One-pot synthesis of N,N-dimethylaniline from nitrobenzene and methanol

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A route for the direct synthesis of N, N-dimethylaniline from nitrobenzene and methanol was developed through the sequential coupling of the hydrogen production from methanol, hydrogenation of nitrobenzene to produce aniline, and N-methylation of aniline over a pretreated Raney-Ni[®] catalyst (at 443 K in methanol). A high yield of N,N-dimethylaniline up to 98% was obtained by the proposed methodology. In this process, aniline was produced from *in-situ* hydrogenation of nitrobenzene with hydrogen generated from methanol, or transfer hydrogenation of nitrobenzene with methanol as donor, while methanol acted as a hydrogen source, alkylating reagent and solvent, simultaneously. Additionally, a plausible mechanism of this one-pot reaction process has been described.

Introduction

As a valuable intermediate in the synthesis of dyes, paints, medicines and pesticides,¹ N,N-dimethylaniline (NNDMA) has been traditionally synthesized by N-methylation of aniline with methylating reagents such as methanol, dimethyl carbonate,² formaldehyde³ and methyl halides. Formaldehyde and methyl halides are not eco-friendly reagents due to their highly noxious nature.⁴ Dimethyl carbonate and methanol are both green reagents but methanol is cheaper than dimethyl carbonate.⁵ However, the synthesis of NNDMA from aniline and methanol in the liquid-phase is no longer a preferred route due to the use of liquid acid, such as sulfuric acid, as the catalyst. Heterogeneous catalytic synthesis of NNDMA in the gas-phase over metallic oxide,⁶ zeolite⁷ or other solid acid⁸ is an environmentally benign process, but it suffers from low conversion of aniline. Recently, Selva et al.5 suggested that NNDMA could not be formed from aniline and methanol at a low temperature (423-473 K) over the NaX-type faujasites, but they interestingly found that it could be produced through a sequential coupling of the transesterification of ethylene carbonate with the selective N-methylation of aniline under identical conditions. However, it should be noted that aniline was used as the starting material in all of the aforementioned routes for the synthesis of NNDMA.

In previous work, we⁹ have coupled the aqueousphase-reforming (APR) of alcohols¹⁰ and the liquid-phase hydrogenation of unsaturated compounds to realize a novel method of liquid-phase hydrogenation (Scheme 1). Additionally, N-monoethylaniline was obtained from nitrobenzene and ethanol directly with a yield up to 86% via

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the coupling of the APR of ethanol, hydrogenation of nitrobenzene and N-ethylation of aniline. In this paper, we report a one-pot synthetic method for NNDMA from nitrobenzene and methanol (Scheme 2). This process was realized through the coupling of hydrogen production from methanol, hydrogenation of nitrobenzene for aniline, and N-methylation of aniline for NNDMA, simultaneously.

Results and discussion

As shown in Table 1, the conversion rate was significantly influenced by the temperature and amount of Raney-Ni[®]. but the selectivity of products was almost unchanged (Table 1, entries, 1-10). The yield of NNDMA was decreased with an increase of nitrobenzene or water (Table 1, entries 8 and 11-19). An optimal yield of NNDMA up to 98% (isolated yield 92.5%) was obtained from nitrobenzene and methanol in a one-pot reaction at 443 K and 3.0 MPa (N₂ pressure) in a stainless-steel autoclave (500 ml), which was higher than the yield obtained by Selva et al. (89%) through the sequential coupling of the transesterification of cyclic carbonates with selective N-methylation of anilines.⁵ In particular, the reaction was not only carried out under a mild condition, but also has high conversions of aniline (100%) and N-methylaniline (99.7%).

To investigate the hydrogen source of the nitrobenzene hydrogenation for aniline, methanol (with or without water) was tested for hydrogen production. Catalyzed by the Raney-Ni[®] catalyst, more H₂ (8.3%) and CO₂ (10.4%) were produced from methanol and water than from only methanol

$$CH_{3}OH + H_{2}O \longrightarrow [H] + CO_{2}$$

$$+$$

$$PhNO_{2}$$

$$\downarrow$$

$$PhNH_{2} + H_{2}O$$



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$$CH_{3}OH \longrightarrow [H]$$

$$PhNO_{2} \longrightarrow PhNH_{2}$$

$$CH_{3}OH \longrightarrow PhNHCH_{3}$$

$$CH_{3}OH \longrightarrow PhN(CH_{3})_{2}$$

Scheme 2 One-pot synthetic method for NNDMA.

