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# Intermolecular [8+2] cycloaddition reactions of 2*H*-3-methoxycarbonylcyclohepta[*b*]furan-2-one with vinyl ethers: an approach to bicyclo[5.3.0]azulene derivatives

Wellington Pham, Ralph Weissleder and Ching-Hsuan Tung*

*Center for Molecular Imaging Research, Massachusetts General Hospital, Harvard Medical School, 149 13th Street, Charlestown, MA 02129, USA*

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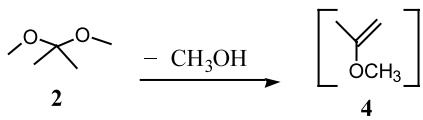
**Abstract**—Substituted bicyclo[5.3.0]azulene compounds are synthesized by intermolecular [8+2] cycloaddition reactions of lactone **1** with vinyl ethers—acetal decomposition products—are described. The reactions were found to be temperature and solvent dependent. 

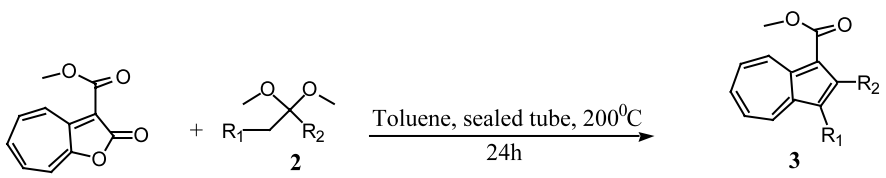
Azulene compounds have recently attracted attention due to their specific physical and chemical properties.[1] Depending on the substituents attached to the rings, azulene derivatives have a range of color spectra from red, blue, purple to green. The aromaticity of the five-membered ring of azulene has been a subject for several important modifications, namely Friedel–Crafts acylation, Mannich aminomethylation, condensation, Vilsmeier formylation, among others. An azulene ring has been synthesized by cycloaddition reactions of the activated troponoid and the active methylene compound.[2] In addition to the [6+4] addition mode, some of these systems are known to undergo [8+2] cycloaddition.[2] In an effort to synthesize azulene derivatives as chromophores, we were interested in starting with the lactone **1**. There are few reports for the synthesis of azulene compounds.[2] However, for the reaction intermediate, conditions had not been clearly defined, resulting in unreproducible results. In this communication, we report an improved procedure toward the synthesis of the [5.3.0] ring system of azulenes (Scheme 1).

Upon thermolysis, the acetal **2** was decomposed into the active vinyl ether **4** and methanol. The cycloaddition reaction between the lactone **1** and **4** forms azulene **3** as a single product.




**2** **4**

The yield of the product was significantly improved by optimizing the reaction conditions. For this type of acetal the thermal decomposition usually requires highly pressurized conditions.[3] In addition, we found the reaction was homogeneous at high temperature, and methanol released from the decomposition did not




**1** **2** **3**

(a) $R_1$= H, $R_2$= $CH_3$
(b) $R_1$, $R_2$= H
(c) $R_1$= $CH_3$, $R_2$= H

(a) $R_1$= H, $R_2$= $CH_3$ (100%)
(b) $R_1$, $R_2$= H (86%)
(c) $R_1$= $CH_3$, $R_2$= H (60%)

**Scheme 1.**

* Corresponding author. E-mail: tung@helix.mgh.harvard.edu

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**Table 1.**

| Entry | Reactant | Product | Yield (%) | | | | $\lambda_{max}$ (nm) MeCN |
|---|---|---|---|---|---|---|---|
| | | | Neat[a] | 140°C | 160°C | 200°C | |
| 1 | **2a** | **3a** | Dec.[b] | 40 | 81 | 100 | 524 |
| 2 | **2b** | **3b** | Dec.[b] | 0[c] | 0[c] | 86 | 535 |
| 3 | **2c** | **3c** | Dec.[b] | 0[c] | 0[c] | 60 | 559 |

