DABCO-Induced [2+2+2]-Cycloaddition Reaction of Ethyl Propiolate and Aryl Aldehydes for the Synthesis of 4-Aryl-4*H*-pyrans

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Abstract: The first DABCO-induced [2+2+2]-cycloaddition reaction of ethyl propiolate and aryl aldehydes is reported for selectively constructing 4-aryl-4*H*-pyrans in moderate to good yields.

Key words: DABCO, [2+2+2]-cycloaddition reaction, ethyl propiolate, aldehydes, 4-aryl-4*H*-pyrans

The development of new methods leading to the carbon–carbon and carbon–heteroatom bonds that would rapidly transform readily accessible starting materials into functionalized complex molecules is of considerable current interest in organic synthesis.[1] Great progress has been achieved during the past decades in these methodologies which have mainly focused on transition-metal-catalyzed procedures with palladium, rhodium, nickel, ruthenium, copper, silver, and gold.[2] Recently, significant efforts have been made to develop cascade reactions with organocatalysts, such as enamine, 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 4-(dimethylamino)pyridine (DMAP), triphenylphosphine (Ph_3P), tributylphosphine (Bu_3P), pyridine, and dimethyl sulfoxide (DMSO) activation modes.[3] DABCO is a commercial available small molecule, which has been found various applications in catalyzing ring-formation reactions[4] and provides an important platform for the development of novel cascade strategies for its reactivity. As a part of an ongoing program to develop novel protocols that are capable of building molecular complexity from simple substrates, herein we wish to describe a new cascade protocol: an unprecedented coupling of ethyl propiolate and aryl aldehydes catalyzed by DABCO to afford diverse and structurally meaningful 4-aryl-4*H*-pyrans, which are one of the structural units in many natural products and important synthons to construct other heterocyclic compounds,[5] and show a broad range of biological and pharmacological activities.[6]

Initial efforts were focused on the systematic evaluation of various conditions for the ring formation to synthesize 4*H*-pyrans starting from ethyl propiolate (**1**) and benzaldehyde (**2a**). Among the seven common used Lewis bases as the organocatalysts, only DABCO proved to be effective for this transformation (Table 1, entries 1–7), and diethyl 4-phenyl-4*H*-pyran-3,5-dicarboxylate (**3a**) was obtained in 26% GC yield. The structure of **3a** was fully characterized by NMR spectra and further confirmed by C–H COSY (HMQC) spectra.[7] The DABCO-based catalytic system was further improved by optimizing other reaction conditions, such as solvent, reaction temperature, reaction time as well as the amount of the catalyst (Table 1, entries 8–22). As the results showed, 1,4-dioxane was found to be suitable for this cyclization reaction (Table 1, entries 3, 8–15). The yield of **3a** can be improved to 40% when raising the temperature from room temperature to 90 °C. However, the yield was not very sensitive to the reaction time (Table 1, entries 16–19).

As shown in Table 2, the substrate scope of DABCO-catalyzed system was then examined under our optimized reaction conditions.[8] The reaction of a wide range of aromatic aldehydes with ethyl propiolate proceeded smoothly to furnish the corresponding 4-aryl-4*H*-pyrans in moderate to good isolated yields. The steric hindrance and electronic properties of the substituents on the aromatic aldehydes have significant influence on the reaction (Table 2, entries 1–7). The aromatic ring with electron-donating groups, such as methyl and methoxy groups, failed to produce the products. *para*-Halogen-substituted aryl aldehydes afforded the corresponding products in 30%, 55%, and 60% yields accompanied by the increase of atomic weight of halogen (Table 2, entries 2–4). The aldehydes bearing electron-withdrawing groups at *para* or *meta* position could be successfully used to furnish the products in good yields (Table 2, entries 5–7).

A likely mechanistic scenario for the catalytic ring formation is outlined in Scheme 1.[9] The reaction is initiated by DABCO nucleophilic attack on the carbon–carbon triple bond of ethyl propionate **1**, resulting in the formation of 1,3-dipole **4**. Subsequent carbon anion nucleophilic attack occurs on the carbonyl carbon of aldehyde leading to intermediate **5**, which then undergoes intramolecular ring formation to give the [2+2]-addition product **6**, accompanied with the regeneration of DABCO. Finally, driven by the release of the four-membered ring strain, intermediate **6** then reacts with a second molecule **4**, allowing for the formation of the final product **3**.

