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Tandem sp^3 C−H Functionlization/Decarboxylation of 2-Alkylazaarenes with Coumarin-3-carboxylic Acids

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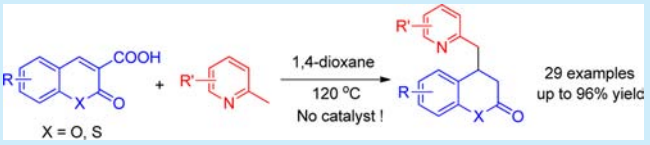
Supporting Information

ABSTRACT: The catalyst-free sp^3 C−H functionalization of 2-alkylazaarenes has been achieved in the reaction with (thio)coumarin-3-carboxylic acids. Followed by a tandem decarboxylation, this method provides facile synthesis of biologically important azaarene-substituted 3,4-dihydro(thio)-coumarins in a single step in high yields.



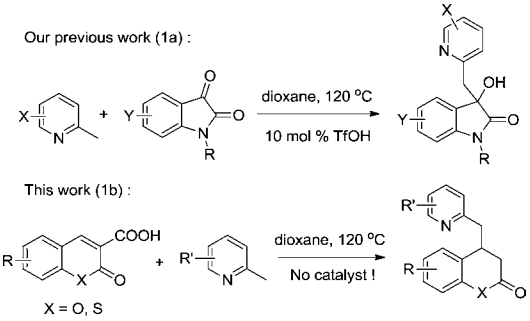
3,4-Dihydrocoumarins constitute an exceptional class of structural motifs which have been found widely present in natural products and biologically active molecules.[1] The compounds of this family exhibit a broad spectrum of pharmacological properties such as protein transacetylase, protein kinase, reductase inhibitory, antioxidant, and blocking of ATP-sensitive potassium channel activities.[2]

Furthermore, this type of compound can be applied as a flavoring agent in the food industry.[3] Consequently, there has been growing interest in modification and functionalization of this class of compounds from both organic and medicinal chemists, aiming to find new applications from these compounds. Among this, the conjugate addition of various nucleophiles to coumarins provides one of the most straightforward methods for the synthesis of diversified 3, 4-dihydrocoumarins.[4] However, much remains to be explored on the derivatization of heteroarenes with coumarins and 3,4-dihydrocoumarins despite universal biological properties and applications in drug discovery and material sciences of heteroarenes.[5]

Significant progress has been achieved for the development of direct sp^3 C−H bond functionalization of 2-alkylazaarenes without resorting to the expensive noble transition metals such as Pd and Rh.[6,7] Various alkylated pyridine derivatives can be synthesized using much cheaper and greener Lewis acid catalysts in an efficient manner, which are important structural motifs present in natural products, pharmaceuticals, and functional materials.[8] However, the research on nonmetal or catalyst-free versions of this reaction is highly desirable and environmentally valuable since no extra effort is needed to remove the toxic metal residues. In this context, we presented the first Brønsted acid-catalyzed sp^3 C−H functionalization of 2-methylazaarenes, leading to facile synthesis of biologically important azaarene-substituted 3-hydroxy-2-oxindoles in one step (Scheme 1a).[9a]

As further research in this field, we proposed that if introducing a carboxyl group in some electron-deficient olefins, the substrate could be served as a Brønsted acid to activate 2-alkylazaarenes, thus triggering the reaction in the absence of catalyst, which can be called "self-activation", to functionalize 2-alkylazaarenes in a more efficient way. As such, coumarin-3-carboxylic acid came into our sight and was selected as a suitable substrate for this purpose. Although pyridine and 3,4-dihydrocoumarin are all important motifs in natural products, to the best of our knowledge, no direct method for the synthesis of azaarene-substituted 3,4-dihydrocoumarins has been reported, while it holds great potential for production of new biologically important compounds and new pharmaceuticals. As a continuation of development of an efficient and green manner to construct biologically and medicinally important molecules,[9] herein we present the catalyst-free tandem sp^3 C−H activation/decarboxylation of 2-alkylazaarenes with coumarin-3-carboxylic acids to furnish the azaarene-substituted 3,4-dihydrocoumarin derivatives in one step (Scheme 1**b**).

