Indian Journal of Fundamental and Applied Life Sciences ISSN: 2231– 6345 (Online)
An Open Access, Online International Journal Available at www.cibtech.org/sp.ed/jls/2015/01/jls.htm
2015 Vol.5 (S1), pp. 5421-5427/Anaraki and-Ardakani and Zaki
Research Article

CuO NANOPARTICLES AS AN EFFICIENT AND RECOVERABLE CATALYST FOR THE SYNTHESIS OF 3-AMIDO-ALKYL-4-HYDROXYCOUMARIN DERIVATIVES IN SOLVENT-FREE CONDITIONS

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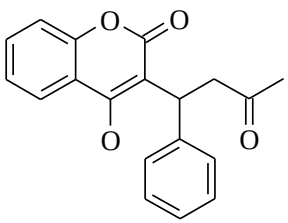
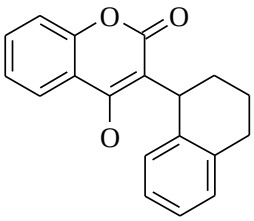
ABSTRACT
One pot, three-component reaction between 4-hydroxycoumarin, aromatic aldehydes and amide catalyzed by Nano CuO in solvent-free conditions provided a simple and efficient one-pot route for the synthesis of 3-amido-alkyl-4-hydroxycoumarin derivatives in excellent yields.

Keywords: *CuO nanoparticles (NPs), 4-Hydroxycoumarin, Aromatic Aldehydes, Solvent-free, 3-Amido-alkyl-4-Hydroxycoumarin*

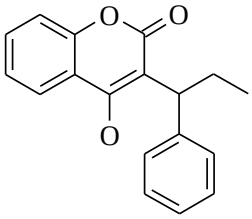
INTRODUCTION
The synthesis of coumarins and their derivatives has attracted considerable attention from organic and medicinal chemists for many years as a large number of natural products contain this heterocyclic nucleus. They are widely used as additives in food, perfumes, cosmetics, pharmaceuticals (O'Kennedy and Thornes, 1997) and optical brighteners (Zabradnik**,** 1992) and dispersed fluorescent and laser dyes (Murray *et al.*, 1982). Among the various substituted coumarins, 3-(benzyl)-substituted 4-hydroxycoumarins represents a significant class of compounds as biologically active compounds (Figure 1) (Raj *et al.*, 1994; Hadler and Shadbolt, 1975) and useful scaffolds, which can be used for the synthesis of 3,4-substituted compounds (Dittmer, 2005; Kalinin and Snieckus, 1998; Kalinin *et al.*, 1998; *Davis et al.*,1997).



Warfarin



Coumatetralyl



Phenprocoumon

Figure 1

Multicomponent reactions (MCRs) have emerged as a vital field of chemistry and a powerful tool in modern synthetic organic chemistry, allowing the facile synthesis of complicated compounds in a one-pot reaction without the isolation of any intermediates. Clearly, for multi-step synthetic procedures the number of reaction and purification steps is among the most important criteria for the efficiency and practicability of the process and should be as low as possible. Therefore, it has drawn the attraction of organic chemists to develop novel MCRs for a broad range of products (Domling and Ugi, 2000). Recently, heterogeneous catalysts have attracted the attention of researchers due to their economic and industrial significance and published reports indicate that they scored over homogeneous catalysts. Among these, nanoscale heterogeneous catalysts are highly preferred as they offer high surface area and

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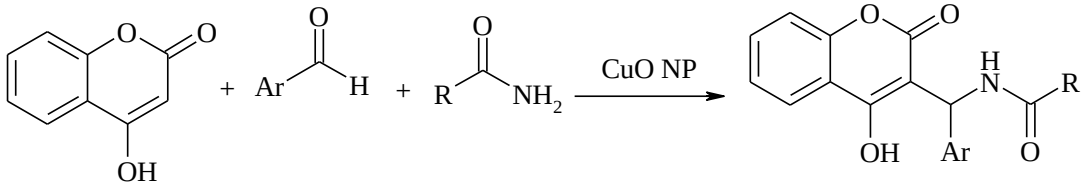
low-coordinated sites, which are responsible for the higher catalytic activity (Pacchioni, 2000; Knight *et al.*, 1984; Gribble, 1996), having the advantage of easy product purification and reusability of the catalyst. Recently, we reported the reaction of 4-hydroxycoumarin, aromatic aldehydes, and acetonitrile in the presence of chlorosulfonic acid to produce 3-acetamido-alkyl-4-hydroxycoumarin derivatives (Anary-Abbasinejad *et al.*, 2007; Anary-Abbasinejad *et al.*, 2008). also we reported the reaction of 4-hydroxycoumarin, aromatic aldehydes and amides in the presence *p*-toluene sulfonic acid in solvent-free conditions to produce 3-(α-amidobenzyl)-4-hydroxycoumarin derivatives (Malekpour *et al.*, 2012), but these methodologies have been associated with some shortcomings such as long reaction times, and difficulty in recovery and reusability of the catalysts. One of the best ways to overcome these difficulties is to employ heterogeneous catalysis, as it enables a convenient recovery and reuse of the catalyst from the reaction mixture through simple filtration or decantation (Kantam *et al.*, 2006; Islam *et al.*, 2011; Bermudez *et al.*, 2013). Considering the above reports and in continuation of our research on multi-component reactions (Anaraki-Ardakani *et al.*, 2012; Anaraki-Ardakani *et al.*, 2012), Herein we have researched for three-component coupling of 4-hydroxycoumarin 1, aryl aldehydes **2**, and amides **3**, in the presence of CuO nanoparticles as heterogeneous catalyst to the synthesis of 3-Amido-alkyl-4-Hydroxycoumarin Derivatives **4** (Scheme 1).



