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Facile Synthesis of Azaarene-substituted Hydroxycoumarins Possessing High Biological Activities via Three-Component C(sp^3)-H Functionalization

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KEYWORDS: three-component, C(sp^3)-H functionalization, 2-alkylazaarenes, aryl aldehydes, 4-hydroxycoumarins, 3-benzyl-4-hydroxycoumarins, biological activities.

ABSTRACT: An unprecedented three-component C(sp^3)-H functionalization of 2-alkylazaarenes with aryl aldehydes and 4-hydroxycoumarins was realized, providing azaarene-substituted 3-benzyl-4-hydroxycoumarins in good to excellent yields. These new target compounds displayed broad-spectrum antibacterial activities, providing a new type of antibacterial skeleton.

INTRODUCTION

4-Hydroxycoumarin and its derivatives are core fragments which have been found in numerous natural products, drugs, pesticides and rodenticides.[1] Among these compounds, 3-benzyl substituted 4-hydroxycoumarins have attracted much attention recently owing to their ever-increasing application in biological and medicinal fields. A number of 3-benzyl-4-hydroxycoumarins, for examples, Phenprocoumon, Difenacoum, Coumatetralyl and Warfarin have exhibited multifarious biological activities such as anti-HIV,[2] antiviral,[3] anticoagulant,[4] antioxidant[5] and anticancer activities[6] (Figure 1). On account of these findings, much attention has been directed towards the synthesis of 3-benzyl substituted 4-hydroxycoumarins.[7] However, to the best of our knowledge, there is still no protocol available for straightforward synthesis of azaarene-substituted 3-benzyl-4-hydroxycoumarins, which might have great potential for production of new biologically and medicinally important compounds.

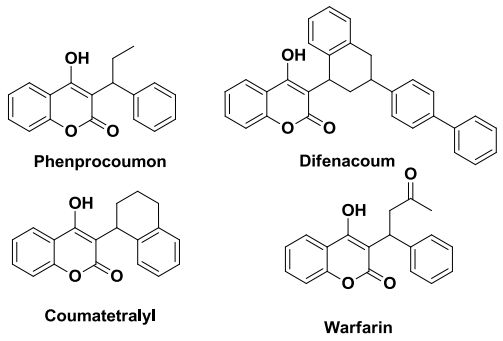
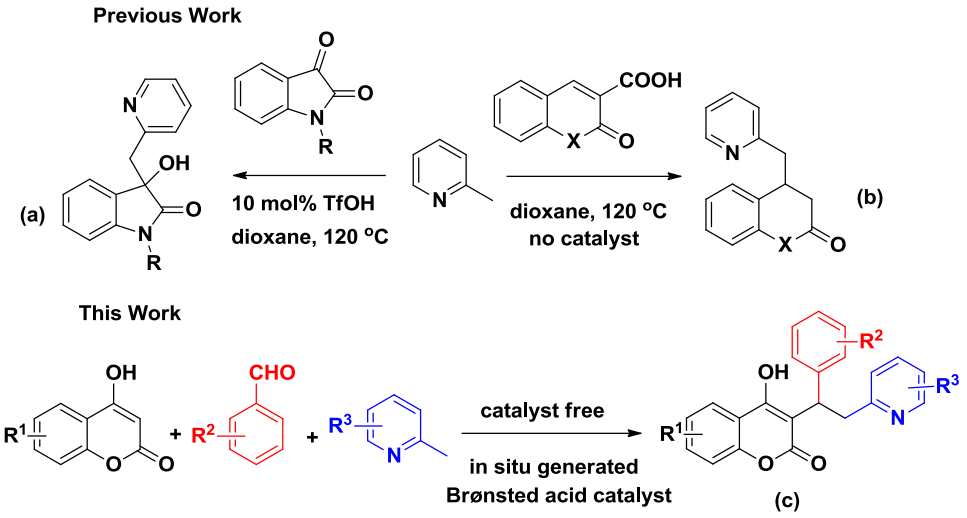


