RSC Advances

ROYAL SOCIETY OF CHEMISTRY

PAPER

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Cite this: *RSC Adv.*, 2022, **12**, 14435

Rh(III)-catalyzed synthesis of dibenzo[*b*,*d*]pyran-6-ones from aryl ketone *O*-acetyl oximes and quinones *via* C–H activation and C–C bond cleavage†

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Received 31st March 2022
Accepted 5th May 2022

DOI: 10.1039/d2ra02074b

rsc.li/rsc-advances

A redox-neutral synthesis of dibenzo[*b*,*d*]pyran-6-ones from aryl ketone *O*-acetyl oximes and quinones has been realized *via* Rh(III)-catalyzed cascade C–H activation annulation. A possible Rh(III)–Rh(V)–Rh(III) mechanism involving an unprecedented β-C elimination step was proposed.

The dibenzo[*b*,*d*]pyran-6-one is one of the most important structural motifs widely present in natural products with pharmacological relevance,[1] such as gut microbiota metabolites urolithins (**1–4**) that show anti-inflammatory, antiglycative and neuroprotective effects,[2–4] and the extracts of an endophytic fungus *Cephalosporium acremonium* IFB-E007 (**5–7**) that have pronounced anticancer activities.[5] In addition, the related heterocyclic structure benzo[*d*]naphtho[1,2-*b*]pyran-6-one is found in some bactericidal and antitumor natural products including gilvocarcins[6,7] (**8–10**) chrysomycins[8,9] (**11–13**), *etc.* (Fig. 1). Therefore, a number of approaches to access dibenzo[*b*,*d*]pyran-6-ones have been developed *via* the intra- or intermolecular biaryl formation as the key step.[10] However, many of these methodologies require multi-step reactions, and the development of new efficient synthetic methods, especially those easy one-step reactions that are still of great interest.

In the past decade, transition-metal-catalyzed C–H bond activation has proven to be a powerful tool in organic syntheses[11] and several methods for the synthesis of dibenzo[*b*,*d*]pyran-6-ones *via* C–H activation have been reported.[12] Actually, in 2015, our group reported Rh(III)-catalyzed synthesis of dibenzo[*b*,*d*]pyran-6-ones from *N*-methoxybenzamides and quinones through C–H activation annulation.[13] Interestingly, we obtained the same products using aryl ketone *O*-acetyl oximes as substrates to react with quinones under Rh(III)-catalyzed conditions in this work. Rh(III)-catalyzed C–H activation using ketoximes as substrates has been developed for synthesis of various substituted heterocycles.[14] Compared to the previous reports, this reaction undergoes a novel mechanism involving an unexpected C–C bond cleavage, which is attractive. Moreover, our study demonstrated that solvent is vital to these reactions. In 2018, we reported Rh(III)-catalyzed annulation of aryl ketone *O*-acetyl oximes with quinones to synthesize 6*H*-benzo[*c*]chromenes with acetone as a co-solvent.[15] Herein, we described Rh(III)-catalyzed synthesis of dibenzo[*b*,*d*]pyran-6-ones using the same substrates without acetone (Scheme 1).

Initially, the reaction of acetophenone *O*-acetyl oxime **1a** with benzoquinone **2a** was employed to optimize the reaction conditions (Table 1). When the reaction was conducted in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%) and PivOH (100 mol%) in MeOH at 50 °C for 12 h, 2-hydroxy-6*H*-dibenzo[*b*,*d*]pyran-6-one **3a** was obtained in 12% yield (Table 1, entry 1). Elevating the reaction temperature led to a higher yield of **3a** (Table 1, entries 1–4). Solvent screening (Table 1, entries 4–9) revealed that reaction in MeOH gave a higher yield of **3a** (Table 1, entry 4). Among the additives tested, benzoic acid was the most favorable with respect to product yield (Table 1, entries