1 **2** **3** **4**

Scheme 1

RESULTS AND DISCUSSION

Firstly, in order to optimize the reaction conditions, the model reaction was carried out by using 4-hydroxycoumarin, 4-chlorobenzaldehyde, and acetamide under solvent-free conditions in the presence of different nanoparticle as catalysts and the results are listed in Table 1 (Scheme 2).

Table 1: Optimization of the nanoparticles catalysed model reaction for synthesis of 3-acetamido-4-chlorophenyl -4-hydroxycoumarin under solvent-free condition [a]

Entry	Catalyst	Catalyst (mol%)	Time(h)	Yield[b] (%)
1	Non	30	7	trace
2	NiO	30	5	30
3	Fe_3O_4	30	5	40
4	MgO	30	5	45
5	CuO bulk	30	5	50
6	CuO	30	3	85

[a] Reaction conditions: 4-hydroxy coumarin (1.0 mmol), acetamide (1.1 mmol), 4-chlorobenzaldehyde (1.0 mmol), neat 130 °C.
[b] Isolated yield

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We examined this reaction in the presence of various nanoparticle catalysts in hand including Fe_3O_4 nanoparticles, MgO nanoparticles, NiO nanoparticles, CuO nanoparticles (Table 1). It was showed that CuO nanoparticle was the most efficient catalyst for the reaction in Solvent-Free condition (Table 1, entry 6). However, only a trace amount of the product was formed in the absence of catalyst (Table 1, entry 1). Afterward, optimization of catalyst amounts was carried out in the model study by using different amounts of the CuO NPs. The higher yield was obtained with increasing the amount of catalyst from 10 mol% to 30 mol%. However, further increase of the molar amount of the catalyst from 30 mol% to 40 mol% did not significantly increase the yield of the product (Figure 2). Hence, the optimum concentration of CuO NPs was chosen 30 mol% in the model reaction.

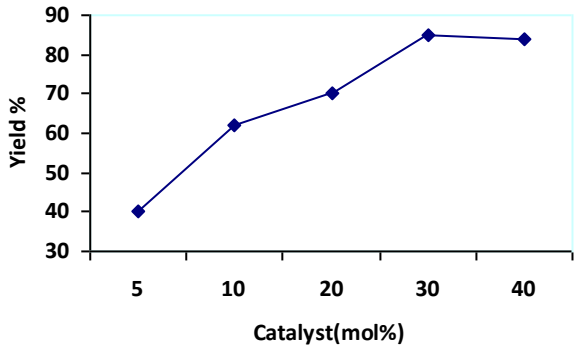

Figure 2: Influence of the amount of the catalyst on the model reaction

To improve the yield of the target product, we carried out the test reaction in presence of various solvents and the results are presented in Table 2.
As can be seen from this table, solvent- free conditions accelerated the rate of reaction and also high yields were obtained for all products.

Table 2: Solvent effect on the reaction between 4-hydroxycoumarin (1eq), 4-chlorobenzaldehyde (1 eq) and acetamide(1 eq) catalyzed by CuO(30mol%)

Entry	Solvent	Temp(^{0}C)	Time(h)	Yield(%)
1	Ethanol	Reflux	5	50
2	Dichloromethane	Reflux	5	45
3	1,2 Dicholoroehane	Reflux	5	50
4	THF	Reflux	5	60
5	Toluene	Reflux	5	55
6	Solvent- free condition	130	3	85

To study the scope of the reaction, a series of aldehydes and amides were employed. The results are shown in Table 3. In all cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in good yields. It could also be concluded that the aldehydes bearing electron-withdrawing groups required shorter time and gave higher yields (Table 3).

