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Cycloaromatization of a Solvolytically Generated Ene-yne-allene

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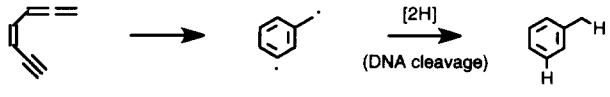
Summary: *The diethylphospate ester of 1-(2-ethynylphenyl)-4-trimethylsilyl-4-(trimethylsilyloxy)-2-pentyn-1-ol solvolyzes in 9:1 THF-H_2O to afford 5-(2-ethynylphenyl)-3-trimethylsilyl-3,4-pentadien-2-one which cyclizes in situ to 1-(2-naphthyl)-1-trimethylsilyl-2-propanone.* Copyright © 1996 Elsevier Science Ltd

Simple acyclic ene-yne-allene systems were shown independently by Saito[1] and Meyers[2] to undergo facile cycloaromatization to biradical species (eq. 1) which mimic to some extent[3] the DNA-cleaving ability of neocarzinostatin, a cyclic enediyne antibiotic whose action has been proposed to occur similarly via an ene-yne-[3]-cumulene cyclization.[4] Since then, the preparations of variously substituted acyclic ene-yne-allenes have been reported, and thermal cyclizations of these species have been observed to display characteristics of diradical intermediates.[5] However, the chemistries employed in these preparations are not compatible with physiological conditions. Other approaches have utilized inter-[2b] and intramolecular[6] thiolate addition as the trigger which generates the allenic functionality in situ, thereby mimicing the natural mode of neocarzinostatin activation. More recently, an in situ acid-catalyzed ionization approach to an ene-yne-allene appeared during our work in this area.[7]



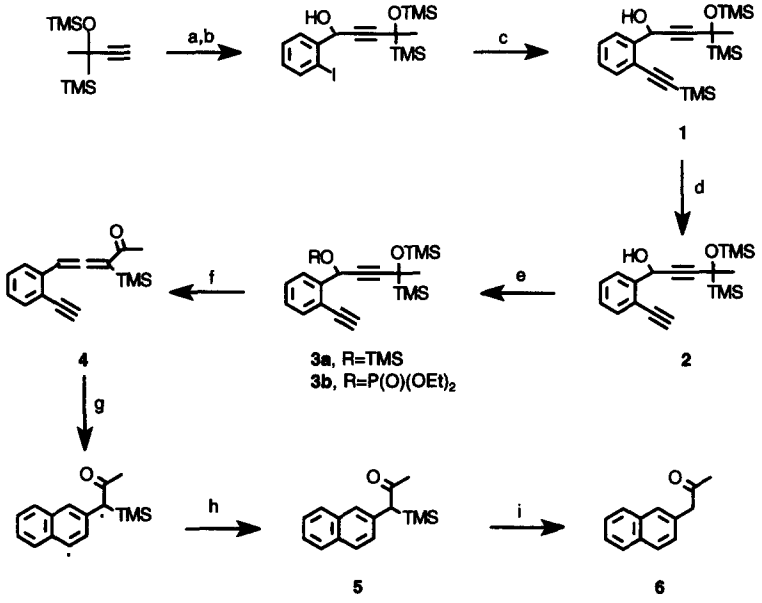
(1)

Our approach to in situ formation of an ene-yne-allene diyl precursor was based on earlier findings of facile elimination-trimethylsilyl (TMS) group migration within the propargylic framework of structures

similar to **3** (Ar = Ph, R = TMS, TMSOTf catalysis).[8] It was reasoned that an appropriately substituted allene precursor of this type could be *solvolytically* triggered near neutral pH, thus affording a physiologically-compatible alternative to the natural process.

Scheme 1 outlines the chemistry selected.[9] All steps to **3** and **4** proceeded in good yields, with the selective desilylation of **1** to **2** especially noteworthy.[10] The allenyl ketone **4**[11] was first isolated after preparation from **3a** in order to directly assess its cyclization behavior (Table 1). Use of 1,4-cyclohexadiene (CHD) as hydrogen donor in benzene resulted in a crude mixture consisting mostly of the expected **5**.[12] Chromatographic purification (silica gel) of this material, however, led to desilylation,[13] and quantitation was made on the basis of **6**[14] thereby obtained. Further solvent selection was made with a view towards a

Scheme 1



a) nBuLi, THF, -78 °C. b) o-iodobenzaldehyde, 77%. c) HCCTMS, $Pd(PPh_3)_4$, CuI, Et_3N, 92%. d) KF, DMF-H_2O, 85%. e) **3a**: TMS-imidazole, CH_2Cl_2, 0 °C, 16h, 87%; **3b**: LDA, -78 °C, then $(EtO)_2P(O)Cl$, 80%. f) **3a**→**4**: TMSOTf, 0 °C, 91%. g) Table 1. h) H donor: CHD or THF. i) Silica gel.