Scheme 1. sp^3 C−H Functionalization of 2-Alkylazaarenes



To test our hypothesis, the initial study was conducted on the reaction of 2,6-lutidine **1a** and coumarin-3-carboxylic acid **2a** in 1,4-dioxane under catalyst-free conditions. To our delight, the reaction proceeded successfully and the corresponding product **3a** was obtained in 94% yield without any catalyst in dioxane at 120 °C (Table 1, entry 1). The lower temperature gave inferior results (Table 1, entries 2 and 3), and no reaction occurred when the temperature was decreased to 80 °C (Table

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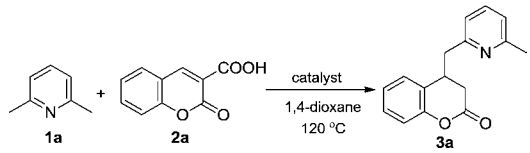
Table 1. Optimization Studies[a]



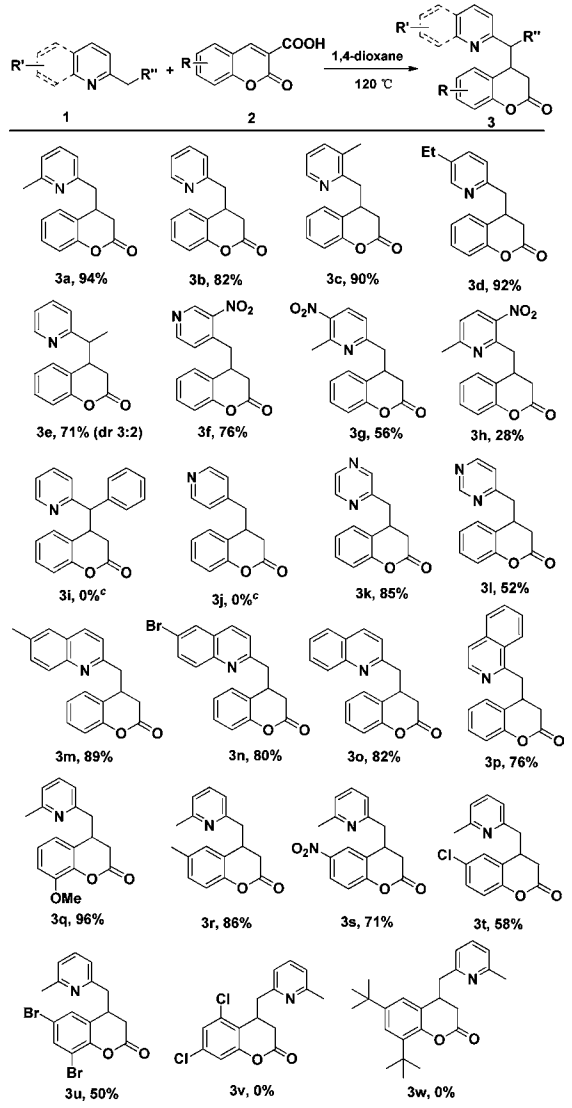
entry	catalyst	solvent	temp (°C)	yield[b] (%)
1		dioxane	120	94
2		dioxane	100	90
3		dioxane	90	77
4		dioxane	80	0
5		THF	120	64
6		DMF	120	69
7		toluene	120	87
8		DMSO	120	62
9	$Sc(OTf)_3$	dioxane	120	62
10	$Yb(OTf)_3$	dioxane	120	64
11	$La(OTf)_3$	dioxane	120	67
12	$Cu(OTf)_2$	dioxane	120	88
13	AgOTf	dioxane	120	66
14	$Zn(OTf)_2$	dioxane	120	75
15	TFA	dioxane	120	52
16	TfOH	dioxane	120	76
17	CH_3COOH	dioxane	120	86
18	p-FC_6H_4COOH	dioxane	120	74

[a]Reactions were conducted with **1a** (0.75 mmol), **2a** (0.3 mmol), and catalyst (10 mol %) in 1 mL of solvent for 48 h. [b]Isolated yield.

1, entry 4). Other solvents also worked well at 120 °C without catalyst, although the yield was not improved (Table 1, entries 5−8). A variety of Lewis acids and Brønsted acids (10 mol %) were also investigated at 120 °C for comparison with the catalyst-free condition, and it was found that all of the tested Lewis acids and Brønsted acids catalysts gave moderate to good yields (Table 1, entries 9−18), which provides the rare example that both Lewis acids and Brønsted acids catalysts are all effective in a single sp^3 C−H activation reaction. However, all of the results were inferior to those under catalyst-free conditions, which eventually corroborated our hypothesis.

