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Enyne and dienyne metathesis reactions in β-carbolines

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Abstract—New indolic enynes and dienynes, based on the β-carboline system, give metathesis products with ruthenium catalysts. The synthesis of the starting materials is readily achieved from tryptamine. The tuning up of the conditions for the metathesis is discussed. Cascade metathesis gives an oxidized pentacyclic product.

The enyne metathesis reaction[1] is completely atom economical and formally implies the formation of a carbon–carbon bond and the migration of the alkylidene part onto the alkyne carbon, to form a diene. In recent years, there has been great interest in intramolecular enyne metathesis[2] especially with regard to further transformations of the resulting conjugated dienes. Thus, domino transformations, including tandem RCM of dienynes,[3] have lead to synthetic applications in the field of polycycle construction and natural product syntheses.

Enynes connected through an aromatic ring are interesting substrates that have found scarce use in this chemistry. We have used benzenic and indolic enynes to construct complex polycycles.[4] In this paper, we describe the first use of β-carboline derived enynes and dienynes in metathesis processes involving tandem metathesis reactions.

This new approach is a powerful entry into polycyclic structures related to alkaloids containing the β-carboline unit such as those depicted in Figure 1.

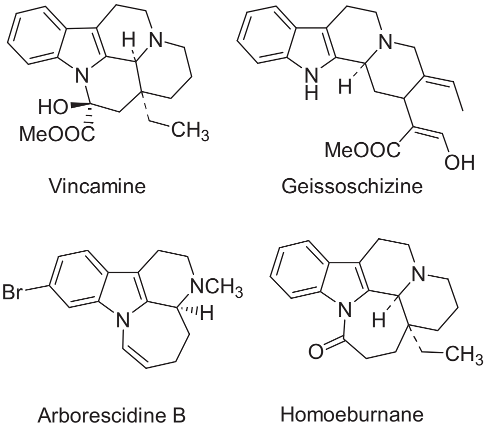

Figure 1. Some β-carboline alkaloids.

The synthesis of the starting enynes was accomplished from tryptamine. The reaction of tryptamine with ethylformate gives formamide **1** which, when treated with NaH and allyl bromide gives a mixture of monoallyl derivatives **2** and **3** and diallylcompound **4**. With a careful selection of the reaction conditions mono- or diallyl products can be made selectively (Scheme 1). Thus, excess of base and allyl bromide gave **4** as the only reaction product in 65% yield, while the use of 1 equiv of base and 2 equiv of allyl bromide gave a 2:1 mixture of **2** and **3** which was separated by column chromatography, yielding pure **2** (64%) and **3** (30%). Compound **3** was protected on the indole nitrogen with tosyl chloride using NaH as the base, giving **5** in 80% yield.

Compound **2** was cyclized using the Bischler–Napieralski reaction, giving the corresponding 9-allyldihydro-β-carboline which was reacted with an alkynylmagnesium bromide and protected, to afford the desired enynes **6a**,**b**. Best yields were achieved when isolating the intermediate cyclic imine (Scheme 2a). On the other hand, compounds **4** and **5**, were reacted with $POCl_3$ and the

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Keywords: Enynes; β-Carboline; Metathesis; Cascade reactions; Ruthenium.

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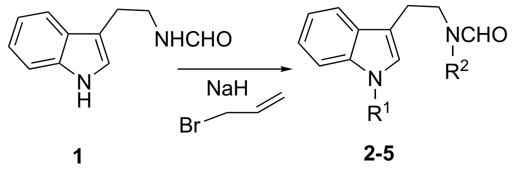


	R_1	R_2	Prod.	Yield	Conditions^a
	Allyl	H	**2**	64%	1:1:2
	H	Allyl	**3**	30%	1:1:2
NaH	Allyl	Allyl	**4**	65%	1:5:5
p-TsCl	Ts	Allyl	**5**	80%	

^{a} Proportion of indole:base:allylbromide.

Scheme 1. Synthesis of enyne precursors.

