Anomalous metathesis reactions of 3,4-disubstituted indoles

Leticia Pérez-Serrano,[†] Gema Domínguez, and Javier Pérez-Castells*

Departamento de Química, Facultad de Ciencias Experimentales y de la Salud. Universidad San Pablo-CEU. Urb. Montepríncipe, Boadilla del Monte 28668-Madrid, Spain
E-mail: jpercas@ceu.es

Dedicated to Prof. Benito Alcaide on the occasion of his 60th birthday

Abstract
3,4-Enynoindoles undergo metathesis reactions leading to structures related to alkaloids. The formation of an unexpected product is reported and discussed

Keywords: Metathesis, indoles, enynes, ruthenium

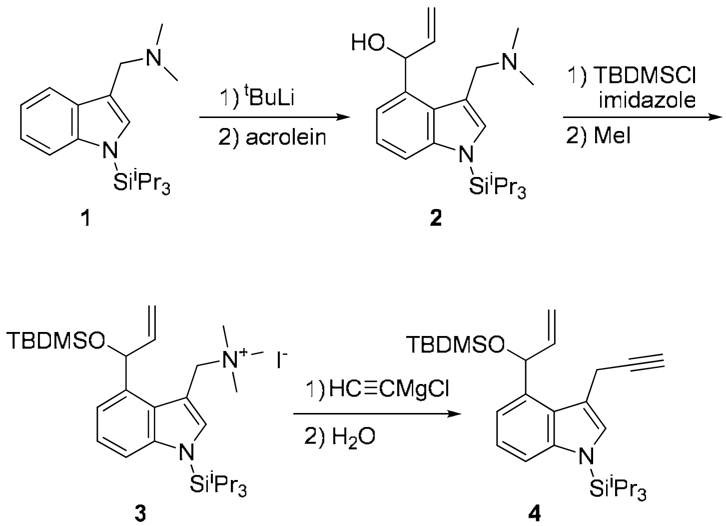
Introduction

The use of the new ruthenium carbene complexes introduced by Grubbs as efficient catalysts for metathesis reactions[1] has led to a great increase in the synthetic applications of these processes. New generations of catalysts have increased the scope of the reaction.[2] Following our ongoing program consisting of the use of aromatic enynes and dienes as starting materials for the synthesis of natural products,[3] we were interested in obtaining polycycloindoles[4] by metathesis reactions. In previously published results, some 3,4-enynoindoles were prepared in our group and gave smoothly the desired 1,3-dienes.[5] These compounds only reacted at high temperatures using second generation Grubbs catalyst **7**. We herein report an anomalous result with one compound similar to those used in our previous report that gives an un-precedent product in metathesis catalysed by ruthenium carbene complexes.

Results and Discussion

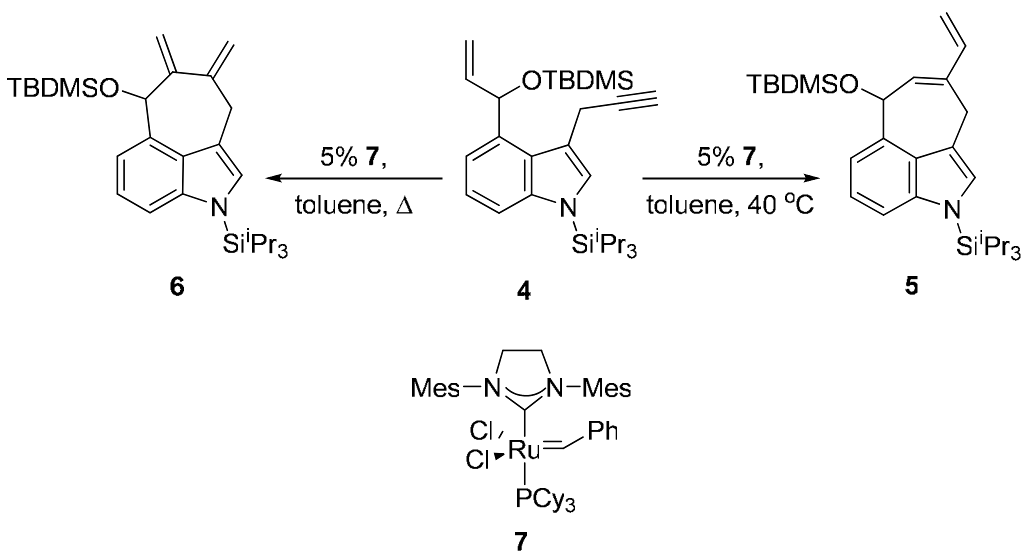
The synthesis of the starting material was carried out following our reported procedure which is an extension of previous works by Iwao.[5] Thus, protected gramine **1** was lithiated at the 4 position. This lithiation is directed by the tertiary amine group. The 4-lithioindole derivative was treated *in situ* with acrolein giving **2**, with good yield. This intermediate was protected as

TBDMS derivative and transformed into the corresponding ammonium salt **3**. The reaction of this salt with ethynyl magnesiumchloride gave the enynoindole **4** (Scheme 1).



