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# INTRAMOLECULAR CYCLIZATION OF ENYNE [3]CUMULENALS

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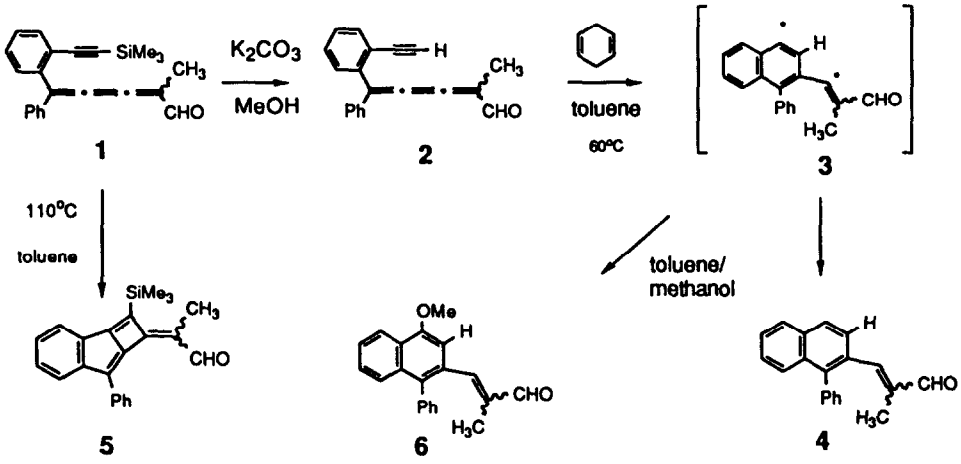
**Abstract:** Enyne [3]cumlenals have been shown to undergo a Bergman cyclization or an intramolecular [2+2] cycloaddition depending on the nature of substituents on the yne carbon. A hydrogen substituted [3]cumulenal is cleanly converted to a naphthalene product while a trimethylsilyl substituted substrate produces a cyclobutene product.

The cycloaromatization of the anti-tumor agent neocarzinostatin chromophore and analogs has been postulated to occur through a cyclic enyne[3]cumulene intermediate.[1] Surprisingly, there are only a few reports of enyne[3]cumulenes that have been studied as models for neocarzinostatin mode of aromatization.[2] Our interest in the design of cumulene based DNA cleaving agents has promted us to examine further these reactions.

We developed a simple methodology for the synthesis of stable diaryl [3]cumulenals based on the rearrangement and dehydration of epoxy-alcohols.[3] In this report, application of this reaction for the synthesis of cumulenal **1** and conversion to naphthalene **4** and cyclobut[a]indene **5** via intramolecular reactions is described.

