



Synthesis of aromatic natural product frameworks using enyne metathesis

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Abstract—Enynes, easily obtained by the Sonogashira coupling reactions of aromatic iodides, undergo, with good yields, enyne metathesis using the Grubbs catalyst. The resulting dienes are interesting carbo- and heterocycles which can give complex natural frameworks by Diels–Alder reactions. Thus, an estradiol type skeleton is obtained in two steps from the corresponding enynes. An example of a metathesis–Diels–Alder cascade one-pot process is reported. © 2001 Elsevier Science Ltd. All rights reserved.

Multiple bond metathesis reactions have become synthetically powerful tools to achieve molecular complexity in an elegant way.¹ Among the different possibilities, the ring closing alkene–alkyne reaction is the one which has received less attention.² This process formally implies the formation of a carbon–carbon bond and the migration of the alkylidene part onto the alkyne carbon, to form a diene (Fig. 1). On the contrary to other metathesis reactions, the mechanism is not completely clear.

The use of aromatic enynes has hardly been reported in this reaction.³ These compounds can be easily prepared and, after the metathesis process, would lead to inter-

esting dienes which can be used in Diels–Alder reactions. The combination of enyne metathesis followed by Diels–Alder reactions has been recently explored for the synthesis of other compounds like perhydroindenes,⁴ tetrahydropyridines⁵ or polycyclic- β -lactams.⁶ Thus, we have prepared a series of enynes following Scheme 1.

The starting products were the 2-trimethylsilyl ethynyl substituted phenol, aniline and benzaldehyde **1–3** obtained by Sonogashira coupling from the corresponding iodo compounds.⁷ The allyl and homoallyl ethers **4** were obtained by Mitsunobu reactions. Amides **5** were synthesized by alkylation of the corresponding acetamide in phase transfer conditions with allyl and

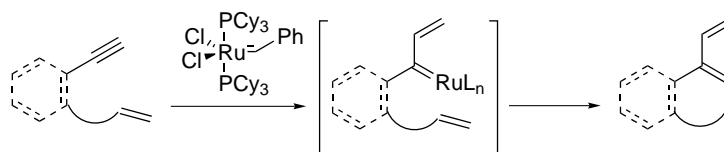
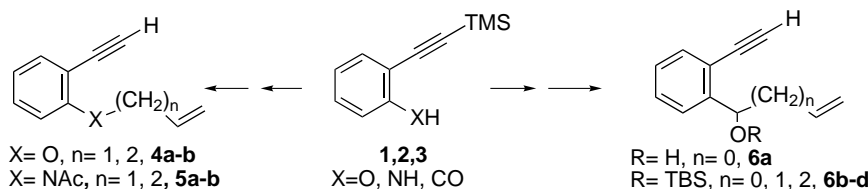


Figure 1.



Scheme 1.

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homoallyl bromide. The reaction of an appropriate Grignard reagent with **1** ($X=CO$), and further protection of the resulting alcohol allowed us to obtain substrates **6**.

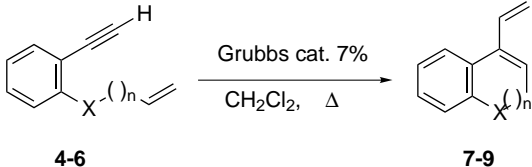
These substrates were submitted to metathesis using 7% of Grubbs catalyst and the reactions were carried out in refluxing dichloromethane.⁸ Among the different solvents used (toluene, benzene), and catalyst proportions (3, 5, 7 and 10%), these were the conditions which gave better results. Table 1 summarizes the results obtained in these reactions.

The yields summarized in Table 1 go from reasonable to good in all cases but some comments ought to be made. The reaction of the two ethers **4**, gave only 50% conversion after 2 h, and was not improved after 18 h or when adding more catalyst to the reaction. Thus, we added a total of 10% of catalyst divided into four equal portions, which were added every 30 min. Before each addition, the reaction mixture was filtered through Celite. With this procedure, the remaining starting material was reduced to less than 10% and we isolated

the dienes **7** with good yields. Alcohol **6a** gave the corresponding diene, which could only be observed in the spectrum of the crude mixture. This reaction product decomposed after few hours at room temperature. All attempts to isolate it were unsuccessful. In addition, no reaction was observed with the TBS protected compound **6b**. We opted thus to react **6a** and protect the hydroxydiene in the crude mixture obtaining **9b** with 50% yield after the two reaction steps. On the other hand, the TBS protected compounds **6c** and **6d** reacted smoothly to give the dienes **9c–d** with good yields. Amides **5a–b** reacted with excellent yields.⁹

The dienes obtained in these metathesis reactions are related to Dane's diene which has been much used as starting material for the synthesis of several natural products.¹⁰ In particular, the Diels–Alder reactions with suitable dienophiles would lead to tetracyclic structures. Thus, we carried out the synthesis of substrate **11** by reduction of the hydroxyl group in compound **10** with superhydride (Scheme 2).¹¹ The metathesis reaction proceeded with good yield (70%), and the obtained diene **12** gave, upon reaction with maleic anhydride, a

