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A Mn(III)-catalysed domino process for C-3 substituted dihydrocoumarins from 2-hydroxybenzyl alcohols and 4-hydroxy-2*H*-chromen-2-ones†

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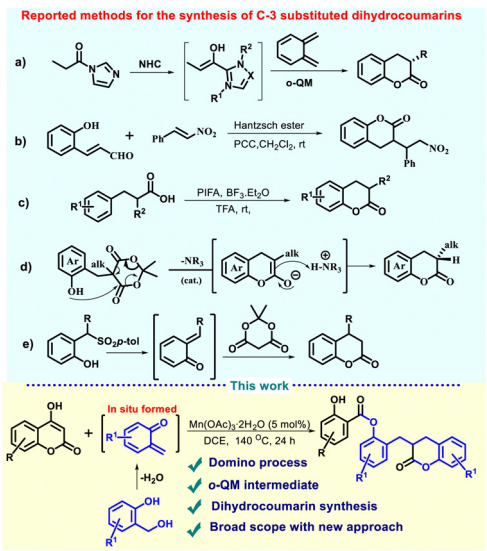
A Mn-catalysed efficient domino process for the synthesis of new C-3 substituted dihydrocoumarins from 2-hydroxybenzyl alcohols and 4-hydroxy-2*H*-chromen-2-ones under one-pot conditions is described. This reaction proceeds *via* a series of reactions in one-pot, such as *o*-quinone methide formation, Michael addition, intramolecular trans-esterification, and skeletal rearrangement to access dihydrocoumarins.

Dihydrocoumarin serves as an important natural compound, known to be an exclusive class of lactone and characterized by its distinctive sweet, vanillin-like olfactory profile.[1] Therefore, it has been used as a key compound in many fragrance and flavor industries. Several natural products and drug molecules possessing these structural motifs exhibit promising biological activities, such as anti-inflammatory, antibiotic, anticancer, *etc.*[2,3] Owing to its significance in the scientific community, many synthetic methods have been documented in the literature for the synthesis of dihydrocoumarins by using various reagents and catalysts.[4] Notably, the synthesis of C-3 substituted dihydrocoumarins was also demonstrated in the literature due to their promising biological significance. For instance, NHC-catalysed synthesis of dihydrocoumarin has been presented by Scheidt using *ortho* quinone methides (Scheme 1a).[5] Then, Liu and coworkers reported the synthesis of C3 alkylated dihydrocoumarins from conjugated aldehydes and nitro compounds using Hantzsch ester as a catalyst (Scheme 1b).[6] The PIFA-based oxidative cyclization of 3-arylpropionic acids to 3,4-dihydrocoumarins has also been demonstrated to investigate the reaction mechanism (Scheme 1c).[7] Recently, an organocatalytic asymmetric version of the synthesis of dihydrocoumarins was developed by Sylvan and coworkers *via trans*esterification using pre-functionalized Meldrum's acid derivatives (Scheme 1d).[8] Previously, this approach was studied for the synthesis of 4-substituted dihydrocoumarin using specially designed sulfonate derivatives as a source of *ortho*-quinone methide with Meldrum's acid through Michael addition and transesterification (Scheme 1e).[9] In recent studies, the *ortho* quinone methides (*o*-QMs) have been extensively used for the synthesis of substituted dihydrocoumarins.[10,11] Although the synthesis of substituted dihydrocoumarins is well documented, very few studies are present in the literature, specifically for the synthesis of C-3 substituted dihydrocoumarins.[5–8] These methodologies are constrained by a few aspects, such as the use of expensive catalysts and pre-functionalized substrates, a multistep approach, hazardous reagents, and the requirement for harsh reaction conditions with low yields. Consequently, to address such drawbacks, and increase the significance of C-3 substituted dihydrocoumarins, the development of a direct and step-economical process to access structurally diverse and elegant compounds by exploiting readily accessible substrates is always intended in synthetic organic chemistry.



