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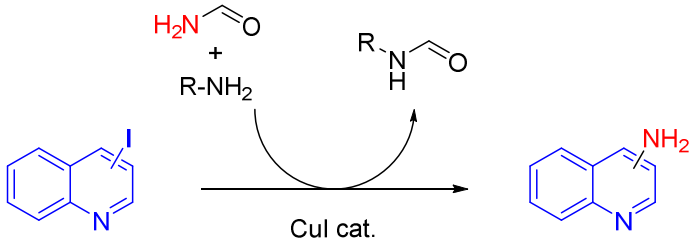

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ARTICLE TYPE

In-situ generation of ammonia for the copper-catalyzed synthesis of primary aminoquinolines

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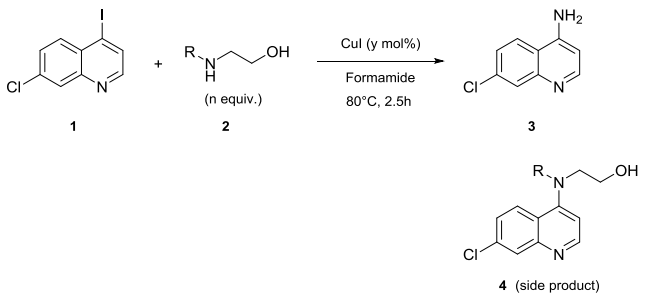
A synthesis of primary aminoquinolines from iodoquinoline was developed in the presence of copper(I) iodide and formamide as solvent and source of ammonia generated *in-situ*. The reaction proceeded in mild conditions within few hours and was applicable on various iodoquinolines.

Aminoquinoline scaffold and derivatives are found in numerous natural products and drug-like compounds.[1-6] Among them, chloroquine is a well-known 4-aminoquinoline class of drugs that is widely used for the prophylaxis treatment of malaria[1] but can be also a useful agent for the treatment of rheumatoid arthritis,[2] lupus erythematosus[3] by means of its anti-inflammatory properties. Besides, some other derivatives exhibit remarkable analgesic[4] or antibacterial activities[5] and more recently 2-aminoquinoline derivatives were identified as efficient BACE1 inhibitors for the treatment of Alzheimer's disease.[6]

Starting from halogenoquinolines, several synthetic approaches have been described for the synthesis of primary aminoquinolines. The traditional strategy involves the use of ammonia or masked ammonia to generate the C-N bond.[7-9] This bond formation was first performed in the presence of ammonia gas with a large excess of phenol and required high temperature (over 150°C).[7] Later, the emergence of transition-metal catalysts has enabled this reaction to take place at lower temperature from a large variety of halogenoquinolines. Typically, the latter reactions were conducted in aqueous ammonia or dioxane/ammonia solution with copper or palladium catalysts.[8] The use of ammonia surrogate in cross-coupling reactions involving aryl halide has been described but usually requires an additional step to release the primary amine moiety.[9]

Herein we wish to report the use of the inexpensive formamide as solvent and ammonia source by means of an *in situ* reaction with an amine for a copper-catalyzed amination of iodoquinolines. This new reaction was inspired from the observation that ammonia is released when formamide is heated with amines.

Our first attempt to check the feasibility of the reaction was realized on 7-chloro-4-iodoquinoline **1** in the presence of ethanolamine (66 equiv.), formamide and 30 mol% of copper(I) iodide (Scheme 1 and Table 1). The flask was capped with a balloon filled with nitrogen (procedure A) to control the ammonia formation. To our delight, the expected 4-amino-7-chloroquinoline **2** was isolated with 63% yield (Table 1, entry 1). The use of an aminoalcohol in the reaction allows to get rid of the side product **4** and derivatives by washing during the work-up. Replacing the ethanolamine by the *N*-methylethanolamine improved the yield to 84% (entry 2). Hence, encouraged by this result, investigations were performed to determine the optimal conditions (Scheme 1 and Table 1). From this optimization, it appears that decreasing the loading of catalyst to 10 mol% was slightly detrimental for the yield (entry 2 vs entry 3). The yield dropped to 60% when the reaction vessel was not capped (entry 6, procedure B). This result can found the explanation in the decrease of ammonia concentration in solution. However, setting up the procedure C (closed vessel) maintained the yield to a satisfying level of 80% (entry 7).



