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Short Communication

One-pot synthesis of *N,N*-dimethylanilines from nitroarenes with skeletal Cu as chemoselective catalyst

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ABSTRACT

A range of *N,N*-dimethylanilines were synthesized with excellent yields in one-pot by the hydrogenation and alkylation of nitroarenes with H_2 and HCHO over quenched skeletal Cu catalyst, which provides a facile, economical, and environmentally benign alternative methodology for C-N bonds formation.

1. Introduction

N,N-dimethylanilines (NNDA) are valuable compounds in pharmaceutical, agrochemicals and fine chemical industries [1–5]. Currently, NNDA are mostly produced from a two-step process involving the reduction of nitroarenes into anilines and the subsequent alkylation (Scheme 1) [6–10]. In contrast, one-pot reactions are of much interest since they are more favorable process avoiding intermediate separation and purifications steps, and therefore minimizing energy during reaction [11,12]. However, it remains challenging to perform the reduction and alkylation simultaneously in the same reaction vessel due to the distinct optimal reaction conditions for each step such as catalyst functionality and hydrogen donor source uniformity. So there are few reports on one-pot synthesis of NNDA during last decades [13].

Recently, several research groups reported the synthesis of *N*-alkylated anilines from nitroarenes using alcohols as the alkyl-source in the presence of $(P \sim N)Ru(CO)_2Cl_2$ [14], $[Ru(p\text{-cymene})Cl_2]_2$ [15] and Ag/Al_2O_3 [16]. However, the secondary amines instead of the tertiary amines were obtained by the *N*-monoalkylation due to the bulkiness of alkylating agents. Li utilized methanol acting as an alkylating reagent, hydrogen source and solvent, simultaneously [17]. *N,N*-dimethylaniline was obtained from in-situ hydrogenation of nitrobenzene with hydrogen generated from methanol over Raney-Ni catalyst followed by alkylation. However, the major drawbacks were low efficiency with a large quantity of catalysts (370–440 mol% Raney Ni with respect to nitrobenzene), harsh reaction conditions and long reaction time [16].

In this study, we have developed a simple one-pot synthesis of NNDA through the hydrogenation of nitroarenes and subsequent dimethylation with HCHO as the alkyl source. Skeletal Cu prepared by the quenching techniques plays dual roles in this hydro-dialkylation process, which has never been reported to the best of our knowledge.

2. Experimental section

The catalytic hydrogenation reaction was conducted in a stainless-steel autoclave reactor (70 mL capacity) heated in oil bath. Substrate (6 mmol), solvent (20 mL) and catalyst (0.5 g) were directly added into the reactor. The autoclave was purged with N_2 and H_2 three times before the reaction started. The reaction process was monitored by gas chromatography (GC) (Agilent 6890) with a flame ionization detector (FID) system.

The catalyst's preparation and characterization were detailedly described in the supporting information.

3. Results and discussion

Similar to the preparation of skeletal Ni catalyst [18], the skeletal Cu catalyst was obtained by leaching Al with 20 wt.% NaOH solution from Cu–Al alloy. Fig. 1 shows some representative SEM images of Cu–Al alloy and the skeletal Cu catalyst. It was clearly found that the alloy possessed uniform structure (Fig. 1a,b). The rich dislocation array in alloy provided high active centre for skeletal Cu catalyst (Fig. 1c). The possible active site for hydrogenation and alkylation was composed by the terraces, corners (Fig. 1d) and holes (Fig. 1e,f).

To better understand the structure–activity relationship, the skeletal Cu catalyst was also analyzed by XPS and results were presented in

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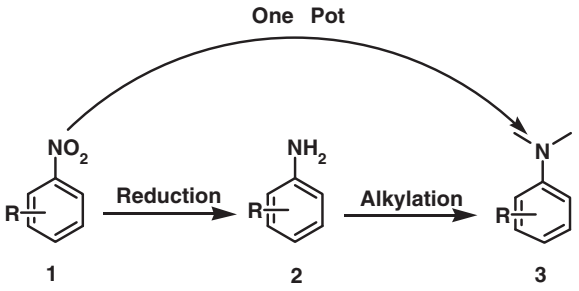


Scheme 1. The hydro-dimethylation of nitroarenes.

