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Research Article

$Zn(OAc)_2.2H_2O$-Catalyzed C3-alkylation and *O*-alkylation of 4-Hydroxycoumarin derivatives

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Abstract

For the C3-alkylation and O-alkylation of 4-hydroxycoumarins with benzylic, allylic, and corresponding acetates, respectively, under neat conditions at 60 ^{0}C with high product yield, $Zn(OAc)_2.2H_2O$ has been found to be an effective reusable solid superacid catalyst.

Keywords: C-C and C-O bond formations; $Zn(OAc)_2.2H_2O$; 4-Hydroxy coumarin; secondary benzyl alcohol; secondary benzyl *O*-acetate

Introduction

Among heterocycles, coumarin is a preferred scaffold and is known to have a variety of biological effects, including antibiotic, anti-malarial, anti-fungal, anti-viral, and cytotoxic effects[1-8]. Due to their effectiveness as "anticoagulant rodenticides as well as antithrombotic agents," such as warfarin, brodifacoum, difethialone, bromadiolone, coumatetralone, and flocoumafen[9] (Figure 1), as well as nonpeptide human immunodeficiency virus (HIV) protease inhibitors[10], the 4-hydroxycoumarins and its derivatives (3-alkylated Due to its pharmaceutical utility, which was previously mentioned, and the ability to be diversified to synthesise 3,4-substituted compounds[11-14], the C3 or O-alkylation of 4-hydroxycoumarin (formation of new C–C and C–O bonds) is without a doubt one of the most significant and difficult reactions in synthetic chemistry. Even though there have been numerous studies on the C3-alkylation of 4-hydroxycoumarins, the majority of them require organic halides or boronic acid as substrates for Pd-catalyzed C-C bond formation or base-mediated alkylation reactions[15-19]. Because starting ingredients are readily available and water is the sole byproduct produced, alcohols are more desirable from a synthetic standpoint than the comparable halides or boronic acid.

Alcohols can also be used as alkylating agents to achieve the alkylation, which is a less well-known alternative. There are a few techniques for C3-alkylating 4-hydroxycoumarin with alcohols that have been documented thus far, including those that use potent acids like HCl, H_2SO_4, etc.[20-22], $Yb(OTf)_3$[23], $FeCl_3.6H_2O$[24], Amberlite IR-120[25], molecular iodine[26], $Bi(OTf)_3$[27] $Fe(ClO_4)_3.xH_2O$[28], TMSOTf[29], $Bi(NO_3)_3.5H_2O$/Ionic liquid system[30], sulphated tin oxide[31] and Ir-Sn bimetallic conventional acid methods[32], however, are inevitably accompanied by issues such high toxicity, corrosion, catalyst waste, and difficulty in separation and recovery. Some of these catalytic systems have a number of drawbacks, including prolonged reaction durations, a lack of reusability, and low yields.

Therefore, it is more crucial and highly desirable to design a brand-new effective, catalytic process for the direct C3-alkylation of 4-hydroxycoumarin employing alcohols. Non-polluting and effective catalytic

technologies have become increasingly important in recent years, especially in light of the numerous international laws that restrict emissions for environmental reasons. In this context, tidy reactions are regarded as one of the key advancements in accomplishing the objective of Green chemistry[33].

Among the several zinc complexes, zinc acetate ($Zn(OAc)_2$) is easily accessible and stable in the presence of moisture and air at room temperature. The effectiveness of $Zn(OAc)_2$•$2H_2O$ as a catalyst has been shown in several papers[34-38]. Furthermore, $Zn(OAc)_2$•$2H_2O$ hasn't been investigated as a catalyst for the C3- and O-alkylation of4-hydroxycoumarins to the best of our knowledge. The C3-alkylation and O-alkylation reactions of 4-hydroxycoumarins with available benzylic alcohols and benzyl *O*-acetates, respectively, are catalysed by $Zn(OAc)_2$•$2H_2O$. Here, we discuss our brief findings for a highly effective technique for the creation of C-C bonds and C-O bonds in these reactions (see Tables 2 and 3).

