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Preparation of phenalenes and hydronaphthacenes through tandem alkyne Fischer–carbene complex coupling and inter- or intra-molecular Diels–Alder reactions

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ABSTRACT

The rapid construction of phenalenes through the reaction of 8-alkynyltetralones with Fischer–carbene complexes followed by either an inter- or intra-molecular Diels–Alder reaction is presented. As a showcase of the synthetic utility of this process, the rapid construction of polycyclic ring systems containing the tetracycline core has been demonstrated through an iterative application of this reaction sequence.

1. Introduction

The phenalene ring system comprises the core of several natural products, including the pseudopterosins and helioporins, compounds which possess antiinflammatory[1] and antitumor[2] activities. Non-natural phenalenes have been evaluated as dopamine receptors.[3] Higher annulated aromatic species (e.g., pyrenes and benzo analogs) form the core structures of several antibiotics[4] and of various fluorophores are useful as biological probes.[5] Phenalenes are substructures of benzo[*a*]pyrene, which is one of the most persistent environmental carcinogens and synthetic benzo[*a*]-pyrene derivatives are frequently required to assess mechanisms of carcinogenesis.[6] The phenalene ring system is most commonly accessed through intramolecular electrophilic aromatic substitution reactions[7] and occasionally through Diels–Alder processes.[8] The phenalene ring system is potentially accessible in a single reaction event through a recently-discovered sequence involving tandem carbene complex alkyne coupling[9] / isobenzofuran formation[10] / and Diels–Alder reaction (Scheme 1).[11] Operationally this is a very simple process involving only thermolysis and avoids a multi-step series of reactions required to perform similar transformations without chromium.[12] Formation of phenalenes requires the use of alkynylbenzenes fused to cyclic ketones (**A**), which are likely ideal substrates for isobenzofuran formation since the carbonyl group is locked in the orientation required for the key C–O bond formation step. In this manuscript the synthesis of 8-alkynyl-2-tetralone derivatives and their subsequent reaction with Fischer–carbene complexes is presented. An iterative version of this process leads to compounds possessing the hydronaphthacene skeleton, a ring system that is potentially useful in the development of organic semiconductors.[13]

2. Results and discussion

The preparation of the *o*-alkynylbenzocycloalkanones (**1**, **3**, **5**) used in this study from commercially-available starting materials is depicted in Scheme 2. Alkynyltetralone **1** was prepared from 1-amino-5,6,7,8-tetrahydronaphthalene via the known transformation to 8-bromo-1-tetralone[14] followed by Sonogashira coupling. This method, though lengthy, is superior to the alternative preparation of 8-bromo-1-tetralone from α-tetralol,[15] since the *ortho*-metallation process would never go to completion and separation of tetralol and bromotetralol was quite difficult. The five-membered ring analog **3** was prepared from 2-bromobenzoyl chloride using Nazarov cyclization as a key step.[14] The bis(alkyne) derivative **5** was synthesized from 1,3-dibromobenzene through regioselective lithiation,[16] followed by formylation and double Sonogashira coupling.

Initial studies focused on the systems depicted in Scheme 3, involving the three-component coupling of alkynyltetralone **1**, methylcarbene complex **7**, and either dimethyl acetylenedicarboxylate (DMAD) (**9**) or dimethyl fumarate. A complex reaction