## Scheme I

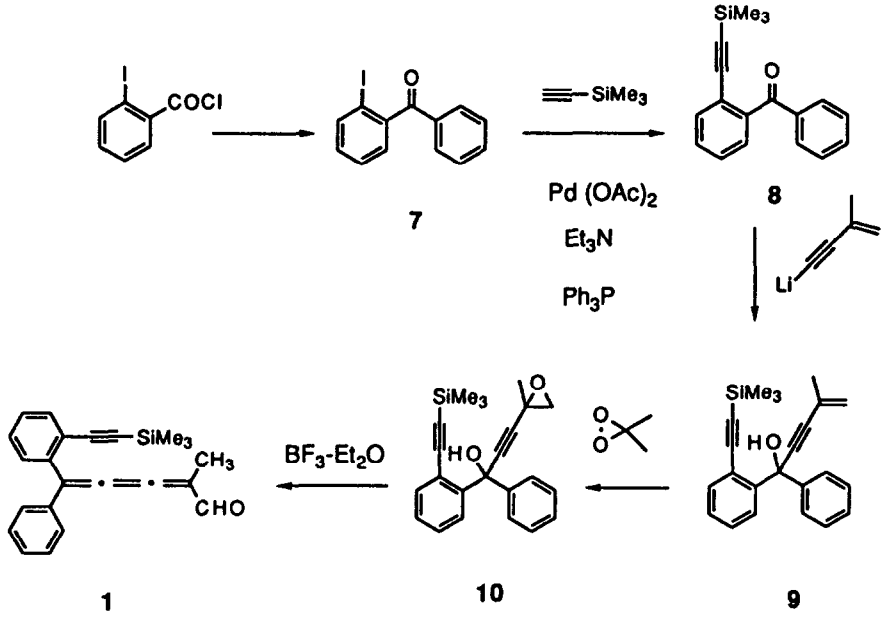



Cumulenal **1** was prepared following the sequence shown in scheme II. Commercially available 2'-iodobenzoyl chloride was converted to 2'-iodobenzophenone **7** in 95% yield by a Friedel-Crafts acylation. Heck coupling of **7** with trimethylsilyl acetylene gave ketone **8** (95%) which was then treated with the lithium anion of 2-methyl-3-buten-1-yne to render alkynol **9** in 85% yield. Epoxidation of **9** with dimethyldioxirane (63% yield)

followed by treatment with 1 equivalent of boron trifluoride etherate gave a 1:1 E:Z mixture of cumulenal **1** in 44% yield.[4]

Heating **1** in toluene gave the [2+2] cycloadduct **5** (1:1 E:Z) in 66% yield.[5] The structure of **5** was established with the aid of a $^{13}C$ NMR DEPT experiment. Cyclobut[a]indene **5** showed 7 methine carbon signals in the aromatic region and one methine signal corresponding to a carbonyl carbon at 190 ppm. Cumulenal **1** when desilylated ($K_2CO_3$/MeOH) gave cumulenal **2**. Heating a toluene solution of **2** containing an excess (5 eq.) of 1,4-cyclohexadiene gave naphatalene **4** in 53% yield.[6] The formation of naphthalene **4** is thought to proceed via a Bergman type cycloaromatization generating diyl **3**. Trapping of diyl **3** was accomplished using a solvent mixture of toluene and methanol and observing (via GC/MS) methoxy naphthalene **6** as the major product.[7]

**Scheme II**




Our results represent the first example of a carbonyl conjugated [3]cumulene undergoing Bergman-type cycloaromatizations. This work complements the earlier study by Hirama in which it was found that enyne-cumulenes undergo both a Bergman and [2+2] cyclization pathways.[2b] Furthermore, the Hirama group demonstrated that a [2+2] pathway occurs exclusively at the terminal cumulene bond giving rise to 1,2,3 cyclohexatriene intermediates (Scheme III). Our experimental observations are in marked contrast to these earlier studies and suggest that cumulenals containing bulky substituents at the terminal alkynyl carbon will not undergo Bergman cycloaromatization but rather cycloadd in a [2+2] fashion across the central bond of [3]cumulenal to render indane **12**.

In order to understand these divergent pathways, semiempirical PM3 calculations[8] on the three different modes of cyclization were performed (Table I). Calculations reveal that the formation of diradical **11** is the most exothermic reaction of the three shown. The TMS group disfavors the Bergman type cyclization by 6-8 kcal/mole. Substitution of the aldehyde functionality by a methyl group was shown to have little effect on the cyclization energy, with a $\Delta\Delta H$ of 2.0 kcal/mole or less. The formation of indane **12** is only 2-4 kcal/mole higher

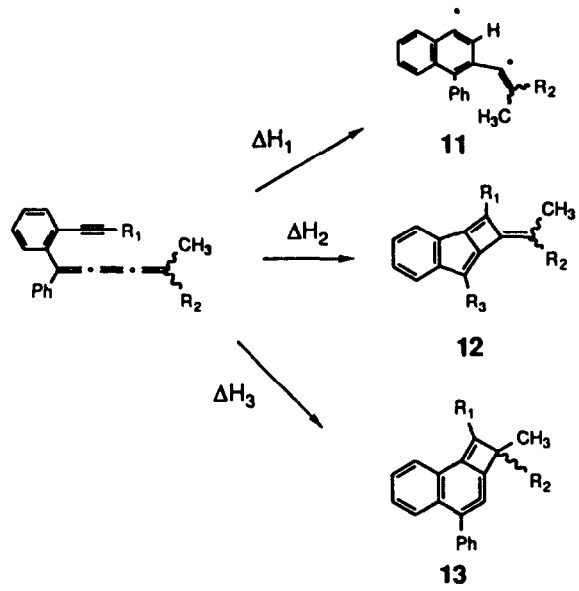
in energy than the formation of diradical **11**. The strained cyclic allene **13** was found to be energetically unfavored regardless of the substitution pattern. These results coupled with our experimental observations indicate that the Bergman cyclization of enyne [3]cumulenals is subject to steric effects.

