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Highly Selective One-Pot Coupling Reaction of Indole, Aromatic Aldehydes, and 4-hydroxycoumarin Using Copper Octoate as a Homogeneous Catalyst

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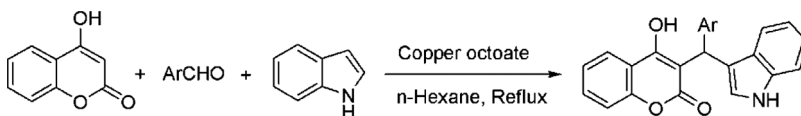
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HIGHLY SELECTIVE ONE-POT COUPLING REACTION OF INDOLE, AROMATIC ALDEHYDES, AND 4-HYDROXYCOUMARIN USING COPPER OCTOATE AS A HOMOGENEOUS CATALYST

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GRAPHICAL ABSTRACT



Abstract A facile protocol for the one-pot, multicomponent reaction of indole, 4-hydroxycoumarin, and aromatic aldehydes was developed using copper octoate as an inexpensive, commercially available, and efficient catalyst. This highly selective reaction eliminates the formation of homodimeric by-products (bisindoles and biscoumarins) and selectively results in the formation of heterodimeric adducts containing both indole and coumarin heterocycles.

Keywords Copper octoate; 4-hydroxycoumarin; indole; multicomponent reaction

INTRODUCTION

In the present era of organic synthetic chemistry, convenient and practical preparation of complex molecules from simple and available starting materials is one of the most challenging areas. In this context, one-pot, multicomponent coupling reactions are efficient alternatives that introduce several elements of diversity into a molecule in a single step.^[1–6] The resulting reduced number of synthetic and purification steps, with much less time and cost, are the desired features of an ideal synthesis.

Indole and coumarin are the most predominant heterocycles in nature.^[7–13] The homodimeric forms of these compounds, bisindoles and biscoumarins, have been well identified as natural products with various biological activities. For instance, bis(3-indolyl)-3,4-dihydroxyphenyl methane **1** acts as a HIV-1 integrase

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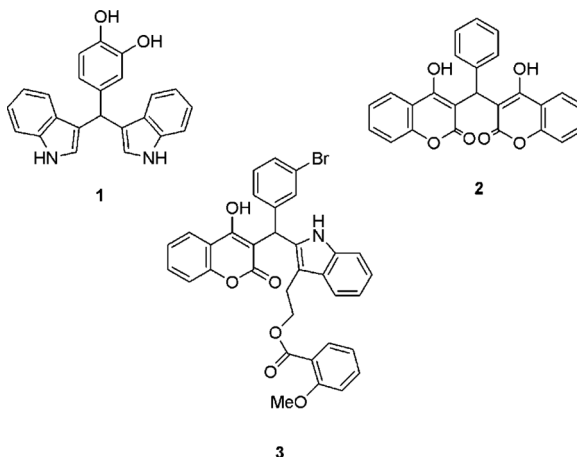


Figure 1. Samples of biologically active bisindole and biscoumarin and their corresponding heterodimer.

inhibitor^[14,15] and bis(4-hydroxycoumarin-3-yl)phenylmethane **2** and its derivatives can exhibit *in vitro* anti-DNA and RNA virus activity.^[16] Recently, a heterodimeric form containing both indole and coumarin motifs **3** was reported to exhibit substantial antibacterial activity.^[17] Interestingly, it is indicated that in some cases heterodimeric structures emerge more efficiency than their homodimeric analogs.^[18–20]

Although homodimeric compounds can be easily synthesized via Lewis acid-catalyzed condensation of aldehydes with electron-rich nucleophiles (indole and 4-hydroxycoumarin),^[21] the preparation of heterodimers still needs more study and exploration. One serious challenge that arises in the synthesis of heterodimeric compounds is the formation of homodimeric by-products. In some of the reported strategies these by-products are separated by tedious and time-consuming chromatography.^[22,23] Producing a stable intermediate containing one of the nucleophilic aromatic moieties and formation of the heterodimeric end product with the nucleophilic attack of the other aromatic moiety to that intermediate is another synthetic approach, which usually comprises a multistage procedure.^[24–26] Applying specific reaction conditions such as ultrasonic irradiation,^[23] nitrogen atmosphere,^[27] and catalysts with hardly available and expensive ligands^[28,29] is the major drawback observed in some other presented methods. In this article, a one-pot synthesis of compound **4a** as a heterodimeric entity, with aldehyde, indole, and 4-hydroxycoumarin

