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Redox Neutral [4 + 2] Benzannulation of Dienals and Tertiary Enaminones Toward Benzaldehyde Synthesis

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By employing the featured amine elimination of tertiary enaminones as a key transformation, the cascade reactions of dienals and tertiary enaminones involving the [4 + 2] annulation, the Hofmann-like amine elimination and the aromatization are devised for the benzaldehyde synthesis. This method is of particular interest by providing benzaldehydes containing an electron withdrawing group in C3 poistion which are hard to access by previous methods on benzadehyde synthesis.

Aldehydes are fundamental chemicals with probably the most universal application in organic synthesis. The flexible reactivity of aldehydes toward numerous transformations such as oxidation, reduction, condensation, addition, cycloaddition, polymerization, to name but a few, determines their irreplaceable role in both industrial and laboratory scale syntheses.[1] A plethora of textbook reactions such as Wittig, Ugi, Biginelli, Hantzsch, Henry, Mannich, Aldol, Perkin as well as many other named reactions employ aldehyde as an indispensable synthon.[2] Moreover, emerging applications of aldehyde reagents in organocatalysis, photocatalysis and the preparation of chiral reagents etc keep getting discovered, demonstrating that even broader room remains in the valuable application of aldehydes.[3] In this context, developing synthetic methods for aldehyde synthesis, especially the synthesis of those unprecedented polyfunctionalized aryl aldehydes is presently an imperative issue.

Currently, the formylation of precursor functional groups such as carboxylic acid, alcohols, C-halogen bond, and even C-H bonds constitutes the dominant methods for aldehyde synthesis.[4] For example, the Gattermann-Koch reaction,[5] Reimer-Tiemann reaction,[6] Duff reaction,[7] Vilsmeier-Haack reaction,[8] and Rieche reaction[9] are classical tactics of the category. In addition, new formylation-based aldehyde syntheses featuring extended substrate scope, product diversity, or catalytic sustainability have recently won notable advances.[10] In contrast to the impressively enriched methods in the formyl generation-based aryl aldehyde synthesis (Mode I, Fig. 1), however, the counterpart synthetic strategy by constructing the aryl ring remains hardly available (Mode II, Fig. 1). Therefore, developing methodology for the synthesis of aromatic aldehydes by means of aryl ring construction is highly desirable since such methods will bring new opportunities not only to aldehyde chemistry, but also numerous other syntheses involving the participation of aryl aldehydes.

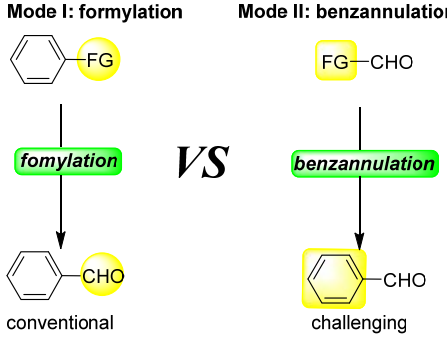

Figure 1 Two major strategies for aryl/benzaldehydes synthesis

By analyzing the reaction process, it can be easily found that the challenge lying in the synthetic model II is the contradiction between the oxidation condition required by the conventional aromatization and the sensitivity of the CHO group to oxidant. Consequently, the benzannulation reactions involving aldehyde substrate are usually accompanied with formyl oxidation. For instance, Chi and Song et al,[11] as well as other groups[12] have reported seminal benzannulation reactions of such kind (Scheme 1A). On the other hand, equivalent annulation reactions allowing the retaining of the formyl group tend to yield non-aromatic products. Enders et al[13] provided one such classical example in the enantioselective synthesis of cyclohexenyl carbaldehydes (Scheme 1B), which has later on become a model tool in devising asymmetric synthesis.[14] In some cases, enamine-

