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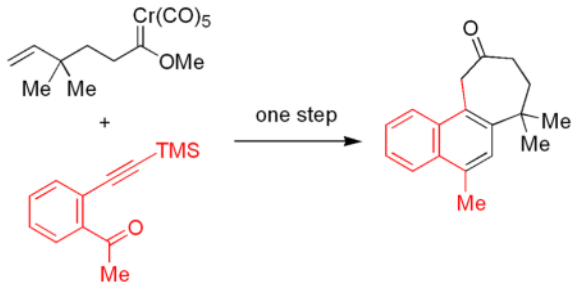
Synthesis of benzocycloheptanones through coupling of δ,ε-unsaturated chromium carbene complexes and 2-alkynylbenzoyl derivatives

Rajesh Kumar Patti, **Kristopher V. Waynant**, and **James W. Herndon***
Department of Chemistry and Biochemistry, New Mexico State University, MSC 3C, Las Cruces, New Mexico 88003, USA

Abstract



The coupling of pentenylcarbene complexes and 2-alkynylbenzoyl derivatives affords naphthocycloheptanones in a single step involving simultaneous construction of both the seven–membered ring and one of the aromatic rings. Aryl tethered systems undergo intramolecular cyclopropanation.

The hydrophenanthrene carbon skeleton (*i.e.* **E** and **F**, Scheme 1) is readily accessed through coupling of 2-alkynylbenzaldehyde derivatives (**A**) and γ,δ-unsaturated chromium carbene complexes (**B**, n= 1).[1] This net [5+5]-cycloaddition approach to hydrophenanthrenes results from a series of reactions involving (1) regio-and stereoselective carbene-alkyne coupling,[2] (2) carbonyl ylide formation,[3] (3) isobenzofuran **C** formation,[4] and (5) intramolecular Diels-Alder reaction. Subsequent transformations of the strained and electronically activated oxanorbornenes **D** leads to the observed products, dihydrophenanthrenes[1] **F** (via dehydration and hydrolysis) or hydrophenanthrenones[5] **E** (via ring opening and hydrolysis). Intramolecular Diels-Alder reactions of isobenzofurans and unactivated alkenes are limited by the instability of isobenzofurans, and nearly all of the examples involve the formation of five- and/or six-membered ring systems.[6] Higher yields and a greater substrate range are generally observed with chromiumgenerated systems compared to acid-generated systems,[7] however even in the chromium-based systems primarily six-membered ring formation has been documented.[8] This manuscript focuses on the formation of seven-membered rings employing this reaction. Furan and/or isobenzofuran Diels-Alder reactions that result in seven-membered and larger rings are comparatively rare.[9] Likely complications in this investigation include: (1) competing intramolecular cyclopropanation,[10] (2) competing

jherndon@nmsu.edu.

Supporting Information. Complete experimental procedures and photocopies of ^{1}H and ^{13}C NMR spectra for compounds **1**, **2**, **7**, **10**, **11**, **12b**.

alkene migration,[11] and (3) a slower intramolecular Diels-Alder event, thus allowing for competing isobenzofuran decomposition.

The coupling of δ,ε-unsaturated carbene complexes (**B**, n = 2) and alkynylbenzaldehydes would hypothetically lead to seven-membered rings fused to a naphthalene ring system (**F**, n = 2). Benzo-fused cycloheptanones and their simple derivatives are a very important structural feature in numerous medicinal compounds, including the anti-HIV drug TAK-779,[12] intermediates for colchicine synthesis,[13] numerous experimental anticancer drugs,[14] and treatments for neurodegenerative disorders.[15] The title reaction is a two component coupling where a diverse array of synthetic routes exists for both of the coupling partners. The basic coupling process is an intermolecular coupling requiring no pre-organization of the reactants and thus is inherently versatile compared to any process limited to intramolecular systems. In this manuscript, the use of this reaction for the preparation of the more challenging seven-membered ring systems is investigated.

Alkene-containing carbene complexes (**1** and **2**, Scheme 2) were synthesized from known or commercially-available compounds according to the Fischer synthetic routes depicted in Scheme 2. The organolithium reagents were generated through reaction of the bromides with lithium metal wherever possible due to safety concerns. In more sluggish cases, lithiation of the iodide with *t*-butyllithium was employed. Competing Bailey cyclization of the organolithium intermediates[16] was not a problem under the conditions employed. The aryl-tethered carbene complexes were prepared from 2-bromobenzyl bromide through halogen-metal exchange followed by analogous conversion to the carbene complex. Compound **2a** was a very unstable compound and had to be used immediately after its synthesis.