Scheme 1 General reaction for the optimization

Table 1 Amination of 7-chloro-4-iodoquinoline under different conditions

Entry	**2** (n equiv.)	CuI (y mol%)	Procedure[a]	Conversion[b]	Yield (%)[b]	
					3	**4**
1	R = H (66)	30	A	nd	63[c]	nd
2	R = Me (66)	30	A	97	84 (84)[c]	6
3	R = Me (66)	10	A	86	78	9
4	R = Me (22)	10	A	76	69	3
5	R = Me (22)	30	A	93	78	1
6	R = Me (66)	30	B	68	60	8
7	R = Me (66)	30	C	98	80	6
8	R = Me (22)	30	C	95	89 (86)[c]	2

[a] Procedure A: reaction vessel closed with a balloon of nitrogen. Procedure B: reaction vessel opened to air. Procedure C: reaction vessel sealed. [b] Determined by calibration curve using the authentic compounds and the 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yields.

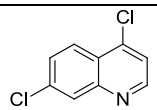
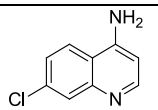
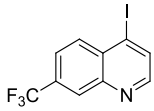
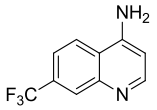
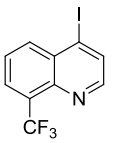
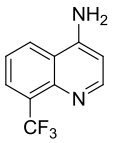
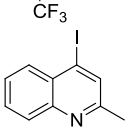
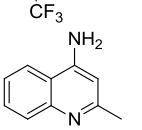
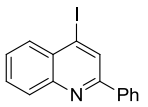
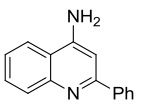
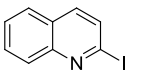
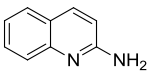
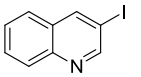
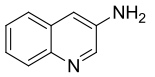
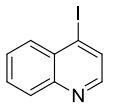
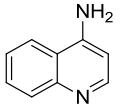
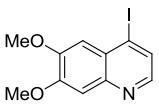
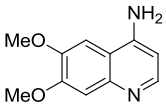
Furthermore, with this last procedure, the amount of aminoalcohol was decreased to 22 equivalents furnishing the 4-amino-7-chloroquinoline with 86% yield (entry 8).

In all cases, a side product corresponding to the cross coupling between the iodoquinoline and the *N*-methylethanolamine was

observed. Fortunately, although its level of formation is affected by the operating conditions, this side reaction is negligible.

With the optimized conditions in hand, the scope of the reaction was explored on various substituted quinolines (Table 2).

Table 2 Amination of various quinolines

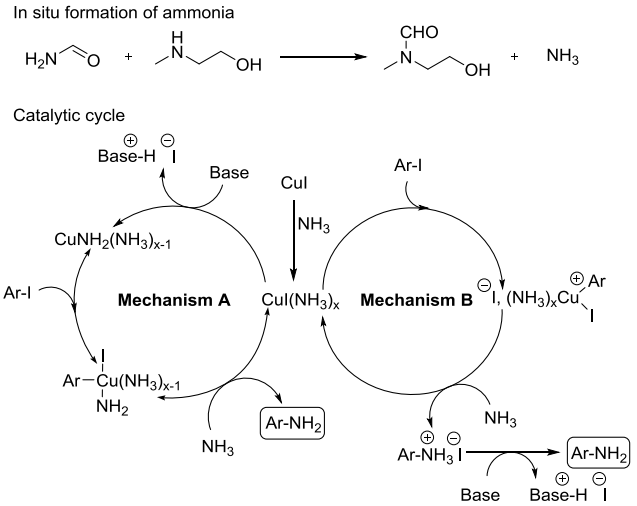
Entry	Halogenoquinoline	Product	Yield (%)[a]
1			0
2			55
3			59
4			62
5			73
6			65
7			71
8			64
9			35

[a] Isolated yields.