Scheme 1. Synthesis of enynoindole **4**.

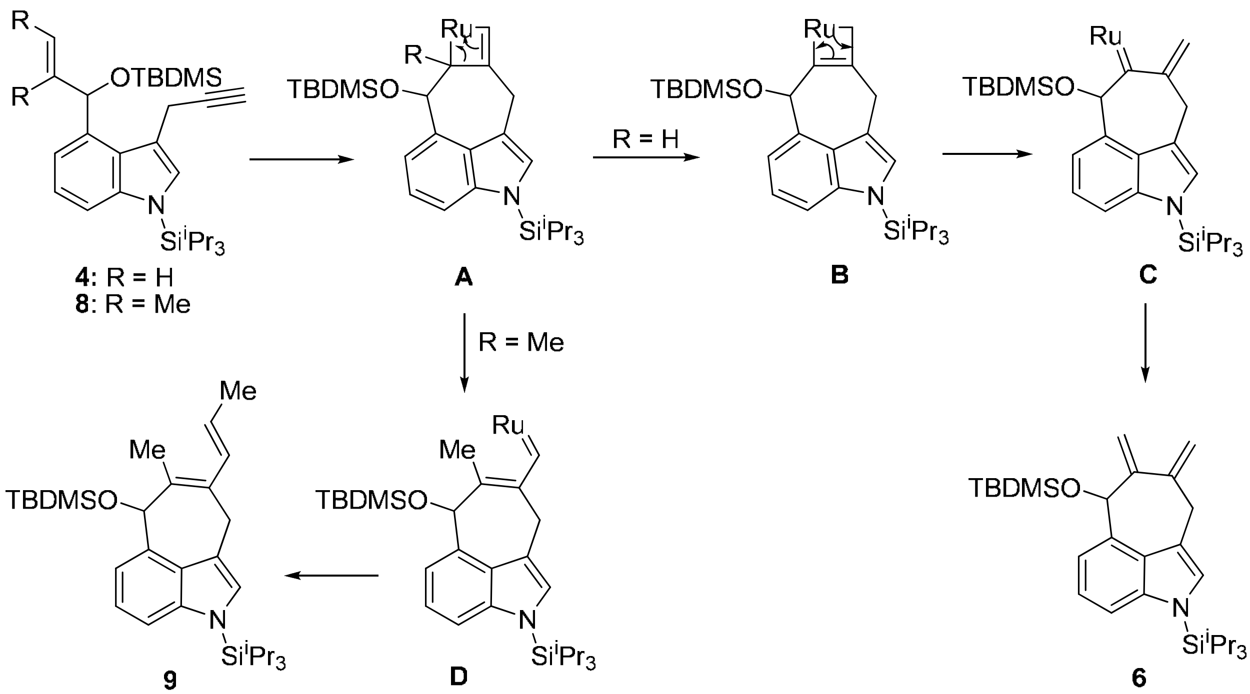
This compound was submitted to metathesis reactions under several conditions. As first generation ruthenium catalysts decomposes at high temperatures, complex **7** was added slowly to a 40 ^{o}C solution of **4** obtaining **5** in low yield (Scheme 2). However, this compound could not be fully characterized as it decomposed in few minutes.



Scheme 2. Metathesis reactions of **4**.

When adding catalyst **7** to a refluxing toluene solution of **4** we obtained only one reaction product without recovery of any starting material. The structure of this compound was unambiguously assigned to compound **6**. This is the first time a compound with this structure is obtained in an enyne metathesis. The enyne metathesis is thought to proceed by coordination of the ruthenium with the double bond followed by cycloreversion and metathesis with the triple bond. There is some controversy on which is the bond that coordinates first with the Ruthenium and Mori has described some products that are compatible with a course of reaction implying an yne-ene pathway.[6]

Nevertheless, we and others have seen by NMR studies of other enyne metathesis, that some signals of new carbenic species compatible with an ene-yne pathway are observed during the reactions with first generation catalyst.[7] This prompts us to think that the formation of a compound like **6** is possible through coordination with the double bond, formation of the metalacyclobutene **A** and isomerization into **B**, involving an hydride abstraction. This intermediate evolves into the carbene **C** which finally gives **6** upon reaction with another molecule of the starting material. This process only occurs at high temperatures. In the case of compound **8**, as the presence of the methyl group inhibits the isomerization of the metalacyclobutene, this intermediate follows the general metathesis pathway onto **D**, which finally gives the expected enyne metathesis product **9**, as we have reported before (Scheme 3).[5c]



Scheme 3. Possible reaction pathway for the formation of **6**.