Scheme 1 State of the art for the synthesis of C-3 substituted dihydrocoumarins.[a–e]

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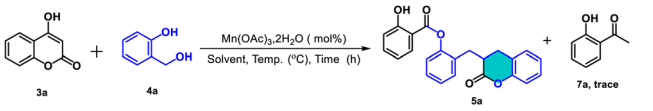
The domino process refers to a sequence of multiple bond-forming reactions that occur under the same reaction conditions, without isolating intermediates or adding new reagents throughout the whole process.[12] This process plays a pivotal role in modern synthetic chemistry due to its selectivity, sustainability, and efficiency. To the best of our knowledge, there is no existing report on an Mn(III) catalyzed domino process for the synthesis of C3-substituted dihydrocumarins utilizing 4-hydroxy coumarins and 2-hydroxy benzyl alcohols. Herein, we report an earth abundant and inexpensive $Mn(OAc)_3$ catalyzed synthetic protocol to synthesize C3-substituted new dihydrocumarins using a domino process through *ortho*-quinone methide (*o*-QM) as a reactive intermediate.

Our investigation was commenced by taking 4-hydroxy-2*H*-chromen-2-one **3a** and 2-(hydroxymethyl)phenol **4a** as model substrates to optimize the reaction conditions for the synthesis of 2-((2-oxochroman-3-yl)methyl)phenyl 2-hydroxybenzoate **5a**. A control experiment in the absence of a catalyst using toluene as a solvent at 140 °C revealed that the catalyst is necessary to conduct the reaction towards the desired product **5a** (Table S1, entry 1, ESI†). Subsequently, we examined various metal complexes as a catalyst, such as Ru, Fe, In, Ni, Cu, Mn, *etc.*, indicating that Mn complexes are more efficient (see Table S1, ESI†). As a result, $Mn(OAc)_3$ rendered 55% yield (Table S1, entry 12, ESI†) and other complexes conferred 23% to 51% yields. From these studies, we observed that the metal complexes bearing –OAc ligand are more efficient for this transformation. The more feasibility of these catalysts might be due to the formation of the acetate ion in the process, which can abstract the proton from phenol to form acetic acid, which can drive the intramolecular esterification (refer to the mechanism). To confirm this, a reaction was performed with 5 mol% and stoichiometric amounts of acetic acid to afford 16% and 40% yields of the product **5a**, respectively (Table S1, entries 26 and 27, ESI†). When we examined the Brønsted acid catalysts such as Amberlyst-15 and *p*-toluene sulfonic acid (*p*-TSA), no product formation was observed. All these results reveal that $Mn(OAc)_3$ is an efficient catalyst for the synthesis of product **5a**. Increasing the catalyst loading up to 10 mol% and extending the reaction time to 48 h resulted in no improvement in the yields (Table 1, entries 1 and 2). In order to improve the product yield, a reaction was performed with different solvent media such as 1,4 dioxane, 2-methyl THF, ethyl acetate (EtOAc), acetonitrile (ACN), dichloroethane (DCE), dimethyl sulfoxide (DMSO), and *N*,*N*-dimethyl formamide (DMF). Among all the solvents tested, dichloroethane (DCE) was found to be the most suitable solvent, providing a 74% yield of **5a** after 36 h (Table 1, entry 7). DMSO was an inefficient solvent for this transformation (Table 1, entry 9). However, other solvents have produced poor to moderate yields (Table 1, entries 3 to 6 and 10). Other reaction conditions were tested and did not improve the yield of product **5a** (Table 1, entries 11 to 14). From the optimisation studies, 5 mol% $Mn(OAc)_3$ catalyst and 24 h reaction time were found to be the best reaction conditions for the synthesis of product **5a**.

