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A carbene insertion route to β-lactam fused cyclic enediynes

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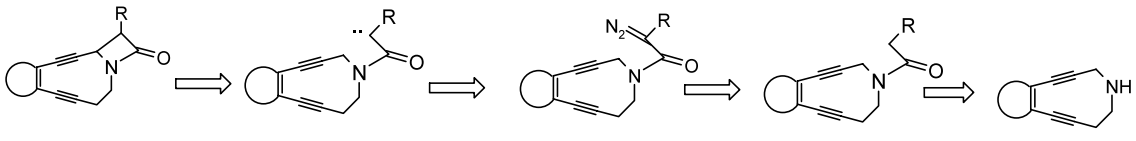
Abstract—A new methodology has been developed for the synthesis of biologically important β-lactam fused enediynes **1** and **2**. The key step is the successful insertion of the carbene generated from the diazo enediynes **3** and **4**. The result is in sharp contrast to the fate of the carbene generated from acyclic enediyne **5** in which case the rearrangement product **6** and the dimer **7** were obtained. © 2002 Elsevier Science Ltd. All rights reserved.

The successful design of enediynes[1,2] requires the incorporation of a locking device the purpose of which is to stabilize the otherwise unstable enediynes. One of the most common ways of stabilizing a reactive enediyne is to fuse a small strained ring with the enediyne framework.[3] For example, in dynemicin the epoxide ring serves this purpose.[4] Recently, Banfi and Guanti[5] as well as our group[6] have independently reported the synthesis of β-lactam fused enediynes (lactenediynes). The strained four-membered lactam ring has been shown to prevent the enediynes from undergoing the Bergman cyclization[7] at room temperature and opening of the β-lactam ring caused the molecule to undergo the same under ambient conditions.[5] In this paper, we report a new approach to the synthesis of these molecules. The salient feature of this new methodology is that it provides functionality at C-3 of the β-lactam that can, in principle, be further elaborated or attached to other entities to boost up its recognition to the target molecules, namely DNA and proteins.[8]

The retrosynthetic analysis of the target enediynes **1** and **2** is shown in Scheme 1. It differs from the earlier reported ones[5,6] in many ways; unlike the previously reported syntheses, in the present case our strategy was to first make the cyclic enediynes and then through appropriate reactions, construct the β-lactam ring. The benzene fused enediynes have previously[9] been shown to be stable at room temperature, which is not the case with the aliphatic one which has a half life of 36 h at 30°C.[10] Thus, the synthetic manipulation to construct the β-lactam ring, especially for the nonaromatic one, should be conducted under mild conditions, preferably below room temperature and over a short period of time.

Since there was always a possibility of the carbene adding to the unsaturation,[11] a model study seemed important before executing the actual chemistry. Towards this end, the *N*-homopropargyl-*N*-propargyl diazo amide **5** was prepared, which was then subjected to the rhodium acetate-catalyzed conditions for carbene generation.[12] However, to our dismay, no β- or γ-lactam containing products were obtained and instead the rearrangement product **6** (via addition to the triple bond) along with the dimer **7** were obtained. Although this result did dampen our spirits to some extent, we were still hopeful about the positive outcome in the actual system because of the rigidity of the cyclic framework of the enediynes and the reported success[13] of carbene insertion to form the oxapenam skeleton (Scheme 2).

Because of the better thermal stability of the benzene fused enediyne, we began to study the feasibility of the carbene chemistry in this system first, to be followed by



Scheme 1.

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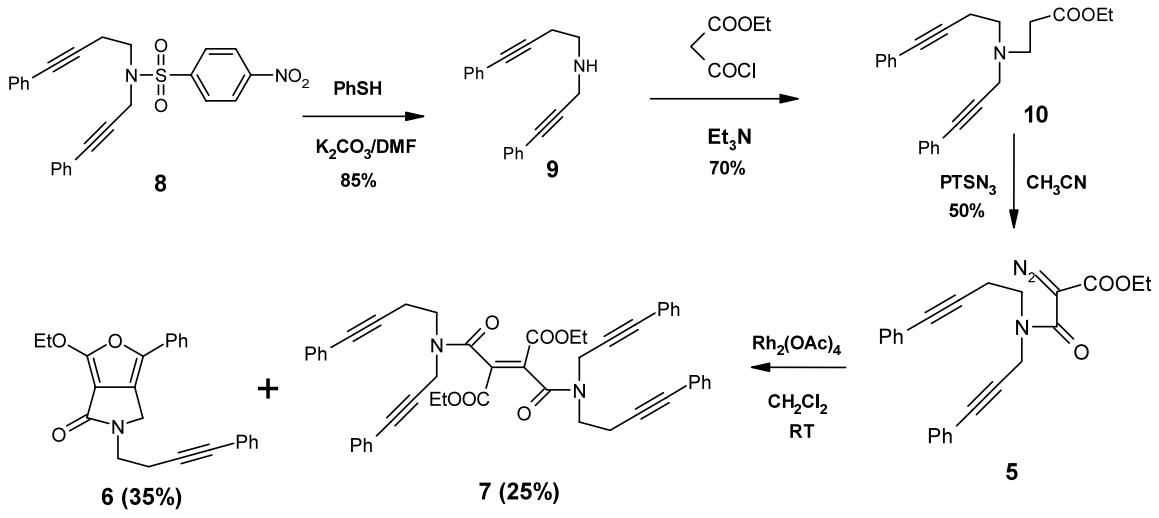

Scheme 2.

non-aromatic enediynes, depending upon the result obtained. Towards this goal, we synthesized the enediynyl amide **13** by acylating the known amine **12**[14] with ethyl malonyl chloride in the presence of triethylamine. The amide on treatment with *p*-toluene sulphonyl azide on potassium carbonate as solid support[15] for 10 min furnished the diazo enediyne **3**. Carrying out the diazo transfer in solution phase (CH_3CN)[16] gave a lower yield (50%) and that too after carrying out the reaction for 36 h! When a solution of the diazo enediyne **3** was treated with a catalytic amount of rhodium acetate for 30 min, the starting material disappeared completely and the β-lactam fused enediynes was obtained as the only isolable product.[17] The yield in the carbene insertion step was about 50%, the rest being base line decomposition products (Scheme 3).

