The synthesis and reactivity of novel azetidinyl enediynes

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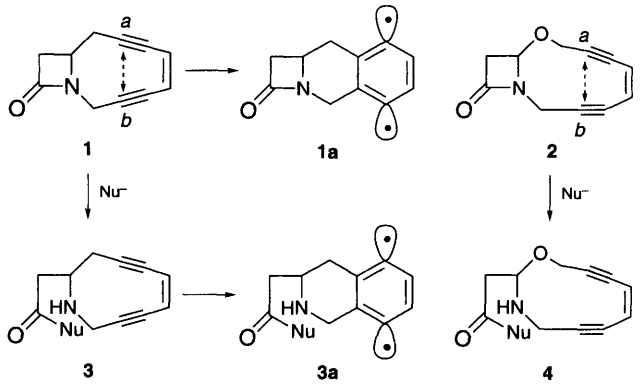
Novel bicyclic azetidinyl enediynes 1 and 2 are synthesized *via* Pd^0 catalysed coupling followed by *N*-alkylation; their thermal properties are also evaluated.

The enediyne class of antitumour antibiotics has recently become the focus of intense biochemical research.[1] These molecules undergo Bergman cyclization[2] under suitable conditions to generate benzene-1,4-diradicals which can then damage DNA.[3,4] A number of new model enediynes have been recently synthesized.[5–7] The key feature in all these designs is the enediyne core coupled to a triggering device. Here we report the synthesis of two novel bicyclic enediynes **1** and **2** which both have a biorecognisable β-lactam ring fused to the lethal enediynes to control their reactivities. Nicolaou *et al.*[8] have proposed the distance between the reacting acetylenic carbons as the major factor for Bergman cyclization,[2] the key process involved with all the enediynes. However, according to Magnus and Snyder[9] the ease of cyclization is mainly dependent upon the difference in molecular strain between the ground state (GS) and the transition state (TS). The presence of the β-lactam ring in **1** and **2** is expected to enhance the strain difference between the bicyclic GS and the partially tricyclic TS. Calculations using PCMODEL† on these molecules revealed the *a,b*-distance in **1** to be 3.27 Å. In the corresponding ring opened system **3** the distance was calculated to be 3.41 Å. For the 11-membered enediyne **2** the *a,b*-distance (3.75 Å) came out to be slightly more than that in the corresponding ring opened system **4** (Nu = OMe, 3.72 Å). The value of 3.27 Å predicts rapid spontaneous aromatization of **1** at ambient temperature. However, the high strain energy of **1** [calculated to be 33.4 kcal mol^{-1}, 1 cal = 4.184 J)] may have an adverse effect upon such a process at ambient temperature. Thus it is expected that the bicyclic enediynes will be locked against cycloaromatization at least in the temperature range present in the biological system. Nucleophilic ring opening of the β-lactam will release the strain to lead to species **3** and **4** which will have a better chance of undergoing cycloaromatization at a lower temperature (Scheme 1).

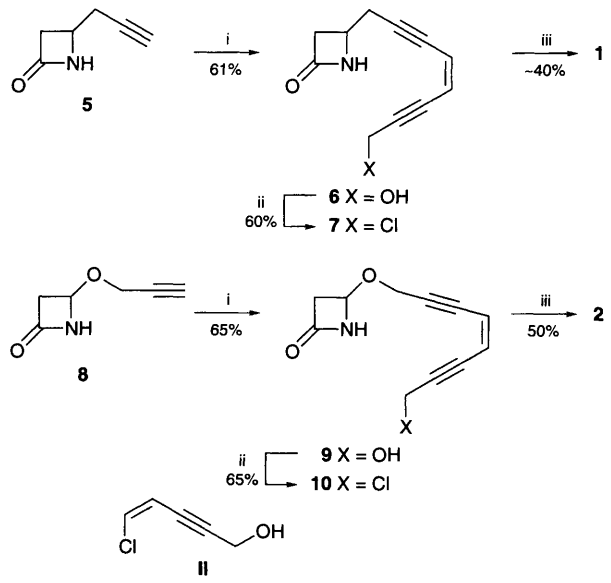
With this in mind, we synthesized the target molecules **1** and **2** according to Scheme 2.