Figure 1. Examples of 3-benzyl-4-hydroxycoumarins

C2-alkylated azaarenes are key structural motifs of numerous natural products, pharmaceuticals, catalysts and functional materials.[8] Therefore, it is extremely valuable to develop an efficient method for preparation of highly functionalized C2-substituted azaarenes.[9] Traditionally, harsh conditions, e.g. stoichiometric amount of strong bases like BuLi or LDA, are

required for functionalization of 2-methylazaarenes via deprotonation of the acidic protons on methyl group, followed by nucleophilic additions to electrophiles.[10] Recently, the direct functionalization of 2-methylazaarenes could be implemented under the catalysis of transition metal.[11] However, the employment of transition metal catalysts suffers from enviromental detriment and high cost, as well as tedious purification of the final products. To circumvent these drawbacks, we developed the first organocatalyic or Brønsted acid catalyzed C(sp^3)−H functionalization of 2-alkylazaarenes with isatins, leading to facile synthesis of biologically important azaarene-substituted 3-hydroxy-2-oxindoles in one step (Scheme 1, a).[12a] On the basis of that work, a catalyst-free direct C(sp^3)−H functionalization of 2-alkylazaarenes by use of carboxylic acid-tethered substrates were further developed in our group to synthesize the azaarene-substituted 3,4-dihydro(thio)-coumarins in a single step (Scheme 1, b).[12b] The above success inspired us to conduct in-depth studies of *in situ* generated Brønsted acid catalyzed C(sp^3)−H functionalization for efficient construction of highly functionalized azaarenes (Scheme 1, c).

Scheme 1. Synthesis of Azaarene-substituted 3-Benzyl-4-hydroxycoumarins via Three-component C(sp^3)−H Functionalization



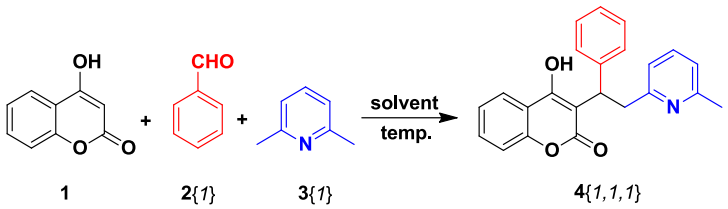
As a continuation of developing efficient C(sp^3)−H functionalization strategy to construct biologically and pharmaceutically important molecules,[12-13] herein, we reported an unprecedented three-component C(sp^3)−H functionalization process[14] for one step construction of azaarene-substituted 3-benzyl-4-hydroxycoumarins in good to excellent yields. This protocol has the advantages of direct C(sp3)-H functionalization and multi-component reaction, which features high atom-economy, operational simplicity, and no environmentally detrimental byproducts. Notably, although multi-component reactions have been in-depth investigated for creation of structurally diverse compound libraries, the catalyst-free multi-component reaction still remains a great challenge.[15]

RESULTS AND DISCUSSION

Initially, the three-component reaction of 4-hydroxycoumarin, benzaldehyde and 2,6-lutidine in dioxane was examined under catalyst-free conditions (Table 1, entry 1). Consistent with our hypothesis, this reaction proceeded smoothly at 120°C, furnishing the desired product **4**{*1,1,1*} in 91% yield. Decreasing the temperature to 100 °C resulted in lower yield, and no reaction occurred at 80 °C (Table 1, entries 2-3). Remarkably, screening of solvents indicated that the

option of solvent was crucial to the success of this transformation, which did not work in other solvents such as DMSO, THF and DCE (Table 1, entries 4-8).

Table 1. Optimization of Reaction Conditions[a]



Entry	Solvent	T (°C)	Yield (%)[b]
1	dioxane	120	91
2	dioxane	100	85
3	dioxane	80	0
4	DMSO	120	trace
5	EtOH	120	0
6	THF	120	0
7	DCE	120	0
8	H_2O	120	0

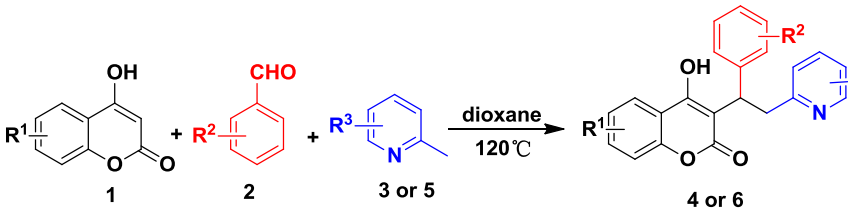
[a] Reactions were conducted with **1** (0.5 mmol), **2**{*1*} (1 mmol), **3**{*1*} (1 mmol) in 1 mL of solvent for 48 h in a sealed tube. [b] Isolated yield.

Under the optimized conditions, a series of substituted 4-hydroxycoumarin derivatives **4** and **6** were synthesized in a 10 mL glass vial using 1:2:2 molar ratio of 4-hydroxycoumarin/aromatic aldehydes/azaarenes (Scheme 2).