As expected, the 4,7-dichloroquinoline did not provide the amino derivative (entry 1). Although aryl chlorides could undergo in some specific conditions cross-coupling transformations, it is known that these substrates are less reactive than the corresponding iodo derivatives.

Replacing of the chloride atom in position 7 by a more electron withdrawing trifluoromethyl group furnished the aminoquinoline with 55% yield (entry 2). When this trifluoromethyl group was positioned in position 8, the yield of the product remained modest (59%, entry 3). The presence of methyl or phenyl substituents on the nitrogen ring allowed the formation of the desired product with good yields (entries 4 and 5). Next, we wanted to evaluate the feasibility of the reaction when changing the position of the iodide atom. To our delight, the 2, 3 and 4-aminoquinolines were obtained with satisfying yields from the corresponding iodoquinolines (entries 6-8). However, the presence of two methoxy electron donating groups on the iodoquinoline was detrimental to the yield (entry 9). This can be attributed to the slower rate of the oxidative addition step.

Although the mechanism of this reaction is not established yet, investigations are ongoing to understand clearly the role of each partner. However, at this stage, it is assumed that the ammonia molecule required for the cross-coupling reaction is generated by condensation of the aminoalcohol on the formamide (Scheme 2).



Scheme 2 Mechanisms of the copper-catalyzed amination reaction

Two main mechanisms are generally considered for the copper-mediated cross-coupling step.[10] In the first one (mechanism A), copper catalyst reacts with ammonia in the presence of the base before the oxidative addition while the mechanism B begins with the oxidative addition of the aryl halide to copper, to form a copper(III) intermediate. We believe that the generated ammonia would act both as reagent and as ligand while the aminoalcohol would operate as base.

In summary, we have developed an unconventional cross-coupling reaction of iodoquinoline catalyzed by copper(I) iodide. The originality of the method resides in the *in situ* formation of ammonia from formamide. Although the yields are not particularly high, the process can be extended for the preparation of a variety of primary aminoquinolines under relatively smooth conditions and within short reaction times. One convenient aspect of this reaction is the water solubility of the formamide, the aminoalcohol and the side product facilitating the isolation of the desired aminoquinolines. This strategy involving this particular formation of ammonia could be a good alternative tool to access different types of primary amino structures.

Experimental

A typical procedure for the preparation of 4-amino-7-chloroquinoline **3**.

A Schlenk tube containing a mixture of 7-chloro-4-iodoquinoline (1 eq.), *N*-methylethanolamine (22 eq.), formamide (126 eq.) and copper iodide (0.3 eq.) was sealed and heated to 80°C for 2.5 h. During this time, the resulting blue solution turned green. After cooling to room temperature, the reaction mixture was diluted with an aqueous KOH 1N solution and extracted five times with AcOEt. The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (AcOEt/Et_3N 10/0 to 9/1) to give the desired aminoquinoline with 73% yield.

^{1}H NMR (300 MHz, MeOD-d_4): δ 8.27 (d, J = 5.5 Hz, 1H), 8.07 (d, J = 9.0 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.39 (dd, J = 9.0, 2.0 Hz, 1H), 6.61 (d, J = 5.5 Hz, 1H), 4.91 (bs, 2H); ^{13}C NMR (75 MHz, MeOD-d_4): δ 154.5, 151.9, 149.9, 136.6, 127.3, 125.8, 125.1, 118.3, 103.9.

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Notes and references

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