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Synthesis of Constrained α-Amino Acid Derivatives *via* Enyne Metathesis Reaction*

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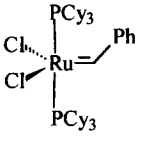
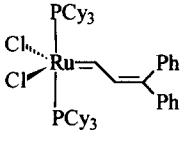
Abstract: Synthesis of a diene building block *via* enyne metathesis reaction and its usage in the preparation of constrained α-amino acid derivatives is described.

In recent years, the catalytic ring-closing metathesis (RCM) reaction has been employed in the construction of carbocyclic, heterocyclic and macrocyclic frames at an accelerated pace. In this regard, introduction of new catalysts such as Grubb's ruthenium catalysts (**A** & **B**) and Schrock's molybdenum catalyst (**C**) have imparted significant impetus to this method.[1] As a variant on RCM reaction of diene, the enyne metathesis reaction offers a novel and simple route to 1-vinylcycloalkenes from acyclic building blocks.[2] The intramolecular enyne metathesis reaction involves a formal 2+2 cycloaddition followed by ring opening of the resulting cyclobutene to generate an inner-outer diene.



A



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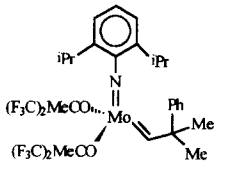
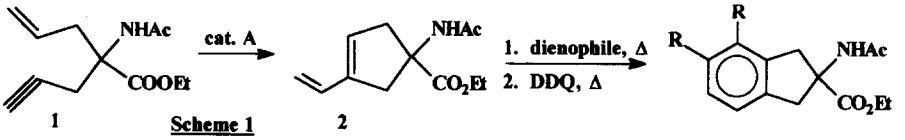


C

In view of our interest in the preparation of useful building blocks containing the α-amino acid (AAA) moiety,[3] we were intrigued with the possibility of using the enyne metathesis reaction for the preparation of dienes (e.g., **2**). Applying this concept to diene indicates its precursor should be 1,6-enyne and the basic idea is displayed in Scheme 1. In this communication we disclose our preliminary results for the synthesis of the building block **2** using enyne metathesis as a key step and its subsequent utility in the preparation of unusual AAA derivatives in Diels-Alder fashion.



1 **Scheme 1** **2**

Initially, we prepared the enyne building block **1** from ethyl isocyanoacetate **3** by two independent pathways (Scheme 2). Reaction of **3** with allyl bromide under phase-transfer conditions (tetrabutyl ammonium hydrogen sulfate and potassium carbonate in acetonitrile reflux)[4] gave diallyl compound as the major product (57 %) and mono allyl derivative as the minor product (13 %).[5] Mono allyl compound was subjected to propargylation under similar reaction conditions to those described earlier to generate the

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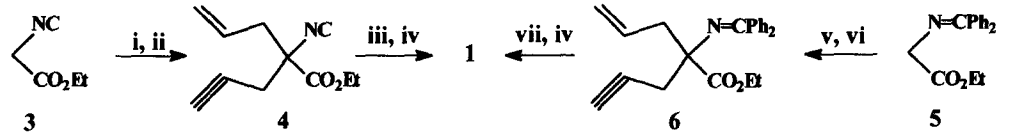
isonitrile derivative **4** (68 %). Hydrolysis of **4** at room temperature using HCl/EtOH gave amino ester (95%), which upon acetylation with acetic anhydride in the presence of a catalytic amount of 4-dimethyl-aminopyridine in dichloromethane gave the enyne derivative **1** (70 %, mp. 91-92 °C). The structure of **1** is supported by spectral data (^{13}C NMR 75 MHz, $CDCl_3$: δ 171.9, 169.6, 131.6, 119.6, 79.4, 70.9, 62.7, 62.2, 39.1, 25.1, 23.9, 14.2).

In order to improve the yield of the enyne building block **1**, we also attempted its preparation by a propargylation and allylation sequence and found no advantage over the earlier route. Despite these successes, the low yields for the formation of the building block **1** forced us to search for alternative methods. In 1976 Stork reported [6] that the benzylidene derivative of glycine ester can be selectively α-alkylated with one or two electrophiles in a stepwise manner leading to non-cyclic mono and dialkylated amino esters. Based on these findings, we reasoned that it may be possible to introduce propargyl and allyl function in a stepwise fashion. Moreover, in recent times, this idea was refined by the usage of more stable glycine equivalents such as **5** [N-(diphenylmethylene)glycine ethyl ester]. [7] Thus, the two-step alkylation of **5** with propargyl and allyl bromide under solid-liquid phase-transfer conditions furnished **6**. Hydrolysis of **6** gave an amino ester which was protected as the acetyl derivative **1** (42 % overall yield from **5**) and the spectral data of this compound is found to be identical to the material obtained from the ethyl isocyanoacetate route.