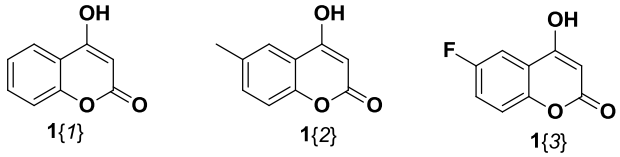
A wide range of sterically and electronically diverse aldehydes, azaarenes and 4-hydroxycoumarins were examined to investigated the generality of this transformation, and the results are shown in Scheme 3. Most of the sterically and electronically diverse substrates were well tolerated. Good yields could be achieved with either electron-donating or electron-

withdrawing group substituted aromatic aldehydes as substrates (Scheme 3, **4**{*1,1-7,1*}). Notably, 2-bromobenzaldehyde (**4**{*1,4,1*}, 37%) gave lower yield than 3-bromobenzaldehyde (4{1,3,1},

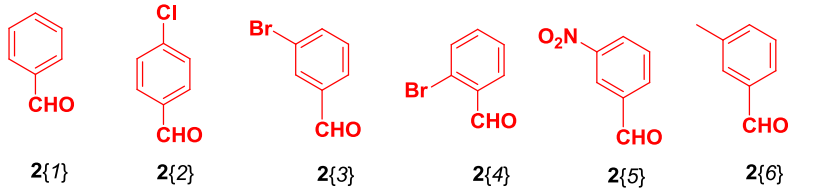
Scheme 2. Synthetic Route and Building Blocks for **4** and **6**.