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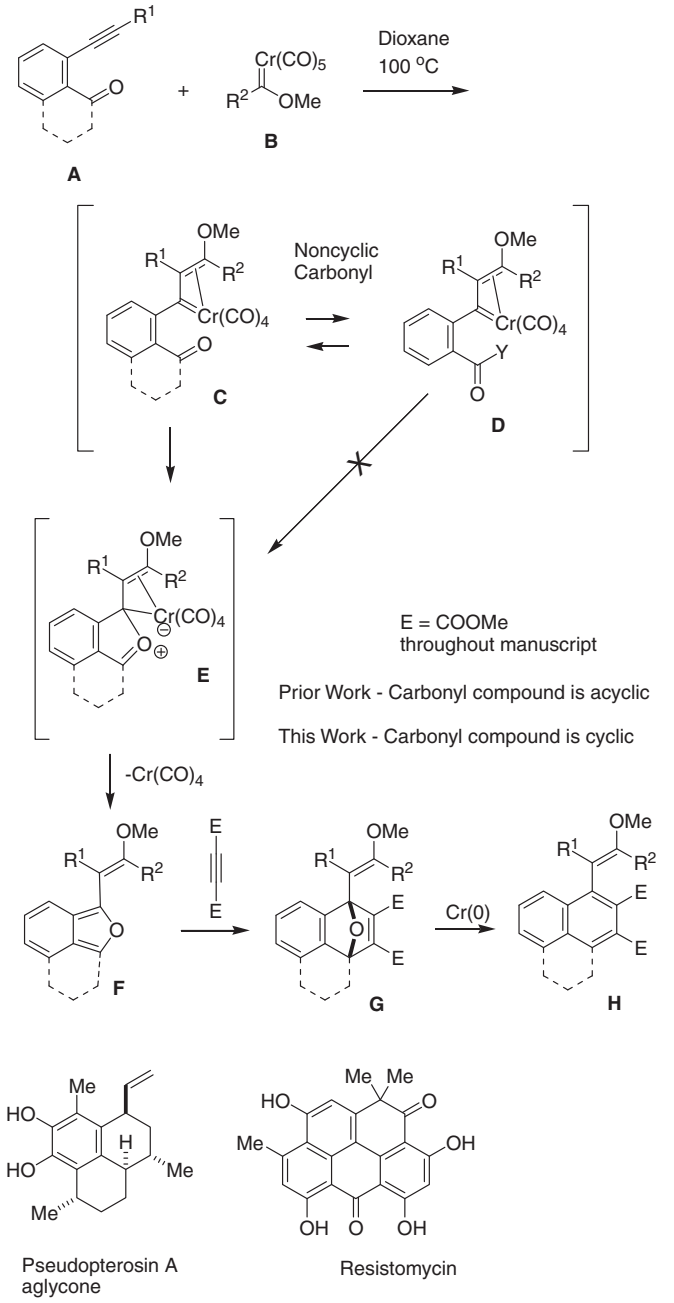
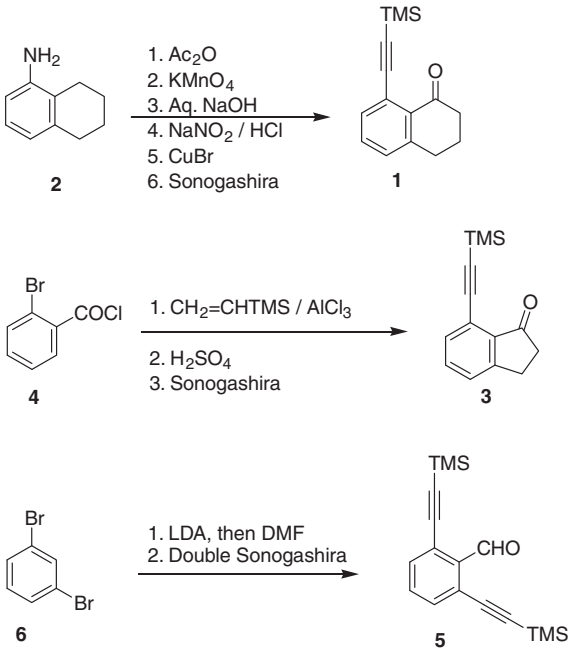


Scheme 1.

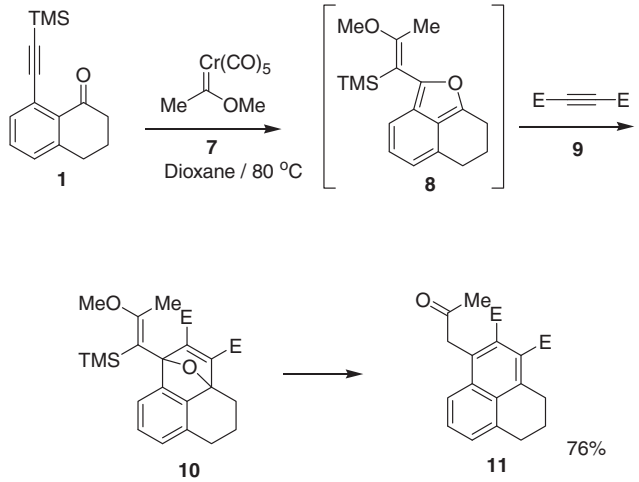
mixture resulted when all three components were present at the onset of the reaction, presumably due to multiple components present in solution that are reactive to carbene complexes.[17] If a sequential addition involving (1) reaction of the carbene complex and alkyne at 100 °C for 1 h and (2) addition of DMAD was employed, a surprisingly excellent yield of phenalene-containing product **11** was observed after silica gel purification. Initially, an efficient process was not anticipated under these conditions since isobenzofurans bearing α-hydrogens are unstable with respect to conversion to alkylidenephthalans,[18] and success thus requires this critical intermediate to survive intact for more than 1 h at 100 °C. Aromatized products analogous to naphthalene **11** have been obtained directly using *N,N*-dimethylhydrazones,[19] however the yield of **11** was lower using the *N,N*-dimethylhydrazone of ketone **1**. A problem with this alternate strategy is that hydrazone formation



