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FACILE SYNTHESIS OF GUAIAZULENE-HETEROCYCLE HYBRIDS VIA MULTICOMPONENT REACTIONS INVOLVING FORMATION OF ZWITTERIONIC INTERMEDIATES

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Abstract – The synthesis of a series of guaiazulene-heterocycle hybrids via zwitterionic intermediates was performed. The multicomponent reactions of 3-isocyano-7-isopropyl-1,4-dimethylazulene **1**, dimethyl acetylenedicarboxylate **2**, and a third reactant **3** (cyclic CH-acids, phenols, aldehydes or amines) proceeded to afford heterocyclic guaiazulene derivatives **4**.

Azulene derivatives are widely used in the design of pharmaceutically active compounds and advanced organic materials because of their numerous applications.[1,2] In particular, azulenes bearing a heterocycle have attracted much attention because of their promising properties.[3] Therefore, efficient and facile approaches to introducing heterocycles into the azulene skeletons have been extensively explored.[4] A general approach to the preparation of heteroarylazulene derivatives involves transition-metal-catalyzed coupling reactions with haloazulenes or azulenyl-metal reagents.[3,4f-4g] Though this method is versatile and reliable and is widely used, but it sometimes requires synthetically difficult starting materials. Imafuku and coworkers stepwise introduced a pyridine ring into azulenes via the prepared azulene derivatives bearing an α, β-unsaturated ketone in a side chain.[4h] Recently Shoji and coworkers established an efficient and unique strategy using triflates of N-containing heteroarenes, and succeeded in preparing various heteroarylazulenes.[4i-4p] Although these methods are undoubtedly useful, most of these studies did not use guaiazulene, which is a practical and cheap starting material for synthesizing azulene nucleus.

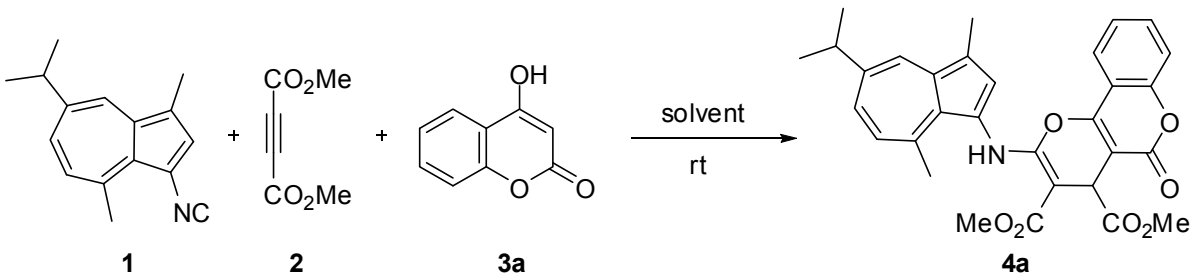
Guaiazulene (7-isopropyl-1,4-dimethylazulene), derived from an abundant sesquiterepene, is a known

active component of the essential oil of *Guaiacum officinalis* L., and many reports have described the anti-allergenic- and anti-inflammatory activities of guaiazulene derivatives.[5] For example, guaiazulene sodium sulfonate, a hydrophilic guaiazulene derivative, has found widespread clinical applications as anti-inflammatory and anti-ulcer agents.[6] Since the past few decades, we have been investigating the development of convenient and safe methods for synthesizing azulene derivatives from guaiazulene, which is a commercially available and cheap starting material.[7] In order to find agents that have attractive biological activities, we have attempted to introduce pharmacologically active skeletons into the guaiazulene framework. However, the use of guaiazulene as a starting material puts additional limitations on the reactive positions because of the occupied 1,4,7-substituted positions, which could cause steric hindrance in various reactions. At the same time, such investigations are worthwhile in view of the increasing demand for more practical processes in the pharmaceutical industry. For example, Yin and coworkers recently reported that a simple modified guaiazulene derivative possessed excellent *in vivo* anti-gastric ulcer activity.[8] In this paper, we describe a simple approach to prepare of guaiazulene derivatives bearing a heterocycle.

Multicomponent reactions (MCRs),[9] especially isocyanide based MCRs (IMCRs),[10] meet the need for practical and efficient preparation of libraries of structurally diverse compounds. It has been shown that the addition of isocyanide to dimethyl acetylenedicarboxylate (DMAD, **2**) generates reactive zwitterionic species, which can be captured by a third component to form diverse heterocyclic scaffolds.[10c] We investigate several IMCRs of **2** with 3-isocyano-7-isopropyl-1,4-dimethylazulene **1**,[7d] which is readily prepared in two steps.