Having obtained the enyne building block **1**, the next task was to demonstrate the key enyne metathesis reaction (Scheme 1). Exposure of enyne **1** to ruthenium catalyst **A** (10 mol %) in dichloromethane at room temperature for 37 h effects smooth conversion to the desired vinylcyclopentene derivative **2** (53-75% yield, mp. 85-86 ° C). The spectral data confirmed the structural assignment [^{13}C NMR, 75 MHz, $CDCl_3$: δ 173.5, 170.0, 140.2, 132.5, 126.6, 115.1, 64.1, 61.5, 44.3, 42.6, 23.0, 14.0].

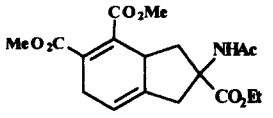
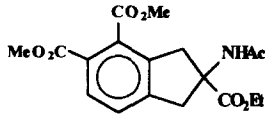
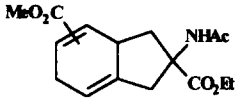
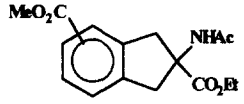
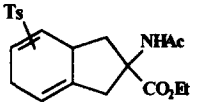
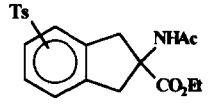
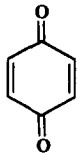
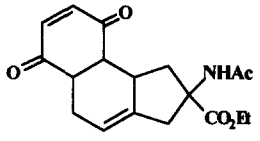
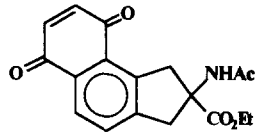
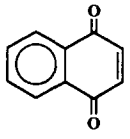
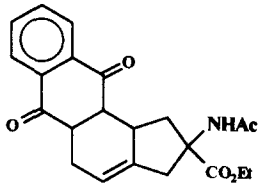
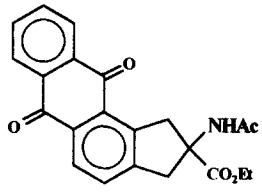


Scheme 2: **i. Allyl bromide, ^{n}Bu$_4$NHSO$_4$, K_2CO_3 ii. propargyl bromide, ^{n}Bu$_4$NHSO$_4$, K_2CO_3 iii. HCl, EtOH iv. Ag_2O, DMAP, CH_2Cl_2 v. propargyl bromide, K_2CO_3 vi. allyl bromide, KOH, ^{n}Bu$_4$NBr vii. 1N HCl, ether**

With the synthon **2** in hand, we examined its Diels-Alder (DA) reaction [8] with various dienophiles. On completion of the cycloaddition as determined by TLC, the DA products were isolated by flash chromatography. Various substrates that have undergone DA reaction and oxidative elimination to generate angularly substituted indane AAA derivatives are shown in Table 1. In the case of entries 2, 4 & 5, we found that DA products were contaminated with aromatized compounds. In other examples, aromatization was carried out by treating the total reaction mixture with DDQ (benzene reflux) [9] and the final products were isolated by flash chromatography. Of particular interest is entry no. 3 where the alkynyl sulfone group provides an additional handle for further synthetic manipulation. [10]

In conclusion, we have shown that the enyne metathesis reaction and DA strategy is very useful to generate angularly substituted indane-based AAA derivatives. Given the dearth of constrained AAA derivatives, [11] this methodology may find useful applications in bioorganic and medicinal chemistry.

TABLE 1: Synthesis of AAAs Using Diene Building Block Prepared by Enyne Metathesis

S. No.	Dienophile	D. A. Product [a]	Oxidation Product [b]	Yields [c]
1				88%
2				67%
3				82%
4				67%
5				87%

[a] Diels-Alder reaction conditions: entry 1. PhH/reflux, 32 h, PhMe/reflux, 37 h, 98 %; entry 2. PhH/reflux, 7 days, 69 %;. entry 3. PhH/reflux, 25 h, PhMe/reflux, 40 h, 91 %; entry 4. PhH/reflux, 40 h, 93 %; entry 5. PhH/reflux, 24 h, PhMe/reflux, 72 h, 99 %. [b] All reactions carried out in benzene reflux in presence of DDQ. [c] Isolated combined yield for two steps.

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References and Notes:

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