Synthesis and Thermal Reactivity of Pyrrolidine- and 2-Pyrrolidinone-Fused Cyclic Enediynes

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Abstract: Various bicyclic enediynes containing pyrrolidine and pyrrolidinone moieties were synthesised. Thermal reactivity studies indicated the lowering of the onset temperature for Bergman cyclisation upon fusion of these heterocyclic systems onto the cyclic enediyne.

Key word: enediynes, pyrrolidines, pyrrolidinones, heterocyclic systems, Bergman cyclisation

Bicyclic enediynes are attractive targets[1] because the reactivity of their monocyclic counterparts towards Bergman cyclisation (BC)[2] can be perturbed by fusion of another ring; the effect is significant if the fused ring is small.[3] Over the past few years, we have been interested in the synthesis of nitrogen-containing cyclic enediynes,[4] which have assumed significant importance in recent years. These compounds possess a good thermal profile under ambient conditions, especially the non-benzenoid ones.[5] Fusion of four-membered rings like β-lactams has been reported to deactivate the parent enediyne system.[6,7] This has prompted us to know whether similar effect exists if the β-lactam ring is replaced by five-membered heterocyclic systems like pyrrolidine or 2-pyrrolidinone (γ-lactam) rings. Thus, we have designed and subsequently synthesised enediynes **1**–**3**. For comparison of thermal reactivity, the enediyne **4** was synthesised (Figure 1). Their synthesis and reactivity studies are reported herein.

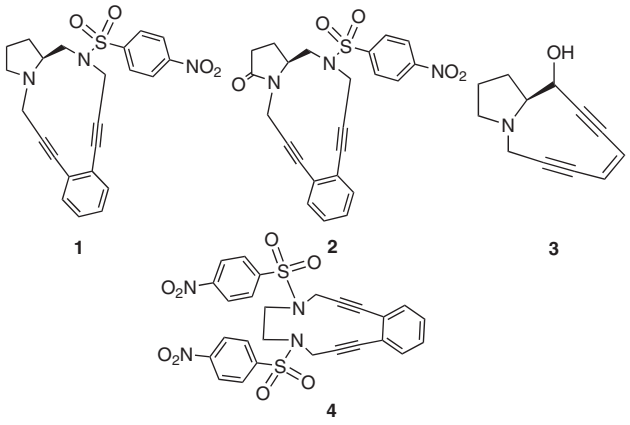
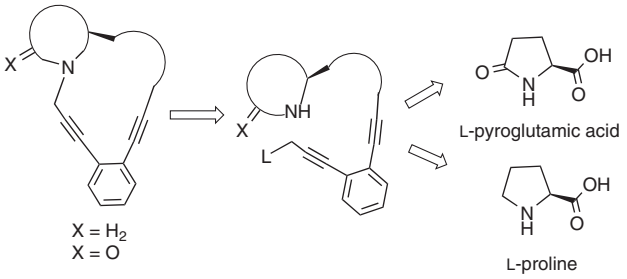


Figure 1

The retrosynthesis of the target molecules, as shown in Scheme 1, has a common final intramolecular N-alkylation step. This was based upon the consideration of our success in the synthesis of β-lactam-fused enediynes involving a similar intramolecular N-alkylation between the lactam N and propargyl halide.[7]



Scheme 1

As a first step towards the synthesis of **1** and **2**, the azides **5** and **9** were prepared from L-proline and L-pyroglutamic acid, respectively. These were reduced with PPh_3/water[8] and the resulting amines were then protected as the sulfonamides **6** and **10**. The enediyne **1** was obtained as a white solid in a single step when the sulfonamide trifluoroacetate **7** was treated with enediynyl dibromide **8** in the presence of anhydrous K_2CO_3 and DMF at 0.005 M concentration (Scheme 2). This approach, however, failed for the synthesis of enediyne **2**. In this case, bisalkylation of sulfonamide **10** yielded compound **16** because of the reduced nucleophilicity of the amide nitrogen. The scheme was modified and the synthesis was accomplished as follows: a) initial N-alkylation of sulfonamide **10** with protected bromoalcohol **11**, b) conversion of the resulting acyclic enediyne **12** into the bromide **15** in a three-step protocol and c) final ring closure using NaH in THF under high dilution condition (Scheme 3).

