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Pyrrolidine catalyzed novel domino reaction for the synthesis of polysubstituted 4-oxocyclohexanecarbaldehyde derivatives

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ABSTRACT

A novel domino reaction catalyzed by an organic molecule based on α,β-unsaturated aromatic aldehydes and methylethylketones has been developed. The progress allows one-pot and efficient synthesis of polysubstituted 4-oxocyclohexanecarbaldehyde derivatives via pyrrolidine mediated under mild conditions. The reaction consists of three consecutive reactions: an aldol condensation reaction and a tandem inter-Michael–intra-Michael addition reaction.

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Over the past few decades, creation of molecular complexity and diversity from simple and readily available substrates has inspired most interest in organic chemists. One aspect in this area that draws much attention is the development of novel tandem or domino reactions catalyzed by organic molecules.[1] Those processes allow multiple bond-forming events to occur in a single vessel with lower costs, shorter reactions, and higher efficiency. Recently, methodologies relying on the tandem/domino/cascade catalytic strategies have received increasing attention in the synthetic community.[2] The ability to promote domino reactions by organocatalysts further expands the realm of its synthetic applications.

However, to the best of our knowledge, an effective triple-cascade and multi-component organocatalytic reaction for the synthesis of polysubstituted 4-oxocyclohexanecarbaldehyde derivatives remains elusive. Moreover, polysubstituted cyclohexanones are prevalent in natural products that display biological activities, and their derivatives have long served as important intermediates in organic synthesis.[3] To extend the application of the organocatalysts in tandem reactions,[4] a reaction that intrigued us most was the pyrrolidine mediated novel domino reaction between cinnamaldehyde and benzylacetone observed in our laboratory, which provided polysubstituted 4-oxocyclohexanecarbaldehyde in one pot (Scheme 1). Our literature survey at this stage revealed that use of small organic molecules as catalysts in the domino aldol–Michael–Michael reaction for the synthesis of polysubstituted 4-oxocyclohexanecarbaldehydes has not been reported. Our goal in this work is to develop inexpensive reagents, short reaction time, and high yield methodology.

As an initial study for the pyrrolidine catalyzed novel domino reaction, some simple starting materials, such as cinnamaldehyde and benzylacetone were optimized. At the outset of our work, benzylacetone reacted with cinnamaldehyde using pyrrolidine as catalyst and acetic acid as additive,[5] diethyl ether as solvent under the condition of room temperature for 60 h. The procedure successfully obtained the desired functionalized polysubstituted 4-oxocyclohexanecarbaldehyde **3a** in poor yield (Table 1). The structure of the polysubstituted 4-oxocyclohexanecarbaldehyde **3a** (mp 146–147 °C) was confirmed on the basis of spectra (IR, ^{1}H NMR, ^{13}C NMR, DEPT, COSY, HSQC, HMBC, NOESY, and HRMS).[6] In order to improve the yield, the reaction condition was optimized under different solvents and temperatures. The observed results are summarized in Table 1. Since the choice of solvent plays an important role in domino reactions,[7] the effect of various solvents including diethyl ether, ethanol, dichloromethane, tetrahydrofuran, DMF, acetonitrile, and toluene in this reaction was investigated (Table 1, entries 1–10) under the specified conditions first.[8] Unfortunately, solvents like dichloromethane and toluene afforded a trace amount of product. Moreover, the yield is lower when the reaction was carried out in ethanol, tetrahydrofuran, acetonitrile, and DMF than that afforded in diethyl ether. So, diethyl ether as solvent is suitable for the reaction. With the optimized solvent in hand, we further observed the effect of temperature on the reaction.[9] Using the same

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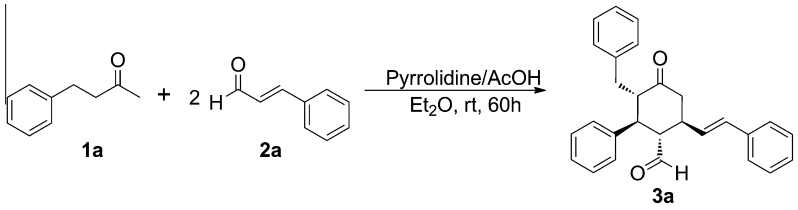


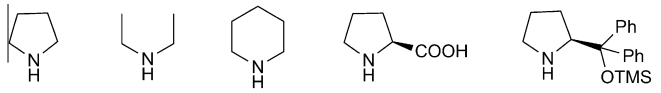
Scheme 1. Pyrrolidine-mediated novel domino reaction.