Fig. 2. Detailed description in high-resolution XPS spectra clearly indicates that surface active sites are mainly consisted of metallic Cu, which provides three response spectra for binding energy. The Cu 2p spectrum exhibits two contributions, 2p3/2 and 2p1/2 (resulting from the spin-orbit splitting), located at respectively 932.6 eV and 952.5 eV (Fig. 2b). The 122.6 eV was assigned to the Cu 3 s orbit (Fig. 2c). The 75 eV and 77 eV were assigned to Cu 3p orbit (Fig. 2d). The O 1 s spectrum (Fig. 2e) allows identifying Cu-O that was obtained by the oxidation of skeletal Cu in the preparation of detected sample. The skeletal Cu was unstable in air due to its porous structure filled with hydrogen, which was formed in Al leaching process. Finally, the binding energy scale was calibrated using the C 1 s at 284.6 eV (Fig. 2f).

The crystallite morphology of Cu–Al alloy and skeletal Cu catalyst were characterized by XRD (seeing the supporting information). It could be concluded that the alloy was mainly composed of $CuAl_2$ phase (Fig. S-1). In addition, typical Cu (111), Cu (200) and Cu (220) peaks were detected in the skeletal Cu sample (Fig. S-2). Using Scherrer's equation, the average crystalline size of skeletal Cu was estimated to be about 14 nm. The surface area and pore distribution for skeletal Cu were also measured by nitrogen adsorption isotherms at 77 K using BET method (Fig. S-3 and S-4). Type IV adsorption isotherms (IUPAC classification) [19,20] indicates that the skeletal Cu catalyst was mainly composed of the mesoporous structure. The BET surface area for skeletal Cu was 29.9 m^2/g and the pore diameter was 6.7 nm by using BJH method calculation.

We initiated the hydrogenation and dimethylation of nitroarenes by screening 8 different catalysts using *p*-chloronitrobenzene (*p*-CNB) as substrate and 37 wt% HCHO as the alkylating agent under the same reaction conditions (373 K and 15 bar H_2, Table 1). Among the noble metal catalysts Pd/C, Pt/C, Ru/C and Rh/C, Rh/C provided 87% conversion to *p*-chloro-*N*,*N*-dimethylaniline (*p*-CDMA), but the selectivity to *p*-CDMA was only 56.6%. Besides, the condensation by-products due to high activity of noble metal catalysts were also detected by GC analysis. In addition, skeletal Ni, Fe, Co and Cu were investigated in this model reaction. Up to 100% *p*-CNB conversion was achieved when S-Ni, S-Co, and S-Cu were used. Obviously, S-Cu showed best performance in the control experiment and the selectivity was up to 99.4% (entry 8).

Employing S-Cu catalyst, effect of temperature, pressure, solvent, the amounts of formaldehyde and catalyst were investigated (Table S2–6, see the supporting information). The optimal reaction conditions were 373 K, 13 bar H_2, which were much milder comparing with the reported results [17] and the catalyst's dosage was significantly reduced, simultaneously. Furthermore, the relationships of components concentration versus reaction time were investigated and shown in Fig. 3. The hydrogenation and methylation of *p*-CNB should be practically more complicated, *p*-chloroaniline (*p*-CAN, ***2-b*** in Scheme 2), *p*-chloro-*N*-methyleneaniline (Schiff's base, ***2-c***), *p*-chloro-*N*-methylaniline (imine, ***2-d***) and 4-chloride-*N*,*N*-bis(methoxymethyl)-benzenamine (***2-e***) may exist as the main intermediates in the reaction system.

Based on the above results and parallel experiments (Table S-8), a mechanism is proposed shown in Scheme 2. Firstly, ***2-a*** was hydrogenated to ***2-b*** over S-Cu catalyst (Entry 1) and ***2-c*** was obtained through next addition-elimination of ***2-b*** and HCHO [13] (Entry 2 and 3). Judged by the main intermediates, ***2-c*** was probably converted into the *p*-CDMA (***2-f***) through two routes in this reaction system. ***2-c*** was hydrogenated into ***2-d*** [15,16], and then converted into ***2-f*** through Route 1 [17,21]. Alternatively, ***2-c*** was presumably converted into ***2-e*** and further **2-f** with multiple steps of addition and elimination through Route 2, which have never been reported to the best of our knowledge.

