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An efficient synthesis of symmetrical N,N-alkylidine bis-amides catalysed by nano copper ferrite

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ABSTRACT

Bis-amide derivatives were synthesized employing nano copper ferrite catalyst. XRD and TEM data of $CuFe_2O_4$ exhibited cubic phase morphology with an average partial size of 10-15 nm. The remarkable advantages are recyclability of catalyst, simple workup procedure and excellent yields.

KEYWORDS

Bis-amides;
Aldehyde;
$CuFe_2O_4$;
Reusability;
Catalyst.

INTRODUCTION

Bis-amides are an important class of organic compounds because of the amide motif present in many biologically significant substances[1]. The first synthesis of *gem*-bis-amides was achieved via condensation reaction between an aldehyde and an amide by Noyes *et al*[2] in 1933. Further literature survey reveals that the application of H_2SO_4[3], CH_3SO_3H[4], PTSA[5], $FeCl_3$, $ZnCl_2$[6], $BaCl_2$[7] as catalyst in the synthesis of bis-amides. Though the methodologies used were good, but they had their own disadvantages viz., i) longer reaction time, ii) lower yields, iii) use of toxic metals as catalysts, iv) use of hazardous organic solvents and tedious workup procedures. $CuFe_2O_{4,a}$ nano catalyst is being used in many other reactions till date. Herein we report the preparation, characterization of nano copper ferrite and its applications in the synthesis of bis-amides.

The advantage of the $CuFe_2O_{4,}$ catalyst is its easy recoverability from the reaction mixture by using an external magnet, efficient recycling and high stability; make it very useful for other applications also. This attracted the focus of synthetic chemist of late, and thus being used in many reactions.

The synthetic scheme for the synthesis of Bis-amides is presented in (scheme-1)

Preparation and Characterization of the nano copper ferrite was taken up by employing the standard procedure and the nano catalyst was characterized by XRD, SEM, TEM. The results indicate an average particle size of 10-15nm

RESULTS AND DISCUSSIONS

Initially the reaction was carried out without any catalyst, where benzaldehyde and benzamide were employed as standard substrates. A trace amount of product was observed even the reaction proceeded for 24hours. After employing the nano $CuFe_2O_4$ catalyst and toluene as solvent, high yields are observed in shorter reaction time. The reaction at different mole quantities of catalysts at different temperatures and in different solvents was screened for further

