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

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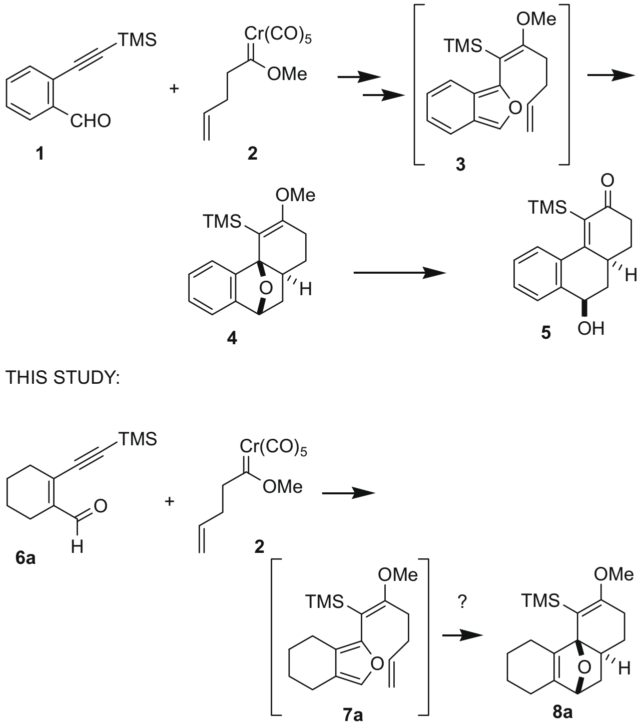
A B S T R A C T

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 selected 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.

1. 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 Letter, 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] and 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 hydronaphthalene[9] from two five-carbon pieces where both components contribute at least one carbon to both of the newly formed rings.



Scheme 1.

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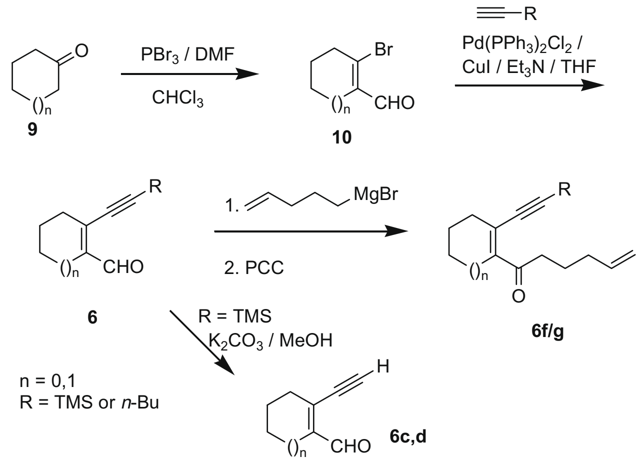
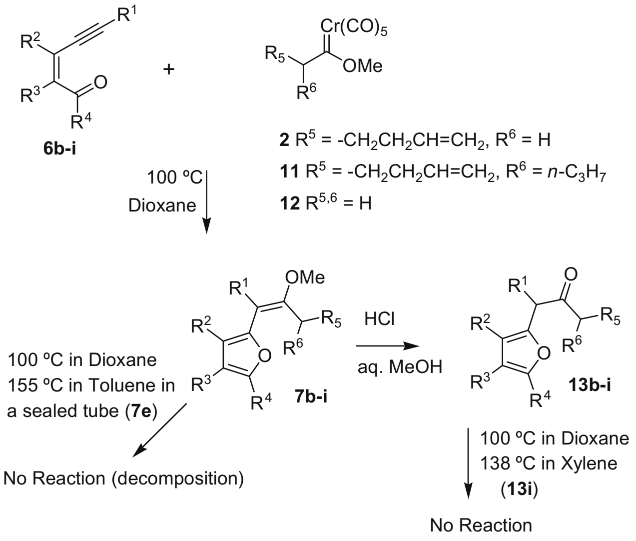


Scheme 2.

2. Results and discussion

Enyne-carbonyl compounds were readily prepared using the synthetic routes depicted in Scheme 2. Haloformylation of either cyclohexanone or cyclopentenone[10] to afford the β-bromoenal 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.



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**)

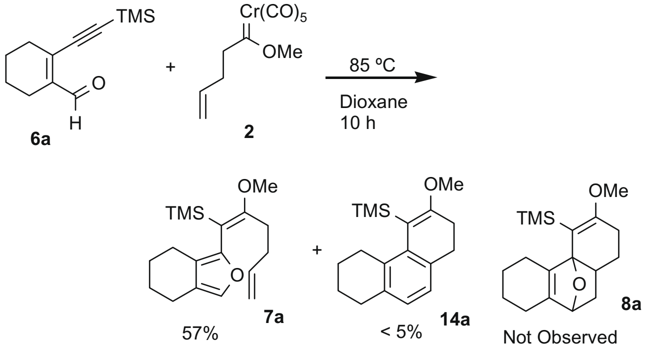
Scheme 3.

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.

