactions performed at room temperature in 1:1 mixtures of ethylene glycol and glyme afforded **16** in yields as high as 87%. LC/MS indicated that hydrolysis and solvolysis products accounted for the remaining UV-active species (260 nm). Note that secondary or tertiary amines, resulting from amination of **8** with **16**, were not detected throughout the course of these investigations.

Applying the conditions optimized for **8** to **9**−**11**, **14**, and **15** afforded the corresponding aminonaphthyridines **17**−**21** in 10−65% yield (Table 3). No attempt was made to optimize these reaction yields, which appear to correlate with hydrolytic stability of the amide. Bromides featuring alkyl amides gave the highest yields while yields for aryl and benzyl substrates were significantly lower. Indeed, amination of **15** and **11** gave 25% and up to 60% yield of 2-amino-7-bromonaphthyridine, respectively, resulting from amide hydrolysis. In the case of **11**, the desired product **19** could be neither isolated nor detected by LC/MS. Although >10 wt % Cu^I is used as precatalyst, ICP-MS analysis for Cu indicates samples of **16** and **17** contain ≤0.1 wt % Cu upon purification by column chromatography.

Conditions for the preparation of functional, nonsymmetric diamidonaphthyridines were sought. Coupling of **16** and **21** with various carboxylic acids was carried out with *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2. The desired diamidonaphthyridines **22**−**27** were readily obtained in 60−95% yield (Table 4). Through this methodology, mono- and heterobifunctional diamidonaphthyridines amenable to copper-catalyzed azide−alkyne cycloaddition (CuAAC),[23] and those bearing polymerizable vinyl moieties, or atom-transfer radical polymerization[24] initiators can be prepared without protecting group chemisry.

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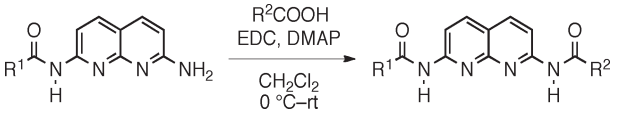
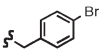
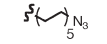
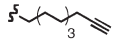
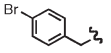
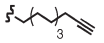
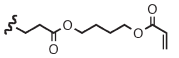
TABLE 4. Nonsymmetric Diamidonaphthyridines via Carbodiimide Coupling of Aminonaphthyridines with Functional Carboxylic Acids



entry[a]	R^1 =	R^2 =	product (yield, %)
1			**22** (97)
2			**23** (87)
3			**24** (98)
4[b]			**25** (59)
5			**26** (95)
6			**27** (83)

[a] 350 μmol of amine, 0.25 equiv of DMAP, 2 equiv of acid, 2 equiv of EDC. [b] 45 °C.

In summary, we have disclosed a route to nonsymmetric 2,7-diamido-1,8-naphthyridines that relies on copper-mediated amination of bromonaphthyridines, which are prepared from the corresponding naphthyridinones via treatment with PBr_3. The amination can be performed in ethylene glycol/aqueous ammonia solution at room temperature, in the presence of Cu_2O, and is effective for preparation of alkyl 2,7-diaminonaphthyridine monoamides. This approach may offer an alternative to that reported by Sijbesma and Meijer[14] in cases where the substrate prevents the use of palladium catalysis or where the required primary amide is not readily available. In the present case, the synthesis of "clickable" and polymerizable diamidonaphthyridines without use of protecting group chemistry may make this an appealing route to functional materials.

Experimental Section

Procedure for Bromination of 7-Amidonaphthyridinones. A three-necked round-bottomed flask, equipped with a stir bar, reflux condenser, and thermometer, containing a slurry of 1 equiv of amidonaphthyridinone in 20 equiv of PBr_3 was heated in a 110 °C oil bath for 6−72 h under a nitrogen atmosphere. The mixture was cooled to 0 °C then diluted with CH_2Cl_2, and the slurry was poured carefully over crushed ice/water. The mixture was extracted with organic solvent, dried over Na_2SO_4, filtered through Celite, and dried in vacuo. Characterization data for **8**: mp 130−131 °C; ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.62 (d, J = 8.9 Hz, 1H), 8.37 (s, 1H), 8.19 (d, J = 8.9 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 2.30−2.21 (m, 1H), 1.78−1.69 (m, 2H), 1.63−1.53 (m, 2H), 1.33−1.31 (m, 4H), 0.97 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 175.7, 154.8, 154.2, 145.7, 139.5, 138.3, 125.7, 119.5, 115.7, 51.2, 32.5, 29.9, 26.2, 22.9, 14.1, 12.1; IR (Nujol, cm^{-1}) 3168 (NH), 1691 (C=O); UV λ_{max} ($CHCl_3$) 340 nm; ESI-HRMS calcd for $[C_{16}H_{20}BrN_3O\cdot H]^+$ 350.0868, found 350.0866. Anal. Calcd for $C_{16}H_{20}BrN_3O$: C, 54.87; H, 5.76; N, 12.00. Found: C, 55.22; H, 5.81; N, 11.82. ICP-MS: 0.003 wt % Cu.

