Practical synthesis of N-substituted naphthyridine.

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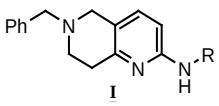
1-INTRODUCTION

➢ Metal catalyzed C-N bond formation reactions of aromatic compounds have made significant advances in the past decade.
Innovations from the Hartwig and Buchwald groups have continued to inspire researchers to discover milder and more selective conditions. Heteroaromatic amines are ubiquitous in biologically active molecules. In one of our Med. Chem. Program we found the need to prepare a variety of N-disubstituted-5,6,7,8 terahydro 1,6 naphthyridine-2-ylamine such as **I**.



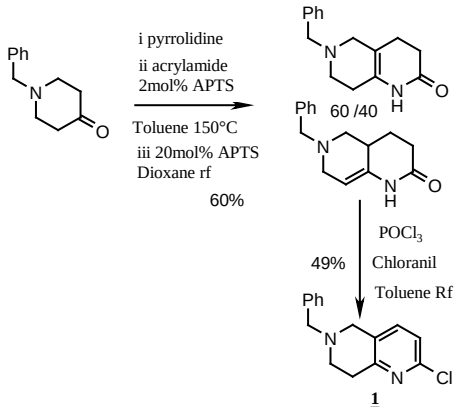
I

R= alkyl or COAr

2-PREPARATION OF NAPHTHYRIDINE CORE 1

Compound **1** was chosen as one key synthetic intermediate, as it was already described in patent literature.[1]

Scheme 1



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3- PRACTICAL Cu CATALYZED AMINATION

➢ We used the coupling of **1** and benzyl amine as a test case and examined a number of literature methods[2] using a variety of ligands combined with both Pd and Cu. Selected results are summarized in Table 1. It quickly became apparent that the CuI/ proline method reported by Ma consistently outperformed all the other methods.
To optimize this reaction, we examined the conditions more in detail and selected examples are summarized in Table 2. The conversion of each reaction was analyzed by LCMS. In most of the cases a mixture of four main products was observed:
Desired product **2**, remaining starting material **1**; dechlorination product (de-Cl) and traces of the ligand addition product (LA) (under Cu conditions).

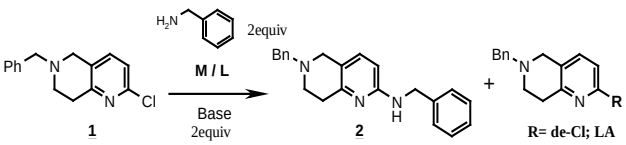


Table 1, Metal catalyzed amination of **1**

Entry	Catalyst condition*	Ligand	%conversion** (**2**/**1**/de-Cl/LA)
1[2a]	$Pd_2(dba)_3$ 5% K_3PO_4 toluène 120°C	x-phos 20%	7/45/35/-
2[2a]	CuI 10% K_3PO_4 toluène 120°C	 30%	5/50/15/-
3[2b]	CuI 10% K_2CO_3 DMSO 120°C	Proline 20%	45/35/5/3

*Microwave heating, 30min.
Conversion based on LCMS. (de-Cl**) dechlorination product (**LA**) ligand addition.
x-Phos: 2dicyclohexyphosphino-2'-4'-6'-triisopropylbiphenyl

➢Proline proved to be the optimal ligand in terms of yields (Table 2).
We attempted to reduce the reaction time by increasing the reaction temperature
in microwave conditions (entry 6), unfortunately more dechlorination was observed. Finally, the selected method was:
*1mmol of **1**, benzylamine (2 equiv), CuI (40%),*
K_2CO_3 (3 equiv); 500 µL DMSO microwave heating at 140°C, for 90min.

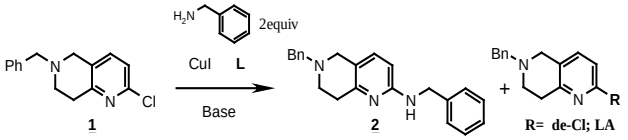
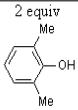


Table 2. Optimization of Cu catalyzed amination of **1**.

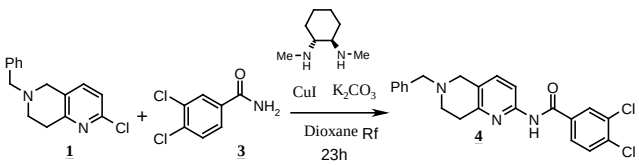
Entry	CuI %	Base	Ligand	Conditions*	%conversion** (**2**/**1**/de-Cl/LA)
1	0.1	2 equiv K_3PO_4	-	NMP 140°C 1h	4/42/-/-
2[2c]	0.1	2 equiv $K_3PO_4H_2O$	10 equiv 	135°C 1h	2/40/16/11
3	0.1	2 equiv $K_3PO_4H_2O$	2 équiv Proline	DMSO 140°C 1h	49/20/2/-
4[2d]	0.1	2 equiv K_3PO_4	2 equiv 	Isopropanol 100°C 1h	25/30/-/-
5[2b]	0.1	2 equiv K_2CO_3	Proline 20%	DMSO 160°C 2h	40/30/2/-
6	0.1	2 equiv K_2CO_3	Proline 20%	DMSO 175°C 2h	33/25/18/-
7	0.2	3 equiv K_2CO_3	Proline 40%	DMSO 140°C 90min 2h	42/30/2/- 44/20/6/-

*Reaction performed on 1mmol scale, microwave heating.

4- PRACTICAL Cu CATALYZED AMIDATION

➢Amidation of the 2 position was successfully obtain by applying Buchwald method.[3] Thus, reaction of the substrate **1** with the primary amide **3** under Buchwald conditions gave compound **4** (scheme 2). We found that the reaction could be accelerated by microwave heating which significantly reduced the reaction time (1h vs 23h).

Scheme 2



➢Those reactions generally gave good conversion and acceptable isolated yields. Typically the compound of type **I** was obtained with a yield ranging from 13% to 45% of isolated yields.
➢ The selected method was : *1mmol of **1**, primary amide **3** equiv. CuI (20%),trans -cyclohexanediamine (40%), K_2CO_3 2 equiv;1ml Dioxane and microwave heating at 150°C, for 40min.*

5-SUMMARY

➢We have prepared a series of type **I** compounds.
Amines were successfully obtained.The straight amidation approach was successful too: the amidation of naphthyridine-2-chloro was accomplished using an air-stable CuI catalyst in combination with cheap racemic *trans* cyclohexanediamine. In this case, rate acceleration was achieved with microwave heating.

➢In conclusion, we have established a practical an efficient route towards aminale and amidated tetrahydro naphthyridine. This methodology is also amenable to parallel synthesis.

References

1. Pfizer US 6,169,093
2. (a) Buchwald, S.L. *J. Am. Chem. Soc.* **2003**, 125, 6653.
   (b) Ma, D. *Synthesis* **2005**, 496.
   (c) Twieg R.J. *Tetrahedron Lett*. **2003**,44,6289
   (d) Buchwald, S.L.*Org. Lett.* **2002**,581
3. Buchwald, S.L. *J. Am. Chem. Soc.* **2001**, 123,7727.