CuO-Al₂O₃ catalyzed oxidation of primary benzylamines and secondary dibenzylamines to N-benzylbenzaldimines

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Abstract: CuO-Al₂O₃ catalyzed one-pot oxidation with O₂ and self-coupling of benzylamines to give N-benzylbenzaldimines was described in good yields. Similarly, secondary dibenzylamines were oxidized to N-benzylbenzaldimines.

1. Introduction

Imines or Schiff bases and its derivations have attracted increasing attention as one of the basic building blocks of modern synthetic organic chemistry.[1,2,3,4] Particularly, aldimines and its metal-compounds are of great importance as intermediates in biochemistry and pharmaceutical chemistry.[5,6,7] Although the reactions of aldehydes or alcohols with primary amines[8,9,10,11,12,13,14] and oxidation of secondary amines[15,16] are used for the syntheses of simple aldimines traditionally, there still remain many problems. For example, the reactions are conducted at oxygen atmosphere,[8] in critical experimental facilities,9 or reaction media.11 Expensive and toxic metal catalysts, such as Pd,[17] Ru,[15] [18] Rh,[19] Au,[20] Ir[21], etc are essential in the preparation imines used secondary amines. Furthermore, the catalyzed oxidations of primary amines always produce various by-products, such as nitriles,[22,23,24,25,26] amides,[27,28] oximes,[29,30] enamines,[31] and so on.

Self-coupling or cross-coupling to primary amines are reported in the last few decades. Some organic compounds as catalysts were reported, such as polyaniline derivatives with Cu(BF₄)₂[32] or (NH₄)₂S₂O₈[33], 3-methyllumiflavin (3MLF) and its derivations,[34,35] quinonoids[36,37,38], etc. The oxidation of alkylamines on the surface of cuprate superconductors (YBa₂Cu₃O₇) is used to study the important monolayer self-assembly process[39]. Simultaneously, Ohshiro and his co-workers utilized binuclear copper (II) complex of 7-azaindole as catalyst for oxidizing benzylamine to N-benzylbenzylimine[40]. Recently, Bela's laboratory used microwave-assisted oxidative self- and cross-coupling of amines to imines with K-10 montmorillonite (K-10), a solid acid catalyst.[41] High yields are reported to oxidize primary amines by transition-metals covered with peroxides as co-catalyst, for example Cu/garvinoxyl,[22c] Cu(bpy)₂/tert-BuOOH,[42] HgO/I₂,[43] Mn(III)/tert-BuOOH.[44] Recently, CuCl was used as catalyst with BrOH as oxidizing agent to synthesize imines from amines by Adimurthy's group.[45]

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Again, some transition-metals as oxidation catalysts, such as $Fe(NO_3)_3 \cdot 9H_2O$ or $FeCl_2 \cdot 4H_2O$,[46] $Au(OAc)_3/CeO_2$,[47] were used in self-coupling benzylamines for the synthesis of imines. However these systems are not generally useful because of these reactions needing peroxides and excess catalysts, the formation of significant amounts of by-products.

Copper compounds as cheap and low toxicity catalysts, have initially shown in the coupling reactions in the catalytic potential.[48,49,50] Herein, we report an effective method for catalyzed oxidation and self-coupling of amines to imines by CuO on HCl-treated Al_2O_3 with molecular oxygen in toluene. The major advantages of the process are the use of a readily available and economic catalyst, the less toxic solvent system and no other additive. This prompted us to study the self-coupling reaction of benzylamines on solid and acid catalysts. The products can be easily separated after the reaction. Furthermore, secondary amines could be oxidized to imines under these mild conditions.

2. Results and discussion

Some diverse copper salts, copper oxides and metallic copper were used as catalysts. The copper salts show a moderate yield of the reaction which suggests that copper is the active site in the present catalytic reaction, so metallic copper is used instead as the catalyst. The reaction shows a low yield of 45%. But the color of nano-copper changes to black which suggests an oxidation to cupric oxide. When cuprous oxide is used as the catalyst, a better yield of 80% is received. But there also exists an apparent color change from red to black under oxygen, air, and even nitrogen atmosphere, which implies an oxidation from cuprous oxide to cupric oxide. Based on the above knowledge, cupric oxide was used directly as the catalyst. The result of a 97% yield indicates that cupric oxide is the most effective catalyst among the copper salts, metallic copper and oxides.