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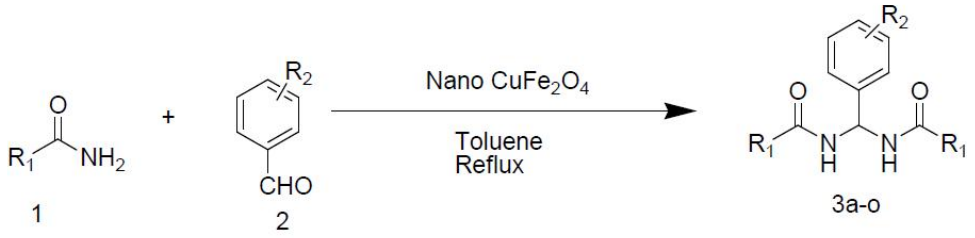
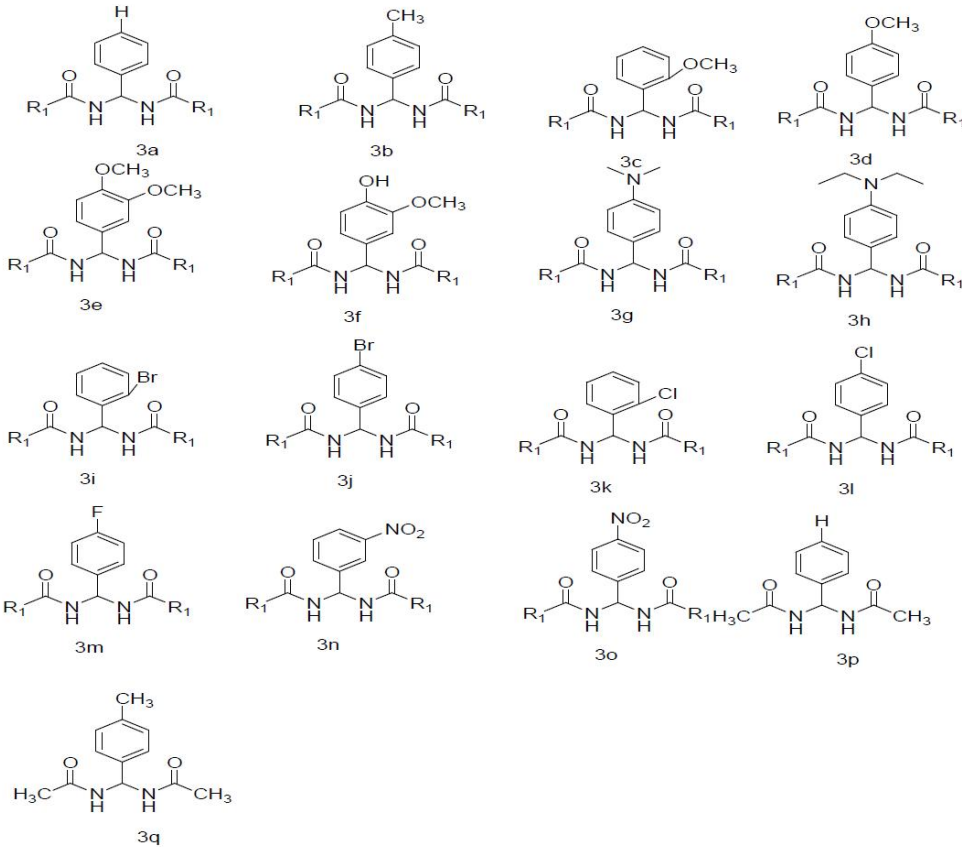


$R_{1=}$ Ar or CH_3; R_2: a = H, b = -CH_3,c = *o*-OCH_3, d = *p*-OMe ; e = *m*,*p*-$(OCH_3)_2$, f = *m*-OCH_3, *p*-OH, g = *p*-$N(CH_3)_2$, h = *p*-NEt_2, i = *o*-Br, j = *p*-Br, k = *o*-Cl, l = *p*-Cl, m = p-F, n = *m*-NO_2, o = *p*-NO_2, p = H, q = *p*-CH_3.

Scheme-1



evaluation, and the results are discussed below.

It is clear from this TABLE 1, that the reaction in the absence of catalyst gave very poor yield of the product after 24 h. More yield of the product was observed under the same reaction conditions; with different amounts of the nano $CuFe_2O_4$ catalyst. (TABLE-1)

The reaction was monitored by employing the prepared nano catalyst and the yields of the products increased to above 90%. Further it is observed that the optimized quantity of 10 mmol of the catalyst is ideal. (TABLE-1).

Further TABLE 1, it is evident that nano $CuFe_2O_4$ was very efficient for the reaction, giving 3a in 96% yield (TABLE 1, entry 8). Other catalysts $ZnCl_2$, $ZrCl_4$, $ZnBr_2$, NH_4Cl and P-TSA, were substantially less effective (TABLE 1, entries 2-7). The amount of Nano $CuFe_2O_4$ and reaction temperature were investigated (TABLE 1, entries 8-10) with amounts of 5 mol%, 10 mol%, 15 mol%, 20 mol% of Nano $CuFe_2O_4$ and it was found that 10 mol% of Nano $CuFe_2O_4$ was enough to accomplish the reaction. Increase in the amount of catalyst did not obviously improve the yield (TABLE 1, entry 8, 11&12).