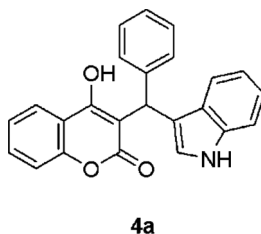
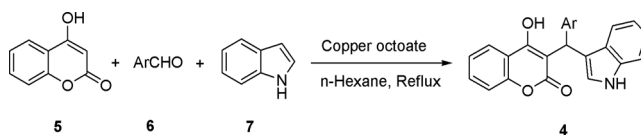


Figure 2.



Scheme 1. One-pot coupling reaction of 4-hydroxycoumarin, indole, and aromatic aldehydes using copper octoate as catalyst.

constituents using copper octoate as a very low-cost and readily available catalyst is presented.

Appendino et al.^[18] recommended an elegant procedure utilizing a biphasic system containing chloroform and water (1:1) in which water was attributed to act as a promoting agent. However, the reaction time was 48 h, and the products were isolated by column chromatography. Our strategy for the synthesis of this compound is via a one-pot multicomponent fashion using Lewis acidic activity of copper octoate to accelerate the reaction and improve the yields. According to the high nucleophilic activity of indole and 4-hydroxycoumarin, one-pot application of both nucleophiles is often restricted by the formation of a multitude of products such as bisindole, biscoumarin, and the desired crossed adduct. However, by optimizing reaction conditions, a logically designed one-pot multicomponent reaction resulting selectively in the formation of heterodimer can be obtained.

Transition metal-catalyzed processes have long been powerful tools for the development of organic reactions.^[30–32] Copper octoate or copper(II) 2-ethylhexanoate is the copper salt of 2-ethylhexanoic acid. This compound is a fungicide and bactericide used to control a wide range of plant diseases. Copper carboxylate systems have been studied as wood preservatives for several years.^[33] An outstanding feature that may distinguish this salt is its high solubility in organic solvents such as xylene and oils, furnishing it to act as a homogeneous catalyst in organic reactions.^[34–36] Copper octoate is commercially available solvated in organic solvents in various concentrations with quite low costs. Because of interest for both academic as well as the industrial community, it is desirable to expand the application scope of copper octoate catalyst in organic transformations because of its unique and remarkable advantages.

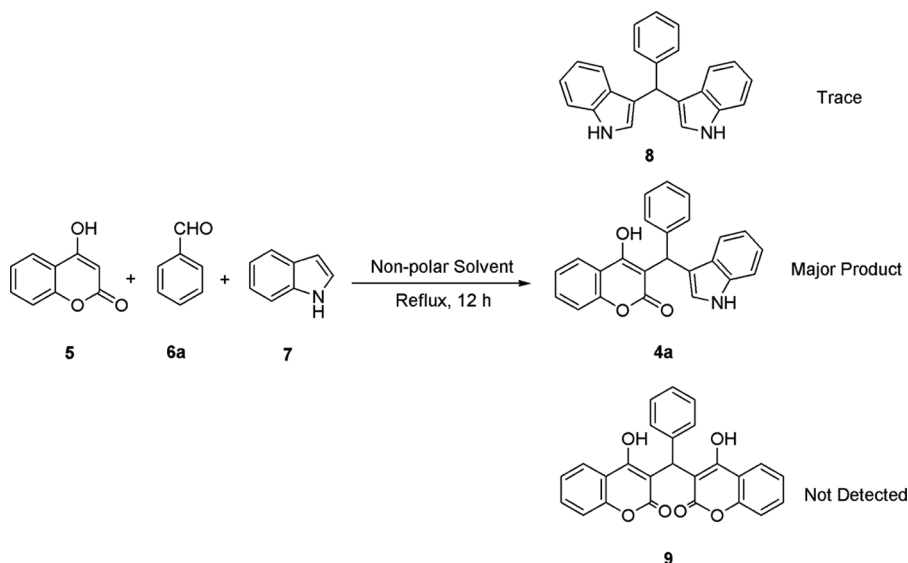
We report here a practical protocol for the one-pot coupling reaction of indole, 4-hydroxycoumarin, and aromatic aldehydes, using copper octoate as a homogeneous catalyst in n-hexane under reflux condition (Scheme 1). Various aromatic aldehydes bearing electron-donating and electron-withdrawing components have been applied for this reaction.