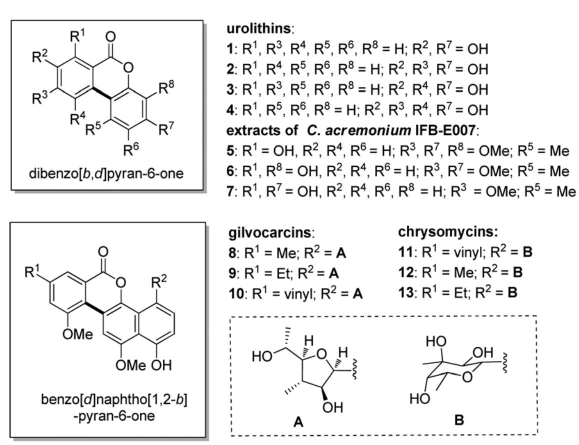

Fig. 1 Selected representative natural products.

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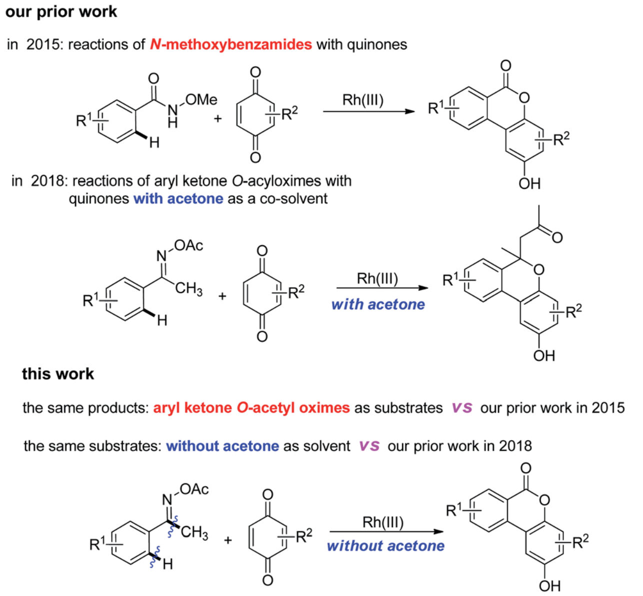
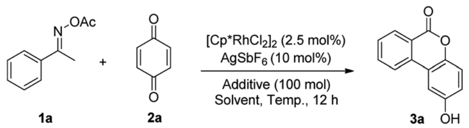
† Electronic supplementary information (ESI) available. See https://doi.org/10.1039/d2ra02074b



Scheme 1 Rh(III)-catalyzed divergent C–H activation annulation with quinones.

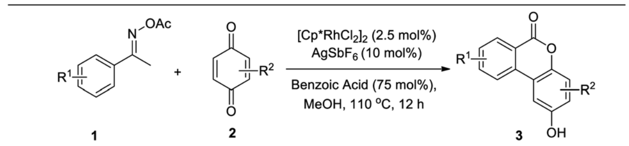
Table 1 Optimization of the reaction conditions[a]

