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Direct C-3 Alkylation of Coumarins *via* Decarboxylative Coupling with Carboxylic Acids

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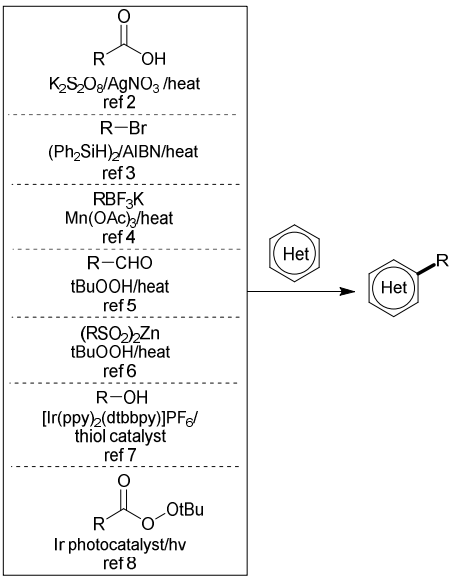
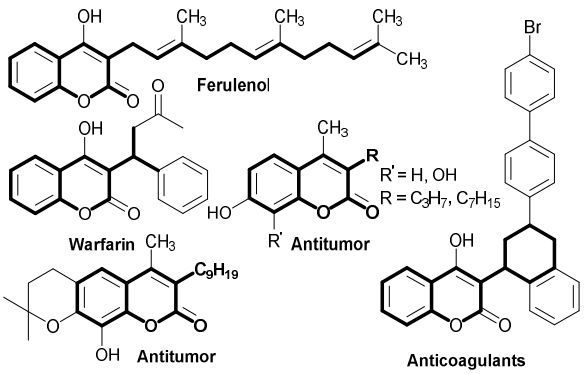
A new method for selective C-3 alkylation of coumarins using carboxylic acids as alkyl sources is reported. This process offers a practical method for the facile construction of 3-alkyl coumarins with a broad substrate scope. The reaction works under metal-free and aqueous media and both cyclic and acyclic aliphatic carboxylic acids participate in this radical C-C cross coupling reaction.

In the past decades, sustainable chemistry as a tremendous challenge has fascinated chemists to develop facile, efficient and environmentally friendly protocols. Among various approaches toward the green chemistry, a great emphasis was placed on protocols which avoid or minimize the use of transition metals in organic synthesis.[1]

Direct C-H functionalization of heteroaromatic scaffolds has become a valuable tool in organic chemistry for the synthesis of biologically active molecules. Alkylation of heteroarenes as one of the most impressive C-C bond-forming reactions provides convenient access to pharmaceutically active compounds. Direct C−H alkylation of heteroaromatic scaffolds by alkyl radicals has been brought to the spotlight consequently, bringing about the substantial development of this type of reactions over the past few years. The seminal work regarding direct C−H alkylation of heteroarenes is often known as 'Minisci' reaction in which carboxylic acids are used as alkylating reagent.[2] Henceforward, several protocols have been evolved using a variety of alkylating agents (Scheme 1).[3-8] Coumarins, significant compounds ubiquitous in plants, are well-known due to their wide array of pharmacological and optical properties.[9] In particular, 3-Alkyl-substituted coumarins are tremendously important molecules because of the occurrence of these structural motifs in a vast range of highly potent drug candidates, many of which have been used in cancer chemotherapy and also as anticoagulants (Scheme 2).[10]



Scheme 1. Previous reports on direct alkylation of heteroarenes



Scheme 2. Biologically active 3-alkyl coumarin derivatives

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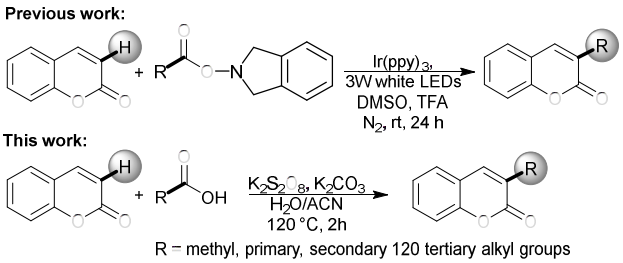


