



Original Research Article

Pseudo-three component reaction of indole with benzaldehyde derivatives for the preparation of bis(indolyl)methanes in the presence of nano-CuO-CeO₂

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ARTICLE INFORMATION

Received: 23 March 2021

Received in revised: 18 May 2021

Accepted: 7 June 2021

Available online: 3 October 2021

DOI: 10.22034/ajgc.2021.288567.1304

KEYWORDS

Nano

Recyclable

Bis(indolyl)methanes

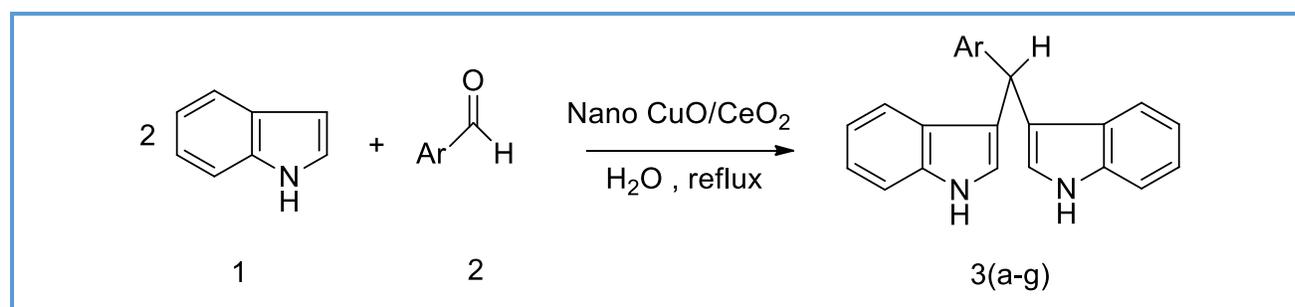
CuO-CeO₂

ABSTRACT

In this research study, a nano-CuO-CeO₂ catalyzed environmentally benign strategy for the preparation of bis(indolyl)methane derivatives via the three-component reaction between indoles and aldehyde in aqueous media under reflux conditions in excellent yields was established. The structure of the prepared compounds was confirmed using IR, ¹H-NMR. The elemental analysis and morphology of the catalyst was characterized using transmission electron microscopy (TEM) and scanning electron microscopy (SEM). The results revealed that this synthetic reaction is very simple and bis(indolyl)methane derivatives produced with good yields compared to other articles. The advantages of this method include catalyst recovery, high efficiency, and easy operation method. The highest efficiency (96%) in a short time (15 min) was obtained, which is very important compared to other previous methods presented.

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Graphical Abstract



Introduction

Bis(indolyl)methane derivatives are used as important mediators for the synthesis of organic compounds and medicinal chemistry and have a lot of medicinal, antimicrobial and physiological properties [1, 2]. In the structure of many natural compounds, the indole ring is found as an important heterocyclic compound.

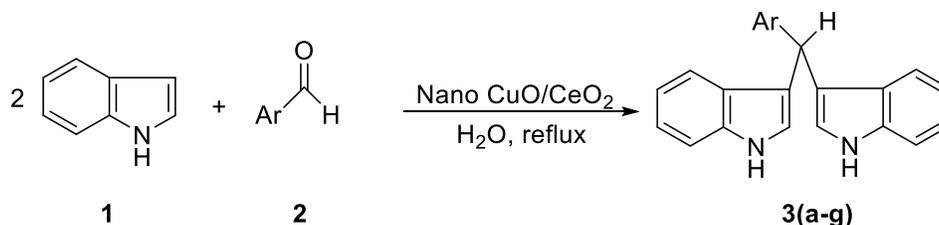
Tenidap and indomethacin are derivatives of indole that exhibit anti-inflammatory, febrile and analgesic activity. By inhibiting cyclooxygenase (COX), they prevent the production of eicosanoids, thereby reducing pain.

Bis(indole)methane is found in cruciferous plants and has been shown to boost estrogen metabolism and help heal human cancer cells [3]. In recent years, indole methane has received much attention [4]. These compounds have an interesting biological activity and are used as antibacterials and to prevent breast cancer [5, 6]. Bis(indole)methane are effective in replicating and inducing apoptosis in human prostate cancer cells [7, 8]. Bis(indole)methane also has several useful biological activities,

including antipyretic, anti-inflammatory, antifungal, antimicrobial, cardiovascular and anticonvulsant [9]. Therefore, synthesis of bis(indolyl)methanes is of a great importance for organic chemists due to their high pharmacological and biological activities. There are several procedures for the synthesis of bis(indolyl)methanes, which can be single-stage or multi-stage. In most methods of preparing of bis(indolyl)methanes, carbonyl compounds and indoles have been used using Lewis acids [10] and protic acids [11].

