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A new efficient approach to 3-methylindole: Vapor-phase synthesis from aniline and glycerol over Cu-based catalyst

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1. Introduction

For several years, indole and its derivatives are widely used in medicine, agriculture and industry [1-3]. 3-Methylindole, an important nitrogen-containing heterocyclic chemical, has received considerable attention owing to its potential application as perfume and synthesizing herbicides, antidiuretic, stimulant antihypertensive, muscular relaxant, respiratory inhibitor and heart stimulant medicaments, etc. [4,5].

To date, many synthetic routes have been developed for the synthesis of indoles (Scheme 1). Among them, liquid-phase method is often considered conventional because it can give the product in a good yield. However, many starting materials are expensive and some catalysts preparations are complicated as well as its stringent environmental concern on the reactions, which limited the further development of indole and its derivatives [6-8]. Hence, the development of vapor-phase synthesis is of general interest. Although many vapor-phase syntheses of indoles are reported [9,10], only a few reports are available about the vapor-phase synthesis of 3-methylindole. One synthesis from indole and methanol (molar ratio of indole/ methanol was 1:6) took place over CeHY zeolite catalyst with 30% yield of 3-methylindole, in which, however, expensive reagent of indole and large amount of toxic methanol were used [11]. Recently, ZrO₂/SiO₂ catalyst was used in the synthesis of alkylindoles, just a yield of 12% was obtained for 3-methylindole from aniline and 1,2-propanediol [12]. Our research found that Ag/SiO₂ was an active catalyst for the vapor-phase

ABSTRACT

A novel efficient method for vapor-phase synthesis of 3-methylindole from aniline and glycerol has been developed over Cu-based catalysts. The catalysts were characterized by BET, XRD, H₂-TPR and NH₃-TPD techniques. The results indicated that Cu/SiO₂-Al₂O₃ catalyst exhibited high activity. The yield of 3-methylindole could be up to 40% when the Cu loading was 5.41 wt% and the reaction temperature was 240 °C. Moreover, the catalyst could be reused without obvious loss of the yield even after reaction time of 46 h. Copper-based catalyst with good dispersion and large amount of weak acid sites was favorable for producing 3-methylindole. A possible reaction pathway for the catalytic synthesis of 3-methylindole was proposed.

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synthesis of 3-methylindole from aniline and 1,2-propanediol, a yield of 35% was obtained [13]. However, the Ag/SiO₂ catalyst showed poor stability and was deactivated rapidly with time on stream. Thus, the development of an efficient approach for the vapor-phase synthesis of 3-methylindole is an important research target.

Glycerol is not only cheap and abundant, but also known as a green feedstock for the production of various chemicals [14–17], such as 1,3-propanediol, succinate, xylitol, propionate, etc. [18–20]. In this paper, we report a new vapor-phase approach to 3-methylindole, in which glycerol was employed as one of the reactants. A series of materials were tested to find out an efficient catalyst for the reaction. Active component loading, reaction temperature and the stability of catalyst were investigated. BET, XRD, H₂-TPR and NH₃-TPD techniques were used to reveal the relationship between the structure of Cu-based catalysts and their catalytic performances.

2. Experimental

2.1. Preparation of catalysts

The catalysts were prepared by incipient wetness impregnation using SiO₂, γ -Al₂O₃ or SiO₂-Al₂O₃ as support. After impregnating support (20 – 40 mesh) with appropriate amount of nitrate aqueous solution for 15 h at room temperature, the sample was dried at 120 °C for 4 h, and then calcined at 500 °C for 4 h to obtain the catalyst precursor. Prior to activity test, the catalyst precursor (3 mL) was *in situ* reduced in a mixture gas composed of N₂ (30 mL/min) and H₂ (30 mL/min) at 250 °C for 2 h, then heated or cooled to reaction temperature in 0.5 h and kept at the temperature for another 0.5 h.

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Scheme 1. Synthesis of 3-methylindole from aniline and glycerol.

2.2. Catalytic activity testing

The catalytic reactions were carried out in a fix-bed continuous flow glass reactor with inside diameter of 12 mm under atmospheric pressure. The mixture of reactants (molar ratio of aniline/glycerol = 3:1, SV = 1700 h⁻¹, LHSV = 0.4 h⁻¹) was pumped through the preheater where they were vaporized and then entered into the reactor with flowing H₂ (10 mL/min), steam (12 mL/h) and N₂ (58 mL/min). The quantitative analysis of the reactants and products was carried out on the SP-6890A gas chromatograph equipped with an SE-54 capillary column. 1-Hexyl alcohol was used as an internal standard. 3-Methylindole selectivity was calculated based on glycerol conversion and 3-methylindole yield.