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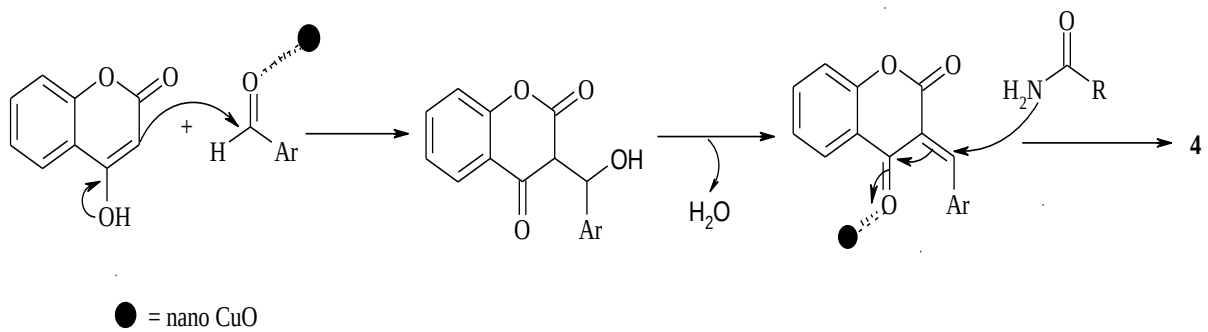
Compounds **4a-j** were known and their structures were deduced by comparison of melting points and spectral data with authentic samples (Anary-Abbasinejad *et al.,* 2007; Anary-Abbasinejad *et al.,* 2008; Malekpour *et al.,* 2012).

Table 3: Three-component reaction of aromatic aldehydes, 4-hydroxycoumarin and amides catalyzed by CuO NP

Entry	R	Ar	Time(min)	Yield(%)	mp (°C)[lit]
4a	CH_3	4-Cl-C_6H_4	180	85	177-179(175-177)[14-15]
4b	CH_3	2-Cl-C_6H_4	180	80	209(208-210)[14-15]
4c	CH_3	4-Br-C_6H_4	185	82	174(172-174)[14-15]
4d	CH_3	C_6H_5	190	80	183(184-186)[14-15]
4e	CH_3	4-NO_2-C_6H_4	180	85	179-183(179-182)[14-15]
4f	CH_3	3-NO_2-C_6H_4	185	82	193-195(195-196)[14-15]
4g	CH_3	3-CH_3O-C_6H_4	195	76	202-204(203-206)[14-15]
4h	CH_3	2-CH_3O-C_6H_4	190	75	192(190-191)[14-15]
4i	CH_3	2-HO-C_6H_4	180	80	146-147(146-148)[14-15]
4j	C_2H_5	C_6H_5	185	78	185(184-186)[16]

Although it is not clear how CuO acts as a catalyst for the reaction, on the basis of the surface of metal oxides exhibit both Lewis acid and Lewis base character (Tanabe, 1970), and according to the literature survey (Azarifar and Yami , 2010; Shaterian and Moradi 2013; Shaterian and Azizi 2013), the suggested mechanism for the formation of the products is shown in Scheme 2. The reaction of 4-hydroxycoumarin with aromatic aldehydes in the presence of CuO NPs catalyst is proposed to give 3-benzylidine-chroman-2,4-diones. These 3-benzylidine-chroman-2,4-diones, generated *in situ*, react with amide to form the 3-acetamido -alkyl-4-hydroxycoumarin products (Scheme 3)



Scheme 3: Suggested pathway for the formation of compounds 4a-j

The reusability of the catalyst was tested in the synthesis of 3-acetamido-alkyl-4-hydroxycoumarin derivatives, as shown in Figure 2. The catalyst was recovered after each run, washed with ethanol, dried in an oven at 100 °C for 20 min prior to use and tested for its activity in the subsequent run. The catalyst was tested for 3 runs. It was seen that the catalyst displayed very good reusability (Figure 3).

