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Cu(I)-catalyzed three component coupling protocol for the synthesis of quinoline derivatives

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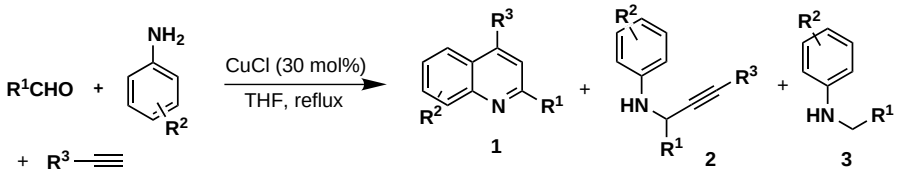
Abstract—Synthesis of 2,4-disubstituted quinolines has been achieved in a one-pot reaction from an aryl amine, an aldehyde and a terminal alkyne using CuCl (30 mol%) as a catalyst.

Quinolines and their derivatives are very important in medicinal chemistry because of their wide occurrence in natural products[1] and drugs.[2] The classical method of quinoline synthesis is Skraup's procedure.[3] Quinolines can be prepared from aminoarenes and olefins using transition metal complexes as catalysts.[4,5] Also, quinolines can be synthesized from aminoarenes and aliphatic aldehydes under non-acidic conditions.[6] Most of these synthetic protocols for quinolines suffer from harsh reaction conditions, poor yields and/or the use of expensive catalysts.

In an ongoing project in our laboratory on the synthesis of functionalized quinolines, we required an efficient route for the synthesis of these heterocycles. To the best of our knowledge there is no simple and efficient method for the formation of a functionalized quinoline. Herein we report a novel, efficient and general route for the synthesis of 2,4-disubstituted quinolines **1** (Scheme 1) in a one-pot synthesis from an aryl amine, an aldehyde and a terminal alkyne using a cheap catalyst, CuCl.[7]

Typically, the arylamine (1.5 mmol) and an aromatic aldehyde (1.5 mmol) were taken along with a catalytic quantity of CuCl (30 mol%) in dry THF. The resulting mixture was stirred at 25°C for 15 minutes. At this stage the terminal alkyne (1 mmol) was introduced into the reaction mixture and the temperature was raised to 60–70°C for 6–10 hours. The solvent was removed under reduced pressure and the resulting mixture was purified by column chromatography to afford 2,4-disubstituted quinoline **1** in satisfactory to good yields (Scheme 1, Table 1). Benzaldehyde and *p*-anisidine reacted with 1-hexyne or 1-octyne to give the corresponding disubstituted quinolines **1a** and **1b**, respectively, in good yields (Table 1, entries 1 and 2). It is interesting to note that propargyl alcohol and propargyl acetate reacted with the aldehyde and amine to give the corresponding disubstituted quinolines **1c**–**g**, which are amenable to further functionalization at the 4-position (Table 1, entries 3–7). A careful analysis of the reaction mixture revealed that benzylamines **3** (reduced product of the in situ formed Schiff base) obtained from the aldehyde and amine were present as by-



Scheme 1.

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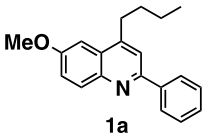
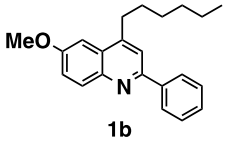
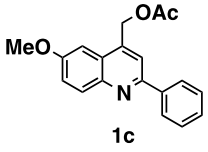
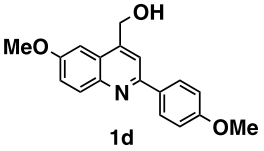
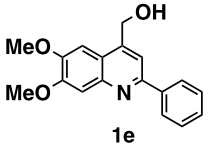
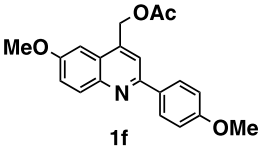
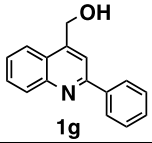
Table 1. Cu(I)-catalyzed synthesis of quinoline derivatives

