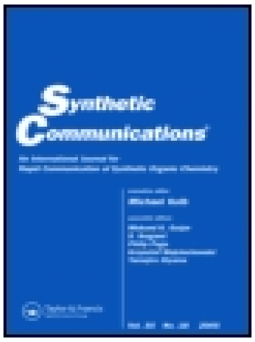

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Copper-Mediated monochlorination of anilines and nitrogen-containing heterocycles

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ABSTRACT
A simple and selective copper(II) chloride-mediated monochlorination of anilines and nitrogen-containing heterocycles has been developed. Stirring a mixture of aniline, copper(II) chloride, lithium chloride in EtOH under reflux condition produced 4-chloroaniline with high yield. Eighteen substrates including substituted anilines, *N*-substituted anilines, *N*,*N*-disubstituted anilines, 5-nitroindole and carbazole were all reactive and afforded desired products in moderate to excellent yields (52%–98%).

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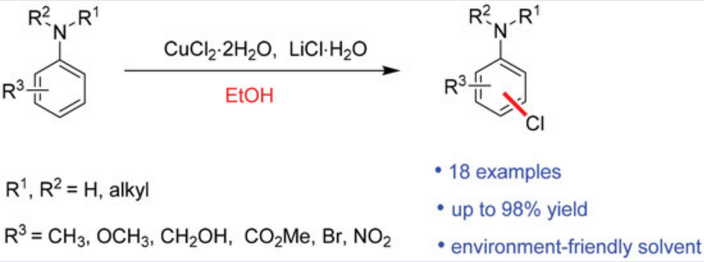
KEYWORDS
Aniline; chlorination; copper chloride; lithium chloride

GRAPHICAL ABSTRACT



Introduction

Aryl chlorides are found in a wide variety of natural products[1,2] and are widely used as building blocks for drugs,[3] pesticides,[4] and other valuable compounds. As a special class of aryl chlorides, chlorinated aryl amines are involved in many organic reactions,[5] especially coupling[6–8] and substitution reactions. Therefore, much attention has been paid to the synthesis of chlorinated aryl amines. Traditionally, aromatic chlorides are obtained through electrophilic aromatic substitution (EAS)[9] using Cl_2 or NCS[10,11] as a chlorine source and by Sandmeyer reaction of anilines.[12] However, due to the harsh conditions and long reaction time of these methods, a series of new methods have been developed for the chlorination. In 2010, Saikia put forward a novel way to chlorinate aniline in the presence of HCl/H_2O_2 using a mixture of CH_3CN and H_2O as solvent, but the use of expensive catalyst and nanoparticle group limited its application.[13] Then

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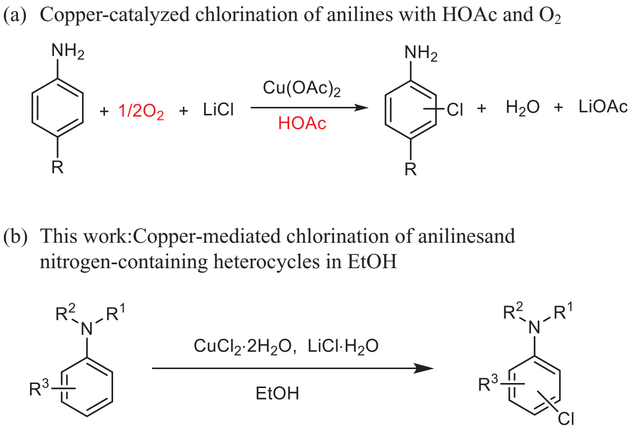


Scheme 1. (a) Copper-catalyzed chlorination of anilines with HOAc and O_2. (b) Copper-mediated chlorination of anilines and nitrogen-containing heterocycles in EtOH.

attention was paid to transition-metal-catalyzed reactions, especially the transition-metal-catalyzed chelation-directed aryl C–H activation.[14] For example, nickel-catalyzed *ortho*-chlorination of aryl C–H bonds using a removable auxiliary was reported in 2016.[15] In the same year, Rh(III)-catalyzed *ortho*-chlorination of benzene derivatives was demonstrated by Lied.[16] In 2017, Sutherland brought up a new way for *ortho*-chlorination of activated arenes using iron(III) catalyst.[17] However, all of these reported reactions required the pre-installation of directing group, which reduced the scope of substrates. A metal-free protocol for chlorination of a range of 8-substituted quinoline derivatives using trichloroisocyanuric acid (TCCA) as efficient chlorine source was established by Motati.[18]

In 2008, Gusevskaya reported copper-catalyzed chlorination of aniline derivatives. However, environment-unfriendly acetic acid was used as solvent under oxygen atmosphere in the reaction (Scheme 1a). In addition, *N*-substituted aniline exhibited very low reactivity under the reported reaction conditions.[19] Hence, it is necessary to develop a more environment-friendly and operationally simple method for the synthesis of chlorinated aniline derivatives or analogs with a broader range of substrates.

