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FACILE SYNTHESIS OF GUAIAZULENE-HETEROCYCLE HYBRIDS VIA UGI MULTICOMPONENT REACTIONS

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Abstract – The Ugi reaction with isocyanoazulene **1** afforded a variety of azulene-heterocycle hybrids. The described approach could be applied to combinatorial synthesis of biologically active compounds of the azulene series.

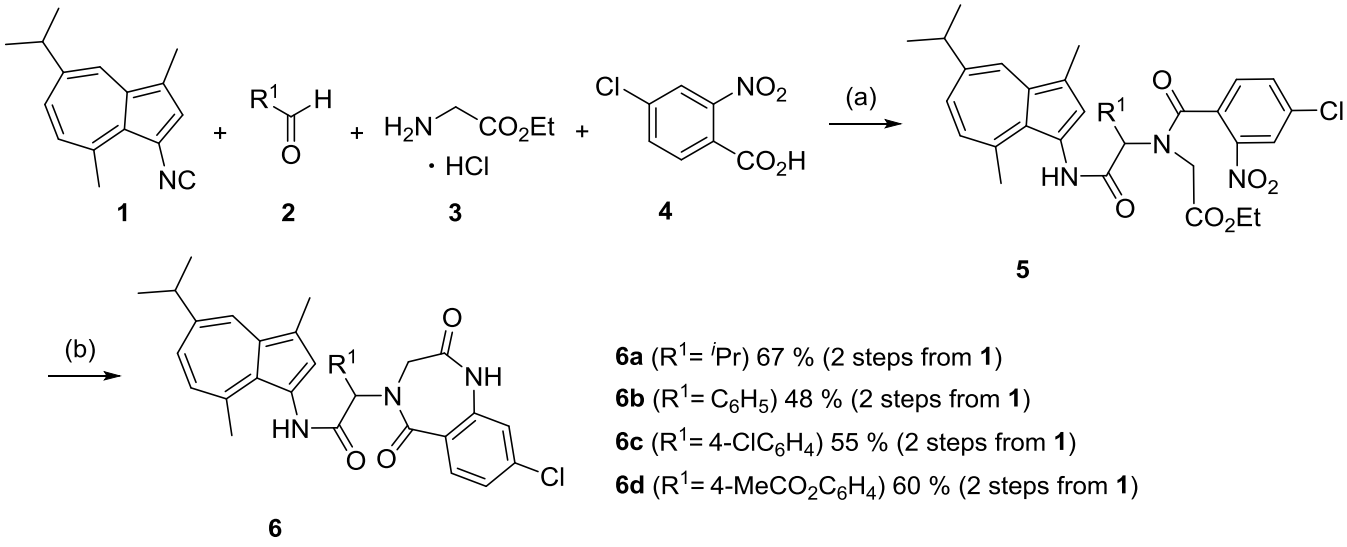
In Celebration of Professor Dr. Isao Kuwajima on His 77th Birthday

Azulene derivatives have been widely used as clinical anti-inflammatory and anti-ulcer agents for a long time.[1] Recently they have also been used in the design advanced organic materials that have numerous applications.[2,3] Of these, azulenes bound to a heterocycle through an linker have attracted much attention because of their promising properties.[4] For example, HNS-32 [N^1,N^1-dimethyl-N^2-(2-pyridylmethyl)-5-isopropyl-3,8-dimethylazulene 1-carboxamidine], an azulene derivative bound to a pyridine ring via a carboxamidine group, was examined as a potential antiarrhythmic agent.[4f] Therefore, practical methods of obtaining a variety of azulene derivatives bound to a heterocycle through an linker are needed.

Guaiazulene (7-isopropyl-1,4-dimethylazulene) is derived from an abundant sesquiterepene and many reports have described the anti-allergenic- and anti-inflammatory activities of guaiazulene derivatives.[5] 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.[6] In order to find agents that have attractive biological activities, we have attempted to

introduce pharmacologically active skeletons into the guaiazulene framework. Previously we were the first to report that 3-isocyano-7-isopropyl-1,4-dimethylazulene **1** could be prepared in two steps from readily available guaiazulene.[6d] Isocyanoazulene **1** forms stable dark green needles and does not have the objectionable odor typical of isonitriles, making it more amenable as a useful synthetic intermediate. Herein, we elucidate the possibility of using isocyanoazulene **1** in the Ugi reaction[7] to meet the need for a practical and efficient preparation of libraries of structurally diverse compounds, with a view to obtain a wide series of guaiazulene derivatives bound to a heterocycle via an amide group.

