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A Lewis acid-catalyzed tandem reaction enabling 2-arylglycerol derivative as a versatile 1,3-biselectrophile for the synthesis of 4*H*-chromenes and 2-pyridinones

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ABSTRACT

Acid-catalyzed tandem reactions were established by employing a novel class of 2-arylglycerol derivative, 5-aryl-1,3-dioxan-5-ol, as versatile 1,3-biselectrophile. In the reactions, 5-aryl-1,3-dioxan-5-ol works like atropaldehydes or 2-aryl malondialdehydes, and can react with 2-naphthols and β-keto amides, allowing the synthesis of 4*H*-chromenes and 5-aryl-2-pyridinones. High yields, good functional group tolerance, broad substrate scope and simple reaction operation make this protocol attractive.

Six-membered heterocycles are highly significant in the synthetic and pharmaceutical chemistry fields since they are widely spread in natural products and medicinally important agents [1–5]. The cycloadditions have been established as one of the most efficient tools to construct these skeletons. In particular, the organic small molecules [6], transition metals [7], or Lewis acids [8] catalyzed [3 + 3] cycloadditions offer advantages for the synthesis of a substantial variety of six-membered heterocyclic compounds, and they are receiving considerable attention. Different from the well-known Diels-Alder reaction, the [3 + 3] cycloadditions are generally stepwise processes. The development of [3 + 3] cycloaddition transformations is greatly facilitated by the identification of novel 1,3-dipoles or 1,3-biselectrophiles, which also offers opportunities in the construction of functionalized heterocycles [9].

In recent years, the conversion of glycerol into value-added chemicals has become attractive due to the large surplus of glycerol [10]. Among these, 1,3-dihydroxyacetone, as a sort of oxidative product of glycerol, is of high value and it has been widely applied to cosmetic, pharmaceutical and food industries [11]. Considering that 2-susbtituted glycerol analogues can be easily prepared from 1,3-dihydroxyacetone [12], it can be expected that exploiting novel reactivity of 2-susbtituted glycerol will further extend the utilization of 1,3-dihydroxyacetone. Mechanically, 2-susbtituted glycerol analogues can undergo the dehydration and tautomerization to generate aldehyde. We envision that the highly reactive aldehyde combined with residual hydroxyl group might enable the 2-susbtituted glycerol analogues as promising 1,3-biselectrophiles to deliver some valuable heterocyclic molecules if accompanied by other cascade process.

Our research commenced from 5-aryl-2,2-dimethyl-1,3-dioxan-5-ol (**1a** in Table 1), which was prepared from Grignard reagent and hydroxyl protected dihydroxyacetone [13]. Initially, 2-naphthol was used as a bis-nucleophile to react with **1a** in 1,4-dioxane for the condition optimization. Several metal Lewis acids were examined (Table 1, entries 1–5), it was found that most of triflates showed poor catalytic efficiencies on this reaction, except for $Al(OTf)_3$, which could generate a cyclization product, 4*H*-chromene **3a** in a moderate yield of 67% (entry 2). In addition, other commonly used catalysts, $BF_3{\cdot}Et_2O$ and PTSA, were also tested, but they were not suitable for the transformation (entries 6 and 7). Subsequently, the evaluation of solvents disclosed that all of the investigated solvents were not as effective as 1,4-dioxane in the reaction, in which CH_3CN and toluene could deliver the desirable product in 58% and 42%, respectively (entries 8 and 11), and DCE