These steps were repeated for the synthesis of the non-aromatic enediyne **2**. Thus, the amine **15** was isolated via deprotection of the corresponding sulphonamide.[18] Acylation followed by diazo transfer furnished the diazo enediyne. This on treatment with rhodium acetate in dichloromethane for 30 min furnished the β-lactam fused enediyne **2** which was purified by column chromatography. However, the yield of the carbene insertion step was lower (35%) as compared to formation of the corresponding aromatic enediyne (Scheme 4).

In conclusion, we have successfully developed an alternative route to β-lactam fused enediynes. The activity, both chemical and biological, of these molecules are currently under study and will be reported in due course.

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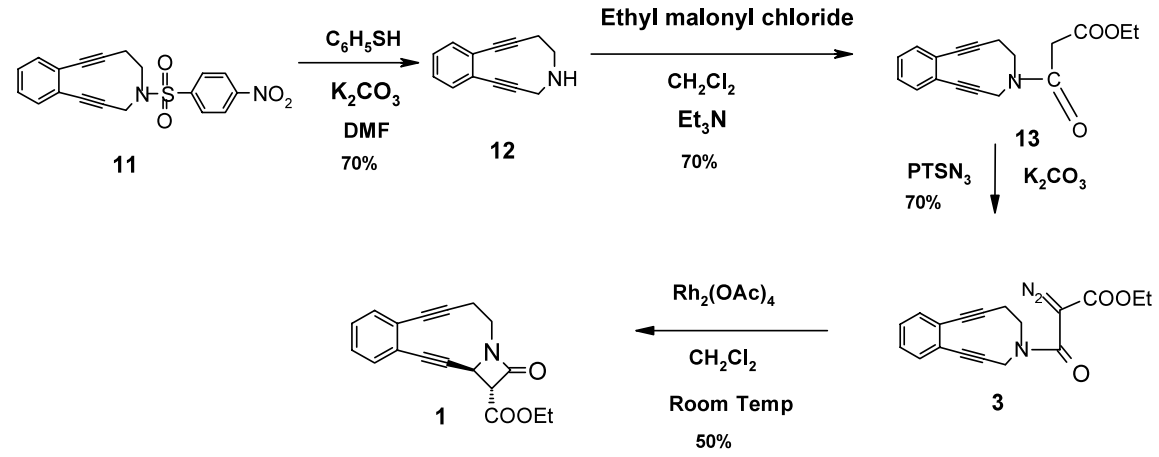
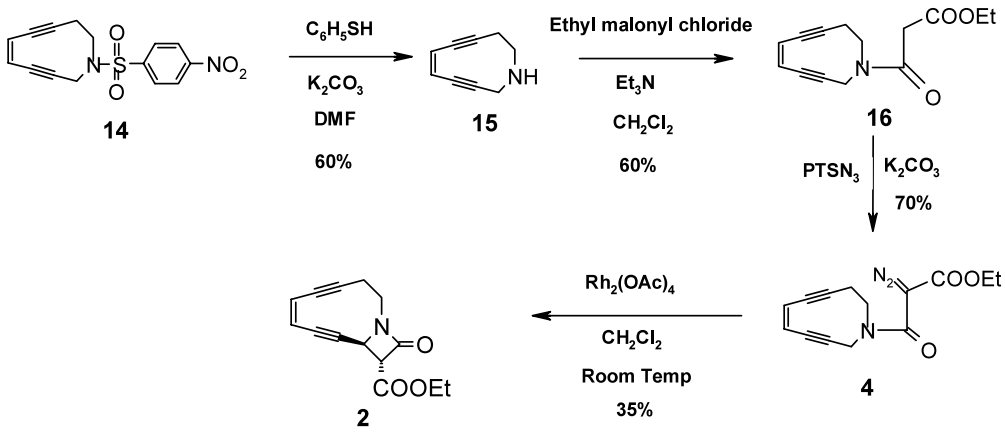


Scheme 3.



Scheme 4.

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18. All new compounds have been fully characterized by various spectral data. Representative NMR data for compound **1**: δ_H ($CDCl_3$, ppm) 7.40–7.15 (4H, m, Ar-H), 4.76 (1H, d, $J=2.5$ Hz, H-4), 4.32 (2H, q, $J=7.0$ Hz, CH_2CH_3), 4.09 (1H, d, $J=2.5$ Hz, H-3), 4.04 (1H, dt, $J=2.8$, 15.7 Hz, H-16), 3.34–2.98 (2H, m, H-15, H-16), 2.50 (1H, dt, $J=2.9$, 17.3 Hz, H-15), 1.29 (3H, *m*, $J=7.0$ Hz); δ_C ($CDCl_3$, ppm) 166.33, 162.07, 129.95, 129.02, 128.63, 128.05, 127.73, 100.56, 94.90, 89.07, 81.12, 62.18, 60.82, 47.53, 44.66, 20.99, 14.15.