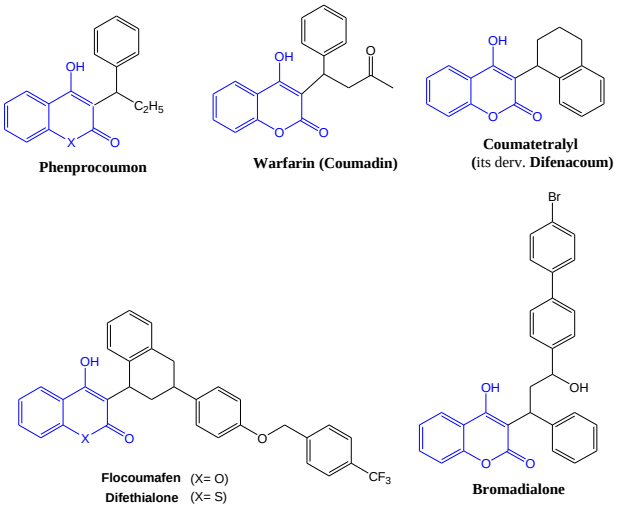


Figure 1. Well known 4-hydroxy coumarin containing drugs.

Experimental

On an Electrothermal Gallenkamp device, all melting points were calculated. On a Varian Gemini Spectrometer operating at 300 and 400 MHz, respectively, ^1H and ^{13}C NMR spectra were captured. On a Nicolet Fourier Transform spectrometer, IR spectra were captured. LSIMS technology was used to obtain mass spectra using a 7070H or VG Autospec mass spectrometer. Silica gel glass-backed plates and GF-25U (Anal. Tech) plates were used for thin-layer chromatography (TLC). Regular column chromatography was carried out on silica gel with a mesh size of 100-200.

General experimental procedure for the C3-alkylation of 4-hydroxycoumarins

To a mixture of 4-hydroxycoumarin (1, 1.0 mmol) and secondary benzyl alcohol (2a-h, 1.1 mmol) under neat conditions, $Zn(OAc)_2.2H_2O$ (0.1 mmol) was added and the reaction mixture was stirred for the given time (see Table 2) at 60 ^{0}C. After completion of the reaction (monitored by TLC), the reaction mixture was added into water. Adjusted to pH neutral with sodium carbonate and extracted in ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by silica gel column with petroleum ether/ethyl acetate (1:3) as eluent to afford the corresponding C3-alkylated 4-hydroxycoumarin (**3a-f**).

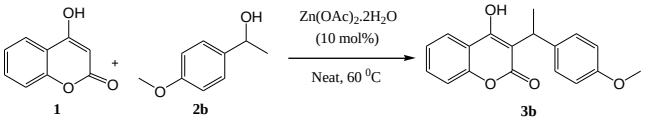
General experimental procedure for the *O*-alkylation of 4-hydroxycoumarins

To a mixture of 4-hydroxycoumarin (1, 1.0mmol) and secondary *O*-acetyl compound (4a-f, 1.1 mmol) under neat conditions, $Zn(OAc)_2.2H_2O$ (0.1 mmol) was added and the reaction mixture was stirred for the given time (see Table 3) at 60 ^{0}C. After completion of the reaction (monitored by TLC), to the reaction mixture was added into water. Adjust pH neutral with sodium carbonate and extracted in ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by silica gel column with petroleum ether/ethyl acetate (1:3) as eluent to afford the corresponding *O*-alkylated 4-hydroxycoumarin (**5a-f**).

All synthesized compounds [**3a-f** and **5a-f**] are known and accordingly reference numbers are provided.[23-32]

Results & Discussion

To provide the ideal reaction conditions, the reaction of 4-hydroxycoumarin (1 mmol) and 4-methoxy-1-phenylethanol (**2b**, 1.1 mmol) in the presence of $Zn(OAc)_2$•$2H_2O$ was initially selected as the model reaction (Scheme 1). It is clear that at RT/reflux or in the absence of a catalyst, the reaction cannot advance. Then, various solvents were examined. As clean conditions proved to be the most effective for generating good yields at 60 $^{\circ\circ}$C for 5 h, we discovered a significant solvent impact (Table 1, entry 6). Other solvents like MeOH, EtOH, CH_3CN, and IPA produced no product or produced product yields and strating material was recovered intact (Table 1, entries 1-4). Despite having a longer response time, toluene had a reasonable yield.



