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# Reaction of 4-methoxy-4-(1-methylethenyl)-2-cyclobutenone derivatives with 2-lithiopropene and $\alpha$ -lithiostyrene: synthesis of eight-membered ring carbocycles

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## Abstract

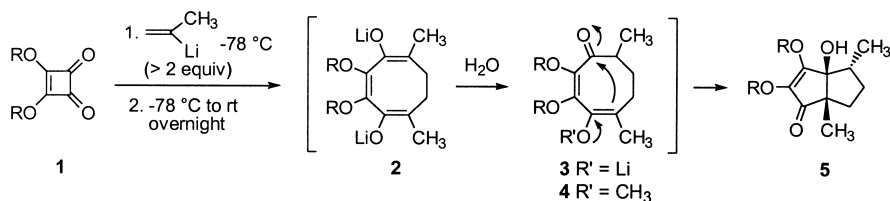
2-Alkyl- or phenyl-substituted 4-methoxy-4-(1-methylethenyl)-2-cyclobutenones react with 2-lithiopropene or  $\alpha$ -lithiostyrene to produce 4-methoxy-2,4-cyclooctadienones in moderate yield, accompanied by varying amounts of 4-methoxy-4-(1-methylethenyl)-2-cyclohexenones. The reaction is general for 2-alkyl substituted 4-methoxy-4-(1-methylethenyl)-2-cyclobutenones. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* cyclooctadienones; cyclohexenones; cyclobutenones; eight-membered rings; cycloadditions.

Recently, the construction of eight-membered ring compounds has attracted considerable attention since they constitute common structural cores of a large number of biologically important compounds.<sup>1</sup> Among the numerous methods available, ring enlargement of small ring compounds occupies an important position.<sup>2</sup> For this purpose, squaric acid is a fascinating C<sub>4</sub>-synthon with four-membered ring strain to drive reactions. The ready availability of numerous cyclobutenediones and cyclobutenones from squaric acid has opened the way to development of the syntheses of highly functionalized ring systems.<sup>3</sup> In this regard, the syntheses of polyquinanes from squarate esters have been intensively studied by the Paquette research group.<sup>4–6</sup> They have shown that the reaction of cyclobutenedione **1** with 2-lithiopropene afforded 5,5-fused ring carbocycle **5** as a major product (Scheme 1).<sup>4</sup> Although 5,5-fused ring formation proceeds via eight-membered ring intermediates such as **2** and **3**, no eight-membered structure has been observed as an end product in these reactions, due to a spontaneous transannular ring closure of **3** to **5** via intramolecular aldol reaction.<sup>4–6</sup>

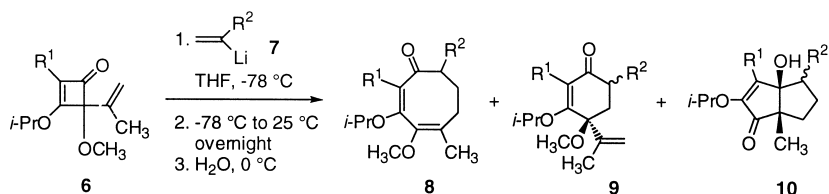
A new synthetic route to eight-membered ring carbocycles can be realized if the reaction sequence in Scheme 1 is stopped at the stage of eight-membered ring intermediate **3**. This may be achieved by replacing the lithium enolate moiety of **3** by an enol ether, i.e. by forming the stable

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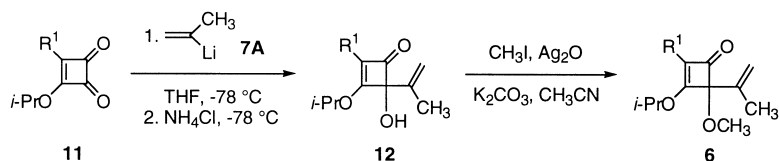
Scheme 1.

derivatives of general structure **4** by alternative reaction processes. As part of a program to develop a new cycloaddition reaction for the preparation of carbocyclic eight-membered rings, we have investigated the reaction of cyclobutenones **6** with vinylolithiums **7**, which afforded cyclooctadienones **8**, accompanied by varying amounts of cyclohexenones **9**, or 5,5-fused ring carbocycles **10** (Scheme 2). We herein report the preliminary results of our study.