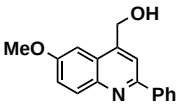
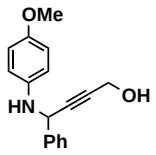
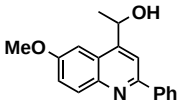
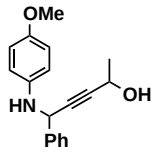
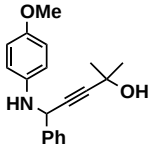
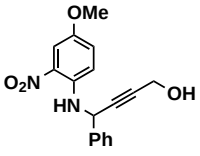
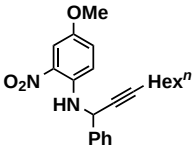
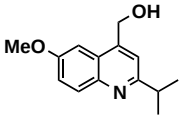
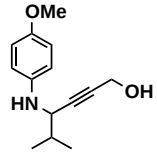
Entry	Aldehyde R^1	Aniline R^2	Alkyne R^3	Quinoline	Yield(%)[a]
1	Ph	*p*-OMe	*n*-Bu	 **1a**	48
2	Ph	*p*-OMe	*n*-Hex	 **1b**	45
3	Ph	*p*-OMe	CH_2OAc	 **1c**	45
4	*p*-$OMeC_6H_4$	*p*-OMe	CH_2OH	 **1d**	34
5	Ph	*p*-OMe *p*-OMe	CH_2OH	 **1e**	40
6	*p*-$OMeC_6H_4$	*p*-OMe	CH_2OAc	 **1f**	34
7	Ph	H	CH_2OH	 **1g**	40

[a]isolated yield

products (~40%) along with the expected quinoline derivatives (Scheme 1).

We have also studied the effect of the nature of the alkyne on the outcome of these reactions. Accordingly, propargyl alcohol when reacted with benzaldehyde and anisidine afforded a mixture of the corresponding quinoline **1h** and the substituted propargyl amine **2a** (Table 2, entry 1). A similar mixture of products **1i** and **2b** was obtained when benzaldehyde and anisidine were reacted with 1-methylprop-2-yn-1-ol (Table 2, entry 2). Interestingly, the reaction of 1,1-dimethylprop-2-yn-1-ol with benzaldehyde and *p*-anisidine gave the corresponding propargyl amine **2c** as the only product in good yield (Table 2, entry 3). It is also interesting to note that the reaction of propargyl alcohol, benzaldehyde and *o*-nitro-*p*-methoxyaniline gave the corresponding propargylamine **2d** as the only product (Table 2, entry 4). Similarly the reaction of 1-hexyne with benzaldehyde and *o*-nitro-*p*-methoxyaniline afforded the corresponding propargylamine **2e** as the sole product (Table 2, entry 5). The reaction of isobutyraldehyde, *p*-anisidine and propargyl alcohol gave a mixture of the corresponding quinoline **1j** and the propargyl amine **2f** derivative (Table 2, entry 6). A careful analysis of the reaction mixtures affording only the propargylamine, revealed the absence of any benzylamine derivative **3**. It appears that the propargylamine **2** is a precursor to quinoline **1** as we have observed that **2a** is transformed to the corresponding quinoline **1h** when heated with

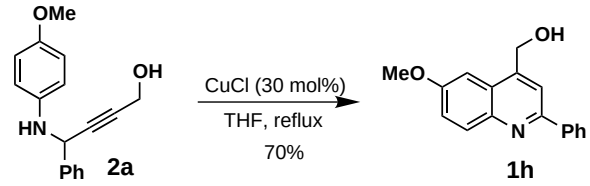
Table 2. Cu(I)-catalyzed synthesis of propargyl amine and quinoline derivatives

Entry	Aldehyde R^1	Aniline R^2	Alkyne R^3	Quinoline yield[a]	Propargyl amine yield[a]
1	Ph	*p*-OMe	-CH_2OH	 **1h (37%)**	 **2a (15%)**
2	Ph	*p*-OMe	-$CH(CH_3)OH$	 **1i (35%)**	 **2b (14%)**
3	Ph	*p*-OMe	-$C(CH_3)_2OH$		 **2c (47%)**
4	Ph	*p*-OMe *o*-NO_2	-CH_2OH		 **2d (48%)**
5	Ph	*p*-OMe *o*-NO_2	*n*-Hex		 **2e (30%)**
6	-$CH(CH_3)_2$	*p*-OMe	-CH_2OH	 **1j (31%)**	 **2f (9%)**