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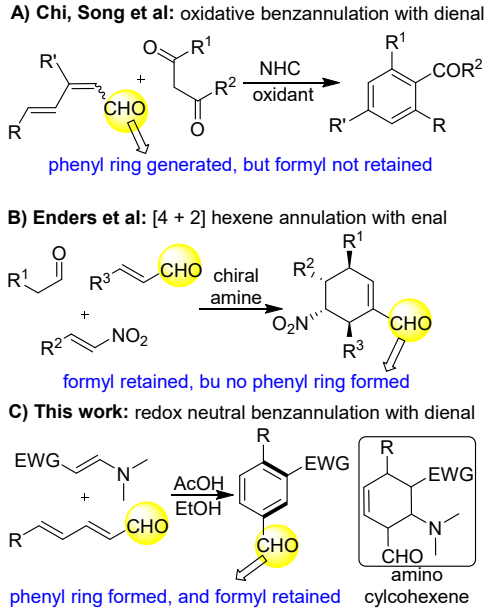
based [4 + 2] cyclization has been used for the construction of cyclohexadiene which could be transformed into benzenes or fused arenes by subsequent operation under harsh dehydration conditions, or by means of tautomerization of the additional C=C double bond preinstalled in the substrate.[15] The one-step benzannulation under redox neutral condition by employing specifically functionalized substrates such as coumarin-fused electron deficient 1,3-diene or 3-formyl chromones are also known.[16] Yet, not any of these methods tolerate aryl aldehyde synthesis.

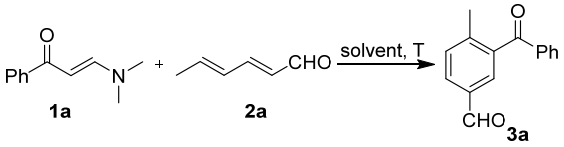


Scheme 1 Different protocols of aldehyde participated annulation

During our research exploring tertiary enaminones in organic synthesis,[17] we noticed that the Hofmann-like amine elimination generating a C=C bond is a featured transformation of these synthons. Thus, we envisaged that the [4 + 2] annulation of a tertiary enaminone with a dienal may quickly undergo this featured elimination to produce cyclohexa-1,3-diene intermediate which can possibly get aromatized to form benzene under the driving force to access stable aryl ring without relying on oxidant, thus providing a practical formyl tolerating methodology for benzaldehyde synthesis (Scheme 1C). Herein, we report the first enaminone-based benzannulation strategy for the synthesis of benzaldehydes by using directly linear aldehydes as the formyl donors.

To start the exploration, the reaction of enaminone **1a** and dienal **2a** was first conducted in different reaction media, including AcOH, DMF, MeCN, toluene etc. It was found that only those protic solvent such as AcOH, EtOH and ethyl lactate (EL) could mediate the reaction to give benzaldehyde **3a** (entries 1-8, Table 1). On the basis of these results, we then attempted to employ the mixed EtOH/AcOH as the medium of the expected reaction. To our delight, the yield of **3a** was drastically increased in this experiment (entry 9, Table 1). Decreasing the amount of AcOH or employing $(CF_3)_2CHOH$ as alternative protic solvent, however, were found to be not helpful for the reaction (entries 10-11, Table 1). The subsequent efforts in varying the ratio of substrates and the reaction temperature did not afford further improved result, either (entries 12-15, Table 1). Notably, a control experiment conducted under N_2 gave **3a** with 59% yield (entry 16, Table 1), supporting that the reaction was independent of external oxidant. A control experiment employing $PhNO_2$ as medium gave **3a** with 20%, further indicating that even a mild oxidant didn't promote this reaction (entry 17, Table 1).

Table 1 Optimization of reaction conditions[a]