In summary, a formal [2+2+2]-cycloaddition cascade reaction for the synthesis of 4-aryl-4*H*-pyrans via organocatalytic reaction was developed. DABCO was found to provide the best results in this reaction. This practical protocol will be the choice for chemists to prepare this type of 4-aryl-4*H*-pyrans in a highly concise fashion. Current

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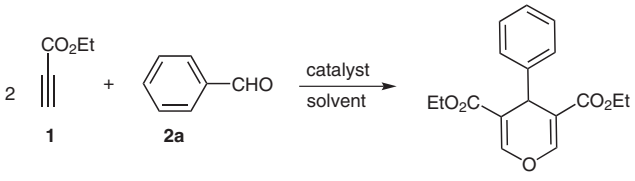
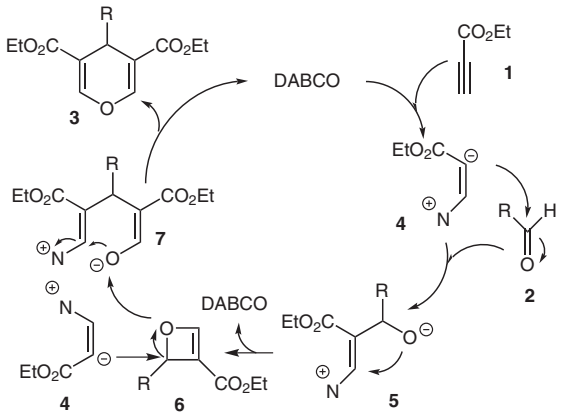
efforts directed towards the mechanism studies of this reaction as well as extension of the substrate scope are ongoing in our laboratory.

Table 1 Optimization of the Reaction Conditions for the Organocatalyzed Cycloaddition Cascade of Ethyl Propiolate (**1**) with Benzaldehyde (**2a**)[a]



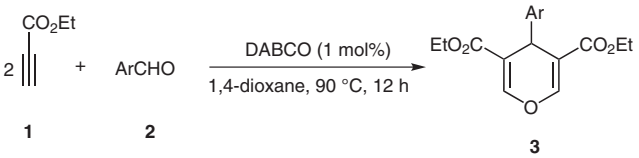
Entry	Cat.	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	pyridine	1,4-dioxane	r.t.	12	trace
2	Et_3N	1,4-dioxane	r.t.	12	trace
3	DABCO	1,4-dioxane	r.t.	12	26
4	PBu_3	1,4-dioxane	r.t.	12	none
5	DBU	1,4-dioxane	r.t.	12	none
6	Ph_3P	1,4-dioxane	r.t.	12	none
7	urotropine	1,4-dioxane	r.t.	12	none
8	DABCO	MeOH	r.t.	12	trace
9	DABCO	MeCN	r.t.	12	6
10	DABCO	DMSO	r.t.	12	16
11	DABCO	DMF	r.t.	12	13
12	DABCO	$CHCl_3$	r.t.	12	10
13	DABCO	THF	r.t.	12	20
14	DABCO	cyclohexane	r.t.	12	trace
15	DABCO	toluene	r.t.	12	8
16	DABCO	1,4-dioxane	90	6	30
17	DABCO	1,4-dioxane	90	10	37
18	DABCO	1,4-dioxane	90	12	40
19	DABCO	1,4-dioxane	90	24	40
20	DABCO[c]	1,4-dioxane	90	12	30
21	DABCO[d]	1,4-dioxane	90	12	10
22	none	1,4-dioxane	90	12	none

[a] The reaction was carried out using 0.5 mmol of **1**, 0.25 mmol of **2a**, and 1 mol% of the catalyst in solvent (6.0 mL).
[b] GC yield.
[c] Conditions: 5 mol% of DABCO.
[d] Conditions:10 mol% of DABCO.



