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**RESEARCH ARTICLE**

# CARBON MICROSPHERE SUPPORTED COPPER NANOPARTICLES (CU-NP/C) IS A HIGHLY EFFICIENT CATALYST FOR THE SYNTHESIS OF CHROMENO [4,3-B] CHROMENE DERIVATIVES

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## ABSTRACT

Cu-NP/Chave been effectively used as catalyst for the synthesis of novel chromeno [4,3-b] chromene derivatives. Herein, a novel and convenient protocol have been developed for the synthesis Chromeno-chromene derivatives via multicomponent one pot reaction. We describe a one-pot three-component synthesis of novel derivatives starting from substituted salicylaldehyde, 4-hydroxy coumarin and indole/ barbituric acid using Cu-NP/C as an efficient catalyst at ambient temperature condition in ethyl alcohol with good yield.



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# INTRODUCTION

Multicomponent reactions (MCR) offer notable advantages in terms of normal linear-step synthesis, simplified workup procedures and purification, short reaction times, and savings in energy and raw material consumption. Thus, MCR provide both economic and environmental benefits.[1,2] Heterogeneous catalysts constitute the heart core of synthetic organic chemistry due to easily separable and reusable make chemical processes economically viable.[3]As of the efficiency of heterogeneous catalyst to catalyse organic transformations, have been focused as intense research area. Heterogeneous catalysts, via MCR approaches for the synthesis of bioactive heterocyclic compounds contribute for the design and development of environmentally benign synthetic routes.The heterogeneous catalysts including metals, metal oxides, fluorides, clays and hybrid materials are mostly used and developed for organic transformations. Nanoparticles constitute the attractive candidates as catalysts due to small size and a large surface to volume ratio as compared to bulk materials. A significant feature of Nano catalyst is its selectivity, high activity, low energy consumption and sustainable life. Widely, medicinally and pharmaceutically significant target molecules have been synthesized by catalysing Nanoparticles of metals, oxides and composites. During the past decade, due to the particle size, shape, spatial distribution, surface composition and thermal as well as the chemical stability of nanoparticles the arena of Nano-catalysis has been enormously increases. Nano-catalysts provide new opportunities, challenges and a wide-ranging plat-form for the design and development of novel routes in synthetic organic chemistry. Nowadays the development of catalytic NPs is highly desirable which are inexpensive, non-poisonous, highly active, selective, robust and easily separable from the reaction mixture.[4] Many coumarin-containing compounds are known to exhibit medically useful properties including anti-HIV, anticancer, antifungal, antibacterial, and anticoagulant activities.[5–10]Phenprocoumon, for example, is a competitive HIV-1 PR inhibitor and has served as a lead compound in the design of nonpeptide inhibitors.[11–16]

A range of methods has been reported for the synthesis of coumarin derivatives including a one-pot, three-component condensation of 4-hydroxycoumarin, aldehydes, and Meldrum's acid, malononitrile or α-cyanocinnamonitrile in the presence of [bmim]OH,[17] HPAs,[18] MGT,[19] MgO,[20]DAHP,[21]TBAB,[22] DBU,[23]$KAl(SO4)_2 \cdot 12H_2O$,[24] $[DMDBSI] \cdot 2HSO_4$,[25] piperidine,[26] or $InCl_3$,[27] and L-proline.[28]These methods have their merits but are often applied to the synthesis of only a narrow range of coumarin derivatives and may necessitate using an expensive catalyst, forcing conditions, and long reaction times or result in low yields and poor selectivity. The present article,copper–based nano catalyst is applied efficiently for the synthesis of biologically significant chromeno [ 4,3-b] chromenes. In this context, we present herein a one-pot multicomponent protocol for the synthesis of chromeno-chromene derivatives by the reaction of 4-hydroxycoumarin, substituted salicylaldehydes, and indole catalysed by copper-based nano catalyst.

**Table 1. Optimization of catalyst and solvent for the synthesis of 9, 11-dibromo-7-(1H-indol-3-yl)-6H,7H-chromeno [4,3-b] chromen-6-one[a]**

| Entry | Catalyst | Catalyst (mol %) | Solvent | Time(hrs) | Yield (%) |
|---|---|---|---|---|---|
| 1 | - | 10 | EtOH | 23 | 45 |
| 2 | $I_2$ | 10 | $H_2O$ | 21 | 42 |
| 3 | $ZnCl_2$ | 10 | DMF | 16 | 53 |
| 4 | $InCl_3$ | 10 | EtOH | 17 | 56 |
| 5 | $Sc(OTf)_3$ | 10 | EtOH | 16 | 50 |
| 6 | Ru(II)/PEG-400 | 10 | - | 14 | 65 |
| 7 | Cu-NP/C | 10 | EtOH | 3 | 96 |
| 8 | Cu-NP/C | 15 | EtOH | 5 | 88 |
| 9 | Cu-NP/C | 20 | EtOH | 8 | 76 |
| 10 | Cu-NP/C | 10 | Tolune | 12 | 59 |
| 11 | Cu-NP/C | 10 | DCM | 18 | 62 |
| 12 | Cu-NP/C | 10 | DMF | 15 | 40 |

