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Metal-Free, Regioselective, Dehydrogenative Cross Coupling between Formamides/Aldehydes and Coumarins *via* C-H Functionalization

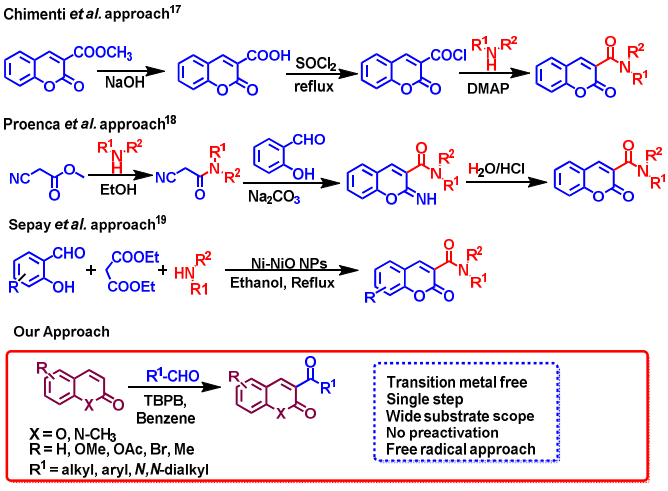
Mohit Gupta, [a] Prashant Kumar, [a] Vijay Bahadur, [a] Krishan Kumar, [a] Virinder S. Parmar [a],[b] and Brajendra K. Singh*[a]

Abstract: A highly efficient, single-step, metal-free synthetic approach for the synthesis of coumarin-3-carboxamides has been developed. The protocol employs TBPB (*tert*-butylperoxybenzoate) as a radical initiator to achieve regioselective C-3 carboxamidation of coumarins in good to moderate yields. The established reaction protocol offers a wide substrate scope as it employs both formamides as well as aldehydes as coupling partners with excellent regioselectivity. Furthermore, mechanistic investigations illustrate that the reaction proceeds via a free radical pathway.

Introduction

During the past decade, significant achievements have been made in the field of C-H activation, which allow the formation of new bonds between unactivated coupling partners without any prefucntionlization.[1] Transition metal catalyzed cross dehydrogenative coupling (CDC) reactions have proven to be a powerful tool in the recent years for the construction of C-C and C-heteroatom bonds *via* the direct functionalization of C-H bonds.[2] CDC inherently avoids the pre-functionalization of the substrates and offers the atom economical shorter routes for important organic transformations.[3] Although transition metal catalysis has become an indispensable tool for the direct transformations, yet it suffers from several limitations such as the use of expensive catalysts, toxicity of catalysts, air and moisture sensitivity of catalysts, addition of expensive and exotic ligands and the presence of transition metals as trace impurities in the final products which restrict its practical applicability in pharmaceutical industries.[4] Therefore, the development of metal free strategies for organic transformations is highly desirable and has become the subject of immense research among researchers.

Coumarins and their derivatives have gained tremendous scientific attention due to their wide range of pharmacological properties such as anti-oxidant activity,[5] HIV protease inhibition,[6] anti-cancer activity,[7] anti-Alzheimer activity,[8] Monoamine oxidase (MAO) inhibition,[9] etc. Apart from their remarkable biological importance, coumarins also attract great attention from the scientific community due to their interesting chemical framework which enables the regioselective C-H functionalization at the C-3 position due to the generation of resonance stabilized benzylic radical.[10] Thus, using the inherent selectivity of coumarin for its C-3 functionalization, various regioselective arylation,[11] alkylation,[12] phosphorylation,[13] aroylation[14] olifination,[15] and trifluoromethylation[16] have been developed to provide simple and shorter routes for its direct functionalization. However, to the best of our knowledge there is no report that discusses the direct carboxamidation of coumarin to afford coumarin-3-carboxamide derivatives till date (Scheme 1). Nevertheless, methods reported so far include multistep approaches which involve the coupling between amines and activated coumarin derivatives.[17] Apart from having several steps, these approaches suffer from various other shortfalls such as prefunctionalization of the substrates, harsh reaction conditions, expensive reagents, long reaction times and laborious workup. In 2008, Proenca et al. have developed a Knoevenagel condensation using salicyaldehydes and N-substituted cynoacetamides.[18] Non-availability of readily available starting materials, multi steps involved and limited substrate scope do not allow this approaches for general application. Recently, Sepay *et al*. have developed Ni-NiO nanoparticles mediated one pot three component reaction to afford coumarin-3-carboxamides,[19] however preparation, characterization and high toxicity[20] of Ni nanocatalyst restricts its practical applicability. Limitations of these reported procedures encouraged us to develop an efficient and regioselective methodology for the C-3 derivatization of coumarins.