Nanocatalyst and nanomagnetic catalysts are widely used in organic synthesis today [12-17]. In this study, we used a nano-CuO-CeO₂ catalyst for the synthesis of bis(indolyl)methanes.

As a part of our work on multicomponent reactions (MCRs) and developing new methodologies for the synthesis of various heterocyclic compounds, and in continuation of our research on the use of water as solvent, we are going to introduce nano-CuO-CeO₂ as a suitable catalyst for the synthesis of bis(indolyl) methanes at ambient conditions (Scheme 1).



Scheme 1.

Results and Discussion

We have established a one-pot reaction of various aldehydes with malononitrile and indole in water in the presence of nano-CuO-CeO₂ as available, green, and inexpensive catalyst in good yields for synthesizing of bis(indolyl)methanes (Table 1).

After optimizing the reaction conditions, different aldehydes, both with electron donating and electron withdrawing groups were investigated for the present protocol. It can be clearly seen from data that, all reactions proceeded were performed well and produced the corresponding products in good yields and in very short reaction times (Table 1).

We evaluated the synthesis of compound **3a** in the presence of different solvents to compare the effects of the solvent on the reaction. As you can see in the Table 2, the best efficiency and the shortest time were obtained in water (Table 2).

The reaction was investigated with different amounts of nano-CuO-CeO₂. In all cases, with 0.05 g catalyst, the maximum yield of products was obtained and using more catalysts has no effect on the reaction efficiency (Table 3).

Table 1. Nano-CuO-CeO₂ catalyzed the preparation of bis(indolyl)methanes

Entry	Ar	Product	Time (min)	Mp (°C)		Yield (%) ^a
				Observed	Reported ¹⁸	
1	Ph	3a	15	124-125	125-126	96
2	4-Me-Ph	3b	15	95-97	94-96	92
3	4-Cl-Ph	3c	15	76-77	77-79	97
4	4-OH-Ph	3d	15	121-123	120-122	93
5	3-NO ₂ -Ph	3e	15	217-219	215-217	97
6	4-MeO-Ph	3f	15	188-190	187-189	93
7	4-NO ₂ -Ph	3g	15	226-228	229-230	97

^aIsolated yields

Table 2. Synthesis of **3a** using different solvents

Entry	Solvent	Yield (%) ^a
1	THF	68
2	C ₂ H ₅ OH	87
3	CH ₃ CN	90
4	EtOAc	88
5	water	96

^aYields were analyzed by GC

Table 3. Preparation of **3a** using various amount of nano-CuO-CeO₂

Entry	nano-CuO-CeO ₂ (g)	Time (min)	Yield (%) ^a
1	No catalyst	24h	No reaction
2	0.02	50	88
3	0.03	50	90
4	0.05	50	96
5	0.08	50	96

^aYield of isolated products

After the reaction, 10 mL of ethyl acetate was added to the compounds on filter paper containing catalyst. The mixture was stirred at room temperature for 5 min using a magnetic stirrer. The reaction mixture was filtered, and the catalyst remained on filter paper due to its insolubility in ethyl acetate solvent. Then, to reuse the catalyst, the filter material was washed several times with acetone. After drying, the reaction was repeated to check the

potency of the catalyst (Table 4). As seen in Table 4, the reaction can be performed up to five times with good efficiency by the recycled catalyst.

By comparing the reaction results with other methods, we find that the nano-CuO-CeO₂ catalyst performs the reaction in shorter time (15 min) and with higher efficiency (96%) (Table 5).

Table 4. Comparison of catalyst recycling for synthesis of **3a**

Entry	Time(min)	Yield (%) ^a
First run	15	96
Second run	15	94
Third run	15	92
Fourth run	15	89
Fifth run	15	88

^aIsolated yields**Table 5.** Comparison of various catalysts for the synthesis of **3a**

Entry	Catalyst	Solvent	Time (min)	Yield (%)	Reference
1	TiO ₂	Solvent Free	3 Hour	92	[19]
2	ALPW ₁₂ O ₄₀	Solvent Free	30	91	[20]
3	Zr(DS) ₄	Water environment	20	92	[21]
4	15-ZTPA	Solvent Free	45	84	[22]
5	ZrOCl ₂	Acetonitrile	20	90	[23]
6	TBATB	Methanol	35	85	[24]
7	Zeokarb-225	Acetonitrile	8/5 Hour	70	[25]
8	Nano-CeO ₂	CH ₃ Cl	20	95	[26]
9	Nano-CuO-CeO ₂	water	15	96	This Research

Experimental

Materials and methods

Chemicals were purchased from the Merck (Darmstadt, Germany) and Sigma-Aldrich chemical Co. All products were characterized using spectra and physical data. Characterizations were carried out using the Melting points(Electrothermal 9100), ¹H NMR(Bruker 500 MHz), TEM (HRTEM, TF 20 Tecnai G2 200 kV FEI), Fourier transform infrared (model Nexus-870, Nicolet Instrument), thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel.