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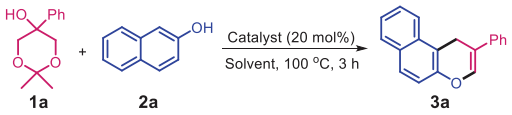
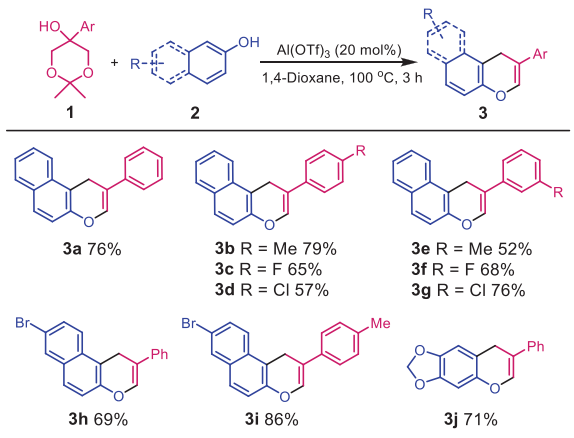
Table 1
Optimization of the reaction conditions.[a]



Entry	Catalyst	Solvent	Yield (%)[b]
1	$Sc(OTf)_3$	1,4-Dioxane	Messy
2	$Al(OTf)_3$	1,4-Dioxane	67
3	$Bi(OTf)_3$	1,4-Dioxane	13
4	$Fe(OTf)_3$	1,4-Dioxane	26
5	$Ni(OTf)_2$	1,4-Dioxane	9
6	$BF_3{\cdot}Et_2O$	1,4-Dioxane	Trace
7	PTSA	1,4-Dioxane	Trace
8	$Al(OTf)_3$	CH_3CN	58
9	$Al(OTf)_3$	DCE	Messy
10	$Al(OTf)_3$	CH_3NO_2	Trace
11	$Al(OTf)_3$	Toluene	42
12[c]	$Al(OTf)_3$	1,4-Dioxane	76
13[c,d]	$Al(OTf)_3$	1,4-Dioxane	31
14[c,e]	$Al(OTf)_3$	1,4-Dioxane	33

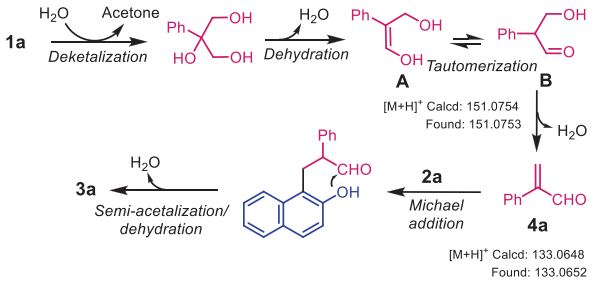
[a] Unless otherwise noted, all reactions were performed with **1a** (0.20 mmol), **2a** (0.20 mmol), catalyst (20 mol%), solvent (1 mL) at 100 °C under air atmosphere for **3h**.
[b] Isolated yield.
[c] **2a**, 1.2 equiv.
[d] $Al(OTf))_3$, 10 mol%.
[e] Performing the reaction at 80 °C.



Scheme 1. The synthesis of 4*H*-chromenes.

and CH_3NO_2 led to inseparable mixture or trace product (entries 9 and 10). When the ratio of **1a** and **2a** was adjusted to 1:1.2, the yield of **3a** increased to 76% (entry 12). Also, the reaction was sensitive to the amount of catalyst and temperature. Further investigation revealed that decreasing the dosage of catalyst or reaction temperature, the yields of the reactions diminished drastically, presumably due to the low conversion of starting materials (entries 13 and 14). Thus, the conditions in entry 12 of Table 1 were identified as the optimal choices.

Afterwards, we explored the substrate scope of this cascade transformation. As demonstrated in Scheme 1, the reaction showed a wide substrate scope. Several tertiary alcohols with different functional groups on the phenyl ring were compatible with the reaction conditions, furnishing the corresponding products with moderate to good yields. Thereinto, tertiary alcohols containing methyl at the *para*-position of phenyl gave a much higher yield than those with halogen groups (**3b**–**3d**), while a contrary electronic effect emerged with regard to the C3 position of this one (**3e**–**3g**). Furthermore, 6–bromo-2-naphthol also readily underwent the transformation, affording the desired products, **3h** and **3i**. Notably, this example represents an alternative strategy to access