Table 1
Screening of the reaction conditions for the domino reaction

Entry[a]	Solvent	Temp (°C)	Yield[b] (%)
1	Et_2O	25	37
2	EtOH	25	13
3	CH_2Cl_2	25	Trace
4	THF	25	18
5	Et_2O	0 → rt	45
6	Et_2O	15	42
7	Et_2O	5	48
8	Et_2O	0	54
9	Et_2O	−20	35
10	DMF	0	17
11	CH_3CN	0	32
12	Toluene	0	Trace

[a] Reactions were carried out on a 1.0 mmol scale in 25.0 mL of solvent with cinnamaldehyde (2.0 equiv), benzylacetone (1.0 equiv) for 60 h.
[b] Yield of isolated product.

Table 2
Screening of the catalyst and additive for the domino reaction



I II III IV V

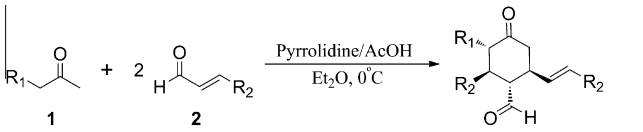
Entry[a]	Catalysts		Solvent	Yield[b] (%)
	Amide (equiv)	Additive (equiv)		
1	I (0.2)	—	Et_2O	Trace
2	I (1.0)	—	Et_2O	12
3	—	AcOH (1.0)	Et_2O	N[c]
4	I (1.0)	AcOH (1.0)	Et_2O	54
5	I (1.5)	AcOH (1.5)	Et_2O	54
6	I (1.0)	PNB (1.0)	Et_2O	Trace
7	I (1.0)	$BF_3{\cdot}OEt_2$ (1.0)	Et_2O	34
8	I (1.0)	TFA (1.0)	Et_2O	7
9	I (1.0)	HCl (1.0)	Et_2O	N
10	II (1.0)	AcOH (1.0)	Et_2O	Trace
11	III (1.0)	AcOH (1.0)	Et_2O	23
12	IV (0.2)	—	DMF	N
13	IV (1.0)	—	Toluene	N
14	V (0.2)	PNS (0.2)	Toluene	N

[a] Reactions were performed under 0 °C and 1.0 mmol scale in 25 mL of solvent with benzylacetone (1.0 equiv), cinnamaldehyde (2.0 equiv).
[b] Yield of isolated product.
[c] Not detected.

substrate and solvent, good yield was achieved by decreasing the temperature to 0 °C. But as the temperature decreased, the yield refused to increase. Therefore, diethyl ether at 0 °C is suitable for the novel organic catalyzed domino reaction.

After optimization of the reaction conditions, we performed a catalyst screening with various common imine catalysts,[10] and found that pyrrolidine could catalyze the reaction efficiently to furnish the desired product in good yield, but the other catalysts, such as II, IV as well as catalyst V,[11] could not effectively catalyze the reaction (Table 2, entries 9, 11–13). When catalyzed with piperidine, the reaction afforded the desired product with lower yield. Next, we examined the effect of additive on the organic catalyzed novel domino reaction, various additives were employed (Table 2, entries 4–8) and found that all additives promoted the reaction to afford the desired product in lower yield compared to acetic acid. Thus we preferred to perform this domino reaction with acetic acid as the additive.

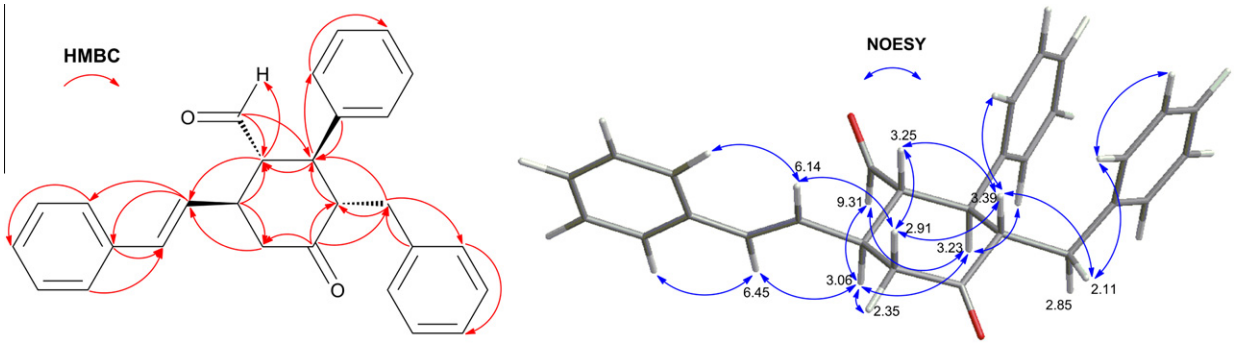
Table 3
Scope and limitations of the domino reaction



