Activation of Enediynes via Intramolecular Iodoetherification

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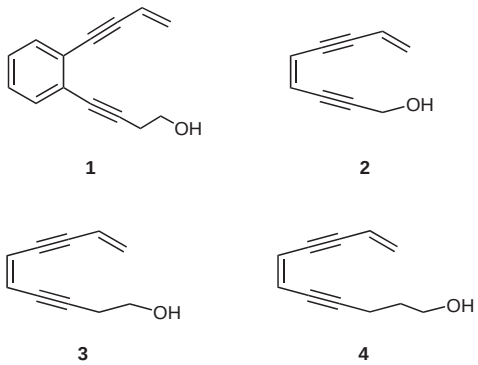
Received 8 August 2007

Abstract: Intramolecular iodoetherification can be a powerful method for activation of acyclic enediyne. However, the activation depends upon the chain length and the electronic nature of the enediyne (whether aliphatic or benzo-fused).

Key words: enediyne, iodoetherification, Bergman cyclization

Bergman cyclization (BC)[1] of enediynes converts them into 1,4-dihydrobenzene (or *p*-benzene) diradicals capable of abstracting H atoms from the sugar-phosphate backbone of the DNA ultimately leading to its cleavage.[2] This ability of enediynes to inflict damage to DNA is dependent upon their reactivity towards undergoing BC under ambient conditions. In general, controlling of the reactivity of enediynes can be achieved through either strain or electronic effects.[3,4] The strain factor can be incorporated by putting the enediyne framework in a cyclic network of size 9 or 10 which in turn also brings the acetylenic carbons (the *c*,*d*-distance[5]) undergoing covalent linkage closer. Thus conversion of an acyclic endiyne into a cyclic system of appropriate size is an attractive strategy to activate the otherwise ambiently benign precursors. In a recent work,[6] we have shown that an intramolecular azide–alkene cycloaddition can be employed for such purpose. In this communication, we describe an intramolecular iodoetherification[7] approach for the triggering of acyclic enediynes of different chain lengths in the two arms of the acetylenic moieties. The results are quite interesting and underline the importance of electrophilic addition to a double bond in enediyne activation.



