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COMMUNICATION

Amide exchange reaction: A simple and efficient CuO catalyst for diacetamide synthesis

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A highly copper-catalysed amide exchange reaction of hexamethylenediamine (HDA) with CH_3CN and H_2O for the synthesis of hexamethylenebisacetamide (HMBA) without organic solvent or gas protection has been developed. One hundred percent HDA conversion and > 99% HMBA selectivity was obtained. X-ray diffraction, scanning emission microscopy, and temperature-programmed reduction of hydrogen were used to characterize the structural properties of the catalyst. The reaction mechanism was also investigated.

Diacetamide products (DAPs), which are amongst the simplest imides, model compounds of biochemical relevance, and good co-crystallising agents, have a variety of applications in many industrially important processes, as well as in medicine, as pesticides, and in organic synthesis.[1-5] The molecular conformation and basic applications have attracted much attention. In recent years, the amide exchange reaction (AER) has increasingly been used to synthesize DAPs by pharmaceutical companies and in research laboratories.[6, 7] Among the many different DAPs, hexamethylenebisacetamide (HMBA)[8-10] is a major anti-carcinogen and medical-chemical intermediate used in the synthesis of different organic chemicals,[11-25] including hexamethylenetertamine (HMTA), diethyl hexamethylenedicarbamate (EHDC), and diphenyl hexamethylenedicarbamate (PHDC), (Figure 1).

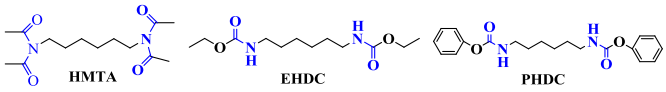
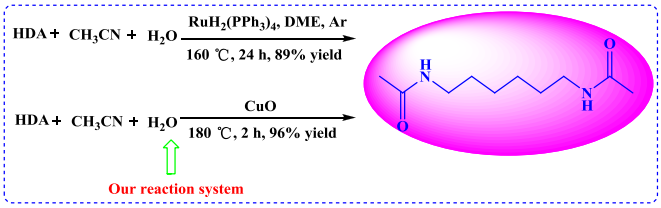


Figure 1 Selected products produced from HMBA.

Given the potential applications of HMBA, much work has gone into its production.[26-28] The traditional preparation method of HMBA, however, still utilises a noble metal complex catalyst and organic solvent under an inert atmosphere and has a low yield. As shown in Scheme 1, $RuH_2(PPh_3)_4$ was employed in the reaction of HDA, CH_3CN, and H_2O to prepare HMBA using dimethoxyethane (DME) as the solvent under an argon atmosphere, with only 89% yield.[29, 30] However, the development of method using mild conditions and a non-noble metal catalyst for the conversion of diamine to diacetamide is still required. Much effort has gone into identifying alternative non-noble metal catalysts and green ways to produce HMBA. Recently, there has been a lot of focus on different copper-catalysed reaction systems. Copper catalysts have been used as simple and efficient promoters in various reaction systems, such as photo-catalytic reactions.[31, 32]

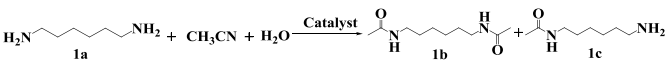


Scheme 1 Synthesis of HMBA from HDA, CH_3CN and H_2O.

Herein, a simple and efficient copper catalyst was used to replace noble metal catalysts in the reaction of HDA, CH_3CN, and H_2O without organic solvent or gas protection, with an isolated yield of 96%.

The catalytic performance of different metal oxide catalysts was studied (see Supporting Information Table 1). From the results, it was identified that the CuO catalyst shows better catalytic performance than others in this reaction, with 100% HDA conversion and > 99% HMBA selectivity. However, the use of other copper catalysts including Cu, Cu_2O, CuCl, CuBr, and $CuSO_4$ was less successful, leading to poor HMBA selectivity compared with CuO. The CuO catalyst was therefore deemed to be more suitable for the reaction of HDA, CH_3CN, and H_2O (Table 1).