Scheme 1. Methods for the Synthesis of coumarin-3-carboxamides.

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Thus, in continuation of our research to develop metal-free protocols[21] to resolve inherent issues and our ongoing efforts for the functionalization of coumarin,[22] herein we report a metal free, regioselective cross coupling reaction of coumarins with formamides to afford industrially and biologically important coumarin-3-carboxamides (Figure 1).[17], [23], [24a-24f]

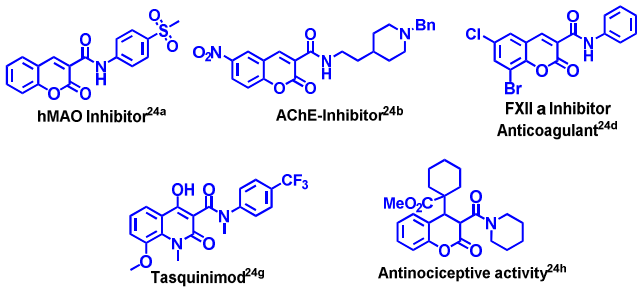
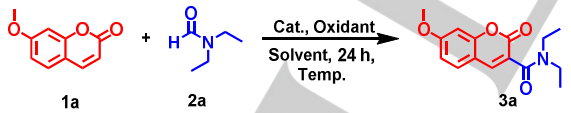


Figure 1. Selected biologically active compounds containing coumarin-3-carboxamide and azacoumarin-3-carboxamide skeleton.

Results and Discussion

During the course of our investigation on regioselective C-H functionalization of coumarin, 7-methoxycoumarin (**1a**) and *N*,*N*-diethylformamide (DEF) (**2a**) were taken as model substrates. Initially regioselective oxidative cross coupled product at C-3 position of coumarin (**3a**, 27% yield, Entry 1, Table 1) was obtained when 3 equiv. of *tert*-butyl hydrogen peroxide (TBHP) was heated at 150 ^{o}C for 24 h with excess of DEF, leaving majority of coumarin unreacted. Encouraged by these preliminary results, a variety of solvents, catalysts and additives were screened but no significant improvement in yields was observed due to the incomplete conversion (Table S2). However, a maximum of 35% yield was obtained with 3 equiv. of anhydrous $ZnCl_2$ (Entry 4, Table 1).

Table 1. Optimisation of the reaction conditions.[a]



1a 2a 3a

Sr. No	Oxidant	Catalyst	Temp. ^{o}C	Solvent	Additives	Yields[b]
1	TBHP	-	150	DEF	-	27
2	TBHP	-	150	Benzene	-	NR
3	TBHP	-	90	DEF	-	32
4	TBHP	-	90	DEF	$ZnCl_2$	35[c]
5	TBPB	-	150	DEF	-	24
6	DTBP	-	150	Benzene	-	23
7	$K_2S_2O_8$	-	150	DEF	-	5
8	H_2O_2	-	150	DEF	-	NR
9	TBPB	-	90	DEF	-	42
10	TBPB	-	90	DEF	-	43
11	TBPB	-	90	DEF	-	69
12	TBPB	-	90	DEF	-	31
13	TBPB	-	90	DEF	-	NR
14	TBPB	AgOAc	90	Toluene	-	41
15	TBPB	$FeCl_2.2H_2O$	90	Benzene	-	31
16	TBPB	$Cu(OAc)_2$	90	DCE	-	NR[d]
17	TBPB	CuO	90	CH_3CN	-	26
18	TBPB	$CuCl_2$	90	Benzene	-	NR[d]
19	TBPB	$FeCl_3$	90	Benzene	-	Traces
20	TBPB	-	90	Benzene	DABCO	41
21	TBPB	-	90	Benzene	NaOAc	61
22	TBPB	-	90	Benzene	KOAc	37
23	TBPB	-	90	Benzene	CuBr	24
24	TBPB	-	90	Benzene	$ZnCl_2$	59[c]

