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Synthesis of hydronaphthalenes through coupling of enyne carbonyl compounds that contain pendant alkene groups with Fischer carbene complexes

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Abstract

The coupling of enyne carbonyl compounds that contain pendant alkene groups with Fischer carbene complexes to afford furans that contain pendant alkene groups is described. Subsequent intramolecular Diels-Alder reactions are effective in select cases, resulting in hydronaphthalene systems after dehydration. Although the Diels-Alder event is thermodynamically unfavorable, the overall transformation of alkene-furans to dihydronaphthalenes is a favorable process.

Introduction

Recently, a novel synthesis of hydrophenanthrenes (*e.g.* **5**, Scheme 1) involving the coupling of 2-alkynylbenzoyl systems (*e.g.* **1**) with γ,δ -unsaturated Fischer carbene complexes (*e.g.* **2**) was reported.¹ This reaction proceeds through a series of tandem events that eventually lead to the formation of an isobenzofuran ring system containing a pendant alkene group (**3**), which undergoes intramolecular Diels-Alder reaction and oxanorbornene ring opening to afford the observed product **5**. In this manuscript, attempts to effect an analogous process using simple furans (*e.g.* **7a**) generated from non-aromatic enyne carbonyl compounds (*e.g.* **6a**) is reported.² The net conversion represents construction of two new ring systems in a single reaction event. This latter process is considerably more challenging than generation of oxanorbornene **4** from isobenzofuran **3** since the Diels-Alder step involves furans and not isobenzofurans. Examples of successful intramolecular Diels-Alder reactions have been reported for simple furans,³ however they appear to be less reliable relative to analogous reactions involving isobenzofurans. Most of the high-yielding reactions involve activated systems such as electron-deficient alkenes,⁴ allenes,⁵ or a favorable gem dialkyl effect.⁶ Six-membered ring forming intramolecular furan Diels-Alder reactions involving unactivated alkenes are often low-yielding,⁷ although several high-yielding processes have been reported.⁸ The net transformation is a unique construction of a hydronaphthalene⁹ from two five-carbon pieces where both components contribute at least one carbon to both of the newly-formed rings.

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Results and Discussion

Enyne-carbonyl compounds were readily prepared using the synthetic routes depicted in Scheme 2. Haloformylation of either cyclohexanone or cyclopentenone¹⁰ to afford the β -bromoaldehyde derivative **10**, followed by Sonogashira coupling afforded the enyne-aldehyde derivative **6**. Subsequent desilylation and/or synthetic manipulation of the aldehyde carbonyl group led to additional enyne-carbonyl systems.

In the initial studies, the carbene alkyne coupling reactions were conducted in dioxane. As noted in Scheme 3, there is NO reason for optimism concerning the Diels-Alder reactions of **7b-i**. The carbene coupling reaction provides the vinylfuran derivatives **7b-i**, which do not undergo Diels-Alder reactions in any of the systems depicted. Extended heating at reflux results in a slow decomposition process. Heating at higher temperatures also results in decomposition. Hydrolysis affords a more robust compound, furan-ketones **13a-i** that is also thermally inert with respect to the Diels-Alder reaction.

The reaction depicted in Scheme 4 is the only evidence of possible successful execution of the original objective. In this reaction, a low yield of a secondary cyclization product, hexahydrophenanthrene **14a**, was observed. Compound **14a** hypothetically results from dehydration of Diels-Alder adduct **8a**, which was not observed under these conditions. Two of the examples in Scheme 3 bear remarkable similarity to this system, the five-membered analog **7b** and the hydrolysis product **13b**, yet no Diels-Alder derived products were observed in these relatively similar systems. Greater focus was thus placed on **7a** since it is only system where there is any remote glimmer of success.

Computational evaluation (DFT-B3LYP, 6-31G*) of selected Diels-Alder reactions reveal that all of these reactions will be difficult (see Scheme 5). Although most of the simple intramolecular Diels-Alder events are exothermic, all are very slightly endergonic when entropic considerations are taken into consideration. Even though the cyclohexane-fused system **7a** was the only system where there is any hint of the Diels-Alder event, there is very little energetic difference in the five- and six-membered ring systems (**7a,b**). Hydrolysis of enol ether **7d** to the ketone **13d** results in a less favorable intramolecular Diels-Alder reaction. Successful Diels-Alder reaction in the five-membered ring alkene-tethered system (conversion of **13g** to **15g**) is very highly unlikely. The tandem Diels-Alder reaction and dehydration process (conversion of **7a** to **14a** and water) is however highly exothermic and exergonic.