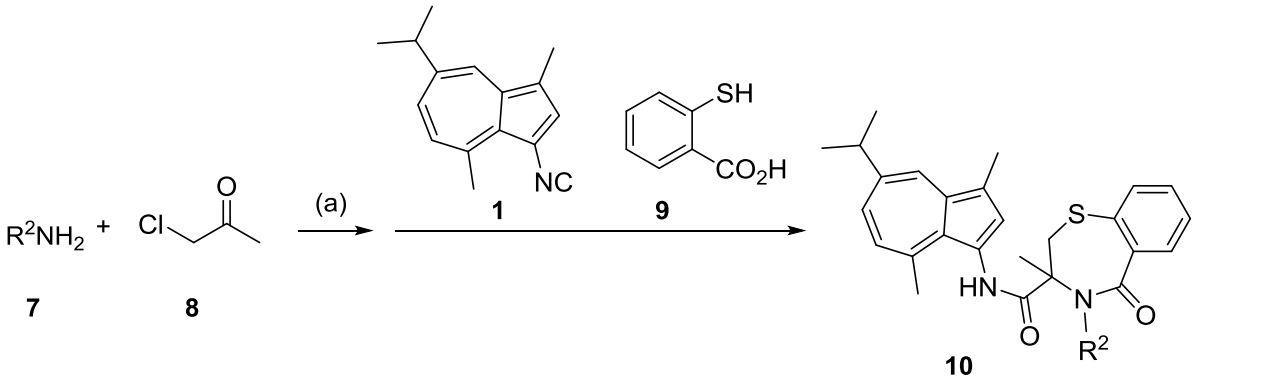
In a pilot experiment, we applied isocyanoazulene **1** to the reported two-step synthesis of 1,4-benzodiazepine-2,5-dione via the Ugi reaction.[8] The Ugi four-component condensation between **1**, aldehyde **2**, ethyl glycine ethyl ester hydrochloride **3**, and 4-chloro-2-nitrobenzoic acid **4** afforded the expected nitro compound **5**, which was reductively cyclized to the desired 1,4-benzodiazepine-2,5-dione derivative **6** in moderate yields (Scheme 1).[9]



Scheme 1. Synthesis of 1,4-benzodiazepine-2,5-dione derivatives. Conditions: (a) KOH, MeOH, rt, 2 h. (b) Fe powder, AcOH, 70 °C, 1 h.

To explore the scope of application of isocyanoazulene **1**, we next tried the synthesis of 1,4-benzothiazepin-5-one derivatives. We first tried Mironov's optimized procedure[10]; thiosalicylic acid **9** and chloroacetone **8** were stirred in methanol in the presence of K_2CO_3. Then *n*-propylamine **7a** and isocyanoazulene **1** were added to the solution. However, it did not result in the effective formation of the 1,4-benzothiazepine-5-one derivative **10a**. We obtained **10a** in 52% yield and isocyanoazulene **1** was recovered in 37% yield. Therefore, we tried to develop a more efficient protocol. As shown in Scheme 2, isocyanoazulene **1** and thiosalicylic acid **9** were added to a premixing solution of amine **7a**, chloroacetone **8** , and K_2CO_3 in methanol to afford **10a** in 82% yield.[11,12] Applying this protocol to aryl amines **7b-7d**

caused reactions to proceed smoothly to afford guaiazulene-1,4-benzothiazepin-5-one hybrids **10b**-**10d** in moderate to good yields.