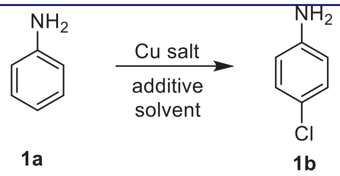
In this article, we describe the synthesis of chlorinated aniline derivatives and nitrogen-containing heterocycles employing cheap and readily available copper(II) chloride as a chlorinated reagent in EtOH without additional need of an oxidant (Scheme 1b). A wide range of substrates can be site-selectively and efficiently monochlorinated under optimized conditions. In general, the advantages of this method include the use of EtOH as solvent, simple operation, a wide range of substrates and high selectivity.

Results and discussion

Optimization of reaction conditions

Initially, the reaction of **1a** with $CuCl_2{\cdot}2H_2O$ (120 mol%) was investigated in the presence of Bu_4NCl in THF at 60 °C for 10 h, and only trace amount of 4-chloroaniline (**1b**) was detected (Table 1, entry 1). Then a solvent screen was performed using dioxane, CH_3CN,

Table 1. Optimization of reaction conditions for chlorination[a].



Entry	Cu salt (mol %)	Additive	Solvent	T (°C)	Time (h)	Yield (%)[b]
1	$CuCl_2{\cdot}2H_2O$ (120)	Bu_4NCl	THF	60	10	16
2	$CuCl_2{\cdot}2H_2O$ (120)	Bu_4NCl	Dioxane	80	10	15
3	$CuCl_2{\cdot}2H_2O$ (120)	Bu_4NCl	CH_3CN	80	10	15
4	$CuCl_2{\cdot}2H_2O$ (120)	Bu_4NCl	DCE	80	10	<10
5	$CuCl_2{\cdot}2H_2O$ (120)	Bu_4NCl	DMSO	80	10	<10
6	$CuCl_2{\cdot}2H_2O$ (120)	Bu_4NCl	DMF	80	10	<10
7	$CuCl_2{\cdot}2H_2O$ (120)	Bu_4NCl	EtOH	reflux	10	19
8	$Cu(OAc)_2{\cdot}H_2O$ (120)	Bu_4NCl	EtOH	reflux	10	0
9	$CuCl_2{\cdot}2H_2O$ (120)	–	EtOH	reflux	10	22
10	$CuCl_2{\cdot}2H_2O$ (200)	–	EtOH	reflux	10	34
11	$CuCl_2{\cdot}2H_2O$ (300)	–	EtOH	reflux	10	61
12	$CuCl_2{\cdot}2H_2O$ (300)	$LiCl{\cdot}H_2O$	EtOH	reflux	10	85
13	$CuCl_2{\cdot}2H_2O$ (300)	$LiCl{\cdot}H_2O$	EtOH	reflux	10	83[c]
14	$CuCl_2{\cdot}2H_2O$ (300)	NH_4Cl	EtOH	reflux	10	28
15	$CuCl_2{\cdot}2H_2O$ (300)	NaCl	EtOH	reflux	10	48

[a]Reaction conditions: **1a** (1 mmol), additive (1 mmol), solvent (2 mL); [b]Isolated yield; [c]Under argon.