RESULTS AND DISCUSSION

The critical factor in driving the reaction specifically toward the synthesis of the desired heterodimers **4** and minimizing the formation of homodimeric by-products, bisindole **8** and biscoumarin **9**, is the proper selection of the solvent. To study the solvent effect, the model reaction of benzaldehyde, indole, and 4-hydroxycoumarin was carried out in a variety of solvents from protic polar solvents such as water, acetic acid, and ethanol to aprotic polar solvent such as acetonitrile. In addition, this reaction was performed in nonpolar solvents such as toluene, 1,2-dichloroethane,

and n-hexane and also in solvent-free conditions. It was obviously indicated that the selectivity of reaction is extremely associated with the solvent of choice and the best results are obtained when relatively nonpolar solvents such as n-hexane, toluene, and 1,2-dichloroethane are utilized. The reluctance of nonpolar, solvents to the formation of biscoumarins **9** can be explained by negligible solubility of 4-hydroxycoumarin in such solvents, which reduces its high nucleophilic activity and moderates its consecutive nucleophilic attacks. This subsequently prevents the formation of biscoumarins **9** (Scheme 2).

To evaluate the efficiency of the aforementioned nonpolar solvents, the model reaction was carried out under reflux conditions, loading 10 mol % of copper octoate as catalyst. As shown in Table 1, entries 1, 2, and 3, maximum yield is achieved in n-hexane as reaction medium. Indeed, application of this solvent is preferred from the environmental point of view. To optimize the amount of catalyst, the model reaction was performed at the same conditions, in the presence of different quantities of copper octoate. As revealed in Table 1, entries 3–7, addition of small amounts of catalyst to the reaction mixture accelerates the reaction considerably, with improved yields of the products. Regarding entry 5, the reaction seems to be very sluggish in the absence of the catalyst because even after 48 h the outcome of the reaction was only 61 %. One could claim that the relatively poor yield obtained is due to longer reaction time, which results in decomposition of the product. Nevertheless, tracking the progress of the reaction by thin-layer chromatography (TLC) in short time intervals indicates the presence of significant amounts of all three starting materials even after 48 h. This could somehow prove that inactivity of the starting materials, especially 4-hydroxycoumarin as the initiator of the reaction, which is intentionally caused by chosen reaction medium, is the main reason for poor yields. Moreover, short reaction



Scheme 2. High selectivity of nonpolar solvents for the synthesis of desired heterodimers rather than homodimeric adducts.

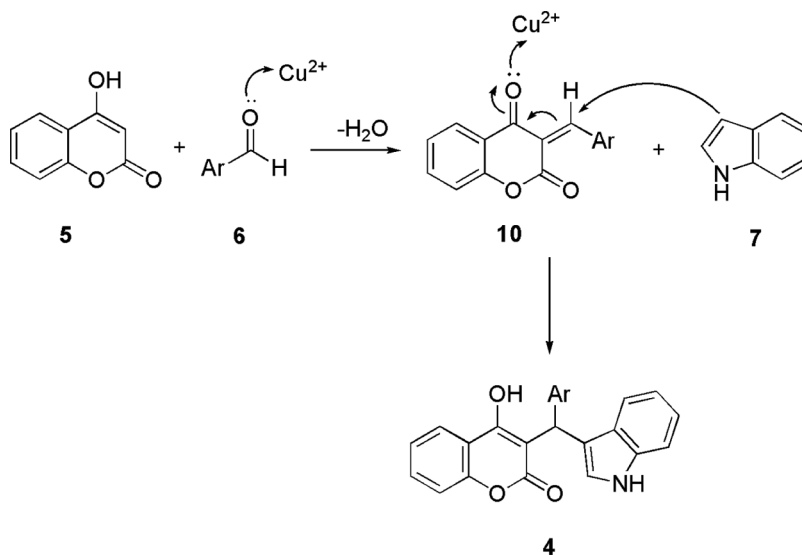
Table 1. Effect of solvent and catalyst loading on time and yield of the reaction