2-e is unstable when concentrating solvent or purification with gel chromatography. Therefore it could not be separated from the reaction system and presumably identified by GC-MS and HPLC-MS (see the supporting information). Comparing with Entry 4 and 5, ***2-e*** disappeared

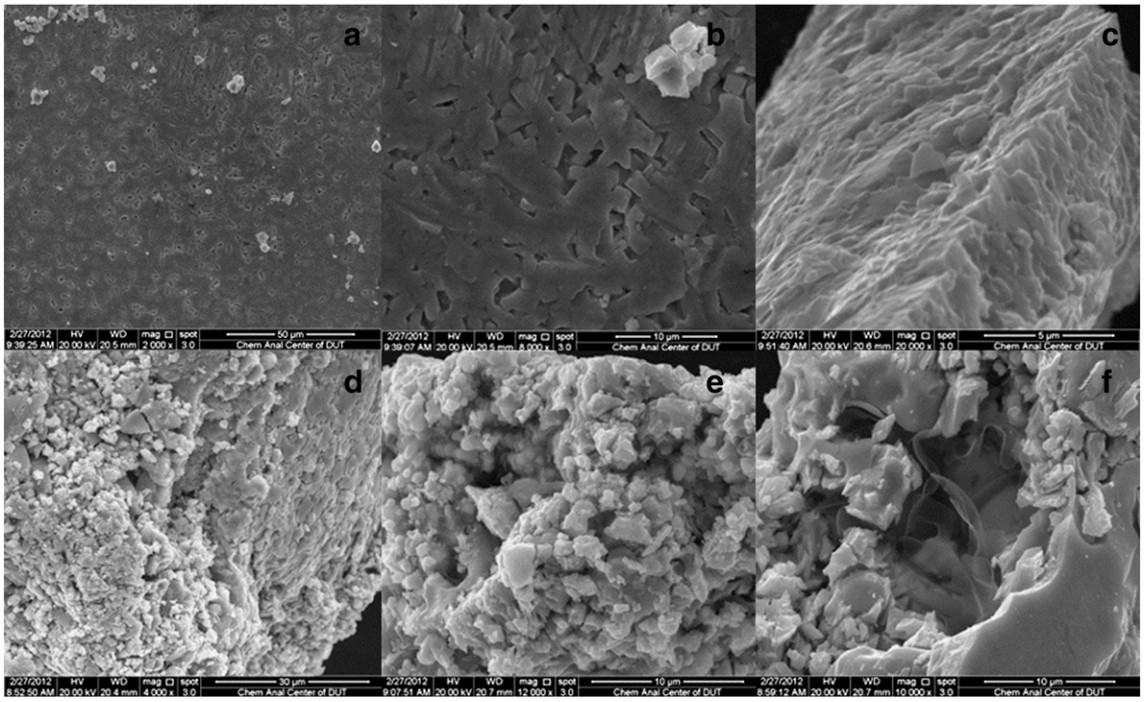


Fig. 1. Scanning electron microscope (SEM) images for the Cu–Al alloy (a,b,c) and the skeletal Cu catalyst (d,e,f).

