Tandem Enediyne-Radical Cyclization Expansion to Nonaromatic Enediynes

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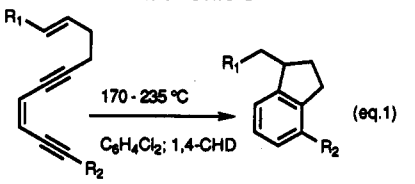
Summary: The nonaromatic enediynes **6-9**, **11**, and **14** upon thermolysis at 170–245 °C in the presence of 1,4-cyclohexadiene will undergo a tandem enediyne-radical and bis-tandem enediyne-radical cyclization to give 2,3-dihydroindenes **15-19** and **20** in moderate to excellent isolated yields.

With the recent emergence of enediyne antitumor antibiotics,[1] a renewed interest has been sparked in the Bergman cyclization[2] which was reported in the early 1970's. While the majority of the research in this area has been focused toward the synthesis of enediyne natural products and their synthetic analogs, our research has focused on using the aromatic diyl as a radical precursor for further radical cyclizations.[3] Until now, in our laboratories, only aromatic enediynes have been utilized to form 2,3-dihydrobenz[*e*]indenes or phenanthralenes in good to excellent yields.[4] Here, we would like to communicate an expansion of this methodology to the synthesis and thermolysis of nonaromatic enediynes where one or both acetylenes can be substituted to yield 2,3-dihydroindenes in moderate to excellent yields (Scheme I, eq 1). These reactions proceed at lower temperatures than the corresponding aromatic enediynes resulting in a product with one less aromatic ring. Therefore, application of this methodology toward the synthesis of natural products should be possible.

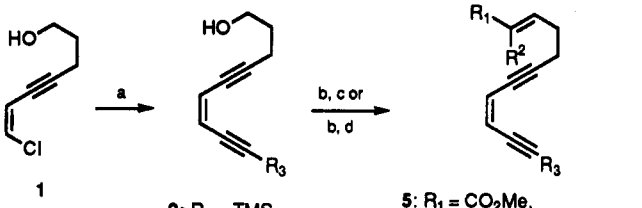
Enediynes **5–9** with one olefinic tether were synthesized in four or five easy high yielding steps starting from commercially available *cis*-dichloroethylene (Scheme II). 4-Pentynol was coupled to *cis*-dichloroethylene under modified Castro–Stephens conditions to yield the monocoupled vinyl chloride **1** in 95% yield.[5] The second acetylenic coupling was achieved under the same conditions with the respective acetylene to yield enediynes **2–4** in 62, 88, and 99% yields, respectively. Elaboration to the α,β-unsaturated ester was accomplished by PCC oxidation of the respective enediynes followed by a Roush–Masamune variation of the Horner–Emmons reaction[6] to yield **5–7** with the radical accepting tethers in place. Desilylation of **5** with TBAF in THF and subsequent solvent removal *in vacuo* at 0 °C yielded enediyne **8** in 82% yield from **2**. Enediyne **9** was synthesized in a similar manner by PCC oxidation followed by a Horner–Emmons reaction with isopropyl dimethyl-2-methylphosphonoacetate[7] and desilylation with TBAF in THF in 64% yield over two steps.

Scheme I



(eq.1)

Scheme II[a]



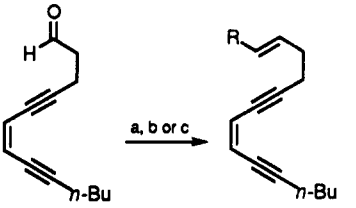
1

2: R_3 = TMS
3: R_3 = CH_2OTBS
4: R_3 = *n*-Bu

5: R_1 = CO_2Me, R_2 = H, R_3 = TMS
6: R_1 = CO_2Me, R_2 = H, R_3 = CH_2OTBS (80%)
7: R_1 = CO_2Me, R_2 = H, R_3 = *n*-Bu (89%)
8: R_1 = CO_2Me, R_2 = H, R_3 = H (82%)
9: R_1 = CO_2i-Pr, R_2 = Me, R_3 = H (64%)

[a]Key (a) **2**, TMS–acetylene, 1, $(Ph_3P)_4Pd$ (0.017 equiv), CuI (0.04 equiv), *n*-$BuNH_2$ (1.7 equiv), PhH 62% or **3** same conditions, TBS–propargyl alcohol, >99% or **4** same conditions, 1-hexyne, 88%; (b) PCC (3 equiv), CH_2Cl_2, Celite; (c) trimethyl phosphonoacetate (1.5 equiv), DBU (1.5 equiv), LiCl (2 equiv), yield from alcohol 82% for **8** following desilylation with TBAF in THF, 80% for **6**, 89% for **7**; (d) (i) 1.5 equiv of isopropyl dimethyl-2-methylphosphonoacetate, 1.5 equiv of DBU, 2 equiv of LiCl, CH_3CN, (ii) TBAF, THF, 64% over two steps.