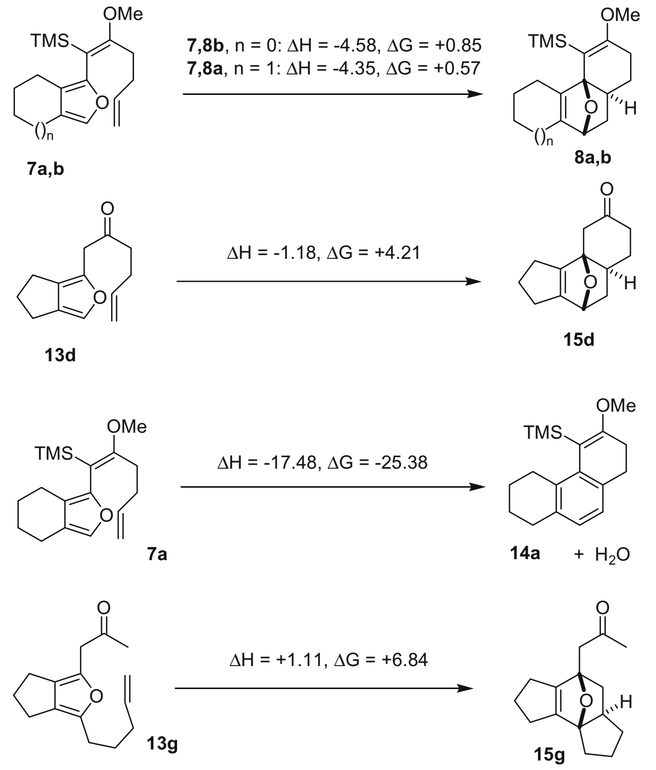
The reaction depicted in Scheme 4 is the only evidence of possible successful execution of the original objective. In this reaction, a low yield of a secondary cyclization product, hexahydrophenanthrene **14a**, was observed. Compound **14a** hypothetically results from dehydration of Diels–Alder adduct **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 the 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.

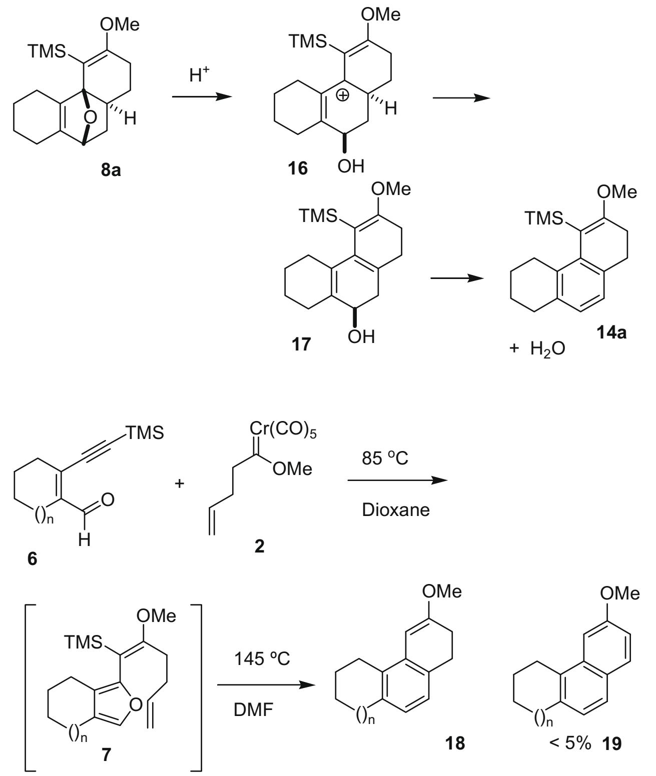
The calculations suggest that successful cyclization might be achieved if the Diels–Alder reaction is coupled with the dehydration step. Tandem Diels–Alder reaction followed by oxanorbornene ring opening and/or aromatization is a feature in many examples of the highly successful amidofuran-based intramolecular 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



Scheme 4.



Scheme 5.



n	yield **18**
1 (a series)	60%
0 (b series)	64%

Scheme 6.

145 °C for 10 h, which affords the hydrophenanthrene **18a** in 60% yield[12] 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.

Acknowledgment

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12. *Spectral data for* **18a**: ^{1}H NMR ($\mathrm{CDCl_3}$): 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 ($\mathrm{CH_3}$), 30.1 ($\mathrm{CH_2}$), 29.0 ($\mathrm{CH_2}$), 27.4 ($\mathrm{CH_2}$), 26.3 ($\mathrm{CH_2}$), 23.5 ($\mathrm{CH_2}$), 22.8 ($\mathrm{CH_2}$); IR (neat): 1660 (s) cm^{-1}; HRMS (ESI): Calcd for $\mathrm{C_{15}H_{19}O}$ $(\mathrm{MH})^+$ 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 dropwise a solution of carbene **2** (0.392 g, 1.35 mmol) in dioxane (5 mL) over a 5-min period. The mixture was stirred for 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 then 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. ^{1}H NMR ($\mathrm{CDCl_3}$): 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 ($\mathrm{CDCl_3}$): 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 $\mathrm{C_{14}H_{17}O}$ $(\mathrm{MH})^+$ 201.1274, found 201.1278.