Scheme 2. Compound **6**: (A)  $\text{R}^1 = \text{Me}$ ; (B)  $\text{R}^1 = \text{Bu}$ ; (C)  $\text{R}^1 = \text{Ph}$ ; (D)  $\text{R}^1 = i\text{-PrO}$ ; Compound **7**: (A)  $\text{R}^2 = \text{Me}$ ; (B)  $\text{R}^2 = \text{Ph}$ ; compounds **8**, **9** and **10**: see footnote *a* in Table 1

The starting cyclobutenones **6** were readily prepared from the corresponding cyclobutenediones **11**<sup>7</sup> according to known literature procedures (Scheme 3). Addition of 2-lithiopropene (**7A**)<sup>4</sup> to cyclobutenedione **11** led to formation of cyclobutenone **12**,<sup>7</sup> which was then methylated by using iodomethane and silver oxide to afford the cyclobutenone **6**.<sup>8</sup>



Scheme 3. Compounds **6**, **11** and **12**: (A)  $\text{R}^1 = \text{Me}$ ; (B)  $\text{R}^1 = \text{Bu}$ ; (C)  $\text{R}^1 = \text{Ph}$ ; (D)  $\text{R}^1 = i\text{-PrO}$ . Yields: **12A**: 70%; **12B**: 84%; **12C**: 72%; **12D**: 78%; **6A**: 56%; **6B**: 67%; **6C**: 44%; **6D**: 70%

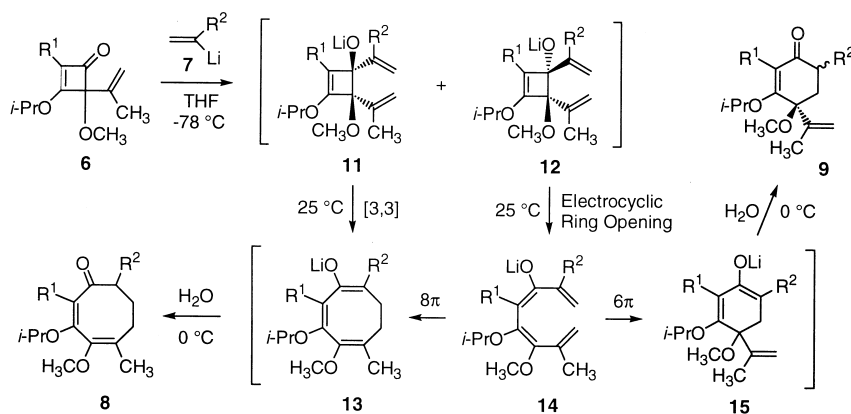
As depicted in Scheme 2, cyclobutenone derivatives (**6A–D**)<sup>7</sup> were reacted with equimolar amounts of 2-lithiopropene (**7A**)<sup>4</sup> or  $\alpha$ -lithiostyrene (**7B**)<sup>4</sup> at  $-78^\circ\text{C}$  in THF under argon for 3 hours. Upon further stirring the mixture at room temperature overnight, followed by hydrolysis, the products were isolated by column chromatography. The results are summarized in Table 1. The reaction of **6A** with **7A** produced the cyclooctadienone derivative **8A** (Entry A).<sup>9</sup> A complication in this reaction was the formation of the cyclohexenone derivative **9A** as a mixture of two diastereomers.<sup>10</sup> A similar trend was observed in the reaction of cyclobutenone **6B** with **7A**, where cyclooctadienone **8B** and cyclohexenones **9B** were obtained (Entry B). However, the reaction