The effects of solvents, temperature, atmosphere, and additive were studied by the controlled experiments. The solvent shows apparent effect on the yield. When the amount of toluene is increased to 2 mL with other experimental parameter unchanged, a drastic yield decrease is received. Although the detail of the effect is not quite clear, we suspect the competition of the solvent with the reactant on the surface of the catalyst accounts for the decreased yield. The temperature is another factor for the high yield. When the reaction is conducted at 90°C, a 23% yield is the result. Compared with data at 110°C, an elevated temperature above 100°C is prerequisite for the reaction in our experimental situation. Furthermore, the atmosphere is also very important in this reaction. Only trace yield can be received with the reaction is conducted under N_2 (Table 1, Entry 12), while the yield increases evidently in air (50%, Table 1, Entry 13). Anyway, these yields can not overcome the results of the reaction conducted under O_2 (97%, Table 1, Entry 8). Al_2O_3 additive also plays a key role in this catalytic reaction. When cupric oxide is used without any support, only a trace yield is received. While cupric oxide is used on other support, for example SiO_2, a yield of 45% is the result (Table 1, Entry 16). To illustrate the catalytic effect is result from cupric oxide and Al_2O_3 provides only the co-effects, a reaction without cupric oxide is conducted. A yield of 25% is obtained, which strongly support that Al_2O_3 can only take effect when cupric oxide is used as the catalyst in this reaction. So the highest yield can be obtained when cupric oxide is used as the catalyst on Al_2O_3 when the reaction is conducted at 110°C under O_2 atmosphere.

There is an interesting and key factor in the present study that the acidification of Al_2O_3 addition is very important for the increasing of yield. Al_2O_3 is by itself a solid acid catalyst, when it is supported with other catalysts,[29,30,51,52] the oxidations of various compounds are reported. In the present study, if the Al_2O_3 is used without further treatment, only a yield of 45% is received. We suspect that a part of primary amine might be oxidized to nitrile before they could not be catalyzed by cupric oxide to the target compounds. Furthermore, the catalyzed reactions to imines are routinely conducted at acid conditions. So we try to reduce the oxidative ability of the addition Al_2O_3 by an acidification process. Al_2O_3 was soaked by HCl then washed by distilled water until pH≈3 or 4. The acidified Al_2O_3 was heat treated 70°C for 18 h. As shown in Table 2, using Al_2O_3 (pH≈7 or 4) had low yields (45% and 72%), between which, Al_2O_3 (pH≈4) results in a better yield than Al_2O_3 (pH≈7).

Table 1. Oxidative coupling of benzylamine under diverse reaction conditions

$$2 \ \text{PhCH}_2\text{NH}_2 \xrightarrow[\text{O}_2]{\text{CuO/Al}_2\text{O}_3} \text{PhCH=N-CH}_2\text{Ph}$$
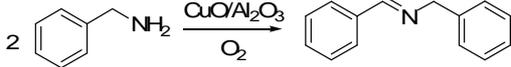
Entry	Solvent/ml	Time/h	t/°C	Cu catalyst	Additive[a]	GC/% Imine
1	Toluene /1	24	110	CuCl$_2$ 2mol%	Al$_2$O$_3$ 1mmol	40
2	Toluene /1	24	110	Cu(OAc)$_2$ 2mol%	Al$_2$O$_3$ 1mmol	29
3	Toluene /1	24	110	Cu(NO$_3$)$_2$ 2mol%	Al$_2$O$_3$ 1mmol	65
4	Toluene /1	24	110	Nano-Cu[b] 2mol%	Al$_2$O$_3$ 1mmol	45
5	Toluene /1	24	110	Cu$_2$O[c] 2mol%	Al$_2$O$_3$ 1mmol	80
6	Toluene /1	24	110	CuO 5mol%	Al$_2$O$_3$ 1mmol	83
7	Toluene /1	24	110	CuO 10mol%	Al$_2$O$_3$ 1mmol	88
8	Toluene /1	24	110	CuO[d] 2mol%	Al$_2$O$_3$ 1mmol	97
9	Toluene /2	24	110	CuO 10mol%	Al$_2$O$_3$ 1mmol	64
10	Toluene /1	20	110	CuO 2mol%	Al$_2$O$_3$ 1mmol	63
11	Toluene /1	24	90	CuO 2mol%	Al$_2$O$_3$ 1mmol	23
12	Toluene /1	24	110	CuO 2mol%	Al$_2$O$_3$ 1mmol	Trace[e]
13	Toluene /1	24	110	CuO 2mol%	Al$_2$O$_3$ 1mmol	50[f]
14	Toluene /1	24	110	CuO 2mol%	-	Trace
15	Toluene /1	24	110	-	Al$_2$O$_3$ 1mmol	25
16	Toluene /1	24	110	CuO 2mol%	SiO$_2$ 1mmol	45
17	DMSO/1	24	110	CuO[d] 2mol%	Al$_2$O$_3$ 1mmol	Trace
18	DMF/1	24	110	CuO[d] 2mol%	Al$_2$O$_3$ 1mmol	Trace
19	Benzene/1	24	110	CuO[d] 2mol%	Al$_2$O$_3$ 1mmol	45

a. Al$_2$O$_3$ pH≈3. b. nano-Cu was made by ourselves. c. nano-Cu$_2$O was made by ourselves. Its color changes to black when dispersed in water. d. CuO is made by ourselves, benzylamine 0.2 ml (1.83mmol), under O$_2$. e. under N$_2$. f. under aerobic air.