Next, the scope of this reaction was elaborated with various coumarins and benzylic alcohols under the optimal conditions (Scheme 2). 4-Hydroxy-2*H*-chromen-2-ones with diverse substituents,

Table 1 Optimization study for dihydrocoumarin **5a**

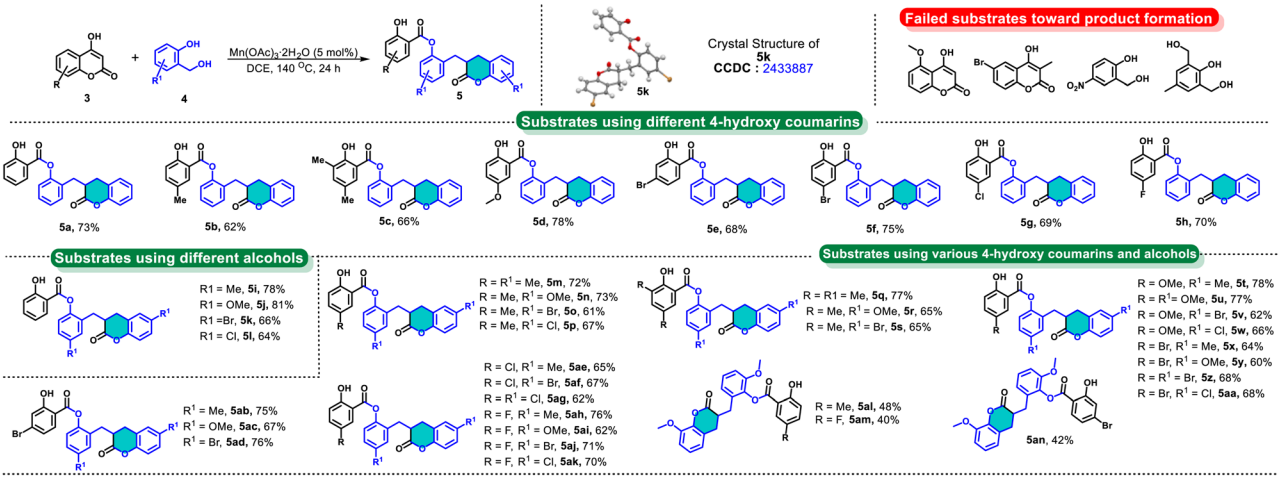


S. no.	$Mn(OAc)_3{\cdot}2H_2O$ (mol%)	Solvent	% Yield (**5a**)
1.	$Mn(OAc)_3{\cdot}2H_2O$ (10)	Toluene	54
2.[a]	$Mn(OAc)_3{\cdot}2H_2O$ (5)	Toluene	55
3.	$Mn(OAc)_3{\cdot}2H_2O$ (5)	Dioxane	20
4.	$Mn(OAc)_3{\cdot}2H_2O$ (5)	2-Me-THF	25
5.	$Mn(OAc)_3{\cdot}2H_2O$ (5)	EtOAc	20
6.	$Mn(OAc)_3{\cdot}2H_2O$ (5)	ACN	54
7.	$Mn(OAc)_3{\cdot}2H_2O$ (5)	DCE	74
8.	$Mn(OAc)_3{\cdot}2H_2O$ (10)	DCE	75
9.	$Mn(OAc)_3{\cdot}2H_2O$ (5)	DMSO	ND
10.	$Mn(OAc)_3{\cdot}2H_2O$ (5)	DMF	12
11.[a]	$Mn(OAc)_3{\cdot}2H_2O$ (10)	DCE	75
12.[b]	$Mn(OAc)_3{\cdot}2H_2O$ (5)	DCE	71
13.[c]	**$Mn(OAc)_3{\cdot}2H_2O$ (5)**	**DCE**	**73**
14.[d]	$Mn(OAc)_3{\cdot}2H_2O$ (5)	DCE	58

Reaction conditions: $Mn(OAc)_3{\cdot}2H_2O$ (mol%), compound **3a** (0.3 mmol), compound **4a** (0.6 mmol), and solvent (3 mL) were stirred in a sealed tube in a preheated oil bath at 140 °C for 36 h. [a] 48 h. [b] **4a** (0.75 mmol). [c] 24 h. [d] 120 °C, ND = not detected. All mentioned yields are isolated yields.

such as 5-Me, 2,4-di-Me, 5-OMe, 4-Br, 5-Br, 5-Cl, and 5-F, were reacted with 2-(hydroxymethyl)phenol to achieve the respective 2-((2-oxochroman-3-yl)methyl)phenyl 2-hydroxybenzoates **5b** to **5h** in good yields (62% to 78%). Subsequently, several 2-(hydroxymethyl)phenols were subjected to reaction with different 4-hydroxy-2*H*-chromen-2-ones to deliver the associated 2-((2-oxochroman-3-yl)methyl)phenyl 2-hydroxybenzoates **5i** to **5l** in good to excellent yields (64% to 81%). Afterward, the compounds **5m** to **5p** were synthesized in good yields (61% to 72%) by reacting them with 4-hydroxy-6-methyl-2*H*-chromen-2-one under the standard reaction conditions.