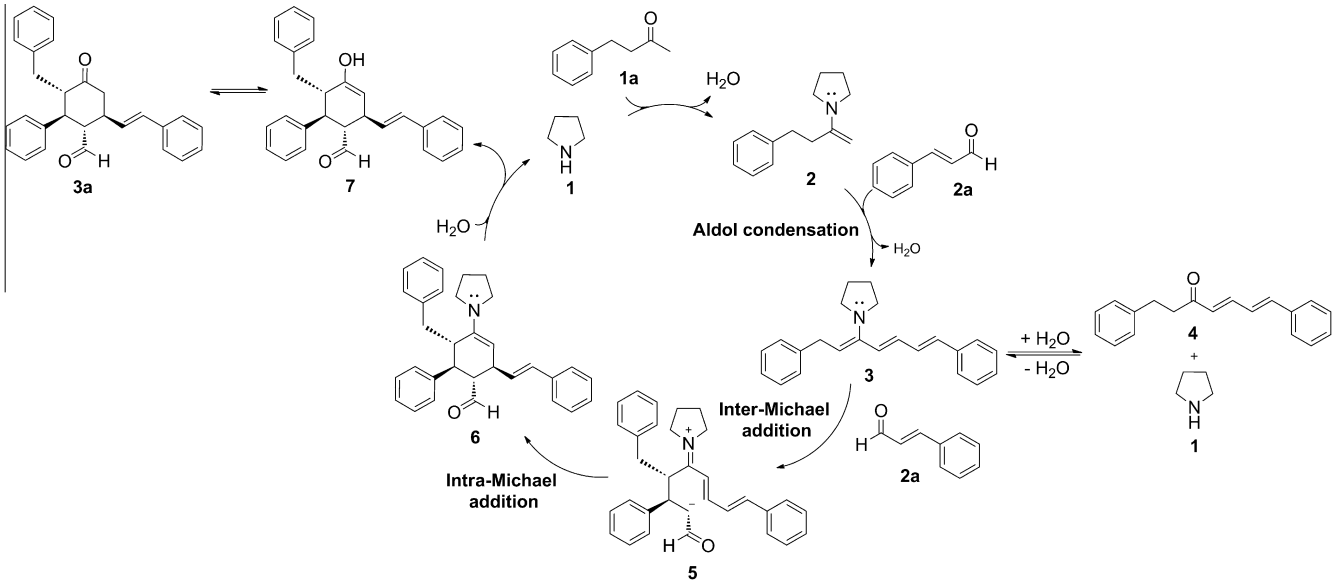
Entry[a]	R_1	R_2	Time (h)	Product	Yield[b] (%)
1	$C_6H_5CH_2$	Ph	60	**3a**	54
2	4-$MeOC_6H_5CH_2$	Ph	60	**3b**	58
3	$C_6H_5CH_2$	4-$MeOC_6H_4$	60	**3c**	47
4	Me	Ph	48	**3d**	39
5	H	Ph	48	**3e**[c]	78
6	4-$MeOC_6H_4$	Ph	48	**3f**	60
7	4-$MeOC_6H_4$	4-$MeOC_6H_4$	48	**3g**	55
8	4-MeC_6H_4	Ph	48	**3h**	55
9	4-BrC_6H_4	Ph	48	**3i**	43
10	4-$MeOC_6H_4$	4-BrC_6H_4	48	**3j**	49
11	4-MeC_6H_4	4-BrC_6H_4	48	**3k**	42
12	4-MeC_6H_4	4-$MeOC_6H_4$	48	**3l**	51
13	4-BrC_6H_4	4-$MeOC_6H_4$	48	**3m**	43
14	4-$MeOC_6H_4$	4-MeC_6H_4	48	**3n**	58
15	4-MeC_6H_4	4-MeC_6H_4	48	**3o**	53
16	4-BrC_6H_4	4-MeC_6H_4	48	**3o**	36
17	Et	Ph	48	**3q**	41
18	Et	4-$MeOC_6H_4$	48	**3r**	43
19	$C_6H_5CH_2$	4-$NO_2C_6H_4$	48	**3s**	37

[a] Unless otherwise specified, all reactions were carried out with **1** (1.0 mmol), **2** (2.0 mmol), catalyst (1.0 equiv), and additive (1.0 equiv) in 25 mL solvent.
[b] Isolated yield of the products after flash chromatography.
[c] Only the corresponding aldol condensation product was obtained.