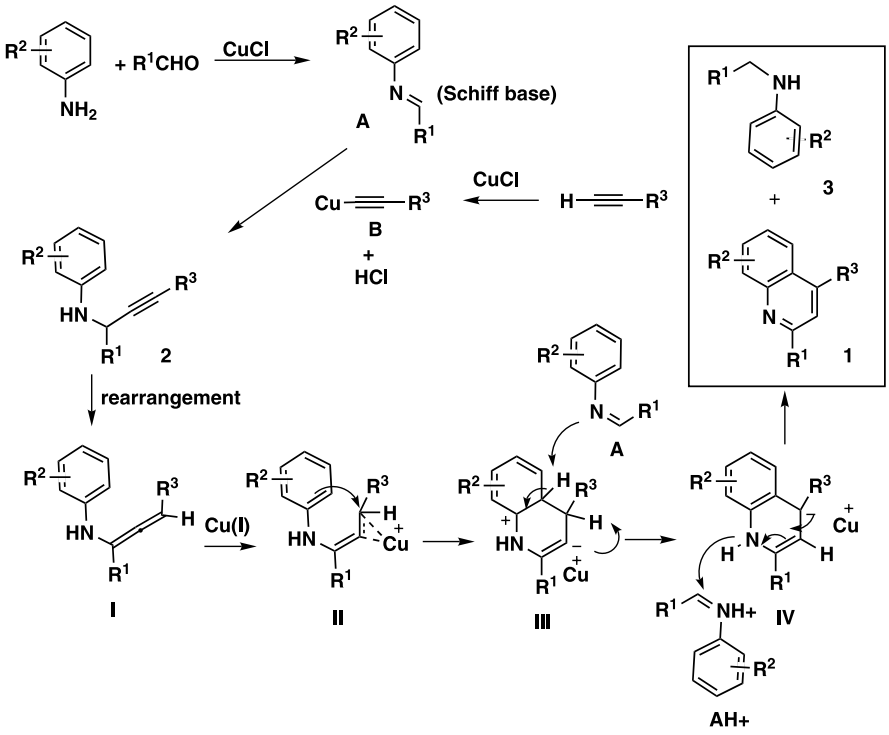
[a]isolated yield

CuCl under the reaction conditions described above (Scheme 2).

Based upon these findings we propose the following mechanism for the conversion of the three components to a quinoline. At first, a Schiff's base **A** is formed from the aldehyde and the amine under the reaction conditions. Cu-acetylide **B**, generated in situ then adds to imine **A** to give intermediate **2** which in turn undergoes



Scheme 2. Cu-catalyzed conversion of a propargylamine to a quinoline.



Scheme 3. Proposed mechanism for Cu(I)-catalyzed quinoline synthesis.

propargyl–allenyl isomerization to form **I** (Scheme 3). Next, coordination of copper(I) to the terminal bond of allene **I** would give intermediate **II** which will trigger an intramolecular nucleophilic attack to produce the zwitterion **III**.[8] The latter would then isomerize via a 1,2-shift and proton transfer to **A** into the more stable zwitterionic intermediate **IV**, and protonated **A** (i.e. **AH+**). The intermediate **IV** would transform into quinoline **1** and benzylamine **3** by an oxidative process (hydride transfer to **B**) (Scheme 3). It may be noted here that the cyclization of compound **2** to quinoline **1** involves an oxidative process in which the Schiff's base may play the role of a sacrificial oxidizing agent leading to the benzylamine derivatives **3** (40%). *However the role of oxygen in this oxidation cannot be ruled out, as these reactions are not conducted under rigorously anaerobic conditions.*

In summary, irrespective of mechanism, we have developed an efficient and general route to 2,4-disubstituted quinolines in a one-pot synthesis from an arylamine, an aldehyde and a terminal alkyne. This methodology appears very attractive for a combinatorial synthesis of quinolines for which efforts are in progress in our laboratory.

Acknowledgements

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8. A similar step has been proposed for the silver-assisted cycloisomerization of the allenyl ketone into furans, see: Marshall, J. A.; Bartley, G. S. *J. Org. Chem.* **1994**, *59*, 7169.