Scheme 3. Strategies for decarboxylative alkylation of coumarin at C-3

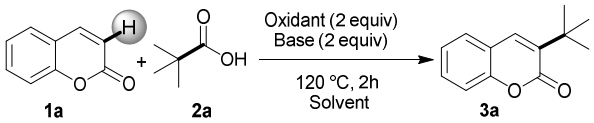
As a result, the development of new and effective strategies on regioselective C-3-alkylation of coumarins is highly desired. Thus far, several developments have been achieved for the synthesis of C-3 alkylated coumarins using various transition metal catalysts, including Cu, Fe and Co. For instance in 2014 Duan and co-workers described a copper catalyzed regioselective benzylation of coumarins at C-3.[11] In other efforts the copper-catalyzed and also the iron-catalyzed C-3-alkylation of coumarins with the use of cycloalkyl ethers and cycloalkanes were demonstrated.[12] Moreover, Du *et. al.* have recently disclosed a cobalt-catalyzed C-3-alkylation of coumarins with alkyl ethers.[13]

Despite the importance of these contributions unfortunately, all these methods are restricted to transition metals and the substrate scope is rather limited and works only with cycloalkanes/ethers and benzyl groups. We have also recently reported a metal-free cross dehydrogenative coupling of coumarins and ethers where, the substrate scope for direct alkylation was limited and a single example of cyclohexane was disclosed.[14]

Carboxylic acids owing to their attractive features such as low cost, high stability and easy availability, represent valuable starting materials in synthetic organic chemistry. Given that, transition metal catalyzed decarboxylative couplings have been an important and very attractive research point of organic synthesis in recent years.[15]

Following our interest in direct functionalization of coumarins[16] herein, we disclose a transition-metal-free alkylation of coumarins with carboxylic acids through a direct decarboxylative cross-coupling process. This protocol features good yields and high regioselectivities, is water compatible, and has environmentally friendly conditions excluding any toxic metals and could open a route for direct instalment of alkyl groups at C-3 of coumarins. Moreover, this protocol affords an unprecedented approach for chain alkylation of coumarins using primary alkyl carboxylic acids under metal-free conditions. The only report in this area is limited to Jin's and Sun's work reported very recently, and could provide alkylated coumarins only under Ir-catalyzed photocatalytic decarboxylative reaction using TFA as an additive (Scheme 3).[17] Some progress in direct arylation of coumarins through an unprecedented metal-free decarboxylative functionalization of arene carboxylic acids is also achieved. Although, there are many reports on transition metal catalyzed decarboxylative coupling of arene carboxylic acids with alkenes,[18] aryl halides,[19] (hetero)arenes[20] and organoboron reagents[21] to the best of our knowledge a transition metal-free decarboxylative cross-coupling of arene carboxylic acids and (hetero)arenes is not precedented.

Table 1. Screening optimal conditionsa



1a 2a 3a

Entry	Oxidant	Base	Solvent	Yield%[a]
1	$K_2S_2O_8$	K_2CO_3	DMSO	25
2	$K_2S_2O_8$	K_2CO_3	DMF	trace
3	$K_2S_2O_8$	K_2CO_3	DCE	0
4	$K_2S_2O_8$	K_2CO_3	ACN	0
5	$K_2S_2O_8$	K_2CO_3	toluene	0
6	$K_2S_2O_8$	K_2CO_3	PhCl	0
7	$K_2S_2O_8$	K_2CO_3	H_2O	45
8	$K_2S_2O_8$	K_2CO_3	DMSO/H_2O (1/1)	0
9	$K_2S_2O_8$	K_2CO_3	DMF/H_2O (1/1)	0
10	$K_2S_2O_8$	K_2CO_3	DCE/H_2O (1/1)	trace
11	$K_2S_2O_8$	K_2CO_3	PhCl/H_2O (1/1)	0
12	$K_2S_2O_8$	K_2CO_3	ACN/H_2O (1/1)	55
13	$(NH_4)_2S_2O_8$	K_2CO_3	ACN/H_2O (1/1)	30
14	TBHP	K_2CO_3	ACN/H_2O (1/1)	0
15	DTBP	K_2CO_3	ACN/H_2O (1/1)	0
16	BQ	K_2CO_3	ACN/H_2O (1/1)	0
17	DDQ	K_2CO_3	ACN/H_2O (1/1)	0
18	—	K_2CO_3	ACN/H_2O (1/1)	0
19	$K_2S_2O_8$	NaOAc	ACN/H_2O (1/1)	43
20	$K_2S_2O_8$	DABCO	ACN/H_2O (1/1)	0
21	$K_2S_2O_8$	$NaHCO_3$	ACN/H_2O (1/1)	50
22	$K_2S_2O_8$	LiOAc	ACN/H_2O (1/1)	35
23	$K_2S_2O_8$	KOAc	ACN/H_2O (1/1)	42
24	$K_2S_2O_8$	—	ACN/H_2O (1/1)	Trace
25	**$K_2S_2O_8$**	**K_2CO_3**	**ACN/H_2O (1/5)**	**74**

