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Synthesis of 1,8-naphthyridines from 2-aminonicotinaldehydes and terminal alkynes

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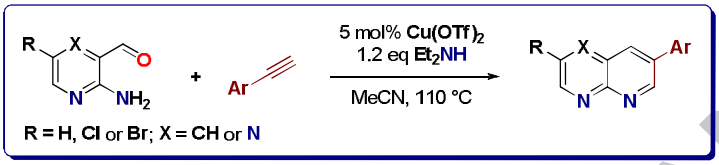
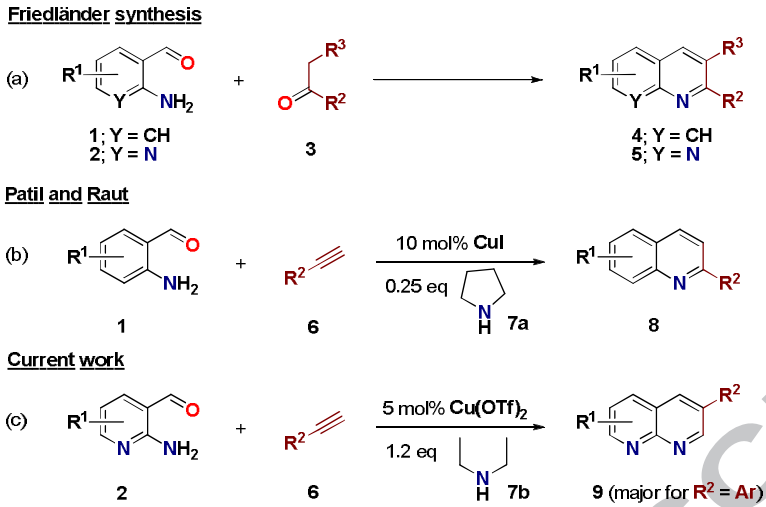


ABSTRACT. A copper (II) triflate-catalyzed diethylamine-assisted protocol for the reaction of 2-aminonicotinaldehydes and terminal alkynes leading to 1,8-naphthyridines is described. The overall process presumably involves a copper (II) triflate-catalyzed hydroamination of the triple bond followed by the Friedländer-type condensation of the resulting enamine with 2-aminonicotinaldehyde.

Keywords: 1,8-naphthyridines, 2-aminonicotinaldehydes, alkynes, copper catalysis, hydroamination, Friedländer synthesis

1,8-Naphthyridine is important heterocyclic motif that is present in a large number of biologically active compounds.[1] In addition, 1,8-naphthyridines and their dimer derivatives have been investigated for the applications in host-guest and self-assembling systems[2] and in organic light-emitting diodes.[3]

The Friedländer synthesis[4] is a classical way to access quinolines **4**[5] and 1,8-naphthyridines **5**[6] through the condensation of aromatic 2-aminoaldehydes **1** or **2** with aldehydes or ketones **3** containing a methylene group in the alpha position to the carbonyl moiety (Scheme 1a). In 2010, Patil and Raut described a complimentary copper (I) iodide/pyrrolidine-co-catalyzed reaction of 2-aminobenzaldehydes **1** with terminal alkynes **6** leading to 2-substituted quinolines **8** (Scheme 1b).[7,8] Following the success of their procedure, we decided to evaluate the reactivity of 2-aminonicotinaldehydes **2** in the analogous process. As a result of these efforts we were able to establish a novel route towards 3-substituted 1,8-naphthyridines **9** (Scheme 1c) that features different regioselectivity compared to the parent Patil and Raut's transformation. Herein we wish to outline the scope and limitations of our procedure.

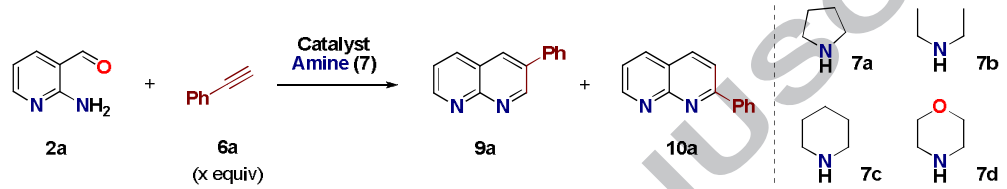


Scheme 1. Approaches to quinolines **4** and **8** and 1,8-naphthyridines **5** and **9**

