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DABCO Catalyzed Unusual Formal [4+2] Cycloaddition of 3-Acyl (or alkoxycarbonyl)-1,4-enediones with 2,3-Butadienoates: An Effective Access to Construct Highly Functionalized Pyrans

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Xiang-Suo Meng[a], Shan Jiang[a], Xiao-Yun Xu[a], Qiang-Xian Wu[a], Yu-Cheng Gu[b], and De-Qing Shi*[a]

A convenient and efficient DABCO-catalyzed formal [4+2] cycloaddition of 3-acyl(or alkoxycarbonyl)-1,4-enediones with 2,3-butadienoates is presented. This transformation takes advantages of mild condition, wide substrate scope and significant functional group tolerance as well as excellent regioselectivity，which makes this method powerful for one-pot synthesis of highly functionalized pyrans in moderate to excellent yields.

Multi-substituted pyran ring is an important framework which can be found in biologically active compounds and natural products.[1] Despite many strategies have been developed to synthesize substituted pyrans.[2] However, the development of novel methodology for the convenient and effective synthesis of high functionalized pyrans remains highly desirable.

In the past decades, Lewis base catalyzed reactions of allenoates have attracted much attention for constructing molecular diversity and complexity.[3] Since 1995, Lu et al. first published phosphine-catalyzed [3+2] cycloaddition reaction of allenoates with alkene; [4] in 2003, Kwon et al. reported a novel [4+2] annulation of α-alkylallenoates with imines; [5] In addition, several other reactions, such as Kwon's [3+3] annulations with aziridines [6]and Tong's [4+n], [3+n] annulations were well established.[7] Compared to phosphines, the corresponding amine analogues usually display markedly different reaction modes in these types of transformations. However, the cycloaddition of allenoates catalyzed by amine is relatively rare[8] and only a few [4+2] cycloadditions have been developed (Figure 1).[9] As shown in **Fig. 1**, in most cases，when amine was used as the catalyst, allenoate acted as a surrogate of a "1,2-dipole" and underwent β,γ-addition, exocyclic double bond adducts were formed.[9a-9e] However, when H-bond bifunctional organocatalyst derived from Cinchona alkaloid was used, the mixture of two regioisomers was yielded, the major isomer was the α,β-adduct. [9f]

On the other hand, the 1,4-enedione is an important structural motif that is not only widely presented in natural products and medicinal molecules,[10] but also served as versatile building blocks in a variety of transformations, such as Diels-Alder cyclization and Michael addition [11] as well as precursors for the preparation of many heterocyclic compounds such as furans, thiophenes, pyrroles etc. [12]

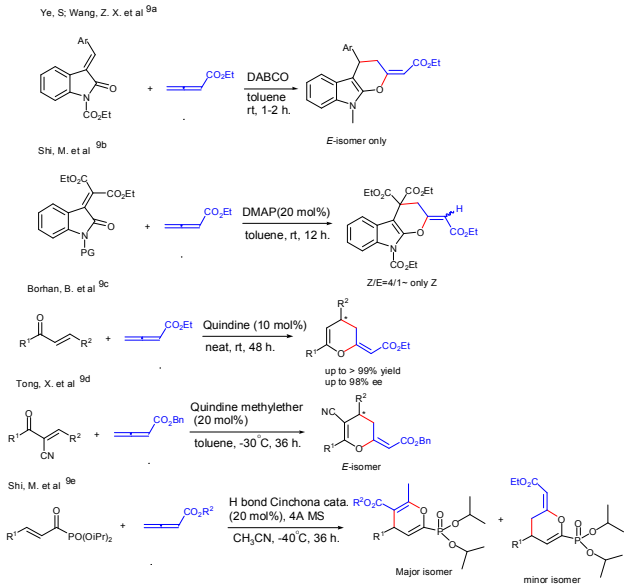

Fig.1 Amine-catalyzed [4+2] cycloaddition of allenoates.

