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Magnetic $CuFe_2O_4$ nanoparticles: a retrievable catalyst for oxidative amidation of aldehydes with amine hydrochloride salts

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ABSTRACT

The application of magnetic $CuFe_2O_4$ nanoparticles for the oxidative amidation of aldehydes with amine hydrochloride salts is described. A wide range of amides have been synthesized in good to excellent yields under mild conditions. Chiral amide also synthesized from its corresponding chiral amine salt with retention of the stereochemistry. In particular, the performance of the magnetic separation of the catalyst was very efficient and an alternative to time, solvent and energy-consuming separation procedures. The catalytic activity of the catalyst remains unaltered after five consecutive cycles, making it environmentally benign and widely applicable due to its efficiency, ease of handling and cost effectiveness.

1. Introduction

The development of more direct catalytic approaches towards synthesis of chemical products represents one of the key efforts of achieving chemical sustainability.[1] On the other hand, the use of more benign catalysts and the simple separation of catalysts from reaction mixtures provide both economical and ecological benefits.[2] In the last few decades, global concern for environment protection boosted the development of cost effective eco-friendly catalytic processes. In this context, magnetic nanoparticles have emerged as a new generation of catalysts or catalyst supports owing to their large surface area, easy dispersion in several solvents and more remarkably, their efficient recovery from the reaction medium by magnetic separation.[3] The magnetic nanoparticles have been widely employed as novel magnetically recoverable catalysts in traditional metal catalyzed reactions,[4] organocatalysis and enzymatic catalysis.[5] They are valuable addition to sustainable methodologies as the demand for benign nanocatalysts and their applications in synthesis is on the rise.

Amide bond is one of the most important functional groups in contemporary chemistry. It plays a major role in the elaboration and composition of biological systems such as making up of peptide bonds in proteins. It is a versatile building block in synthetic organic chemistry and also exhibits a wide range of industrial applications and pharmacological interest (Fig. 1).[6] A comprehensive survey revealed that the leading pharmaceutical companies Glaxo Smith-Kline, Astra Zeneca and Pfizer utilized amide bond formation in the synthesis of 66% of the drug molecules.[7] Recently, the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable identified amide formation as one of the most utilized and problematic synthesis in the pharmaceutical industry and has been labeled as a high priority research field.[8]

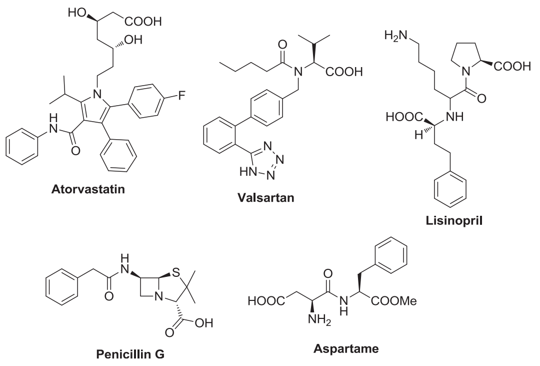

Fig. 1. Molecules containing an amide group.

Traditionally, amides were prepared by the reaction of an amine with a carboxylic acid derivative (acyl halide or anhydride) or by using a coupling reagent.[9] However, these methods suffered from the lability of activated carboxylic acid derivatives, use of hazardous reagents, harsh conditions, tedious workup and generation of

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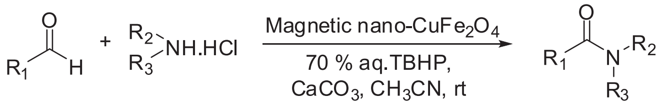
wastes that not only reduce process efficiency but also pose environmental problems. To circumvent these problems, alternative strategies toward the synthesis of amides have been explored. These includes an azide based modified Staudinger reaction,[10] hydrative amide synthesis with alkynes,[11] thio-acid/ester ligation methods.[12] Due to the advanced properties, use of transition-metal catalysts has developed rapidly in organic synthesis, and was also employed to promote the formation of amides. For example, transition metal catalyzed amidations of nitriles,[13] aldehydes,[14] aldoximes,[15] alcohols,[16] alkenes,[17] alkynes,[18] and haloarenes[19] with amines have been reported. Although significant achievements were made, the high cost of transition metals and harsh reaction conditions restricted the large scale industrial application.

Among these the oxidative amidation of aldehydes with amine salts is an attractive method with practicality and potential industrial applications as both starting materials are readily available and less hazardous than those traditionally used. Recently, Li et al., reported an efficient and greener method for amide formation through the oxidative amidation of aldehydes with amine hydrochlorides using CuI–$AgIO_3$ as catalyst.[20] However, this protocol required a dual catalyst system and limited substrate scope. More recently, Chen group identified iron and copper salts as effective catalyst for the oxidative amidation of aldehydes with amine hydrochloride salts.[21]

Nanoparticles of spinel type $CuFe_2O_4$ have been recognized as magnetic material with catalytically active copper centers, which has resulted in a number of catalytic applications.[22] The characteristics of this catalyst, such as easy recovery of catalyst from the reaction mixture by using an external magnet, efficient recycling, and high stability make it very attractive for further applications. Recently, we have reported the preparation, characterization, and application of magnetic $CuFe_2O_4$ for the synthesis of tetrazoles, triazoles and aryl amines. In continuation of our research endeavors on the applications of magnetic nanocatalysts,[23] herein, we have exploited magnetic $CuFe_2O_4$ nanoparticles[22k] for the oxidative amidation of aldehydes with amine hydrochloride salts (Scheme 1).