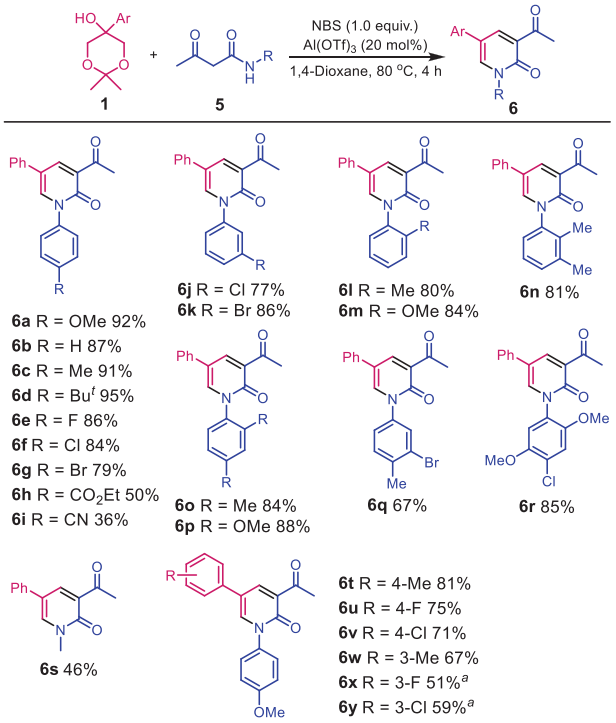
Scheme 2. The proposed mechanism for the synthesis of 4*H*-chromene.

2,3-dihydrophenalenone compared with direct cyclization from 1-naphthylpropionic acid [14]. Unexpectedly, sesamol was also applicable to the tandem process with the production of compound **3j** in a satisfying yield. However, no target product was obtained when the simple phenol was engaged as the substrate.

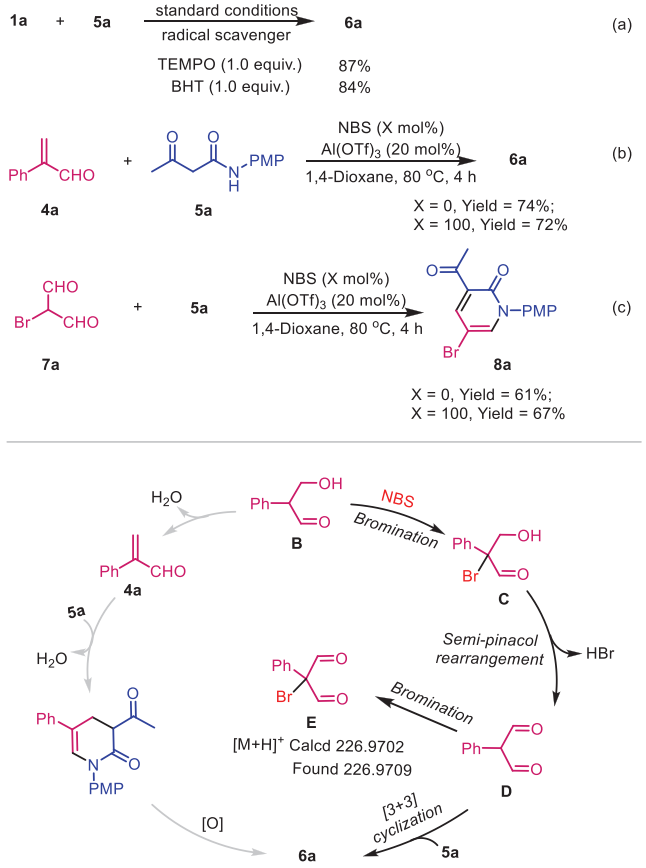
To probe the reaction mechanism and verify the conversion pathway of 2-arylglycerol functionalized as 1,3-biselectrophile in the reaction, the crude HRMS analysis experiment was conducted. The peaks at 151.0753 and 133.0652 were detected (Fig. S1 in Supporting information), which were assigned to 2-phenylpropene-1,3-diol or 3–hydroxy-2-phenylpropanal and atropaldehyde, respectively (**A** or **B** and **4a** in Scheme 2). Then, the atropaldehyde was directly reacted with **2a** under standard conditions, in which **3a** was successfully obtained in a good yield of 79%. Based on these observations, a plausible mechanism for the synthesis of 4*H*-chromene was proposed as depicted in Scheme 2. In the presence of acid catalyst, the deprotection of ketal from **1a** occurred to afford 2-arylglycerol, which went through dehydration to give the intermediate **A**. After that, the tautomerization of **A** occurred to result in the intermediate **B**, followed by an elimination of H_2O to generate the key intermediate, atropaldehyde **4a**. Subsequently, a Michael addition of **4a** with 2-naphthol occurred, followed by a successive Michael addition/intramolecular semi-acetalization/dehydration process to give the desired product **3a**. It was worth noting that the atropaldehyde was a kind of important biselectrophile, which was widely used in synthesis of heterocycles [15–18]. However, they are generally synthesized from styrenes [16] or α-hydroxyacetophenones [19] by multistep reactions (Scheme S1 in Supporting information), which restricts their wide uses in a large extent. Currently, our protocol offers a more expedient and efficient approach to *in situ* generate atropaldehyde, to rapidly synthesize some important scaffolds.