In order to get more information on this metathesis reaction, we proceeded to follow it by ^1H NMR. The reaction was carried out with 25% catalyst in 0.025 M solution of starting material at 40 °C and in xylene-d_{10}. We registered a proton spectrum every 15 minutes as depicted in Figure 1. The ruthenium complex is partially transformed into a new complex. Nevertheless at this temperature the product being formed is **5** instead of **6**. It seems this temperature is not enough to promote isomerization of the metalacyclobutene. Our efforts to monitor this reaction at higher temperatures gave sluggish spectra that we could not analyse (Figure 1).

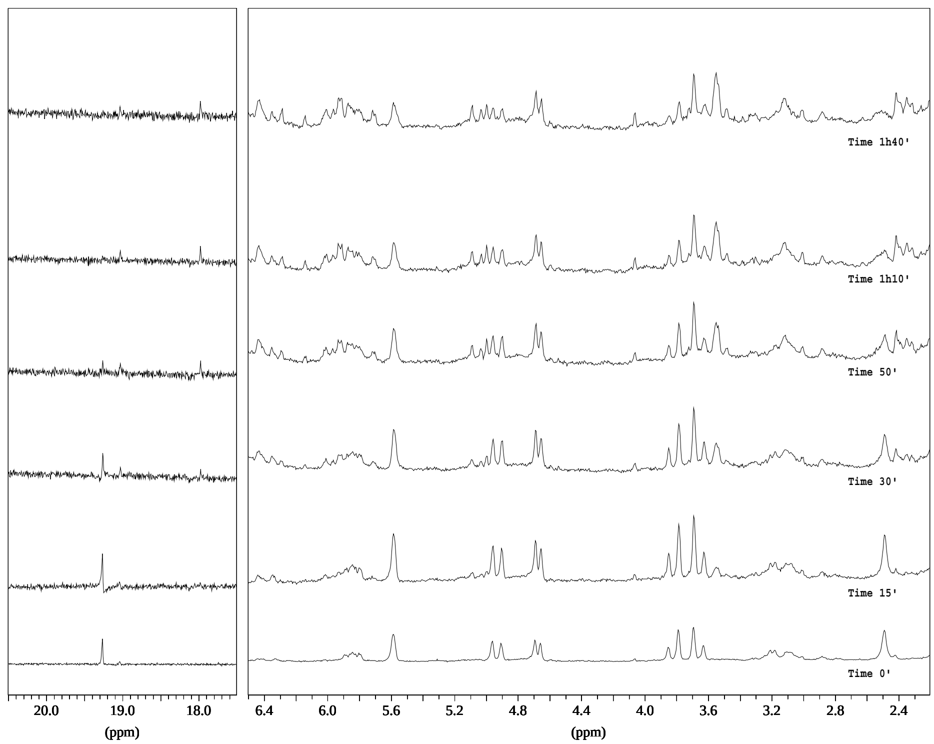


Figure 1. ^1H NMR monitorization of the reaction of **4** at 40 °C.

Conclusions

In conclusion, we show here an anomalous result in enyne metathesis reactions catalysed by ruthenium complexes. We are currently investigating if this behaviour is extensible to other substrates.

Experimental Section

General Procedures. Thin layer chromatography (t.l.c.) was accomplished using Merck TLC aluminium sheets (silica gel 60 F_{254}). Flash column chromatography was carried out on Merck silica gel (230-400 mesh). The IR spectra were recorded on a Perkin Elmer 1330 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-300 instrument in $CDCl_3$ with TMS. The following NMR abbreviations are used: b (broad), s (singlet), d (doublet), t (triplet), m (multiplet), Elemental analyses were performed in the Facultad de Farmacia (Universidad Complutense Madrid); all analytical values for C, H and N were within ± 0.4% of the theoretical values.