The side products were analyzed on a gas chromatograph with a mass spectrometer (Shimadzu GCMS-QP2010) using a DB-5 capillary column and a gas chromatograph connected to a hydrogen flame ionization detector (FID-GC, SP-6800A) using OV-17 column.

2.3. Regeneration of catalyst

The inactivated catalyst was regenerated in the flow of O_2 (3 mL/min) and N_2 (57 mL/min) from ambient to 500 °C at a linearly programmed rate of 5 °C/min and kept at the temperature for 4 h. Prior to activity test, the catalyst was *in situ* reduced and the process was the same as the reduction step of catalyst preparation in 2.1.

2.4. Characterization of catalysts

BET surface areas of Cu-based catalysts were measured by an AUTOSORB-1MP apparatus using ultra pure nitrogen as the analysis gas. Before each measurement, the sample was outgassed overnight at 200 °C under 10^{-3} torr. The pore-size distribution curves were obtained from the analysis of the desorption portion of the isotherms using the BJH (Barrett–Joyner–Halenda) method.

X-ray diffraction (XRD) patterns were recorded by using a D8 Advance diffraction meter with Cu K_{α} source at radiation rate 0.5°/min in the 2 θ range of 30–80°. The voltage and current were 40 kV and 40 mA, respectively.

The temperature programmed reduction (H₂-TPR) experiments were performed in a quartz reactor with inside diameter of 6 mm and length of 350 mm. The sample (100 mg) was pretreated in a flow of ultra pure nitrogen gas of 50 mL/min at 100 °C for 1 h to remove water and other contaminants. TPR profiles were obtained by heating the samples under a 10% H₂/Ar flow (50 mL/min) from 50 to 450 °C at a linearly programmed rate of 10 °C/min. The hydrogen consumption was recorded with a thermal conductivity detector.

The temperature programmed desorption of ammonia (NH₃-TPD) experiments were carried out in a quartz reactor used as in H₂-TPR experiment. 150 mg of the sample was firstly pretreated at 500 °C for 1 h in a flow of ultra pure helium gas (50 mL/min) to remove water from the catalyst. In the following steps, the sample was saturated with ammonia gas at 100 °C for 1 h and subsequently flushed with He (50 mL/min) at 100 °C for 3 h to remove the physisorbed ammonia. Hereinto, the heating rate for the TPD measurements was 10 °C/min and the temperature range was from ambient to 700 °C.

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The activity and selectivity of the catalysts.

Catalyst	Glycerol conversion (%)	3-Methylindole yield (%)	3-Methylindole selectivity (%)
SiO ₂	85	0	0.0
γ -Al ₂ O ₃	100	13	13.0
SiO ₂ -Al ₂ O ₃	100	15	15.0
FeO/SiO ₂	82	1	1.2
CoO/SiO ₂	83	1	1.2
Ni/SiO ₂	100	0	0.0
Ag/SiO ₂	100	5	5.0
Cu/SiO ₂	100	12	12.0
FeO/r-Al ₂ O ₃	94	6	6.4
$CoO/r-Al_2O_3$	96	4	4.2
Ni/r-Al ₂ O ₃	100	1	1.0
Ag/r-Al ₂ O ₃	100	12	12.0
Cu/r-Al ₂ O ₃	100	18	18.0
FeO/SiO2-Al2O3	100	9	9.0
CoO/SiO ₂ -Al ₂ O ₃	100	9	9.0
Ni/SiO ₂ -Al ₂ O ₃	100	5	5.0
Ag/SiO ₂ -Al ₂ O ₃	100	17	17.0
Cu/SiO2-Al2O3	100	38	38.0

Reaction conditions: 240 °C, aniline/glycerol = 3:1 molar ratio, $SV = 1700 h^{-1}$, LHSV = 0.4 h^{-1} , H₂ = 10 mL/min, steam = 12 mL/h, N₂ = 58 mL/min. Catalyst loading: 3.67 wt%. The results were taken at the fourth hour.

3. Results and discussion

3.1. Performances of various catalysts in the synthesis of 3-methylindole

For the synthesis of 3-methylindole from aniline and glycerol, the activity and selectivity over various catalysts are presented in Table 1. When Fe, Co or Ni was employed as active component respectively, glycerol conversion of 82–100% was obtained, but the selectivity of 3-methylindole was low (less than 10%). Based on the GC-MS analysis, the main side products were *N*-methylaniline, *N*-ethylaniline and indole, etc. Over the silver-based catalysts, the selectivity of 3-methylindole reached 5–17%. It is clearly observed that Cu-based catalysts afforded 3-methylindole in higher yields than those obtained over other catalysts. Besides, SiO₂-Al₂O₃ support seemed to be favorable for the desired transformation. Compared with the catalysts of SiO₂ or γ -Al₂O₃ supported, SiO₂-Al₂O₃ supported catalysts showed higher activity and selectivity. Among all the examined catalysts, Cu/SiO₂-Al₂O₃ exhibited the highest catalytic activity, which the yield of 3-methylindole reached 38%.