Table I: Reaction enthalpies (kcal/mole) for the cyclization of enyne-cumulenes

| $R_1$ | $R_2$ | $\Delta H_1$ | $\Delta H_2$ | $\Delta H_3$ |
|---|---|---|---|---|
| H | $CH_3$ | -16.3 | -12.7 | -5.8 |
| H | CHO (Z) | -14.6 | -11.7 | -4.5[a] |
| H | CHO (E) | -14.3 | -12.0 | |
| TMS | $CH_3$ | -8.7 | -0.2 | -0.7 |
| TMS | CHO (Z) | -8.8 | -8.1 | 0.5[a] |
| TMS | CHO (E) | -7.3 | -7.1 | |

a. Z and E isomers become enantiomers on the timescale of a 45° rotation of the phenyl group, and therefore have the same energy. The lowest calculated reaction energy is shown.

## Scheme III



The evaluation of cumulenal **1** as a DNA cleaving agent and the intramolecular [2+2] cycloaddition reactions of cumulenals are the subject of ongoing investigations.

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3. Wang, X.; Ramos, B.; Rodriguez, A. *Tetrahedron Lett.* **1994**, *35*, 6977.
4. $^1$H NMR (400 MHz, δ, $CDCl_3$): two distinguishable stereoisomers: 9.76 (s, 1H), 9.52 (s, 1H), 2.18 (s, 3H), 2.09 (s, 3H), 0.06 (s, 9H), 0.04 (s, 9H). FT-IR ($cm^{-1}$): 3065, 2960, 2164, 2045, 1953, 1664. MS: 359 ($M^+ + H_2O$ - H), 73 (100%).
5. $^1$H NMR (400 MHz, δ, $CDCl_3$): two distinguishable stereoisomers: 10.07 (s, 1H), 9.63 (s, 1H), 7.54-7.32 (m, 9H), 1.98 (s, 3H), 1.75 (s, 3H), 0.48 (s, 9H), 0.47 (s, 9H). MS: 360 ($M^+ + H_2O$), 73 (100%).
6. $^1$H NMR (400 MHz, δ, $CDCl_3$): two distinguishable stereoisomers: 9.99 (s, 1H), 9.34 (s, 1H), 7.90-7.25 (m, 12H), 2.05 (d, 3H, $J$ = 1.3 Hz), 1.83 (d, 3H, $J$ = 1.5Hz). MS: 272 ($M^+$, 100%), 257, 246, 195, 165, 152.
7. MS: 302($M^+$) 271 (100%), 287, 234, 215, 165, 152, 113, 77, 51.
8. Semiempirical PM3 (Stewart, J. J. P. *J. Comp. Chem.* **1989**, *10*, 209) calculations were performed either with the MOPAC 6.0 program (Stewart, J. J. P MOPAC, A Semiempirical Molecular Orbital Program, **1983**, QCPE 455) and the Insight II graphical interface, produced by Biosym (Biosym Technologies of San Diego, CA) on a Silicon Graphics Indigo 2 workstation, or with MOPAC 7.0 on an IBM 370 or 590 workstation. All PM3 geometry optimizations were performed in Cartisian coordinates without symmetry constraints, using the PRECISE keyword, which improves the convergence criteria by a factor of one hundred. Both open and closed shell molecules were optimized using the unrestricted Hartree-Fock (UHF) method, to allow a direct comparison of the energies of open and closed shell systems.

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