[a] Reaction conditions: Coumarin **1a** (0.2 mmol), pivalic acid **2a** (2 equiv), oxidant (2 equiv), base (2 equiv), solvent (0.6 ml) were heated in a sealed tube at 120˚C for 2 h.

At the outset, decarboxylative alkylation of coumarin **1a** employing pivalic acid **2a** was chosen as a benchmark reaction for the optimization of the reaction conditions and different oxidants, bases and solvents were screened (Table 1). The reaction of coumarin and pivalic acid in the presence of $K_2S_2O_8$ as oxidant and K_2CO_3 as base in various solvents at 120˚C, was explored and fortunately the desired product was detected in 25% yield in DMSO (entries 1-6). Fortunately, conducting the reaction in water, increased the yield of the desired product to 45% (entry 7). According to the low solubility of the substrates in water, co-solvents (v/v: 1/1) were chosen and the best result was obtained in ACN/H_2O (entries 8-12). Inferior results were obtained when various oxidants including $(NH_4)_2S_2O_8$, DTBP, TBHP, BQ and DDQ were employed (entries 13-17). The reaction did not proceed in the lack of the oxidant, suggesting

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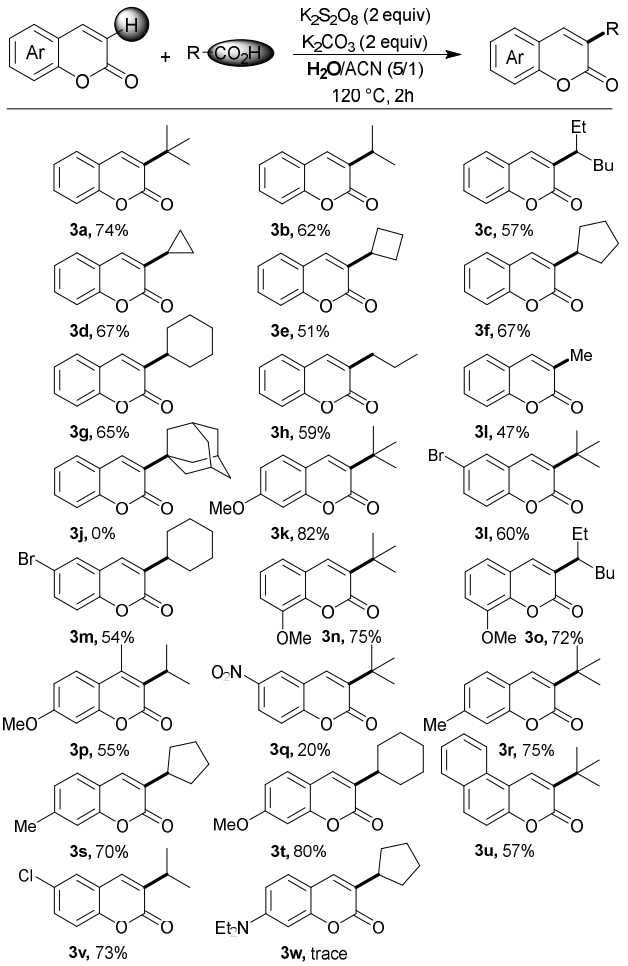
its crucial importance for this type of transformation (entry 18). A screening of various bases was also performed and among the bases surveyed, K_2CO_3 proved to be the best (entries 19-23). Due to the great environmental concerns of solvents and to improve the sustainability of this transformation, the water content was gradually increased and gratefully a 74% of the desired product was obtained in 2h in H_2O/ACN with 84% of water content (v/v: 5/1) (entry 25). Applied reaction condition is appreciated due to water compatibility of the reaction, and toxic metal- and waste-free production of alkyl coumarins in short reaction times.