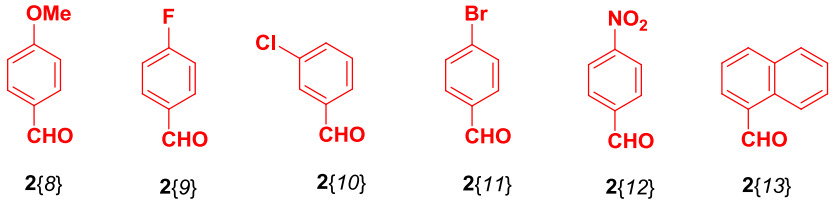


substituted 4-hydroxycoumarins 1

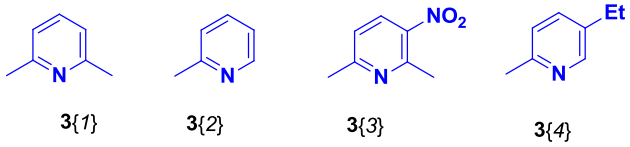


aromatic aldehyde 2

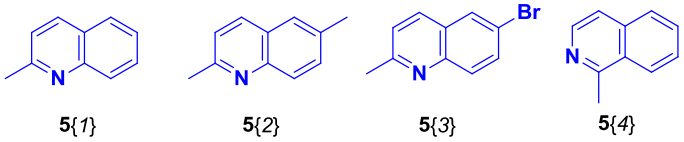




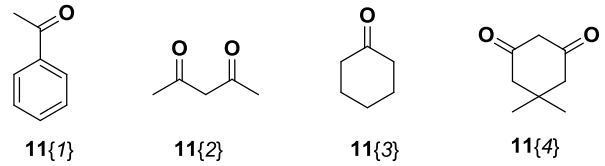
substituted methylpyridines 3



substituted methylquinolines 5



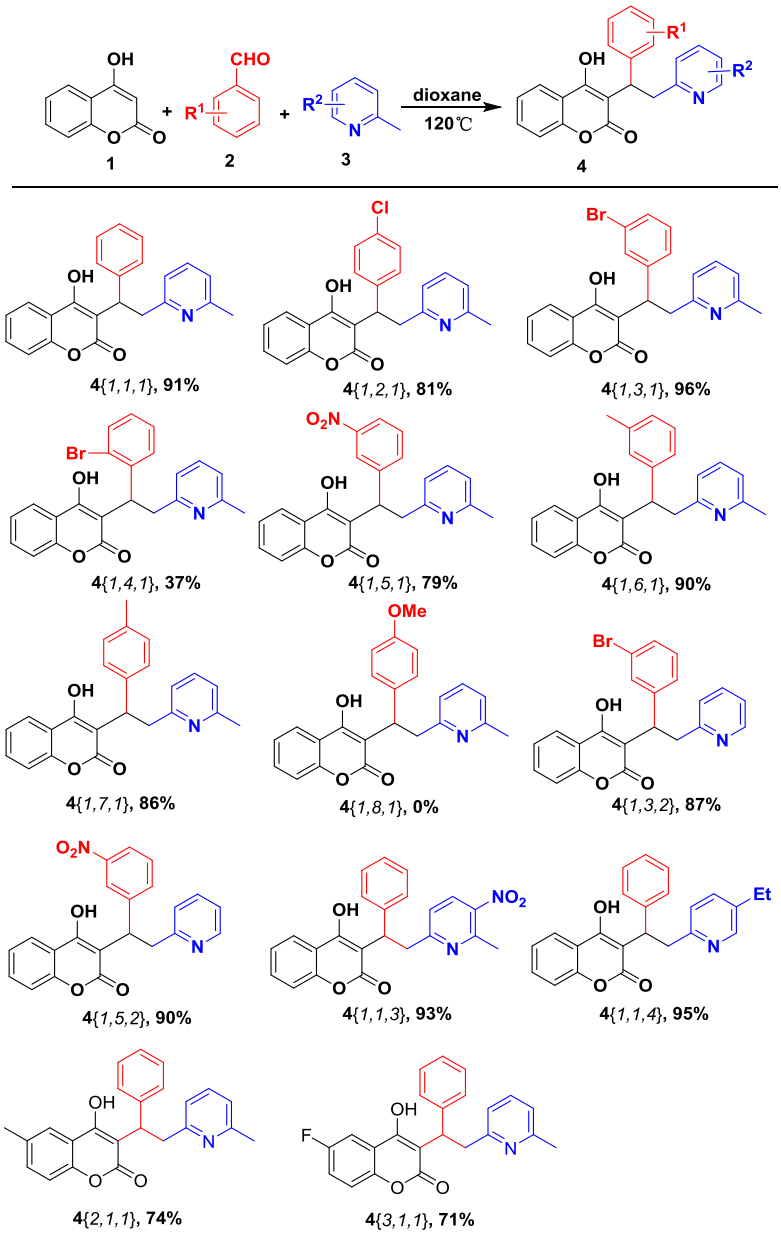
ketones 11



96%), probably due to the steric hindrance. When anisaldehyde was employed, the analogous product 4{1,8,1} was not detected, even under the catalysis of strong Lewis acids and Bronsted

acids, which might be ascribed to the strong electron-donating effect of methoxyl group. Subjection of other 2-methylpyridines to this reaction could also furnish the desired products in

Scheme 3. Three-Component Reactions of 4-Hydroxycoumarin, Aromatic Aldehyde and 2-Alkylpyridines.