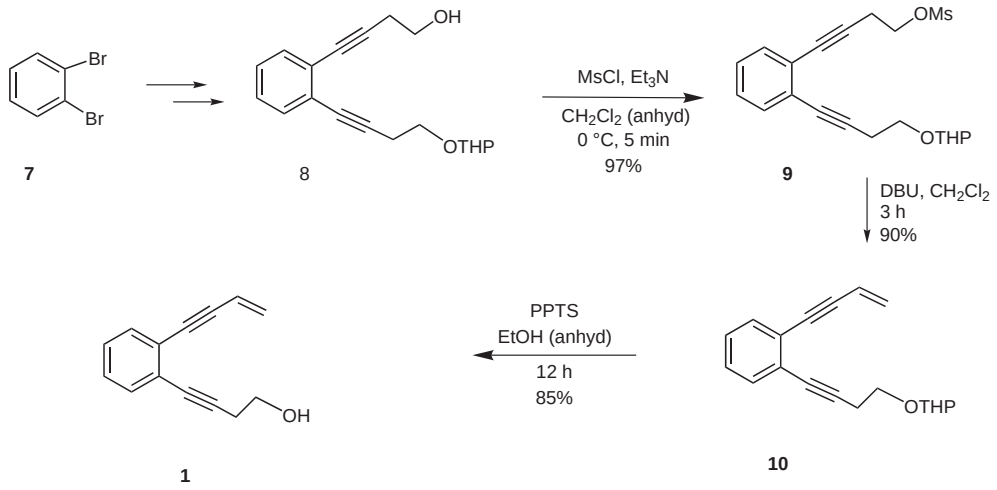
1 2 3 4

Figure 1

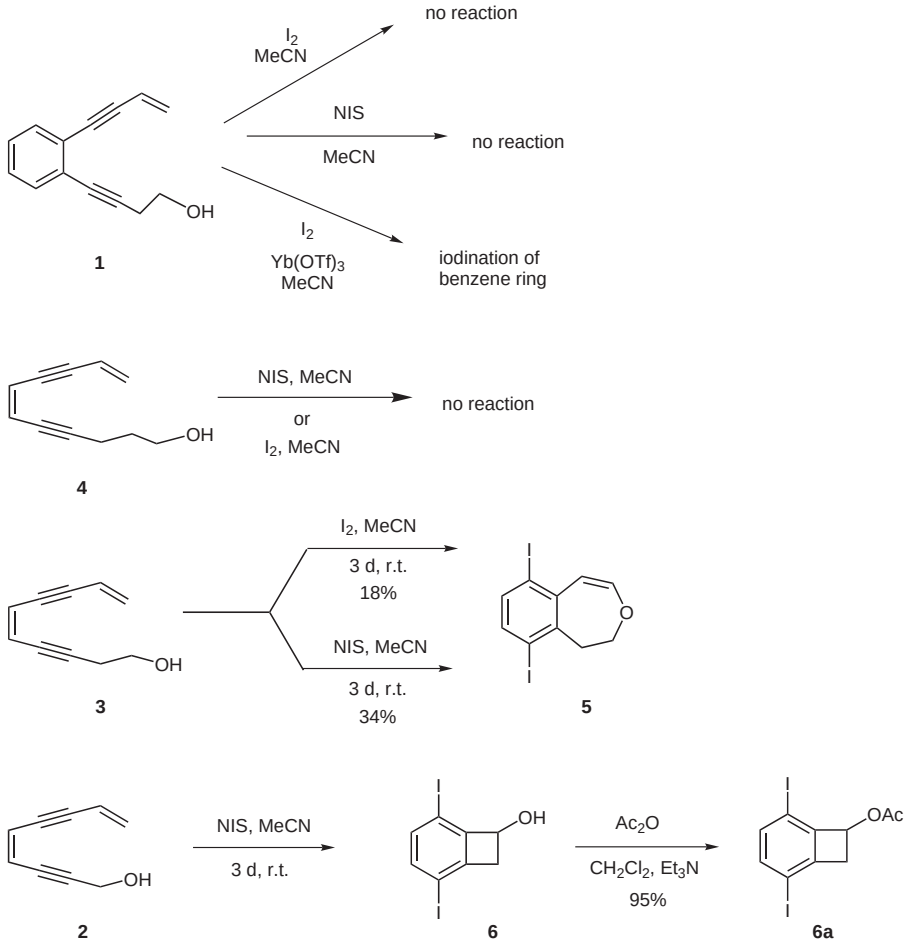
The starting precursor **1** (Figure 1) for our iodotherification study was prepared as described in Scheme 1. It involved sequential Sonogashira couplings[8] followed by β-elimination and deprotection of THP ether. The nonaromatic enediynes **2**–**4** were prepared in the same way as compound **1** starting from *cis*-dichloroethylene. The iodoetherification was first attempted on the aryl-fused enediyne **1** with both I_2/MeCN and NIS/MeCN. With both these reagents, no meaningful reaction took place; with the latter reagent, some decomposition product could be seen. Attempted reaction with I_2/Yb(OTf)$_3$[9] led to electrophilic iodination of the aromatic ring. Realizing that the presence of an aromatic ring is posing problem due to electrophilic substitution, we decided to study the reactivity of the nonaromatic enediynes **2**–**4** (Scheme 2). Thus the enediyne **3** was treated with I_2/MeCN for three days at room temperature. It afforded only one distinct product characterized as the diiodobenzooxepine **5** in 18% yield. With NIS/MeCN the reaction was better in terms of yield (34%) and side products. The higher homologous enediyne **4**, however, failed to react under both the conditions, thus indicating the importance of ring size to be formed by iodoetherification. The lower homologous enediyne **2** when subjected to iodoetherification conditions (NIS/MeCN) gave one major product that could be isolated by column chromatography (hexane–EtOAc, 10:1) followed by HPLC (ODS column, 87% MeOH and 13% H_2O at 0.6 mL/min flow rate). The compound showed pair of doublets at δ = 7.34 and 7.25 (*J* = 8 Hz) ppm typical of a 1,2,3,4-tetrasubstituted benzene ring. There were three other signals at δ = 5.09, 3.42, and 2.84 ppm characteristic of an ABX system. The absence of a benzylic methylene in the ^{1}H NMR spectrum indicated that perhaps the benzylic carbon has undergone oxidation under the reaction conditions. The ^{13}C NMR spectrum showed the presence of eight carbons, which indicated loss of one carbon during the process. Analysis of mass spectral data as well as NMR spectral analysis showed the structure to be a benzocyclobutane derivative **6**. The structure was further confirmed by the isolation of monoacetate **6a** by treatment with acetic anhydride and pyridine.