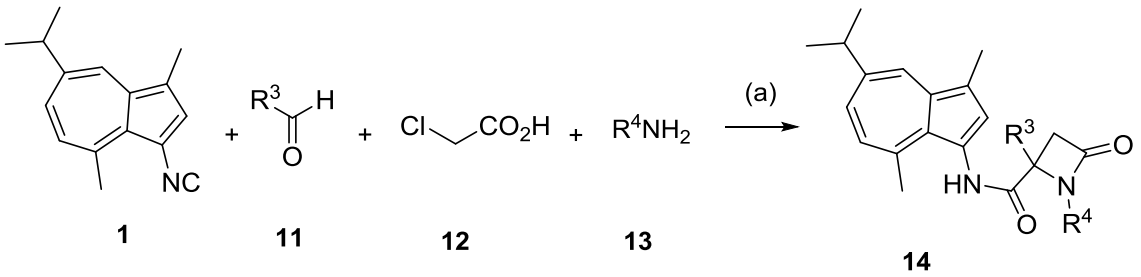


7 8 1 9 10

10a (R^2=^{n}Pr) 82% **10c** (R^2=4-ClC_6H_4) 59%
10b (R^2=C_6H_5) 46% **10d** (R^2=4-$MeOC_6H_4$) 66%

Scheme 2. Synthesis of 1,4-benzothiazepin-5-one derivatives. Conditions: (a) K_2CO_3, MeOH, rt.

In continuation of our investigations on the synthesis of guaiazulene-heterocycle derivatives from isocyanoazulene **1**, we carried out the synthesis of β-lactams according to Marcaccini's report.[13] Although they synthesized β-lactams in a stepwise fashion, we carried out a one-pot synthesis (Scheme 3) by mixing isocyanoazulene **1**, aldehyde **11a**, chloroacetic acid **12**, amine **13a**, and KOH in methanol to smoothly afford **14a** in 91% yield.[14] In addition to aliphatic substrates, aromatic aldehyde **11c** and amine **13c** also afforded the corresponding product **14c** in good yield.



1 11 12 13 14

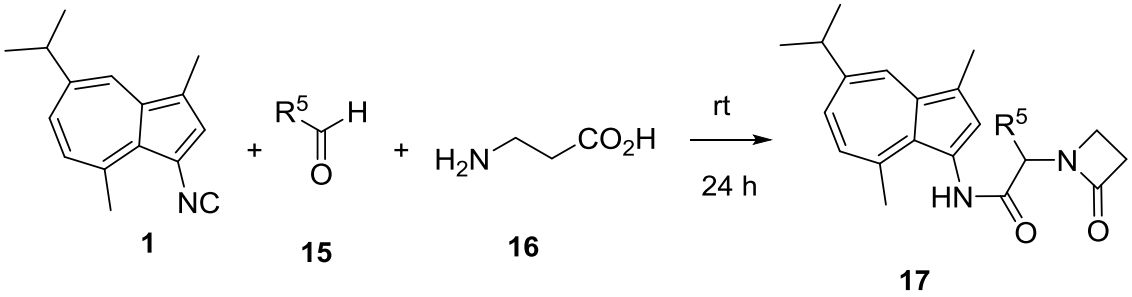
14a (R^3= ^{i}Pr, R^4= ^{n}Pr) 91%
14b (R^3= ^{i}Pr, R^4= ^{i}Pr) 75%
14c (R^3= C_6H_5, R^4= C_6H_5) 97%

Scheme 3. Synthesis of β-lactam derivatives. Conditions: (a) KOH, MeOH, rt, 4 h.

β-Lactam-guaiazulene hybrids were also synthesized using the following procedure.[15] The Ugi reaction of isocyanoazulene **1**, aldehyde **15**, and β-alanine **16** in MeOH afforded **17** in 89% yield (Table 1, entry 1-3). With the aim of establishing greener synthetic processes, we also attempted the aqueous β-lactam

synthesis using an anionic or canionic surfactant (entries 4-6);[16] SDS or CTAB assist the aqueous reaction to proceed in good yield.

Table 1. Synthesis of β-lactam derivatives.



Entry	R^5	Product	Solvent	Yield (%)	Entry	R^5	Product	Solvent	Yield (%)
1	^{i}Pr	**17a**	MeOH	89	4[a]	^{i}Pr	**17a**	H_2O	67
2	C_6H_5	**17b**	MeOH	88	5[a]	C_6H_5	**17b**	H_2O	64
3	H	**17c**	MeOH	29	6[b]	H	**17c**	H_2O	73

[a] Reaction was performed using 0.5 equiv of SDS (sodium dodecyl sulfate, $C_{12}H_{25}OSO_3Na$) as a surfactant.
[b] Reaction was performed using 0.5 equiv of CTAB (cetyltrimetylammonium bromide $C_{16}H_{33}N(Me_3Br)$ as a surfactant.