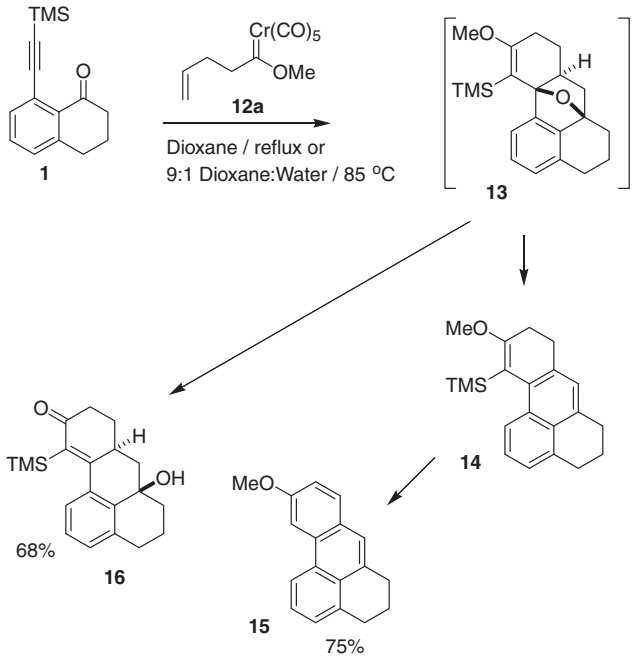
Scheme 2.

from **1** would never go to completion, and the reaction was initiated using a 2:3 mixture of the ketone and hydrazone as the starting material.

Ketone **1** was also tested as a substrate for the net [5+5]-cycloaddition process employing the butenylcarbene complex **12a** (see Scheme 4). In this case the reaction was highly efficient leading to the tetracycle **15**. The anticipated product is simple dehydration product **14**,[11] which undergoes an unanticipated oxidation under the reaction conditions. Interestingly, the product containing the phenanthrene ring was obtained when the reaction was conducted in anhydrous dioxane, however, high yields of alcohol **16** were obtained when the reaction was conducted in dioxane/water mixtures.[20] This latter process was completely diastereoselective. The stereochemistry of compound **16** was assigned based on the known exo preference for intramolecular six-membered ring-forming reactions involving isobenzofurans,[21] which would afford the depicted stereoisomer after the ring opening.

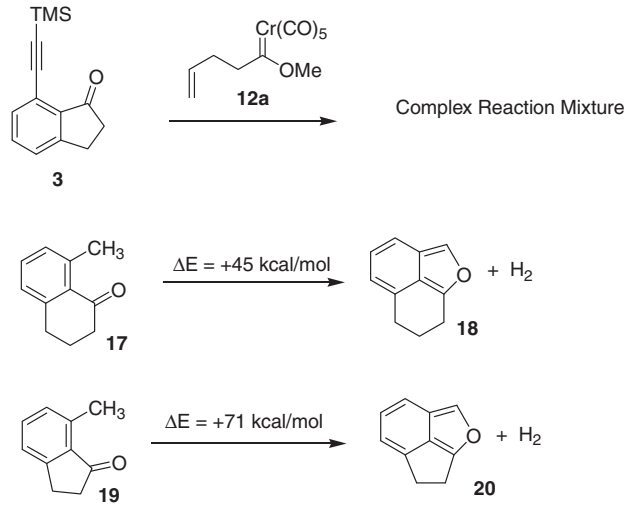


Scheme 3.