Table 2. Oxidative benzylamine with Al$_2$O$_3$ different pH

Entry	Al$_2$O$_3$ (≈pH)	Conv (%)	Isolated yields/%
1	7	>70	45
2	4	>90	72
3	3	> 99	89

CuO (2 mol%) was based on benzylamine; Al$_2$O$_3$ 1 mmol; under O$_2$, 110°C; 24h; benzylamine 0.20 ml (1.8 mmol).

Table 3. CuO-catalyzed oxidation of various amines with Al$_2$O$_3$

$$2\ R\!-\!CH_2NH_2 \xrightarrow[O_2]{CuO/Al_2O_3} R\!-\!CH=N\!-\!CH_2\!-\!R$$
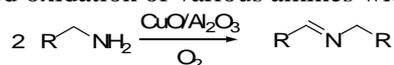
Entry[a]	R	Conv.[b](%)	Isolated yield/%
1	-C$_6$H$_5$	>99	89
2	p-F-C$_6$H$_4$-	>90	75
3	m-F-C$_6$H$_4$-	>90	76
4	o-F-C$_6$H$_4$-	>99	95
5	p-CH$_3$-C$_6$H$_4$-	>99	98
6	p-OCH$_3$-C$_6$H$_4$[b]	>90	85
7	m- OCH$_3$-C$_6$H$_4$	>60	55
8	p-Cl-C$_6$H$_4$	>99	94
9	o-Cl-C$_6$H$_4$	>99	93
10	p-OH-C$_6$H$_4$-	-	Trace
11	p-COOH-C$_6$H$_4$-	-	Trace

[a] CuO 2mol%. Al$_2$O$_3$ (pH≈3) 1mmol. under O$_2$; 110°C, 24h. R-CH$_2$NH$_2$ 1.8 mmol. b. Conversion was determined by GC.

Table 4. Oxidative secondary amines to imines with CuO/Al$_2$O$_3$

$$R_1\!-\!CH_2\!-\!NH\!-\!R_2 \longrightarrow R_1\!-\!CH=N\!-\!R_2$$

Entry[a]	Substrate	Product	Isolated yield/%
1	N-benzylaniline[b]	N-benzylideneaniline	30
2	Dibenzylamine	Dibenzylimine	65
3	1,2,3,4-tetrahydroquinoline	quinoline	25[c]
4	N-benzyl(p-tolyl)methanamine	N-benzyliden(p-tolyl)methanamine	-
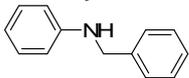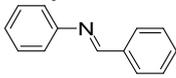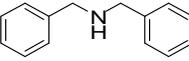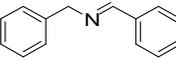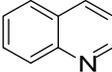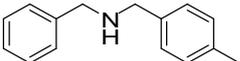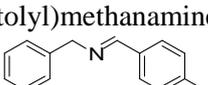
[a]Amines 0.2 ml, CuO 2mol%, Al$_2$O$_3$ 1mmol, toluene 1ml, 110°C, 24 h, under O$_2$. b. isolated yield, 48 h. c. Yield determined by GC using naphthalene as an internal.

As results are listed in Table 3, the CuO/Al$_2$O$_3$ catalyst showed high activity and selectivity of the oxidation of aryl amines with molecular oxygen. (Entry 1-9) 4-hydroxybenzylamine hydrobromide and 4-aminomethylbenzoic acid are polar compounds, so they have no reactive activity under this solvent environment. As summarized in Table 4, this catalytic system was adequate for the secondary amines. N-benzylaniline was oxidized 48h, but a low selectivity and conversion was

obtained. (30%, Entry 1) Dibenzylamine was converted to N-benzylidenebenzylamine in a higher yield. (65%, Entry 2) There was no expected product received when N-benzyl(p-tolyl)methanamine was oxidized. (Entry 4) When 1,2,3,4-tetrahydroquinoline used as substrates were oxidized to quinoline through removal two molecular hydrogen. (25%, Entry 3)
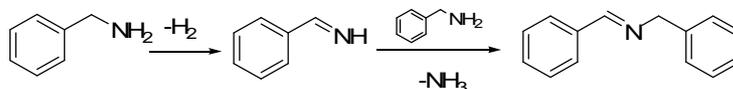
Scheme 1. The mechanism of reactions used CuO/Al$_2$O$_3$ as catalyst