Scheme 1. Reaction of 4-hydroxycoumarin with 4-methoxy-1-phenylethanol in the presence of $Zn(OAc)_2$•$2H_2O$

Table 1: Screening for the reaction conditions[a]

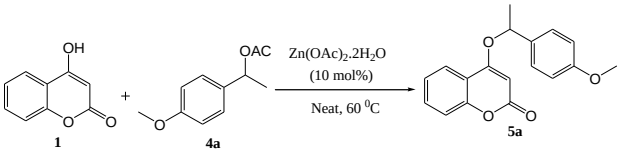
Entry	Cat. (mol%)[a]	Solvent	Temp	Time (h)	Yield[b] (%)
1	10	MeOH	Reflux	1	0
2	10	EtOH	Reflux	1	0
3	10	CH_3CN	Reflux	1	0
4	10	IPA	Reflux	1	0
5	10	Toluene	Reflux	10	50
6	10	Neat	60 ^{0}C	5	78
7	5	Neat	60 ^{0}C	12	61
8	20	AcOH	Reflux	5	58

[a]1.0 mmol**1,** 1.1 mmol **2b**, cat. $Zn(OAc)_2.2H_2O$ in 5 mL solvent; [b] Isolated yield

It just took 10 mol% of $Zn(OAc)_2$•$2H_2O$ as catalyst to get the desired product in good yield. Increasing the catalyst loading has no discernible impact on yields (Table 1, entry 8). The reaction time was extended to 12 hours when 5 mol% $Zn(OAc)_2$•$2H_2O$ was used to catalyse the reaction, and only 61% of the intended product (3b) was produced (Table 1, entry 7). As a result, the ideal reaction conditions for 3b's formation were identified (Table 1, entry 6).

With the optimized reaction conditions in hand (10 mol% $Zn(OAc)_2.2H_2O$, Neat, 60 ^{0}C), we then evaluated the scope of the benzylation of 4-hydroxycoumarin 1 using a variety of structurally divergent reactants and the results are summarized in Table 2.

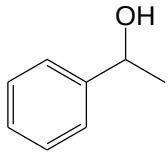
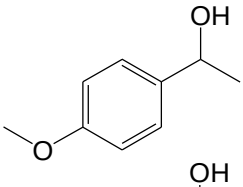
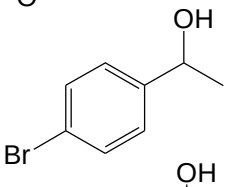
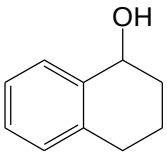
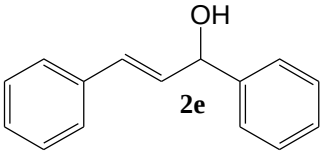
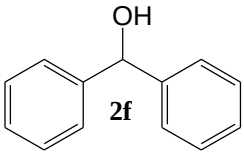
After 5 hours, we achieved the matching C3-alkylated compounds in yields of 68-78%. (entries 1-3, Table 2). When benzylic alcohols contain electron-donating groups, such as methoxy, the reaction produced better yields (entry 2, Table 2). Additionally, we carried out this reaction with substituted allylic alcohols (entry 5, Table 2) and got fantastic yields. Primary benzyl alcohols did not produce the desired outcome when employed. These findings unequivocally show that secondary benzylic alcohols are the only source of success for the direct C3-alkylation of 4-hydroxycoumarin. Even after 20 h of refluxing, the reaction between benzhydrol (2h) and 4-hydroxycoumarin did not continue (entry 6, Table 2). We focused on testing the viability of secondary benzyl acetates (prepared instantly for the purpose) reacting with 4-hydroxycoumarin under the above optimized conditions to generate novel compounds (**5a-e**) in the designated time, and were successful in C3-alkylation of 4-hydroxycoumarin with secondary benzyl alcohols (new C-C bond formation) (Scheme 2 and Table 3). Prenyl acetate (4f) and 4-hydroxycoumarin were unexpectedly combined to produce pyranocoumarin in good yield (entry 6, Table 3), as opposed to the anticipated O-alkylated result. This process offers a simple and safe way to obtain multi-substituted pyranocoumarins.



Scheme 2. Reaction of 4-hydroxycoumarin with secondary benzyl acetates in the presence of $Zn(OAc)_2$•$2H_2O$

The proposed mechanism of this reaction can be conceptualized as occurring through a tandem sequence of reactions that removes water as a by-product by forming stabilised carbocations from alcohol that act as the alkylating species (or else by forming dimeric ether) in the presence of $Zn(OAc)_2.2H_2O$ using its Lewis acidic site (C3-Alkylation). Zn metal uses Lewis acid catalysis to activate the enolic hydroxyl group, making the 3-position more nucleophilic. While in the instance of *O*-alkylation, Zn uses Lewis acid catalysis to activate the carbonyl functionality of acetate, making it the leaving group. The stabilised carbocation that is subsequently created then interacts with enolic hydroxide, producing AcOH as a by-product (Figure 2).