Preparation of Bis(indolyl)methanes, typical procedure

A mixture of indole (2 mmol), aldehyde (1 mmol) and nano-CuO-CeO₂ (0.05 g) in water (5 mL) was refluxed. After completion of the reaction, as indicated by TLC, the reaction mixture is cooled, and the precipitate is

filtrated. The precipitate was recrystallized in ethanol.

3g: IR (KBr) (ν_{\max} / cm⁻¹): 3463, 1642, 1509, 1458, 1416, 1345, 1108, and 749. ¹H NMR (400 MHz, DMSO): δ 10.93 (s, 2H), 8.17 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.39(d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 7.09 (t, *J* = 7.5 Hz, 2H), 6.97–6.79 (m, 4H), 6.07 (s, 1H). ¹³C NMR (100 MHz, DMSO): δ 153.5, 146.3, 137.1, 129.9, 124.3, 123.9, 121.6, 119.3, 118.9, 112.0, 40.6, 40.4, 40.2, 40.0, 39.8, 39.6, 39.4.

3b: IR (KBr) (ν_{\max} / cm⁻¹): 3411, 3063, 2967, 1609, 1505, 1459, 1219, 1093, and 737. ¹H NMR (400 MHz, DMSO): δ 2.39 (s, 3H), 5.96 (s, 1H), 6.82 (s, 2H), 7.07-7.59 (m, 12H, Ar-H), 8.07 (br s, 2H, NH). ¹³C NMR (100 MHz, DMSO): δ 143.9, 137.8, 136.7, 128.6, 128.1, 125.4, 122.5, 121.5, 119.3, 119.0, 110.9, 37.0.

Preparation of catalyst Nano-CuO/CeO₂

The mixture of Ce (NO₃)₃.6H₂O and Cu(NO₃)₂.3H₂O were dissolved in distilled water at equal molar ratios. Then, two times molar

PVP was added to the stirred mixture solution containing cerium and copper nitrate. The solution is heated in a water bath to obtain a viscous gel. In the process, the color of the mixture changed from blue to green. The

resulting gel is placed at 110 °C overnight. It is then calcined at 600 °C for 4 h [27]. The dimensions of nanoparticles were determined by SEM and TEM (Figures 1 and 2).