Table 1 Synthesis of HMBA from HDA, CH_3CN, and H_2O with different copper catalysts[a]



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Electronic Supplementary Information (ESI) available: Details of experimental procedures of preparation and characterization of catalysts and catalytic data, and characterization of the product. See DOI: 10.1039/x0xx00000x

Entry	Catalyst	Conv. (%)	Sel. (%)[b]
1	CuO	100	>99
2	Cu	98	61
3	Cu_2O	98	72
4	CuCl	93	70
5	CuBr	90	84
6	$CuSO_4$	89	60

[a] Reaction conditions: 0.01 mol HDA, 0.03 mol CH_3CN, 0.06 mol H_2O, 0.00625 mol catalyst, 180 °C, 2 h. Conversion and selectivity were determined by gas chromatography. [b] Selectivity of 1b.

Then, we optimised the reaction conditions of the model reaction of HDA, CH_3CN, and H_2O (see Supporting Information, Figure S1). Primarily, the influence of the ratio of reagents was investigated. In the presence of 0.00625 mol catalyst at 180 °C for 2 h, the optimal molar ratio of HDA, CH_3CN, and H_2O was found to be 1:3:6.

The recyclability of the CuO catalyst was also investigated (Figure 2). The results show a slight decrease in activity after each run, corresponding to a drop in HDA conversion from 100 to 98%. This could be ascribed to the fact that CuO recovered only 95% of the charged amount after each run by simply centrifuging, washing, and drying, and it was slightly influenced by water, suggesting that the CuO catalyst could be reused without significant loss of activity. As shown in Figure 2, HMBA selectivity was also influenced by the slight decrease in activity of the CuO catalyst.

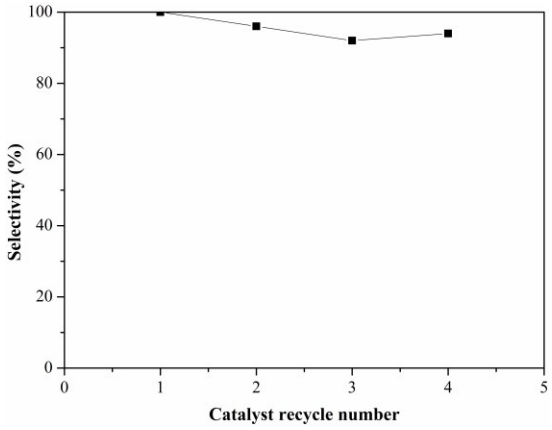
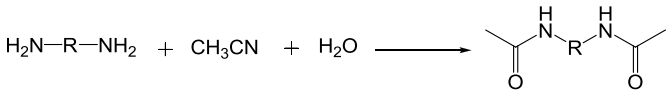
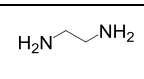
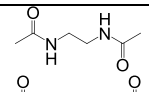
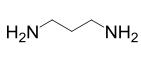
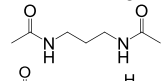
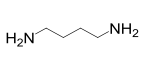
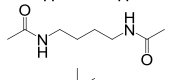
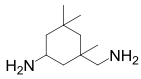
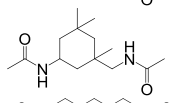
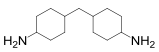
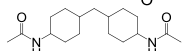
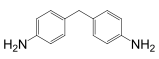
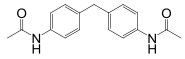
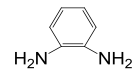
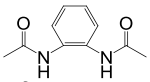
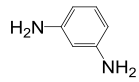
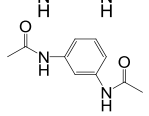
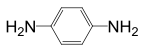
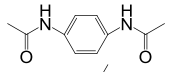
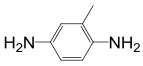
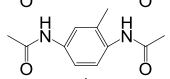
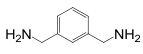
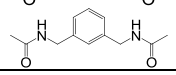


Figure 2 Cycling tests of CuO. Reaction conditions: 0.01 mol HDA, 0.03 mol CH_3CN, 0.06 mol H_2O, recovered catalyst, 180 °C, 2 h. The selectivity in this figure was assigned to HMBA.