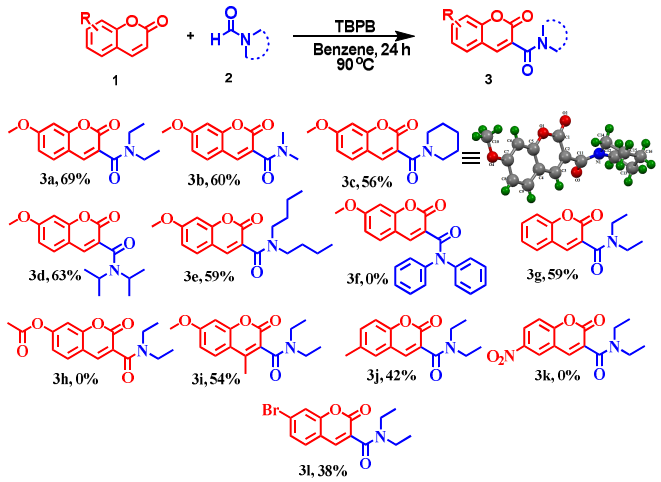
[a] Reaction conditions: a mixture of 7-methoxycoumarin (**1a**) (1 equiv.), DEF (**2a**) (3 equiv.), catalyst (20 mol-%), oxidant (3 equiv.) and additive (1 equiv.) was heated at indicated temperature for 24 h; [b] Isolated yield of product was calculated using coumarin as limiting reagent; [c] equiv. of $ZnCl_2$ was used; [d]Cross coupled product of DEF and oxidant was formed.

Further, different oxidants other than TBHP were screened (Entry 5-8, Table 1), interestingly TBPB and DTPB afforded 24 % and 23 % yields, respectively without the addition of any additive (Entries 5 and 6, Table 1), however no product formation was observed when hydrogen peroxide was used as an oxidant (Entry 8, Table 1). Improvement in the product yields was observed when the reaction temperature was changed from 150 ^{o}C to 90 ^{o}C using TBPB as the oxidant. Under these conditions, various solvents were screened (Entries 10-13, Table 1). TBPB in benzene furnished gratifying results by delivering the desirable product in 69 % yields (Entry 11, Table 1). Next, different catalysts and additives were investigated (Entries 16-24, Table 1), unfortunately all these catalysts and additives exhibited a deteriorating effect on the product yields. It is worth mentioning here that in the cases where $Cu(OAc)_2$ and $CuCl_2$ were used as catalysts, a cross coupled product of TBPB and DEF was obtained[25] without any formation of the desired product even in traces (Entries 16 and 18, Table 1). After several permutations and combinations, the optimized reaction conditions were established as 1.0 equiv. of coumarin, 3.0 equiv. of TBPB, 3.0 equiv. of formamide in benzene as solvent at 90 ^{o}C for 24 h.

Further, the substrate scope of this optimized protocol was evaluated. During the investigations, 7-methoxycoumarin was first treated with different disubstituted aliphatic, alicyclic and aromatic formamides (Table 2). The reactions went smoothly

and delivered the regioselective C-3 functionalized products in moderate to good yields with aliphatic as well as alicyclic formamides (Entries 3a-3e, Table 2). However, no product was observed with diphenylformamide, probably due to steric reasons[24] (Entry 3f, Table 2).

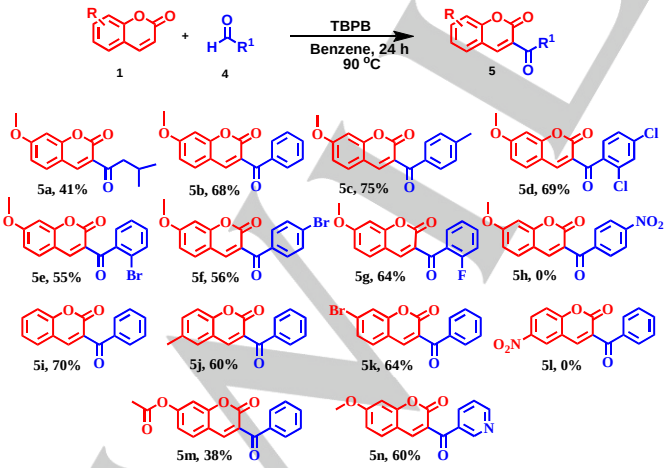
Table 2. Direct formimidation of coumarins.[a],[b]