Table 2 exhibits the yields of 3-methylindole over Cu/SiO₂-Al₂O₃ catalyst with different Cu loadings. It can be seen that the yield of 3-methylindole increased with the increase of Cu loading from 1.87 to 5.41 wt%. When the Cu loading was 1.87 wt%, the yield of 3-methylindole was only 33%. When the Cu loading was 5.41 wt%, the desired product could attain a yield as high as 40%. A further increase in Cu loading again, however, the yield of 3-methylindole decreased. 5.41 wt% of the Cu loading was the best choice for Cu/SiO₂-Al₂O₃ catalyst to produce 3-methylindole.

Table 2	
Effect of Cu loading on the activity and selectivity of Cu/SiO_2 - Al_2O_3 catalyst.	
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Cu loading	Glycerol	3-Methylindole	3-Methylindole selectivity (%)
(wt%)	conversion (%)	yield (%)	
1.87	100	33	33.0
3.67	100	38	38.0
5.41	100	40	40.0
7.08	100	37	37.0
8.70	100	34	34.0

Reaction conditions: 240 °C, aniline/glycerol = 3:1 molar ratio, $SV = 1700 h^{-1}$, LHSV = 0.4 h^{-1} , $H_2 = 10 mL/min$, steam = 12 mL/h, $N_2 = 58 mL/min$. The results were taken at the fourth hour.

Table 3

Effect of the reaction temperature on the activity and selectivity of $\mbox{Cu/SiO}_2\mbox{-Al}_2\mbox{O}_3$ catalyst.

Temperature (°C)	Glycerol conversion (%)	3-Methylindole yield (%)	3-Methylindole selectivity (%)
220	100	34	34.0
240	100	40	40.0
260	100	36	36.0
280	100	31	31.0

Reaction conditions: aniline/glycerol = 3:1 molar ratio, SV = 1700 h⁻¹, LHSV = 0.4 h⁻¹, H₂ = 10 mL/min, steam = 12 mL/h, N₂ = 58 mL/min. Copper loading: 5.41 wt%. The results were taken at the fourth hour.

The effect of reaction temperature was investigated over $Cu/SiO_2-Al_2O_3$ catalyst. As shown in Table 3 the yield of 3-methylindole increased at first, then decreased as the temperature shifted from 220 to 280 °C. At 220 °C, a 34% yield of 3-methylindole was obtained. To our delight, the target product yield can be enhanced to 40% when increased the reaction temperature to 240 °C. In the case of higher temperature such as 260 °C or 280 °C, the lower yield of 36% or 31% was obtained, respectively. 240 °C was propitious temperature to the production of 3-methylindole.

The stability of the Cu/SiO₂-Al₂O₃ catalyst in the synthesis of 3-methylindole was examined under the reaction temperature of 240 °C and the Cu loading of 5.41 wt%. It can be seen in Fig. 1 that although the yield of 3-methylindole dropped to about 30% after reaction time of 10 h, the yield could be recovered when the catalyst was regenerated in the flow of O₂ (5%) and N₂ (95%). The yield of 3-methylindole was up to 37% after the catalyst was reused successively five times (nearly 46 h), indicating that the stability of the Cu/SiO₂-Al₂O₃ catalyst was good.

3.2. Catalyst characterization

Table 4 showed the specific surface areas and total pore volumes for different Cu-based catalysts. It can be seen that the specific surface area and total pore volume on Cu/SiO₂-Al₂O₃ were all smaller than those on Cu/ γ -Al₂O₃ or Cu/SiO₂. Considering the activities of Cu-based catalysts it can be obtained that the specific surface area and total pore volume were not the crucial factors for the vapor-phase synthesis of 3-methylindole.

The X-ray diffraction patterns of Cu-based catalysts are shown in Fig. 2. Two big diffraction peaks at about 43.1° and 50.3°, assigned to



Fig. 1. The stability of Cu/SiO₂-Al₂O₃ catalyst.

Table 4

The specific surface area and total pore volume of Cu-based catalysts.

