



Copper-catalyzed C–N cross-coupling reactions for the preparation of aryl diamines applying mild conditions

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ABSTRACT

In this work, aryl diamines were prepared by C–N cross-coupling reactions between aryl halides and ethylenediamine. These reactions were successfully catalyzed by low quantities of Cu₂O or CuO (1 mol %) employing low reflux temperature and low diamine excess. Products were afforded in good yields (up to 95%).

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Polyamines represent a class of compounds of great importance both in coordination and biological chemistry, being involved with cation complexation,¹ cellular growth, and ribonucleic acid transcription. Besides, their participation in protein synthesis and regulation of immune responses² are also described. In particular, N-aryl substituted diamines are subject of interest from the pharmaceutical industry, since they can regulate the growth of cancerous cells.³ In this context, the development of N-arylation methods of diamines/polyamines constitutes an important area of research. The formation of the C–N bond has been a strategic subject within organic synthesis field evidenced by the growing number of manuscripts in the last years.⁴ Besides the use of palladium based catalysts, the employment of copper in these reactions has been re-evaluated due to its chemical stability under air atmosphere as well as its low cost and toxicity.

Recently, Han and co-workers reported both the use of diamines and aminoalcohols in the N-arylation of several aryl halides, employing the ratio 1:3 equiv (halide:amine/aminoalcohol). These reactions were catalyzed by 10 mol % of CuCl and the respective products were obtained in moderate to good yields at 0–90 °C for 8 h in the absence of solvents.⁵

Motivated by the plethora of subjects surrounding the polyamines chemistry, we have been studying copper-catalyzed C–N cross-coupling reactions aiming to develop a synthetic method to obtain aryl diamines. Herein, we firstly report the use of Cu₂O

and CuO nanoparticles (NPs) and CuO microparticles (MPs) as catalysts in the model reaction between ethylenediamine and 4-iodo-1-nitrobenzene (Scheme 1). For comparison, CuI was also evaluated, since it is often applied as the catalyst in C–N cross-coupling reactions.⁶ Moreover, several conditions were investigated such as the ethylenediamine amount, the reaction time, and inert atmosphere use in the reaction medium.

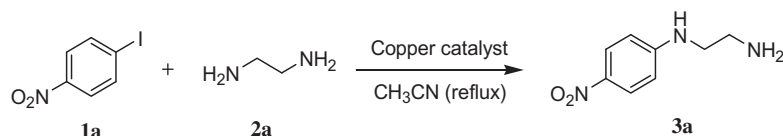
Initially, the ratio of 1:7.4 equiv between 4-iodo-1-nitrobenzene and ethylenediamine was assayed. The results are summarized in Table 1. Firstly, we verified that the non-employment of a catalyst did not allow an appreciable yield, 26% (entry 1). With this in mind, Cu₂O catalyst was applied. Entries 2 and 3 (Table 1) evidence that dropping the Cu₂O amount from 10 to 1 mol % did not influence significantly the reaction yield (94–95%). In contrast, further diminishment of the catalyst amount to 0.5 mol % (entry 4) was sufficient to slow the reaction (87% after 10 h).

Comparing Cu(I) catalysts, reactions employing CuI, entries 6 and 7, afforded less coupled product than those of entries 3 and 4, revealing the superior catalytic activity of copper oxide.

Furthermore, entries 2 and 8 allow comparing Cu₂O and CuO NPs performance. Here it is noticed that Cu₂O NPs permitted enhanced catalytic activity (entry 2), signaling to the need of having Cu(I) species in the reaction medium.⁷ However, the employment of N₂ atmosphere in CuO catalyzed reactions (entries 11 and 13) afforded good to excellent yield (79–99%) even in low amounts of catalyst (1 mol %). On the other hand, when this procedure was applied to Cu₂O (entry 5) it did not offer an appreciable yield enhancement (compare entries 4 and 5). The deficient O₂ atmosphere possibly aids the creation of Cu(I) sites in the CuO lattice⁸

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Scheme 1. N-arylation of ethylenediamine.

Table 1

Reaction yields regarding the catalyzed C–N cross-couplings between 4-iodo-1-nitrobenzene (**1a**) and ethylenediamine (**2a**) using a variable ratio **1a:2a** in acetonitrile applying different copper catalysts

