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Synthesis of secondary amines via amination of alcohols with benzylamine using the magnetic nano-catalyst $Fe_3O_4@SiO_2@CS@EDTA/Cu(II)$

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Abstract: In this article, the core-shell nanoparticle $Fe_3O_4@SiO_2@CS@EDTA/Cu(II)$ is employed as an environmentally friendly and efficient magnetic catalyst for converting various benzyl alcohols with electron-donating or electron-withdrawing groups into their corresponding amine derivatives with high efficiency. The investigation entailed optimizing reaction conditions, including factors such as the presence of a base, the operation temperature, the reaction duration, and the quantity of catalyst to determine the optimal parameters. The best results were achieved using 0.3 mmol of catalyst per 1 mmol of benzyl alcohol derivatives under reflux conditions for 10h. The reaction proceeds by converting the alcohol into a carbonyl compound, forming an imine between the amine and the generated carbonyl and reducing the imine. The results indicated that electron-donating groups enhanced the reaction rate, while electron-withdrawing groups, such as nitro, reduced the overall yield. Furthermore, this reaction exhibited high efficiency, and due to the straightforward catalyst separation facilitated by an external magnetic field, along with its stability and recyclability, it holds significant relevance in organic chemistry and industrial applications.

Keywords: Amination, Magnetic nanocatalyst, Core-shell nanoparticle, Benzyl amin, Benzyl alcohol.

Introduction

The formation of carbon-amine bonds is a fundamental concept in organic chemistry, holding significant importance in constructing and synthesizing organic molecules [1]. Nitrogen-containing compounds, particularly amines and their derivatives are recognized as versatile building blocks for generating a wide range of organic molecules and diverse precursors used to produce biologically active compounds [2].

Considering the diversity and versatility of applications of nitrogen-containing compounds in the fields of chemistry and medicine, the development of efficient methods for amine synthesis remains a prominent and active challenge in research areas [3].

Due to their significance, various methods have been introduced for their synthesis, including the Hofmann alkylation [4], Buchwald-Hartwig reaction[5], Ullmann reaction [6], hydroamination [7], and hydrogen transfer processes [8], amination or hydroamination of alkenes and alkynes [7, 8], as well as reduction of nitriles and nitro compounds [9], and amine production through the reduction of carbonyl compounds [10, 11]. However, these methods present challenges, such as the activation of aryl/alkyl halides, the utilization of hazardous reagents, and potent reducing agents, which are environmentally detrimental. One of the interesting methods in this field is the amination of alcohols using intermediate metal catalysts [12, 13]. An exciting aspect of this approach is the substitution of aryl/alkyl halides with alcohols as alkylating agents. These alcohols, by

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losing hydrogen, form a carbonyl intermediate, which, in the presence of amines, is transformed into an imine or iminium species. Subsequently, in the presence of a water molecule, the carbonyl intermediate undergoes the transformation into a new amine that carries a newly attached alkyl group. This method is considered one of the more sustainable and environmentally friendly approaches to the production of amines. It has garnered significant attention in the field of organic chemistry due to its abundance and easy access to alcohol [14]. The development of efficient and useful catalytic systems for alcohol amination represents a significant step towards greener synthetic processes in the production of various organic molecules and biologically active compounds. Some of the catalysts used in this reaction recently include copper-aluminum hydrotalcite (CuAl-HT)/K_2CO_3[15], CuO-NiO/γ-Al_2O_3[16], $Cu(OH)_x/TiO_2$ [17], $Cu(OH)_x/Al_2O_3$[17], heterogeneous catalyst with a mesoporous magnesium structure[18], Cu-Fe[19], and iron-based heterogeneous catalysts[20].

So, this result indicated that the presence of transition metals like Cu and Fe facilitates the conversion of alcohols into amines [20, 21]. Considering the presence of intermediate metals, the Fe_3O_4@SiO_2@CS@EDTA nanocomposite is recognized as an advanced and multilayered catalyst with a core-shell structure[22]. This composite, in its layers, is initially coated with iron oxide nanoparticles with silica, then with chitosan, and ultimately with EDTA. Some part of this catalyst such as Fe_3O_4@SiO_2 [23, 24] or Fe_3O_4@SiO_2@CS [25, 26] or Fe_3O_4@SiO_2@EDTA [27-29] and Fe_3O_4@SiO_2@CS@EDTA has been reported. They are utilized in various processes, including color removal and pollution reduction. For simplicity, we will use the term NCM@EDTA to denote Fe_3O_4@SiO_2@CS@EDTA.This catalyst is of special significance due to its unique properties within its composition, including the capacity for easy separation from the solution in the presence of a magnetic field and stability in the reaction environment facilitated by the attachment of functional groups through chemical bonds. The synthesis of this catalyst is relatively straightforward, and it has not been previously employed in organic syntheses. Consequently, in our research, we utilized this catalyst as a practical and cost-effective tool for the synthesis of amines. This synthesis involves the amination of alcohols with the assistance of NCM@EDTA in the presence of Cu(II) ions as a catalyst in the presence of a base. The presence of a catalyst in the amination of alcohol offers several advantages, including the ability of recyclability, effortless separation of the catalyst from the reaction medium when exposed to an external magnetic field, straightforward synthesis, and exceptional selectivity, rendering it particularly attractive to researchers and industries.