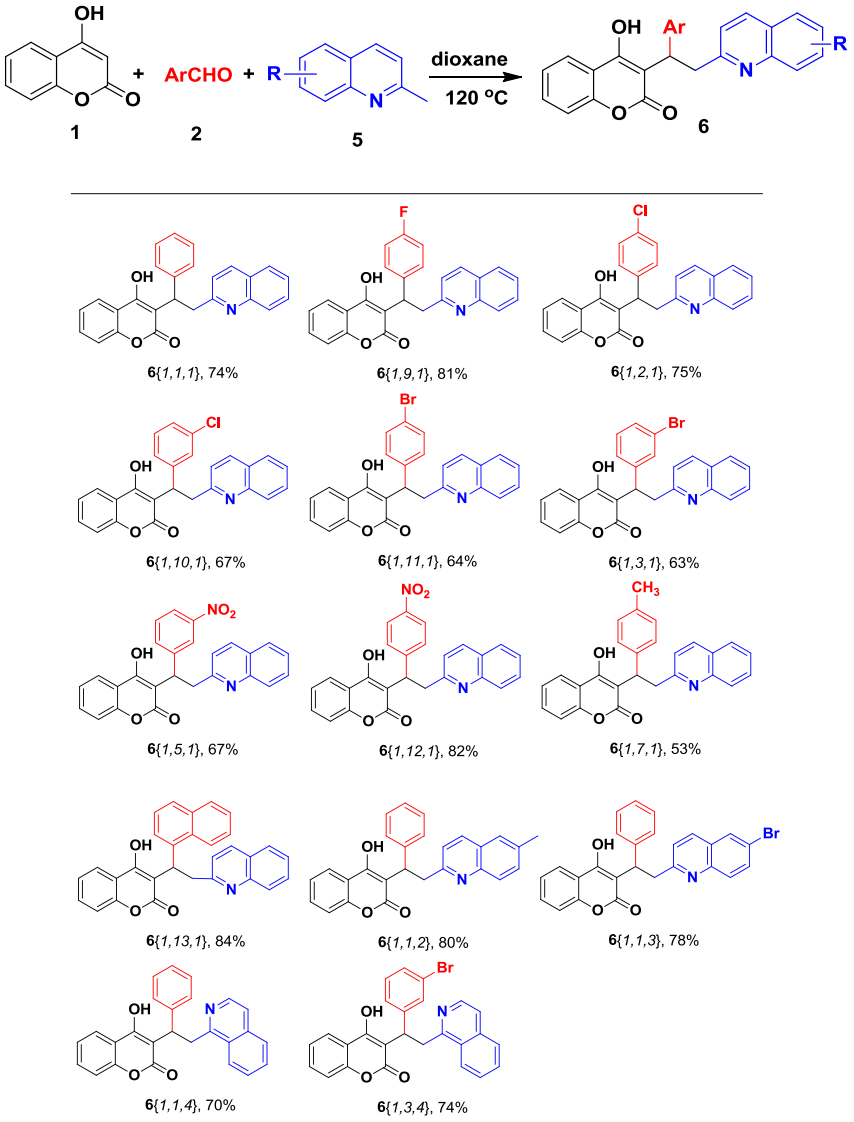


excellent yields (Scheme 3). Notably, when 2, 6-dimethyl-3-nitropyridine was employed, only less sterically hindered 6-methyl was functionalized (**4**{*1,3,1*}), whereas the regioisomeric 2-methyl product was not detected. Subsequently, substituted 4-hydroxycoumarins were also evaluated under the optimal condition. Both the electron-donating group such as methyl substitutent and electron-withdrawing group such as fluoro substitutent could provide the desired product 4{2,1,1} and 4{3,1,1} in 74% yield and 71% yield correspondingly.

When 2-methylquinolines were employed as substrates, the desired products **6** were obtained in good yields (Scheme 4), along with 2-alkenylquinolines as byproducts.[16] The comparatively lower yields illustrated the different reactivity between C(sp^3)−H bond of 2-methylquinolines and 2-methylpyridines. As shown in Scheme 4, formation of product **6**{*1,1-13,1*} was more favored for electron-deficient aldehydes than electron-rich ones. 2,6-dimethylquinoline 5{2} and 1-methylisoquinoline 5{4} were also well tolerated to furnish the desired products in good yields. Considering that 3-benzyl substituted 4-hydroxycoumarins exhibit multifarious biological activities and have promising application in medicinal chemistry, the current protocol provides an efficient strategy to construct such type of compounds.

When aliphatic aldehydes were subjected to this reaction, disappointedly, no desired products were obtained. Ketones were also examined under the standard reaction condition, however, no C(sp^3)-H functionalization products were obtained and only nucleophilic coupling products between 4-hydroxycoumarin with ketones were observed, in which 2,6-lutidine served as a base. The employment of ketones like acetophenone, cyclohexanone and 1, 3-diketone afforded the products **7**{*1,3,1*}[17], **8**{*1,3,3*}[18] and **9**{*1,3,2*}[19] in 47%, 88% and 77% yields, respectively (Scheme 5). The structure of product **7**{*1,3,1*} has been unambiguously confirmed

Scheme 4. Three-Component Reactions of 4-Hydroxycoumarin, Aromatic Aldehyde and 2-Methylquinolines[a, b]



