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Visible-light synthesis of 4-substituted-chroman-2-ones and 2-substituted-chroman-4-ones *via* doubly decarboxylative Giese reaction†

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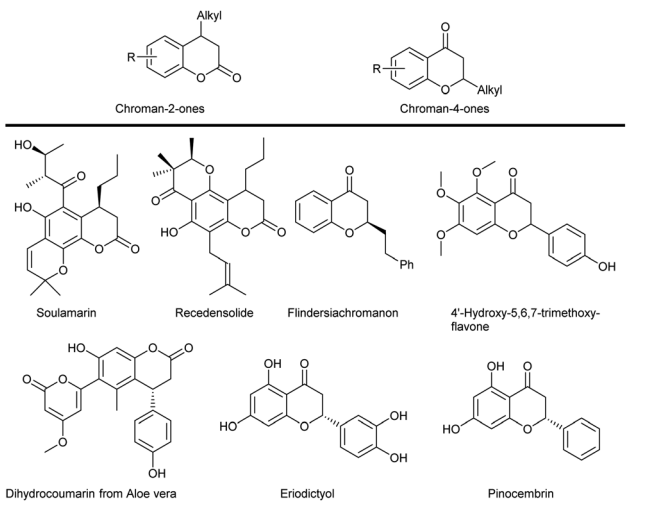
Doubly decarboxylative, photoredox synthesis of 4-substituted-chroman-2-ones and 2-substituted-chroman-4-ones is described. The reaction involves two independent decarboxylation processes: the first one initiating the cycle and the second completing the process. Visible light, photoredox catalyst, base, anhydrous solvent and inert atmosphere constitute the key parameters for the success of the developed transformation. The protocol proved applicable for coumarin-3-carboxylic acids and chromone-3-carboxylic acids as well as *N*-(acyloxy)phthalimide which served as precursors of the corresponding alkyl radicals.

Chroman-2-ones and their derivatives constitute privileged structural motifs present in various natural products (Scheme 1).[1] Similarly, the chroman-4-one ring system can be found in various bioactive molecules relevant for the life-science industry.[2] Representative examples of both groups of compounds are shown in Scheme 1. Soulamarin, isolated from stem bark has found application in folk medicine to treat rheumatism, varicose veins, haemorrhoids and ulcers.[3] Recedensolide shows activity against human cervical epitheloid carcinoma.[4] Flavanoids, such as eriodictyol and pinocembrin, are associated with reducing risk of certain chronic diseases.[5] Natural flavanones isolated from flowers of *Chromolaena odorata* such as 4′-hydroxy-5,6,7-trimethoxyflavanone are reported to have antimycobacterial activity.[6]

The addition of free radicals to electron-deficient olefins is known in the literature as Giese reaction (Scheme 2).[7] Recently, owing to the development of photocatalysis, the synthetic potential of this and related reactions has been vastly expanded.[8] Advancements in this field arises from the development of photo-initiated methods allowing for free radical formation under mild and non-toxic conditions. An interesting way to generate free radicals involves the usage of *N*-(acyloxy) phthalimides.[9] The formation of free radical is initiated by one-electron reduction with subsequent decarboxylation. Recently, the potential of this method has been confirmed in the Giese reaction with various electron-poor olefins.[10]

Decarboxylative Michael reaction that involves the addition to carboxylic-acid-activated olefins followed by decarboxylation reaction constitutes a powerful synthetic tool.[11] Coumarin-3-carboxylic acids **2** and chromone-3-carboxylic acids **4** are useful reactants participating in this reaction opening access to biologically relevant chroman-2-ones **3** and chroman-4-ones **5**.[12,13] Recently, doubly decarboxylative reactions involving these reagents have also been developed.[14] Surprisingly, decarboxylative Giese reaction with carboxylic-acid-activated olefins has not been a subject of studies so far. Herein, we report the first photocatalytic, doubly decarboxylative Giese reaction



Scheme 1 The importance of chroman-2-ones and chroman-4-ones.