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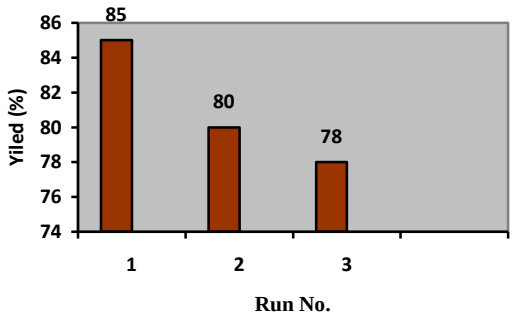

Figure 3: Reusability of the catalyst

In summary, we have described a simple, efficient, and environmentally benign one-pot procedure for the synthesis of 3-acetamido-alkyl-4-hydroxycoumarin derivatives by using catalytic amount of CuO-NPs under solvent-free conditions. The advantages of the reported method are inexpensive and easily available starting materials, simple reaction conditions, low loading of catalyst, safety and reusability of catalyst, high yields, single-product reaction and simple workup procedure.

Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at in DMSO-d_6 solution using TMS as internal standard. The chemicals used in this work purchased from fluka (Buchs, Switzerland) and were used without further purification.

Synthesis of nano-CuO

Copper oxide nanoparticles were prepared as previously described in the literature (Kantam *et al.*, 2008; Diego *et al.*, 2009).

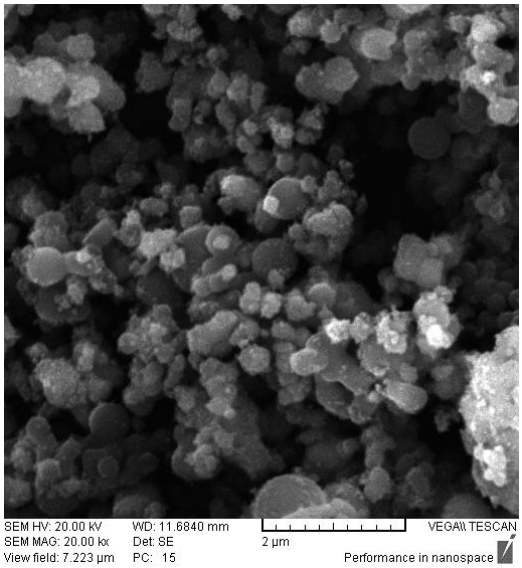

Figure 4: SEM image of synthesized CuO nanoparticles

In a typical procedure Solution of NaOH (100 mL, 0.1 mol/L) was added to solution of $Cu(CH_3COO)_2{}^{-}2H_2O$ (0.1 mol/L) in ethanol/ water. The obtained mixtures were sonicated for 30 min

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with 30 W ultrasound power. To investigate the role of surfactants on the size and morphology of nanoparticles, we used 1 g of polyvinyl alcohol (PVA) in the reaction. The morphology, structure and size of the samples were investigated by Scanning Electron Microscopy (SEM). Figure 4 indicates that the original morphology of the particle was approximately spherical with the diameter varying between35 and 103 nm.

General Procedure

A mixture of 4-hydroxycoumarin (1.0 mmol), aromatic aldehyde (1.0 mmol), amide (1.0 mmol), and nano-CuO (30 mol %) was heated at 130 ºC for 180-195 min. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature. The solid residue was dissolved in hot ethanol and centrifuged to separate the catalyst. By recrystallization from ethanol, pure products were obtained.

N-[(4-Hydroxy-2-oxo-2H-chromen-3-yl)phenylmethyl propionamide **(4j).** white powder, m.p. 184 - 186°C, IR (KBr) (ν_{max} cm^{-1}): 3320 (NH), 1674, 1629 (2 C=O). Analyses: Calcd. for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33%. Found: C, 70.71; H, 5.22; N, 4.35%. MS (m/z, %): 323 (10). ^{1}H NMR (500 MHz, d_6-DMSO): δ = 0.91 (t, J_{HH} = 7.6 Hz, 3 H, CH_3), 2.27 (q, J_{HH} = 7.6 Hz, 2 H, CH_2), 6.58 (1 H, d, J_{HH} = 8.8 Hz, C*H*), 7.20 (1 H, t, J_{HH} = 7 Hz, C*H* of C_6H_5), 7.26-7.31 (4 H, m, 4 C*H* of C_6H_5), 7.36-7.41 (2 H, m, 2 C*H* of coumarin moiety), 7.65 (1 H, t, J_{HH} = 8 Hz, C*H* of coumarin moiety), 8.05 (1 H, d, J_{HH} = 8 Hz, C*H* of coumarin moiety), 8.38 (1 H, d, J_{HH} = 8.8 Hz, N*H*), 10.15(1 H, broad, OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ = 10.16 (CH_3), 28.69 (CH_2), 47.39 (*C*H), 106.69, 116.62, 116.77, 124.29, 124.50, 126.98, 152.82, 161.99, and 162.30 (carbons of coumarin moiety), 126.49, 128.17,132.87 and 141.07 (carbons of C_6H_5), 174.21 (N*C*=O).

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