Entry	Solvent	Amount of catalyst (mol%)	T (°C)	Time (h)	Yield (%)
1	Toluene	10	111	1	86
2	1,2-Dichloroethane	10	84	1	78
3	n-Hexane	10	68	1	88
4	n-Hexane	0	68	1	23
5	n-Hexane	0	68	48	61
6	n-Hexane	5	68	3	59
7	n-Hexane	15	68	1	84

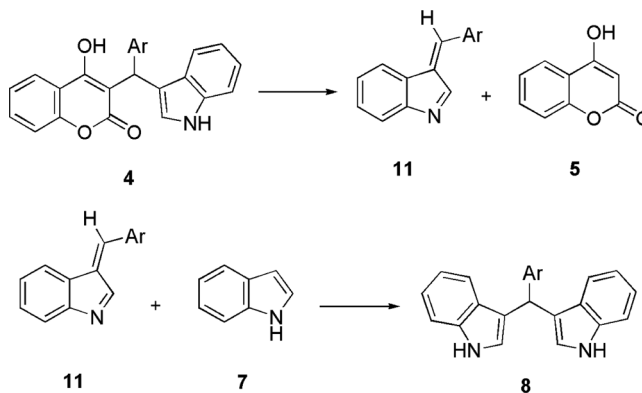
time did not improve the yields, revealing the necessity of applying catalyst. The optimum amount of catalyst was 10 mol %.

A plausible mechanism of the reaction is presented in Scheme 3. Lewis acid-catalyzed Knoevenagel condensation of 4-hydroxycoumarin **5** with aldehyde **6** generates the intermediate **10**, which undergoes conjugate addition with indole **7** to give the heterodimeric adduct **4**. In addition, it is postulated that according to the nonpolar character of 2-ethylhexanoate groups in catalyst, coordination of the catalyst to 4-hydroxycoumarin could drag this constituent to the nonpolar phase in which other starting materials exist and consequently facilitates the progress of the reaction this way as well.

In addition to the heterodimeric products, formation of trace amounts of bisindole by-product **8** occurred. One pathway for the formation of this by-product could simply be the coupling reaction of aldehyde with 2 mol of indole without interference of 4-hydroxycoumarin. Another possible mechanism for this side reaction, which was suggested by Appendino et al.,^[18] is outlined in Scheme 4. Initially, the



Scheme 3. Plausible mechanism for one-pot coupling reaction of indole, 4-hydroxycoumarin, and aromatic aldehydes utilizing copper octoate as catalyst.



Scheme 4. Possible mechanism for the formation of bisindole by-products.

4-hydroxycoumarin moiety is eliminated from the heterodimeric adduct **4**. The remaining intermediate **11** suffers a nucleophilic attack by indole **7**, giving the bisindole by-product **8**. To investigate the accuracy of the proposed mechanism for the formation of bisindoles, equimolar amounts of heterodimer **4** and indole **7** were refluxed in *n*-hexane. After 3–4 h, very slight amounts of 4-hydroxycoumarin **5** and bisindole **8** were detected by thin-layer chromatography. It was observed that protic solvents such as ethanol enhance this side reaction. This might be due to the high solubility of 4-hydroxycoumarin **5** in such solvents, which stabilizes this nucleus and thus makes it a better leaving group. Moreover, it is speculated that coordination of protic solvents to the oxygen atom of hydroxyl group in 4-hydroxycoumarin enhances the elimination process.