Encouraged by above result, we subsequently attempted to employ β-keto amide **5a** as a nucleophile to couple with **1a** (Scheme 3), since β-keto amides are frequently used as potential precursors for the construction of heterocyclic systems because of the existence of multiple reactive sites [20,21]. To our delight, a 5-aryl-2-pyridone **6a** was obtained in 28% yield under the identical reaction conditions with the reaction of **1a** and **2a** (Table S1 in Supporting information). Considering the fact that an oxidation process may be involved in the new transformation, different oxidants were screened and we found that the combination of $Al(OTf)_3$ and NBS could lead to a huge improvement, providing **6a** with an excellent yield, up to 92% (Table S1 in Supporting information).

Following this, the substrate scope of the protocol was explored (Scheme 3). Acetoacetanilides bearing various functional groups at the *para*-position of aromatic ring all proceeded smoothly, affording the desired 5-aryl-2-pyridone compounds **6c**–**6i** in moderate to excellent yields. A significant electronic effect was observed on the reaction yields. The acetoacetanilides attached to electron-donating groups, such as methyl and *tert*–butyl, on the



Scheme 3. Investigation of substrate scope for the synthesis of 5-aryl-2-pyridones. Reaction conditions: **1** (0.20 mmol), **5** (0.24 mmol), $Al(OTf)_3$ (0.04 mmol), NBS (0.20 mmol), 1,4-dioxane (1.0 mL), 80 °C, 4 h under air atmosphere, and isolated yields based on **1**. [a] 100 °C, 8 h.



Scheme 4. The control experiments and proposed mechanism for the synthesis of **6a**.

aromatic ring gave rise to higher efficiency than those with electron-withdrawing groups (including –F, –Cl, –Br, –CN). Most importantly, the acid-sensitive ester group could be also delivered uneventfully into the anticipated product, **6h**, without causing any structural damage. Also, substituents at the *ortho* and *meta*-position of benzene ring were also amenable to the transformation, delivering the desired products, **6j**–**6m**, in good yields. Of note, *ortho*-substituted substrates **6l** and **6m**, exhibited a slight decrease in yields, perhaps due to the influence of steric hindrance. Moreover, the two- or three-substituted acetoacetanilides were proven to be compatible substrates for the transformation, providing the 2-pyridone-type products (**6n**–**6r**) with satisfying yields. Impressively, *N*-methyl β-keto amide could be favorably used in this sort of transformation, offering the anticipated product **6s**, albeit with a relatively low yield, 46%. Subsequently, numerous decorated 5-aryl-1,3-dioxan-5-ols were also employed to examine the generality. Delightedly, they were well tolerated with the standard reaction conditions, producing the corresponding products **6t**–**6y** with yields ranging from 51% to 81%. Intriguingly, the position of groups on the phenyl of tertiary alcohol, played a crucial role in the reaction. Tertiary alcohols with substituents at the *para*-position performed higher reactivities in this catalytic system compared to those endowed with groups at the *meta*-position. In addition, the electron-rich 5-aryl-1,3-dioxan-5-ols converted more efficiently than their electron-deficient analogues, even enabling that the conversion of tertiary alcohols bearing 3-F and 3-Cl on the phenyl required a higher temperature and longer reaction time. It should be pointed out that 2-pyridones [22,23], especially for 5-aryl-2-pyridones, such as Tenellin, Sambutoxin and Pretenellin B, are important natural products that display a broad range of physiological activities, including antifungal, antitumoral, MEK-1 inhibitors [24,25]. However, there are only a few methods to access 5-aryl-2-pyridones, and the common one is transition-metal catalyzed oxidative coupling between acrylamides and diary alkynes [26,27]. Apparently, our method is simple and practical by employing tertiary alcohols as the materials through the acid-catalyzed tandem pinacol rearrangement reaction.