[a] 200°C.
[b] Dec., decomposed.
[c] Lactone **1** can be recovered by flash column chromatography.

reverse the reaction nor did it react with the reactants. Contradictory to previous reports[2] the reaction could not be carried out neat in most of the syntheses. In the absence of toluene the expected brownish–red liquid products did not form. Instead, black tar-like decomposition material was recovered. This observation suggests that solvation of the vinyl ether is needed for the cycloaddition step to proceed. Initially, we thought the reaction could be done neat if the thermolysis product of the vinyl ether was a gas. Therefore, we decided to start with **2b** as a model experiment. However, the observation was consistent to that of **2a** (Table 1). The activation volume under high pressure is similar to that of a typical Diels–Alder reaction in these reactions, which proves that high pressure is effective for enhancing reactivity.[4] At high temperature (200°C) and high pressure we isolated product **3a** in 100% yield by flash column chromatography. The yield was diminished at lower temperature. In the characterization of the products by $^1$H NMR spectroscopy, a first order splitting pattern of the AX system was observed.

In summary, we demonstrate a convenient synthesis of the [5.3.0] bicyclo systems of azulene derivatives. The yield was significantly improved under high temperature and pressure in the presence of aprotic solvent. The azulene products **3** are key intermediates for synthesizing diagnostic and potential therapeutic agents. Finally this work may contribute to the synthesis of more complex systems of a similar type.

**Typical experimental procedure for the preparation of 3a**: A yellow suspension of 2*H*-3-methoxycarbonylcyclohepta[*b*]furan-2-one **1** (4 g, 19.6 mmol) and 2,2-dimethoxypropane **2a** (12.1 ml, 98 mmol) in anhydrous toluene (10 ml) in an ACE pressure seal tube was heated slowly from room temperature to 200°C for 24 h. (**CAUTION**: The total materials inside the seal tube should not fill more than half of the tube; when the volume reaches 3/4 of the tube, explosion is likely to occur. In addition, a safety shield should be used.) After 24 h, the brownish-red solution was introduced directly onto a silica gel flash column using 1:1 chloroform: hexane as an eluent to afford the brownish-red viscous liquid **3a** (3.92 g, 100%); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.83 (s, 3H), 3.98 (s, 3H), 7.13 (s, 1H), 7.39 (t, $J=11.1$ Hz, 1H), 7.50 (t, $J=11.1$ Hz, 1H), 7.69 (t, $J=11.1$ Hz, 1H), 8.28 (d, $J=10.6$ Hz, 1H), 9.48 (d, $J=10.6$ Hz, 1H); MS (MALDI-TOF) calcd: 200, found: 201 $(M+H)^+$; UV (MeCN) $\lambda_{max}$ 524 nm.

Compound **3b**: $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 3.96 (s, 3H), 7.33 (d, $J=5.0$ Hz, 1H), 7.45 (t, $J=10.1$ Hz, 1H), 7.55 (t, $J=10.5$ Hz, 1H), 7.81 (t, $J=9.8$ Hz, 1H), 8.37 (d, $J=4.5$ Hz, 1H), 8.46 (d, $J=10.5$ Hz, 1H), 9.66 (d, $J=10.5$ Hz, 1H); MS (MALDI-TOF) calcd: 186, found: 187 $(M+H)^+$; UV (MeCN) $\lambda_{max}$ 535 nm.

Compound **3c**: $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 2.63 (s, 3H), 3.98 (s, 3H), 7.26–7.50 (m, 2H), 7.79 (t, $J=9.2$ Hz, 1H), 8.2 (s, 1H), 8.37 (d, $J=9.2$ Hz, 1H), 9.55 (d, $J=9.2$ Hz, 1H); MS (MALDI-TOF) calcd: 200, found: 200 $(M+H)^+$; UV (MeCN) $\lambda_{max}$ 559 nm.

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