The mechanism of amines self-coupling had been reported.[39,53,54,55] It is commonly believed that this typical reaction is conducted through two steps to synthesize imines, which was conjectured Scheme 1. First, primary amine is oxidized through dehydrogenation to intermediates imine. Then this imine undergoes a deamination step, through reaction with benzylamine to form benzylidene-benzylamine. As the mechanism of primary amines' self-coupling was speculated, acidic Al$_2$O$_3$ is important function in the step of deamination. It can facilitate the reaction of synthesis imines from primary amines.

3. Conclusion

Generally aldimines are unstable because C=N double bond is relatively active. In summary, we used CuO/Al$_2$O$_3$ as an high efficiency catalyst for oxidative coupling of primary amines to give N-benzylbenzaldimines. Particularly, co-catalyst Al$_2$O$_3$ was a crucial element for improving catalytic activity of CuO. Though, good to excellent yields can be obtained in these uncomplicated, low-toxicant, economy and reactive activity conditions.

4. Experimental

4.1. General Procedures: NMR spectra were recorded on ANAVCF 300 MHz and ANAVCF 400 MHz instruments. CDCl$_3$ was used as solvent and Me$_4$Si as an internal standard. IR spectra were recorded on EQUINX 55 FT-IR spectrometer using KBr pellets. Analytical thin-layer chromatography (TLC) was performed with silica gal 60 F-254 plates. The columns were hand packed with Silica Gel 60 (200-300). GC was obtained Agilent GC 6890N and with FID as detector. All primary amines and 1,2,3,4-tetrahydroquinoline were commercial products and were not purified before used.

4.2. Synthesis of Secondary Amines: The secondary amines were synthesized as previously reported.[15] A mixture of an alkyl chloride (10 mmol), an amine (11 mmol) and K$_2$CO$_3$ (20 mmol) in DMF (20 mL), unless otherwise noted, stirred until the chloride disappeared being monitored with TLC. The reaction mixture was dissolved in Et$_2$O (50 mL) and water (50 mL). Et$_2$O layer was separated, and washed with water (3 x 20 mL) and saturated brine (20 mL), dried (MgSO$_4$), and concentrated. The residue was concentrated and isolated by column chromatography, with petroleum ether (60-90°C)-ethyl acetate as an eluent and silica gel as stationary phase.

4.3. Typical Procedure for the Oxidation of Primary amines with CuO/Al$_2$O$_3$: CuO was made from Cu$_2$O, which was roasted in electric muffle furnace, at 300°C and for 4h. Industrial Al$_2$O$_3$ was soaked by HCl then washed by distilled water until pH≈3 or 4. The acidified Al$_2$O$_3$ was heated at 70°C for 18 h, then roasted in muffle furnace in order to receive objective Al$_2$O$_3$, at 900°C for 10 h, and then washed by distilled water.
CuO (2 mol%) based on primary amines and Al$_2$O$_3$ 1 mmol (0.102 g), was added to reaction vessel full of O$_2$. Primary amines (1.8 mmol) were dissolved in toluene (1 mL) and then the mixture was injected into the vessel simultaneously inflating O$_2$. The reaction vessel was closed and placed under

stirring in a preheated oil bath at 110ºC for 24 h, under O_2. After cooling to room temperature, the solid was dissociated by filter funnel (100 mL-G3) with Silica Gel 60 (200-300), and washed with ethyl acetate (5×10 ml). The organic phase was conflated in flask and concentrated. For isolation of the products the solvent was evaporated and the residue was purified by column chromatography, petroleum ether (60-90ºC)-ethyl acetate as an eluent, and identified by ^{1}H NMR and IR. The data is listed as follows:

4.4. N-benzylbenzaldimine:
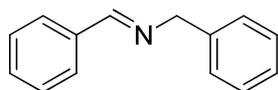
^{1}H NMR (CDCl$_3$, 300 MHz): δ 4.80 (s, 2H), 7.24-7.78 (m, 10H, Ar-H), 8.35 (s, 1H).

4.5. N-(4-Methylbenzyl) 4-methylbenzaldimine:
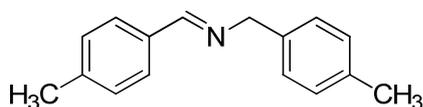
^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.33 (s, 3H), 2.37 (s, 3H), 4.76 (s, 2H), 7.12-7.25 (m, 6H), 7.64-7.67 (d, 2H; J=7.8Hz), 8.33 (s, 1H).