Table 1  
Reaction of cyclobutenones **6** with vinylolithiums **7**

Entry <sup>a</sup>	Reacting Partners	R <sup>1</sup>	R <sup>2</sup>	Yields of Products, <sup>b,c</sup> %		
				<b>8</b>	<b>9</b> <sup>d</sup>	<b>10</b> <sup>d</sup>
<b>A</b>	<b>6A</b> + <b>7A</b>	Me	Me	40	25 <sup>e</sup>	0
<b>B</b>	<b>6B</b> + <b>7A</b>	Bu	Me	42	28 <sup>e</sup>	0
<b>C</b>	<b>6C</b> + <b>7A</b>	Ph	Me	25	<i>f</i>	0
<b>D</b>	<b>6A</b> + <b>7B</b>	Me	Ph	44	0	0
<b>E</b>	<b>6B</b> + <b>7B</b>	Bu	Ph	45	0	0
<b>F</b>	<b>6D</b> + <b>7A</b>	<i>i</i> -PrO	Me	0	0	50 <sup>e</sup>

<sup>a</sup>Entry letters define R<sup>1</sup> and R<sup>2</sup> for compounds **8–15**. <sup>b</sup>Isolated yields. <sup>c</sup>All new compounds were adequately characterized. <sup>d</sup>Refers to combined yield of two diastereomers. <sup>e</sup>A nearly 1:1 mixture of two diastereomers was obtained. <sup>f</sup>This product could not be isolated.

between **6C** and **7A** revealed a complex reaction mixture; only the cyclooctadienone **8C** could be isolated (Entry C). The reaction of  $\alpha$ -lithiostyrene (**7B**) with cyclobutenones **6A** and **6B** produced the expected cyclooctadienones **8D** and **8E**, respectively, without formation of any cyclohexenones such as **9D** and **9E** (Entries D and E). These results imply that both processes, cyclooctadienone- and cyclohexenone-forming reaction, or one of them can be operative depending upon the substitution pattern of starting cyclobutenones **6** and vinylolithiums **7**. Interestingly, the reaction of **6D** with **7A** led to a formation of two diastereomers of 5,5-fused ring carbocycle **10F**;<sup>5</sup> none of the expected cyclooctadienone **8F** and cyclohexenone diastereomers **9F** were observed (Entry F). Formation of the diastereomeric 5,5-fused ring carbocycles **10F** may not actually represent a different reactivity pattern, since they are secondary products of the reaction and result from the initially formed cyclooctadienone **8F** by a transannular ring closure, as in the case of conversion of **3** to **5** as shown in Scheme 1.<sup>6</sup> For instance, compound **8A** yields **10A** when subjected to acidic hydrolysis. Apparently, the substituent at the 2-position of cyclooctadienone **8** (i.e. R<sup>1</sup>) controls whether transannular cyclization to **10** occurs. As can be seen in Table 1, cyclooctadienone formation is general for 2-alkyl or phenyl substituted cyclobutenones (**6A–C**).



Scheme 4. R<sup>1</sup> and R<sup>2</sup> for compounds **6** and **7**: see Scheme 2; compounds **8–15**: see footnote *a* in Table 1

The mechanism proposed for the formation of products **8** and **9** is outlined in Scheme 4.<sup>11</sup> It first involves the addition of vinylolithium **7** to cyclobutenone **6**, leading to a mixture of *cis*- and *trans*-divinyl substituted cyclobutenes **11** and **12**.<sup>11</sup> Cyclobutene **11** undergoes anionic oxy-Cope rearrangement to give **13**. However, cyclobutene **12** experiences a conrotatory electrocyclic ring opening to afford **14**, which yields the enolates **13** and **15** by  $8\pi$  and  $6\pi$  electrocyclization, respectively.<sup>10,11</sup> Hydrolysis of **13** and **15** produces the compounds **8** and **9**. As noted before, the substitution pattern of the reactants determines the reaction pathway leading to formation of **8** and/or **9**.

In summary, we have developed a new method for the synthesis of cyclooctadienones. Further investigation of the mechanism, scope and limitations of this process is currently under investigation, as well as delineation of the factors which influence cyclooctadienone versus cyclohexenone and cyclooctadienone versus 5,5-fused ring formation.

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