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Journal Name

COMMUNICATION

Synthesis of fused oxazole containing coumarin derivatives via oxidative cross coupling reaction using a combination of $CuCl_2$ and TBHP

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Md. Belal[a] and Abu T. Khan[a,b]*

Various fused oxazoles containing coumarin derivatives was accomplished via oxidative cross coupling reaction by employing 20 mol% $CuCl_2$ as the catalyst and TBHP as an oxidant. The reaction proceeds through functionalization of a C-H bond by cross-dehydrogenative coupling (CDC) pathway to produce various oxazole derivatives. The reaction protocol gives an easy access to a number of oxazole derivatives containing coumarin moiety at room temperature from various 3-(benzylamino)-2*H*-chromen-2-one derivatives.

Coumarins are biologically active compounds widely distributed in nature. Many biologically important fused coumarin derivatives have been reported by our research groups as well as by others.[1] Also, a number of naturally occurring fused coumarin derivatives having oxazole moiety exhibit interesting biological properties such as anticancer, antifungal, antiviral, which is shown in Figure 1.[2] Many methods have been reported for the synthesis of various oxazole derivatives in the literature.[3] But, a very few methodologies are available for the synthesis of fused oxazoles containing coumarin derivatives except some classical methods (scheme 1).[4] Therefore, there is a scope to synthesize these compounds by a simpler approach avoiding harsh reaction condition.

Transition metal catalysed oxidative coupling reactions have been widely explored for functionalization of C-H bond.[5] These methodologies are being used for formation of diverse heterocyclic molecular entities in recent time.[6] Functionalization of a sp^3 C-H bond through cross dehydrogenative coupling reaction adjacent to a nitrogen atom is an interesting approach

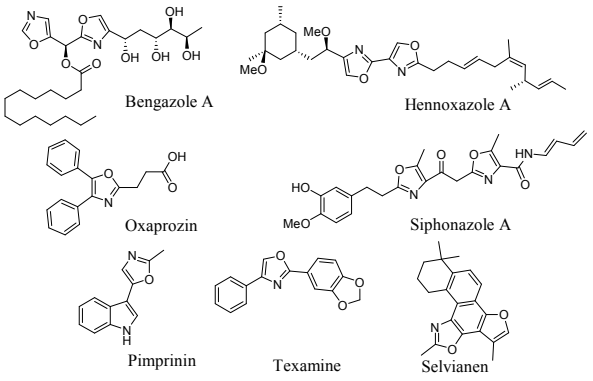
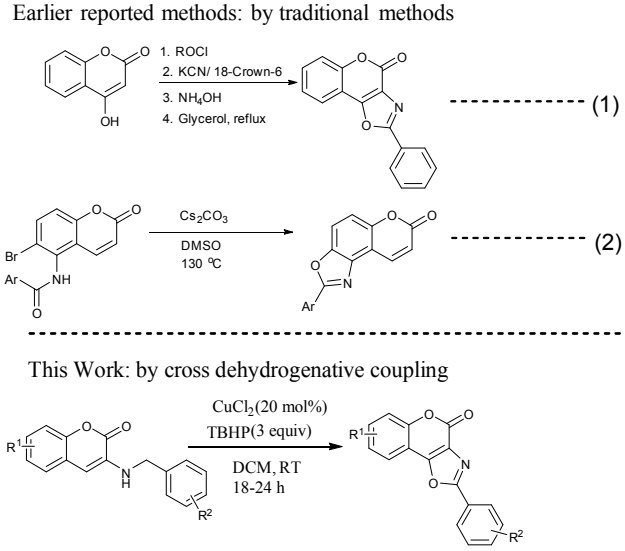


Figure 1. Some biologically active oxazole derivatives[2a, 2d]



Scheme 1. Methods for synthesis of various coumarin fused oxazoles

[a]*Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781 039, India*
[b]*Vice-Chancellor, Aliah University, IIA/27, New Town, Kolkata-700 156, West Bengal, India*
Tel.: +91 361 2582305; fax: +91 361 2582349
E-mail address: atk@iitg.ernet.in (A.T. Khan)
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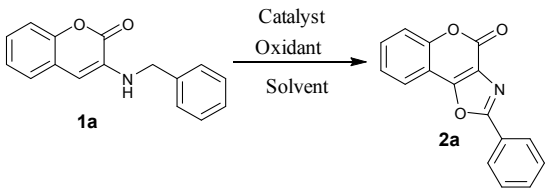
to access various molecular transformations.[7] Literature survey reveals that a number of oxidants have been employed for oxidative coupling reaction to avoid the use of stoichiometric amount of the catalyst.[8] TBHP has been extensively used as a useful oxidant for oxidative cross coupling reactions.[9] Li et al. have reported the use of TBHP and a copper salt to achieve various C-C bond formation adjacent to a nitrogen atom.[10]