We have started our investigation with a search for the optimal reaction parameters employing 2-aminonicotinaldehyde **2a** and phenyl acetylene **6a** as model substrates (Table 1). The first trial was performed under the conditions adopted from the Patil and Raut's report utilizing slight access of phenyl acetylene **6a**, 10 mol% of copper (I) iodide as a catalyst, 0.25 equivalents of pyrrolidine **7a** as a secondary amine additive and 3.3 mL of MeCN as a solvent. However, conducting this reaction at 100 °C for 14 hours resulted in only 50% conversion of **2a** producing only very small amounts of two isomeric 1,8-naphthyridines **9a** and **10a** (Table 1, entry 1). Increasing the reaction time to 26 hours or decreasing the amount of solvent did not affect the reaction outcome (Table 1, entries 2 and 3). Switching to the use of diethylamine **7b** as an additive slightly affected the regioselectivity but the yields remained poor (Table 1, entry 4). At this point, we decided to switch to the use of stoichiometric amounts of the amine additive. Simultaneously, we have opted to pre-treat **2a**, **6a** and a copper catalyst prior to the addition of the secondary amine. Conducting the reaction with 5 mol% of copper (I) iodide and 1.2 equivalents of diethylamine **7b** in 1 mL of MeCN led to almost complete conversion of **2a** producing 3-substituted 1,8-naphthyridine **9a** in 32% yield (Table 1, entry 5). At the same time the yield for the isomeric 2-substituted 1,8-naphthyridine **10a** remained poor directing the focus of our optimization efforts towards the 3-substituted isomer **9a**. Next we have found that the copper (I) bromide is a less efficient catalyst compared to copper (I) iodide (Table 1, entry 6) whilst copper (II) triflate demonstrated superior performance furnishing **9a** in 47% yield (Table 1, entry 7) thus making it a catalyst of choice for further screening. An attempt to lower the amount of diethylamine **7b** met with failure leading to diminished yield of **9a** (Table 1, entry 8). Omitting the pretreatment step resulted in lower yield of **9a** and an incomplete conversion of **2a** despite the prolonged reaction time of 17 hours (Table 1, entry 9).[9] Employing copper (II) triflate in a combination with other secondary amine additives such as pyrrolidine **7a**, piperidine **7c** or morpholine **7d** significantly decreased the regioselectivity of the process (Table 1, entries

10-12). The use of other solvents such as dioxane or toluene also proved to be disadvantageous leading to diminished yield of **9a** and incomplete conversion of **2a** (Table 1, entries 13 and 14). Finally, some improvements were made by decreasing the amount of acetonitrile solvent (Table 1, entry 15) and shortening the pretreatment time (Table 1, entry 16) that allowed to upgrade the NMR yield of **9a** up to 57%, which corresponds to the isolated yield of 55%. The use of copper (II) triflate catalyst in the absence of diethylamine **7b** additive or visa versa gave no 1,8-naphthyridines **9a** and **10a** (Table 1, entries 17 and 18) despite the partial consumption of starting **2a** that, thus, could be ascribed to decomposition.

Table 1. Optimization of the reaction parameters[a]