Table 2: C3-Akylation of 4-hydroxycomarin with various alcohols

Entry	Alcohol	Product	Time (h)	Yield (%)[a]
1	 **2a**	**3a**	**5**	**72**
2	 **2b**	**3b**	**5**	**78**
3	 **2c**	**3c**	**5**	**68**
4	 **2d**	**3d**	**5.5**	**70**
5	 **2e**	**3e**	**6**	**81**
6	 **2f**	**3f**	**20**	**0**

[a] Isolated yields after column chromatography.

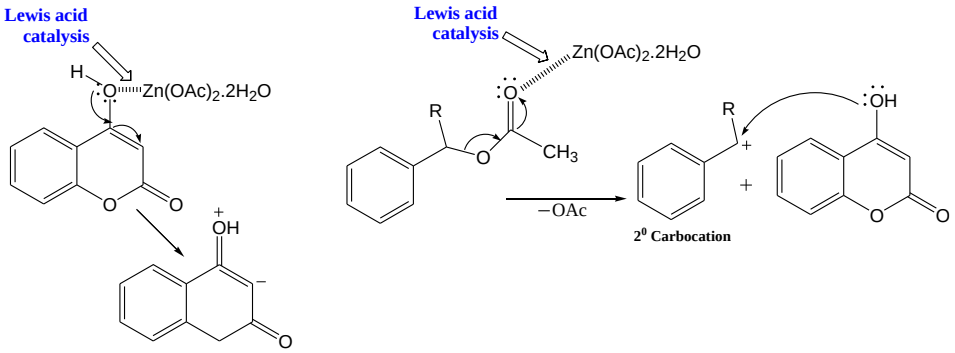
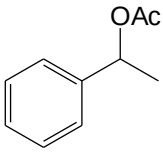
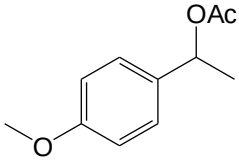
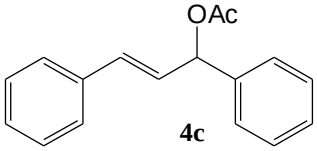
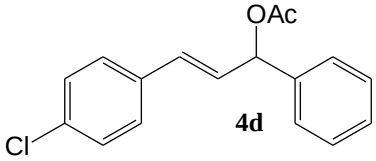
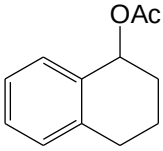
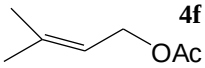
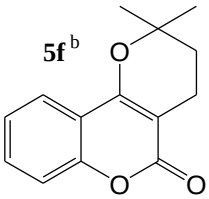


Figure 2. Mechanism for C3/O-Alkylation via Lewis acid Catalysis using Zn catalyst.

Table 3: *O*-alkylation of 4-hydroxycomarin (1) with various acetates

Entry	Acetate	Product	Time (h)	Yield (%)[a]
1	 **4a**	**5a**	**4**	**67**
2	 **4b**	**5b**	**4**	**78**
3	 **4c**	**5c**	**5**	**73**
4	 **4d**	**5d**	**5**	**70**
5	 **4e**	**5e**	**6**	**82**
6	 **4f**	**5f**[b] 	**5**	**65**

[a] Isolated yields after column chromatography.

[b] Intramolecular cyclization.

Conclusion

In conclusion, in this preliminary communication, we have successfully used $Zn(OAc)_2.2H_2O$ as an effective catalyst to promote *O*-alkylation using secondary benzyl acetates and *C3*-benzylation utilising secondary benzyl alcohols, such as benzylic and allylic alcohols, of 4-hydroxy-coumarin. This procedure has the following benefits: a broad application, mild conditions, the use of a cheap, reusable catalyst, and ease of operation under orderly circumstances. Additionally, this approach offers a simple and gentle path to multi-substituted pyranocoumarins.

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Supporting Information

All data and material are available upon request.

Conflict of interests

The authors claim that there is no conflict of interest.

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NA

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