The present protocol gives access to various oxazoles derivatives of coumarin through cross dehydrogenative coupling at room temperature. Initially, 3-(benzylamino)-2*H*-chromen-2-one (**1a**) was synthesized using 3-aminocoumarin and benzyl bromide in presence of K_2CO_3 in DMF at 100 ^oC by a previously reported

Table 1. Optimization of reaction condition



Entry	Catalyst (mol%)	Solvent	Oxidant	Time/h	Yield (%)[b]
1	CuI (10)	DCM	TBHP	18	50
2	CuBr (10)	DCM	TBHP	18	50
3	$CuBr_2$ (10)	DCM	TBHP	20	52
4	$Cu(AcO)_2.H_2O$ (10)	DCM	TBHP	24	10
5	$CuCl_2$ (10)	DCM	TBHP	18	64
6	$CuCl_2$ (15)	DCM	TBHP	18	66
7	**$CuCl_2$ (20)**	**DCM**	**TBHP**	**20**	**72**
8	$CuCl_2$ (5)	DCM	TBHP	18	61
9	CuCl (10)	DCM	TBHP	12	58
10	$Cu(NO_2)_2$ (10)	DCM	TBHP	20	60
11	$CuSO_4$ (10)	DCM	TBHP	20	57
12	$CuCl_2$(10)	DCE	TBHP	14	62
13	$CuCl_2$(20)	DCE	TBHP	14	69
14	$CuCl_2$ (10)	CH_3CN	TBHP	24	45
15	$CuCl_2$ (10)	$CHCl_3$	TBHP	32	45
16	$CuCl_2$ (10)	DMF	TBHP	32	NR
17	$CuCl_2$ (10)	DMSO	TBHP	32	NR
18	$FeCl_2$ (10)	DCM	TBHP	24	NR
19	$FeCl_3$ (10)	DCM	TBHP	24	NR
20	$CuCl_2$ (10)	DCM	-------	24	NR
21	-------	DCM	TBHP	24	NR
22	$CuCl_2$ (10)	DCM	H_2O_2	24	NR
23	$CuCl_2$ (10)	DCM	$(PhCO)_2O_2$	24	NR

[a]Unless otherwise stated all the reactions were carried out with 3 mmol of **1a** , 3 equiv. of oxidant, in 3 mL of solvent at RT.
[b]Isolated yield

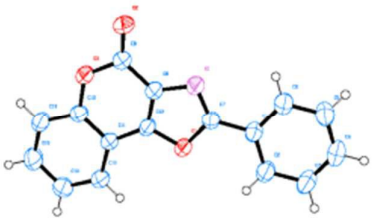


Figure 2 ORTEP diagram of **2a (**CCDC number 1405370)

method by our group (ref: 1a)The substrate **1a** was treated with 10 mol% CuI and TBHP in DCM at room temperature and the desired the product **2a** was obtained in 50 % yield (entry 1, Table 1). The product was characterized by H^1 NMR, ^{13}C NMR and HRMS spectra. Further, the structure of **2a** was also established from single XRD data (Figure 2)

To find out the optimal reaction condition, a number of reactions were executed using different copper salts like CuBr, $CuBr_2$, $Cu(OAc)_2.H_2O$,$CuCl_2$, CuCl, $Cu(NO_2)_2$, $CuSO_4$ as the catalyst and TBHP as the oxidant in DCM at room temperature. The desired product **2a** was obtained from moderate to good yields (entries 2-5 and 9-11). Among various copper salts, $CuCl_2$ was found to be the optimized catalyst for the reaction. The desired product **2a** was obtained in 64%, 66% and 72% yield with 10 mol%, 15 mol% and 20 mol% of $CuCl_2$ respectively employing 3 equivalent of TBHP as oxidant in DCM at room temperature (entry 5-7). Lowering the amount of catalyst from 10 mol% to 5 mol%, yield of desired product was decreased to 61% (entry 8). Apart from DCM, the desired oxazole product was also obtained in 1,2-dichloroethane (DCE), acetonitrile and chloroform (entries 12-15) whereas no product was formed in DMF or DMSO (entry 16 and 17). Furthermore, iron salts like $FeCl_2$ and $FeCl_3$ were found ineffective to produce the desired product (18 and 19). Also, the reaction was unsuccessful without any catalyst or oxidant (entry 20 and 21) indicating that both are crucial for the formation of product. The reaction was not feasible with other oxidants like H_2O_2 and benzoyl peroxide (entry 22 and 23).