In summary, we demonstrate that isocyanoazulene **1** could be used as a starting material for the synthesis of various guaiazulene derivatives bearing a heterocycle, such as benzodiazepine, benzothiazepine, and β-lactam derivatives via the Ugi reaction. 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.[17]

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9. *General procedure for the synthesis of guaiazulene-1,4-benzodiazepine-2,5-dione hybrids* ***6a-6d***: (Scheme 1) To a solution of isocyanoazulene **1** (0. 20 mmol) in MeOH (3 mL), aldehyde **2d** (0.24 mmol), **3** (0.24 mmol), **4** (0.24 mmol) and KOH (0.24 mmol) was added and stirred at room temperature for 2 h. After completion of the reaction, the resultant mixture was extracted with $CHCl_3$, dried (Na_2SO_4), and concentrated. The residue was purified using silica gel column chromatography (hexane-acetone as eluent) to give **5d**. Then, to a solution of **5d** in AcOH (10 mL), Fe powder (0. 40 mmol) was added and stirred at 70 ^oC for 1 h. The resultant mixture was extracted with $CHCl_3$, dried (Na_2SO_4), and concentrated. The residue was purified using silica gel column chromatography (hexane-acetone as eluent) to give **6d** as green needles (60%, 2 steps from **1**). mp 253-254 ^oC. ^{1}H-NMR (DMSO-d_6) δ: 1.27 (6H, d, J = 6.8 Hz), 2.56 (3H, s), 2.72 (3H, s) 2.99-3.06 (1H, m), 3.78-3.93 (5H, m), 6.56 (1H, s), 6.79 (1H, d, J = 10.8 Hz), 7.14 (1H, d, J = 2.4 Hz), 7.29 (1H, dd, J = 2.4, 2.0 Hz), 7.33 (1H, dd, J = 2.0, 1.6 Hz), 7.58 (3H, t, J = 7.8 Hz), 7.88 (1H, d, J = 8.8 Hz), 8.04-8.06 (3H, m), 10.16 (NH, s), 10.40 (NH, s). MS *m/z*: 597 (M^+) 2.18% (Calcd for $C_{34}H_{32}ClN_3O_5$ (M^+): 597.2030), Found: 597.5002.
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11. Mironov *et al.* reported that simple mixing of amine, chloroacetone, thiosalicylic acid, and alkyl

cyanide gave polymeric compounds, not the desired 1,4-benzothiazepin-5-ones. Then they optimized procedure and concluded that premixing of thiosalicylic acid and chloroacetone before adding amine and alkyl isocyanide was effective (ref. 10). On the other hand, considering the mechanism of the Ugi reaction, we assumed that formation of the imine intermediate was important for the reaction to proceed smoothly; *in situ* preparation of imine by premixing of amine and chloroacetone could be more efficient protocol.