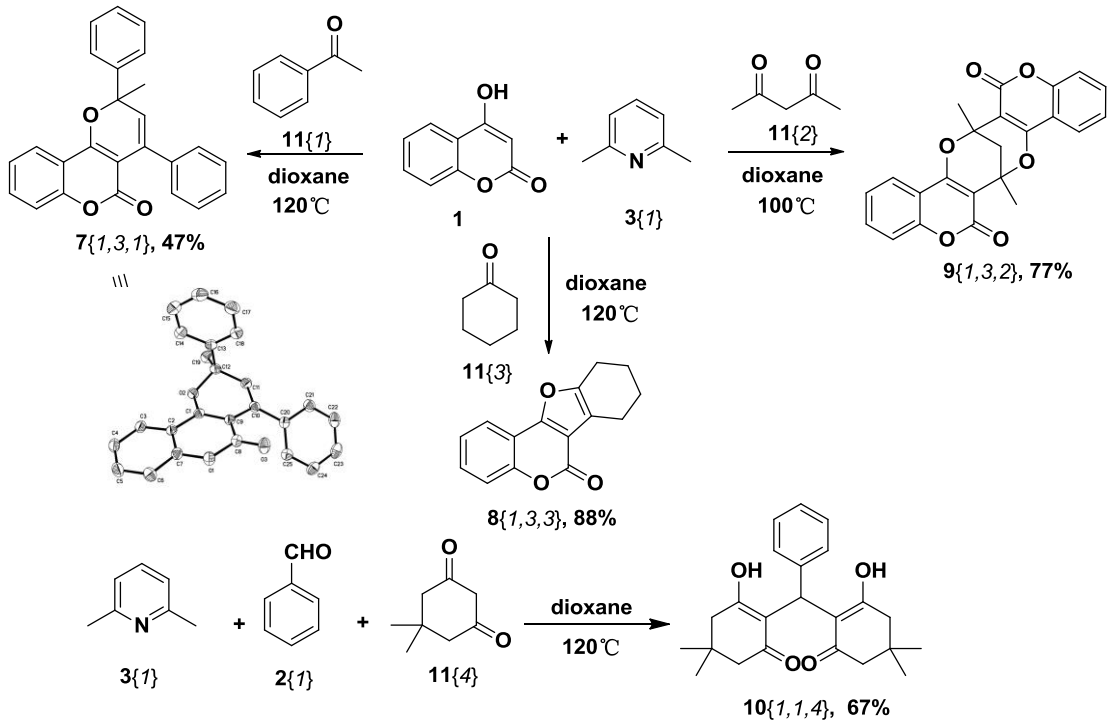
[a] Reactions were conducted with **1** (0.5 mmol), aromatic aldehyde **2**{*2,3,5,9-13*} (1 mmol) and azaarene **5**{*1-4*} (1 mmol) in 1 mL of dioxane at 120 °C for 48 h. [b] Isolated yield of purified products.

by X-ray crystallography. Intriguingly, when 5,5-dimethylcyclohexane-1,3-dione was subjected to the reaction instead of 4-hydroxycoumarin, only bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-

ones) **10**{*1,1,4*} was isolated in 67% yield.[20] These results indicated that this three component C(sp^3)-H functionalization could work merely with aromatic aldehydes, not working for aliphatic aldehydes and ketones. Ketone substrates such as cyclohexanone and 1,3-diketone operate by the other reaction pathway, which could be explained by the fact that ketones are less electrophilic than aldehyde.

To probe the mechanistic pathway, control experiments were conducted as shown in Scheme 6. The formation of benzoic acid was observed when benzaldehyde was dissolved in dioxane under 120 ºC under air atmosphere, and this reaction could proceed via addition of