Scheme III[a]



10

11: R = CH_2OH
12: R = OMe

[a]Key: (a) trimethyl phosphonoacetate (1.5 equiv), DBU (1.5 equiv), LiCl (2 equiv), CH_3CN; (b) DIBAL (2.1 equiv), CH_2Cl_2, 57%; (c) methoxymethyltriphenylphosphonium chloride (5.1 equiv), potassium *tert*-butoxide (5 equiv), THF, –78 °C, 38%.

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(1) For a general overview on the enediyne antibiotics see: (a) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (b) Nicolaou, K. C.; Smith, A. L. *Acc. Chem. Res.* **1992**, *25*, 497.

(2) (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660. (b) Lockhart, T.P.; Comita, P.B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082.

(3) In the literature, there have been reports of biradicals generated from eneyne allene and eneyne ketene cyclizations being utilized in radical cyclizations. (a) Xia, H.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 3765. (b) Andemichael, U. W.; Huang, Y.; Wang, K. K. *J. Org. Chem.* **1993**, *58*, 1651. (c) Andemichael, Y. W.; Gu, Y.G.; Wang, K.K. *J. Org. Chem.* **1992**, *57*, 794. (d) Padwa, A.; Austin, D. J.; Chicchio, U.; Kassir, J.M. *Tetrahedron Lett.* **1991**, *32*, 5923.

(4) (a) Grissom, J. W.; Calkins, T. L. *Tetrahedron Lett.* **1992**, *33*, 2315. (b) Grissom, J.W.; Calkins, T.L. *J. Org. Chem.* **1993**, in press.

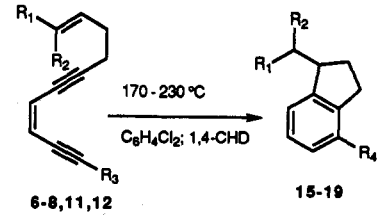
(5) (a) Crévisy, C.; Beau, J.-M. *Tetrahedron Lett.* **1991**, *32*, 3171. (b) Guillerm, D.; Linstrumelle, G. *Tetrahedron Lett.* **1985**, *26*, 3811. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *4467*.

(6) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. P.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(7) Isopropyl dimethyl-2-methylphosphonoacetate was prepared by an Arbuzov reaction between trimethyl phosphite and commercially available (±)-isopropyl 2-bromopropionate.

0022-3263/93/1958-6556$04.00/0

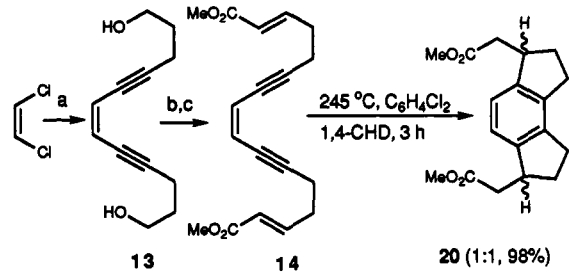
Table I



entry	SM	R_1	R_2	R_3	R_4	temp (°C)	time (h)	product (%)
1	8	CO_2Me	HH	H	H	170	2	15 (11)
2	9	CO_2-*i*-Pr	Me	H	H	170	2	16 (13)
3	6	CO_2Me	H	CH_2OTBS	CH_2OTBS	230	2.5	17 (45)
4	7	CO_2Me	H	*n*-Bu	*a*	230	5	18 (47)
5	11	CH_2OH	H	*n*-Bu	*b*	230	2.5	19 (54)
6	12	OMe	H	*n*-Bu		230		*c*

[a] R_4 = –CH=CHEt as a 1.7:1 mixture of cis/trans isomers; (b) R_4 = –CH=CHEt and –CH_2CH=$CHCH_3$ as a mixture of regio- and stereoisomers; (c) hydrolysis of enol ether to the aldehyde at high temperatures results in an undesired product mixture.

Scheme IV[a]



[a] Key: (a) 2-equiv of 4-pentynol, 0.04 equiv $(PPh_3)_4Pd$, 0.17 equiv CuI, PhH, 40 °C, 87%; (b) 3.5 equiv PCC, CH_2Cl_2; (c) 2.5 equiv trimethyl phosphonoacetate, 2.5 equiv of DBU, 4 equiv of LiCl, CH_3CN, 31% over two steps.

The allylic alcohol 11 was obtained by DIBAL reduction of 7 in 57% yield (Scheme III). The methyl enol ether 12 was synthesized by subjecting 10, which was obtained by PCC oxidation of 4, to Wittig conditions with methoxymethyltriphenylphosphonium chloride in 38% yield.