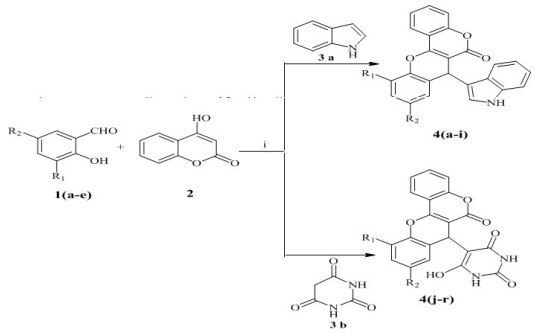
[a]Conditions: 3,5-Dibromo saliycylaldehyde (1 mmol), 4-hydroxy coumarin (1 mmol), indole (1mmol) and solvent (15 mL) on reflux with stirring.The progress of reaction was monitored by thin layer chromatography.

Table 2. Exploration of the substrate scope for the synthesis of chromeno-chromenones

| Entry | Reactant 3 | $R_1$ | $R_2$ | Time (hrs) | Product | M.P. $^oC$ | Yield[a]% |
|---|---|---|---|---|---|---|---|
| 1 | Indole | H | H | 14 | 4a | 270 | 90 |
| 2 | Indole | H | Br | 13.5 | 4b | 277 | 87 |
| 3 | Indole | Br | Br | 12 | 4c | 280 | 96 |
| 4 | Indole | H | Cl | 13 | 4d | 268 | 83 |
| 5 | Indole | I | Cl | 12 | 4e | 272 | 80 |
| 6 | Indole | I | I | 12.5 | 4f | 275 | 91 |
| 7 | Indole | I | Br | 14 | 4g | 282 | 87 |
| 8 | Indole | H | $NO_2$ | 12 | 4h | 265 | 89 |
| 9 | Indole | H | $OCH_3$ | 13 | 4i | 262 | 86 |
| 10 | Barbituric acid | H | H | 14 | 4j | 285 | 89 |
| 11 | Barbituric acid | H | Br | 12 | 4k | 290 | 88 |
| 12 | Barbituric acid | Br | Br | 12.5 | 4l | 292 | 92 |
| 13 | Barbituric acid | H | Cl | 13 | 4m | 286 | 89 |
| 14 | Barbituric acid | I | Cl | 12 | 4n | 288 | 85 |
| 15 | Barbituric acid | I | I | 14 | 4o | 274 | 88 |
| 16 | Barbituric acid | I | Br | 13.5 | 4p | 281 | 85 |
| 17 | Barbituric acid | H | $NO_2$ | 12.5 | 4q | 282 | 86 |
| 18 | Barbituric acid | H | $OCH_3$ | 12 | 4r | 284 | 85 |

[a]Isolated yields

**Present work**




**Scheme 1.** ***Reagent and conditions*****: i) Cu-based NPs, EtOH, reflux, 3-4hrs, 80-96%**

# RESULT AND DISCUSSION

As a prototype, the reaction of 4-hydroxycoumarin, substituted salicylaldehyde, and indole (Scheme 1) was studied under different catalytic conditions summarized in Table 1. It was found that Cu-NP/C was the most efficient catalyst compared with $I_2$, ZnCl2, $InCl_3$, $Sc(OTf)_3$, and Ru(II)/PEG-400, which exhibited from moderate to poor catalytic properties (Table 1). The results showed that a 10% mol amount was sufficient to promote the reaction and larger amounts of the catalyst did not lead to any significant changes in the reaction yield. Also we studied the model reaction catalyzed Cu-NP/C in different solvent. Different organic solvents, such as DMF, DCM, and toluene were used, which afforded 4c in moderate yields (Table 1).

We extremely expected the reaction to perform in EtOH media, the result was satisfactory (Table 1). EtOH was a better solvent than the others were tested. The yields increased, as the solvent was EtOH. When reaction was carried out in EtOH on reflux, the good yield could be obtained in a short time as compared to other mentioned conditions. Finally, it should be mentioned that when the reactions were carried out without catalyst, almost no conversion occurred. With this optimized procedure in hand, a range of chromeno[4,3-b] chromenonederivativeswere synthesized by the one-pot condensation of substituted salicylaldehyde ,4-hydroxy coumarin and Indole/ barbituric acid. The reaction preceded about 3 hrs in excellent yields at reflux after the addition of the catalyst Cu-NP/C (see Table2). Various substituted salicylaldehydes with the both electron donating and withdrawing groups have been used. The electron-donating group on salicylaldehydes resulted in excellent yields. However, good yields are obtained for salicylaldehyde with electron withdrawing groups (Table 2).

## Experimental

**General details:** All solvents were used as commercial anhydrous grade without further purification. Aluminium sheets 20 x 20cm, Silica gel 60 $F_{254,}$Merckgradewas used for thin layer chromatography to determine progress of reaction. Melting points were determined in open capillary tube and are uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded on a Brucker AV-300 MHz spectrometer in $CDCl_3$ solvent. Mass spectra were taken on Polaris-Q Thermoscintific GC-MS.