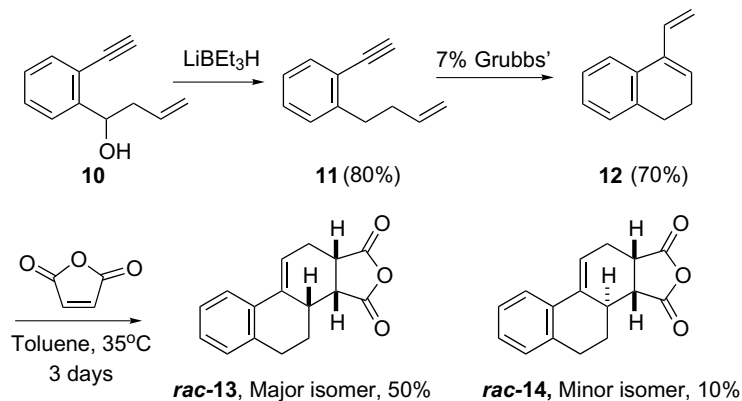
Table 1. Synthesis of dienes **7–9**

					
Entry	Substrate	X	<i>n</i>	Product	Yield (%) ^a
1	4a	O	1	7a	65 ^b
2	4b	O	2	7b	60 ^b
3	5a	NAc	1	8a	95
4	5b	NAc	2	8b	85
5	6a	CHOH	0	9b	50 ^c
6	6b	CHOTBS	0	N.R.	–
7	6c	CHOTBS	1	9c	85
8	6d	CHOTBS	2	9d	85

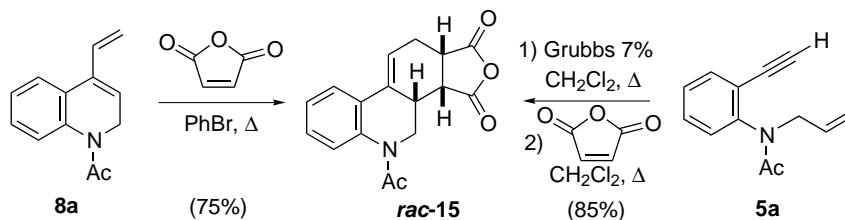
^a Of pure material with correct spectroscopic data (¹H, ¹³C NMR, IR).

^b 10% of total catalyst was added in four portions after filtration.

^c Yield corresponds to TBS protected product **9b** obtained from the crude mixture of the metathesis reaction.



Scheme 2.



Scheme 3.

3:1 mixture isomers where major adduct, **rac-13**, was isolated in 50% yield, and minor compound **rac-14** in 10% yield. These compounds were assigned as the stereoisomers depicted in Scheme 2 by analogy with related structures described by Göbel.^{10a}

On the other hand, compound **8a** reacted with maleic anhydride only in refluxing bromobenzene, yielding, after 2 h, 75% of compound **rac-15** (*endo* adduct). A minor isomer of this compound was detected in less than 10% amount in the crude ¹H NMR spectrum (Scheme 3). The relative configuration of this adduct was determined by analogy with previously reported compounds.¹² In order to avoid these severe reaction conditions we tried the one-pot obtention of compound **rac-15** by adding the dienophile to the metathesis reaction mixture, once total conversion of the enyne was verified (TLC). We were very pleased to obtain the final pure tetracyclic compound **rac-15** in 85% overall yield, after 36 h of reaction in refluxing dichloromethane. This result shows the possible catalytic action of the ruthenium complex in the Diels–Alder reaction. We are currently investigating the generality of this process with other enynes and dienophiles.

In conclusion, we have shown a new entry to the skeleton of steroids and aza- or oxa-steroids based on the enyne metathesis reaction. The tetracyclic structure is constructed in two steps from readily available enynes. Other interesting skeletons like benzoazepines have been obtained with good yields. A cascade metathesis–Diels–Alder example is also shown.

Acknowledgements

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- General procedure follows: 1 mmol of enyne is dissolved in 20 mL of dry dichloromethane under argon. To this solution, 0.07 mmol of benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium is added and the reaction refluxed for 5–15 h (TLC). Filtration through Celite, evaporation of the solvent and purification by chromatography yields the corresponding diene.
- Spectroscopic data for compound **8a**: ¹H NMR (CDCl₃) δ 2.22 (s, 3H), 4.45 (bs, 2H), 5.30 (d, 1H, *J*=11.0 Hz), 5.58 (d, 1H, *J*=17.0 Hz), 6.18 (t, 1H, *J*=4.4 Hz), 6.56 (dd, 1H, *J*₁=11.0 Hz, *J*₂=17.0 Hz), 7.15–7.29 (m, 3H), 7.43 (d, 1H, *J*=7.7 Hz). ¹³C NMR (DMSO-*d*₆, 80°C) δ 168.2, 136.9, 134.1, 132.8, 128.1, 126.9, 124.7, 124.1, 124.0, 123.6, 116.3, 41.3, 21.6. IR (neat) ν 1660, 1600, 1580.
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