(4.9% and 2.6%, respectively). The amount of CO_2 shows that more H_2 was produced from methanol through APR with the addition of water.

The hydrogenation of nitrobenzene with H₂ and methanol, respectively, as the hydrogen source was investigated. Using H₂ as hydrogen source will result in the formation of aniline (Table 2, entry 1), cyclohexylamine,¹¹ and cyclohexanol^{10b} etc., simultaneously. While the hydrogenation of nitrobenzene with methanol as hydrogen source could produce aniline, N-methyleneaniline and N-methylaniline, simultaneously at 353 K (Table 2, entry 2), N-methylaniline could not be produced from aniline and methanol under the identical conditions (Table 2, entry 3), because formaldehyde can not be produced from methanol over the Raney-Ni[®] catalyst without a hydrogen acceptor.¹² These results suggested that the catalytic transfer hydrogenation of nitrobenzene using methanol as hydrogen donor could lead to the formation of aniline and formaldehyde together.^{13a} This transfer hydrogenation process could favor the formation of N-methyleneaniline and N-methylaniline due to the formation of formaldehyde.

Finally, the N-methylation of aniline with methanol or formaldehyde as the methylating reagent was also investigated. When the methanol was used as methylating reagent, a high yield of NNDMA (95.0%) was obtained (Table 3, entry 1). The addition of water, however, decreased the yield of NNDMA (90.8%) with the increase of cyclo-

 Table 1
 Results of one-pot synthesis of N,N-dimethylaniline

Table 2 Reduction of nitrobenzene with H_2 or methanol^{*a*}

Entry	Reactants	T/K	Conv. (%)	Selecti		
1 ^b	$PhNO_2 + H_2$	443	100	NH ₂	он 21.5	NH ₂ 28.6
2 ^{<i>c</i>}	PhNO ₂ + CH ₃ OH	353	45.6	NH ₂	N [™] 57.0	N 12.1
3^d	PhNH ₂ + CH ₃ OH	353	0			

^{*a*} Reaction time = 5 h, 5 g Raney-Ni[®] as catalyst. ^{*b*} 60 ml cyclohexane as solvent, 2 ml PhNO₂, under 3 MPa H₂. ^{*c*} 2 ml PhNO₂, 60 ml CH₃OH. ^{*d*} 2 ml PhNH₂, 60 ml CH₃OH.

hexanol and *N*-methylaniline (Table 3, entry 2). In the case of using formaldehyde as methylating reagent, the results show that *N*-methyleneaniline could be produced from aniline and sequentially hydrogenated into *N*-methylaniline with methanol as hydrogen source (Table 3, entries 3, 4).

As shown above, the generation of NNDMA from nitrobenzene and methanol was carried out by multi-step reaction pathways in one reactor over a multifunctional catalyst. Scheme 3 illustrates the essential features of the one-pot synthesis of NNDMA. It involves first formation of aniline from the *in-situ* and/or transfer hydrogenation of nitrobenzene as described in the follows, these initial steps were followed by stepwise *N*-methylations of aniline to produce NNDMA finally. Methanol in this reaction system could be versatile, since it acted as a hydrogen source, alkylating reagent and solvent, simultaneously. Additionally, the simply pretreated commercial Raney-Ni[®] catalyst seems to be multifunctional for its feasibility on hydrogen production from methanol,^{10d}