Regarding the formation of the benzooxapene derivative **5**, two mechanisms (Scheme 3) can be proposed: one involving a Myers–Saito pathway[10] after initial iodoetherification via an *endo* cyclization. The other involves iodoetherification followed by elimination to lead to the 11-membered system, which underwent BC to give rise to the product. Mass spectrometric study on the various fractions separated by HPLC showed the presence of the com-

SYNLETT 2008, No. 4, pp 0501–0504
Advanced online publication: 12.02.2008
DOI: 10.1055/s-2008-1032077; Art ID: D24507ST



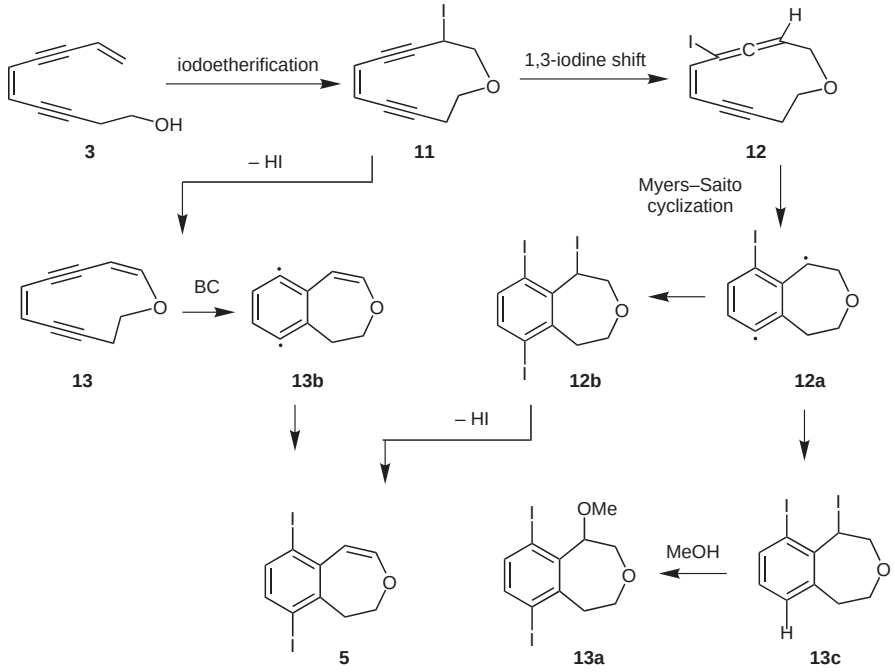
Scheme 1 Synthesis of enediyne **1**



Scheme 2 Iodoetherification of enediynes **1**–**4**

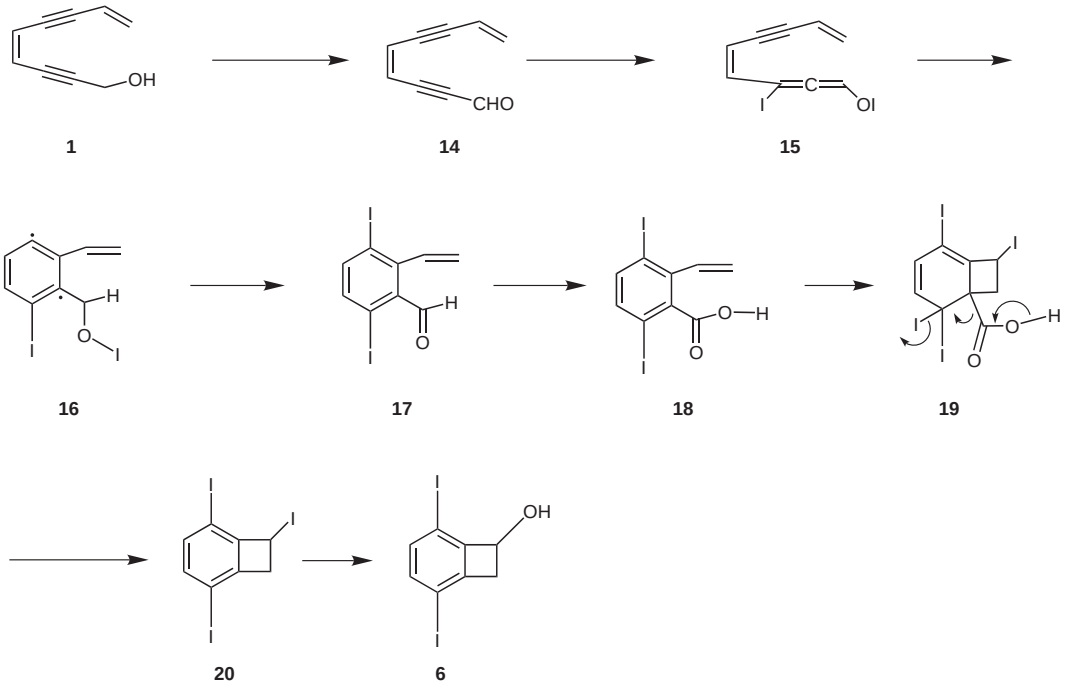
pound **13a** in the fraction (t_R = 14.8 min), which can only arise from the first mechanism. The displacement of benzylic iodide might have taken place during HPLC separation in which methanol was used as the mobile phase.