A number of 3-(benzylamino)-2*H*-chromen-2-one derivatives were synthesized using various 3-aminocoumarin and benzyl bromide derivatives and was examined to evaluate the substrates scope of the present protocol. At first, the group tolerance on the benzyl moiety was studied. Interestingly, the desired oxazole derivatives of coumarin were afforded in good yield with both electron donating-(**2b**, **2e**, **2h** and **2i**, Scheme 2) and withdrawing substituents (**2c**, **2d**, **2f** and **2g**,). Product **2j** was obtained in 68 % yield containing a heteroatom in the benzyl ring. Whereas replacing benzyl moiety with naphthyl moiety, the desired product **2k** were obtained in significant yield, but in lesser time compared to the benzyl derivatives under the optimized condition. The yield was comparable with substituent at the *meta*- and *para* position of the benzyl group indicating no

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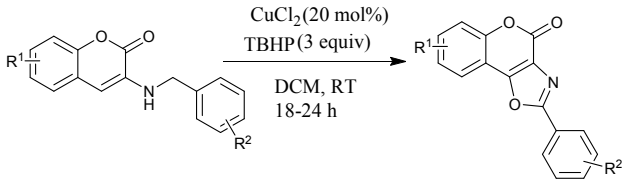
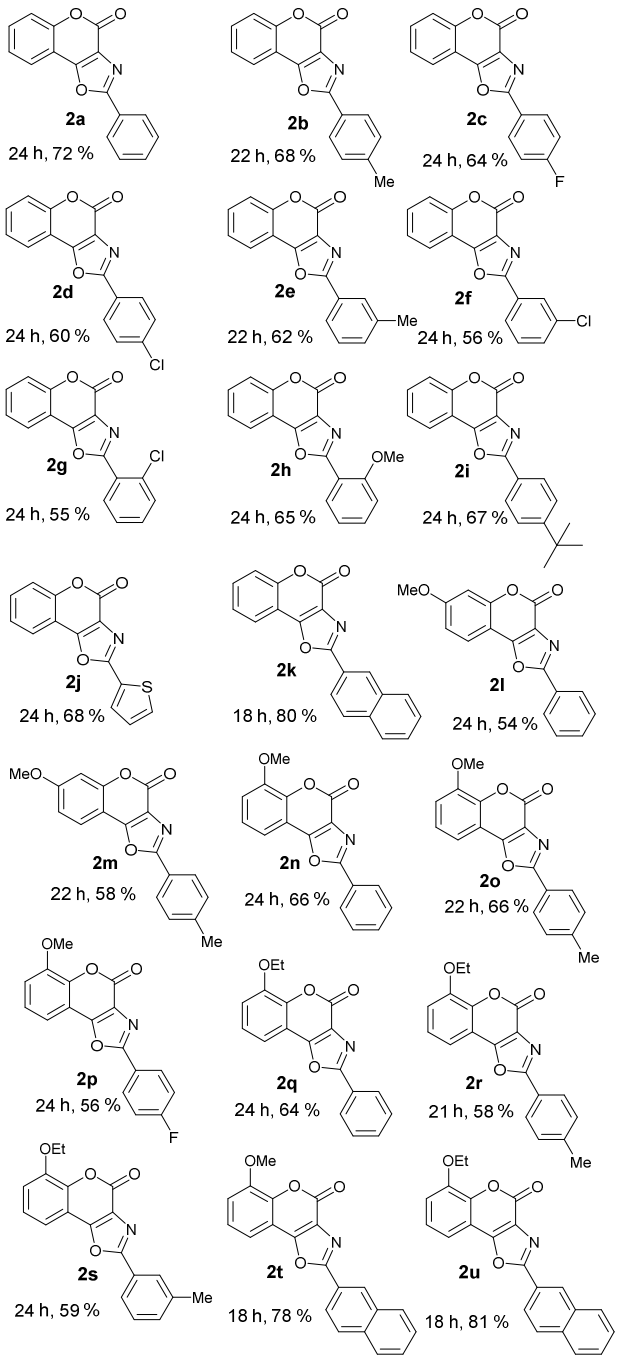
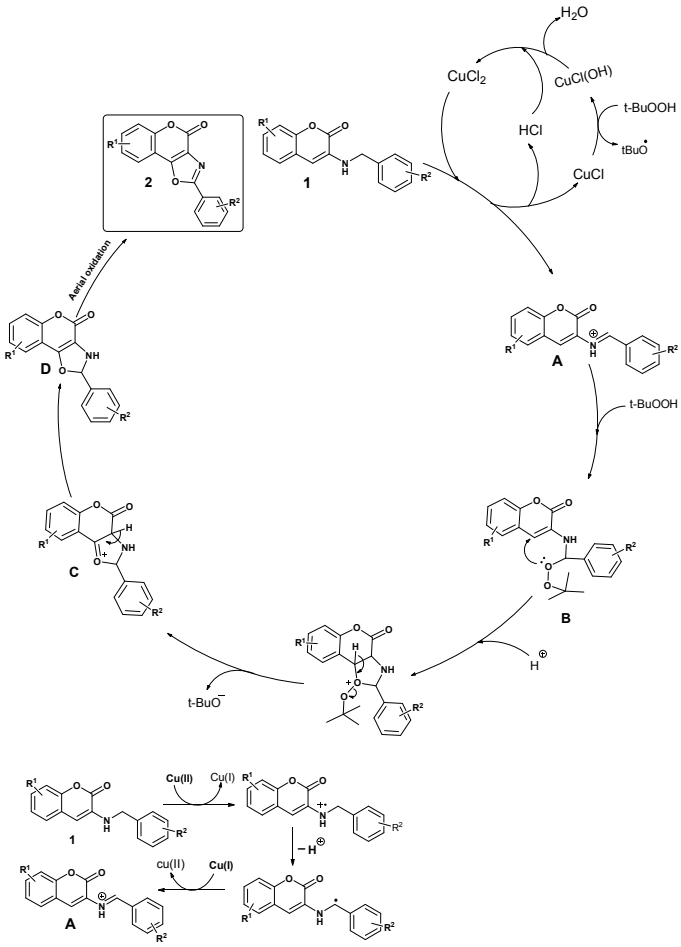
significant role of steric hindrance for the formation of products (**2e**, **2f**. **2g** and **2h**).