The synthesis of the enediynes **1** and **2** was accomplished starting from 4-substituted β-lactams **5** and **8** which were prepared from 4-phenyl sulfonylazetidinones by literature methods.[10,11] Treatment of **5** or **8** with 5-chloropent-4-ene-2-yne **11** in presence of Pd^0 catalyst[12] and excess Et_3N failed to produce any coupled products. However replacing Et_3N by $BuNH_2$ effected smooth coupling and the desired enediyne alcohols were obtained in good yields. Interestingly, contrary to our apprehension, the β-lactam ring remained intact in the presence of a large excess of $BuNH_2$. The alcohols **6** and **9** were then converted to the chlorides **7** and **10** by treatment with tosyl chloride and DMAP. Presumably the chloride ion displaced the highly reactive tosylate formed *in situ* during the reaction.[13] Both the enediyne chlorides are quite stable at room temperature; however their iodo analogues, prepared *via* NaI–acetone and presumably more suitable for *N*-alkylation were extremely unstable, trace of moisture reverted them back to the starting alcohols. The final critical step, *i.e.* intramolecular cyclization was accomplished by treating the chlorides with K_2CO_3–KI in DMF for 18 h to afford the enediynes **1** and **2** in 40–50% yield. To our knowledge, these are the first examples of *N*-containing enediynes with the [8.2.0] and [9.2.0] systems. The enediynes **1** and **2** are stable viscous oils and have been fully characterized.‡

To ascertain the reactivities of the enediyne units, the thermal properties of **1** and **2** were investigated by differential scanning calorimetry (DSC).[14] The plot of heat change as a function of temperature showed an exothermic rise beginning at *ca.* 100 °C for **1** and at *ca.* 125 °C for **2** which reflects the start of the cyclization process. Similar large values for energy change per mole were obtained for both these molecules (150 kcal mol^{-1}) indicating a radical process. Thus the strain in the β-lactam ring is sufficient to lock[15] the otherwise labile enediyne moiety specially in 10-membered rings up to quite high temperature. Interestingly, we have recently demonstrated the ability of the



Scheme 1



Scheme 2 *Reagents and conditions*: i, **11**, $Pd(PPh_3)_4$, CuI, $BuNH_2$, benzene; ii, tosyl chloride, DMAP, CH_2Cl_2; iii, K_2CO_3, KI, DMF, room temp.

β-lactam ring to lock the prop-2-ynyl to allene isomerization.[16]

A. Basak thanks CSIR and DST for financial assistance. We also thank Dr A. Basak, Clinical Research Institute of Montreal, Canada, for the Mass spectra.

Footnotes

† Calculations were done using PCMODEL ver 4.0 (Serena software, Bloomington, Indiana, USA). We are grateful to Dr U. Maitra, IISc, Bangalore, India, for his help in this regard.

‡ *Selected spectral data*: for **1** ν_{max}/cm^{-1} 2926, 2857, 1742, 1523, 1442, 1374, 1249, 1104, 1035, 893, 618; δ_H ($CDCl_3$, 200 MHz) 5.95 (2 H, bm), 4.56 (1 H, d, *J* 18.75 Hz), 4.13 (1 H, d, *J* 18.75 Hz), 4.03 (1 H, m), 3.20 (1 H, dd, *J* 15.6, 6.2 Hz), 2.85–2.77 (2 H, m) and 2.61 (1 H, bd, *J* 15.6 Hz); Mass (EI) *m/z* 171(22), 133(45), 129(50), 115(72), 106(100) and 102(20); HRMS cald. for $C_{11}H_9NO$ 171.0685; found 171.0690. For **2**: ν_{max} cm^{-1} 2925, 2854, 1761, 1533, 1353, 1196, 1076, 1024 and 618; δ_H ($CDCl_3$, 200 MHz) 5.93 (2 H, bs), 5.80 (1 H, dd, *J* 3.8, 1.2 Hz), 4.50, 4.11 (2 × 1 H, 2 × bd, *J* 18.3 Hz), 4.54, 4.30 (2 × 1 H, 2 × d, *J* 17.5 Hz), 3.11 (1 H, dd, *J* 14.5, 3.6 Hz) and 2.83 (1 H, bd, *J* 14.5 Hz). δ_C ($CDCl_3$, 50 MHz) 175.96, 122.03, 121.75, 90.7, 89.3, 84.4, 82.7, 79.22, 57.20, 44.35 and 31.86; Mass (EI) *m/z* 187(9), 149(100), 145(21), 131(50), 118(29), HRMS calcd. for $C_{11}H_9NO_2$ 187.0634 found 187.0638.

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Received, 11th December 1995; Com. 5/08059B