Thermolysis of enediyne 8 in dichlorobenzene in the presence of 1,4-cyclohexadiene at 170 °C yielded the 2,3-dihydroindene 15 (Table I, entry 1). NMR analysis of the crude product mixture revealed only one tandem enediyne-radical cyclization product. A large portion of the mass balance was consumed by the formation of a polymeric product, which was removed from the crude reaction mixture in the initial workup.[8] Isolation of 15 was achieved *via* Kugelrohr distillation of the crude reaction mixture to yield a colorless oil in 11% yield. Compound 9 was thermolyzed under similar reaction conditions to yield 16 in 13% yield as a 2:1 mixture of diastereomers (Table I, entry 2). Apparently, the monosubstituted enediynes do not undergo an efficient radical trapping process, resulting in undesirable side reactions and low isolated yields.

Substitution at the R_3 position seemed to have a beneficial effect on the tandem enediyne-radical cyclization of the nonaromatic enediynes. Thermolysis of enediyne 6 at temperatures ranging from 170 °C to 220 °C showed no product formation. When the temperature was raised to 230 °C, starting material was consumed within 2 h to yield bicycle 17 in 45% yield (Table I, entry 3). Likewise, enediyne 7 required both an increase in reaction temperature (230 °C) and in reaction time (5 h) to yield 18 in 47% as a 1.7:1 mixture of cis/trans isomers (Table I, entry 4).

The formation of the isomers of 18 presumably arises from a very fast 1,5-hydrogen abstraction from the butyl chain followed by a disproportionation to produce an olefin which is thermally isomerized into conjugation with the aromatic ring to yield an inseparable mixture of cis/trans isomers. There was no evidence of any product formation arising from hydrogen abstraction from solvent by the aromatic diyl. This can be explained by a very fast 5-*exo* radical cyclization and 1,5-hydrogen abstraction process, which drastically decreases the lifetime of the biradical intermediate.

To expand the methodology to other radical accepting tethers, the allylic alcohol 11 was thermolyzed to yield the 2,3-dihydroindenes 19 in 54% yield. When 12 was subjected to the same reaction conditions, the methyl enol ether quantitatively hydrolyzed to give the aldehyde 10 which upon thermal cyclization gave a complex mixture of products (Table I, entry 6).

A *bis*-tandem enediyne radical cyclization has been shown to be successful in the case of the aromatic enediynes.[9] Thus, a nonaromatic analog was synthesized to test the feasibility of forming three rings simultaneously in one thermal process. Compound 14 was synthesized in three steps starting with a Castro–Stephens coupling of 2 equiv of 4-pentynol to *cis*-dichloroethylene to yield the *cis*-enediyne 13 in 87% yield, followed by PCC oxidation and a Horner–Emmons reaction with trimethyl phosphonoacetate to yield 14 in 31% yield over two steps (Scheme IV).

Finally, compound 14 was thermolyzed at 245 °C for 3 h in the presence of 1,4-CHD to yield a 1:1 mixture of diastereomers of 20 in 98% yield (Scheme IV). It should be noted that the yield of this substrate is substantially higher than the other tandem enediyne-radical cyclized products. An explanation may be the fact that both tethers of the enediyne 14 possess a radical accepting center which can immediately quench both aromatic radicals formed

(8) General procedure for thermal cyclization of aromatic and nonaromatic enediynes: To a predried screw-top reaction vial was added the enediyne and 8 mL of anhydrous $C_6H_4Cl_2$. Nitrogen was bubbled through the reaction mixture for approximately 20 min after which 20 equiv of 1,4-cyclohexadiene was added *via* syringe. The reaction vial was sealed under an atmosphere of N_2 and heated to the reaction temperature. Temperatures greater than 230 °C required a reaction bomb because at higher temperatures, the vessels tended to burst open. The reaction was then plugged through SiO_2 with hexanes to remove the high boiling reaction solvent and then Et_2O to obtain a crude reaction mixture. Further purification was completed *via* silica gel column or radial chromatography.

(9) Grissom, J. W.; Calkins, T. L.; Egan, M. *J. Am. Chem. Soc.*, in press.

in the cyclization to generate two α-carbomethoxy stabilized radicals which are then quenched by 1,4-CHD. If a rapid quenching process is not available to the aromatic biradical, polymerization is observed causing the yields to be much lower.

In conclusion, the mono- and bis-tandem enediyne-radical cyclization has been expanded to include nonaromatic enediynes, which cyclize in moderate to excellent yields. Substantial mass balance in the reaction is consumed by the formation of a polymeric material which is easily removed in the workup process. Otherwise, the tandem enediyne-radical cyclization of the nonaromatic analogs is a very predictable process. It should also be noted that in all cases only the substituted indene products were obtained and isolated by simple silica gel chromatography. Efforts to lower the reaction temperatures of this methodology and applications toward the synthesis of biologically active natural products are currently underway and will be reported in a timely manner.

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Supplementary Material Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra of compounds (42 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering imformation.