Procedure for Cu-Catalyzed Amination of 2-Bromonaphthyridines. A thick-walled high-pressure tube with cap was charged with bromonaphthyridine (1 equiv), Cu_2O (0.3 equiv), and 0.15 M in either 1:1 (v:v) ethylene glycol:glyme or ethylene glycol (see the Supporting Information for details). To the slurry was added NH_4OH_{aq} (10 equiv). The tube was capped and the reaction was stirred at room temperature (25 ± 3 °C) for 24 h. The vessel was carefully opened, diluted with water and CH_2Cl_2, and stirred, open to air, for 1 h. The crude reaction mixture was extracted with organic solvent, washed with water and brine, dried over Na_2SO_4, filtered, and dried in vacuo. Characterization data for **16**: mp 192−193 °C; ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.26 (br s, 1H), 8.05 (br s, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 6.68 (br s, 1H), 4.91 (br s, 2H), 2.21−2.16 (m, 1H), 1.77−1.70 (m, 2H), 1.64−1.58 (m, 2H), 1.35−1.30 (m, 4H), 0.97 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 175.5, 160.2, 155.5, 153.3, 139.0, 138.0, 115.4, 111.0, 110.7, 51.2, 32.7, 30.0, 26.3, 23.0, 14.2, 12.2; IR (Nujol, cm^{-1}) 3423, 3289, 3102 (NH), 1697 (C=O); UV λ_{max} ($CHCl_3$) 352 nm; ESI-HRMS calcd for $[C_{16}H_{22}N_4O\cdot H]^+$ 287.1872, found 287.1867. Anal. Calcd for $C_{16}H_{22}N_4O$: C, 67.11; H, 7.74; N, 19.56. Found: C, 66.92; H, 7.80; N, 19.18. ICP-MS: 0.09 wt % Cu.

Procedure for Acylation of 7-Amido-2-aminonaphthyridines. A round-bottomed flask equipped with a stir bar was charged with aminonaphthyridine (1 equiv), DMAP (0.25 equiv), carboxylic acid (2−3 equiv), and 0.16 M CH_2Cl_2 and was cooled to 0 °C via an ice−water bath. *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) (2−3 equiv) was added, the vessel was capped with a rubber septum, and the reaction was warmed to room temperature over several hours and kept there for 12−24 h. The solution was diluted with CH_2Cl_2 and washed with water, saturated aqueous $NaHCO_3$, and brine. The combined organic portions were dried over Na_2SO_4, filtered, and were dried in vacuo. Characterization data for **24**: mp 115−116 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.48 (d, J = 8.8 Hz, 1H), 8.44 (d, J = 8.8 Hz, 1H), 8.23 (br s, 1H), 8.21 (br s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 2.46 (t, J = 7.5 Hz, 2H), 2.26−2.21 (m, 1H), 2.18 (td, J = 7.0, 2.7 Hz, 2H), 1.94 (t, J = 2.6 Hz, 1H), 1.79−1.68 (m, 4H), 1.65−1.49 (m, 4H), 1.44−1.30 (m, 12H), 0.98 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 175.5, 172.4, 153.9, 153.9, 153.8, 139.2, 118.5, 113.7, 113.5, 84.9, 68.3, 51.2, 38.2, 32.6, 29.9, 29.3, 29.2, 29.0, 28.8, 28.6, 26.2, 25.4, 22.9, 18.5, 14.1, 12.2; IR (CCl_4, cm^{-1}) 1698 (C=O); UV λ_{max} ($CHCl_3$) 347 nm; ESI-HRMS calcd for $[C_{27}H_{38}N_4O_2\cdot H]^+$ 451.3073, found 451.3084. Anal. Calcd for $C_{27}H_{38}N_4O_2$: C, 71.97; H, 8.50; N, 12.43. Found: C, 71.89; H, 8.66; N, 12.19.

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Supporting Information Available: Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.