4-[1-*tert*-Butyldimethylsilyloxy(prop-2-en-1-yl)]-3-(prop-2-yn-1-yl)-1-(triisopropyl-silyl)-1*H*-indole (4). Compound **3**, (1.75 g, 3.5 mmol) was protected as TBDMS derivative.[8] This compound was transformed into its trimethylammonium salt **3** by reaction with 0.43 mL of CH_3I. Conversion into **4** was achieved by treatment of this salt, solved in 50 mL of THF with 28.0 mL of ethynylmagnesium chloride 1M. The mixture was refluxed under argon overnight, and then was treated with 10 mL of a saturated aqueous NH_4Cl solution and extracted with EtOAc (3x10 L). The organic layer was washed with brine (30 mL), dried ($MgSO_4$) and concentrated. The crude thus obtained, was purified by flash chromatography (hexane-hexane/AcOEt 49:1), yielding pure enyne **5 (**1.43 g 85%) as a colorless oil. IR (neat) 3300, 2110, 1460, 1430 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ -0.11 (s, 3H), 0.02 (s, 3H), 0.89 (s, 9H), 1.13 (d, 18H, *J*= 7.7 Hz), 1.62-1.72 (m, 3H), 2.19 (t, 1H, *J*= 2.2 Hz), 3.86 (dd, 1H, J_1= 19.2 Hz, J_2= 2.2 Hz), 3.93 (dd, 1H, J_1= 19.2 Hz, J_2= 2.2 Hz), 5.00-5.16 (m, 2H), 5.78 (bs, 1H), 6.09-6.20 (m, 1H), 7.08 (t, 1H, *J*= 7.7 Hz), 7.14 (d, 1H, *J*= 7.7 Hz), 7.29 (s, 1H), 7.36 (d, 1H, *J*= 8.2 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ -4.8, -4.6, 12.9, 18.1, 18.2, 18.3, 25.9, 69.5, 73.7, 83.4, 112.3, 113.2, 113.6, 118.4, 121.2, 126.7, 130.4, 135.6, 142.2, 142.4; *Anal.* Calcd. for $C_{29}H_{47}NOSi_2$: C. 72.28; H. 9.83; N. 2.91. Found: C. 72.41; H. 9.99; N. 2.80.

(*E*)-6-(tert-Butyldimethylsilyloxy)-2-(triisopropylsilyl)-8-vinyl-6,9-dihydro-2*H*-cyclohepta[*cd*]indole (5). Compound **4** (0.1 g, 0.21 mmol) was dissolved in 20 mL of dry toluene under argon. To this solution, Ruthenium catalyst **7** (12.5 mg) was added and the reaction was stirred at 40 ºC for 3h. The mixture was filtered through celite and the solvent evaporated under vacuum. The crude thus obtained was purified by flash chromatography (hexane) to obtain 0.010 g (10%) of **5** as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ -0.05 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 1.14 (d, 18H, *J*= 7.7 Hz), 1.59-1.74 (m, 3H), 3.74 (d, 1H, *J*= 12.6 Hz), 3.86 (d, 1H, *J*= 12.6 Hz), 5.30 (d, 1H, 9.9 Hz), 5.36 (d, 1H, 17.6 Hz), 5.99 (dd, 1H, J_1= 14.3 Hz, J_2= 5.0 Hz), 6.16-6.23 (m, 1H), 6.33 (d, 1H, *J*= 5.0 Hz), 6.95 (s, 1H), 7.00-7.10 (m, 2H), 7.34 (d, 1H, *J*= 8.1 Hz)

6-(*tert*-Butyldimethylsilyloxy)-7,8-dimethylene-2-(triisopropylsilyl)-6,7,8,9-tetrahydro-2*H*-cyclohepta[*cd*]indole (6). Compound **4** (0.1 g, 0.21 mmol) was dissolved in 20 mL of dry toluene under argon. To this solution, Ruthenium catalyst **7** (12.5 mg) was added and the reaction was refluxed for 6h. The mixture was filtered through celite and the solvent evaporated under vacuum. The crude thus obtained was purified by flash chromatography (hexane) to obtain 0.04 g (40%) of **6** as a colorless oil. IR (neat) 1460, 1430 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ -0.05 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 1.12 (d, 18H, *J*= 7.7 Hz), 1.59-1.74 (m, 3H), 3.73 (d, 1H, *J*= 16.0 Hz), 4.73 (d, 1H, *J*= 16.0 Hz), 4.94 (s, 1H), 5.03 (s, 1H), 5.28 (s, 1H), 5.32 (s, 1H), 5.63 (s, 1H), 6.95 (s, 1H), 7.00-7.08 (m, 2H), 7.32 (d, 1H, *J*= 7.7 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ -4.9, -4.7, 12.8, 18.2, 18.3, 25.9, 33.1, 77.1, 110.7, 110.8, 113.2, 115.9, 116.6, 121.3, 126.0, 128.7, 136.2, 141.3, 148.26, 151.9; ^{13}C-NMR (300 MHz, C_6D_6): δ -4.6, -4.5, 12.9, 18.1, 18.6, 26.1, 33.7, 78.5, 111.2, 111.3, 113.8, 117.2, 117.4, 122.0, 126.3, 129.6, 136.9, 142.1, 149.0, 152.4; *Anal*. Calcd. for $C_{29}H_{47}NOSi_2$: C, 72.28; H, 9.83; N, 2.91. Found: C, 72.45; H, 9.99; N, 23.07.

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