



# [2+2+1] Cycloadditions of ynol ethers. The synthesis of iron complexes of 3-alkoxycyclopentadienones

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**Abstract**—This Letter reports the synthesis of iron complexes of 3-oxocyclopentadienones from ynol ether–alkyne [2+2+1] cycloaddition reactions as well as the use of 3-alkoxycyclopentadienones in subsequent cycloaddition reactions. © 2001 Elsevier Science Ltd. All rights reserved.

In spite of their vast synthetic potential, cyclopentadienones have not been widely utilized in organic synthesis. This has been due, in part, to the lack of synthetically useful cyclopentadienones that are available and to the enhanced reactivity of cyclopentadienones lacking substitution.<sup>1</sup>

One solution to the reactivity problem has involved the protection of the dienone as the corresponding transition metal complex.<sup>2–4</sup> While not proven in a general sense, metal coordination also presents one with the possibility of carrying out stereoselective reactions on functionality pendant to the cyclopentadienone complex.<sup>5</sup>

From an interest in the use of cyclopentadienones in the synthesis of heterocyclic natural products, we have become fascinated with cyclopentadienone metal complexes that have heteroatom substitution at the 3-position. As an illustration of this, we recently demonstrated that cobalt and iron complexes of 3-aminocyclopentadienones could be generated from ynamine–alkyne [2+2+1] cycloaddition reactions.<sup>6</sup> Following oxidative decomplexation of the metal, we also demonstrated that the free cyclopentadienones could be induced to undergo chemo- and stereoselective cycloaddition reactions with dienophiles.

As a continuation of these studies, we have recently become interested in the analogous [2+2+1] cycloaddition reactions of ynol ethers with pendant alkynes. If successful, we believed that the 3-alkoxycyclopentadienone products from these reactions would have sig-

nificant potential in organic synthesis. Outlined herein are our preliminary results in this area.

Our initial investigations explored unsubstituted ynol ethers **2**, **5**, and **8** having 2-, 3-, and 4-carbon tethers between the alkyne and the ynol ether, respectively. These were synthesized in two steps from the corresponding alkynols (Table 1, entries 1–3). Namely, exposure of the alkynols to KH and trichloroethylene resulted in the formation of the corresponding dichlorovinyl ethers (e.g. **1**, **4**, and **7**). Upon treatment with BuLi, vinyl ethers **1**, **4**, and **7** were converted into ynol ethers **2**, **5**, and **8**, respectively, after trapping of the intermediate dianion with TMSCl.<sup>7,8</sup> With **2**, **5**, and **8** in hand, we exposed them to thermal cycloaddition conditions in the presence of Fe(CO)<sub>5</sub>. This protocol resulted in the isolation of tricarbonyliron cyclopentadienone complexes **3**, **6**, and **9** in relatively low yield.<sup>9</sup>

While pleased that we were able to generate 3-alkoxycyclopentadienones **3**, **6**, and **9**, we were not satisfied with the efficiency of the [2+2+1] cycloaddition reaction. From the hypothesis that the ground state conformation of **3**, **6**, and **9** was responsible for the low cycloaddition yields,<sup>10</sup> we turned to the cycloaddition of the conformationally restricted aryl ynol ether **11** (Table 1, entry 4). To our delight, the cycloaddition of **11** provided iron cyclopentadienone complex **12**<sup>15</sup> in 67% yield in two steps from dichlorovinyl ether **10**.

To further demonstrate the importance of ynol ether conformation on the cycloaddition reaction, we examined *gem*-dimethyl substituted ynol ether **14** (Table 1, entries 5 and 6). When **14** was subjected to the same conditions that we had used for the other substrates

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Table 1.