In a pilot experiment, **1**, **2**, and 4-hydroxy-2*H*-chromen-2-one **3a** were stirred in several different organic solvents at room temperature (Table 1).[11] The reaction proceeded smoothly in dichloromethane and afforded the desired guaiazulene-heterocycle hybrid **4a** in 72% yield (Entry 1). Acetonitrile and tetrahydrofuran as solvents also gave **4a** in moderate yields (Entries 2 and 3), but the use of ethanol was ineffective and resulted in a lower yield (Entry 4).

Table 1. Solvent screening



1 **2** **3a** **4a**

Entry	Solvent	Time	Yield (%)
1	CH_2Cl_2	22 h	72
2	MeCN	24 h	62
3	THF	24 h	66
4	EtOH	23 h	19

To explore the scope of IMCR of **1** and **2**, we extended it to include a third reactant as shown in Table 2. The use of 2-hydroxynaphthalene-1,4-dione **3b** gave the desired 4*H*-benzo[*g*]chromene-3,4-dicarboxylate derivative **4b** (Entry 2). Phenols **3c** and **3d** afforded the corresponding guaiazulene-chromene hybrids **4c** and **4d** in moderate yields (Entries 3 and 4). Once we had ascertained that the reactive zwitterionic intermediate generated by **1** and **2** (Figure 1) could be trapped by a third component, other IMCRs were also examined. The use of aldehydes[12] **3e-3i** afforded the desired furan hybrids **4e-4i** in 50-64% yields (Entries 5-9), while the treatment of amines[13] **3j** and **3k** gave the corresponding 1,2-dihydropyridine hybrids **4j** and **4k** in 20% and 38% yields respectively (Entries 10 and 11). It seemed that the reactivity of sterically demanding isocyanide **1** was fairly different from that of simple alkylisocyanides; steric repulsion between 4-methyl group of azulene ring and methyl carboxylate of 1,2-dihydropyridine ring presumably resulted in low yields.[14]

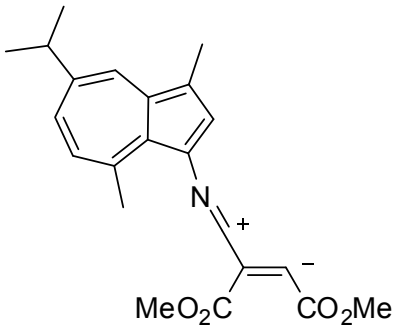
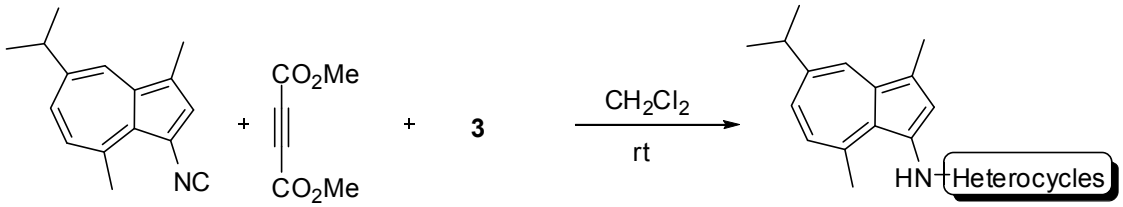
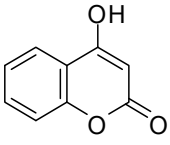
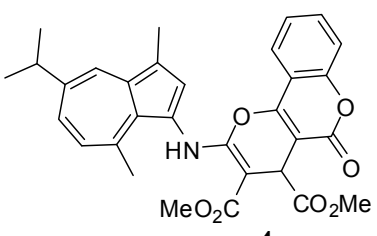


Figure 1. zwitterionic intermediate

Table 2. Synthesis of guaiazulene-heterocycle hybrids **4**[a]

