GRAPHICAL ABSTRACT

Stereocontrolled Intramolecular Iron-mediated Tandem [6+2]-Ene-type Diene/Dienol Ether Double Cyclization Reactions

Anthony J. Pearson* and Sheng Zhang

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106, United States

Stereocontrolled Intramolecular Iron-mediated Tandem [6+2]-Ene-type Diene/Dienol Ether Double Cyclization Reactions

Anthony J. Pearson* and Sheng Zhang

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106, United States

ajp4@case.edu

Abstract

A stereocontrolled intramolecular iron-mediated diene/diene tandem double cyclocoupling reaction has been explored using vinyl ethers as the olefin partners. Diastereomerically pure spirotricyclic products with functionalized (alkoxymethyl) side chains can be formed efficiently under photothermal conditions. With a methoxy substituent on the iron-complexed cyclohexadiene core, demetallation and acidic hydrolysis of the cyclocoupling product afforded a cyclohexenone ring.

Keywords: tricarbonyliron, diene, cycloisomerization, ene reaction

Introduction

Iron carbonyl complexes of alkenes and dienes, as well as their derived allylic and dienyl systems, have found numerous applications as stoichiometric intermediates in organic synthesis, mostly utilizing the ability of the tricarbonyliron group to stabilize otherwise highly reactive species, to act as a stereodirecting moiety, and to act as a protecting group for 1,3-dienes.¹ Our group has developed a promising stereocontrolled intramolecular iron-mediated diene/olefin cyclocoupling procedure, equivalent to a [6+2] ene-type reaction, which generates spirolactams,² spirolactones,² spirothiolactones,³ and spiroalkane derivatives⁴ under thermal or photothermal conditions (eq. 1). Based on this reaction, a double cyclization process, resulting from two consecutive [6+2] ene-type reactions, was also developed in our laboratory (eq. 2).⁵ The overall reaction manifold takes advantage of the ability of a tricarbonyliron group to protect the attached cyclohexadiene moiety and prevent intramolecular Diels-Alder reactions, thus directing the substrate along a normally inaccessible ene reaction pathway. The work described in this report aims to examine the tandem double cyclization using an electron rich 2π component in the second ene reaction, thereby further expanding the scope of

the cyclocoupling to include dienol ethers, which would result in tricyclic molecules having (protected) hydroxymethyl side chains ($R' =$ alkoxy in eq. 2).⁶

Results and Discussion

Known carboxylic acids **5a**⁷ and **5b**⁸ were each coupled via their acyl mesylates with amine **6** to afford amides **7a** and **7b** (Scheme 1). Deprotection of **7a** and **7b** by treatment with an 8:1:1 mixture of MeOH/H₂O/HCl afforded alcohols **8a** and **8b**, which were oxidized using the Mukaiyama protocol⁹ to afford aldehydes **9a** and **9b** without loss of the Fe(CO)₃ moiety. Complexes **9a** and **9b** were each reacted with (methoxymethyl)triphenylphosphorane to afford methoxy dienyl ethers **10a** ($E/Z = 0.9:1$) and **10b** ($E/Z = 1.5:1$). We also planned to study cyclizations of the corresponding benzyl ethers, because a benzyl protecting group is easier to remove from the anticipated cyclization products when required. Accordingly, **9a** and **9b** were each treated with (benzyloxymethyl)triphenylphosphorane to give benzyloxydienyl derivatives **10c** ($E/Z = 1.3:1$) and **10d** ($E/Z = 1.2:1$).

In order to assess the potential for the pendant dienol ethers to engage in our tandem [6+2] ene-type cyclocoupling reaction, we first examined thermal conditions that were successful with complexes **3** (eq. 2). Accordingly, **10a** was heated in *n*-Bu₂O (0.02 mmol/mL) under CO atmosphere at 142 °C for 16 h, which afforded a separable mixture of the anticipated product **11a** and a side product **12** that results from an iron-mediated [4+4] cycloaddition product (eq. 3, 2:1 in favor of **11a** from the ¹H NMR spectrum of the crude product). This type of reaction has been previously observed as the major pathway when complexes related to **3** were treated with a controlled amount of trimethylamine-*N*-oxide to effect loss of a carbonyl ligand from the iron complex,¹⁰ but we have not previously observed formation of

Scheme 1

[4+4] adducts under standard thermal reaction conditions. Similar treatment of complex **10a** with Me₃NO was unproductive. Presumably the electron rich nature of the dienol ether side chain plays a role in the outcome of this reaction. Cyclization of **10a** under photothermal conditions, however, afforded the double-ene cyclization product **11a** together with the demetallated diene **13a** as the major components (see Table 1). The mixture was treated directly with Me₃NO to afford **13a** as the major product in 70% isolated yield, together with a minor amount of **12** (7%).

We were interested in determining whether the nature of the ether group on the pendant diene affects the partitioning between ene- and [4+4]- cyclization pathways. Accordingly **10c**, which has a somewhat more sterically demanding ether group on the side chain, was reacted under purely thermal conditions and gave a mixture of the anticipated product **11c** and the [4+4] cycloaddition product **14** in 2.8:1 ratio, as well as some unidentifiable side products. Reaction of **10c** under photothermal conditions, in contrast, gave an 11:1 NMR ratio of double cyclization products (**11c** and its demetallated form **13c** - see Table 1) over compound **14**. The crude mixture was then stirred with Me₃NO in benzene, affording **13c** in 68% overall yield from **10c**. The results indicate that the nature of the *O*-alkyl substituent has only marginal effect on the outcome of the reaction, and this was not pursued any further.