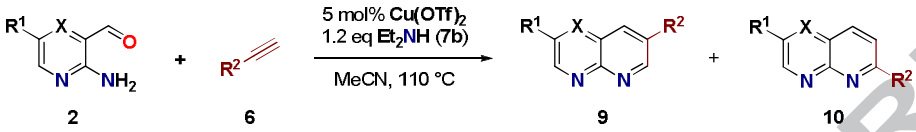
Entry	x	Catalyst (mol %)	Amine **7**	Solvent	Temp, °C[b]	time, h	Yields (%)[c]		
							2a	**9a**	**10a**
1	1.2	CuI (10 mol%)	**7a**; 0.25 equiv	MeCN (3.3 mL)	100	14	50	3	4
2	1.2	CuI (10 mol%)	**7a**; 0.25 equiv	MeCN (3.3 mL)	100	26	30	4	6
3	1.2	CuI (10 mol%)	**7a**; 0.25 equiv	MeCN (1 mL)	100	14	44	3	5
4	1.2	CuI (10 mol%)	**7b**; 0.25 equiv	MeCN (1 mL)	100	14	48	4	3
5	1.5	CuI (5 mol%)	**7b**; 1.2 equiv[d]	MeCN (1 mL)	110	3[e]+12	6	32	4
6	1.5	CuBr (5 mol%)	**7b**; 1.2 equiv[d]	MeCN (1 mL)	110	3[e]+12	25	27	4
7	1.5	$Cu(OTf)_2$ (5 mol%)	**7b**; 1.2 equiv[d]	MeCN (1 mL)	110	3[e]+12	tr	47	4
8	1.5	$Cu(OTf)_2$ (5 mol%)	**7b**; 0.5 equiv[d]	MeCN (1 mL)	110	3[e]+12	tr	27	3
9	1.5	$Cu(OTf)_2$ (5 mol%)	**7b**; 1.2 equiv	MeCN (1 mL)	110	17	9	43	4
10	1.5	$Cu(OTf)_2$ (5 mol%)	**7a**; 1.2 equiv[d]	MeCN (1 mL)	110	3[e]+12	tr	21	16
11	1.5	$Cu(OTf)_2$ (5 mol%)	**7c**; 1.2 equiv[d]	MeCN (1 mL)	110	3[e]+12	tr	33	14
12	1.5	$Cu(OTf)_2$ (5 mol%)	**7d**; 1.2 equiv[d]	MeCN (1 mL)	110	3[e]+12	tr	35 (31)[f]	26 (19)[f]
13	1.5	$Cu(OTf)_2$ (5 mol%)	**7b**; 1.2 equiv[d]	dioxane (1 mL)	110	3[e]+12	49	22	4
14	1.5	$Cu(OTf)_2$ (5 mol%)	**7b**; 1.2 equiv[d]	toluene (1 mL)	110	3[e]+12	24	22	5
15	1.5	$Cu(OTf)_2$ (5 mol%)	**7b**; 1.2 equiv[d]	MeCN (0.5 mL)	110	3[e]+12	tr	53	4
16	1.5	$Cu(OTf)_2$ (5 mol%)	**7b**; 1.2 equiv[d]	MeCN (0.5 mL)	110	1[e]+12	4	57 (55)[f]	4
17	1.5	$Cu(OTf)_2$ (5 mol%)	-	MeCN (1 mL)	110	12	51	-	-
18	1.5	-	**7b**; 1.2 equiv	MeCN (1 mL)	110	12	86	-	-

[a] The reactions were run on 0.5 mmol scale. [b] This refers to the oil bath temperature. [c] Yields are determined by ^{1}H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. [d] Added after the indicated pretreatment time. [e] Pretreatment time. [f] Isolated yield is given in parentheses.

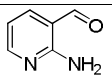
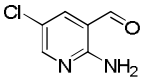
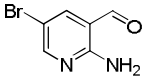
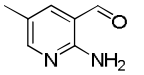
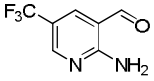
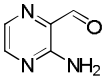
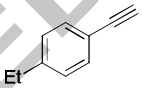
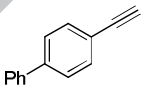
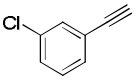
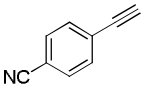
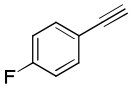
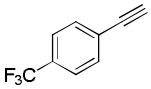
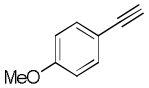
Having these results in hand, we moved to the substrate scope evaluation (Table 2).[10] First, we tested several 2-aminonicotinaldehydes **2a-e** in a combination with phenyl acetylene **6a**. All reactions proceeded with comparable efficiency delivering 1,8-naphthyridines **9a-e** with good isolated yields ranging from 47% to 55% (Table 2, entries 1-5). However, the analogous reaction of 3-aminopyrazine-2-carbaldehyde **2f** gave only poor yield of pyrido[2,3-b]pyrazine **9f** (Table 2, entry 6) restricting the scope of our procedure. Next, we reacted various (hetero)aromatic acetylenes **6b-i** in a combination with 2-aminonicotinaldehyde **2a**. The acetylenes **6b-g** bearing neutral or electron withdrawing substituents on the aromatic ring all gave good results furnishing 1,8-naphthyridines **9g-l** in up to 62% yield (Table 2, entries 7-12). The 4-methoxyphenyl

acetylene **6h** showed inferior reactivity producing 1,8-naphthyridine **9m** in only 22% yield along with 9% of isomeric **10m** (Table 2, entry 11). The heteroaromatic 3-ethynylthiophene **6i** reacted well allowing to isolate 1,8-naphthyridines **9n** and **10n** in 53% and 9% yields, respectively (Table 2, entry 12).