Subsequently, to demonstrate the utility and generality of this approach to the formation of diacetamides, reactions of different diamines, including aliphatic diamines (linear chain and cydic diamines) and aromatic diamines, with CH_3CN and H_2O were carried out under the optimised conditions, the results are shown in Table 2. Excellent yields of the corresponding diacetamides were obtained with the linear chain and cydic aliphatic diamines (entries 1–5). On the other hand, lower activities were obtained with aromatic diamines towards the production of the corresponding diacetamides (entry 6–10), which might be due to the weak nudeophilicity of the nitrogen atom and the conjugative effect derived from the benzene ring. 2-Methyl-1H-benzo[d]imidazole was easily formed, detected using an Agilent GC-MS 7890B (see Supporting Information Figure S4), for the reaction of *o*-phenylenediamine and CH_3CN, which proceeded with only 3% selectivity for the diacetylation product. However, high activity was achieved with 1, 3-bisaminomethylbenzene (entry 11), with 100% conversion and 83% diacetamide selectivity due to the benzyl group of this aromatic diamine. The CuO catalytic system demonstrated to be applicable to a wide range of aliphatic and aromatic diamines.

Table 2 Synthesis of diacetamides from various diamines[a]



Entry	Diamine	Major product	T(h)	Conv. (%)	Sel. (%)[b]
1			2	100	>99
2			2	100	>99
3			2	100	>99
4			8	100	95
5			8	100	93
6			8	56	20
7			8	45	3
8			8	63	15
9			8	75	25
10			8	35	10
11			2	100	83

[a] Reaction conditions: 0.01 mol diamine, 0.03 mol CH_3CN, 0.06 mol H_2O, 0.00625 mol catalyst, 180 °C, 2–8 h. Conversion and selectivity were determined by gas chromatography. [b] Selectivity of diacetamide.

X-ray diffraction (XRD), scanning electron microscopy (SEM), and temperature-programmed reduction of hydrogen (TPR-H_2) were carried out to explore the relationship between the structure of the CuO catalyst and performance of the reaction system. The XRD results of the prepared and used CuO are shown in Figure 3. The diffraction peaks at 32, 35, 38, 48, 53, 58, 61, 66, 68, 72, and 75° of the prepared CuO are in good agreement with pure CuO (JCPDS card No. 801916). In addition, the sharp and narrow peaks indicate that the prepared CuO is well crystallised. The peaks at 18, 33, 43, and 50° in Figure 3b are attributed to Cu, which was formed by the reaction of by-product NH_3 with CuO, causing the slight decrease in activity of the CuO catalyst.

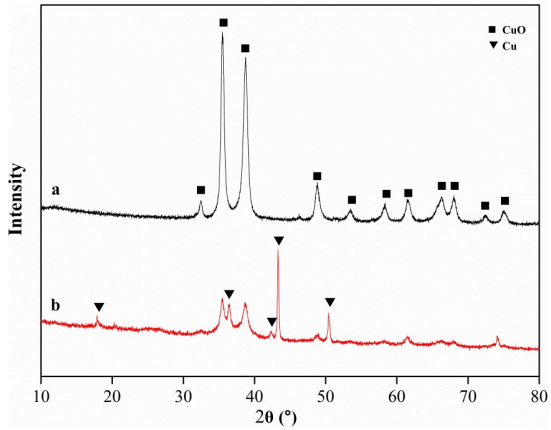


Figure 3 Powder XRD patterns of (a) prepared CuO and (b) used CuO.

It can be seen that the CuO catalyst prepared by the hydrothermal method has a nanorod-like morphology with an average diameter of 200 nm, as shown in Figure 4. For comparison, different morphologies of CuO were also investigated and were found to exhibit similar catalytic activities, indicating that the morphology of the CuO catalyst has little influence in this reaction.