The first reaction examined was the coupling of alkynylbenzophenone derivative **5a** (Scheme 3) with carbene complex **1a**. The benzophenone derivative **5a** had proven to be the most reliable substrate in related [5+5]-cycloaddition processes[17] owing to the enhanced stability of arylisobenzofuran intermediates. After treatment of the crude reaction mixture with aqueous HCl, the naphthalene derivative **7a** was isolated in 77% yield. The more challenging reaction, coupling of complex **1a** alkynylbenzaldehyde derivative **5b**, was examined under a variety of conditions. Thermolysis in dioxane followed by treatment with acid led to naphthocycloheptanone **7b** in 73% yield. As noted in previous manuscripts, addition of water[17] or collidine[1] to [5+5]-cycloaddition reactions often led to improved yields of adducts. Addition of either of these additives led to uncyclized compounds tentatively assigned as alkylidenephthalans (**8b**/**9b**), which result from a net 1,7-hydride shift of the vinylisobenzofuran intermediate[7] and were often produced when a carbene complex incapable of the Diels-Alder step was employed.[18] In related six-membered ring-forming processes, competition from this reaction pathway was seldom an issue. A likely explanation for these results is that the seven-membered ring process is slower than the previously-reported six-membered ring-forming process, and the 1,7-hydrogen shift is the preferred fate of the isobenzofuran intermediate. Unfortunately, all attempts to isolate a single derivative of **6b** prior to HCl treatment were unsuccessful. This might be attributed to a lack of endo-exo selectivity in the Diels-Alder reaction using the longer-tethered system, or could be due to a mixture of ketones and enol ethers, and their respective protiodesilylation products prior to the hydrolysis step.

Several different examples are presented in Table 1, which vary in composition of the carbene complex tether, the alkyne substituent, the benzene ring substituents, and the carbonyl group. As noted in Table 1, the reaction in dioxane is unaffected by all of these variables. Silylated alkynes and alkyl-aryl alkynes all produce the naphthocycloheptanone in similar yield, however the yields were slightly lower using a terminal alkyne (entry 4). The simple benzene ring substrates and the one substrate featuring a highly electron-rich

aromatic ring (entry 7) work equally effectively. The yields for the carbene complex featuring a gem-dimethyl group in the tether (entries 3, 4, and 8) are equal to that for the carbene complex featuring the unsubstituted tether. It appears as though any steric disadvantage has been offset by a favorable gem dialkyl effect. Use of the propargylic ester **5e** (entry 6) led to the elimination product, methylenecycloheptanone **10**. A single example afforded the enone-alcohol derivative **11** (entry 5), which only afforded the naphthalene derivative **7e** with more vigorous HCl treatment. In compound **11**, the hydrogen noted as H_A appears as a doublet of doublets (if D_2O was added to the chloroform NMR) with coupling constants of 12.0 and 3.7 Hz, which suggests that it is in an axial orientation. The indicated stereochemistry is consistent with complete exo selectivity in the intramolecular Diels-Alder step, even in the longer tethered systems employed in these studies.[19]

All attempts to make an eight-membered ring using this methodology failed. Reaction of the hexenylcarbene complex **1c** with either of the substrates **5a** or **5b** resulted in products where no Diels-Alder reaction occurred. The crude ^{1}H NMR spectra exhibited substantial absorptions and δ 5.9 and δ 5.0, which is indicative of a monosubstituted alkene group. The reactions employing the arylcarbene complexes **2a** and **2b** did not result in alkyne-coupled products. Thermolysis of either of carbene complexes with alkyne **5b** led to the simple tetralone derivatives **13** (Scheme 4) after HCl treatment. The yields and product distributions are identical, regardless of whether the alkyne is present. A likely mechanism for the formation of these compounds involves intramolecular cyclopropanation[10b] followed by acid-catalyzed ring opening of the alkoxycyclopropane derivatives.[20] In one case the cyclopropane **12b** was isolated and leads to α-methyltetralone (**13b**) upon exposure to acid.