Scheme 1 A possible reaction mechanism

Table 2 Synthesis of 4-Aryl-4*H*-Pyrans via DABCO-Catalyzed Cycloaddition Reaction of Ethyl Propiolate with Representative Aryl Aldehydes[a]



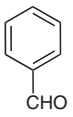
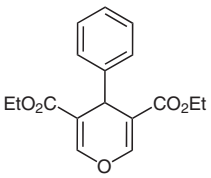
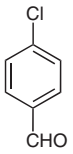
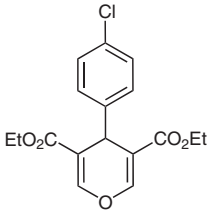
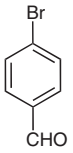
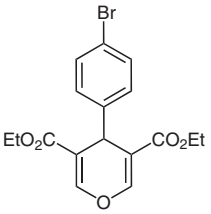
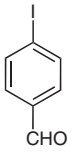
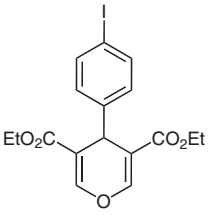
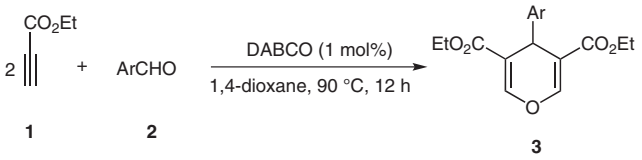
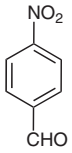
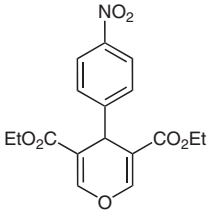
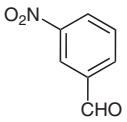
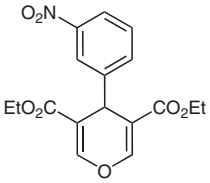
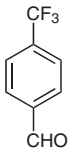
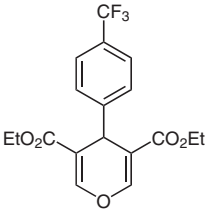
Entry	Aromatic aldehyde	Product	Yield (%)[b]
1		3a 	40
2		3b 	30
3		3c 	55
4		3d 	60

Table 2 Synthesis of 4-Aryl-4*H*-Pyrans via DABCO-Catalyzed Cycloaddition Reaction of Ethyl Propiolate with Representative Aryl Aldehydes[a] (continued)



Entry	Aromatic aldehyde	Product	Yield (%)[b]
5		3e 	80
6		3f 	78
7		3g 	82

[a] All the reactions were carried out using **1** (1 mmol), **2** (0.5 mmol), and DABCO (1 mol%) in 1,4-dioxane (6.0 mL) at 90 °C for 12 h.
[b] Isolated yield.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(7) The HMQC spectrum of diethyl 4-(3-nitrophenyl)-4*H*-pyran-3,5-dicarboxylate enabled assignment of the directly bonded C–H moieties. The results showed that H–C correlations signals were 1.15–1.22/14.0, 4.01–4.13/60.9, 4.78/35.6, 7.41–7.45/128.9, 7.62/148.7, 7.68–7.70/135.1, 8.03–8.12/122.1 and 8.12/123.6, respectively.

(8) **Typical Procedure for the Cascade Reaction of Ethyl Propiolate with Benzaldehyde**
To a stirring mixture of ethyl propiolate (98 mg, 1 mmol) and benzaldehyde (53 mg, 0.5 mmol) in a round-bottom flask, 1,4-dioxane (6 mL), and DABCO (0.56 mg, 0.005 mmol) were added successively, and then the mixture was stirred at 90 °C for 12 h. After the reaction accomplished, the solvent was diluted with H_2O and extracted with Et_2O. The ether layer was washed with sat. salt water, and dried with anhyd $MgSO_4$. The resulting mixture was then analyzed by GC and GC-MS. Volatiles were removed under reduced pressure, and the crude product was subjected to isolation by PTLC (GF254), eluted with a PE–Et_2O (10:1) mixture to afford the desired product diethyl 4-phenyl-4*H*-pyran-3,5-dicarboxylate(**3a**). Colorless viscous oil. IR (KBr): ν_{max} = 1713, 1655, 1616, 1475, 1248, 1178, 1077, 894, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.56 (s, 2 H), 7.22 (m, 5 H), 4.65 (s, 1 H), 4.06 (m, 4 H), 1.17 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 148.0, 143.7, 128.7, 128.1, 126.9, 112.9, 60.6, 35.7, 14.0 ppm. GC-MS: *m/z* (%) = 302.07 (27) [M^+], 225.00(100). Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.52; H, 6.03.

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