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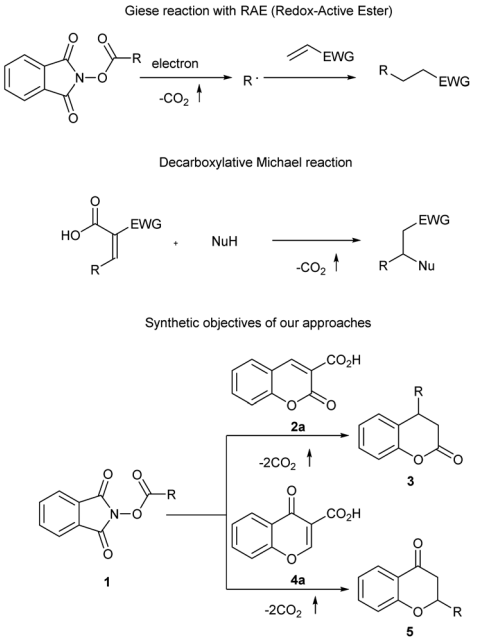
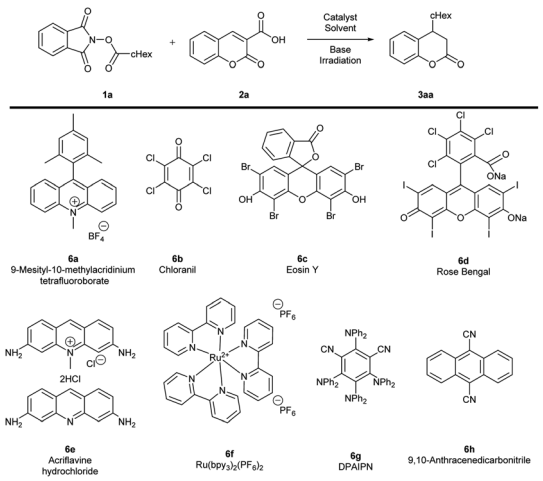


Scheme 2 The importance of decarboxylative approaches in organic synthesis and the synthetic objectives of our study.

which is applicable to electron poor carboxylic acids. The developed strategy benefits from mild reaction conditions.

Optimization studies were performed using coumarin-3-carboxylic acid **2a** and 1,3-dioxoisoindolin-2-yl cyclohexane carboxylate **1a** (NHPI esters) as model substrates (Table 1). Initial experiments were performed in CH_2Cl_2 in the presence of DIPEA as a donor of electron and base the corresponding photoredox catalyst under LED irradiation (with the light source of suitable wavelength) under inert atmosphere. In the first part of the optimization studies, the catalytic activity of eight different photoredox catalysts was tested (Table 1, entries 1–8). When 9-mesityl-10-methylacridinium tetrafluoroborate **6a**, chloranil **6b** or **6h** were used, the formation of target product **3aa** was not observed (Table 1, entries 1 and 2). The best yield was obtained in the presence of $Ru(bpy_3)_2(PF_6)_2$ **6f** (Table 1, entry 6). In the course of further studies, the effect of the solvent on the reaction outcome was evaluated (Table 1, entries 9–13). The use of $CHCl_3$ did not ensure the product formation (Table 1, entry 9). Similar effect was observed in THF and toluene (Table 1, entries 10 and 11). The desired reaction took place also in acetonitrile and DMF, however, lower yield than in the case of CH_2Cl_2 was obtained (Table 1, entries 12 and 13). Subsequently, the effect of base on the reaction outcome was evaluated (Table 1, entries 14 and 15). When triethylamine was used, the yield of the reaction decreased (Table 1, entry 14) and the application of quinine did not result in the product **3aa** formation (Table 1, entry 15). In the course of further studies control experiments were performed (Table 1, entries 16–20). The reaction did not proceed in the absence of neither photoredox catalysts (Table 1, entry 16, presumably electron donor–acceptor complex of DIPEA with NHPI esters was not efficiently formed in this case), nor a base (Table 1, entry 17).[9a] Similar effect was observed

Table 1 Doubly decarboxylative Giese reaction – optimization studies involving coumarin-3-carboxylic acid **2aa**[a]



Entry	Cat	Solvent	Base	Cat. mol%	Yield [%]
1[b]	**6a**	CH_2Cl_2	DIPEA	10	—
2[c]	**6b**	CH_2Cl_2	DIPEA	10	—
3[d]	**6c**	CH_2Cl_2	DIPEA	10	56
4[d]	**6d**	CH_2Cl_2	DIPEA	10	63
5[b]	**6e**	CH_2Cl_2	DIPEA	10	26
6[b]	**6f**	CH_2Cl_2	DIPEA	10	82
7[b]	**6g**	CH_2Cl_2	DIPEA	10	42
8[b]	**6h**	CH_2Cl_2	DIPEA	10	—
9[b]	**6f**	$CHCl_3$	DIPEA	10	—
10[b]	**6f**	THF	DIPEA	10	—
11[b]	**6f**	PhMe	DIPEA	10	—
12[b]	**6f**	DMF	DIPEA	10	61
13[b]	**6f**	MeCN	DIPEA	10	58
14[b]	**6f**	CH_2Cl_2	TEA	10	47
15[b]	**6f**	CH_2Cl_2	Quinine	10	—
16[e]	—	CH_2Cl_2	DIPEA	—	—
17[b]	**6f**	CH_2Cl_2	—	10	—
18[f]	**6f**	CH_2Cl_2	DIPEA	10	—
19[b]	**6f**	CH_2Cl_2	DIPEA	5	53
20[g]	**6f**	CH_2Cl_2	DIPEA	10	35
21[h]	**6f**	CH_2Cl_2	DIPEA	10	—

