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A facile stereoselective synthesis of julolidine hybrid analogs via domino knoevenagel intramolecular hetero Diels–Alder reaction

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ABSTRACT

We have reported here a facile stereoselective synthesis of julolidine hybrid analogs by employing domino Knoevenagel intramolecular hetero Diels–Alder reaction on symmetrical 1,3-diones and unsymmetrical 1,3-diones It was found that the cycloaddition proceeded efficiently under microwave irradiation to afford highly stereoselective cycloadducts in good yields

Heterocyclic compounds are ubiquitous in nature and display a wide range of biological activities[1] and thus have numerous applications in pharmaceutical industry.[2] Development of new strategies is essential for the preparation of such interesting complex heterocyclic frameworks. Usually, a longer synthetic sequence is necessary to synthesize these kinds of complex systems; however the number of steps can be significantly reduced by considering the domino process. Among the domino reactions, Knoevenagel intramolecular hetero Diels–Alder reaction is a highly useful and efficient strategy employed for the synthesis of complex frameworks, particularly for the hetero-polycyclic compounds and natural products.[3]

Julolidine based hetero-polycyclic compounds are extremely useful and found to have applications in photochemical industry as dyes and also in biological systems.[4–9] Although the preparation of such moieties is crucial but fewer attentions have been paid so far.[10] This stimulates our interest on the synthesis of julolidine hybrid analogs and hence we planned to exploit domino Knoevenagel intramolecular hetero Diels–Alder strategy for this purpose. Apparently, symmetrical 1,3-dione **3** as well as unsymmetrical 1,3-dione **4** could be used as one of the components in domino Knoevenagel intramolecular hetero Diels–Alder reaction, especially for the latter, biologically important coumarin derivative and quinoline derivative are used.[11,12] As outlined in Scheme 1, the desired julolidine analogs **6** can be obtained from **2** via the intermediate of **5**.

Our synthesis commenced from the julolidine aldehyde **1**, was obtained from 3-methoxy aniline by the reported literature procedure.[13] Treatment of **1** with prenyl bromide under mild basic condition furnished prenyl derivative **2** in good yields. To check the feasibility of domino Knoevenagel intramolecular hetero Diels–Alder reaction, we screened julolidine derivative **2** with cyclohexane-1,3-dione **3a** under various conditions as shown in Table 1. Treatment of **2** and **3a** either in catalytic $InCl_3$ or EDDA gave the highly functionalized julolidine analog **7** in poor yields. Refluxing **2** with **3a** in ethanol also indicated a similar result; surprisingly the addition of catalytic amount of piperidine dramatically increased the yield of **7**–81%. A further increase in the yield was observed by conducting the reaction in toluene; however the same condition under microwave[14] showed good yields with short reaction time (Table 1). The structure of **7** was revealed by the spectral data, especially H_1 proton appeared as doublet at δ 4.05 with coupling constant (J = 6.0 Hz) confirmed the *cis*-fused cycloaddition product.[15]

Encouraged by this outcome, we applied this methodology on symmetrical 1,3-diones **3** as shown in Table 2. Under the conventional and microwave conditions, dimedone **3b** furnished **8** and 5-phenyl-1,3-cyclohexandione **3c** gave **9** in good yields. Besides,

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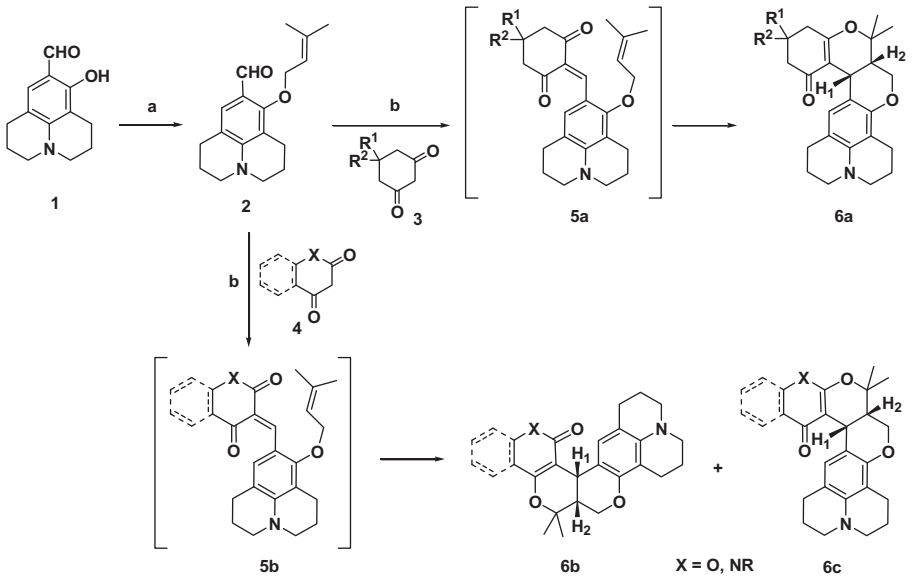
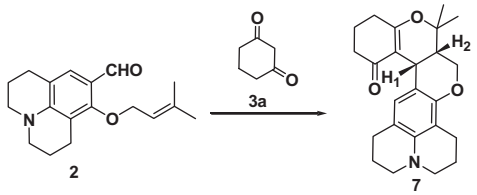