The synthesis of the pyrrolidine-fused ten-membered enediyne **3** was more challenging. In this case, the acetylenic alcohol **19** was first prepared by the addition of TMS-acetylide onto *N*-Boc prolinal **18**. The alcohol **19** was then protected as the THP ether **20** after fluoride-mediated desilylation. Attempted Sonogashira coupling[9] of the alkyne **20** with dibromo- or diiodobenzene failed, very little coupled product was obtained. When we changed the dihalobenzene to chloroeneyne alcohol **21** as the coupling partner, the reaction took place smoothly at room temperature to give the desired acyclic enediyne **22**. This was

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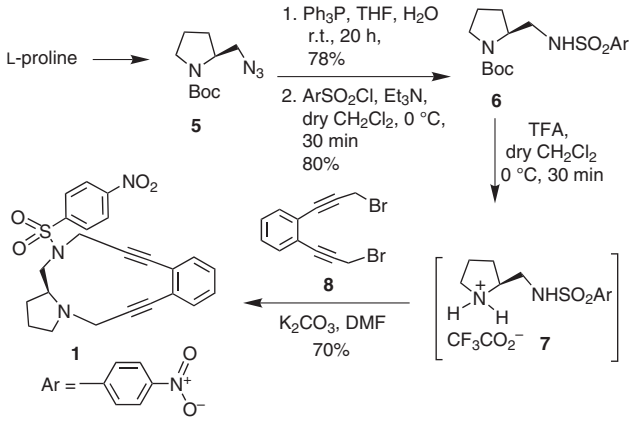
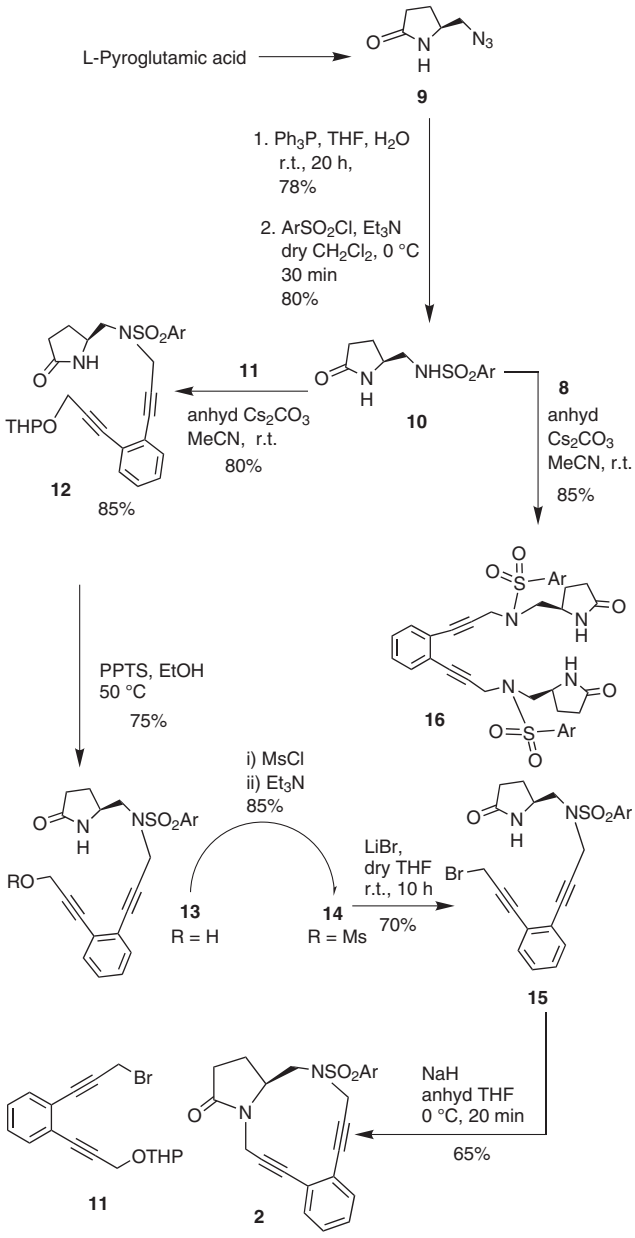
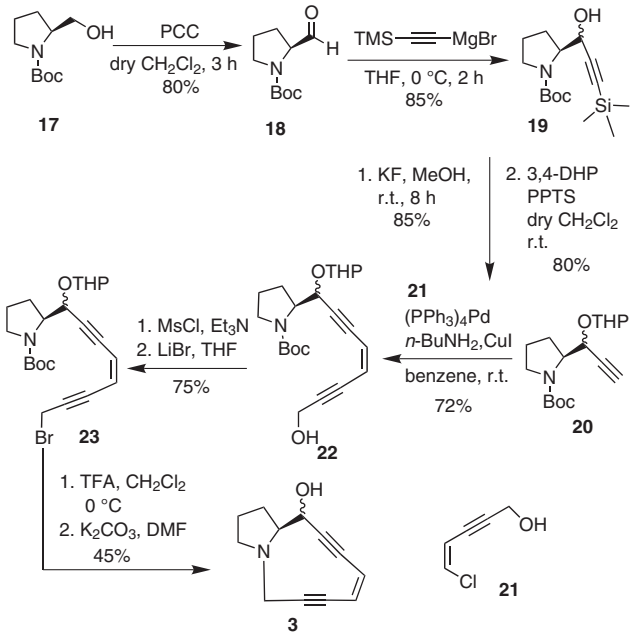