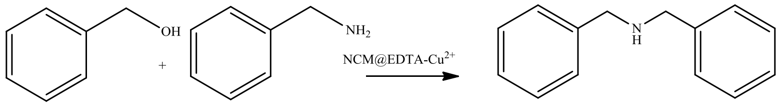
Results and Discussion

To optimize the synthesis of the second type of amines, we initially investigated the amination of benzyl alcohol with benzylamine in the presence of the NCM@EDTA-Cu(II) catalyst as an initial sample. Parameters such as the presence of a base, reaction time, reaction temperature, and the catalyst amount were optimized. The reaction was conducted in the presence of K_2CO_3 as the base at 80°C. Optimization results indicated that the presence of a reducing agent such as $NaBH_4$ in the reaction completion and reduction step improved the reaction yield (Table 1, entry4). However, in the absence of a reducing agent, the reaction could still occur but required a longer time. The best result is achieved with 0.3 mmol of NCM@EDTA-Cu(II) catalyst per 1 mmol of benzyl alcohol at 80 °C, under reflux conditions for 10 h, yielding an 90% conversion (Table 1, entry 6).

The results of titration studies in the presence of a standard Mg^{2+} solution with the Eriochrome Black T (EBT) indicator demonstrated that each gram of the NCM@EDTA catalyst contains approximately 4.0 mmoles of EDTA. Therefore, the optimized 3.0 mmol catalyst contains approximately 0.8g of NCM@EDTA. By adding copper ions, the EDTA ligands coordinate with copper ions, forming complexes.

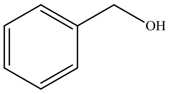
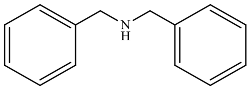
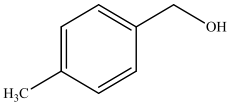
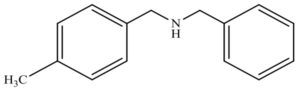
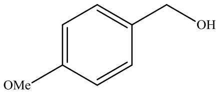
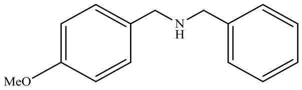
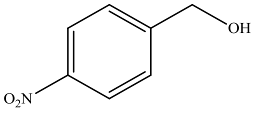
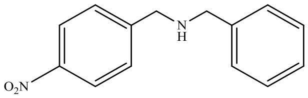
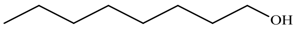
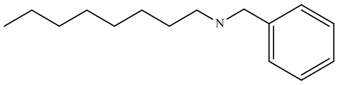
The reactions with benzyl alcohol derivatives bearing various functional groups, including electron-withdrawing groups like nitro and electron-donating groups like methoxy, were investigated. The results showed that the presence of electron-donating groups in the benzyl ring improved the reaction rate, while the presence of electron-withdrawing groups, including nitro, reduced the reaction rate and required more time. Additionally, the overall yield decreased (Table 2, entries 3,4). Regarding aliphatic alcohols, the conversion rate and overall yield showed a significant decrease, and, in general, aliphatic alcohols exhibited lower yields compared to benzyl alcohols (Table 2, entry 5). This was mainly due to the increased complexity of generating carbonyl intermediates from aliphatic alcohols. The results of these studies are summarized in Table 2.

Table 1. Optimization of alcohol (1 mmol) to amine conversion in the presence of NCM@EDTA-Cu(II) catalyst.



Entry	Catalyst (mmol)	Catalyst (type)	Base/ reducing agent	Time(h)	Yield (%)
1	0.4	NCM@EDTA	-	24	-
2	1	NCM@EDTA- Cu(II)	-	24	30
3	1	NCM@EDTA- Cu(II)	K_2CO_3	10	90
4	1	NCM@EDTA- Cu(II)	K_2CO_3/$NaBH_4$	2	100
5	0.5	NCM@EDTA- Cu(II)	K_2CO_3	10	92
6	0.3	NCM@EDTA- Cu(II)	K_2CO_3	10	90

Table 2. Conversion of various alcohols in terms of structure in the reaction with benzylamine to second-type amines in the presence of the NCM@EDTA-Cu(II) catalyst.

