



Consecutive enolate addition/cyclization of Fischer enynyl carbene complexes: facile access to cyclopentenoids

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ABSTRACT

Functionalized cyclopentenoids were synthesized from Fischer enynyl carbene complexes by a sequence that involves regioselective nucleophilic 1,4-addition of enolates and anionic electrocyclization of the resulting intermediate. Moreover, the method is effective for the C2–C3 annulation of heterocyclic rings like benzofuran and indole. The methoxycyclopentadiene thus obtained can be hydrolyzed to substituted cyclopentenones, which are not straightforwardly accessible by other methods.

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Developing new strategies for cyclopentane-based molecules continues to stimulate synthetic chemists. Currently, the Pauson–Khand reaction (alkyne + alkene + CO) is a reference for synthesis of cyclopentenones.¹ Although the cyclopentannulation reaction of functionalized dienyl systems, like dienyl ketones for the Nazarov cyclization, appears to represent an attractive synthetic tool, it remains much less exploited and development of new strategies of this type would be beneficial for cyclopentane-based molecules.²

In the last years, α,β -unsaturated Fischer carbene complexes have demonstrated high potential in the area of carbocyclization reactions.³ One can realize that not only that linear-conjugated dienylcarbenes (1-metalla-1,3,5-hexatrienes) are attractive candidates for the construction of the cyclopentane skeleton, but also their cyclopentannulation would complement the Nazarov reaction which involves the cyclization of a cross-conjugated system (Fig. 1).⁴ We also envisioned that the Michael-type addition to readily available, highly electrophilic enynyl carbenes would give easy access to the required *cis*-dienyl carbenes. Therefore, we report herein on the synthesis of functionalized cyclopentenoids from Fischer enynyl carbene complexes of chromium(0) by a tandem sequence involving addition of enolates and cyclopentannulation.⁵

First, chromium 4-phenyl-3-buten-1-ynyl carbene **1** was treated with lithium enolate **2** at -78°C in THF for ca. 15 min until complete disappearance of the carbene. The mixture was warmed up to room temperature, worked-up (aqueous ammonium chloride), and the resulting crude chromatographed (SiO_2 , hexanes/

ethyl acetate 5:1) to give the cyclopentadiene enoether **3** as a single compound in 82% yield (Scheme 1). The structure of **3** was ascertained on the basis of its NMR spectroscopic and HRMS data,⁶ and confirmed by an X-ray analysis.⁷ The formation of **3** can be explained by nucleophilic 1,4-addition of the enolate to the alkynyl carbene functionality (intermediate **I**) followed by anionic electrocyclic cyclization (intermediate **II**) and hydrolysis (Scheme 1).

The usefulness of this reaction was further expanded to the synthesis of bicyclic ethers **6–12** (65–92%) by using chromium cycloalkenylalkynyl carbenes **4a,b**, and various lithium enolates derived from mono and dicarbonyl compounds **5** (Scheme 2). The reaction was found to work well for unsubstituted and substituted malonate substrates (compounds **6, 8, 9**) as well as for ethyl acetoacetate (compound **7**). On the other hand, simple lithium enolates derived from di- and trisubstituted esters also promote efficiently the cyclopentannulation reaction (compounds **10, 11**).⁸ In the same way, using 1-phenylpropan-1-one yields the cycloadduct **12** as a 2:1 mixture of diastereoisomers.⁹

The chance that an aromatic C–C double-bond might participate in the cyclization was then taken in mind. However, the reaction of

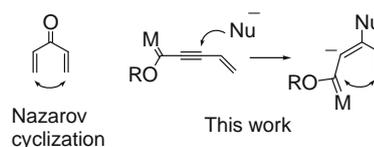
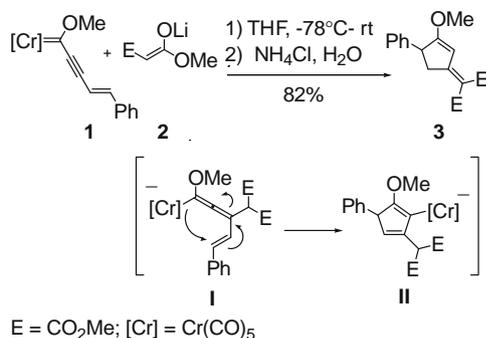


Figure 1.