Having established the optimized reaction conditions, the substrate scope was evaluated (Table 2). Using aliphatic carboxylic acids including primary, secondary and tertiary carboxylic acids in the current approach, a variety of coumarins with linear and branched alkyl groups at C-3 were obtained in good to high yields (**3a**-**3c**). Cyclobutyl, pentyl and hexyl analogues were also obtained in 51%, 67% and 65% yields, respectively (**3e**-**3g**). Cyclopropanes as a common part of many pharmaceuticals[22] provide distinct structural and electronic properties when installed on heteroaryl scaffolds. It has been evidenced however, that cyclopropyl carboxylic acids are traditionally unproductive alkylating coupling partners in Minisci reactions due to the ring-opening of cyclopropyl radicals in the course of the reaction.[23] Fortunately, cyclopropylation reaction of coumarin proceeded smoothly under the presented reaction conditions to afford the desired product **3d** in 67% isolated yield. Furthermore, more challenging linear carboxylic acids producing primary radicals participated well in this alkylation process. Gratifyingly, acetic acid was used successfully and furnished the desired 3-methyl coumarin **3i** in moderate yield considering the high reactivity of methyl radical. There are several reports which highlight the importance of methyl groups in biologically active molecules. Instalment of methyl groups have proved to improve properties of drug candidates and physical properties of molecules.[24]

Moreover, the scope of the methodology was investigated with respect to coumarins. Methyl and methoxy substituted coumarins led to the desired products in yields exceeding 70%. Gratifyingly, 4-substituted coumarin furnished the desired product **3p** in 55% isolated yield despite of steric encumbrance. To our delight, bromo and chloro-substituted coumarins were also found to be suitable for these transformations, which provide useful components for further transformations through traditional cross-coupling reactions (**3m**, **3l** and **3v**). Alkylation of the π–extended coumarin with interesting photophysical and biological properties[25] also proceeded smoothly to afford the desired 3-alkylated adduct **3u** in 57% isolated yield.

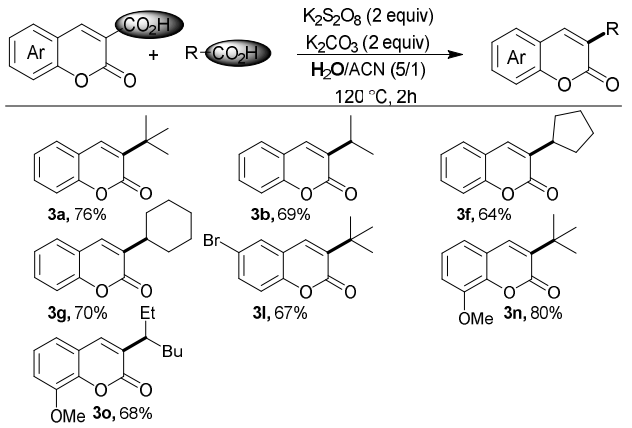
Pleasingly, alkylation of coumarins at C-3 was also achieved *via* a metal-free double decarboxylative cross-coupling of coumarin-3-carboxylic acids and aliphatic acids (Table 3). This transformation removes the surplus carboxylate group left behind as a result of the common synthetic routes[26] in the course of the reaction and protodecarboxylation[27] is not pre-requisite. This transition-metal-free one step sequence was possible using the optimized reaction conditions and a comparable yield of the desired products were obtained.

Table 2. Scope of the alkylation of coumarins with aliphatic carboxylic acids[a].



[a]All reactions were run under the optimized reaction conditions.

Table 3. Scope of alkylation of coumarin-3-carboxylic acids with aliphatic acids[a]



[a]All reactions were run under the optimized reaction conditions.