							Yield (%)					
	Reactants	(mi)						N	N N	`N ́	ОН	
Entry	CH ₃ OH	$PhNO_2$	H_2O	T/\mathbf{K}	Catalyst/g	t/h	P/MPa			\bigcup	\bigcup	Others
1	60	1		413	3.0	25	2.0	4.8	89.4	2.2	0.6	3.0
2	60	1		423	3.0	18	2.0	2.1	91.8	3.1	0.7	2.3
3	60	1		433	3.0	10	2.5	2.6	91.8	2.6	1.1	1.9
4	60	1		443	3.0	7	3.0	1.8	94.4	0.3	0.7	2.8
5	60	1		453	3.0	5	3.5	2.1	93.3	2.5	0.7	1.4
6	60	1		463	3.0	4	4.4	2.3	91.0	2.2	1.4	3.1
7	60	2		443	2.5	15	3.0	0.8	95.7	0.3	1.2	2.0
8	60	2		443	5.0	7	3.0	0.4	97.0	0.6	0.9	1.1
9	60	2		443	7.5	5	3.0	0.3	98.0	0.1	0.8	0.8
10	60	2		443	10.0	4	3.0	0.3	96.7	0.1	1.1	1.8
11	60	3		443	5.0	10	3.0	2.1	94.0	0.2	1.1	2.6
12	60	4		443	5.0	16	3.0	3.6	91.2	0.7	0.9	3.6
13	60	5		443	5.0	20	3.0	3.1	89.2	0.4	2.8	4.5
14	60	5		443	10.0	9	3.0	1.6	88.5	1.0	5.4	2.5
15	60	2	1	443	5.0	8	3.0	0.8	95.0	0.3	1.4	2.5
16	60	2	2	443	5.0	9	3.0	0.8	96.0	0.2	1.2	1.8
17	60	2	3	443	5.0	9	3.0	1.3	93.3	0.2	2.7	2.5
18	60	2	4	443	5.0	9	3.0	2.7	92.8	0.5	2.3	1.7
19	60	$\overline{2}$	5	443	5.0	10	3.0	4.9	89.0	0.9	3.9	1.3

Table 3 N-Methylations of aniline with methanol or formaldehyde

			Selectivity (%)						
Entry	Reactants	Conv. aniline (%)	N [#]	N	`N [_]	`N [_]	OH	Others	
1 ^{<i>a</i>}	$PhNH_2 + CH_3OH$	100	< 0.1	2.2	95.0	1.8	0.2	0.8	
2^b	$PhNH_{2} + CH_{3}OH + H_{2}O$	100	< 0.1	3.8	90.8	0.5	2.3	2.6	
3^c	$PhNH_{2} + CH_{2}O + CH_{3}OH$	68.7	94.8		_			5.2	
4^d	$PhNH_2 + CH_2O + CH_3OH$	95.7	< 0.1	37.0	60.8	< 0.1	< 0.1	2.0	

^{*a*} Reaction conditions: 2 ml PhNH₂, 60 ml CH₃OH, 5 g catalyst, 9 h, at 443 K, under 3 MPa Ar. ^{*b*} Reaction conditions: 2 ml PhNH₂, 60 ml CH₃OH, 10 ml H₂O, 5 g catalyst, 9 h, 443 K, 3 MPa Ar. ^{*c*} Reaction conditions: 2 ml PhNH₂, 8 ml CH₂O, 100 ml CH₃OH, 1 min, at room temperature. ^{*d*} Reaction conditions: 5 g catalyst, 5 h, 443 K, under 3 MPa Ar.



Scheme 3 Reaction pathways for the one-pot synthesis of NNDMA.

hydrogenation of nitrobenzene for aniline¹⁴ and *N*-methylation of aniline (Table 3, entry 1) in the one-pot concurrent catalysis manner. It can also be reused directly after separation from the products (at least six times).

Two plausible routes for the reduction of nitrobenzene are considered to be involved in the proposed methodology. Initially (anhydrous system), aniline is partially produced by the catalytic transfer hydrogenation of nitrobenzene with methanol as hydrogen donor (accompanied with the formation of formaldehyde and water as the by-products). Hydrogen is produced by APR of methanol with water (Scheme 4, eqn (1), and subsequently the produced hydrogen could be used in-situ for the hydrogenation of nitrobenzene into aniline. Additionally, the formaldehyde and water could also result in the formation of formic acid and H_2 (Scheme 4, eqn (3) and (4)).¹³ In summary, aniline is produced from the *in-situ* hydrogenation of nitrobenzene with hydrogen (from any processes that result in the formation of hydrogen as shown in Scheme 4), and the transfer hydrogenation of nitrobenzene with methanol or formic acid as donor.