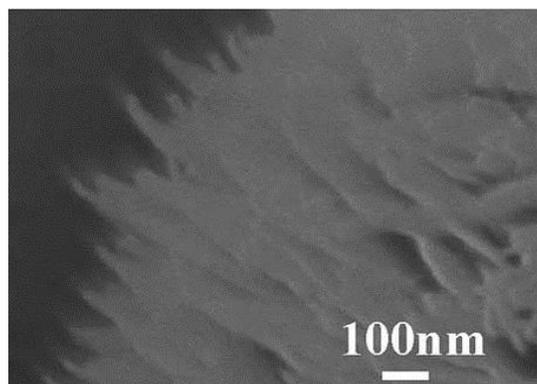


Figure 1. SEM spectra of nano-CuO/CeO₂

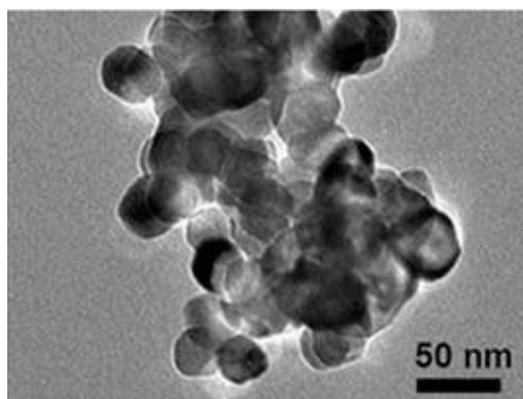


Figure 2. TEM Spectra of nano-CuO/CeO₂

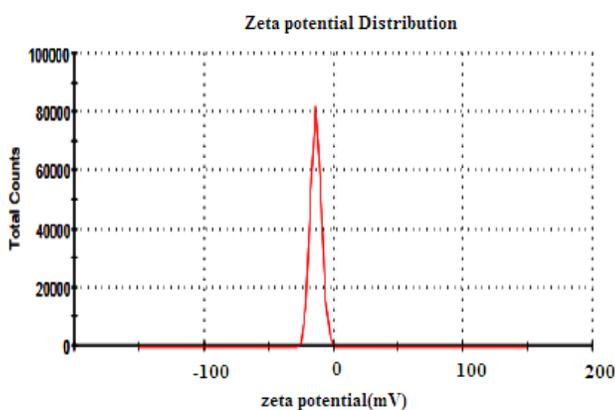


Figure 3. Zeta potential of nano-CuO/CeO₂

The zeta potential for the nano-CuO/CeO₂ was measured as -13.7 ± 1.55 at 25 °C (Figure 3). Zeta potential results were calculated by taking the average of the three measurements and standard deviation.

Thermal analysis (TGA/DTG)

The thermal analysis of bimetallic nitrate and the polymer (PVP) were carried out using thermogravimetric analysis technique (TGA) and differential thermal gravimetry technique (DTG), respectively. The analyses helped in identifying the calcination process's optimal temperature. Figure 4 presents the TG-DTA curves for the developed compound that comprised PVP (M.W.=29000 g/mL) bimetallic nitrate before the calcination process take place. Following completion of calcination process, two distinct weight losses were notified from the TGA curve. At the beginning, a weight loss of ~13% was recorded between the temperature range of 50 °C and 250 °C, which was believed to be caused by water loss. Other weight loss of about (~82%) was observed between the temperature range of 250 °C and 472 °C, which was believed to occur as a result

of inorganic and organic materials decomposition from nitrate salts and PVP, leading to the stable metal oxide formation [28]. Moreover, the DTG curve showed a three-stage weight loss, whose initial stage was characterised by trapping of moisture within the sample, appearing below 100 °C. At 297 °C, a small peak appeared, which was assumed to have been caused by the breakdown of NO_x compounds [29]. Majority of the PVP composition in the sample decomposed in the final stage, at a temperature of 440 °C, which is the temperature the maximum weight loss had occurred [30]. Very little weight loss change was observed at 492 °C this could be due to complete transformation undergone by the remaining PVP content into carbonaceous products [31]. Beyond 492 °C, there was no further weight loss observed as carbonaceous matter had been removed from the sample between the temperature range of 440 °C and 492 °C. After thermogravimetric analysis, there was a change in colour from light blue to crystalline gray, which suggested the formation of high-purity binary oxide nanoparticles [32].

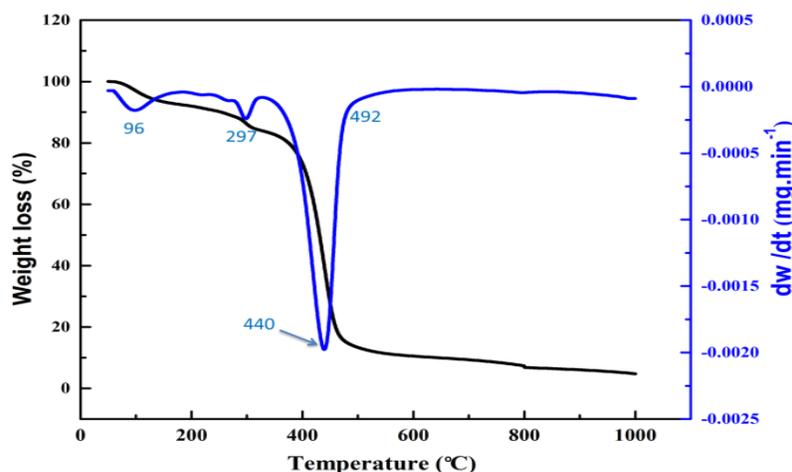


Figure 4. The TGA and DTG curves for copper nitrate and cerium nitrate with PVP at a heating rate 10 °C/min

Conclusions

In this study, we introduced a suitable and green method for to prepare bis(indolyl)methanes through the indole and aldehyde using nano-CuO-CeO₂ as a catalyst in water. This reaction has several advantages that can be explained using green water solvent, the use of a small amount of nano catalyst, catalyst recyclability, high efficiency and short reaction time. In this research study, nano-CuO-CeO₂ as an efficient catalyst was synthesized and characterized by SEM and TEM analysis. According to Table 5, you can see that the highest efficiency (96%) was obtained in a short time (15 minutes) in this study, which is much better and more useful compared to other previous methods. The results also demonstrated that, the best efficiency (95%) was obtained in the water as a solvent.

Disclosure Statement

No potential conflict of interest was reported by the authors.