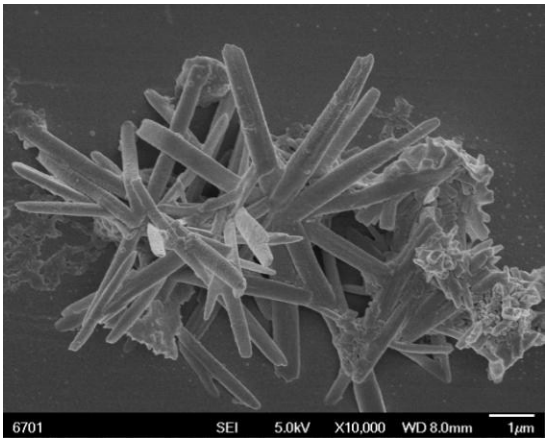


Figure 4 SEM image of the prepared CuO catalyst.

The TPR results of the prepared CuO, commercial CuO, and Cu_2O catalysts are shown in Figure 5. A broad peak at 305 °C can be observed for the prepared pure CuO catalyst (Figure 5a). There are two broad peaks at 367 and 534 °C which are assigned to Cu_2O and CuO, respectively, ascribed to the fact that Cu_2O is more easily reduced than CuO under the same conditions. Additionally, the shift in CuO reduction temperature from 305 to 534 °C indicated some sort of interaction between Cu_2O and CuO, which may inhibit the reduction of CuO (Figure 5b). On the contrary, the introduction of CuO may favour the reduction of Cu_2O, with much lower peaks at 254 and 280 °C observed in Figure 5c compared to Figure 5b.

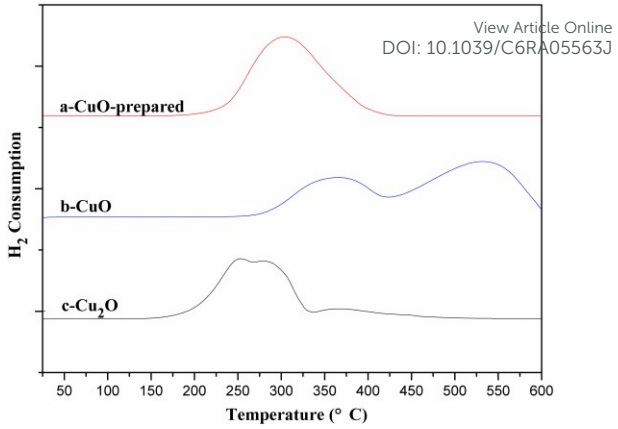


Figure 5 TPR-H_2 results for a) prepared CuO, b) commercial CuO, and c) commercial Cu_2O.

In order to study the mechanism of the reaction of HDA, CH_3CN, and H_2O catalysed by CuO, reactions of different substrates including HDA, CH_3CN, H_2O, and CH_3CONH_2 were carried out and traced by gas chromatography-mass spectrometry (GC-MS), (Table 3).

Table 3 Effect of the CuO catalyst on different combinations of reagents including HDA, CH_3CN, H_2O, and CH_3CONH_2[a]

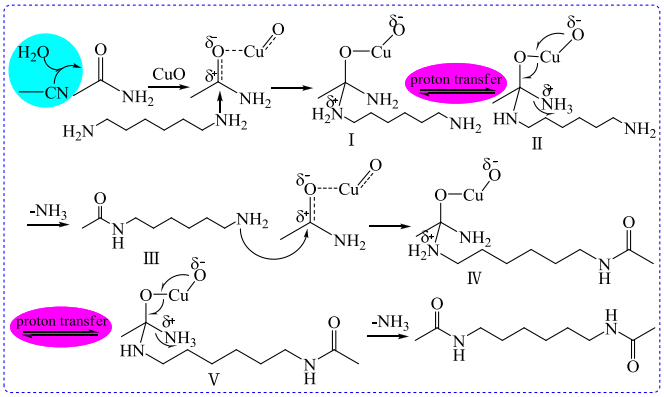
Entry	HDA (mol)	CH_3CN (mol)	H_2O (mol)	CH_3CONH_2 (mol)	Conv. (%)	Sel. (%)[b]
1	0.01	0.03	0.06	-	100[c]	>99
2	0.01	0.03	-	-	-	-
3	0.01	-	-	0.03	82[c]	52
4	0.01	-	0.06	-	-	-
5	-	-	0.06	0.01	-	-
6	-	0.03	-	0.01	-	-
7[e]	-	0.03	0.06	-	6.5[d]	-
8	-	0.03	0.06	-	8[d]	-