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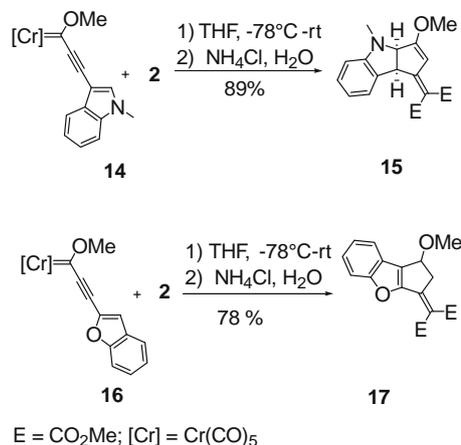


Scheme 1. Cyclopentannulation of chromium enynyl carbene **1** by sequential conjugated addition and cyclization.

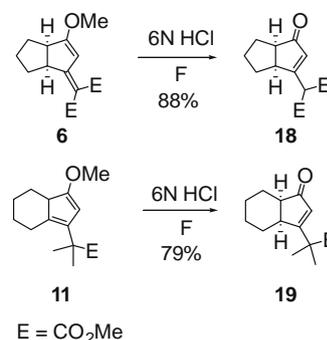
phenylethynyl(methoxy)carbene of chromium with various enolates resulted in the formation of complex mixtures of unidentified compounds. Fortunately, replacing the phenyl group with heteroaryl substituents led to success. Thus, the reaction of (1-methylindol-3-yl)ethynyl carbene **14** with the lithium enolate derived from dimethyl malonate gave rise, under the reaction conditions and after purification (SiO₂, hexanes/ethyl acetate, 5:1), to dihydroindole derivative **15** in 89% yield (Scheme 3). The benzofuran-2-yl substituted carbene **16** also underwent the cyclopentannulation with malonate diester enolate **2** to furnish the benzofuran-fused cyclopentene **17** in 78% yield. The structures of these tricyclic adducts were assigned by means of mono- and bidimensional ¹H and ¹³C NMR experiments, as well as X-ray analysis for **15**.¹⁰

Finally, the hydrolysis of the methoxycyclopentadiene system was accomplished with aqueous HCl. For instance, the treatment of cycloadducts **6**, **11** with 6 N HCl in THF at room temperature provided the cyclopentenone derivatives **18**, **19** in 79–88% yield.¹¹

In summary, we have described a facile access to functionalized cyclopentenoids from Fischer enynyl carbene complexes that involves regioselective addition of enolates and cyclization. Interestingly, the method has proven to serve for the C₂–C₃ annulation of the benzofuran and indole rings, irrespective of the carbon (C₂ or



Scheme 3. Cyclopentannulation reaction of heteroaryl-substituted alkynyl carbenes **14** and **16**.



Scheme 4. Hydrolysis of enoethers **6** and **11** to cyclopentenones **18** and **19**.

C₃) bonded to the alkynyl carbene ligand. These types of cyclopentenones are not at all straightforwardly accessible by the intermolecular Pauson–Khand reaction because of a lack of either reactivity (in particular for unstrained alkenes) or regioselectivity (2,5-disubstituted cyclopentenones are generally formed) (see Scheme 4).