Scheme 2



Scheme 3

converted to bromide **23** via mesylation, which was successfully cyclised to the target enediyne **3** using K_2CO_3 in DMF (Scheme 4). The enediyne **4** was prepared in a single step by bis N-alkylation of ethylene diamine di-4-nitrobenzene sulfonamide following our published procedure.[10] The structures of all enediynes **1**–**4** were confirmed by NMR and mass spectroscopic data.[12]



Scheme 4

The thermal reactivity of all the enediynes was studied using differential scanning calorimetry.[11] The onset temperatures are shown in Table 1. The data clearly demonstrated that fusion of five-membered rings like a pyrrolidine or pyrrolidinone reduces the onset temperature for BC. The effect is more dramatic for the pyrrolidine system. This result is the opposite to what has been observed so far for cyclic enediynes fused to small rings (for example, an epoxide or β-lactam).[3,6,7]

Table 1 Thermal Reactivity of Enediynes **1**–**4** by DSC

Enediyne	Onset temp [T_1, °C]	$\Delta T = T_1$[**4**] – T_1 [**1**, **2**, **3**]
1	159	103
2	220	41
3	62	200
4	262	–

In conclusion, we have developed synthetic routes to pyrrolidine or pyrrolidone fused cyclic enediynes via intramolecular N-alkylation strategy. The role of the five-membered heterocyclic rings in reducing the onset temperature for BC has also been successfully demonstrated.

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(12) Spectroscopic Data: All new compounds were characterised by spectroscopic and analytical data. Compound **1**: ^{1}H NMR: δ = 8.23 (2 H, dd, $J_{o,m}$ = 6.9, 1.9 Hz), 8.00 (2 H, dd, $J_{o,m}$ = 6.9, 1.9 Hz), 7.32–7.07 (4 H, m), 4.68, 4.19 (2 H, AB_q, J = 18.8 Hz), 3.78, 3.52 (2 H, AB_q, J = 16.6 Hz), 3.49–3.17 (5 H, m), 2.04–1.85 (4 H, m). ^{13}C NMR: δ = 150.0, 143.5, 130.5, 129.8, 128.8, 128.7, 127.9, 126.9, 124.7, 123.9, 90.5, 87.2, 84.0, 82.4, 59.2, 56.0, 50.2, 45.1, 28.2, 23.9. MS (ES+): m/z = 436 [M + H$^+$]. Compound **2**: ^{1}H NMR: δ = 8.31 (2 H, dd, $J_{o,m}$ = 7.0, 2.0 Hz), 7.98 (2 H, dd, $J_{o,m}$ = 7.0, 2.0 Hz), 4.62 (2 H, dd, J = 18.6, 6.0 Hz), 4.33 (1 H, m), 4.21 (2 H, dd, J = 18.6,12 Hz), 3.79 (1 H, dd, J = 12.0, 3.4 Hz), 3.44 (1 H, t, J = 2.0 Hz), 2.65–2.37 (2 H, m), 2.27–2.15 (2 H, m). ^{13}C NMR: δ = 174.7, 150.3, 143.4, 130.6, 130.2, 128.9, 128.7, 128.4, 125.9, 124.6, 124.4, 87.2, 86.5, 84.9, 83.7, 54.8, 48.0, 38.0, 32.6, 29.4, 22.1. MS (ES+): m/z = 450 [M+ H$^+$], 263 [M$^+$ – SO_2Ar]. Compound **3**: δ = 6.43 (1 H, d, J = 10.8 Hz), 5.88–5.79 (2 H, m), 5.28 (1 H, d, J = 15.6 Hz), 4.51–4.42 (2 H, m), 4.12–4.04 (2 H, m), 3.69–3.41 (2 H, m), 2.25–2.14 (1 H, m), 1.97–1.88 (3 H, m). ^{13}C NMR: δ = 121.7, 120.8, 94.7, 93.0, 86.6, 83.4, 67.1, 65.0, 55.5, 54.7, 49.0, 32.0, 30.6, 23.7. MS (ES+): m/z = 170 [M – OH]. Compound **4**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.41 (2 H, dd, J = 8.8 Hz), 8.07 (2 H, dd, J = 8.8 Hz), 7.28 (H, m), 4.28 (2 H, s), 3.66 (2 H, s). ^{1}H NMR (200 MHz, DMSO-d_6): δ = 8.39 (2 H, d), 8.13 (2 H, dd, J = 8.8 Hz), 7.32 (2 H, m), 4.40 (2 H, s), 3.53 (2 H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 150.3, 142.5, 130.7, 128.7, 124.7, 124.6, 85.7, 84.7, 46.3, 40.0. ^{13}C NMR (50 MHz, DMSO-d_6): δ = 150.29, 142.4, 130.5, 129.2, 129.1, 124.9, 104.5, 86.7, 84.9, 45.7. MS (ES+): m/z = 598 [M$^+$ + H_2O], 581 [M + H$^+$], 394 [M$^+$ – SO_2Ar].