Entry	substrate	Product	Yield (%)
1			90
2			92
3			94
4			75
5			65

While this method requires relatively high reaction temperatures and additional amounts of amines, the use of the cost-effective and heterogeneous catalyst NCM@EDTA-Cu(II), instead of expensive and non-recyclable homogeneous catalysts, offers the advantage of easy separation in the presence of an external magnetic field. It demonstrates the versatility of the process in converting various aliphatic and benzylic alcohols containing both electron-donating and electron-withdrawing groups into amines.

It seems the carboxylate groups present in EDTA are capable of rapidly forming a complex with copper (II) ions, thereby creating the catalytic ensemble NCM@EDTA-Cu(II). This, in turn, facilitates the conversion of copper (II) to copper (I) and vice versa, easily achievable within the framework of the NCM@EDTA catalyst. To investigate the role of a base in alcohol amination, reactions were carried out in the absence of a base, resulting in no observed product formation. Therefore, it is anticipated that the oxidation step likely occurs through the formation of an alkoxide, involving the dissociation of a proton from the alcohol in the presence of a base, and its coordination with the copper center in NCM@EDTA-Cu (II). The presence of amino groups within the chitosan linked to the catalyst contributes to improved reaction kinetics and the elimination of hydrogen from the alkoxy intermediate, making the reaction feasible under mild alkaline conditions. Copper alkoxy intermediates are then converted to amine products, demonstrating a dynamic process that involves the reversible transformation of copper(I) to copper(II) facilitated by the structure of the catalyst.

The EDTA ligand and the hydroxyl and amino groups associated with chitosan in the nanostructured catalyst create an environment conducive to the facile alteration of the oxidation state of the copper ion. In essence, the presence of EDTA eases the conditions for reverting copper to its copper(II) oxidation state. The reaction mechanism is illustrated in Figure 1.

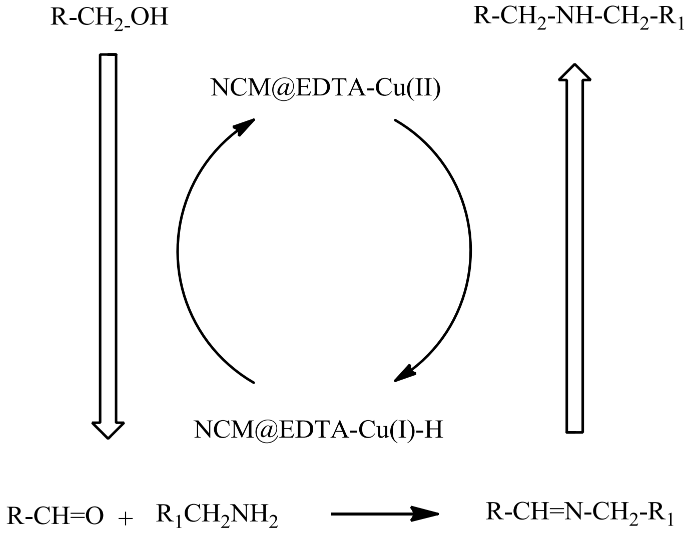
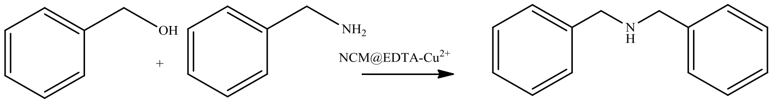


Figure 1. Proposed Mechanism for the Reaction of Alcohols with Amines in the Presence of the NCM@EDTA-Cu(II) Catalyst

The catalyst NCM@EDTA-Cu(II) can be easily separated from the reaction mixture with the assistance of an external magnetic field. The recovered catalyst, after washing sequentially with acetone, ethanol, and water, followed by drying at 65 ˚C, was used in the subsequent cycles to study its reusability and effectiveness (Table 3).

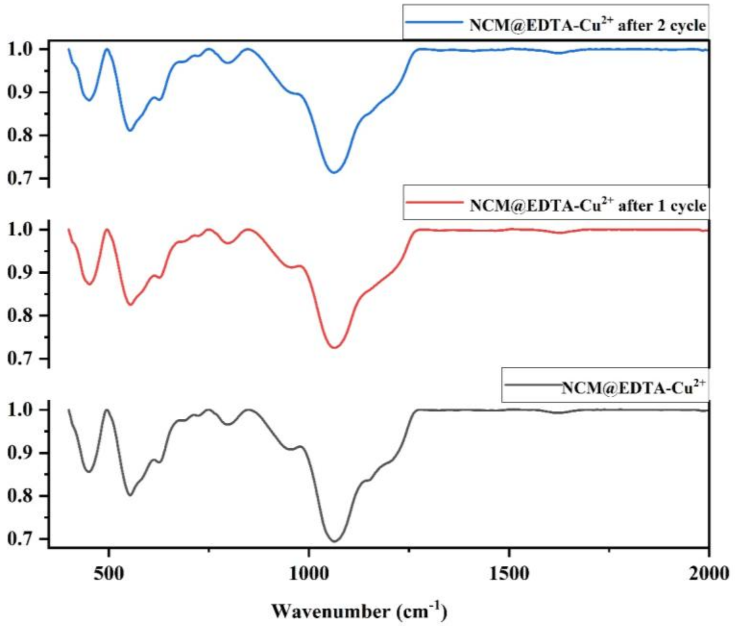
Table 3. Catalyst Recovery in the Reaction of Methoxybenzyl Alcohol and Benzyl Amine