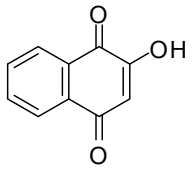
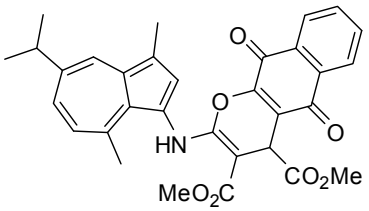
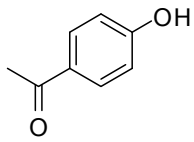
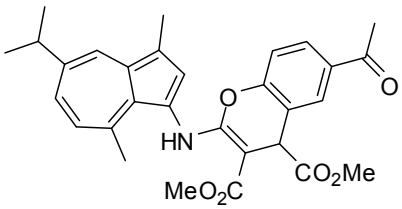
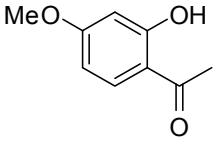
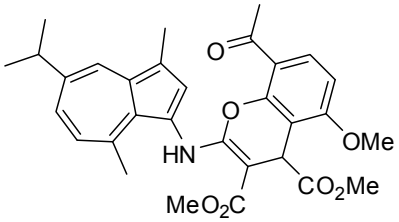
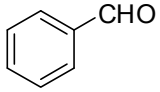
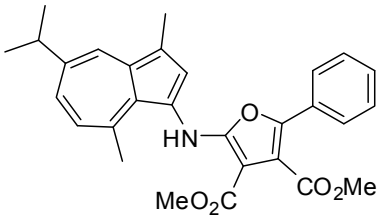
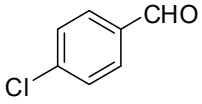
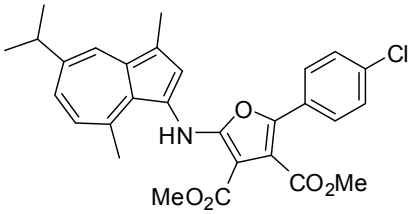
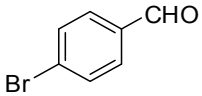
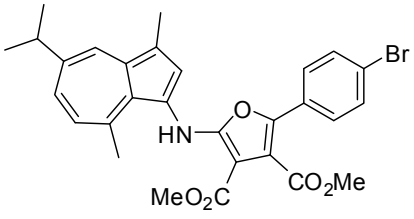
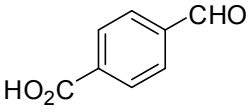
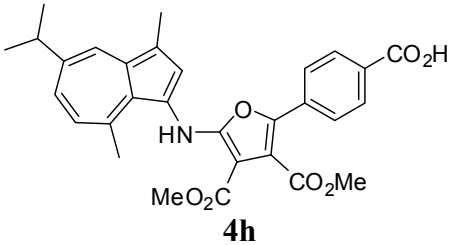


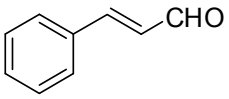
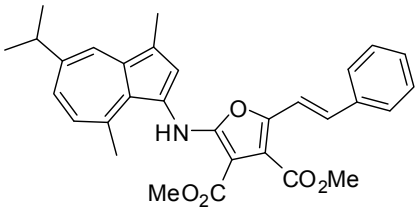
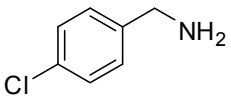
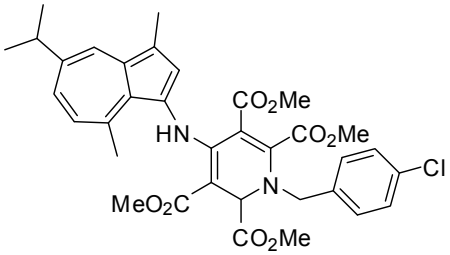
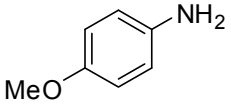
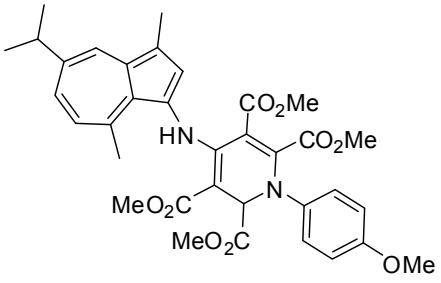
1 **2** **4**

Entry	**3**	Time (h)	Product **4**	Yield (%)[b]
1		22		72

3a

4a

2	 **3b**	20	 **4b**	51
3	 **3c**	20	 **4c**	57
4	 **3d**	20	 **4d**	55
5	 **3e**	20	 **4e**	60
6	 **3f**	20	 **4f**	63
7	 **3g**	20	 **4g**	52
8	 **3h**	20	 **4h**	50

9	 **3i**	20	 **4i**	64
10 [c]	 **3j**	24	 **4j**	20
11 [c]	 **3k**	22	 **4k**	38

[a] Reactions were performed with 1.0 equiv of isocyanide **1**, 2.0 equiv of **2**, and 2.0 equiv of **3** , unless otherwise noted.
[b] Isolated yields after purification.
[c] 3.0 equiv of **2** were used.