Table 2. Scope of the process[a]



2 **6** **9** **10**

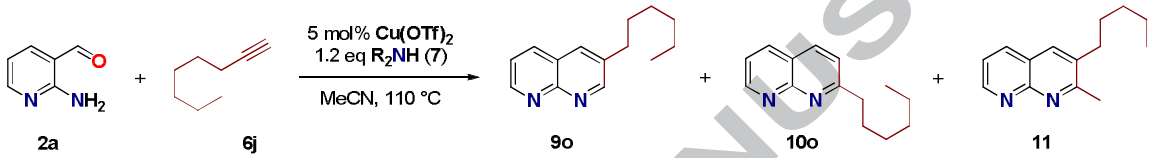
Entry	2	6	Product	Yields[b] 9	10
1	 **2a**	 **6a**	**a**	55	4[c]
2[d]	 **2b**	**6a**	**b**	53	-
3[e]	 **2c**	**6a**	**c**	49	-
4[f]	 **2d**	**6a**	**d**	51	5
5[f]	 **2e**	**6a**	**e**	47	5
6[d]	 **2f**	**6a**	**f**	10	-
7	**2a**	 **6b**	**g**	52	-
8[d,g]	**2a**	 **6c**	**h**	42	-
9	**2a**	 **6d**	**i**	62	-
10[d]	**2a**	 **6e**	**j**	62	-
11	**2a**	 **6f**	**k**	61	-
12	**2a**	 **6g**	**l**	58	-
13	**2a**	 **6h**	**m**	22	9
14	**2a**	 **6i**	**n**	53	9

[a] The reactions were run on 0.5 mmol scale (based on **2)** using 1.5 equiv excess of **6** in 0.5 mL of MeCN for 1+12 hours unless otherwise stated. [b] Isolated yields. [c] Determined by ^{1}H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. [d] The reaction

was run in 0.8 mL of MeCN. [e] The reaction was run in 1 mL of MeCN. [f] The reaction was run on 0.75 mmol scale. [g] The reaction was run for 1+20 hours.

The reaction of aliphatic 1-octyne **6j** and 2-aminonicotinaldehyde **2a** under the standard conditions proceeded completely unselectively yielding monosubstituted 1,8-naphthyridines **9o** and **10o** in comparable yields of 13% and 14%, respectively along with the trace amounts of disubstituted 1,8-naphthyridine **11** (Table 3, entry 1). Interestingly, changing the amine additive from diethylamine **7b** to morpholine **7d** allowed to upgrade the selectivity at the same time diverging it towards 2-substituted 1,8-naphthyridine **10o** that in this case was obtained in 49% yield (Table3, entry 2).

Table 3. Reaction of 2-aminonicotinaldehyde **1a** with octyne **2j**[a]



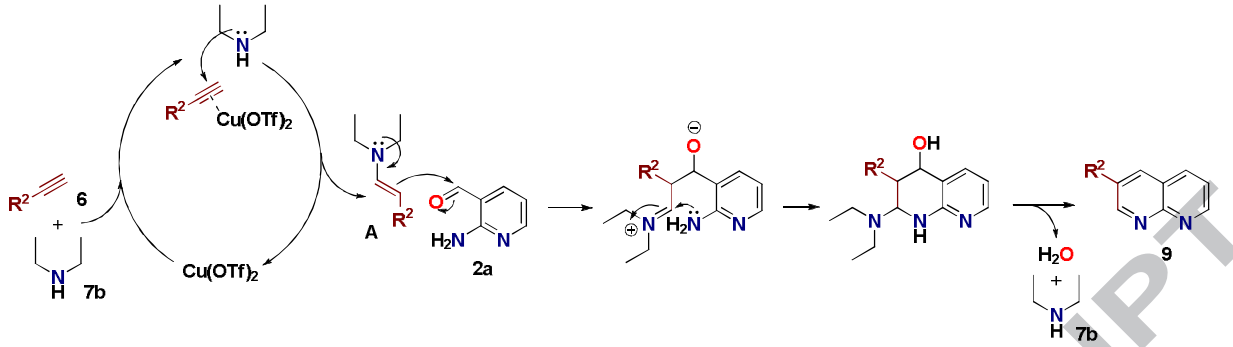
2a **6j** **9o** **10o** **11**

Entry	**7**	Yields[b]		
		9o	**10o**	**11**
1	**7b**	13	14	tr
2	**7d**	10[c]	49	5[c]

[a] The reactions were run on 0.5 mmol scale (based on **2a)** using 1.5 equiv excess of **6j** in 0.5 mL of MeCN for 1+12 hours. [b] Isolated yields. [c] For this entry **9m** and **11** were obtained as a mixture. The individual yields are estimated based on ^{1}H NMR.