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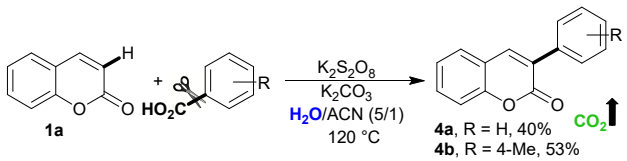
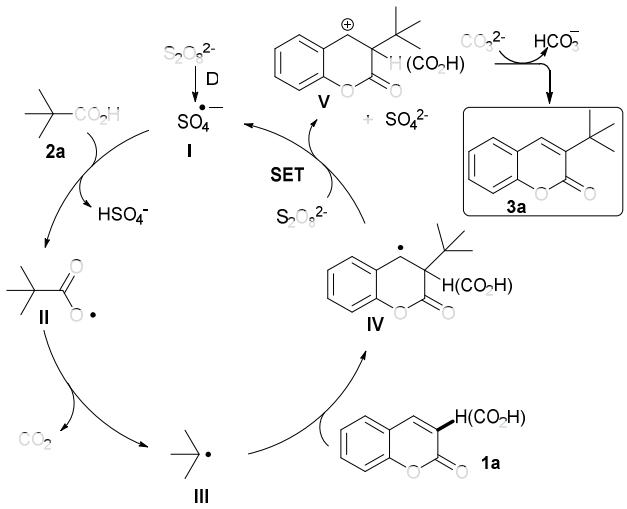


Scheme 4. Decarboxylative coupling of arene carboxylic acids and coumarin.



Scheme 5. Plausible Mechanism for C-3 Alkylation of Coumarin

Previous efforts directed towards functionalization of these scaffolds excluding metals however, provided only esterification products or C-4 functionalization of coumarins with subsequent reduction of the double bond to build up 3,4-dihydrocoumarins.[28]

Fortunately, some aromatic carboxylic acids were also favoured in this system and afforded the corresponding products (Scheme 4).

To get insight to the mechanism of this reaction, 2,2,6,6-tetramethylpiperidyl-1-oxyl (TEMPO) (2.0 equiv.) as a radical scavenger was added into the model reaction mixture of coumarin and pivalic acid and the reaction was fully suppressed. This effect may suggest a radical mechanism for the process. A plausible radical mechanism is accordingly outlined in Scheme 4 based on the control experiment and previous literature. Initially, the thermal decomposition of $S_2O_8^{2-}$ with an estimated standard redox potential of 2.01 V in aqueous solution, affords sulfate radical anion.[29] Hydrogen-atom transfer between the carboxylic acid and the sulfate radical anion, generates the carboxyl radical which quickly undergoes decarboxylation to provide the corresponding alkyl radical.[30] Then the alkyl radical adds to the double bond of the substrate **1a**, which affords the most stable radical intermediate **IV**. Finally, further oxidation of **IV** by another sulfate radical produces the corresponding carbocation **V**,[31] and deprotonation/decarboxylation of intermediate **V** under basic conditions regenerates a double bond leading to **3a**.

Furthermore, considering the results of radical reactions in aqueous media, the origin of the favorable solvent effect would be owing to extremely high polarity of water, strong hydrogen bonding ability, here with carbonyl group of coumarin, and lack of easily transferable hydrogen via a radical process.[32]

Conclusions

In conclusion, we have developed an efficient and practical decarboxylative alkylation of coumarins in an environmental benign manner. This protocol works with a wide spectrum of readily available aliphatic cyclic and acyclic acids and coumarin(-3-carboxylic acid)s affording interesting 3-alkylcoumarins that serve as the key intermediates in the synthesis of drug candidates. Furthermore, this protocol featured simple instalment of primary alkyl groups at C-3 of coumarins which remains a formidable challenge. This simple procedure which proceeds in aqueous solvent mixtures could serve as an alternative approach towards construction of 3-alkyl coumarins.

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Conflicts of interest

There are no conflicts of interest to declare.

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Graphical Abstract:

Direct C-3 Alkylation of Coumarins *via* Decarboxylative Coupling with Carboxylic Acids

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A metal-free direct alkylation of coumarins using carboxylic acids in aqueous media with a broad substrate scope is devised.