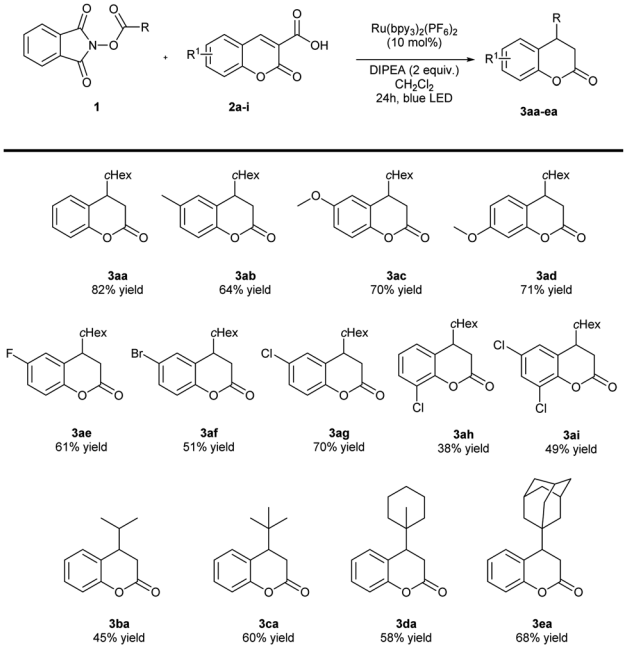
[a] All reactions were performed in a 0.20 mmol scale using **1a** (1.2 equiv.) and **2a** (1.0 equiv.) in the presence of the corresponding photoredox catalyst **6** (10 mol%) and the corresponding base (2 equiv.) in the solvent (3 mL). [b] Reaction performed under irradiation with the blue light. [c] Reaction performed under irradiation with the violet light. [d] Reaction performed under irradiation with the green light. [e] Reaction performed without catalyst. [f] Reaction performed in the dark. [g] The reaction performed in the presence of DIPEA (1.2 equiv.). [h] Reaction performed in the presence of TEMPO (1 equiv.).

when the transformation was attempted in the dark (Table 1, entry 18), thus confirming the crucial effect of photocatalyst and the source of light on the reaction outcome. The amount of the photocatalyst **6f** was possible to be lowered to 5 mol% resulting in decrease of yield to 53% after 24 hours (Table 1, entry 19). On the other hand, it was possible to perform the reaction with DIPEA (1.2 equiv.) but the yield of the reaction decreased (Table 1, entry 20). Noteworthily, the reactivity was quenched in the

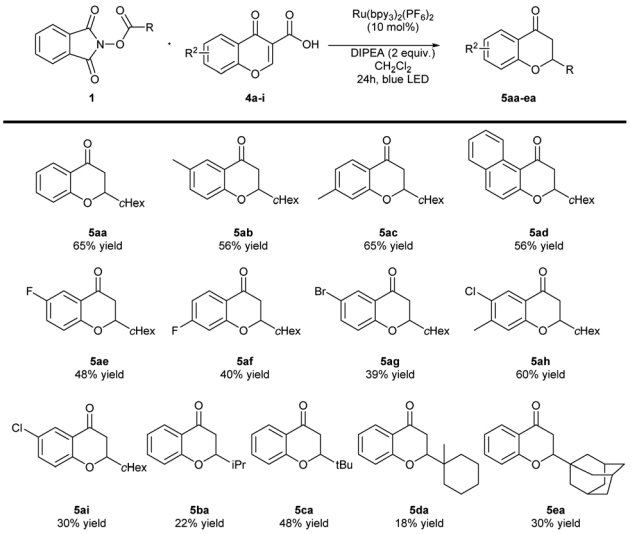
presence of TEMPO confirming the radical mechanism of the process (Table 1, entry 21).

With the optimized reaction conditions in hand (Table 1, entry 6), the applicability of the developed methodology was studied (Schemes 3 and 4). Initially, various coumarin-3-carboxylic acids **2a–i** were tested (Scheme 3). Acids **2b–d** bearing electron-donating groups on the aromatic ring provided products **3ab–ad** with higher yields. Similarly, carboxylic acids **2e–i** with electron-withdrawing groups also provided products with good yields. The lowest yield was obtained for coumarin-3-carboxylic acid **2h** with chlorine substituent in the 8-position. In the second stage of the scope studies various *N*-(acyloxy)phthalimides **1a–e** were investigated (Scheme 3). *N*-(Acyloxy)phthalimides **1a–e** that served as precursors of secondary and tertiary alkyl radicals turned out to be suitable components in the developed reaction. Target products **3ba–ea** were efficiently formed. However, the use of primary radicals turned out to be problematic. In the case of benzylic radical precursor, a dimerization of the corresponding radical was faster than the addition to the electrophile **2a**.