Entry	Enol ether	Yield	Yno-ether	Yield	Cyclopentadienone	Cond's <sup>c</sup>	Yield
1		59% <sup>a</sup>		-----		A	37% <sup>d</sup>
2		54% <sup>a</sup>		-----		A	24% <sup>d</sup>
3		47% <sup>a</sup>		-----		A	21% <sup>d</sup>
4		57% <sup>a</sup>		-----		A	67% <sup>d</sup>
5		-----		83% <sup>b</sup>		A	48%
6	<b>13</b>	-----	<b>14</b>	83% <sup>b</sup>	<b>15</b>	B	71%

<sup>a</sup>yield from the corresponding alkynol

<sup>b</sup>yield is for two steps from 2,2-dimethyl-pent-4-yn-1-ol

<sup>c</sup>conditions: A: Fe(CO)<sub>5</sub>, PhCH<sub>3</sub>, 130 °C; B Fe(CO)<sub>5</sub>, PhCH<sub>3</sub>, 130 °C, alumina

<sup>d</sup>yield is for two steps from the corresponding dichloroenol ether

(i.e. Fe(CO)<sub>5</sub>, PhCH<sub>3</sub>, and 130°C), we isolated **15**<sup>15</sup> in a disappointing 48% yield. In related Pauson Khand cycloadditions of heteroatom bearing substrates, Smit and Caple had found that alumina had dramatic effects on the efficiency of the reaction.<sup>11</sup> With the hope of obtaining similar results, we included alumina in the reaction of **14** with Fe(CO)<sub>5</sub>. We were pleased to isolate cyclopentadienone complex **15** in 71% yield.<sup>12</sup>

Having established that yno-ether [2+2+1] cycloaddition reactions in the presence of Fe(CO)<sub>5</sub> lead to the generation of iron complexes of 3-alkoxycyclopentadienones, we set out to demonstrate the utility of metal-free 3-alkoxycyclopentadienones through their use in cycloaddition reactions with dienophiles. The

decomplexation of **3**, **6**, **12**, and **15** using trimethylamine-*N*-oxide (TMANO) and the use of the resulting 3-alkoxycyclopentadienones in cycloaddition reactions with alkynes is depicted in Table 2.<sup>15</sup> In contrast to the cycloadditions of 3-aminocyclopentadienones, the cycloadditions of 3-alkoxycyclopentadienone with ethyl propiolate gave mixtures of isomeric aromatic products (entries 2–4). As expected, the major product had the ester and ether substituents *para* to one another.<sup>13</sup> As had been our experience with the 3-aminocyclopentadienone cycloadditions, the initial bicyclo[2.2.1]-heptenone adducts were not observed. To the best of our knowledge, these experiments represent the first successful examples of the use of 3-alkoxycyclopentadienones in cycloaddition reactions.<sup>14</sup>

Table 2.

Entry	Complex	Dienophile	Cycloadduct(s)	Ratio <sup>b</sup>	Yield
1	3	DMAD		----	42%
2	6	ethyl propiolate		3:1	60%
3	12	ethyl propiolate		3:1	70%
4	15	ethyl propiolate		3:1	63%

<sup>a</sup>arrows depict observed nOe enhancements that were used to assign regioselectivity

<sup>b</sup>ratio of para product to meta product as determined by <sup>1</sup>H NMR

In summary, we have found that yno1 ethers undergo [2+2+1] cycloaddition reactions with pendant alkynes when subjected to Fe(CO)<sub>5</sub>. We have also found that 3-alkoxycyclopentadienones undergo cycloaddition reactions with ethyl propiolate. Our current efforts in this area are focused on the optimization of the reactions that we have discovered, the use of 3-heterosubstituted iron cyclopentadienones in stereoselective reactions and the use of 3-heterocyclopentadienones in the synthesis of biologically active heterocycles.

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- Pearson has carried out stereoselective additions to ketones pendant to iron cyclopentadienone complexes. See Ref. 3c.