Recently, we reported the Ph_3P and 1,4-diazabicyclo(2,2,2)octane (DABCO) catalyzed cycloaddition of 2,3-butadienoates with 3-acyl-

[a] *Key Laboratory of Pesticide and Chemical Biology of Ministry of Education, College of Chemistry, Central China Normal University, 152 Luoyu Road, Wuhan 430079, P. R. China*
E-mail: chshidq@mail.ccnu.edu.cn; Fax: 86-27-67862041
[b]*Syngenta Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY, U.K.*
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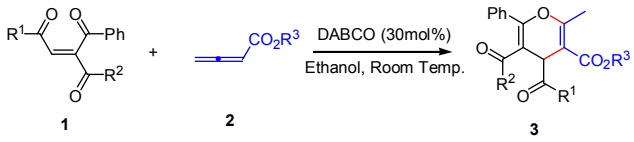
2*H*-chromen-ones for the convenient synthesis of dihydropyran-fused and cyclopenten-fused chromen-2-ones with high regio- and stereo-selectivities.[13]. As part of our continuing interest in cycloaddition involving 2,3-butadienoate and investigating its regioselectivity, herein, we report a DABCO-catalyzed unusual formal [4+2] cycloaddition of 2,3-butadienoates with 3-acyl(or alkoxycarbonyl)-1,4-enediones, the unexpected α,β-adduct regioisomer--highly functionalized pyrans **3** were generated (Scheme 1).



Scheme 1 DABCO-catalyzed unusual formal [4+2] cycloaddition of 2,3-butadienoates with 3-acyl(or alkoxycarbonyl)-1,4-enediones

Initially, the cycloaddition of 3-benzoyl-1,4-biphenyl-1,4-enedione (**1a**) with ethyl 2,3-butadienoate (**2b**) was used as the model substrate to screen for experimental conditions. When 1,4-enedione **1a** was treated with 1.5 equiv of ethyl 2,3-butadienoate **2a** in the presence of 20 mol% of DABCO in toluene (4.0 mL) at room temperature, the reaction afforded the desired multi-substituted pyran **3a** in 57% yield (Table 1, entry 1). Encouraged by this result, different amine catalysts such as DMAP, DBU, TMEDA and Et_3N were examined (Table 1, entries 1–5), DABCO gave the highest yield (Table 1, entry 1). However, a variety of phosphines (Ph_3P, *n*-Bu_3P and Me_3P) cannot trigger the reactions (Table 1, entries 6-8). The effect of solvents was investigated, and EtOH was shown to be the optimal solvent for this reaction (Table 1, entries 9–14).

Subsequently, the effect of reaction temperature was also explored (Table 1, entries 15-18). Increasing or decreasing the temperature did not affect the reaction yield remarkably. The amount of catalyst was also evaluated, and the results showed that a loading of 30 mol% DABCO gave the best result, led to the desired product **3a** in 90% yield (Table 1, entry 19).

With the optimized conditions in hand, initially, a variety of 3-acyl(or alkoxycarbonyl)-1,4-enediones **1** were subjected to the above mentioned optimal conditions to examine the generality of this methodology (Table 2). The 1-substitutedphenyl(or heteroaryl) subsituted 1,4-enediones bearing electron-donating (CH_3, OCH_3) or electron-withdrawing groups (F, Cl, NO_2) or different substituted pattern on the phenyl ring were found to be suitable substrates for this reaction, gave the desired products **3a**-**3j** in a range of 78-91% yields. More importantly, 1-furyl or thienyl substituted 1,4-enediones **1k** and **1l** also proceeded smoothly to give the desired products **3k**-**3l** with satisfactory results (75 and 71% yield, respectively). It was noted that 3-ethoxycarbonyl substituted 1,4-enediones can be also employed in this transformation and provide the desired products **3m** and **3n** in 85% and 68% yield, respectively, and it was found that the 3-substituents has no significant influence on the reaction (**3a**, **3m**-**3n**). However, when trans-1,4-diphenyl-2-butene-1,4-dione was used as the substrate, the formal [3+2] product **3r** was obtained as a light yellow crystal in 76% yield (please see the supporting information), which displayed different reaction mode from the 3-acyl (or alkoxycarbonyl)-1,4-enedione substrates.

Then, we evaluated the scope of 2,3-butadienoates **2**. Methyl or benzyl 2,3-butadienoates (**2b**, **2c**) are also suitable candidates for this transformation, affording the desired products **3o**-**3q** in excellent yields (86-96% yield). Unfortunately, when α- or γ-alkyl substituted allenoates (for example, α-methyl or benzyl substituted or γ-methyl substituted 2,3-butadienoates) were used as the substrates, no reaction occurred under these above conditions (the results are not listed).