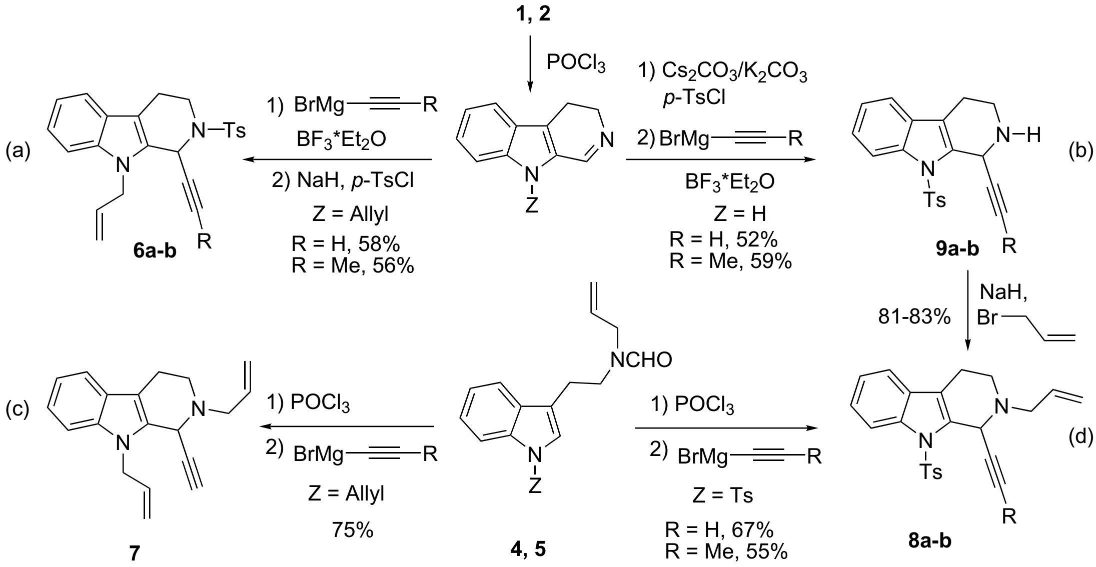
corresponding Grignard reagent in a 'one-pot' fashion, affording **7** and **8a**,**b**, respectively, in good yields (Scheme 2c and d). In this approach the synthesis of **8a**,**b** started from **3** which was a minor product obtained in the alkylation of **1**. As the yield of compound **3** was low, an alternative synthesis of **8a**,**b** was addressed. Thus, we transformed quantitatively formamide **1** into the corresponding dihydro-β-carboline which was protected as the tosyl derivative, using in this case Cs_2CO_3/K_2CO_3 as the base. The reaction with the appropriate alkynylmagnesium bromide yielded **9a**,**b** in 52–59% yield from **1** (Scheme 2b). Subsequent allylation of these intermediates in position 2 gave **8a**,**b**. The global yield of this route from **1** to the enynes **8a**,**b** is 42% and 49%, respectively.

We accomplished next, the metathesis reaction of these starting compounds. The reaction of enyne **6a** was used as a model and was reacted with catalysts **A**, **B** and **C** under different reaction conditions (Scheme 3). While catalyst **A** did not give any conversion (entry 1), both complexes **B** and **C** led to the desired diene product **10a** with similar yields, toluene being a better solvent than dichloromethane (entries 2 and 3). All reactions were carried out at room temperature, as extensive decomposition of the starting material occurred when operating at an elevated temperature.

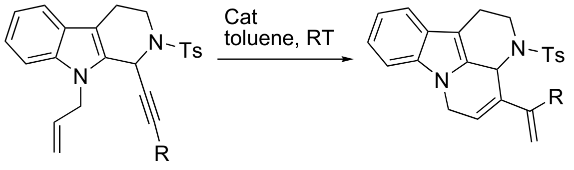
We used a 10 mol% catalyst because we observed a significant decrease in yield when using only 5% of catalyst (entry 4). This point may be surprising as it is thought that complex **B** generates small amounts of $14e^-$ active species that give a high number of catalytic cycles.[5] Our reactions were at that point very slow and needed 3 days to complete. We have monitorized the RCM of **6a**–**10a** by ^{1}H NMR which indicated the progressive conversion of the starting material into the diene.[6] In this context, the need for such a high amount of catalyst might be due to its partial decomposition. We have observed similar yields when adding the catalysts in portions every 12 h (3% at the beginning and 1% additional every 12 h, completing 8%). We used 10 mol% of complex **C**, yielding 55% of **10a** although this reaction needed 6 days to complete (entry 5). In view of these results, cheaper complex **B** was used for the rest of the metathesis reactions. Our results improved remarkably when performing the reaction under an ethylene atmosphere (entry 6).[7] Ethylene is known to have a beneficial effect in metathesis reactions.[8] This conditions allowed the synthesis of **10a** in only 3 h, using 5% of catalysts and in 95% yield.

In the same way compound **6b** was readily transformed into diene **10b**. The use of ethylene allowed raising the yield to 85% (Scheme 3, entries 7 and 8).

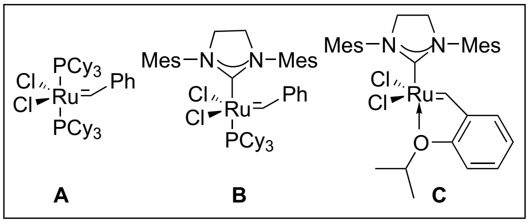
We also used these reaction conditions to carry out the metathesis reactions of **8a**,**b**. These substrates gave the corresponding dienes **11** in good yield along with small amounts of an oxidized pyrrole **12**. This ability to oxidize the reaction product is a known non-metathetic behaviour of ruthenium catalysts and it is particularly observed with complexes of type **B** (Scheme 4).[9]



Scheme 2. Synthesis of starting enynes and dienynes.