[a] Reaction conditions: a mixture of 7-methoxycoumarin (**1**) (0.17 mmol), formamides **2** (0.51 mmol) and TBPB (0.51 mmol) was heated at 90 °C for 24 h; [b] CCDC access number for 3c is 1563897.[27]

Subsequently, several differently substituted coumarins were treated with DEF to investigate the role of electronic factors of the functional groups on the product yields. It was found that the coumarins with electron donating groups (such as -OCH_3, -CH_3) afford the desired product in better yields (Entries 3a and 3j, Table 2) as compared to those carrying the electron withdrawing groups (such as -Br) (Entry 3l, Table 2). However, no product formation was observed with coumarins having the -$OCOCH_3$ and -NO_2 as electron withdrawing groups (Entries 3h and 3k, Table 2).

Table 3. Direct Aroylation of coumarins with aldehydes.[a]

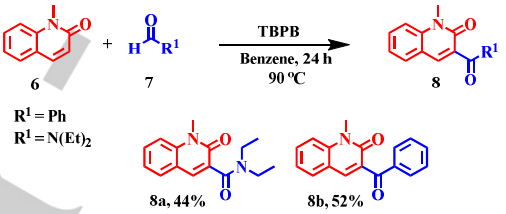


[a] Reaction conditions: a mixture of coumarin **1** (0.17 mmol), aldehyde **4** (0.51 mmol) and TBPB (0.51mmol) was heated at 90 °C for 24 h.

Next, various aliphatic, aromatic and heterocyclic aldehydes were screened with coumarin under optimized reaction conditions and all the screened aldehydes yielded desired products in moderate to good yields (Table 3). Better yields were observed with those aldehydes having electron donating groups on benzene ring whereas electron withdrawing groups present on the aromatic ring of aldehyde provided lower yields. It is worth mentioning here that halogen atoms at *ortho*- and *para*-positions to aldehyde moiety were also tolerated well and yielded the desired products in good yields (Entries 5d-5g, Table 3). However, no product was obtained with *p*-nitrobenzaldehyde as it was completely converted into *p*-nitrobenzoic acid (Entry 5h, Table 3). Moreover, with *iso*-butraldehyde, the desired product was obtained in 41 % yield (Entry 5a, Table 3).

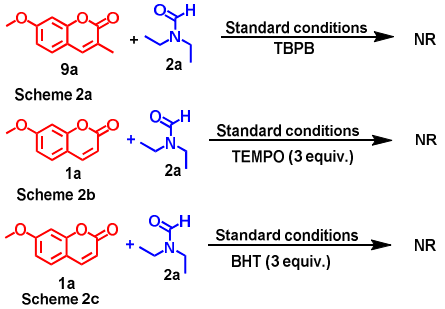
Substrate scope was further investigated with of *N*-methyl quinolone. Both benzaldehyde and DEF afforded the coupling products in moderate yields (Entries 8a and 8b Table 4).

Table 4: Formamidation and aroylation of quinolone.[a]



[a] Reaction conditions: a mixture of N-methyl quinolone **5** (0.17 mmol), compound 7 (0.51 mmol) and TBPB (0.51 mmol) was heated at 90 °C for 24 h.

To get the insight into the reaction mechanism, some control experiments were carried out (Scheme 2). Firstly, the regioselectivity of reaction was studied by treating 3-methyl-7-methoxycoumarin (**9a**) with DEF (**2a**) under optimal reaction conditions (Scheme 2a). Absence of the desired product **3a** as well as C-4 functionalized coumarin derivative, even after exposing the reaction contents for 48 h confirms the regioselectivity of the reaction.