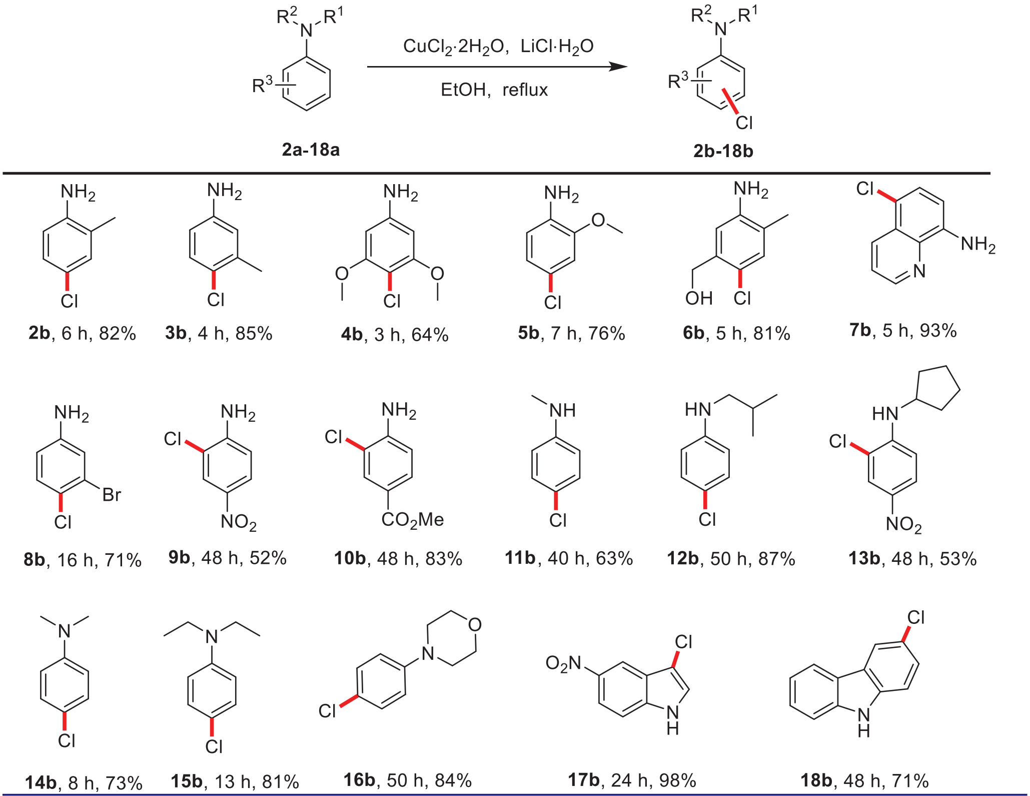
1,2-dichloroethane (DCE), DMSO, DMF, EtOH (Table 1, entries 2–7). The results indicated that EtOH was the best solvent among those examined. When $Cu(OAc)_2{\cdot}H_2O$ replaced $CuCl_2{\cdot}2H_2O$, no product was detected (Table 1, entry 8). To determine the optimal quantity of $CuCl_2{\cdot}2H_2O$ necessary for chlorination, the amount of the salt was varied. The yield improved by nearly 3-fold when the amount of $CuCl_2{\cdot}2H_2O$ was increased from 120 mol% to 300 mol% (Table 1, entries 9–11). In addition, the isolated yield increased to 85% when $LiCl{\cdot}H_2O$ was used as an additive (Table 1, entry 12). The use of NH_4Cl or NaCl as additive was, however, not beneficial (Table 1, entries 14–15). Performing the reaction under the argon atmosphere did not impact on the yield (Table 1, entry 13). To sum up, the optimized reaction conditions were established as follows: 300 mol% of $CuCl_2{\cdot}2H_2O$, 100 mol% of $LiCl{\cdot}H_2O$, EtOH as solvent at reflux.

Scope of substrates

With the optimized conditions in hand, we turned to investigate the substrate scope of chlorination. As shown in Table 2, substituted anilines (**2a–10a**), *N*-substituted anilines (**11a–13a**), *N*, *N*-disubstituted anilines (**14a–16a**), and heterocycles (**17a–18a**) were all reactive and generated anticipative products (**2b–18b**) in moderate to excellent yields (52–98%).

The chlorination of the anilines took place at the *para*–position of the amino group (**2b–8b, 11b–12b, 14b–16b**), while the *ortho*–chlorinated products formed in the case where there was a substituent at the *para*–position of the amino group (**9b–10b, 13b**). In addition, all anilines were reactive irrespective of the electron-withdrawing or electron-donating groups present. However, the yield of the product was higher for the anilines with electron-donating groups (**2b–6b**) than those with electron-withdrawing groups (**8b–10b**). Interestingly, 8-aminoquinoline, which was reported as a directing

Table 2. Reaction scope of chlorination[a,b].



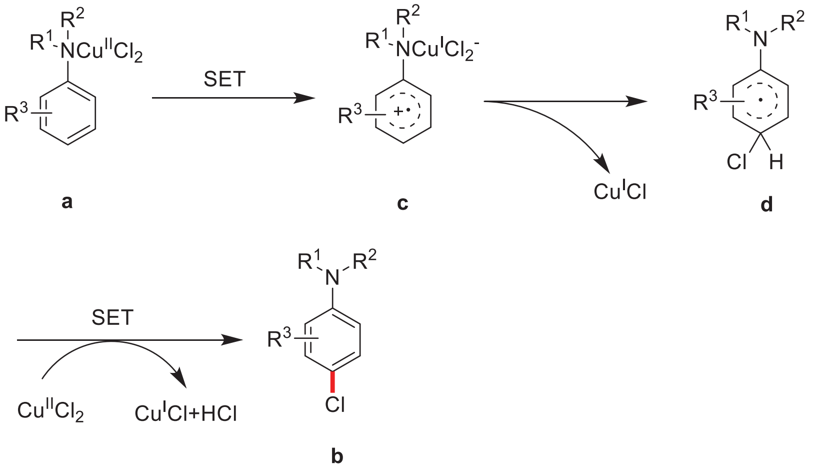
2b, 6 h, 82%
3b, 4 h, 85%
4b, 3 h, 64%
5b, 7 h, 76%
6b, 5 h, 81%
7b, 5 h, 93%
8b, 16 h, 71%
9b, 48 h, 52%
10b, 48 h, 83%
11b, 40 h, 63%
12b, 50 h, 87%
13b, 48 h, 53%
14b, 8 h, 73%
15b, 13 h, 81%
16b, 50 h, 84%
17b, 24 h, 98%
18b, 48 h, 71%