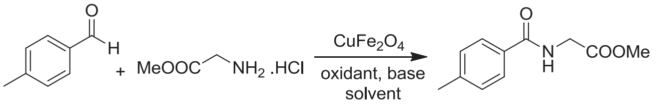
Scheme 1. Magnetically separable $CuFe_2O_4$ nanoparticles catalyzed oxidative amidation of aldehydes with amine hydrochloride salts.

2. Results and discussion

Initial experiments were performed between 4-methylbenzaldehyde and glycine methyl ester hydrochloride to determine the optimized reaction conditions and the results are summarized in Table 1. We first examined different oxidant sources and *tert*-butyl hydroperoxide (TBHP) was identified as the best-suited oxidant, while other oxidants were ineffective in giving the desired product (Table 1, entries 1–6). The effect of the bases was studied and $CaCO_3$ was found to be optimal, among other bases including Cs_2CO_3, Na_2CO_3, K_2CO_3, and $NaHCO_3$ (Table 1, entries 10–13). Screening of solvents was also carried out and it was found that acetonitrile was the best solvent among others solvents screened (Table 1, entries 14–20). Decreasing the reaction temperature from 80 °C to room temperature did not affect the reaction (Table 1, entry 6). The absence and low yield of product formation in control reactions (Table 1, entries 7–9) demonstrates the importance of catalyst, base, and oxidant for this transformation. Optimization of the reaction times showed that the reaction was completed within 10 h at room temperature as comparable yields obtained when the reaction was carried out for 24 h at the same temperature (Table 1, entries 6 and 21).

Table 1

Optimization of the reaction conditions[a]



Entry	Oxidant	Base	Solvent	Yield (%)[b]
1	H_2O_2	$CaCO_3$	CH_3CN	18
2	NaOCl	$CaCO_3$	CH_3CN	10
3	NaO_2Cl	$CaCO_3$	CH_3CN	15
4	$PhI(OAc)_2$	$CaCO_3$	CH_3CN	12
5	O_2 balloon	$CaCO_3$	CH_3CN	0
6	TBHP	$CaCO_3$	CH_3CN	86, 84[c]
7	—	$CaCO_3$	CH_3CN	0
8	TBHP	—	CH_3CN	14
9	TBHP	$CaCO_3$	CH_3CN	10[d]
10	TBHP	Cs_2CO_3	CH_3CN	15
11	TBHP	Na_2CO_3	CH_3CN	25
12	TBHP	K_2CO_3	CH_3CN	20
13	TBHP	$NaHCO_3$	CH_3CN	23
14	TBHP	$CaCO_3$	Toluene	28
15	TBHP	$CaCO_3$	*t*-BuOH	18
16	TBHP	$CaCO_3$	Dioxane	55
17	TBHP	$CaCO_3$	Water	15
18	TBHP	$CaCO_3$	THF	35
19	TBHP	$CaCO_3$	DMF	50
20	TBHP	$CaCO_3$	CH_3CN+H_2O (1:1)	38
21	TBHP	$CaCO_3$	CH_3CN	87[e]
22	TBHP	$CaCO_3$	CH_3CN	0[f], 55[g]

[a] Reaction conditions: 4-methylbenzaldehyde (1.0 mmol), glycine methyl ester HCl salt (1.2 mmol), base (1.1 mmol), oxidant (1.1 mmol), $CuFe_2O_4$ (10 mol %), solvent (2 mL), rt, under nitrogen atmosphere, 10 h.

[b] Isolated yields.

[c] Reaction was carried out at 80 °C.

[d] In the absence of catalyst.

[e] Reaction time was 24 h.

[f] Reaction with Fe_3O_4 nanoparticles (10 mol %) for 24 h.

[g] With 10 mol % CuO nanoparticles for 10 h.

The scope of the reaction was further probed under the established optimal reaction conditions. As depicted in Table 1, a wide range of aldehydes and primary amine hydrochloride salts were reacted to give secondary amides in good to excellent yields in 10 h. Benzaldehyde as well as benzaldehyde with electron-donating substituents at both *para* and *meta* positions reacted well and gave the corresponding products in 68–86% yield (Table 2, entries 1–5). Further, the reaction was extended to di- and tri-substituted aldehydes 3,5-dimethoxyaldehyde and 3,4,5-trimethoxyaldehyde that afforded the corresponding amides in 75 and 78% yield, respectively (Table 2, entries 6–7). Halogen substituted aldehydes, such as 3-fluoroaldehyde, 4-chloroaldehyde, 4-bromoaldehyde reacted smoothly and gave the desired products in 74–79% yield (Table 2, entries 8–10).

Electron withdrawing aldehydes, such as 4-cyanoaldehyde, 4-nitrobenzaldehyde, and 4-chloro-3-nitrobenzaldehyde reacted effectively to give the expected product in 60–78% yield (Table 2, entries 11–13). In addition, 2-naphthaldehyde and 4-phenyl substituted aldehyde reacted smoothly and gave the corresponding products in 72 and 70% yield, respectively (Table 2, entries 14 and 15). Hetero-aromatic and aliphatic aldehydes were reacted well and gave 70 and 68% yield of amide (Table 2, entries 16 and 17). The reaction between hindered aromatic aldehydes and glycine methyl ester hydrochloride also led to the corresponding amide formation in 72–75% yield (Table 2, entries 18–20).

When the oxidative amidation reaction was applied to L-valine methyl ester, the reaction proceeded smoothly in 86% (ee=98%) yield with the retention of configuration (Table 2, entry 23). Good activity of the catalyst for the synthesis of secondary amides from primary amine salts inspired us, to explore its catalytic activity for the synthesis of tertiary amides, yielding the desired amides in