We have previously employed a methoxy substituent at C-3 on the cyclohexadienylcarboxamide-Fe(CO)₃ complexes to control the stereochemical outcome of single ene-type cyclizations as well as to generate useful cyclohexenone functionality in the products that result from both single- and tandem double ene-type reactions.⁸ To assess the outcome of using this moiety in the present reactions, complexes **10b** and **10d** were cyclized under thermal conditions, but each gave a complex mixture containing less than 20% of the desired product (by NMR spectroscopy). Reaction **10b** or **10d** under photothermal conditions, however, gave almost exclusive conversion to the double cyclization products **13b** and **13d** after direct demetallation using excess Me₃NO; no [4+4] adducts were detected in the crude product mixtures from these reactions, the mass balance for the cyclization process being accounted for as unreacted and/or demetallated starting material. Dienes **13b** and **13d** were then each hydrolyzed using oxalic acid, affording α,β -unsaturated ketones **15a** and **15b**, respectively (eq. 4).

Table 1. Photothermal Cyclization of Complexes **10**

reactant	R, R'	product	yield 13 ^a
10a	H, Me	13a	70
10b	OMe, Me	13b	72
10c	H, Bn	13c	68
10d	OMe, Bn	13d	68

^a Overall yield from **10** after demetallation, two steps.

Conclusions

In conclusion, we have shown that a tandem double [6+2] ene-type cyclization, that is mediated by an iron carbonyl moiety attached to a cyclohexa-1,3-diene, can be performed using a dienol ether as the pendant diene, resulting in a spirotricyclic molecule that has alkoxymethyl functionality at the cyclization terminus. Competing [4+4] cycloaddition that occurs during the thermally activated reaction can be ameliorated by using a photochemical procedure at moderately elevated temperature.

Acknowledgements

We are grateful to the National Science Foundation (CHE-0743234) and the Department of Chemistry, Case Western Reserve University, for financial support.

Supplementary Data

Supplementary data (experimental procedures and characterization data for all new compounds) associated with this article, can be found in the online version at:

Literature References

1. Selected reviews and articles: (a) Grée, R. *Synthesis* **1989**, 341-355. (b) Fatiadi, A. J. *J. Res. Natl. Inst. Stand. Technol.* **1991**, 96, 1. (c) Knölker, H.-J. *Synlett* **1992**, 371-387. (d) Knölker, H.-J. *Chem. Rev.* **2000**, 100, 2941-2961. (e) Pearson, A. J. in *Advances in Metal-Organic Chemistry*, Ed. Liebeskind, L. S., Jai Press, Inc., Greenwich, Vol. 1, **1989**, 1-49. (f) Pearson, A. J. *Iron Compounds in Organic Synthesis*, in *Best Synthetic Methods*, Ed. Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W. Academic Press Inc., **1994**. (g) Roush, W. R.; Wada, C. K. *Tetrahedron Lett.* **1994**, 35, 7347-7350. (h) Cleator, E.; Harter, J.; Hollowood, C. J.; Ley, S. V. *Org. Biomol. Chem.*, **2003**, 1, 3263 - 3264, and references cited therein. (i) Lee, D. W.; Pandey, R. K.; Lindeman, S.; Donaldson, W. A. *Org. Biomol. Chem.* **2011**, 9, 7742-7747, and references cited therein. (j) El-Mansy, M. F.; Sar, A.; Lindeman, S.; Donaldson, W. A. *Chem. Eur. J.* **2013**, 19, 2330-2366, and references cited therein.
2. (a) Pearson, A. J.; Zettler, M.; Pinkerton, A. A. *J. Chem. Soc., Chem. Commun.* **1987**, 264-266. (b) Pearson, A. J.; Zettler, M. W. *J. Am. Chem. Soc.* **1989**, 111, 3908-3918.
3. Pearson, A.J.; Alimardanov, A.; Pinkerton, A. A.; Parrish, D. A. *J. Org. Chem.*, **1998**, 63, 6610-6618.
4. Pearson, A. J.; Wang, X.; Dorange, I. B. *Org. Lett.* **2004**, 6, 2535-2538.
5. (a) Pearson, A. J.; Wang, X. *J. Am. Chem. Soc.* **2003**, 125, 638-639. (b) Pearson, A. J.; Wang, X. *Tetrahedron Lett.* **2005**, 46, 3123-3126. (c) Pearson, A. J.; Sun, H.; Wang, X. *J. Org. Chem.* **2007**, 72, 2547-2557.

6. We have previously described the use of vinyl ethers in single ene-type cyclizations related to that shown in eq. 1: Pearson, A. J.; Zhang, S.; Sun, H. *J. Org. Chem.* **2012**, 77, 8835-8839.
7. Birch, A. J.; Williamson, D. H. *J. Chem. Soc. Perkin Trans. 1* **1973**, 1892-1900.
8. Pearson, A. J.; Dorange, I. B. *J. Org. Chem.* **2001**, 66, 3140-3145.
9. Wada, A.; Hiraishi, S.; Takamura, N.; Date, T.; Aoe, K.; Ito, M. *J. Org. Chem.* **1997**, 62, 4343-4348.
10. Pearson, A. J.; Wang, X. *Tetrahedron Lett.* **2005**, 46, 4809-4811.