Scheme 1. Reagents and conditions: (a) Prenyl bromide, K_2CO_3, DMF, rt, 16 h. (b) Piperidine (cat.), toluene, 110 °C.

Table 1
Screening results of **2** and 1,3-cyclohexanedione **3a** under different conditions

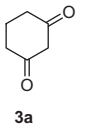
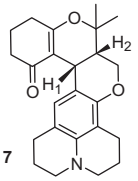
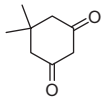
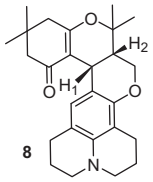
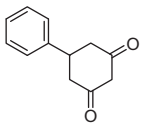
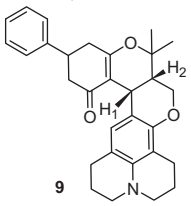
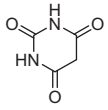
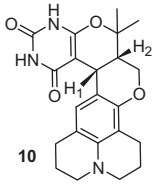
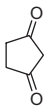
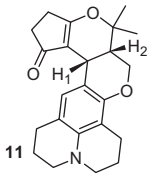


Entry	Catalyst	Solvent	Temp (°C)	Time	Yield (%)
1	$InCl_3$	CH_3CN	100	15 h	15
2	EDDA	Xylene	150	15 h	12
3	—	EtOH	80	15 h	15
4	Piperidine	EtOH	80	15 h	81
5	Piperidine	Toluene	110	15 h	88
6	Piperidine	Toluene	110	25 min	90

pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione **3d** and cyclopenan-1,3-dione **3e** smoothly led to the julolidine analogs **10** and **11**, respectively. It is worth to mention that the domino Knoevenagel intramolecular hetero Diels–Alder reaction is stereoselective with symmetrical 1,3-diones **3a–e** to provide the corresponding **7–11** as a single isomer (Table 2).[16]

After having success with julolidine analogs derived from symmetrical 1,3-diones, we turned our attention on unsymmetrical 1,3-diones which would lead to more complex and interesting julolidine hybrid analogs. Not surprisingly, the reaction of **2** with 4-hydroxy coumarin **4a** under the standard toluene reflux condition gave a mixture of julolidine–coumarin analog **12a** and julolidine–chromene analog **12b** in the ratio of 1.7:1 (Table 3). A similar result was obtained, when we tried under the microwave condition where the ratio of **12a**:**12b** was 1.8:1. The structure of **12a** and **12b** was proved by NMR spectra and further **12a** (Fig. 1) was secured by single crystal X-ray diffraction analysis. Other coumarin derivatives **4b** and **4c** also behaved in a similar manner as **4a** when treated with **2**. 4-Hydroxy-6-methyl coumarin **4b** and 4-hydroxy-7-methoxy coumarin **4c** delivered a mixture of julolidine

Table 2
Reaction summary of symmetrical 1,3-diones with dienophile **2** under various conditions

Entry	Reactants	Products	Conditions	Time	Yield
1			A	10 h	88
			B	25 min	90
2			A	12 h	78
			B	30 min	92
3			A	15 h	75
			B	50 min	80
4			A	12 h	79
			B	50 min	87
5			C	20 h	85
			D	70 min	70

Conditions: A. Toluene, piperidine, reflux; B. Toluene, piperidine, 100 °C, MW; C. Xylene, piperidine, 150 °C; D. Xylene, piperidine, 150 °C, MW.