4.6. N-(3-Fluorobenzyl) 3-fluorobenzaldimine:
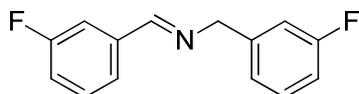
^{1}H NMR (CDCl$_3$, 300 MHz): δ 4.78 (s, 2H), 6.91-6.94 (t, 1H; J=8.4Hz), 7.03-7.17 (m, 3H), 7.25-7.40 (m, 2H), 7.48-7.55 (t, 2H; J=20.4), 8.33 (s, 1H).

4.7. N-(4-Fluorobenzyl) 4-fluorobenzaldimine:
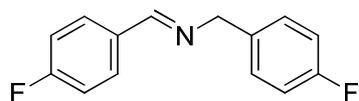
^{1}H NMR (CDCl$_3$, 300 MHz): δ 4.76 (s, 2H), 6.92-7.12 (m, 4H), 7.29 (s, 2H), 7.77 (d, 2H; J=8.7Hz), 8.34 (s, 1H).

4.8. N-(2-Fluorobenzyl) 2-fluorobenzaldimine:
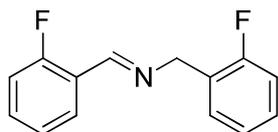
^{1}H NMR (CDCl$_3$, 300 MHz): δ 4.85 (s, 2H), 7.00-7.39 (m, 7H), 8.00-8.05 (t, 1H; J=14.7Hz), 8.70 (s, 1H).

4.9. N-(4-chlorobenzyl) 4-chlorobenzaldimine:
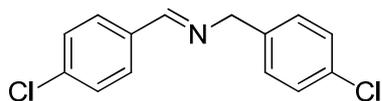
^{1}H NMR (400 MHz, DMSO) δ 4.74 (s, 2H), 7.32-7.39 (AB system, 4H), 7.49-7.50 (d, 2H, J=8 Hz), 7.78 (d, 2H; J=8Hz), 8.47 (s, 1H).

4.10. N-(2-chlorobenzyl) 2-chlorobenzaldimine:
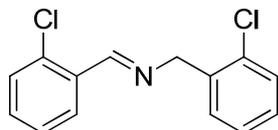
^{1}H NMR (400 MHz, DMSO) δ 4.99 (quasi d, 2H) , 7.31-7.54 (m, 7H, Ar-H), 7.99-8.04 (t, 1H) 8.73 (s, 1H).

4.11. N-(4-methoxybenzyl) 4-methoxybenzaldimine:
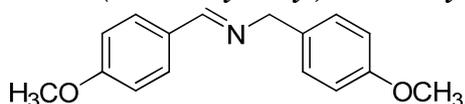
^{1}H NMR (CDCl$_3$, 300 MHz): δ 3.76-3.84 (d, 6H), 4.71 (s, 2H), 6.85-6.92 (t, 4H), 7.22-7.25 (d, 2H; J=9Hz), 7.69-7.72 (d, 2H), 8.28 (s, 1H).

4.12. N-benzylaniline:
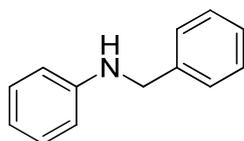
^{1}H NMR (CDCl$_3$, 300 MHz): δ 3.89 (s, 1H), 4.23 (s, 2H), 6.55 (d, 2H, J=8.1 Hz), 6.68 (t, 1H; J=7.2 Hz), 7.09-7.30 (m, 8H, Ar-H).

4.13. N-benzylideneaniline:
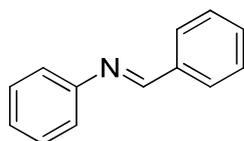
^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.11-7.81 (m, 10H, Ar-H), 8.35 (s, 1H).

4.14. Dibenzylamine:
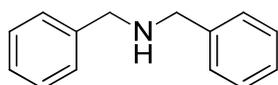
^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.64 (s, 1H), 3.79 (s, 4H), 7.25-7.33 (m, 10H, Ar-H).

4.15. N-benzyl(p-tolyl)methanamine:
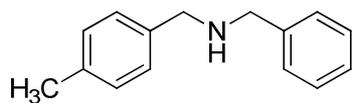
^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.69 (s, 1H), 2.33 (s, 3H), 3.76 (s, 2H), 3.79 (s, 2H,), 7.12-7.33 (m, 9H, Ar-H).

Acknowledgements

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