The structures and configurations of the formal [4 + 2] cycloadducts **3** were assigned via ^{1}H-NMR, ^{13}C-NMR, MS, elemental analysis (see the ESI†). Moreover, the structure of **3q** was unambiguously determined by X-ray crystallographic analysis (Figure 2, CCDC: 1483768).

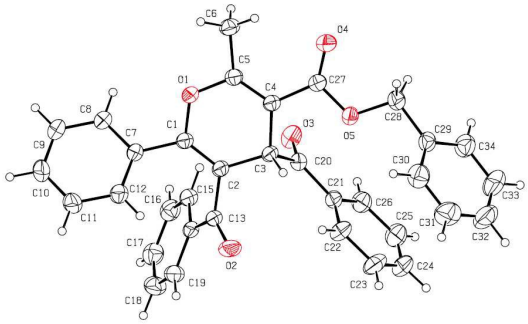
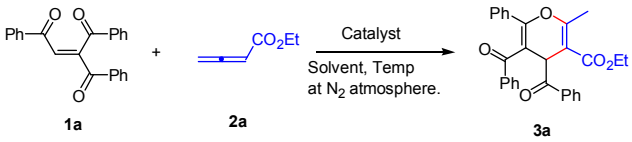


Figure 2. X-ray crystal structure of compound **3q**.

Table 1 Reaction conditions screening[a]



Entry	Catalyst (mol%)	Solvent	Temp(°C)	Time(h)	Yield[b](%)
1	DABCO (20)	toluene	Room Temp.	24	57
2	DMAP (20)	toluene	Room Temp.	24	trace
3	DBU (20)	toluene	Room Temp.	24	trace
4	TMEDA (20)	toluene	Room Temp.	24	40
5	Et_3N	toluene	Room	24	35

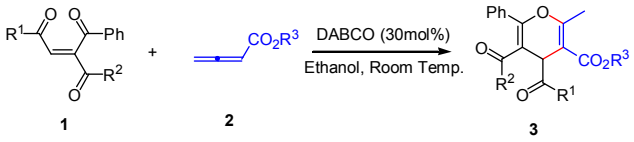
	(20)		Temp.		
6	Ph_3P (20)	toluene	Room Temp.	36	trace
7	*n*-Bu_3P (20)	toluene	Room Temp.	24	trace
8	Me_3P (20)	toluene	Room Temp.	24	trace
9	DABCO (20)	CH_2Cl_2	Room Temp.	24	50
10	DABCO (20)	CH_3CN	Room Temp.	24	73
11	DABCO (20)	THF	Room Temp.	24	60
12	DABCO (20)	C_2H_5OH	Room Temp.	12	87
13	DABCO (20)	DMF	Room Temp.	24	63
14	DABCO (20)	DMSO	Room Temp.	24	71
15	DABCO (20)	C_2H_5OH	-5	40	75
16	DABCO (20)	C_2H_5OH	0	36	85
17	DABCO (20)	C_2H_5OH	40	12	79
18	DABCO (20)	C_2H_5OH	50	12	81
19	DABCO (30)	C_2H_5OH	Room Temp.	10	90

[a] Reaction conditions: 1a (0.50 mmol), 2a (0.75 mmol), catalyst in solvent (4.0 mL) , under N_2 atmosphere .