The calculations suggest that successful cyclization might be achieved if the Diels-Alder reaction is coupled with the dehydration step. Tandem Diels-Alder reaction followed by oxanorbornene ring opening and/or aromatization is a feature in many examples of the highly successful amidofuran-based intramolecular Diels-Alder reactions.¹¹ A likely mechanism for the dehydration step is depicted in Scheme 6, and involves ionization of the C-O bond as a key step. Optimization of this process would ideally involve a high boiling and highly polar solvent, thus DMF was employed for the Diels-Alder reaction. Complete conversion of the furan to the desilylated hydrophenanthrene derivative **18a** occurred upon heating the compound to reflux in DMF. The ideal condition for this process involves performing the carbene-alkyne coupling in dioxane at 85 °C followed by replacing the dioxane with DMF and heating to 145 °C for 10 h, which affords the hydrophenanthrene **18a** in 60% yield¹² accompanied by a trace of the aromatized compound **19a**. Since the thermodynamics for Diels-Alder reaction of five-membered ring analog **7b** are basically identical, this analog was subjected to similar reaction conditions. This process resulted in the five-membered ring fused adduct **18b**, also accompanied by a trace of aromatized compound **19b**.¹³

In summary, we have demonstrated that the net [5+5]-cycloaddition of 2-alkynylbenzaldehydes and γ,δ -unsaturated carbene complexes can be extended to non-aromatic enyne-aldehyde systems. The simple Diels-Alder step of the tandem reaction was unsuccessful, however can be conducted if conditions favoring a Diels-Alder dehydration sequence were employed, resulting in the direct formation of dihydronaphthalene derivatives.

Acknowledgments

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References

1. For the most recent example, see: Menon S, Sinha-Mahapatra D, Herndon JW. *Tetrahedron*. 2007; 63:8788–8793. [PubMed: 18769535]
2. Herndon JW, Wang H. *J Org Chem*. 1998; 63:4564–4565.
3. a Keay BA, Hunt IR. *Adv Cycloadd*. 1999; 6:173–210. b Kappe CO, Murphree SS, Padwa A. *Tetrahedron*. 1997; 53:14179–14233. c Ciganek E. *Org React*. 1984; 32:1–374.
4. For representative examples: a Claeys S, Van Haver D, De Clercq PJ, Milanesio M, Viterbo D. *Eur J Org Chem*. 2002:1051–1062. b Dorr H, Rawal VH. *J Am Chem Soc*. 1999; 121:10229–10230. c Woo S, Keay BA. *Synlett*. 1996:135–137. d Woo S, Keay BA. *Tetrahedron: Asymmetry*. 1994; 5:1411–1414. e Padwa A, Lynch SM, Mejía-Oneto JM, Zhang H. *J Org Chem*. 2005; 70:2206–2218. [PubMed: 15760207]
5. For representative examples, see: a Jung ME, Min SJ. *J Am Chem Soc*. 2005; 127:10834–10835. [PubMed: 16076181] b Wu HJ, Yen CH, Chuang CT. *J Org Chem*. 1998; 63:5064–5070.
6. a Jung ME, Gervay J. *J Am Chem Soc*. 1991; 113:224–232. b Fischer K, Huenig S. *J Org Chem*. 1987; 52:564–569.
7. a Dadwal M, Kesharwani MK, Danayak V, Ganguly B, Mobin SM, Muruganantham R, Namboothiri INN. *Eur J Org Chem*. 2008:6106–6118. b Namboothiri INN, Ganesh M, Mobin SM, Cojocaru M. *J Org Chem*. 2005; 70:2235–2243. [PubMed: 15760210]
8. For examples, see: a Klein LL. *J Org Chem*. 1985; 50:1770–1773. b Padwa A, Ginn JD, Eidell CK, Lynch SM. *J Org Chem*. 2002; 67:3412–3424. [PubMed: 12003554] c Wang Q, Padwa A. *Org Lett*. 2004; 6:2189–2192. [PubMed: 15200317]
9. For a review of naphthalene and hydronaphthalene syntheses, see: de Koning CB, Rousseau RR, van Otterlo WAL. *Tetrahedron*. 2003; 59:7–36.
10. Brahma S, Ray JK. *Tetrahedron*. 2008; 64:2883–2896.
11. a Padwa A, Dimitroff M, Waterson AG, Wu T. *J Org Chem*. 1998; 63:3986–3997. b Padwa A, Ginn JD. *J Org Chem*. 2005; 70:5197–5206. [PubMed: 15960524]
12. Spectral data for **18a**: ^1H NMR (CDCl_3): δ 6.86 (d, 1H, $J = 7.2$ Hz), 6.75 (d, 1H, $J = 7.2$ Hz), 5.63 (s, 1H), 3.72 (s, 3H) 2.83 (t, 2H, $J = 7.5$ Hz), 2.73 (t, 2H, $J = 5.8$ Hz), 2.68 (t, 2H, $J = 5.8$ Hz), 2.35 (t, 2H, $J = 7.5$ Hz), 1.90–1.70 (m, 4H); ^{13}C NMR: δ 160.7 (C), 135.4 (C), 133.2 (C), 130.4 (C), 129.4 (C), 125.2 (CH), 124.3 (CH), 92.6 (CH), 54.7 (CH_3), 30.1 (CH_2), 29.0 (CH_2), 27.4 (CH_2), 26.3 (CH_2), 23.5 (CH_2), 22.8 (CH_2); IR (neat): 1660 (s) cm^{-1} ; HRMS (ESI): Calcd for $\text{C}_{15}\text{H}_{19}\text{O}$ (MH) $^+$ 215.1436, found 215.1431.
13. Preparation of **18b**: To a solution of enyne aldehyde **6b** (0.200 g, 1.00 mmol) in dioxane (20 mL) under nitrogen atmosphere at 85°C added drop wise a solution of carbene **2** (0.392 g, 1.35 mmol) in dioxane (5 mL) over a 5min period. The mixture was stirred 10 h at 85°C and then cooled to room temperature and filtered through Celite. The solvent was removed on a rotary evaporator. The oil obtained was dissolved in dimethylformamide (15 mL) and heated to 145°C for 7 h and the cooled to room temperature. Hexane (20 mL) was added and the mixture was washed two times with water. After removal of the hexane on a rotary evaporator, final purification was achieved using flash chromatography using 19:1 hexane:ethyl acetate as eluent. A colorless oil identified as compound **18b** (0.128 g, 64% yield) was obtained. ^1H NMR (CDCl_3): δ 6.90 (s, 2H), 5.53 (s, 1H), 3.74 (s, 3H), 2.93–2.83 (m, 6H), 2.41 (t, 2H, $J = 6.5$ Hz), 2.09 (quintet, 2H, $J = 7.0$ Hz); ^{13}C NMR