**General procedure for synthesis of Chromeno-chromenonederivatives:** A mixture of salicylaldehyde (1 mmol), 4-hydroxycoumarin (1 mmol) and Cu-NP/C (0.1 mmol) in solvent ethanol (5 mL) was refluxed for 1hours. Then indole (1mmol)/

barbituric acid (1mmol) was added to the reaction mixture and continuously reflux with stirring for further 2-3 hours to get pure crystals (monitored by TLC). It was filtered washed with ethanol then with water to afford analytically pure product.

**Synthesis of Cu-NP/C Catalyst:** A styrene-based commercial cation exchange resin containing divinylbenzene crosslinker (7%), acrylonitrile modifier (2%) and iminodiacetate (-$CH_2N$ ($CH_2COOH)_2$) functional groups (binding capacity of 1mol divalent metal cation per 1 $dm^3$ resin, VARION BIM-7) was used as the starting material. Initially, the resin was saturated with copper(II) ions using an aqueous copper sulphatesolution. The exchanged resin was dried in air followed by in a drying box at 120ºC for 1 day. The dried resin was carbonized at 600ºC for 4 h in a high purity dry nitrogen stream. More details of the carbonization process are provided in previous paper.[29-30]

**Characterization of some representative compounds: 9,11-dibromo-7-(1H-indol-3-yl)-6H, 7H-chromeno [4,3-b] chromen-6-one (4c):** Brownish solid, Yield-90%, M.P. =280°C. IR($cm^{-1}$):3410, 2900, 2350, 2300, 1700, 1600, 1550, 1450, 1400, 1300, 1210, 1150,900, 750, 700.$^1$H NMR (300 MHz, $CDCl_3$): δ 10.29(s 1H,NH), 8.23(d, 1H), 8.03(d, 1H), 7.67(t, 2H), 7.48(m,3H), 7.32(t,1H), 7.21(d,2H), 5.31(s,1H).$^{13}$C-NMR (300MHz, $CDCl_3$): δ164.53, 158.62, 151.25, 149.00, 147.63, 141.00, 140.87, 135.00, 133.39, 132.52, 130.43, 25.55, 125.06, 124.62, 124.25, 123.87, 117.93, 117.13, 116.57, 111.82, 105.03, 104.00, 103.80,30.47.GC-MS:*m/z* 523 ($M^+$)

**9-bromo,11-iodo-7-(1H-indol-3-yl)-6H, 7H-chromeno [4, 3-b] chromen-6-one (4g):** Brownish solid, Yield-85%M.P. = 282°C.IR($cm^{-1}$): 3300, 2910, 2870, 1700, 1610, 1490, 1395, 1210, 1050, 850, 820, 710, 600.$^1$H NMR (300 MHz, $CDCl_3$): δ 10.38 (s, 1H, NH), 8.14 (dd,1H),8.02(dd,1H), 7.65(m,1H),7.55(m,1H),7.52(m,1H),7.49(m,1H),7.41(m,2H), .34(d,1H), 7.24(s,1H), 7.12(s,1H).$^{13}$C-NMR (300 MHz, $CDCl_3$): δ 166.00, 157.12, 153.00, 149.00, 146.00, 143.50, 136.00, 135.39, 134.42, 130.52, 126.85, 125.06, 124.32, 124.25, 124.00, 117.91, 117.12, 116.51, 111.00, 106.00, 101.52,100.00, 31.00.GC-MS:*m/z* 570($M^+$).

**5-(9-chloro-6-oxo-6H,7H-chromeno [4,3-b] chromen-7-yl)-6-hydroxypyrimidine, 4(1H, 3H)-dione (4m):** Brownish solid, Yield-89%, M.P. = 286ºC.IR($cm^{-1}$): 3600, 3420, 3380, 2996, 2817, 1702, 1663, 1611, 1566, 1452, 1400, 1215, 1168, 786, 530.$^1$HNMR (400 MHz, DMSO): 12.87(s,1H,OH), 9.89 (s,1H,NH),8.04(d,1H) , 7.85(s,1H), 7.60(s,1H), 7.49(t,1H), 7.29(t,2H), 7.18(d,1H), 6.81(s,1H,NH), 5.73 (s,1H).$^{13}$C-NMR (300 MHz, $CDCl_3$): δ167.08, 165.76, 163.80, 161.00, 154.29, 152.42, 150.80, 132.36, 131.10, 129.00, 127.63, 127.23, 125.72, 125.12, 120.00, 117.49, 117.12, 115.12, 110.00, 81.50, 29.24.GC-MS: m/z = 410 ($M^+$).

# CONCLUSION

In conclusion, we have reported an easy and efficient protocol for the one-pot synthesis of chromeno [4,3-b] using environmentally benign MCR approach in ethanol as the green solvent. The use of Cu-NP/C catalyst offers several advantages including operational simplicity, environmental friendliness, high yield, reusability of catalyst and green chemical transformation. This method not only provides an excellent harmonize to substituted quinoxaline but also avoids the use of hazardous acids or bases and harsh reaction conditions.

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