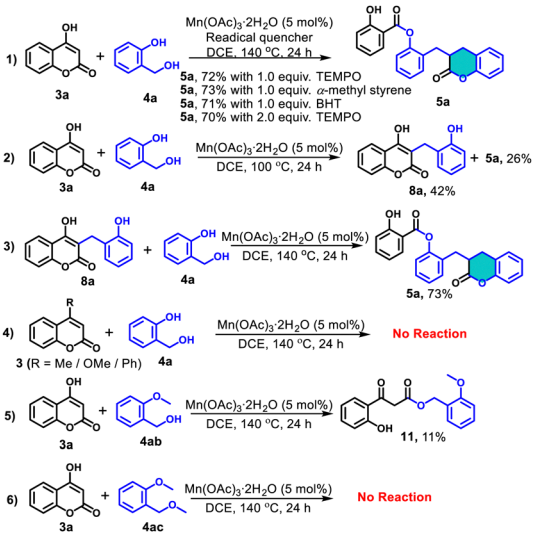
These alcohols reacted smoothly with 4-hydroxy-6,8-dimethyl-2*H*-chromen-2-one to afford the compounds **5q** to **5s** in 65% to 77% yields and with 4-hydroxy-6-methoxy-2*H*-chromen-2-one to generate compounds **5t** to **5w** in good yields (62% to 78%). The reactivity of bromo-substituted 4-hydroxy-6-methoxy-2*H*-chromen-2-ones was also examined with various alcohols to construct the anticipated products **5x–5ad** in 60% to 76% yields. The 5-Me, 5-Br, and 5-Cl-containing benzylic alcohols productively reacted with 6-chloro-4-hydroxy-2*H*-chromen-2-one and 6-fluoro-4-hydroxy-2*H*-chromen-2-one to afford **5ae–5ag** and **5ah–5ak** (62% to 76% yields), respectively. The reaction of 2-(hydroxymethyl)-6-methoxyphenol was performed with different 4-hydroxy-2*H*-chromen-2-ones to deliver products **5al–5an** in moderate yields. In contrast, a few coumarins, namely 4-hydroxy-5-methoxy-2*H*-chromen-2-one and 6-bromo-4-hydroxy-3-methyl-2*H*-chromen-2-one, as well as alcohols such as 2-(hydroxymethyl)-4-nitrophenol and (2-hydroxy-5-methyl-1,3-phenylene)dimethanol were unable to deliver the desired products. The failure of these substrates to yield the desired products could be attributed to steric hindrance and electronic factors that interfere with the reaction. To demonstrate gram-scale synthesis, the reaction of **3a** (10.0 mmol) and **4a** (20.0 mmol) was performed on a large scale in a sealed tube under standard reaction conditions to afford product **5a** (2.47 g, 66% yield).



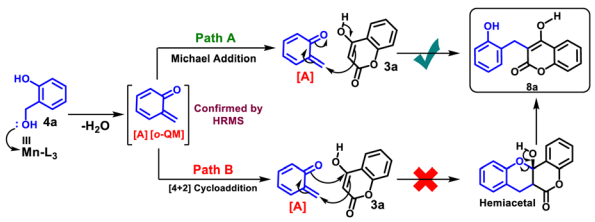
Scheme 2 Substrate scope for the synthesis of diverse C-3 substituted dihydrocoumarins.