(CDCl₃): δ 160.6, 142.3, 138.4, 131.0, 129.5, 125.0, 119.9, 93.5, 54.8, 32.9, 30.7, 28.5, 27.6, 25.1;
HRMS (ESI): calcd for C₁₄H₁₇O (MH)⁺ 201.1274, found 201.1278.

Scheme 1.

Scheme 2.

6, 7, 13 ($R^1 = H$ in **13** if $R^1 = TMS$ in **7**)

a $R^1 = TMS$, $R^{2,3} = -(CH_2)_4-$, $R^4 = H$, $R^5 = -(CH_2)_2CH=CH_2$, $R^6 = H$ (**6a** + **2**)

b $R^1 = TMS$, $R^{2,3} = -(CH_2)_3-$, $R^4 = H$, $R^5 = -(CH_2)_2CH=CH_2$, $R^6 = H$ (**6b** + **2**)

c $R^1 = H$, $R^{2,3} = -(CH_2)_4-$, $R^4 = H$, $R^5 = -(CH_2)_2CH=CH_2$, $R^6 = H$ (**6c** + **2**)

d $R^1 = H$, $R^{2,3} = -(CH_2)_3-$, $R^4 = H$, $R^5 = -(CH_2)_2CH=CH_2$, $R^6 = H$ (**6d** + **2**)

e $R^1 = n-Bu$, $R^{2,3} = -(CH_2)_3-$, $R^4 = H$, $R^5 = -(CH_2)_2CH=CH_2$, $R^6 = H$ (**6e** + **2**)

f $R^1 = TMS$, $R^{2,3} = -(CH_2)_3-$, $R^4 = -(CH_2)_3CH=CH_2$, $R^{5,6} = H$ (**6f** + **12**)

g $R^1 = H$, $R^{2,3} = -(CH_2)_3-$, $R^4 = -(CH_2)_3CH=CH_2$, $R^{5,6} = H$ (**6g** + **12**)

h $R^1 = TMS$, $R^{2,3} = -(CH_2)_4-$, $R^4 = H$, $R^5 = -(CH_2)_2CH=CH_2$,

$R^6 = n-Pr$ (**6a** + **11**)

i $R^1 = H$, $R^{2,3} = -(CH_2)_4-$, $R^4 = H$, $R^5 = -(CH_2)_2CH=CH_2$, $R^6 = n-Pr$ (**6c** + **11**)

Scheme 3.

Scheme 4.

Scheme 5.

Scheme 6.