In summary, we successfully synthesized a series of guaiazulene derivatives bearing a heterocycle via IMCRs involving the reactive zwitterionic intermediate generated by readily available **1** and **2**. The merits of this procedure include operational simplicity and mild condition (reactions were carried out at room temperature). These products may be useful intermediates to develop biologically active agents containing an azulene nucleus. The practical synthesis of other guaiazulene derivatives is in progress in our laboratory.

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14. In reference 13, the use of alkylisocyanides afforded the corresponding 1,2-dihydropyridines in 83-87% yields.
15. *General procedure for the synthesis of guaiazulene-chromene hybrids **4a-4e***: (Table 2, entry 1) To a mixture of **3a** (0.40 mmol) and **2** (0.40 mmol) in CH_2Cl_2 (3 mL), a solution of **1** (0.20 mmol) in CH_2Cl_2 (3 mL) was dropwise added over a 10-min period, and the mixture was stirred at room temperature for 20 h. After completion of the reaction, the resultant mixture was extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated. The residue was purified using silica gel column chromatography (hexane-acetone as eluent) to give **4a** as green needles (72%). Mp 187.7 ^oC. ^1H-NMR ($CDCl_3$) δ: 1.37 (6H, d, J = 6.8 Hz), 2.68 (3H, s), 2.92 (3H, s), 3.06 (1H, sept, J = 6.8 Hz), 3.75 (3H, s), 3.82 (3H,s), 4.84 (1H, s), 6.83 (1H, d, J = 10.4 Hz), 7.01-7.08 (2H, m), 7.30-7.33 (2H, m), 7.47-7.52 (1H, m), 7.57 (1H, s), 8.15 (1H, d, J = 2.4 Hz), 10.65 (NH, s). MS *m/z*: 527(M^+), 100.0% (Calcd for $C_{31}H_{29}NO_7$ (M^+): 527.5751). Found: 527.1944.

16. *General procedure for the synthesis of guaiazulene-furan hybrids **4f-4j***: (Table 2, entry 6): To a mixture of **3f** (0.40 mmol) and **2** (0.40 mmol) in CH_2Cl_2 (3 mL), a solution of **1** (0.20 mmol) in CH_2Cl_2 (3 mL) was dropwise added over a 10-min period, and the mixture was stirred at room temperature for 20 h. After completion of the reaction, the resultant mixture was extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated. The residue was purified using silica gel column chromatography (hexane-acetone as eluent) to give **4f** as green needles (60%). Mp 128.8 ^oC. ^1H-NMR ($CDCl_3$) δ: 1.33 (6H, d, J = 6.8 Hz), 2.66 (3H, s), 2.98 (1H, sept, J = 6.8 Hz), 3.01 (3H, s), 3.85 (3H, s), 3.94 (3H, s), 6.71 (1H, d, J = 10.4 Hz), 7.22 (2H, d, J = 10.0 Hz), 7.32-7.36 (2H, m), 7.52 (2H, d, J = 7.6 Hz), 7.80 (1H, s), 8.03 (1H, d, J = 2.0 Hz), 9.28 (NH, s). MS *m/z*: 471 (M^+), 100.0% (Calcd for $C_{29}H_{29}NO_5$ (M^+): 471.7699). Found: 471.2046.
17. *General procedure for the synthesis of guaiazulene-1,2-dihydropyridine hybrids **4k-4l***: (Table 2, entry 11) To a mixture of **3l** (0.40 mmol) and **2** (0.60 mmol) in CH_2Cl_2 (3 mL), a solution of **1** (0.20 mmol) in CH_2Cl_2 (3 mL) was dropwise added over a 10-min period, and the mixture was stirred at room temperature for 20 h. After completion of the reaction, the resultant mixture was extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated. The residue was purified using silica gel column chromatography (hexane-ether as eluent) to give **4l** as red brown powder (38%). ^1H-NMR ($CDCl_3$) δ: 1.30 (6H, d, J = 6.8 Hz), 2.53 (3H, s), 2.94 (1H, sept, J = 6.8 Hz), 3.04 (3H, s), 3.64 (6H, s), 3.80 (6H, s), 3.83 (3H, s), 3.93 (1H, s), 5.50 (NH, s), 6.65 (1H, d, J = 10.0 Hz), 6.89 (4H, d, J = 8.8 Hz), 7.14 (1H, d, J = 8.4 Hz), 7.40 (1H, s), 7.87 (1H, d, J = 2.0 Hz). MS *m/z*: 630 (M^+), 100.0% (Calcd for $C_{35}H_{38}ClN_2O_9$ (M^+): 630.9125). Found: 630.2577.