Entry	Recovery Steps	Yield (%)
1	first	94
2	Second	90
3	third	85

Furthermore, the FTIR spectra of the fresh NCM@EDTA catalyst and the catalyst recovered from the second and third reaction cycles were analyzed (Figure 2), demonstrating no significant differences between the FTIR patterns of the fresh and recovered catalyst. This study highlights the exceptional resilience and efficiency of the catalyst, as its structure remains intact under reaction conditions.

Figure 2. FTIR Spectra of the Fresh NCM@EDTA Catalyst and the Catalyst Recovered from the Second and Third Reaction Cycles



Conclusion

In conclusion, the NCM@EDTA-Cu(II) catalyst establishes its effectiveness in the amination of benzyl alcohols, and the optimal conditions provide a high conversion yield. This catalytic system holds significant promise in the field of organic chemistry, offering advantages such as easy catalyst separation using an external magnetic field, stability in the reaction environment, and straightforward recyclability.

Experimental Section:

Catalyst Preparation: NCM@EDTA-Cu(II)

All material purchased from Merck company. The catalyst preparation method for NCM@EDTA-Cu(II), as previously reported [22], can be summarized as follows: Chitosan (2.5 g) is initially converted into a gel form using a 2% acetic acid solution and then sonicated for 3h. Simultaneously, in another container, $Fe_3O_4@SiO_2$ (2 g) [23] is mixed with CTAB salt (2.5 g) in deionized water. Then, the prepared chitosan gel is added to the above solution, and glutaraldehyde (30 μl) is introduced as a cross-linking agent for chitosan. Subsequently, EDTA monohydrate (0.5 g) is added to the container contents, and the mixture is stirred for 5h. Following this, NCM@EDTA is separated and, after washing with water, it is dried under vacuum conditions for 24h at 50°C. In continuation, 1.0 M copper nitrate solution (20 mL) is added to 1g of NCM@EDTA and left to equilibrate at room temperature for 24h. Finally, under the influence of an external magnetic field, the nanoparticles of NCM@EDTA-Cu(II) are separated. After washing with water, they are dried at 50°C.

Alkylation of Benzyl Amine with Benzyl Alcohol Derivatives Using NCM@EDTA-Cu(II) Catalyst

In alkylation method, NCM@EDTA-Cu(II) (0.8 g, 0.3 mmol), the relevant benzyl alcohol (1 mmol), and benzylamine (3 mmol) are mixed together in the presence of 10 ml of acetonitrile as a solvent in a round-bottom flask. The mixture is heated and refluxed under argon gas conditions at 80°C for 3 to 4h. Conversion and product yield are examined via Thin-Layer Chromatography (TLC), and the final purification is conducted. The NMR spectrum is compared to a standard sample. All the products are known compounds, and the NMR spectrum characteristics of the products listed in Table 2 are provided, along with their respective CAS numbers:

1. Dibenzylamine: Table 2, entry 1. CAS Number: 100-46-9; 1H NMR ($CDCl_3$) δ(ppm) = 6.12 (m, 10H), 3.67 (s, 4H).
2. N-Benzyl-N-(4-methoxybenzyl)amine: Table 2, entry 3. CAS Number: 43229-65-8; 1H NMR ($CDCl_3$) δ(ppm) = 7.61-7.1 (m, 9H), 3.85 (s, 4H), 3.76 (s, 3H), 1.75 (s, 1H).
3. N-Benzyl-N-(4-nitrophenyl)amine: Table 2, entry 4. CAS Number: 4309-92-3; 1H NMR ($CDCl_3$) δ(ppm) = 8.15 (d, 2H), 7.41-7.16 (m, 5H), 6.6 (d, 2H), 4.75 (s, 1H), 4.67 (s, 1H).
4. N-Benzylheptan-1-amine: Table 2, entry 5. CAS Number: 4309-92-3; 1H NMR (CDCl3) δ(ppm) = 7.51-6.15 (m, 5H), 3.47 (d, 2H), 2.8 (s1, H), 1.56 (m, 2H), 1.35 (m, 2H), 0.88 (m, 3H).

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