Similarly, the effect of temperature was also studied. The yield was low (TABLE 1, entry 9) at 100^{0}C for 35 min, yield 88%). Increasing the temperature did not help obviously to improve the yield (TABLE

TABLE 1 : Yields and optimization of the reaction conditions [a]

Entry	Catalyst	Catalyst (Mole %)	Temperature (^{0}C)	Reaction Time (min)	Yield (%)
1	Without catalyst	0	120	24 h	3
2	$ZnCl_2$	5	120	180	72
3	$ZrCl_4$	5	120	120	68
4	$ZnBr_2$	5	120	90	79
5	NH_4Cl	5	120	120	62
6	P-TSA	5	120	140	70
7	Nano $CuFe_2O_4$	5	120	27	83
8	Nano $CuFe_2O_4$	10	120	15	96
9	Nano $CuFe_2O_4$	10	100	35	88
10	Nano $CuFe_2O_4$	10	140	14	98
11	Nano $CuFe_2O_4$	15	120	15	96
12	Nano $CuFe_2O_4$	20	120	14	97
13	Nano $CuFe_2O_4$[b]	10	120	15	81[b]

[a] Reaction conditions: All reactions were carried out using 1 (2 mmol), 2 (1 mmol), nano $CuFe_2O_4$ catalyst and toluene (4 ml); [b] Recycled catalyst

TABLE 2 : Solvent effect

Entry	Solvent	Time(min)	Yield(%)
1	Acetone	120	61
2	Dichloromethane	130	66
3	THF	120	68
4	Chloroform	150	40
5	1,2-Dichloromethane	120	70
6	Toluene	15	96

1), entries 8-10). The catalyst can be recovered easily and the yields were not reduced drastically when the recycled catalyst was used (TABLE 1, entry 13). The above reaction was carried out with different organic solvents viz) Acetone, Dichloromethane, THF, Chloroform, 1,2-Dichloromethane, Toluene and the data is recorded in (TABLE-2). Interestingly, it is observed that Toluene is the more suitable solvent for higher yields.

In all the cases, substituted aromatic aldehydes with either electron-donating or electron-withdrawing groups reacted with the substituted amide smoothly and gave the products in good to excellent yield. A total of seventeen compounds were prepared and the yields, the reaction times, along with the m.p's were presented in (TABLE-3).

All the above synthesized compounds were characterized by their melting points and comparison of their IR, ^{1}H NMR, and ^{13}C NMR spectra with authentic samples. The structure of unknown compounds was deduced by spectral analysis. Further it was anticipated about the reusability of $CuFe_2O_4$ in this system. Hence after completion of the reaction, under optimized conditions, the reaction mixture was cooled and filtered. The catalyst was recovered from the reaction mixture by magnetization process. The recovered catalyst was reused directly for five subsequent runs and the yields of product decreased slightly after four runs. The results are summarized in TABLE-4.

[a]Catalyst recovered by membrane filtration and washed with diethyl ether and then by distilled water; [b]Yields compared to isolated products

In conclusion, we have synthesized nano $CuFe_2O_4$ particles a heterogeneous catalyst for the synthesis of bis-amides and their derivatives in short reaction time without using any acidic catalyst, solvent or toxic materials. In addition, nano $CuFe_2O_4$ offers the competitive advantage of easy separation from the reaction mixture which can be reused, and the recyclability of the catalyst without any significant degradation of catalytic activity.

EXPERIMENTAL

The preparation and characterization of nano

TABLE 3 : $CuFe_2O_4$ catalyzed synthesis of symmetrical N,N-alkylidine bis-amides

Product	Time(min)	Yield %	m.p(°C)	Lit.m.p(°C)
3a	20	90	237-238	237-238[8]
3b	18	91	240-242	242-243[8]
3c	18	92	224-226	-
3d	17	93	221-223	221-222[8]
3e	16	95	352-259	-
3f	16	95	266-267	-
3g	17	94	230-231	-
3h	16	95	264-367	-
3i	17	94	215-217	-
3j	16	96	259-260	-
3k	16	95	252-253	-
3l	15	98	230-231	230-232[9]
3m	19	95	267-278	-
3n	18	93	192-193	190-192[10]
3o	16	95	265-267	265-267[8]
3p	15	93	238-240	239-240[8]
3q	17	92	272-273	269-271[8]