The generality of this method was studied applying various aromatic aldehydes. The results are collected in Table 2. Aromatic aldehydes with different substitutions on aromatic ring underwent smooth reaction with indole and 4-hydroxycoumarin, furnishing the respective heterodimers in good yields and considerable shortened reaction time in comparison with the previous reported methods. To investigate the function of this method for aliphatic carbonyl

Table 2. Synthesis of (4-hydroxycoumarin-3-yl)(3-indolyl)phenylmethanes using copper octoate as catalyst^a

Entry	Ar	Product	Time (h)	Yield (%) ^b	Mp (°C)
1	C ₆ H ₅	4a	1	88	198–199 ^[18]
2	4-CH ₃ C ₆ H ₄	4b	4	86	169–170
3	4-NO ₂ C ₆ H ₄	4c	45 ^c	96	207 ^[18]
4	2-OCH ₃ C ₆ H ₄	4d	2	81	186–187
5	4-ClC ₆ H ₄	4e	3	95	190
6	3-BrC ₆ H ₄	4f	4	83	206

^aReaction conditions: indole (1 mmol), 4-hydroxycoumarin (1 mmol), aldehyde (1 mmol), 6% xylene solution of copper octoate (0.58 g, 0.1 mmol), *n*-hexane, reflux.

^bYields refer to pure products after recrystallization.

^cMin.

compounds, the reaction was carried out with acetaldehyde and acetone. In the case of acetone, even after 12 h only trace amounts of the corresponding bisindole was formed. This result could be caused by the mildness of the reaction conditions. The same result was obtained for acetaldehyde, while in this case very slight amounts of other products, which were supposed to be the desired product and biscoumarin, were detected, which discloses the lower selectivity for this aliphatic aldehyde. On the other hand, our attempts to perform the reaction with 2-methylindole instead of indole failed. After 2 h of refluxing the reaction mixture of equimolar amounts of benzaldehyde, 4-hydroxycoumarin, and 2-methylindole under reaction conditions, the corresponding bisindole was obtained as the only product. It seems that the methyl substitution on indole ring makes it exceed the nucleophilic activity of 4-hydroxycoumarin and as a result changes the expected selectivity of the reaction in favor of the bisindole by-product.

CONCLUSION

In summary, a practical and highly selective alternative for the one-pot multi-component synthesis of hybridized adducts containing both indole and 4-hydroxycoumarin moieties is established with maximum simplicity and brevity. Taking advantage of copper octoate's substantial catalytic activity, reaction times could be significantly reduced and product yields are improved. Different solvents were studied for this reaction and a pronounced effect was observed: Nonpolar solvents that are unable to dissolve 4-hydroxycoumarin are superior to provide a selective transformation.

EXPERIMENTAL

All the chemicals were purchased from Merck and Sigma-Aldrich companies. Melting points were measured using the capillary tube method with an Electrothermal 9200 apparatus. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AQS Avance-500-MHz spectrometer, using tetramethylsilane (TMS) as an internal standard (CDCl_3 solution). Infrared (IR) spectra were recorded on the FT-IR Bruker Tensor 27. Mass spectra were documented on an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis (% C, H, N) was carried out on a Perkin-Elmer 2400 CHN elemental analyzer.

To a mixture of 4-hydroxycoumarin (1 mmol, 0.162 g), aromatic aldehyde (1 mmol), and indole (1 mmol, 0.117 g) in *n*-hexane (2 mL) was added 0.58 g of a 6% solution of copper octoate in xylene (10 mol%). The mixture was refluxed for an appropriate time (Table 2). After completion of the reaction, as indicated by TLC (petroleum ether–ethyl acetate–ethanol, 4:1:1), the solvent was evaporated and 10 mL of ethanol was added to the residue. The resulting mixture was stirred for 15 min filtered, and washed with ethanol to give the crude product, which was further purified by recrystallization from 95% ethanol.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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