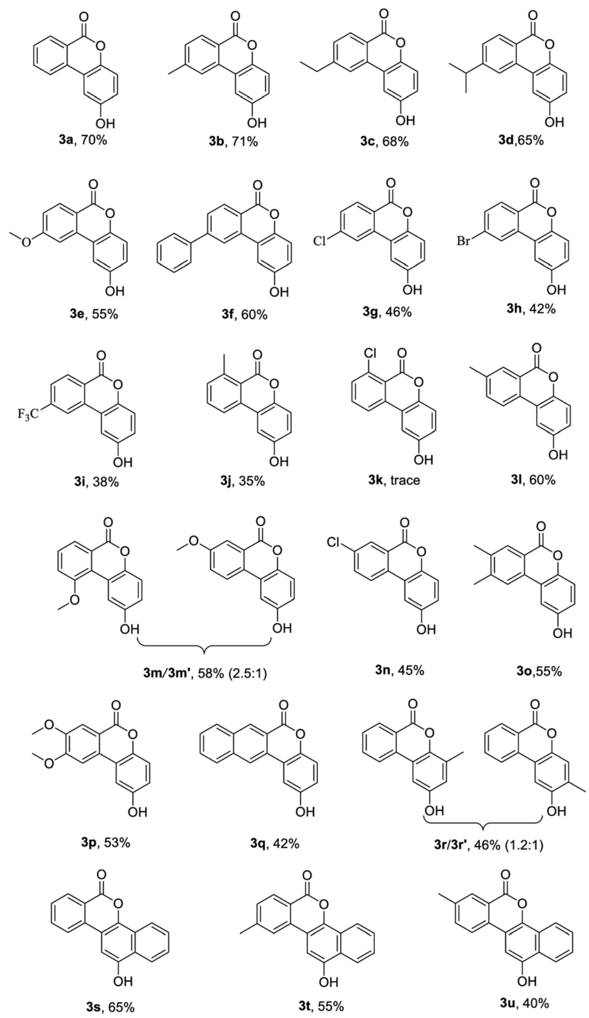


Entry	Additive	Solvent	Temp °C	Yield[b] (%)
1	PivOH	MeOH	50	12
2	PivOH	MeOH	70	20
3	PivOH	MeOH	90	36
4	PivOH	MeOH	110	43
5	PivOH	EtOH	110	26
6	PivOH	DMF	110	37
7	PivOH	THF	110	16
8	PivOH	HFIP	110	0
9	PivOH	Acetone	110	Trace
10	HOAc	MeOH	110	Trace
11	Benzoic acid	MeOH	110	50
12[c]	Benzoic acid	MeOH	110	70
13[d]	Benzoic acid	MeOH	110	63

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), additive (100 mol%), solvent (1 mL) for 12 h. [b] Isolated yields. [c] Benzoic acid (75 mol%) was added. [d] Benzoic acid (50 mol%) was added.

Table 2 The reaction scope[a]

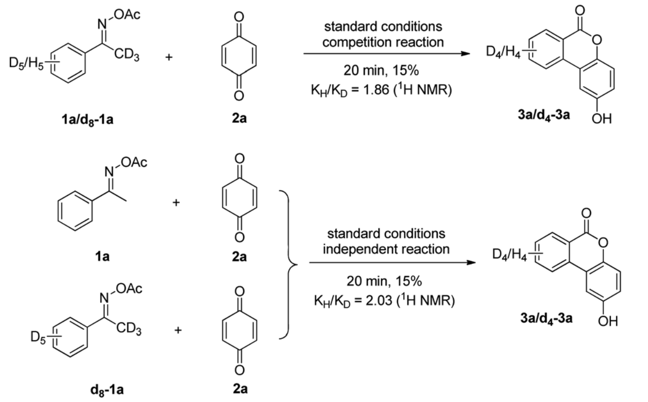




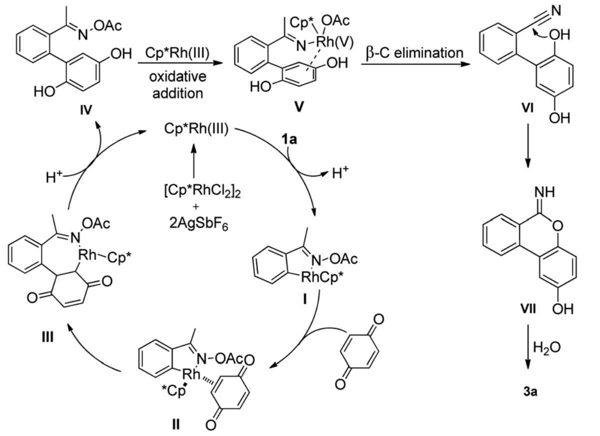
[a] Standard conditions.

4, 10 and 11). Decreasing the amount of benzoic acid to 75 mol% resulted in the best yield of **3a** (Table 1, entry 12).