TABLE 4 : Reusability of nano catalyst

S.No	Catalyst recovery (%)[a]	Yield (%)[b]
1	-	97
2	66	90
3	84	82
4	80	78

copper ferrite[11] has been reported earlier and also used for the synthesis of xanthenes[12] and its derivatives in our previous study. The synthesized nano $CuFe_2O_4$ has been characterized by XRD, SEM and TEM analysis for structural and morphological studies. The XRD pattern shows the formation of cubic phase of maghemite, γ-Fe_2O_3 (matched with PDF No-01-089-5892) and the major XRD peak was obtained at $2\theta = 35.9^o$,while the other observed peaks were at 2θ = 30.5, 43.6, 54.0, 57.5 and 63.2 which suggests strongly that gamma phase of Fe_2O_3 is the major phase in this material. The average grain size of γ-Fe_2O_3 nano particles was calculated using the Scherrer formula and was found to be about 11nm indicating nano crystalline nature. The morphology and size of the γ-Fe_2O_3 nano particles were analyzed by scanning electron microscopy (SEM) and transmission electron microscopy (TEM). The low magnification SEM image shows small nano sized grains having spherical with a narrow size distribution ranging about 150 nm which indicates the nano crystalline nature of γ-Fe2O3 nano particles. The presence of some larger particles attributes aggregating or overlapping of smaller particles. The particle size about 10-15 nm was also determined by TEM and their shape was found spheroidal.

General procedure for the synthesis of Bis-amides

A mixture of amide (2eq), substituted aromatic aldehydes (1eq), toluene and $CuFe_2O_4$ nano particles (10 mol%) were stirred at 100°C in an oil bath for the time indicated in (TABLE-3). The completion of the reaction was followed by TLC [Hexane – Ethyl acetate]. After completion of the reaction, the mixture was cooled and the solid residue was separated and dissolved in methanol and the catalyst was recovered by magnetization. The separated solid was filtered and dried in vacuum, the solid product passed over a column of silica gel 60-100 mesh and finally recycled from alcohol to afford the pure product. All the synthesized products were characterized by IR, NMR and mass spectroscopic data. The NMR spectra obtained in DMSO-d_6, Mass spectroscopic data and their melting points were compared with

authentic samples. The reaction times, percentage of yield and m.p's were presented in (TABLE-3). The spectral data of some of the synthesized compounds are given below.

SPECTRAL DATA FOR SELECTED COMPOUNDS

N-[Acetylamino(4-methoxyphenyl)methyl]-acetamide (3P)

White powder, IR (KBr) (cm $^{-1}$): 3270 (NH), 1686 (C=O); 1H NMR : 1.85 (6 H, s, -CH_3), 3.73 (3 H, s, -OCH_3), 6.45 (1 H, t, -CH), 6.88 and 7.24 (4 H, aromatic), 8.43 (2 H, d, *J* = 8 Hz, -NH). 13C NMR : 21.9, 54.6, 56.3, 113.0, 127.0, 132.0, 158.1 and 167.9.

N-[Benzoylamino (3-nitrophenyl)methyl]-benzamide (3n)

White powder; IR (KBr) (cm^{-1}): 3255 (NH), 1645 (C=O); 1H NMR : 7.09 (1 H, t, -CH), 7.47–8.34 (14 H, aromatic), 9.23 (2 H, d, *J* =8 Hz, -NH). 13C NMR : 58.6, 121.4, 122.7, 129.9, 133.5, 133.7, 147.8, 127.6, 128.3, 131.7, 142.4 and 165.9.

CONCLUSIONS

In conclusion, we have developed a convenient and highly efficient method for the synthesis of bis amides by condensation reaction of aldehydes with amides by the use of nano- $CuFe_2O_4$, an inexpensive and easily recoverable catalyst. The attractive features of this synthetic protocol are easy work up procedure, operational simplicity and reusability of the catalyst with good to excellent yields.

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