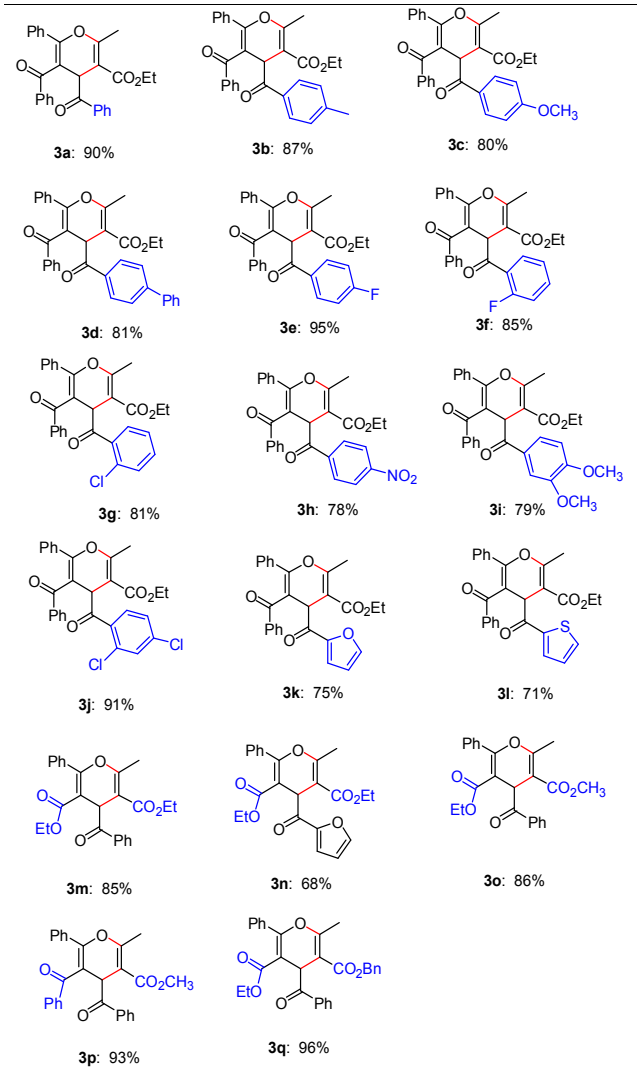
[b]Isolated yield.

Based on our investigations and the reported literatures,[9a,9b,9f] a possible mechanism is suggested as shown in **Scheme 2**. First of all, DABCO attacks the β-carbon of ethyl 2,3-butadienoate **2a** to give intermediate **A**, which can isomerize to the more stable intermediate **B**, because both the ammonium salt ion and ester group can stabilize the β-carbanion of **B**. Subsequently, compound **B** undergoes 1,4-addition with 1,4-enedione **1a** to generate intermediate **C**, which follows by the enolization and 1,3-proton transfer and converts to intermediate **E.** Finally, the formal [4+2] cycloadduct **3a** is formed by the intramolecular nucleophilic attacking and then the release of DABCO.

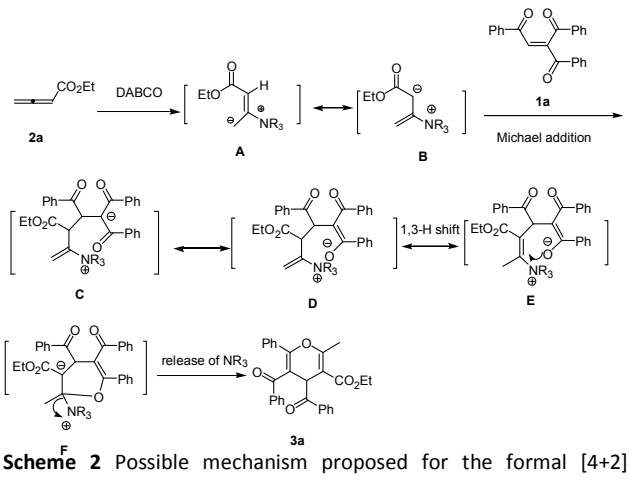
Table2 Substrate Scope[a, b]



1 2 3



[a]Unless otherwise noted, reactions were carried out with **1** (0.50 mmol), **2** (0.75 mmol), DABCO (0.15 mmol) in EtOH (4.0 mL) at room temperature under N_2 atmosphere. [b]Isolated yield.



Scheme 2 Possible mechanism proposed for the formal [4+2] cycloadditions of 3-acyl(or alkoxycarbonyl)-1,4-enediones with 2,3-butadienoates catalyzed by DABCO

Conclusions

In conclusion, we developed a convenient and efficient DABCO-catalyzed formal [4+2] cycloaddition of 3-acyl(or alkoxycarbonyl)-1,4-enediones with 2,3-butadienoates. This methodology possesses mild condition, wide substrate scope and significant functional group tolerance as well as excellent regioselectivity, which provides a convenient and effective pathway for the preparation of highly functionalized pyrans. Further investigation of the chiral amine-catalyzed formal [4+2] annulation of 3-acyl (or alkoxycarbonyl)-1,4-enediones with 2,3-butadienoates is currently underway and will be reported in due course.

Acknowledgements

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