Acknowledgments

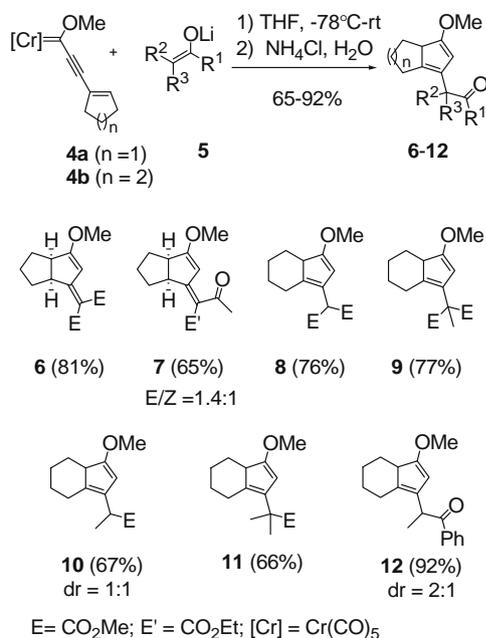
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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.058.

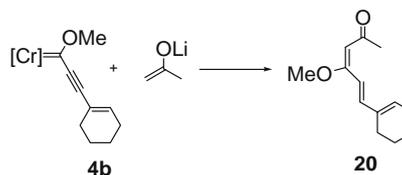
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Scheme 2. Cyclopentannulation of chromium enynyl carbenes **4a,b** using different lithium enolates **5**.

5. The cyclization of 4-amino-1-metalla-1,3,5-trienes to 1,3-cyclopentadienes was reported: Auman, R.; Fröhlich, R.; Prigge, J.; Meyer, O. *Organometallics* **1999**, *18*, 1369–1380.
6. *Synthesis of 3, typical procedure:* Dimethyl malonate (85.9 mg, 0.65 mmol) was added to a solution of lithium diisopropyl amide (0.715 mmol) in THF (1 mL) at -78°C and the mixture was stirred for 15 min at that temperature. A solution of the enynylcarbene **1** (235.5 mg, 0.65 mmol) in THF (0.5 mL) was added and the solution was allowed to warm to room temperature. The resulting mixture was stirred for 15 min, treated with saturated aqueous ammonium chloride (20 mL), and the mixture extracted with ether (3×10 mL). After solvent removal the resulting crude was purified (SiO_2 , hexanes/ethyl acetate 5:1) to give cyclopentadiene enolether **3** (161 mg, 82% yield). Spectroscopic data of **3**: ^1H NMR (300 MHz, C_6D_6): δ 2.93 (s, 3H), 3.48 (s, 6H), 3.58 (s, 3H), 6.49 (s, 1H), 6.88–6.90 (m, 2H), 6.97–7.02 (m, 3H). ^{13}C NMR (75 MHz, C_6D_6): δ 40.2 (CH_2), 40.9 (CH), 51.0 (CH_3), 51.1 (CH_3), 57.6 (CH_3), 103.1 (CH), 111.4 (C), 127.0 (CH), 126.4 ($2 \times \text{CH}$), 128.7 ($2 \times \text{CH}$), 141.4 (C), 166.7 (C), 167.0 (C), 181.1 ($2 \times \text{C}$).; HRMS calcd for $\text{C}_{17}\text{H}_{18}\text{O}_5$ [M^+] 302.1149, found: 302.1144.
7. Crystallographic data for **3** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 721068. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax + 44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
8. All new compounds isolated gave satisfactory analytical figures and were characterized by spectroscopic means (IR, HRMS, ^1H , and ^{13}C NMR).
9. The reaction of the enynyl carbene **4b** with lithium acetone enolate led to trienone **20** as a result of, (i) initial 1,2-addition of the enolate to the metal-carbene functionality, (ii) 1,3-shift of the metal fragment, and (iii) hydrolytic metal elimination. This behavior of Fischer carbene complexes toward carbon nucleophiles has been described. Barluenga, J.; Trabanco, A. A.; Flórez, J.; García-Granda, S.; Llorca, M.-A. *J. Am. Chem. Soc.* **1998**, *120*, 12129–12130.



10. Crystallographic data for **15** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 721067. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax + 44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
11. For cyclopentenone-containing natural and bioactive compounds, see: Gibson, S. E.; Lewis, S. E.; Mainolfi, N. *J. Organomet. Chem.* **2004**, *689*, 3873–3890.