12. *General procedure for the synthesis of guaiazulene-1,4-benzodiazepine-2,5-dione hybrids* ***10a-10d***: (Scheme 2) A solution of amine **7a** (0.40 mmol) and **8** (0.40 mmol) in MeOH (3 mL) was stirred at room temperature for 10 min, and then **1** (0.20 mmol), thiosalicylic acid **9** (0.40 mmol), K_2CO_3 (0.40 mmol), and MeOH (3 mL) was added, and the mixture was stirred at room temperature. After completion of the reaction, the resultant mixture was extracted with $CHCl_3$ dried (Na_2SO_4), and concentrated. The residue was purified using silica gel column chromatography (hexane-acetone as eluent) to give **10a** as dark blue needles (82%). mp 197-198 ℃. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, t, *J* = 7.4 Hz), 1.29 (6H, d, *J* = 6.8 Hz), 1.76 (3H, s), 1.87 (2H, sext, *J* = 7.4 Hz), 2.47 (3H, s), 2.82 (1H, d, *J* = 12.8 Hz), 2.86 (3H, s), 2.93 (1H, sept, *J* = 6.9 Hz), 3.54-3.61 (1H, m), 4.00-4.07 (1H, m), 4.63 (1H, d, *J* = 12.8 Hz), 6.61 (1H, d, *J* = 10.4 Hz), 7.06 (1H, ddd, *J* = 1.2, 1.2, 1.6 Hz), 7.13-7.17 (2H, m), 7.24 (1H, s), 7.29 (1H, ddd, *J* = 1.2, 2.0, 1.6 Hz), 7.45 (1H, dd, *J* = 0.8, 1.2 Hz), 7.92 (1H, d, *J* = 2.0 Hz), 8.29 (NH, s). MS *m/z*: 474 (M^+) 23.02% (Calcd for $C_{29}H_{34}N_2O_2S$ (M^+): 474.2341), Found: 474.5229.
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14. *General procedure for the synthesis of guaiazulene*-β-lactam *hybrids* ***14a-14c***: (Scheme 3) A mixture of **1** (0.20 mmol), **11a** (0.40 mmol), **12** (0.40 mmol), and **13a** (0.40 mmol) in MeOH (6 mL) was stirred at room temperature for 2 h. Then, to the resultant mixture KOH (0.40 mmol) was added and stirred at room temperature for another 2 h. After completion of the reaction, the reaction mixture was extracted with $CHCl_3$, dried (Na_2SO_4), and concentrated. The residue was purified using silica gel column chromatography (hexane-Et_2O as eluent) to give **14a** as dark blue prisms (91%). mp 144-145 ℃. ^{1}H-NMR ($CDCl_3$) *δ*: 0.94 (3H, t, *J* = 7.4 Hz), 1.18 (6H, dd, *J* = 4.8, 5.2 Hz), 1.32 (6H, dd, *J* = 0.8, 1.2 Hz), 1.59-1.73 (2H, m), 2.35 (1H, sept, *J* = 6.5 Hz), 2.60 (3H, s), 2.73 (3H, s), 2.75-2.80 (1H, m), 3.03 (1H, sept, *J* = 6.8 Hz), 4.08 (1H, dd, *J* = 11.2, 11.2 Hz), 4.12-4.18 (1H, m), 4.51 (1H, dd, *J* = 8.4, 8.8 Hz), 6.92 (1H, d, *J* = 10.4 Hz), 7.33-7.39 (2H, m), 8.16 (1H, d, *J* = 2.0 Hz). MS *m/z*: 394 (M^+) 100.00% (Calcd for $C_{25}H_{34}N_2O_2$ (M^+): 394.2620), Found: 394.3008.
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16. *General procedure for the aqueous synthesis of guaiazulene*-β-lactam *hybrids* ***17a-17c***: (Table 1, entry 4) A mixture of **1** (0.20 mmol), **15a** (0.40 mmol), **16** (0.40 mmol), and surfactant (0.10 mmol) in water (6 mL) was stirred at room temperature for 24 h. After completion of the reaction, the reaction mixture was extracted with $CHCl_3$, dried (Na_2SO_4), and concentrated. The residue was purified using silica gel column chromatography (hexane-acetone as eluent) to give **17a** as blue needles (67%). mp 212-213 ℃. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (6H, d, J = 6.8 Hz), 1.29 (6H, d, J = 7.2 Hz), 2.45 (1H, sept, J = 5.0 Hz), 2.57 (3H, s), 2.89 (3H, s), 2.95-3.00 (3H, m), 3.41-3.52 (2H, m), 3.81 (1H, d, J = 10.0 Hz), 6.73 (1H, d, J = 10.8 Hz), 7.20-7.24 (2H, m), 8.02 (1H, d, J = 2.0 Hz), 8.42 (NH, s). EI-MS m/z: 366 (M^+, 28.67%), Calcd for $C_{23}H_{30}N_2O_2$: 366.30, Found: 366.20.
17. The preparation of isocyanoazulene **1** is facile and practical (ref. 6d). On the other hand, the synthesis of guaiazulene substituted by isocyano group at other position is difficult and thus currently under study.