hydrogen-donor system which could also ultimately serve as a good ionizing medium.[15] In THF, **4** was converted in 22% yield to **6**, and in THF containing 10% H_2O (v/v), a 16% yield of cycloaromatized product was isolated. It is of note that this latter yield of two-hydrogen capture product is considerably higher than that obtained by Meyers[2b] from a terminally unsubstituted allene precursor.[16]

Table 1. Cycloaromatization of **4**.[a]

Run	Conditions	Results[b]
1	0.05M in benzene, 20 eq CHD, 60 °C, 1.5h	**5** (→ **6**, 52%)
2	0.05M in THF, 45 °C, 5.5h	**6**, 22%
3	0.09M in 9:1 THF-H_2O, 45 °C, 3h	**6**, 16%

[a] Reaction mixtures deoxygenated by Ar purge. [b] Yields of isolated material.

To ascertain that phosphate **3b**[17] was also capable of affording **4**, a sample in hexane was filtered through a short column of Florisil: **4** of 90% NMR purity was directly obtained from solvent removal. Finally, the phosphate was subjected to solvolytic conditions in 9:1 THF-H_2O (0.10M, 45 °C, 7h) and its disappearance followed by NMR spectroscopy ($t_{1/2}$ ~ 1.5h) to ultimately yield 17% of **6** after isolation by silica gel chromatography. These results suggest that solvolytic triggering may be a viable alternative to the natural *in vivo* process which leads to diradical species. Moreover, perhaps because of the expected stability[18] of the substituted benzylic radical precursor to **5** (after initial hydrogen atom transfer to the aryl site), radical-radical combination[16] may be suppressed, and may thus allow for enhanced double-strand DNA cleavage.

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9. All new compounds except the unstable **3b**, **4** and **5** afforded correct combustion data.
10. A mixture of 3.4 mmol of **1** and 7.2 mmol KF in 22 mL DMF and 5.6 mL H_2O was stirred at 25 °C for 1h and quenched with NH_4Cl-H_2O. Chromatography on Florisil (5% EtOAc-hexane) afforded analytically pure **2.** This site-selectivity for desilylation is not general. For example, similar treatment of 1,3-bis(TMS)-3-(trimethylsilyloxy)-1-butyne did not result in selective desilylation. Participation of the benzylic hydroxyl group of **1** in the cleavage process is suspected.
11. Neat **4** was unstable at 25 °C and was freshly prepared just prior to use. Evacuation at 1 mm Hg, 0 °C, 0.5h, afforded a sample which was >95% pure by NMR. ^{1}H NMR: δ 0.20 (s, 9H); 2.30 (s, 3H); 3.35 (s, 1H); 6.85 (s, 1H); 7.1-7.5 (m, 4H). IR: 3290(m), 2100(vw), 1920(vs), 1670(vs) cm^{-1}.
12. ^{1}H NMR: δ 0.07 (s, 9H); 2.23 (s, 3H); 3.97 (s, 1H); 7.3-7.8 (m, 7H).
13. The sensitivity of α-silyl ketones is well known. See Colvin, E. *Silicon in Organic Synthesis* **1981**, Butterworths, London, Chapter 3.
14. ^{1}H NMR: δ 2.17 (s, 3H); 3.84 (s, 2H); 7.31 (d, 1H); 7.46 (m, 2H); 7.66 (s, 1H); 7.80 (m, 3H). An authentic sample was obtained from $Me_2Cu(CN)Li_2$ and the acid chloride of 2-naphthoic acid (Aldrich Chemical Co.).
15. Methanol was also investigated as a solvent, but disappearance of **4** was not accompanied by formation of **5** or **6**.
16. Meyer's major product (in 20% aqueous THF) is the 2-(benzylic)THF adduct. Small amounts of what may be the corresponding **6**-THF adduct were detected in our runs containing THF.
17. Obtained as a mixture of diastereomers. ^{1}H NMR: δ -0.03, -0.01 (s, 9H); 0.01 (s, 9H); 1.19-1.30 (m, 6H); 1.36, 1.37 (s, 3H); 3.33, 3.34 (s, 1H); 4.0-4.13 (m, 4H); 6.49, 6.53 (s, 1H); 7.22-7.49 (m, 3H); 7.65 (d, J = 7.6 Hz, 1H). IR: 3300, 2219, 2100, 1250 cm^{-1}.
18. Effect of carbonyl functions on the stability of α-radicals: Huang, R.L. *J. Chem. Soc.* **1956** 1747; effect of silyl groups on stability: Doncaster, A.M.; Walsh, R. *Faraday Trans. 1* **1976**, *72*, 2908. Polar or steric effects may also have an influence on combination rates.

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