With the optimized conditions in hand, the substrate scope was investigated and the results are shown in Scheme 2. A series of 2-substituted pyridines were examined under the optimized conditions, and corresponding products **3a−h** were produced in good to excellent yields. No reaction occurred for 2-benzylpyridine (**3i**) probably due to the steric hindrance caused by the phenyl group. Notably, when γ-methylpyridine was employed, the analogous product **3j** was not detected. However, if a nitro group was introduced at the β-position of 4-picoline, the reaction proceeded exclusively in the γ-position and afforded the corresponding product **3f** in 76% yield. Notably, when 2,6-dimethyl-3-nitropyridine was employed, two regioisomeric products (**3g** and **3h**) could be isolated in higher yield (84% yield) with less sterically hindered 6-methyl product **3g** as the major product. Pyrazine and pyrimidine derivatives were also well tolerated to furnish the products **3k** and **3l** in 85% and 52% yields, respectively. This tandem conjugate addition/decarboxylation reaction also worked well with 2-methylquinolines (or 1-methylisoquinoline) bearing a variety of substituents on the ring of quinoline, leading to the products (**3m−p**) in good to excellent yields. Subsequently, a variety of substituted coumarin-3-carboxylic acids were subjected to the reaction (**3q−w**), and it was found that both electron-donating

Scheme 2. Substrate Scope of 2-Alkylazaarenes and Coumarin-3-carboxylic Acids[a,b]



[a]Reactions were conducted with azaarene **1** (0.75 mmol) and coumarin-3-carboxylic acid **2** (0.3 mmol) in 1 mL of dioxane at 120 °C for 48 h. [b]The yields indicated are isolated yields by column chromatography.

and -withdrawing substituents, such as OMe, NO_2, and halogen groups, on the phenyl ring of coumarins were well-tolerated, giving rise to the desired products in yields ranging from 50% to 96% (**3q−u**). The electron-rich aryl-substituted coumarins were more favored for the transformation (**3q**, 96% and **3r**, 86%). If the C5, C7 positions were substituted with two chlorine atoms or the C6, C8-positions were occupied by two *tert*-butyl groups, no desired products could be obtained even when the reactions were heated to 140 °C (**3v** and **3w**), and the reason might be the steric hindrance caused by those substituents.

Inspired by the success in coumarin-3-carboxylic acid, we intended to extend the reaction scope to thiocoumarin-3-carboxylic acid.[10] Thiocoumarins and its derivatives also exhibit a broad spectrum of pharmacological properties although there are no reported methods for functionalization of such compounds.[11] Gratifyingly, when thiocoumarin-3-carboxylic

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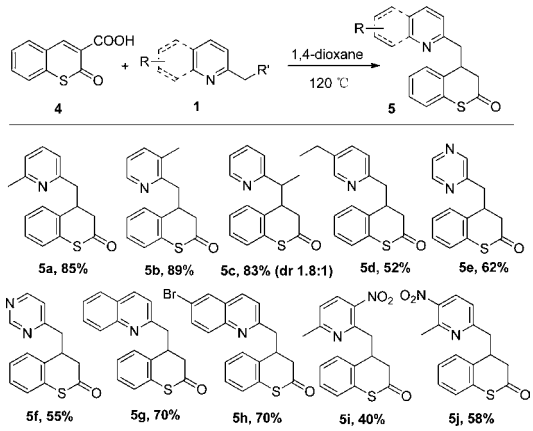
acid **4** was subjected to the reaction, the corresponding product **5** could be isolated in good to excellent yields (Scheme 3).

Scheme 3. Reaction of 2-Alkylazaarenes with Thiocoumarin-3-carboxylic Acid[a,b]

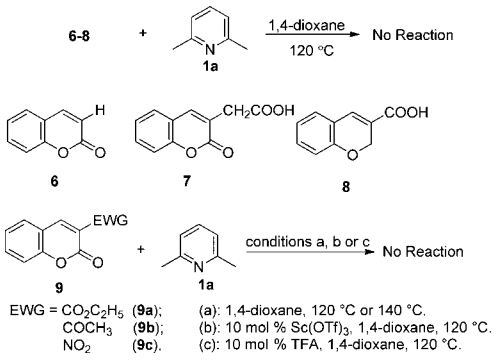


[a]Reactions were conducted with azaarenes **1** (0.75 mmol) and **4** (0.3 mmol) in 1 mL of dioxane at 120 °C for 48 h. [b]Isolated yield.