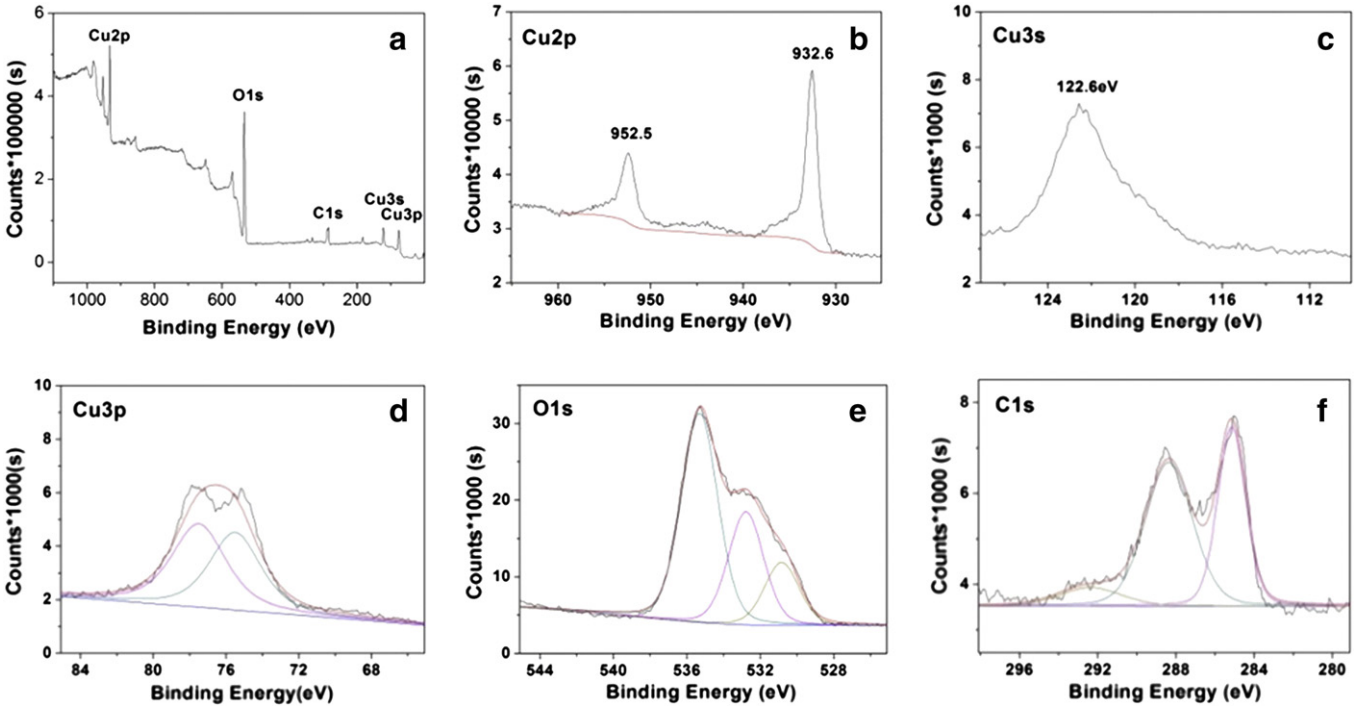


Fig. 2. (a) Survey and high-resolution XPS spectra of (b) Cu 2p (c) Cu 3 s (d) Cu 3p (e) O1s (f) C1s region for skeletal Cu sample.

when THF was used as solvent instead of CH_3OH and the reaction time was prolonged from 60 min to 105 min (Table S-6). So we have reasons to believe that the CH_3OH solvent participates in this reaction, which was confirmed when replacing CH_3OH (Fig. S-10, ***2-e*** m/z = 215) with CD_3OD (Fig. S-11, ***2-e*** m/z = 221). Moreover, we noticed ***2-b*** was easily converted to ***2-f*** even without any catalyst under H_2, N_2 or air (Entries 5–7), which might speed up the reaction rates by transforming the reaction path.

Inspired by these results, we investigated a series of nitroarenes with different substituents on NNDA under optimized reaction conditions and the results are summarized in Table 2. The corresponding NNDA were all obtained with high selectivity (entries 1–11, 83–99%). As expected, the substituent types and relative positions of nitroarenes have important impact on the corresponding products' selectivity. For instance, the selectivity for hydro-dimethylation of *o*-chloronitrobenzene was only 82.9% at 373 K for 250 min, indicating the reaction rate and selectivity are lower compared with *p*-chloronitrobenzene and *m*-chloronitrobenzene (Table 2, entries 2–4). The main by-product is *o*-chloro-*N*-methylaniline via hydrogenation and *N*-monoalkylation of *o*-chloronitrobenzene, which might be attributed to the steric hindrance. The selectivity to NNDA is about 96% under optimal conditions when the para-positions in nitrobenzene were replaced by the –OH, CH_3 and OCH_3 groups, respectively (Table 2, entries 5–7).

Table 1
Effect of the different catalysts on the hydro-dimethylation of *p*-CNB.[a]

Entry	Cat.	Catalysis (g)	*t*(min)	Conversion (%)	Selectivity[b](%)
1	Pd/C	0.04	120	14	30.5
2	Pt/C	0.07	120	14.5	10.7
3	Rh/C	0.04	120	87	56.6
4	Ru/C	0.05	120	32.8	0.8
5	S-Ni	0.5	30	100	91.3
6	S-Fe	0.5	120	43	4.8
7	S-Co	0.5	120	100	16.8
8	S-Cu	0.5	60	100	99.4

[a] Reaction conditions: 373 K, 15 bar H_2, *p*-CNB = 1.0 g, CH_3OH = 20 mL, HCHO (37 wt.%) = 1.35 mL.
[b] Conversion and selectivity were determined by GC.

In entry 9, the hydro-dialkylation of *p*-acetylnitrobenzene was investigated at 373 K for 68 min but the selectivity was only 88.2%, which was caused by excessive hydrogenation of the carbonyl group in products. We also studied the hydro-dialkylation of *p*-nitroaniline and *p*-dinitrobenzene with double-*N* atoms under the optimized reaction conditions. Results showed that *N1,N1,N4,N4*-tetramethyl-1,4-benzenediamine as main product could be obtained with high selectivity in one-pot (Table 2, entries 10–11).