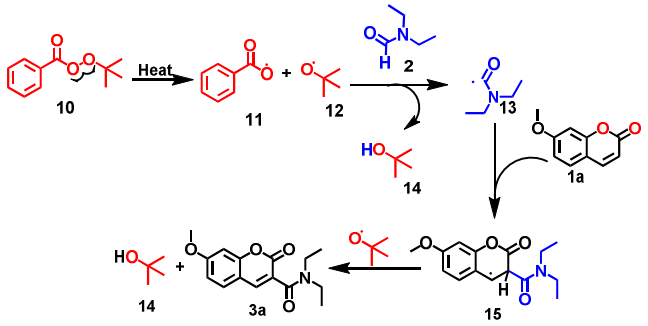


Scheme 2. Control experiments.

Next, when 7-methoxycoumarin (**1a**) and DEF (**2a**) were reacted in the presence of 3 equiv. of TEMPO and 3 equiv. of BHT under the standard reaction conditions, the desired product was also not obtained (Scheme 2b and 2c). The complete suppression of

desired product in presence of TEMPO and BHT confirms the involvement of a radical intermediate in the reaction pathway. Hence, on the basis of these results and literature reports,[10-14] a possible mechanism for the reaction has been proposed (Scheme 3).

Initially, the radical initiator TBPB (**10**) undergoes thermal homolytic cleavage to generate radicals **11** and **12**. Thereafter, these radicals selectively abstract hydrogen atom from DEF (**2**) to generate radical **13**, followed by its addition across the C-3 and C-4 C=C bond of coumarin (**1a**) to afford the intermediate **15**. Subsequently, the intermediate **15** undergoes hydrogen abstraction by tert-butyl radical (**12**) to afford the final product **3a** along with the formation of tert-butyl alcohol (**14**), a useful reagent.



Scheme 3: Plausible mechanisum for the carboxamidation of coumarin

Conclusions

In summary, we have successfully described a general methodology for the regioselective C-3 functionlization of coumarins and aza-coumarin with formamides and aldehydes using radical initiator TBPB in single step. This methodology not only provides a convenient, cost effective and shorter route to access useful products but also includes some characteristic features such as single step reaction, metal free approach, wide substrate scope and excellent regioselectivity, thus making the present methodology superior to the literature precedents.

Experimental Section

General procedure for the cross coupling reaction of coumarins with formamides/aldehydes.

To an oven-dried screw cap reaction tube charged with magnetic bead, 0.17 mmol of coumarin was added to it. Subsequently, 0.51 mmol of TBPB, 0.51 mmol of formamides/aldehyde and 2 mL of benzene were added using micro litre pipette, the reaction mixture was then allowed to heat at 90 ^{o}C for 24 h on a preheated oil bath. After the completion of reaction as monitored by TLC, the reaction mixture was allowed to cool. The solvent present in the reaction mixture was evaporated under vaccum and the residue thus obtained was extracted with ethyl acetate and water (3x50 mL), the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness to yield crude product which was further purified by column chromatography using ethyl acetate and hexane as eluents.

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Keywords: Coumarin-3-carboxamide • Regioselective • Direct amidation • Direct aroylation • Cross dehydrogenative coupling

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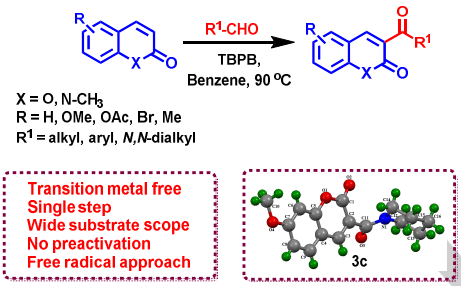
[27] CCDC 1563897 (**3c**) contains the supplementary crystallographic data for this paper. The data could be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Entry for the Table of Contents

FULL PAPER

A general methodology for the regioselective C-3 functionlization of coumarins and aza-coumarin with formamides and aldehydes has been achieved in single step using TBPB as a radical initiator. This methodology provides a convenient and cost effective route to access the products under metal-free conditions with excellent regioselectivity and wide substrate scope.



Key Topic Regioselective carboxamidation of coumarins

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Metal-Free, Regioselective, Dehydrogenative Cross Coupling between Formamides/Aldehydes and Coumarins via C-H Functionalization