In summary, we have presented a versatile two-component coupling approach to form naphthalene-fused cycloheptanones in a net [5+6]-cycloaddition process, where both the seven-membered ring and one of the benzene rings are constructed in a single reaction event. The reaction proceeds in good yields for all systems examined employing sp^3 carbons in the tether however aryl-containing tethers undergo rapid intramolecular cyclopropanation in preference to any intermolecular coupling with alkyne groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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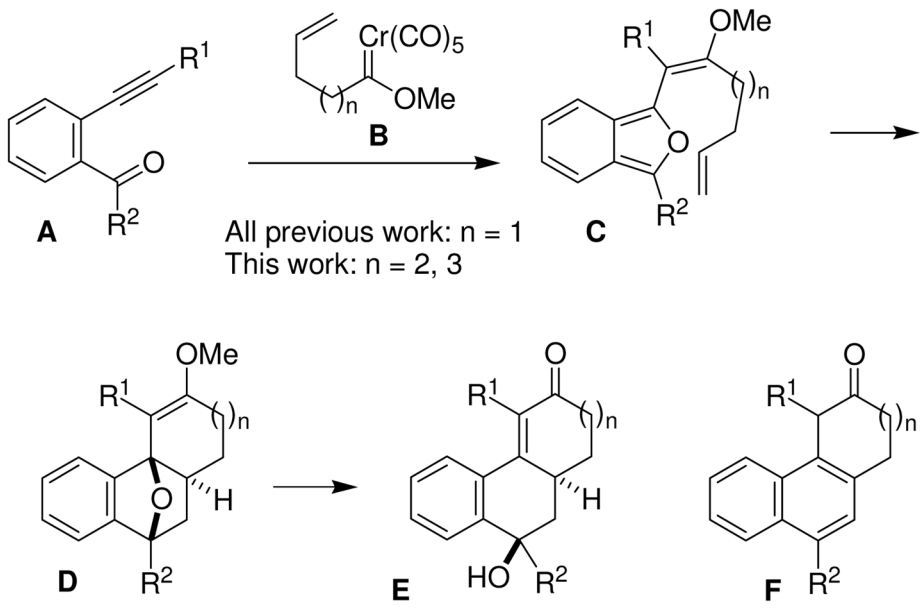
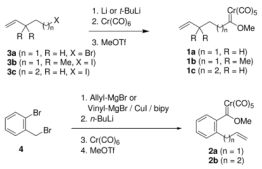
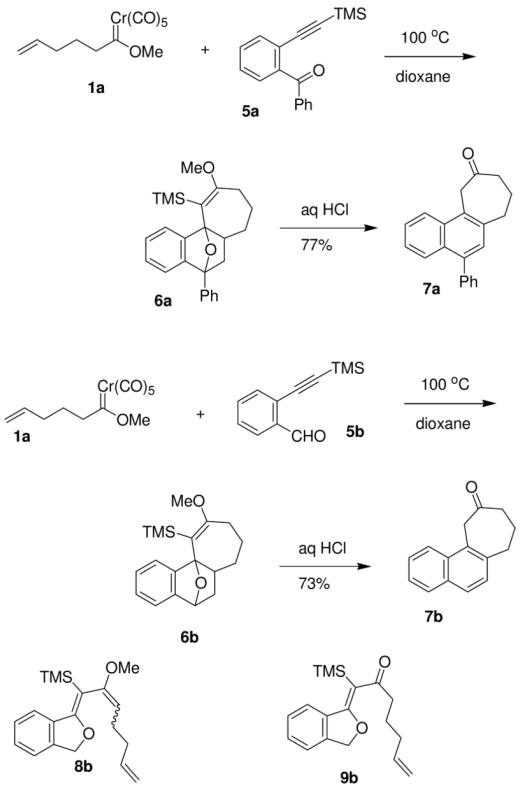


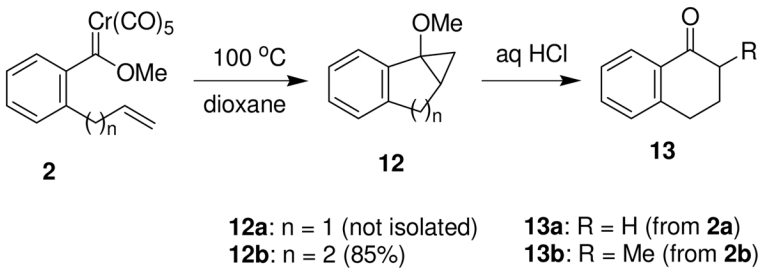
Scheme 1.



Scheme 2.



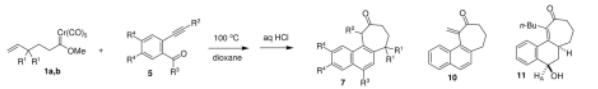
Scheme 3.



Scheme 4.

Table 1

Preparation of naphthocycloheptanones through couplling of δ,ε-unsaturated carbene complexes and 2-alkynylbenzoyl systems.



entry	reactants	R^1	R^2	R^3	R^4	product	yield %
1	**1a** + **5a**	H	TMS[a]	Ph	H	**7a**	77
2	**1a** + **5b**	H	TMS[a]	H	H	**7b**	73
3	**1b** + **5b**	Me	TMS[a]	H	H	**7c**	75
4	**1b** + **5c**	Me	H	H	H	**7c**	62
5[b]	**1a** + **5d**	H	*n*-Bu	H	H	**11**	78
6[c]	**1a** + **5e**	H	CH_2OAc	H	H	**10**	74
7	**1a** + **5f**	H	TMS[a]	H	OMe	**7g**	76
8	**1b** + **5g**	Me	TMS[a]	Me	H	**7h**	80

[a] R^2 = H in **7** when R^2 = TMS in **5**.

[b] The exclusive product was the alcohol derivative **11**.

[c] The exclusive product was elimination product **10**.