Entry	Ratio 1a:2a	Catalyst amount (mol %)	Atmosphere	Reaction time (reflux) (h)	3a ¹³ Yield %
1	1:7.4	—	—	6	26 ^a
2	1:7.4	NPs Cu ₂ O-10	—	6	95 ^b
3	1:7.4	NPs Cu ₂ O-1	—	6	94 ^b
4	1:7.4	NPs Cu ₂ O-0.5	—	10	87 ^b
5	1:7.4	NPs Cu ₂ O-0.5	N ₂	10	89 ^b
6	1:7.4	CuI-1	—	6	90 ^b
7	1:7.4	CuI-0.5	—	6	85 ^a
8	1:7.4	NPs CuO-10	—	10	85 ^b
9	1:7.4	MPs CuO-10	—	10	87 ^b
10	1:7.4	MPs CuO-1	—	6	30 ^a
11	1:7.4	MPs CuO-1	N ₂	6	96 ^b /99 ^a
12	1:7.4	NPs CuO-1	—	6	5 ^a
13	1:7.4	NPs CuO-1	N ₂	6	79 ^a
14	1:4	NPs Cu ₂ O-1	—	6	61 ^a
15	1:4	NPs Cu ₂ O-1	N ₂	6	51 ^a
16	1:4	NPs Cu ₂ O-1	—	8	87 ^b /91 ^a
17	1:4	NPs Cu ₂ O-1	N ₂	8	57 ^a
18	1:4	MPs CuO-1	N ₂	8	68 ^a
19	1:4	NPs CuO-1	N ₂	8	56 ^a
20	1:2	NPs Cu ₂ O-1	—	6	1 ^a
21	1:2	NPs Cu ₂ O-1	—	24	83 ^a
22	1:2	MPs CuO-1	N ₂	24	79 ^a
23	1:2	—	N ₂	48	18 ^a
24	1:2	MPs CuO-1	N ₂	48	95 ^b

^a Molar yield calculated by ¹H NMR.

^b Isolated yield.

generating non-stoichiometric copper(II) oxide (CuO_{1-x}).⁹ In addition, it is noteworthy to say that CuO MPs (1 mol %) were surprisingly more active than CuO NPs (1 mol %; compare entries 10 and 12; and entries 11 and 13).

So far in our study, we evidenced that the employment of 1 mol % of Cu₂O or CuO under N₂ atmosphere afforded yields of 94–99% (results regarding the model reaction, Table 1). However, a 7.4-fold molar excess of ethylenediamine was still being applied, as described in the literature.¹⁰ The use of this excess is not desirable since a residual of the starting diamine still remains at the end of the process, implying either in the discard of the reagent or in extra costs to purify it for re-utilization hence impacting in the global process cost. To search for the motivation to use such an excess, in the next set of model reactions we managed to diminish the molar excess of diamine applying the ratios of 1:4 and 1:2 equiv keeping the best reaction conditions described so far in Table 1. Interestingly, the decrease of ethylenediamine amount in the reaction medium led to lower yields of the coupled product **3a**. This is noticed for all the reactions (compare entry 3 with entries 14 and 20, Table 1), including those in which N₂ atmosphere was applied (compare entries 11 and 13 with entries 18 and 19 of Table 1).

However, the increase of the reaction time allowed obtaining **3a** in a higher yield (compare entries 14 and 16 and also 20 and 21 of Table 1). In addition, it is noteworthy that even for a ratio of 1:2 the model reaction catalyzed by CuO microparticles under nitrogen atmosphere, provided **3a** in significantly high yields. However, to obtain this result longer reaction times (24–48 h) were employed (entries 22 and 24). Once again, we verified that the non-employment of a catalyst did not allow a satisfactory yield, even in a long-

er time (18%; entry 23). From these experiments, it became clear that the employment of smaller proportions of aryl halide to diamine is critical for the kinetics of the C–N cross-coupling reaction. Therefore, it shows that the diamine amount is crucial to carry out the reaction in significant velocity. Such conclusion is supported by a nucleophilic substitution mechanism.

To better understand the mechanism of the C–N cross coupling reaction we carried out reactions employing other substrates and some of the conditions established for the model reaction in Table 1 (1 mol % Cu₂O or CuO under N₂ atmosphere applying reflux for 6–48 h, besides of 2 or 7.4 equiv of the amine). Firstly, the results were obtained upon variation of the aryl iodide employed (**1a–d**; Table 2). A comparison between entries 1–4 discloses that 4-iodo-1-nitrobenzene was more reactive than other aryl iodides, having a major conversion into the product after 6 h (94%, entry 1; Table 2). Couplings with iodobenzene, 4-iodotoluene, and 4-iodoanisole demanded longer reaction time, although not presenting such satisfactory results (Table 2, entries 2–4). These results showed that the presence of electron withdrawing groups in the aromatic ring favored the reaction kinetic, in conformity with the oxidative addition and nucleophilic substitution mechanisms.

Still in search of mechanistic insights on the C–N cross-coupling reaction, we essayed the reactivity of a series of aryl halides composed of iodobenzene, bromobenzene, and chlorobenzene using the same catalytic system (Table 2, entries 2, 5, and 6). It was observed that the reaction between iodobenzene and ethylenediamine provided a superior yield in a reduced time when compared to those employing other halides. In fact, the reaction between chlorobenzene and ethylenediamine did not afford any

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