In order to gain mechanistic insights into the reaction, some control experiments were carried out, and the results were shown in Scheme 4. Firstly, two different radical trappers, TEMPO or BHT, were added to the catalytic system (Scheme 4a), the expected product **6a** was obtained in 87% and 84% yields, respectively, suggesting that a radical pathway might not be involved in this tandem reaction. Given that **1a** could be converted into the corresponding atropaldehyde, the **4a** was directly allowed to react with **5a**. To our surprise, only 72% yield of **6a** was obtained in under standard conditions, which was obviously less than that of **1a** as the starting material (72% *vs.* 92%, Scheme 4b). Further kinetic study showed that NBS could not obviously accelerate the reaction rate towards the desired product in any step (Table S2 in Supporting information), which excluded that NBS served an oxidant to promote the reaction when **4a** was used as the material. However, in the absence of NBS, the reaction of **1a** and **5a** only furnished 28% yield of the desired product (Table S1). All these results indicated that other intermediates might be involved instead of **4a**. Therefore, the LC-MS analysis experiment was conducted, in which some *m/z* peaks were assigned to the substituted malondialdehyde (**E** in Scheme 4) as well as the intermediates **B** and **4a**. Considering the difficulty in synthesis of 2-phenylmalondialdehyde (intermediate **D**) [28], we utilized a readily available analogue **7a** instead to react with **5a**. In this case, the bromo–substituted 2-pyridone product **8a** formed albeit in a lower yield compared with **6a** in the standard conditions (Scheme 4c) that might result from substitution effect.

On the basis of these experimental results, a possible mechanism was proposed for the reaction (Scheme 4). Likewise, **1a** was transformed to intermediate **B** under $Al(OTf)_3$-catalyzed conditions, which underwent either intramolecular dehydration or NBS-mediated bromination to generate the atropaldehyde **4a** and intermediate **C**, respectively. The atropaldehyde **4a** passed through a successive Michael addition/intramolecular semi-aza-acetalization/dehydration/oxidative aromatization process to give the desired product **6a** (Scheme 4, left hemicycle). On the other hand, the semi-pinacol rearrangement of the intermediate **C** might occur to generate the key intermediate **D**, which reacted with **5a** to form the product through [3 + 3] cyclization (Scheme 4, right hemicycle). Taking it into account that the NBS was very important to facilitate the formation of **6a** (92% *vs.* 28% yield), we speculated the 2-phenylmalondialdehyde **D** might be the main intermediate.

In summary, a novel class of 2-arylglycerols derivative, 5-aryl-1,3-dioxan-5-ols, have been successfully developed as versatile 1,3-biselectrophiles, functionalized as atropaldehydes or 2-aryl malondialdehydes, which could be combined with 2-naphthols or β-keto amides for the chemoselective synthesis of diverse heterocycles, 4*H*-chromenes and 2-pyridinones. Good functional group tolerance, broad substrate scope and simple reaction operation are also the attractive features, which render the present protocol more practical.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.108130.

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