In the second part of our studies, chromone-3-carboxylic acids **4** were tested as acceptors in the doubly decarboxylative Giese reaction employing the same conditions that were used in the case of coumarine-3-carboxylic acids **2** (Scheme 4). The use of **4b–d** bearing electron-donating groups provided **5ab**, **5ac**, **5ad** with good results. On the other hand, the reaction of chromone-3-carboxylic acids **4e–i** with electron-withdrawing groups provided products **5ae–5ai** with slightly lower efficiency. Chromone-3-carboxylic acid **4h** bearing two substituents with opposite electronic effects was also well-tolerated. Other alkyl radical precursors **1b–e** were also utilized in the reaction with chromone-3-carboxylic acid **4a**. The *tert*-butyl substituted



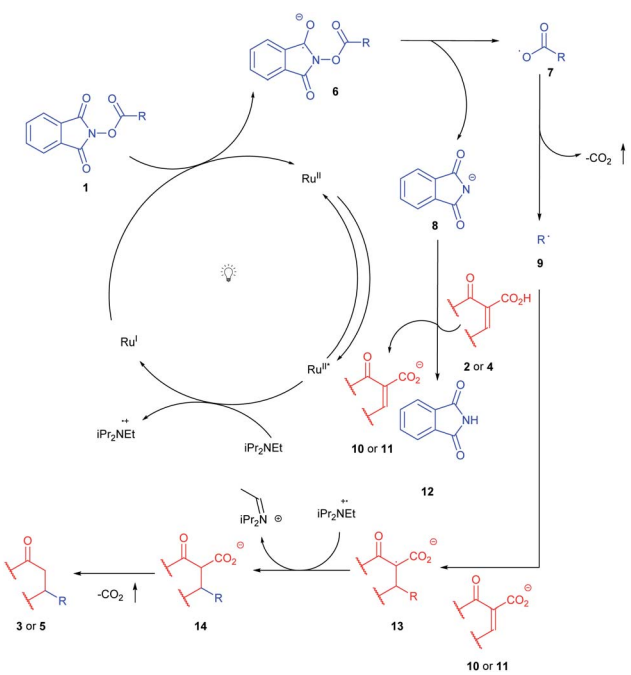
Scheme 3 Doubly decarboxylative Giese reaction – reaction involving coumarin-3-carboxylic acids **2**.



Scheme 4 Doubly decarboxylative Giese reaction – reaction involving chromone-3-carboxylic acids **4**.

product **5ca** was obtained with the highest yield in this part of the study. Unfortunately, the rest of examples showed lower responsiveness to participate in the reaction.

The postulated mechanism of both developed reactions is similar and begins with photocatalyst excitation (Scheme 5). Then the electron transfer from the amine to the photocatalyst takes place. Fluorescence quenching and cyclic voltammetry experiments confirmed the lack of quenching in the case of acids **2a** or **4a** as well as *N*-(acyloxy)phthalimide **1a** (for details see ESI†). Subsequently, Ru(I) species acts as reductant of the *N*-(acyloxy)phthalimide **6**. In turn, **7** undergoes decarboxylative



Scheme 5 Doubly decarboxylative Giese reaction – mechanism.

degradation with the formation of an alkyl radical **9**. The newly formed radical **9** undergoes Giese reaction with the acceptor **10** or **11**. Transfer of the hydrogen atom from the radical cation originating from amine and subsequent decarboxylative protonation terminates the reaction affording **3** or **5** as target products.[10a]

Conclusions

In conclusion, we have developed a doubly decarboxylative photocatalytic Giese reaction. It exemplifies the unique application of a free carboxylic-acid-activated olefins in a radical transformation. The reaction was applicable to a carboxylic acids as various coumarin-3-carboxylic acids **2a–i** and chromone-3-carboxylic acids **4a–i** served as effective Giese acceptors. The reaction can be described as doubly decarboxylation process with the first decarboxylation initiating the cycle and the second completing the process. Target, biologically relevant 4-substituted-chroman-2-ones **3aa–ea** and 2-substituted-chroman-4-ones **5aa–ea** were obtained in good to high yields under mild reaction conditions.

Conflicts of interest

There are no conflicts to declare.

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