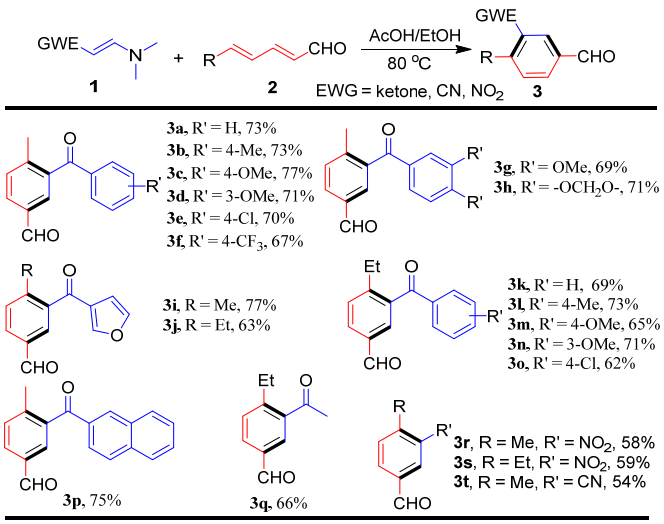


Entry	Solvent	T/°C	Yield (%)[b]
1	AcOH	80	30
2	DMF	80	nr
3	DMSO	80	nr
4	CH_3CN	80	nr
5	H_2O	80	nr
6	toluene	80	nr
7	EtOH	80	27
8	EL	80	25
9	AcOH: EtOH	80	73
10[c]	AcOH: EtOH	80	65
11	$(CF_3)_2CHOH$:EtOH	80	30
12[d]	AcOH: EtOH	80	73
13[e]	AcOH: EtOH	80	72
14	AcOH: EtOH	90	71
15	AcOH: EtOH	70	70
16[f]	AcOH: EtOH	80	59
17[g]	$PhNO_2$	80	20

[a]General conditions: **1a** (0.2mmol), **2a** (0.2mmol), stirred for 12 h in 2 mL or 1 + 1 mL solvent(s). [b]Yield of isolated product. [c]AcOH(0.5 mL) and EtOH (1 mL). [d]The loading of **1a** was 0.4 mmol. [e]The loading of **2a** was 0.4 mmol. [f]Reaction under N_2. [g]In the presence of AcOH (0.6 mmol).

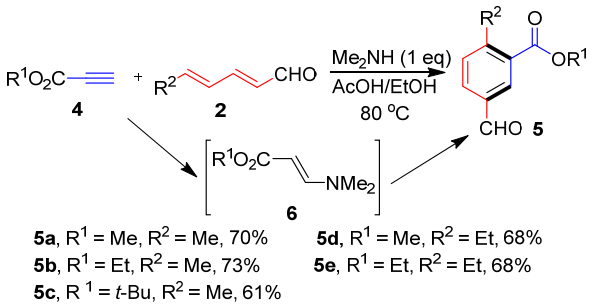
To investigate the application scope, this [4 + 2] benzannulation was then executed by using different enaminones and dienals. Table 2 outlined the results provided by these experiments. It was indicated that this protocol tolerated well to the substrates functionalized with various substituents. The aryl functionalized enaminones containing alkyl, alkoxy, halogen and heteroaryl, for example, all participated the reaction to afford corresponding products with generally good yields. Expected products were also smoothly obtained when the alkyl substituted enaminone was utilized (**3q**, Table 2). What's more, alongside enaminones, analogous enamines such as nitro-enamine and cyano-enamine also took part in the reaction to give the nitro and cyano functionalized benzaldehydes, respectively (**3r**-**3t**, Table 2). The reaction employing an aryl functionalized pentadienal, the (*2E*,*4E*)-5-phenylpenta-2,4-dienal to react with enaminone **1a**, however, didn't provide the corresponding biaryl aldehyde product (R = Ph).

Table 2 Scope of enamines in the synthesis[a,b]



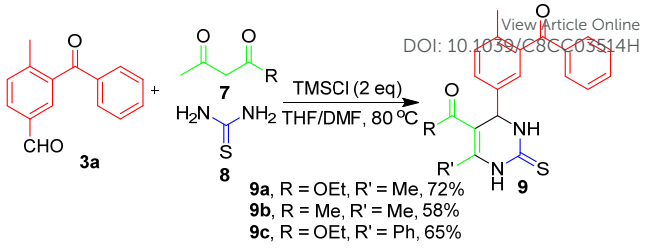
[a]General conditions: **1** (0.2 mmol), **2** (.2 mmol), AcOH/EtOH (1/1 mL), stirred at 80 °C for 12 h. [b]Isolated yield.