[a]Reaction conditions: substrate (2 mmol), $CuCl_2 \cdot 2H_2O$ (6 mmol), $LiCl \cdot H_2O$ (2 mmol) in EtOH (4 mL), 3–50 h; [b]Isolated yields.

group for C–H activation by Dauglis,[20] gave the expectant product in 93% yield. As expected, the secondary anilines, the nitrogen atom of which was attached to either a chain or a cyclic substituent, produced chlorinated products in moderate to high yields (**11b–13b**, 53%–87%). Furthermore, cyclic tertiary aniline and branched tertiary aniline were chlorinated to produce chlorine-substituted products under the reaction conditions (**14b–16b**, 73%–84%). To our delight, nitrogen-containing heterocycles were also active substrates under the present reaction conditions and gave acceptable to excellent yields of the desired products. 5-Nitroindole was selectively chlorinated to provide 3-chloro-5-nitroindole (**17b**, 98%), while carbazole was chlorinated at the *para*-position of the nitrogen atom to give 3-chloro-9*H*-carbazole (**18b**, 71%).

Proposed mechanism

In 2006, Yu put forward a mechanism for chlorination of 2-phenylpyridine.[21] Subsequently, Gusevskaya showed us the mechanism of chlorination of aniline in 2008.[19] Based on the reported mechanisms, we proposed a single electron transfer (SET) mechanism for the chlorination of aniline derivatives. As shown in Scheme 2, intermediate **c** was produced from complex **a** through a single electron transfer process, which was subsequently attacked by chlorine ion to give intermediate **d** and CuCl.



Scheme 2. Proposed mechanism for chlorination of aniline derivatives.

Intermediate **d** went through single electron transfer process to provide chlorinated product **b**, CuCl and HCl. According to the proposed mechanism, the yield of the anilines with electron-donating substituent was higher than those with electron-withdrawing substituent due to the fact that the former was much easier to transfer electron to copper(II).

Conclusions

In summary, an approach for selective monochlorination of the aniline derivatives and nitrogen-containing heterocycles mediated by copper(II) chloride was developed. Substituted anilines, *N*-substituted anilines, *N*,*N*-disubstituted anilines, 5-nitroindole, and carbazole were all reactive. Moreover, we showed the proposed mechanism for the chlorination. These findings provide a simple synthetic strategy to prepare chlorinated anilines and heterocyles.

Experimental section

All the regular chemicals were purchased from commercial sources with purity over 95% and used without further purification. ^{1}H and ^{13}C NMR spectra were received using a Bruker 400 MHz (400 MHz or 100 MHz, respectively) spectrometer. Chemical shifts (δ) and coupling constants (J) were reported in ppm and Hz, respectively. Mass (MS) analysis was obtained using LC-MS1000 (Skyray Instrument) with ESI. Flash chromatography was performed using standard grade silica gel (200–300 mesh). Analytical TLC was performed with GF254 precoated silica gel plates with visualization by UV (254 nm).

General procedure for the synthesis of 1b–18b

A round-bottomed flask (25 mL) was charged with substrate (2 mmol), $CuCl_2{\cdot}2H_2O$ (6 mmol), $LiCl{\cdot}H_2O$ (2 mmol) and EtOH (4 mL). The resulting reaction mixture was stirred at reflux. After the completion of the reaction monitored by TLC, EtOH was removed under reduced pressure. Then ammonium hydroxide (4 mL, 25%) and water (10 mL) were added and the aqueous phase was extracted with ethyl acetate (10 mL ×3). The combined organic phase was washed with brine (8 mL × 3) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by chromatography on silica gel to obtain the desired products.

4 -chloroaniline (1b)[19]

Grey solid; yield: 215.9 mg, 85%; M.p.: 66.7–69.3 °C (lit: 67–70 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, $J = 8.7$ Hz, 2H), 6.60 (d, $J = 8.7$ Hz, 2H), 3.63 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 129.1 (2C), 123.1, 116.3 (2C). MS (ESI$^+$): m/z calcd for C_6H_7NCl $[M+H]^+$ 128.0; found 127.8 (^{35}Cl, 100%), 129.7 (^{37}Cl, 45%). All other characterization data and spectra of compounds are given in Supplementary data.

Funding

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