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8. Because of their instability to chromatographic purification, ynol ethers **2**, **5**, and **8** were used in the subsequent cycloaddition chemistry without purification.
9. In comparison, the tosyl protected ynamines corresponding to **2**, **5**, and **8** underwent [2+2+1] cycloaddition to give cyclopentadienone–iron complexes in 84, 96, and 54% yields, respectively.
10. As has been discussed by others, unsubstituted acyclic ethers adopt a ground state conformation that orients the alkyl substituents *anti* to one another, see: (a) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p. 611; (b) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291; (c) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653.
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12. We saw little to no enhancement in yield when alumina was included in the reaction for the other ynol ether substrates.
13. The regiochemistry of **18** was determined through NOE experiments. The assignments for **19–22** were based upon these experiments.
14. Herndon was unable to trap a 1,2-diphenyl-4-oxocyclopentadienone either intramolecularly with an unactivated alkene or intermolecularly with DMAD. See: Herndon, J. W.; Patel, P. P. *Tetrahedron Lett.* **1997**, *38*, 59.
15. All new compounds were characterized by <sup>1</sup>H, <sup>13</sup>C NMR, IR and HRMS. Selected examples:  
**12**: Viscous oil; <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>) δ 7.68 (d, *J*=8.0 Hz, 1H), 6.99 (d, *J*=8.5 Hz, 1H), 6.93 (t, *J*=7.5 Hz, 1H), 6.87 (t, *J*=7.5 Hz, 1H), 0.54 (s, 9H), 0.49 (s, 9H); <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>) δ 208.4, 177.2, 161.3, 147.1, 128.9, 124.6, 123.9, 123.6, 113.1, 93.9, 62.3, 61.7, 0.21, –0.78; IR (CH<sub>2</sub>Cl<sub>2</sub>) 3056, 2978, 2303, 2062, 2009, 1620 (cm<sup>-1</sup>); MS (FAB<sup>+</sup>) 455 (MH<sup>+</sup>), 398, 307, 289, 154 *m/z*; HRMS calcd for C<sub>20</sub>H<sub>23</sub>O<sub>5</sub>Si<sub>2</sub>Fe (MH<sup>+</sup>) 455.0434, found 455.0440.  
**15**: Pale yellow solid; mp 136–138°C; <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>) δ 3.18 (s, 2H), 2.21 (d, *J*=14.0 Hz, 1H), 1.99 (t, *J*=13.5 Hz, 1H), 0.67 (s, 3H), 0.50 (s, 3H), 0.47 (s, 9H), 0.34 (s, 9H); <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>) δ 209.4, 176.4, 145.2, 88.4, 76, 65.9, 64.9, 35.2, 29.2, 25.5, 23.8, –0.10, –0.58; IR (CH<sub>2</sub>Cl<sub>2</sub>) 3048, 2978, 2061, 1992, 1975 (cm<sup>-1</sup>); MS (FAB<sup>+</sup>) 449 (MH<sup>+</sup>), 393, 392, 246, 185 *m/z*; HRMS calcd for C<sub>20</sub>H<sub>20</sub>O<sub>5</sub>Si<sub>2</sub>Fe (MH<sup>+</sup>) 449.0903, found 449.0904.  
**19**: <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>) δ 8.28 (s, 1H), 8.12 (d, *J*=8.5 Hz, 1H), 7.35 (d, *J*=8.0 Hz, 1H), 7.11 (m, 2H), 4.18 (q, *J*=7.0 Hz, 2H), 1.08 (t, *J*=7.0 Hz, 3H), 0.74 (s, 9H), 0.42 (s, 9H); <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>) δ 169.4, 161.3, 157.3, 136.4, 135.3, 133.4, 130.6, 125.6, 125.1, 124.3, 123.7, 122.6, 121.2, 61.2, 14.3, 1.85, –0.97; IR (CH<sub>2</sub>Cl<sub>2</sub>) 3048, 2987, 2295, 1706, 1455 (cm<sup>-1</sup>); MS (FAB<sup>+</sup>) 385 (MH<sup>+</sup>), 369, 307, 289, 154 *m/z*; HRMS calcd for C<sub>21</sub>H<sub>29</sub>O<sub>3</sub>Si<sub>2</sub> (MH<sup>+</sup>) 385.1655, found 385.1641.  
**21**: <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>) δ 7.99 (s, 1H), 4.14 (q, *J*=7.0 Hz, 2H), 3.37 (s, 2H), 2.52 (s, 2H), 1.05 (t, *J*=7.0 Hz, 3H), 0.68 (s, 6H), 0.50 (s, 9H), 0.39 (s, 9H); <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>) δ 170.5, 160.0, 143.6, 137.9, 127.3, 126.9, 74.9, 60.9, 42.3, 28.5, 24.7, 14.3, 2.9, –1.1; IR (CH<sub>2</sub>Cl<sub>2</sub>) 3048, 2978, 2303, 1715, 1412 (cm<sup>-1</sup>); MS (FAB<sup>+</sup>) 379 (MH<sup>+</sup>), 363, 307, 289, 154 *m/z*; HRMS calcd for C<sub>20</sub>H<sub>35</sub>O<sub>3</sub>Si<sub>2</sub> (MH<sup>+</sup>) 379.2125, found 379.2129.