Scheme 2. Synthesis of various oxazole derivatives via oxidative cross coupling reaction. All the reaction were carried out with 0.3 mmol of **1** ,3 equiv. of TBHP, 20 mol % of the $CuCl_2$ in 3 mL of DCM at RT. [b]Isolated yield.



Scheme 3. Plausible reaction mechanism

Notably, no product was obtained on replacing benzyl moiety with alkyl moiety.

Similarly, 3-(benzylamino)-2*H*-chromen-2-one with substituents on the coumarin moiety such as 7-MeO, 8-MeO and 8-EtO were also examined and the desired products **2l-u** were isolated in satisfactory yield (scheme 2). Unfortunately, the present protocol is not feasible with electron withdrawing substituents like 6-NO_2, 6-Cl and 6-Br on the coumarin moiety.

From literature survey[11] and our experimental results, a plausible mechanism is presented for the formation of **2** from **1**. Initially an iminium ion **A** (Scheme 3) might be formed from **1** with the help of TBHP/$CuCl_2$ and then another molecule of TBHP attacks the electrophilic centre of **A** to form intermediate **B**. Intermediate **B** cyclizes to intermediate **D** through **C** and finally **D** on aerial oxidation provides the desired product **2**.

Conclusions

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In conclusion we have demonstrated a novel approach for the construction of various fused oxazole containing coumarin derivatives under mild reaction conditions. We do hope that the synthesized compounds may exhibit interesting biological activity.

Acknowledgement

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Graphical Abstract

Synthesis of fused oxazole containing coumarin derivatives via oxidative cross coupling reaction using a combination of $CuCl_2$ and TBHP

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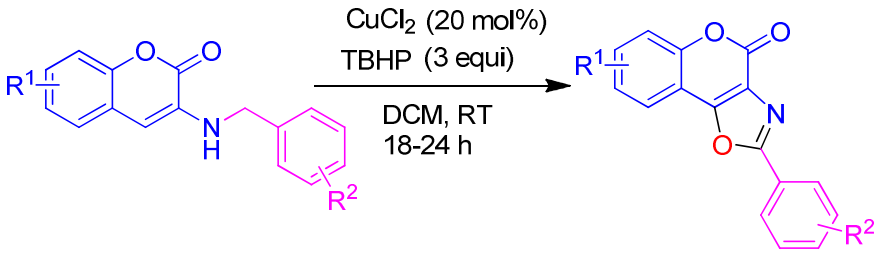

Functionalization of an sp^3 and sp^2 C-H bonds

Formation of two C-O bonds

21 Examples

54 to 81% Yiield