FACILE SYNTHESIS OF GUAIAZULENE-HETEROCYCLE HYBRIDS
VIA UGI MULTICOMPONENT REACTIONS

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Abstract – The Ugi reaction with isocyanooazulene 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.23 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\textsubscript{1},N\textsubscript{1}-dimethyl-N\textsubscript{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 sesquiterpene e 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.5 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.\textsuperscript{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\textsuperscript{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.\textsuperscript{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).\textsuperscript{9}

\begin{center}
\includegraphics[width=\textwidth]{Scheme1.png}
\end{center}

\textbf{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\textsuperscript{10}; thiosalicylic acid 9 and chloroacetone 8 were stirred in methanol in the presence of K$_2$CO$_3$. 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$_2$CO$_3$ in methanol to afford 10a in 82\% yield.\textsuperscript{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.

\[ R^2NH_2 + Cl\text{-}COH \rightarrow (a) \rightarrow \] [Diagram]

10a \((R^2=\text{"Pr}) 82\%
10b \((R^2=\text{C}_6\text{H}_5) 46\%
10c \((R^2=\text{4-ClC}_6\text{H}_4) 59\%
10d \((R^2=\text{4-MeOC}_6\text{H}_4) 66\%

Scheme 2. Synthesis of 1,4-benzothiazepin-5-one derivatives. Conditions: (a) K$_2$CO$_3$, MeOH, rt.

In continuation of our investigations on the synthesis of guaiazulene-heterocycle derivatives from isocyanoazulene 1, we carried out the synthesis of \(\beta\)-lactams according to Marcaccini’s report.\(^{13}\) Although they synthesized \(\beta\)-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.

\[ \text{[Diagram]} \]

14a \((R^3=\text{"Pr}, R^4=\text{"Pr}) 91\%
14b \((R^3=\text{"Pr}, R^4=\text{"Me}) 75\%
14c \((R^3=\text{C}_6\text{H}_5, R^4=\text{C}_6\text{H}_5) 97\%

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

\(\beta\)-Lactam-guaiazulene hybrids were also synthesized using the following procedure.\(^{15}\) The Ugi reaction of isocyanoazulene 1, aldehyde 15, and \(\beta\)-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 \(\beta\)-lactam
synthesis using an anionic or cationic surfactant (entries 4-6); SDS or CTAB assist the aqueous reaction to proceed in good yield.

**Table 1.** Synthesis of β-lactam derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R^5</th>
<th>Product</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>R^5</th>
<th>Product</th>
<th>Solvent</th>
<th>Yield (%)</th>
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<td>17a</td>
<td>MeOH</td>
<td>89</td>
<td>4^a</td>
<td>iPr</td>
<td>17a</td>
<td>H_2O</td>
<td>67</td>
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<tr>
<td>2</td>
<td>C_6H_5</td>
<td>17b</td>
<td>MeOH</td>
<td>88</td>
<td>5^a</td>
<td>C_6H_5</td>
<td>17b</td>
<td>H_2O</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>17c</td>
<td>MeOH</td>
<td>29</td>
<td>6^b</td>
<td>H</td>
<td>17c</td>
<td>H_2O</td>
<td>73</td>
</tr>
</tbody>
</table>

^a Reaction was performed using 0.5 equiv of SDS (sodium dodecyl sulfate, C_{12}H_{25}SO_3Na) as a surfactant.

^b Reaction was performed using 0.5 equiv of CTAB (cetyltrimethylammonium 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

REFERENCES


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 CHCl₃, dried (Na₂SO₄), 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 °C for 1 h. The resultant mixture was extracted with CHCl₃, dried (Na₂SO₄), 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 °C. ¹H-NMR (DMSO-d₆) 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, 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 C₃₄H₃₂ClN₃O₅ (M⁺): 597.2030), Found: 597.5002.


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$_2$CO$_3$ (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$_2$SO$_4$), 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 °C. $^1$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), 4.51 (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: 474 (M$^+$) 23.02% (Calcd for C$_{29}$H$_{34}$N$_2$O$_2$S (M$^+$): 474.2341), Found: 474.5229.


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$_2$SO$_4$), and concentrated. The residue was purified using silica gel column chromatography (hexane-Et$_2$O as eluent) to give 14a as dark blue prisms (91%). mp 144-145 °C. $^1$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$_2$O$_2$ (M$^+$): 394.2620), Found: 394.3008.

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 CHCl₃, dried (Na₂SO₄), 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 ℃. ¹H-NMR (CDCl₃) 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 C₂₃H₃₀N₂O₂: 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.