Under the obtained optimum reaction conditions above (Table 1, entry 12), we surveyed the reaction scope (Table 2). First, the reactions of various aryl ketone *O*-acetyl oximes **1** with **2a** were examined. For acetophenone *O*-acetyl oximes, substrates with electron-donating groups or phenyl at the *para*-position of aryl groups participated well in this reaction and the corresponding products were obtained in good yields (**3a–3f**). Substrates with halogens or strong electron-withdrawing group trifluoromethyl gave the products in lower yields (**3g–3i**). Substrate bearing the methyl or chlorine at the *meta*-position provided the desired products **3l** and **3n** with exclusive regioselectivity toward the less-hindered site, whereas the *meta*-methoxy-substituted derivative gave a mixture of regioisomers (**3m**/**3m′** = 2.5 : 1), revealing that the nature of the substituent at the *meta*-position had an effect on the regioselectivity. 3,4-Disubstituted acetophenone *O*-acetyl oximes smoothly reacted to result the corresponding dibenzo[*b*,*d*]pyran-6-ones **3o** and **3p** in moderate yields. 2-Acetonaphthone *O*-acetyl oxime also produced the target product 2-hydroxy-6*H*-naphtho[2,3-*c*]



Scheme 2 Kinetic isotope effect experiments.



Scheme 3 Proposed mechanism.

chromen-6-one **3q**. Next, we examined the reactivity of quinone derivatives with **1a** under the established conditions. Methyl benzoquinone afforded the desired molecule in 46% yield with regioisomers (**3r**/**3r′**) in a ratio of approximately 1.2 : 1. The naphthoquinone could be also well tolerated, giving benzo[*d*]naphtho[1,2-*b*]pyran-6-one **3s** in 65% yield. Furthermore, *para*-methyl-substituted or *meta*-methyl-substituted acetophenone *O*-acetyl oximes also smoothly reacted with naphthoquinone to give the corresponding products **3t** or **3u**. Thus, several tetracyclic benzo[*d*]naphtho[1,2-*b*]pyran-6-ones were synthesized successfully.

To shed light on the reaction mechanism of this annulation, the reaction of acetophenone *O*-acetyl oxime **1a** with benzoquinone **2a** under standard conditions was detected by GC-MS, and benzonitrile was observed (detected by GC-MS; see ESI†). This result suggested this reaction might undergo a β-C elimination. Then, deuterium-labeling experiments were further carried out to gain some insights into the catalytic mechanism. A competition between protio and deutero **1a** showed a KIE value of 1.86 at early conversion. The KIE was further measured from two side-by-side reactions using protio and deutero **1a** with **2a** and a KIE value of 2.03 was observed (Scheme 2). These results demonstrated that the C–H bond cleavage process might be involved in the rate-determining step.

On the basis of our previous work, present observations and literature precedent,[11,13,15,16] a mechanistic pathway is proposed (Scheme 3, taking the reaction of substrate **1a** with benzoquinone **2a** as an example). First, *O*-acetyl oxime **1a** reacts with the active Cp*Rh(III) species through directed C–H cleavage to form a five-membered rhodacycle intermediate **I**. Next, coordination of the benzoquinone affords intermediate **II**, which undergoes migratory insertion into the incipient Rh–C bond to form a seven-membered rhodacycle **III**. Protonolysis and aromatization deliver biaryl intermediate **IV**. Then, an oxidative addition of Rh(III) into the O–N bond is possible to produce the Rh(V) species **V**,[17] followed by β-C elimination to give the intermediate **VI**.[18] A subsequent intramolecular nucleophilic addition of intermediate **VI** delivers the intermediate **VII**, which undergoes hydrolysis to generate the final product **3a**.

Conclusions

In summary, we have developed a novel Rh(III)-catalyzed cascade C–H activation annulation with readily available and inexpensive substrates for the convenient and direct synthesis of dibenzo[*b*,*d*]pyran-6-ones. In this process, we proposed a possible Rh(III)–Rh(V)–Rh(III) pathway, which might undergo an unprecedented β-C elimination step. This is the first example of β-C elimination *via* Rh(III)-catalyzed C–H bond functionalization. Further studies into the detailed reaction mechanism is ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for financial support from The Education Department of Jilin Province (Grant No. JJKH20190698KJ), Jilin Science and Technology Bureau (Grant No. 20190104142) and Northeast Electric Power University (Grant No. BSZT06202106).

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