References

- [1]. Bell R., Carmeli S., Sar N. *J. Nat. Prod.*, 1994, **57**:1587
- [2]. Sundburg R. *J. The chemistry of Indoles*. Academic Press, New York 1996
- [3]. Zeligs M.A. *J. Med. Food.* 1998, **1**:67
- [4]. Garbe T.R., Kobayashi M., Shimuju N., Takesue N., Ozawa M., Yukawa H. *J. Nat. Prod.*, 2000, **63**:596
- [5]. Michnovicz J.J., Bradlow H.L. *Proc. R. Soc. Edinburg*, 1989, **95**(B):1571
- [6]. Osawa T., Namiki M. *Tetrahedron Lett*, 1983, **24**:4719
- [7]. Hong C., Firestone G.L., Bjeldanes L.F., *Biochem. Pharmacol.*, 2002, **63**:1085
- [8]. Nachshon-Kedmi M.N., Yannai S., Haj A., Fares F.A. *Food. Chem. Toxicol.*, 2003, **41**:745
- [9]. Sujatha K., Perumal P.T., Muralidharan D., Rajendran M., *Ind. J. Chem.*, 2009, **48**(B):267
- [10]. Niknam K., Zolfigol M.A., Sadabadi T., Nejati A., *J. Iran. Chem. Soc.*, 2006, **3**:318
- [11]. Murugesan V., Cheralathan K.K., Karthik M. *Bull. Catal. Soc. Ind.*, 2004, **3**:23
- [12]. Karimirad F., Behbahani F.K. *Inorganic and Nano-Metal Chemistry*, 2020, **51**:656
- [13]. Hasanzade F., Behbahani F.K. *Russian Journal of Organic Chemistry*, 2020, **56**:1070
- [14]. Behbahani F.K., Rezaee E., Fakhroueian Z. *Catalysis Letters*, 2014, **144**:2184
- [15]. Biklarian H., Behbahani F.K., Fakhroueian Z. *Letters in Organic Chemistry*, 2012, **9**:580
- [16]. Behbahani F.K., Ziaei P., Fakhroueian Z., Doragi N. *Monatshefte für Chemie-Chemical Monthly*, 2011, **142**:901
- [17]. Behbahani F.K., Sasani M. *Journal of the Serbian Chemical Society*, 2012, **77**:1157
- [18]. Ri Sh., Sheng Q.Y., Wang Y., Ding X.L., Liu M., Cai Zh. *Catal. Lett.*, 2009, **28**:418
- [19]. Shaterian H.R., Ghashang M., Hassankhani A. *Dyes Pigments*, 2008, **76**:564
- [20]. Gong K., Fang D., Wang H.L., Zhou X.L., Lin Z.L. *Dyes Pigments*, 2009, **80**:30
- [21]. Rostamizadeh S., Amani A.M., Mahdavinia G.H., Shadjou N. *Chin. Chem. Lett.*, 2009, **20**:779
- [22]. Amini M.M., Fazaali Y., Yassae Z., Feizi S., Bazgir A. *Open. Catal. J.*, 2009, **92**:2940
- [23]. Hajipour A.R., Ghayeb Y., Sheikhan N., Ruoho A.E. *Synlett*, 2010, **5**:741
- [24]. Rahmati A. *Chin. Chem. Lett.* 2010, **21**, 761
- [25]. Jaber Z.K., Keshavarzi M. *Chin. Chem. Lett.*, 2010, **21**:547
- [26]. Patil D.V., Salve A., Gharat V.D., Gawand N., *Int. J. Hetero. Chem.*, 2019, **9**:11
- [27]. Muthuchudarkodi R.R., Kalaiarasi S. *J. Scienc. Research.*, 2016, **5**:543
- [28]. Mallakpour S. *Journal of Composite Materials*, 2015, **50**:1181
- [29]. Lee S.J., Kriven W.M. *Journal of the American Ceramic Society*, 1988, **8**:2605

[30]. Maensiri S., Masingboon C., Laokul P., Jareonboon W., Promarak V., Anderson P.L., Seraphin S. *Crystal growth & design.*, 2007, **7**:950

[31]. Patil P.R., Joshi S.S., *Materials Chemistry and Physics*, 2007, **105**:354

[32]. Guo L., Tong F., Liu H., Yang H., Li J. *Materials Letters*, 2012, **71**:32

How to cite this manuscript: Bita Baghernejad*, Asma Zareie Pseudo-three component reaction of indole with benzaldehyde derivatives for the preparation of bis(indolyl)methanes in the presence of nano-CuO-CeO₂. *Asian Journal of Green Chemistry*, 5(4) 2021, 343-350. DOI: 10.22034/ajgc.2021.288567.1304