Next, to understand the reaction pathway, a series of experiments using radical quenchers such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), ∝-methyl styrene and butylated hydroxytoluene (BHT) were performed. This set of experiments indicated that the reaction may not involve the generation of radicals throughout the process and follows the ionic pathway (Scheme 3, entry 1). When the model reaction was tested at low reaction temperature (100 °C), the formation of 4-hydroxy-3-(2-hydroxybenzyl)-2*H*-chromen-2-one **8a** as a major product was observed with 42% yield and **5a** with 26% yield (Scheme 3, entry 2). The formation of **8a** was further confirmed by reacting with 2-(hydroxymethyl)phenol **4a** under the standard reaction conditions, providing **5a** with a 73% yield (Scheme 3, entry 3).

Based on these experiments, two possible mechanistic pathways (path **A** and path **B**) have been depicted for product formation, as disclosed in Scheme 4. Path **A** follows the Michael addition reaction, while Path **B** follows the [4+2] cycloaddition reaction. To gain insights into the reaction pathways, further



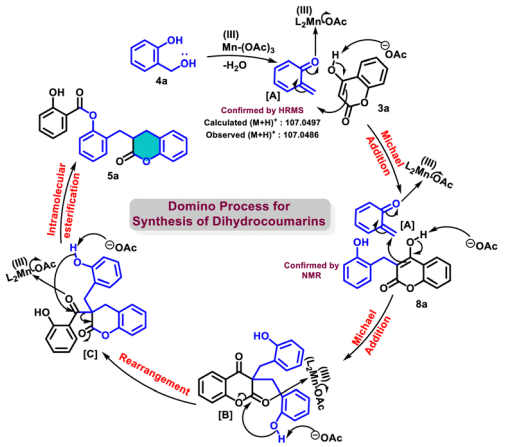
Scheme 3 Control experiments for the reaction pathway.



Scheme 4 Possible mechanistic pathways.

control experiments have been performed. Replacement of the –OH group from 4-hydroxy-2*H*-chrome-2-one with methyl/methoxy/phenyl resulted in no product formation when reacted with 2-(hydroxymethyl)phenol **4a** (Scheme 3, entry 4). This experiment shows that a free –OH is necessary to form the product, and the reaction may not follow the cycloaddition reaction pathway. Furthermore, to confirm the formation of the *o*-QM intermediate, the reaction of 4-hydroxy-2*H*-chromen-2-one **3a** and (2-methoxyphenyl)methanol **4ab**, was performed to obtain 3-(2-hydroxyphenyl)-3-oxopropanoate **11** (Scheme 3, entry 5). In a similar fashion, when fully protected alcohol, 1-methoxy-2-(methoxymethyl)benzene **4ac**, was reacted with 4-hydroxy-2*H*-chromen-2-one **3a**, no reaction was observed under the standard conditions (Scheme 3, entry 6). These reactions clearly indicate that the free –OH is required to generate an *o*-QM intermediate, which is formed in our model reaction and confirmed by HRMS.

From the control experiments and literature findings,[8,10,11] we proposed the transformation route for the current protocol (Scheme 5). The process initiates with the Mn(III)-catalyzed dehydration of 2-(hydroxymethyl)phenol **4a** to generate an *o*-QM intermediate **[A]**. The acetate ion generated from $Mn(OAc)_3$ abstracts a proton from 4-hydroxy-2*H*-chromen-2-one **3a** and reacts with intermediate **[A]** *via* Michael addition through the C-3 carbon to deliver mono-alkylated product **8a** and bis-alkylated product **[B]**. This species, upon skeletal rearrangement in the presence of an Mn(III) catalyst, forms a compound **[C]**. In the last step, the desired product **5a** was formed by



Scheme 5 Proposed mechanistic pathway.

intramolecular transesterification of compound **[C]** promoted by an Mn(III)-catalyst under the standard reaction conditions.

In conclusion, we developed a $Mn(OAc)_3$-catalysed domino process for the synthesis of diverse C-3 substituted dihydrocoumarins using several coumarins and hydroxybenzyl alcohols under one-pot conditions. This process involves a series of reactions, such as *o*-QM formation, Michael addition, and intramolecular transesterification, followed by skeletal rearrangement. This protocol enables the synthesis of a library of C-3 substituted dihydrocoumarins (40 compounds) with moderate to good yields. The proposed mechanistic pathway has been supported by the detection of the reactive intermediate (*o*-QM) and several control experiments.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the ESI.†

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