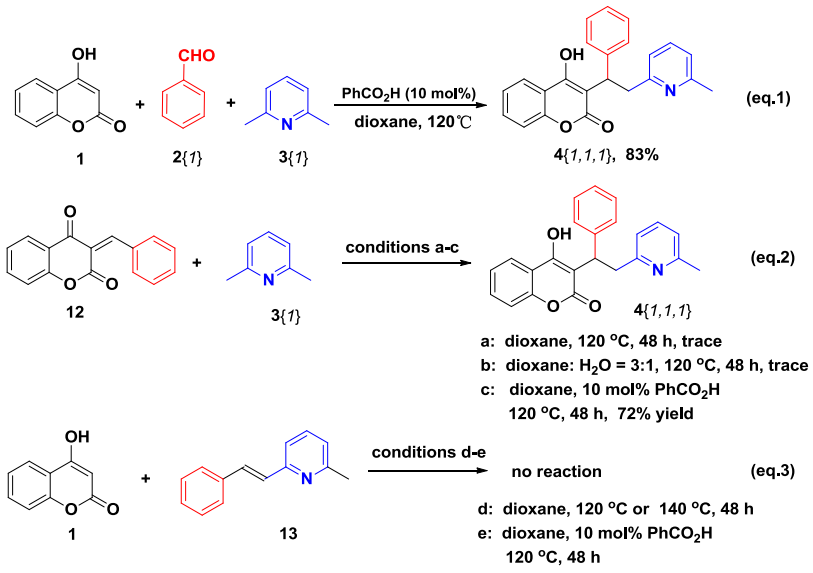
Scheme 5. Ketones as Substrates



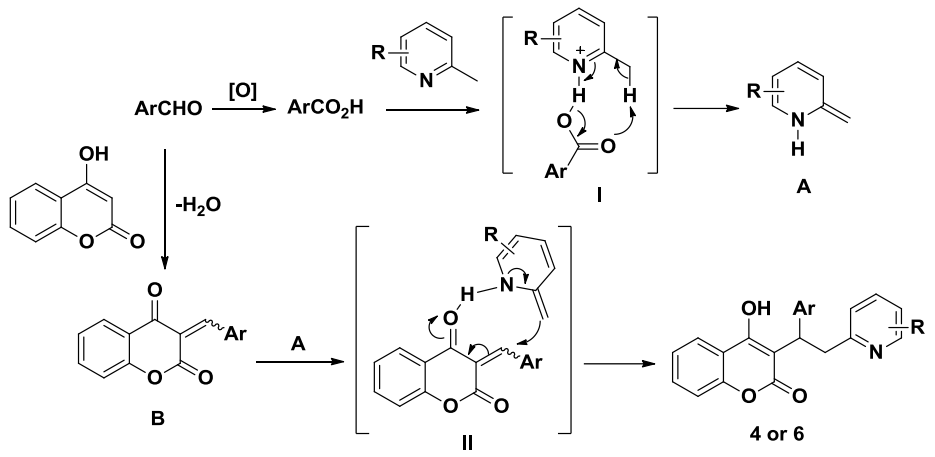
10 mol% benzoic acid, affording the desired product **4**{***1,1,1***} in 83% yield (eq. 1). Compound **12**{*1*} and **13**{*1*} were prepared and subjected to the standard reaction conditions (eq. 2 and 3).

However, only trace of **4**{*1,1,1*} was detected even in the presence of water (eq. 2, condition a-b). In contrast, 10 mol% benzoic acid could catalyze this reaction smoothly to afford the product **4**{*1,1,1*} in 72% yield, demonstrating that the direct addition of C(sp^3)−H bond to *ortho*-quinone methides intermediate[21] was possible (eq. 2, condition c). The direct addition of 4-hydroxycoumarin to 2-alkenylazaarenes was also examined, however, no desired product **4**{*1,1,1*} could be obtained, even under the catalysis of 10 mol% benzoic acid (eq. 3). On the basis of the experimental results, a plausible reaction mechanism is proposed as outlined in Scheme 7. Trace of aryl aldehyde is oxidized to aryl carboxylic acid under air atmosphere at high temperature, which serves as Brønsted acid catalyst to activate the 2-methylazaarenes, affording an enamine intermediate **A** via transition state **I**. Condensation of aryl aldehyde with 4-hydroxycoumarin produces *ortho*-quinone methide intermediate **B,** which is then attacked by electron-rich intermediate **A** to furnish the product **4** or **6** via the well-organized transition state **II**.

Scheme 6. Control Experiments



Scheme 7. The Proposed Reaction Pathway



To examine the biological activities of these synthetically new molecules, the antibacterial activities of products **4** and **6** were evaluated (Table 2). It was found that they were against a panel of pathogenic bacteria such as *S. epidermidis*, *S. aureus* and *B. cereus*, etc. For instance, compound **6**{*1,13,1*} exhibited strong inhibitory activity against *S. aureus* and *B. cereus* with the MIC value of 1.56 μM, which were 80 percent and 40 percent, respectively than that of ciprofloxacin (MIC = 1.25 μM). The preliminary bioassay results showed that these new synthetic compounds had broad-spectrum antibacterial effects and potentially acted as lead compounds for further modification and commercial application.

Table 2. Antibacterial Test for Compound **4** and **6**[a]

Compound	*S.epidermidis*	*T.halophilus*	*B.subtilis*	*K.rhizophila*	*V.parahaemolyticus*	*S.aureus*	*B.cereus*	*N.brasiliensis*
4{*1,2,1*}	50.0	100	50.0	50.0	>100	50.0	>100	100
4{*1,3,1*}	25.0	25.0	50.0	50.0	50.0	25.0	25.0	50.0
4{*1,5,1*}	50.0	100	100	100	25.0	25.0	25.0	>100
4{*1,6,1*}	>100	50.0	100	100	100	100	100	>100
4{*1,7,1*}	100	100	50.0	100	25.0	100	>100	100
4{*1,3,2*}	50.0	25.0	50.0	50.0	100	50.0	25.0	100
4{*1,5,2*}	100	100	100	100	>100	100	50.0	>100
4{*1,1,3*}	50.0	50.0	50.0	25.0	>100	50.0	>100	50.0
6{*1,1,1*}	25.0	50.0	25.0	25.0	>100	50.0	>100	50
6{*1,2,1*}**c**	6.25	12.5	12.5	>100	25.0	3.13	6.25	12.5