The N-methylation of aniline was realized by two pathways including substitution N-alkylation with methanol as alkylating reagent and reductive N-alkylation with formaldehyde

$CH_3OH + H_2O \longrightarrow CO_2 + 3H_2$	(1)			
CH ₃ OH - 2[H]	(2)			
$CH_2O + H_2O \longrightarrow HCOOH + CH_3OH$	(3)			
HCOOH 2[H] + CO₂	(4)			
Scheme 4 Hydrogen production from methanol.				

as alkylating reagent. The substitution N-alkylation of aniline with methanol could take place more easily and effectively than with ethanol *etc.* because the C–O bond dissociation energy of methanol is lower $(384.93 \pm 0.71 \text{ kJ mol}^{-1})^{15}$ than those of other primary aliphatic alcohols (ethanol 391.2 ± 2.9 kJ mol⁻¹, 1-butanol 392.0 ± 2.9 kJ mol⁻¹).¹⁵ In the stepwise N-methylations of aniline for NNDMA production, *N*-monomethylaniline is first produced through two individual pathways with methanol and formaldehyde as methylating reagents, respectively. The produced *N*-monomethylaniline further underwent substitution N-methylation with methanol as methylating reagent, resulting finally in the formation of NNDMA.

The main by-products are cyclohexanol and N,N-dimethylcyclohexanamine and their formation mechanisms are shown in Scheme 5. It suggested that rich H₂ and water conditions should thus be avoided for the proposed methodology. However, much H₂ and water remained on the fresh Raney-Ni[®], so that pretreatment of Raney-Ni[®] was essential.



Scheme 5 Formation of cyclohexanol and *N*,*N*-dimethylcyclohexanamine.

Conclusions

A novel one-pot synthesis of NNDMA from nitrobenzene and methanol in the presence of pretreated Raney-Ni[®] at 443 K and 3 MPa N₂ with an overall yield of up to 98% was described. During the reaction procedure, aniline was produced *in-situ* from the hydrogenation of nitrobenzene. Methanol acted as a hydrogen source, alkylating reagent and solvent, simultaneously.

Experimental

Reagents and apparatus

Nitrobenzene (AR/99.0%) and aniline (AR/99.0%) were purchased from Shanghai Chemical Reagents Factory. Methanol (AR/99.5%) and aqueous formaldehyde (37–40%) were purchased from Juhua Group Corporation, Cyclohexylamine (AR/99.5%) was purchased from Hangzhou Shuanglin Corporation.

Catalyst

The Raney-Ni[®] catalyst was obtained from Hangzhou Jiali metal Co. Ind. Before reaction, the Raney-Ni[®] was pretreated with methanol at 443 K under about 2 MPa N₂ for 8 h, and then stored in methanol.

The porous structural parameters of Raney-Ni[®] (before and after pretreatment), including BET surface area, pore volume, and pore size were obtained from conventional analysis of the nitrogen adsorption–desorption isotherms by Nova 1000e. The amounts of hydrogen adsorbed on the fresh and pretreated Raney-Ni[®] catalyst were calculated from the hydrogenation of nitrobenzene at 323 K without the supply of extra hydrogen. The BET surface area, pore volume, and pore size of Raney-Ni[®] were not changed after the pretreatment. However, the amounts of hydrogen absorbed on the Raney-Ni[®] catalyst were significantly decreased from 108.7 to 22.2 ml g⁻¹ after the pretreatment.

Reactions

A stainless-steel autoclave (500 ml) was charged with the mixture of reagents and catalyst, air was purged for 3–4 times with 1 MPa N₂, and kept under N₂ pressure (0.5–1 MPa) at room temperature, and subsequently heated to the desired temperature in about 1 h. Finally, the N₂ pressure was adjusted to a desired value, and the reactions were initiated by starting magnetic stirring and set for a given time. After each reaction, gaseous products were analyzed *in-situ* by a Gas-Chromatogram (Fuli GC-9790) equipped with 2 m

Porapak Q column and TCD detector. Liquid products were analyzed by GC-MS (Agilen GC-6890-MS-5973) (for qualitative analysis) and/or Gas-Chromatogram (Japan Shimadzu GC-2014B) equipped with a 30 m HP-5 capillary column (for quantitative analysis). The content of products was determined by the peak area normalization method.

Isolation of N,N-dimethylaniline (Table 1, entry 9)

The liquid product mixture was filtered after reaction, and 5 ml of the mixture (total 60 ml) was selected for isolation. Methanol was removed by rotary evaporation, the residues were purified by column chromatography on silica gel (200–300 mesh, eluent: petroleum ether–ethyl acetate, 15 : 1 v/v). 0.185 g (92.5%) *N*,*N*-dimethylaniline was obtained.

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