Secondary amine was known to be capable of generating enaminoesters of type **6** by incorporating propiolates through aza-Michael addition.[18] As further investigation, the reactions of alkyl propiolates **4** and dienals were also examined in the additional presence of dimethylamine. As expected, the corresponding ester functionalized benzaldehydes **5** were practically furnished with good yields (**5a**-**5e**, Scheme 2), demonstrating the broad scope of this strategy in the synthesis of divergent benzaldehydes.



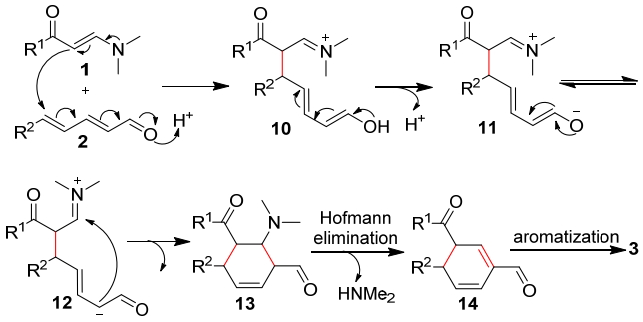
Scheme 2 Benzaldehyde synthesis via in situ enamine formation

Subsequently, to explore the synthetic application of these newly synthesized polyfunctional benzaldehydes, we employed benzaldehyde **3a** in the three-component Biginelli reaction. The expected products would be potentially valuable since the substitution on the C4 phenyl ring of Biginelli compounds was known to play crucial role in determining their biological profile.[19] As a result, the reactions of **3a**, methylene substrates **7** and thiourea **8** successfully provided 3,4-dihydropyrimidinthiones **9** via simple operation (Scheme 3).



Scheme 3 Application of the benzaldehydes in Biginelli reaction

According to the known transformation pathways of the electron deficient enamines[17] and the present results, the mechanism of this benzannulation is proposed and outlined in Scheme 4. Initially, in the presence of protic acid, the dienal **2** is activated in the δ position, which undergoes the attack of the nucleophilic α-carbon in enaminone **1** to generate intermediate **10**. The zwitteric ion **11** resulting from the deprotonation of **10** then gives rise to intermediate **12** by tautomerization. After the subsequent formation of **13** via intramolecular cyclization, the featured Hofmann-like elimination in **12** then enables the formation of cyclohexa-1,3-diene **14** by releasing dimethyl amine. Because of the increased acidity of the C-H bond in the ketone (R^1CO) α-site, the aromatization of **14** then easily takes place to yield products **3** under the driving force of forming stable aromatic system.



Scheme 4 The proposed mechanism for the benzannulation-based synthesis of benzaldehydes

Conclusions

In conclusion, by making use of the featured amine elimination in the tertiary enaminones, we have realized for the first time the benzannulation-based synthesis of benzaldehydes using linear aldehydes. The key factor allowing the tolerance of the unprotected formyl group to this benzannulation protocol is the redox neutral reaction conditions. Besides providing a new option for the synthesis of polyfunctionalized benzaldehydes, the present work is also pivotal by disclosing new synthetic application of tertiary enaminones in addressing current synthetic challenges.

Conflicts of interest

There are no conflicts to declare.

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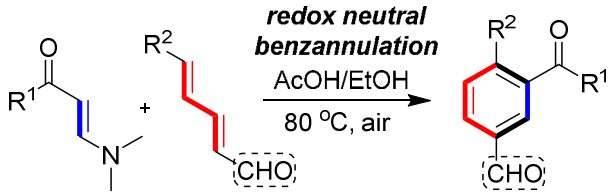

✔ **Selective aryl aldehyde formation without further oxidation**
✔ **New application model of tertiary enaminones**
✔ **Environmentally benign & simple condition**

The [4 + 2] benzannulation reactions between tertiary enaminones and dienals have been developed for the synthesis of polyfunctionalized benzaldehydes, providing a new access to benzaldehydes alongside the classical formylation strategy.