6{*1,10,1*}	100	12.5	6.25	12.5	50.0	6.25	3.13	12.5
6{*1,11,1*}	6.25	25.0	6.25	6.25	25.0	6.25	12.5	6.25
6{*1,3,1*}	6.25	3.13	3.13	3.13	25.0	6.25	25.0	6.25
6{*1,5,1*}	25.0	>100	12.5	6.25	100	6.25	6.25	12.5
6{*1,12,1*}	12.5	6.25	12.5	6.25	100	6.25	12.5	25.0
6{*1,7,1*}	25.0	12.5	25.0	3.13	25.0	12.5	25.0	50.0
6{*1,13,1*}	3.13	3.13	6.25	3.13	>100	1.56	1.56	6.25
6{*1,1,2*}	12.5	6.25	12.5	25.0	25.0	6.25	6.25	25.0
6{*1,1,3*}	3.13	6.25	3.13	12.5	12.5	3.13	12.5	6.25
6{*1,1,4*}	12.5	6.25	25.0	12.5	>100	3.13	6.25	25.0
Ciprofloxacin[b]	0.625	2.50	0.156	0.313	5.00	1.25	0.625	0.313

[a] Data are expressed in MIC values (μM). [b] Ciprofloxacin was used as a positive control.

CONCLUSION

In conclusion, an unprecedented three-component C(sp^3)-H functionalization of 2-alkylazaarenes with aryl aldehydes and 4-hydroxycoumarins was realized, providing azaarene-substituted 3-benzyl-4-hydroxycoumarins in good to excellent yields. The mechanistic studies imply that *in situ* oxidation of aryl aldehydes to aryl carboxylic acids is crucial to the success of this transformation. Furthermore, these new target compounds displayed broad-spectrum antibacterial activities, providing a new type of antibacterial skeleton. The subsequent in-depth studies on bioactivity and structure-activity relationship as well as further application of this synthetic strategy are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

Experimental details and spectroscopic characterization of all the compounds and ^{1}H and ^{13}C spectra for all products.

Crystallographic information file for compound **7{*1,3,1*}**.

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Author Contributions

[§] These authors contributed equally to this work.

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Notes

The authors declare no competing financial interest..

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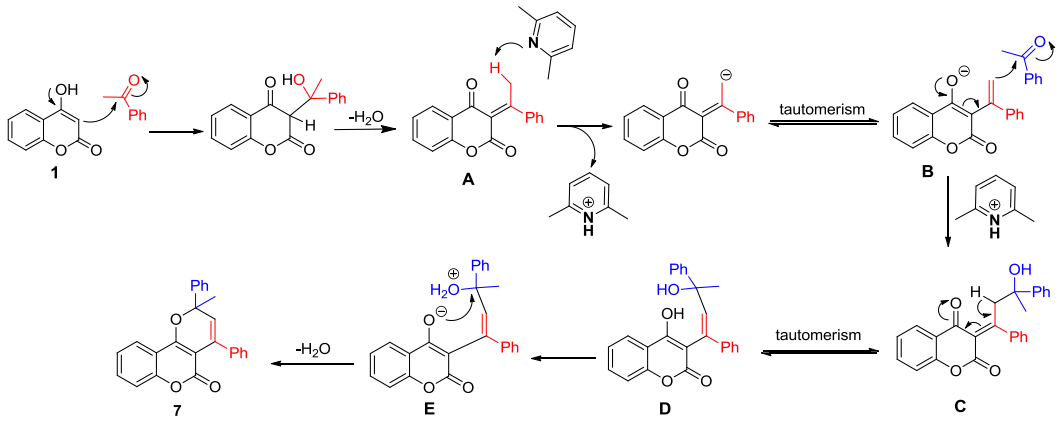

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Facile Synthesis of Azaarene-substituted Hydroxycoumarins Possessing High Biological Activities via Three-Component C(sp^3)-H Functionalization

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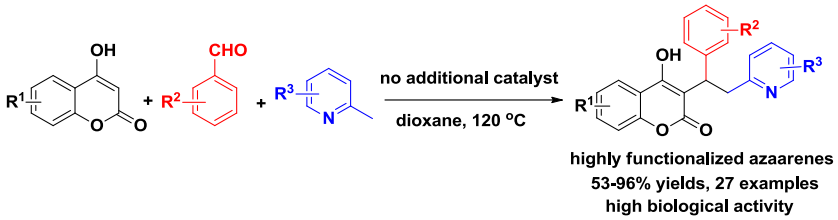

An unprecedented three-component C(sp^3)-H functionalization of 2-alkylazaarenes with aryl aldehydes and 4-hydroxycoumarins was realized, providing azaarene-substituted 3-benzyl-4-hydroxycoumarins in good to excellent yields. These new target compounds displayed broad-spectrum antibacterial activities, providing a new type of antibacterial skeleton.