For the formation of the benzocyclobutane product, because of loss of a carbon, some kind of oxidative pathway can be thought of. A possible mechanism has been proposed in Scheme 4. Initial oxidation to the aldehyde followed by a Myers–Saito-type cyclization, as shown in Scheme 3, is a possibility. Subsequent oxidation to the acid followed by a decarboxylative[11] ring closure can lead to the final product. At this point the only support that we have is that the aldehyde **14**, when subjected to the same conditions, led to the formation of **6** as the only isolable



Scheme 3 Probable mechanism of formation of **5**

product.[12,13] The displacement of the benzylic iodide probably has taken place during work up.



Scheme 4 Probable mechanism of formation of **6**

In conclusion, we have shown that intramolecular iodoetherification can be a powerful method for activation of acyclic enediyne. The importance of chain length and the electronic nature of the enediyne, aromatic or not, is important in such an activation process.

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(12) To a solution of compound **3** (150 mg, 1.03 mmol) in anhyd MeCN (10 mL), NIS (278 mg, 1.23 mmol) was added and stirred for 3 d under inert atmosphere. The reaction mixture was extracted with Et_2O, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude was purified via chromatography (SiO_2, hexane–EtOAc = 30:1) to yield the desired compound **5** (34%).
Selected Spectral Data
Compound **5**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.35 (2 H, t, *J* = 4.0 Hz, C*H*$_2$CH$_2$O), 4.26 (2 H, t, *J* = 4.1 Hz, CH$_2$C*H*$_2$O), 5.64 (1 H, d, *J* = 8.4 Hz, ArC*H*CHOCH$_2$), 6.54 (1 H, d, *J* = 8.4 Hz, ArCHC*H*OCH$_2$), 7.28 (1 H, d, *J* = 8.3 Hz, ArH), 7.38 (1 H, d, *J* = 8.3 Hz, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 43.02, 71.28, 100.68, 100.76, 108.71, 136.99, 138.08, 139.11, 142.38, 146.99. MS (EI): *m/z* = 398.87 [MH$^+$]. Compound **6**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.84, 4.42 (2 H, ABX, J_{AX} = 4.2 Hz, J_{BX} = 0.0 Hz, J_{AB} = 14.6 Hz, ArC*H*$_2$CHOH), 5.09 (1 H, dd, *J* = 1.8, 4.7 Hz, ArC*H*OHCH$_2$), 7.25 (1 H, d, *J* = 8.2 Hz, ArH), 7.34 (1 H, d, *J* = 8.3 Hz, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 42.84, 68.66, 87.07, 89.96, 137.35, 138.69, 149.76, 153.60. MS (EI): *m/z* = 395.88 [MNa$^+$], 354.85 [M – H_2O].
(13) To a solution of alcohol **6** (10 mg, 0.037 mmol) in CH_2Cl_2 (5 mL), Ac_2O (4 μL, 0.044 mmol), Et_3N (6 μL, 0.044 mmol), and DMAP (5 mol%) were added at 0 °C. The reaction mixture was stirred for 10 min after which it was poured into H_2O and CH_2Cl_2. The organic layer was washed with H_2O, dried, and then evaporated. The compound **6a** was then isolated by column chromatography (SiO_2, hexane–EtOAc = 30:1) as a white solid (98%).
Selected Spectral Data
Compound **6a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (3 H, s, C*H*$_3$COOCH), 2.94, 3.50 (2 H, ABX, J_{AX} = 4.4 Hz, J_{BX} = 0.0 Hz, J_{AB} = 14.8 Hz, ArC*H*$_2$CHOH), 5.87 (1 H, d, *J* = 4.0 Hz, ArC*H*OHCH$_2$), 7.28 (1 H, d, *J* = 8.4 Hz, ArH), 7.36 (1 H, d, *J* = 8.0 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.87, 40.93, 69.12, 87.09, 88.71, 138.09, 139.96, 148.64, 150.16, 170.50. MS (EI): *m/z* = 413.35 [M$^+$].