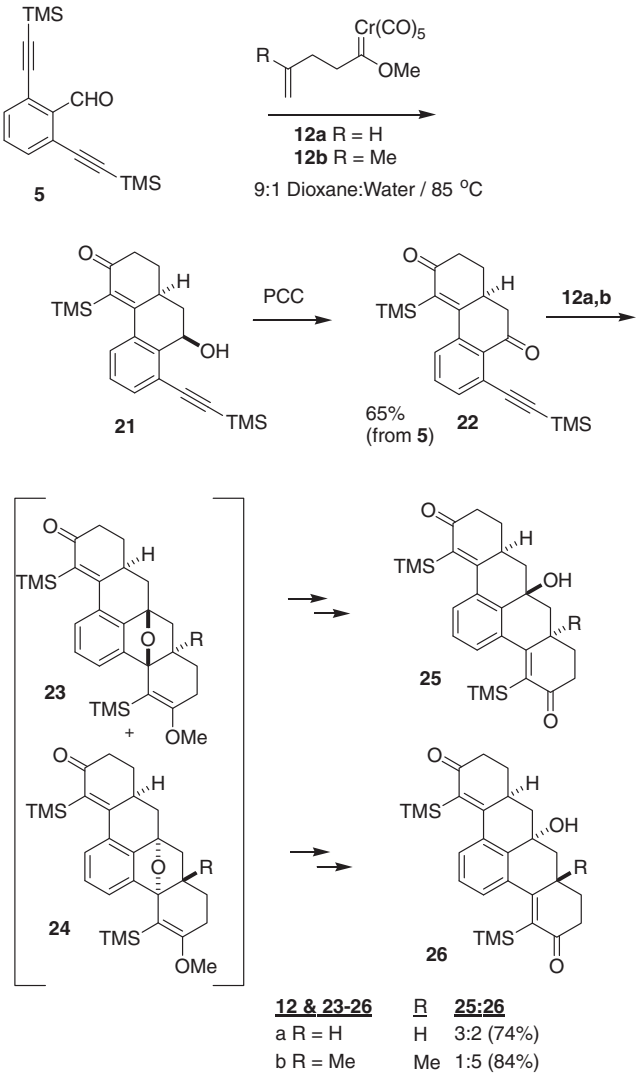


Scheme 4.

Unfortunately, reactions involving the related five-membered ring systems were unsuccessful (Scheme 5). Coupling of alkynylindanone **3** and carbene complex **12a** afforded a complex reaction mixture where the pattern for a monosubstituted alkene is a predominant feature of the crude ^{1}H NMR spectrum. This observation suggests a failure in the formation of the isobenzofuran intermediate,[20] which is likely due to ring strain.[22] An examination of the isodesmic reactions in Scheme 5 (based on DFT calculations employing the B3LYP method and 6-31G(d) basis sets) reveals that formation of the five-membered fused ring system **20** is unfavorable relative to the six-membered fused ring-fused system **18**. The energy for the isodesmic reaction is 26 kcal/mol greater in the five-membered ring case. A simple MM2 calculation revealed the angle strain in the five-membered fused ring system to be 34.1 kcal/mol while the strain in the six-membered ring case was considerably less at only 15.5 kcal/mol.



Scheme 5.



12 & 23-26	R	25:26
a R = H	H	3:2 (74%)
b R = Me	Me	1:5 (84%)

Scheme 6.

This novel [5+5]-cycloaddition reaction was also examined iteratively as a synthetic route to the hydronaphthacene ring system. The initial product (**21**, Scheme 6) of net [5+5]-cycloaddition employing bis(alkyne) derivative **5** and butenylcarbene complex **12a** is an incipient alkynyltetralone system, and thus the iterative [5+5]-cycloaddition can provide rapid access to this medicinally-important ring system. The crude product from cycloaddition of bis(alkyne) **5** and carbene complex **12a** was subjected to oxidation with PCC, affording alkyne-dione **22**, followed by an additional [5+5]-cycloaddition sequence. This reaction sequence resulted in a 3:2 mixture of diastereomers (out of four possible) favoring the symmetrical isomer **25a**. The stereoisomers arise through exo selective intramolecular Diels–Alder reaction, which proceeds with relative asymmetric induction from the only stereocenter present in **22** to afford either of intermediates **23** or **24**. The stereochemistry of the major isomer (**25a**) was assigned based on the appearance of only 13 signals in the ^{13}C NMR spectrum, compared with 21 signals in the unsymmetrical minor isomer (**26a**). This chromium(0-6-0)-based synthesis of the tetracyclines was also demonstrated for a system employing two different carbene complexes. Reaction of alkynone **22** with methylbutenylcarbene complex **12b** afforded a 5:1 mixture of diastereomers. The structure of the minor isomer was determined by X-ray crystallography and was determined to be stereoisomer **25b** (see Supplementary data).

The crystal consisted of two independent enantiomeric molecules where one molecule of the pair shows a disorder at the chiral centers and the other member of the pair is well-resolved. The reactions of alkyne-dione **22** with the γ,δ-unsaturated carbene complexes **12a** and **b** proceeded with the opposite stereoselectivity in the [5+5]-cycloaddition event. The carbene complex featuring a 1,1-disubstituted alkene group likely affords an alkene-isobenzofuran that undergoes a slower and more thermodynamically selective Diels–Alder reaction due to the more electron rich nature of the dienophile.

In summary, tandem isobenzofuran generation/Diels–Alder processes that employ 8-alkynyltetralone systems are quite efficient. In these systems one can employ ketones as substrates in sequential addition processes due to the enhanced lifetime of the isobenzofuran intermediate, despite the presence of hydrogens poised for rearrangement to alkylidenephthalans. Use of dialkylbenzaldehydes allows for a rapid gain in molecular complexity through an iterative process leading to selective formation of two out of the possible four diasteromers in the resulting complex hydronaphthacene ring systems in three reaction events.

3. Experimental

See Ref. 23.

Acknowledgments

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Supplementary data

Supplementary data (general experimental, X-ray parameters and ORTEP drawing for compound **25b**, photocopies of NMR spectra for new compounds employed in successful investigations, SCF energies for compounds in Scheme 5, and a cif file for the X-ray structure of **25b**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.006.

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