Catalyst	Specific surface area (m^2/g)	Total pore volume (mL/g)
$\begin{array}{c} Cu/SiO_2\text{-}Al_2O_3\\ Cu/\gamma\text{-}Al_2O_3\\ Cu/SiO_2 \end{array}$	308.4 332.5 381.3	0.6029 0.8807 0.9403

(111) and (200) reflections of crystalline copper, were observed on Cu/SiO₂ catalyst and no distinct copper diffraction peaks were found on Cu/SiO₂-Al₂O₃ or Cu/ γ -Al₂O₃, suggested that copper existed in bigger particles on the surface of SiO₂ and presented in an amorphous state on CuO/SiO₂-Al₂O₃ or Cu/ γ -Al₂O₃ [21]. This was ascribed to the interactions between copper and the supports. For the Cu/SiO₂ catalyst, in spite of its relatively large specific surface area, the interaction between Cu and SiO₂ was weak, as a result, it was easy for the Cu particles to get together on the surface of SiO₂, whereas, the interaction between Cu and SiO₂-Al₂O₃ or γ -Al₂O₃ was strong, which resulted in the good dispersion of copper particles on the support of SiO₂-Al₂O₃ or γ -Al₂O₃. From the results of XRD and Table 1 it can be deduced that bigger copper particles on Cu-based catalyst took disadvantage of the synthesis of 3-methylindole.



Fig. 2. XRD patterns of Cu/SiO₂-Al₂O₃ (1), Cu/ γ -Al₂O₃ (2) and Cu/SiO₂ (3).



Fig. 3. H_2 -TPR profiles of CuO/SiO₂-Al₂O₃ (1), CuO/ γ -Al₂O₃ (2) and CuO/SiO₂ (3).



Fig. 4. NH₃-TPD profiles of Cu/SiO₂-Al₂O₃ (1), Cu/γ-Al₂O₃ (2) and Cu/SiO₂ (3).

The reducibility of supported CuO samples was investigated by H₂-TPR experiments and the profiles are given in Fig. 3. On the sample of CuO/SiO₂-Al₂O₃ or CuO/ γ -Al₂O₃, more than two reduction peaks were observed. Considering the results of XRD it can be deduced that the big reduction peak at the relative lower temperature was the dispersed CuO species and the small peaks at relative higher temperature were attributed to the reduction of very small amount of bulk CuO particles [22]. On the sample of CuO/SiO₂, only one reduction peak existed at about 260 °C, assigned to the reduction of bulk CuO phase [21]. Moreover, the main reduction peak on CuO/SiO₂-Al₂O₃ or CuO/ γ -Al₂O₃ shifted towards the lower temperature compared with the reduction of CuO/SiO₂, suggested that the dispersed CuO particles were more easily reduced than the bulk CuO ones.

NH₃-TPD profiles can be used to illuminate the distribution and the amount of acid sites of catalyst. From Fig. 4 it can be seen that three desorption peaks existed on the Cu-based catalysts. The peak at lower temperature (<150 °C) was assigned to the weak acid sites, while the others at higher temperature (150–350 °C) were corresponded to the middle-strong acid sites. The amount of weak acid sites on Cu/SiO₂-Al₂O₃ was largest, followed by that on Cu/ γ -Al₂O₃ and Cu/SiO₂. Considering the results in Table 1 it can be obtained that copper-based catalyst with large amount of weak acid sites was favorable for the synthesis of 3-methylindole.



Fig. 5. Proposed reaction pathway for the synthesis of 3-methylindole over Cu-based catalyst.

It is well known that acid sites facilitated the reactants of aniline and glycerol to adsorb on the catalyst. However, it was unfavorable for the synthesis of 3-methylindole if the acidity of the catalyst was strong because 3-methylindole desorbed from the catalyst difficultly and as a result, the further reaction of 3-methylindole happened easily and the selectivity of the target product was low.

4. Reaction pathway

For the vapor-phase synthesis of 3-methylindole, a possible reaction pathway over Cu-based catalyst was proposed (Fig. 5) [23–25], in which 2-hydroxypropylaldehyde (2-HPAL) might be formed from glycerol, then 2-HPAL produced a Schiff's base (SB) by N-alkylation of aniline, SB cyclized to 3-methylindole. Because 2-HPAL and SB was not detected by GC-MS, it could be deduced that steps 2 and 3 were fast.

5. Conclusion

A new efficient and convenient route was developed for the vaporphase synthesis of 3-methylindole from readily available reactants of aniline and glycerol under mild conditions. Cu/SiO₂-Al₂O₃ catalyst showed high activity. A 40% yield of 3-methylindole was obtained when the Cu loading was 5.41 wt% and the reaction temperature was 240 °C. Moreover, the stability of Cu/SiO₂-Al₂O₃ catalyst was good. The catalyst could be reused without obvious loss of the yield even after reaction time of 46 h. There existed the strong interaction between Cu and SiO₂-Al₂O₃, which promoted copper dispersed on the surface of the support commendably. Copper-based catalyst with good dispersion and large amount of weak acid sites was favorable for the synthesis of 3-methylindole because small copper particles could provide large amount of active sites and weak acid sites could facilitate the adsorption of reactants on the catalyst and the desorption of 3-methylindole from the catalyst. A possible reaction pathway for the catalytic synthesis of 3-methylindole was proposed.

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