4. Conclusion

In conclusion, we have demonstrated a simple and efficient protocol for the synthesis of NNDA in one-pot with skeletal Cu catalyst, which was prepared by the quenching technique and played bifunctional roles in the hydrogenation and alkylation process. The reaction conditions are very mild with less catalyst's dosage. Mechanism studies indicate that nitroarene converts to NNDA through two pathways. Methanol solvent participated in this process through Route 2 and obviously accelerated the reaction rate comparing with THF solvent. Furthermore, a wide

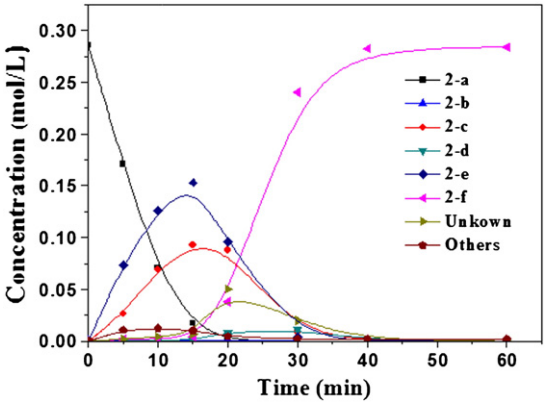
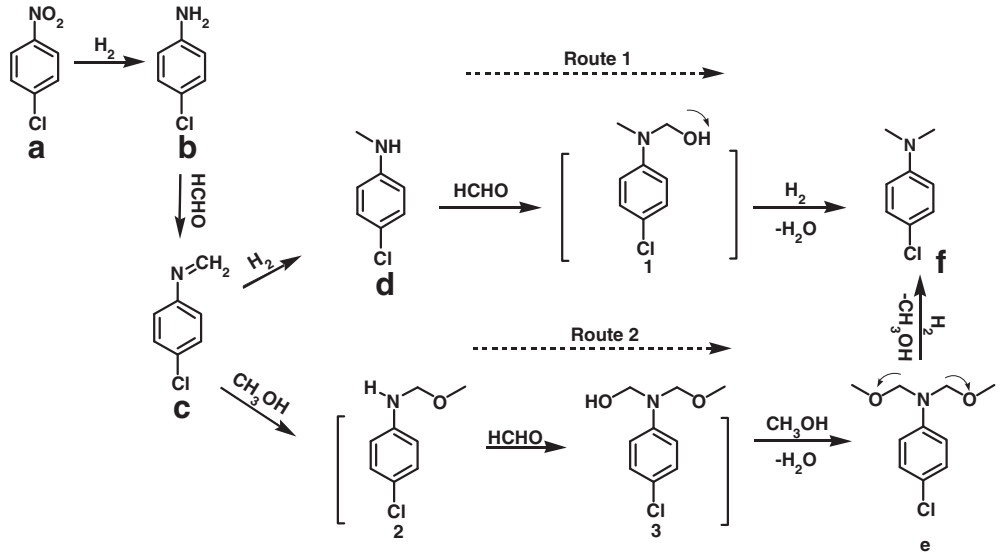
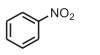
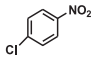
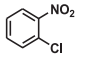
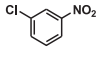
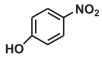
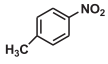
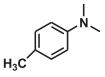
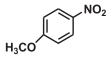
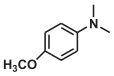
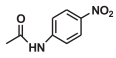
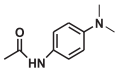
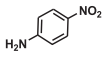
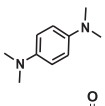
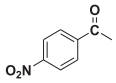
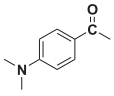
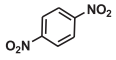
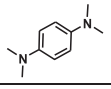


Fig. 3. The concentration–time plots for the hydro-dimethylation of p-CNB (reaction conditions: 373 K, 13 bar H_2, *p*-CNB = 6 mmol, CH_3OH = 20 mL, HCHO (37 wt.%) = 1.35 mL, S-Cu(wet) = 0.5 g).



Scheme 2. The possible pathway for hydro-dimethylation of *p*-CNB.

Table 2
Hydro-dimethylation of different nitroarenes to NNDA over skeletal Cu catalyst.[a]

Substrate	T(K)	*t*(min)	Product	Conversion (%)	Selectivity[b](%)
	353	85		100	90.5
	373	60		100	99.4
	373	127		100	82.9
	373	75		100	99.6
	373	57		100	96.0
	343	80		100	96.4
	353	60		100	96.1
	373	37		100	99.2
	373	98		100	97.8
	373	68		100	88.2
	373	110		100	99.2

[a] Reaction conditions: substrate = 6 mmol, HCHO = 18 mmol, CH_3OH = 20 mL, 0.5 g S-Cu catalyst, 13 bar H_2.
[b] Conversion and selectivity were determined by GC.

range of nitroarenes were converted to the corresponding NNDA with high selectivity, which provided an attractive and useful methodology for organic synthesis.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2013.07.023.

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