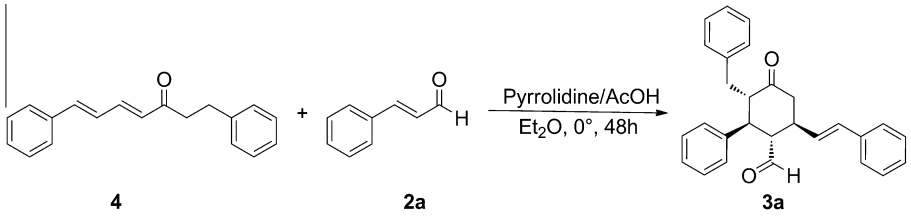
Having established optimal reaction conditions, the scope and generality of the reaction were next explored, and the results are summarized in Table 3. First of all, a series of ketones (1.0 mmol) were reacted with cinnamaldehyde **2a** (2.0 mmol) under the optimized conditions (Et_2O, 0 °C, pyrrolidine catalysis and acetic acid as additive). The reaction with methylethylketones proceeded smoothly to afford the corresponding products in moderate to good yields. However, for acetone the corresponding tandem reaction product could not have been obtained. Similar to the results reported, only the aldol condensation product **3e** was separated in 78% yield.[12] Then we set out to examine the scope of the domino reaction with a series of α,β-unsaturated aromatic aldehydes and methylethylketones with different substituted groups. Consequently, all reactions with cinnamaldehyde (entries 1, 2, 4–6, 8, 9, and 17), α,β-unsaturated aromatic aldehydes with electron-rich groups (entries 3, 7, 12–16, and 18), and α,β-unsaturated aromatic aldehydes with electron-deficient groups (entries 10, 11, and 19)



Scheme 2. Selected HMBC (→) and ROESY (↔) correlations of **3a**.



Scheme 3. Proposed mechanism for the pyrrolidine-catalyzed domino reaction.



Scheme 4. The reaction between 1,7-diphenylhepta-4,6-dien-3-one and cinnamaldehyde.

afforded desired products. But the reactions with electron-deficient groups gave lower yields than those α,β-unsaturated aromatic aldehydes with electron-rich groups. Thus, we have developed a domino reaction which provides a highly efficient method to construct the 4-oxocyclohexanecarbaldehyde backbone with multifunctional groups in one step.[13]

All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS studies.[14] Purities of the compounds were determined by HPLC analysis (>95%), which were performed on an Agilent 1200 equipment with a reversed-phase C18 column. The relative configuration of the product was confirmed by HMBC correlations and ROESY correlations as illustrated for **3a** as a representative example (Scheme 2).[15]

Based on previous experiences with imine catalyzed aldol condensation as well as Michael addition reactions,[16] a mechanistic rationalization for the pyrrolidine-mediated novel domino reaction is proposed as shown in Scheme 3, taking the synthesis of **3a** as an example. The novel organic catalyzed domino reaction process initiates with benzylacetone **1a** and pyrrolidine **1** reacting to form enamine **2**, which undergoes aldol condensation reaction with a molecule of cinnamaldehyde **2a** to generate **3**. The aldol product **3** would then release the catalyst to provide 1,7-diphenylhepta-4,6-dien-3-one **4** or undergoes tandem inter-Michael–intra-Michael addition reaction to give **6** with another molecule of cinnamaldehyde **1a**. Moreover, the aldol condensation product **4** would further react with pyrrolidine **1** to form enamine **3** to continue the domino reaction. And the tandem reaction product **6** would then release the catalyst to afford the final polysubstituted 4-oxocyclohexanecarbaldehyde **3a**. This novel domino reaction consists of three consecutive reactions: an aldol condensation reaction and a tandem inter-Michael–intra-Michael addition reaction.

In order to gain insights into the novel domino reaction and confirm the proposed mechanism, the reaction between 1,7-diphenylhepta-4,6-dien-3-one[17] and cinnamaldehyde was investigated as shown in Scheme 4. The 1,7-diphenylhepta-4,6-dien-3-one reacted with cinnamaldehyde smoothly to afford the tandem inter-Michael–intra-Michael addition product in 68% yield under the optimal reaction conditions. That proved the proposed mechanism of the novel domino reaction is reasonable.

In conclusion, we have developed a novel synthetic method to construct the polysubstituted 4-oxocyclohexanecarbaldehyde derivatives via a pyrrolidine-mediated novel organic catalyzed domino cyclization reaction. The reaction consists of three consecutive reactions that include an aldol condensation reaction and a tandem inter-Michael–intra-Michael addition reaction in one pot with moderate to good yields. Further study on its asymmetric version and applications of this methodology toward total synthesis of natural products as well as pharmaceutical agents are in progress in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.125. These data include MOL files and InChiKeys of the most important compounds described in this article.

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