A tentative mechanistic pathway for the formation of 3-substituted 1,8-naphthyridines **9** is depicted on Scheme 2. [11] The copper catalyst activates the alkyne **6** towards the nucleophilic attack by the amine **7b** resulting in the enamine **A** formation. Such copper-catalyzed alkyne hydroaminations are well known[12,13] and typically are accompanied by the addition of the second alkyne molecule to the generated enamine **A** yielding propargylamines as final products. In our case, the enamine **A** chooses to react with 2-aminonicotinaldehyde **2a** through the Friedländer-type sequence that starts from the nucleophilic attack onto the carbonyl group of **2a** and follows by the cyclization into the aminal **B**. Finally, **B** converts into naphthyridine **9** with concomitant elimination of water and amine **7b**.

Following the above considerations, it is reasonable to assume that the regioselectivity of the overall process arises from the regioselectivity of the alkyne hydroamination step where the anti-Markovnikov pathway seems to be predominant leading to the formation of 3-substituted 1,8-naphthyridine **9** as a major product. Thus, the minor 2-substituted 1,8-naphthyridine **10** should result from the following the Markovnikov pathway during the hydroamination.



Scheme 2. Tentative mechanism

In conclusion, we have discovered and documented a novel copper (II) triflate-catalyzed reaction of 2-aminonicotinaldehydes with terminal alkynes providing access to 1,8-naphthyridine core. The reaction requires the presence of secondary amine and presumably involves a copper (II) triflate-catalyzed hydroamination of alkyne followed by the Friedländer-type condensation of resulting enamine with 2-aminonicotinaldehyde. The scope and limitation of the process have been briefly assessed resulting in a generation of a mini library of 1,8-naphthyridines.

Acknowledgements

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Supplementary data

Full experimental procedures as well as copies of ^{1}H and ^{13}C NMR spectra of the compounds associated with this article can be found, in the online version, at http://dx.doi.org/.

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[8] For other related processes involving reactions of 2-aminobenzaldehydes or 2-acylanilines with alkynes for the synthesis of quinolines, see: (a) Li, H.; Wang, C.; Huang, H.; Xu, X.; Li, Y. *Tetrahedron Lett.* **2011**, *52*, 1108-1111; (b) Zhou, W.; Lei, J. *Chem. Commun.* **2014**, *50*, 5583-5585.

[9] We have no precise explanation for this result. Probably, the pretreatment of Cu salt with **2a** and **6a** in the absence of amine **7b** leads to the generation of more reactive catalytic species.

[10] *Representative procedure exemplified by the synthesis of 3-phenyl-1,8-naphthyridine (**9a**).* 2-Aminonicotinaldehyde **2a** (61 mg, 0.5 mmol) and copper (II) triflate (9 mg, 0.025 mmol) were placed in a screw cap vial followed by addition of acetonitrile (0.5 ml) and phenyl acetylene **6a** (77 mg, 0.75 mmol). The resulting mixture was flushed with argon, submerged in the oil bath preheated at 110 °C and kept with a stirring for 1 hour. Upon completion of this time, the mixture was cooled down and the diethylamine **7b** (44 mg, 0.6 mmol) was added. The reaction mixture was again flushed with argon, submerged in the oil bath preheated at 110 °C and kept with a stirring for another 12 hours. The resulting mixture was diluted with EtOAc and evaporated with silica gel. Column chromatography with PE-EtOAc (40→50 %) followed by washing with diethyl ether delivered pure **9a** (57 mg, 55 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.38 (bs, 1H), 9.10 (bs, 1H), 8.29 (d, *J* = 2.3 Hz, 1H), 8.23 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.76–7.64 (m, 2H), 7.58-7.47 (m, 3H), 7.47-7.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 153.4, 153.2, 137.3, 137.0, 135.0, 134.0, 129.4, 128.6, 127.5, 122.6; HRMS (ESI, $[M+H]^+$) for $C_{14}H_{10}N_2$ calcd. 207.0917, found 207.0918.

[11] In the paper of Patil and Raut (ref.[7]) a different mechanism for the analogous reaction of 2-aminobenzaldehydes **1** was proposed. According to them, **1** reacts with secondary amine to form the iminium cation that subsequently undergoes the attack of copper acetylide. The resulting propargylamine intermediate undergoes 6-*endo-dig* cyclization and aromatization to give 2-substituted quinoline **8**. However, for the reactions with 2-aminonicotinaldehydes **2** this mechanism seems to be not operational as can be judged from the different regioselectivity of our process.

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*Highlights

- 1,8-Naphthyridine core can be assembled from 2-aminonicotinaldehydes and terminal alkynes.
- The developed procedure utilizes copper (II) triflate catalyst in the presence of diethylamine.
- The developed procedure selectively yields 3-substituted 1,8-naphthyridines.