When 2,6-dimethyl-3-nitropyridine was exploited, two regioisomeric products (**5i** and **5j**) were isolated in similar yield, which implies that the 2- and 6-methyl groups are of comparable reactivity associated with the thiocoumarin-3-carboxylic acid **4**.

To shed light on the reaction mechanism, coumarin **6**, coumarin-3-acetic acid **7**, and 2*H*-chromene-3-carboxylic acid **8** were prepared and subjected to the standard conditions (Scheme 4). All of these substrates did not react with 2,6-

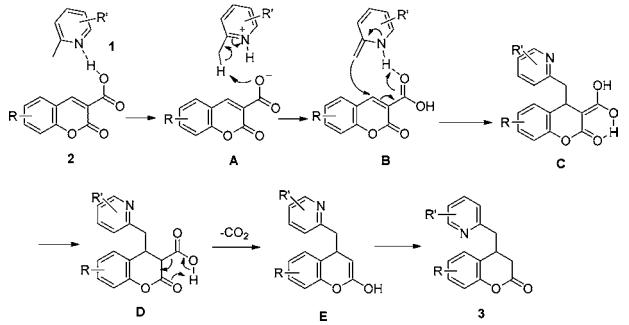
Scheme 4. Control Experiment



lutidine **1a** under standard reaction conditions. No reaction of coumarin **6** and coumarin-3-acetic acid **7** indicated that the direct connection of carboxyl group to the alkene at C-3 position was a crucial factor for this reaction. Failure of the reaction of 2*H*-chromene-3-carboxylic acid **8** implied that electron deficiency of alkene was indispensable. Toward this end, more control experiments were carried out with the introduction of ester, acetyl, and nitro groups (**9a**, **9b**, and **9c**) into the C-3 position of coumarin instead of the carboxyl group. However, no reaction occurred under the standard conditions (condition a), even in the presence of $Sc(OTf)_3$ (condition b) or TFA (condition c). Base addition such as Et_3N and DBU was also detrimental to this reaction. In view of the above-mentioned experimental results, it can be concluded that the carboxyl group in C-3 position of coumarin was crucial for the success of this reaction, which not only rendered the alkene electron deficient but also activated the 2-methylpyridine substrate to drive the reaction to completion. Furthermore, the carboxyl group brings the nucleophile closer to the Michael acceptor by hydrogen bonding so that the nucleophile can approach the electron-deficient alkene more readily. These factors caused by the carboxyl group can facilitate the transformation dramatically, thus rendering the reaction proceed very well in the absence of catalyst.

On the basis of the above-mentioned information, the proposed reaction mechanism is outlined in Scheme 5. It could

Scheme 5. Proposed Reaction Mechanism



be conceived that 2-methylazaarenes **1** and coumarin-3-carboxylic acid **2** were bound together via a hydrogen-bonding interaction, followed by protonation of 2-methylazaarenes **1** to give pyridinium **A**. As a result of the enhanced acidity of the benzylic protons, C−H cleavage would occur to afford an enamine intermediate, which attacked the electron-deficient alkene via the well-organized transition state **B** to form the intermediate **C**. In the transition state **B**, hydrogen-bonding interaction helps the enamine approach the electron-deficient alkene moiety. The next tautomerization, decarboxylation, and isomerization would produce **3**. In the whole process, it was proposed that hydrogen bonding plays a key role for the success of this transformation.

In summary, we present a facile catalyst-free tandem conjugate addition/decarboxylation of 2-alkylazaarenes with (thio)coumarin-3-carboxylic acids via sp^3 C−H activation for the efficient construction of azaarene substituted 3,4-dihydro-(thio)coumarins. A broad scope of coumarins, thiocoumarins, and azaarenes can be tolerated, and the coupled products were isolated in good to excellent yields. This method proves to be an efficient and innovative approach to this biologically important architecture in a single step. The success of this reaction should broaden the library of coumarins or thiocoumarins in pharmaceutical chemistry and extend the synthetic utility of sp^3 C−H functionalization in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Additional experimental procedures and spectrascopic data of new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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