[a]Reaction conditions: 180 °C, 2 h, magnetic stirring speed of 960 rpm, 100 mL high pressure reactor. Conversion and selectivity were determined by gas chromatography. [b] Selectivity of HMBA. [c]Conversion of HDA. [d]Conversion of CH_3CN. [e]Without the CuO catalyst.

Initially, HDA, CH_3CN, and H_2O (molar ratio, 1:3:6) were added into the reactor, and 100% HDA conversion and > 99% HMBA selectivity were obtained (entry 1). Then, the reactions of HDA with CH_3CN, H_2O, and CH_3CONH_2 were investigated, respectively. As shown in Table 3 entry 2, no HDA consumption or HMBA detected in the reaction solution. These results and those of previous reports reveal that the polymerization reaction of CH_3CN was promoted by a catalytic amount of HDA to form 1,3,5-trimethyl-triazine, which was detected by GC-MS in this experiment. Only 82% HDA conversion and 52% HMBA selectivity were obtained when HDA reacted with CH_3CONH_2 directly (entry 3). There was no reaction between HDA and H_2O, CH_3CONH_2 and H_2O, and CH_3CONH_2 and CH_3CN in the presence of the CuO catalyst under the reaction conditions (entries 4–6). In the end, compared with entry 7 which has 6.5% CH_3CN conversion under no CuO catalyst , the reaction of CH_3CN with H_2O catalyzed by CuO showed 8% CH_3CN conversion to CH_3CONH_2 (entry 8), indicating that CuO has little effect on the reaction of CH_3CN with H_2O.

Based on the reactions discussed above, a feasible reaction pathway for the AER of HDA, CH_3CN, and H_2O catalysed by CuO is proposed, as shown in Scheme 2. The results indicate that HMBA was generated in two consecutive steps. Initially,

CH_3CONH_2 was formed by reaction of CH_3CN and H_2O, followed by the formation of HMBA in the second step via the AER of HDA with CH_3CONH_2, the former reaction was promoted by the latter. It is worth noting that in the second step, CuO plays a significant role in the nucleophilic addition reaction of HDA and CH_3CONH_2. The electrophilicity of the carbonyl carbon atom in CH_3CONH_2 was promoted by the CuO catalyst. The carbonyl was then attacked by nucleophilic HDA.



Scheme 2 The proposed mechanism for the AER of HDA, CH_3CN, and H_2O.

As shown above, nucleophilic addition of CH_3CONH_2 activated by CuO with HDA occurred to form I, followed by proton transfer to generate II. Elimination of ammonia from II affords intermediate III, which goes on to react with activated CH_3CONH_2 to afford IV. Then, V forms HMBA via elimination of ammonia.

Conclusions

In conclusion, we have proposed a highly copper-catalysed AER of HDA with CH_3CN and H_2O for the synthesis of HMBA. Under the optimised reaction conditions, good yields of various diacetamides were obtained with different diamines. This optimised catalytic system for the AER of diamines, CH_3CN, and H_2O is preferable for the synthesis of diacetamides via an environmentally benign route. Further development and application of this reaction are underway.

Acknowledgements

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Notes and references

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Synthesis of hexamethylenebisacetamide (HMBA) from hexamethylenediamine (HDA), CH_3CN and H_2O catalyzed by CuO without organic solvent and gas protection