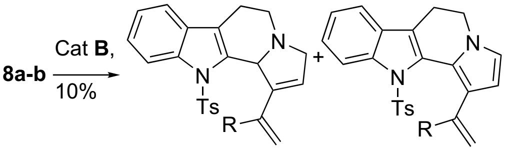
6a-b **10a-b**



No.	R	Cat.	Solv.	Time	Prod.	Yield(%)
1	H	**A,** 10%	DCM	5d	**10a**	-
2	H	**B,** 10%	DCM	3d	**10a**	45
3	H	**B,** 10%	Tol.	3d	**10a**	60
4	H	**B,** 5%	Tol.	3d	**10a**	52
5	H	**C,** 10%	Tol.	6d	**10a**	55
6	H	**B,** 5%	Tol.	3h[a]	**10a**	95
7	Me	**B,** 10%	Tol.	3d	**10b**	72
8	Me	**B,** 5%	Tol.	3h[a]	**10b**	85

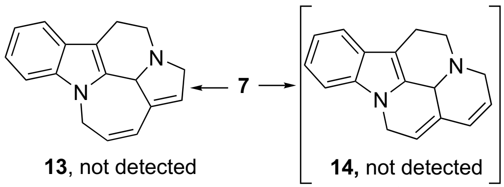
[a] Performed under a 1 atm of ethylene.

Scheme 3. Metathesis reaction and tandem metathesis-Diels–Alder reaction of compounds **6a**,**b**.



11a, 62%
11b, 51%

12a, 9%
12b, traces

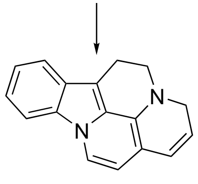


13, not detected

14, not detected

Cat., %	Time	Temp.	Yield
A, 10%	5d	r.t.	-
B, 10%	5d	r.t.	15%
B, 6%[a]	3d	80 °C	45%
C, 6%[a]	3d	80 °C	67%

[a] 2 mol% added every 24 h.



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Scheme 4. Metathesis of **8a**,**b** and cascade metathesis of **7**.

Finally, we present the first example of a tandem metathesis reaction on a β-carboline derivative. When reacting compound **7** under the above conditions we isolated in low yield a new pentacyclic structure whose analytical and spectroscopical data corresponded to compound **15**. The cascade metathesis of compound **7** starts by reaction of one of the double bonds with the ruthenium carbene. The formation of **15** implies the coordination of the ruthenium first with the allyl group in position 9 of the starting material to give **14** which is oxidized under the reaction medium to **15**. Reaction with the allyl group in first would have produced **13** which was not detected in any of the reactions. In addition, raising the reaction temperature to 80 °C gave better yields of **15**. Thus, we switched to catalyst **C**, a more stable complex towards heat, and 2% catalyst was added to the reaction every 24 h during 3 days. In this case we found no improvement by working under an ethylene atmosphere.[10]

In conclusion, we show here the first enyne metathesis reactions in β-carbolines leading to polycyclic systems related to alkaloids. The synthesis of natural products using this methodology is currently underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.07.140. Experimental procedures and full spectroscopical data for all new compounds.

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6. An aliquot was taken from the reaction every 12 h, and after workup the crude was analyzed by ^{1}H NMR showing progressive conversion of **6a** into **10a.**
7. Experimental procedure for the synthesis of **10a** is as follows: To a 0.01 M solution of **6a** (0.200 g, 0.512 mmol) in anhydrous toluene, 0.022 g (0.026 mmol) of Grubbs catalysts **B** was added and the resulting mixture was stirred at room temperature under a ethylene atmosphere for 3 h. The reaction mixture was filtered off through a Celite pad and washed with toluene. The solvent was removed under reduced pressure and purified by column chromatography (hexane–EtOAc, 9:1) giving pure **10a** (0.190 g, 95%) as yellow oil. ^{1}H NMR (C_6D_6, 60 °C) δ (ppm): 1.76 (s, 3H), 2.17–2.21 (m, 2H), 3.88–4.05 (m, 4H), 5.11 (d, 1H, $J = 12.1$ Hz), 5.48 (d, 1H, $J = 17.0$ Hz), 5.68 (br s, 1H), 6.30 (s, 1H), 6.59 (d, 2H, $J = 8.2$ Hz), 6.97 (d, 1H, $J = 7.7$ Hz), 7.01–7.13 (m, 3H), 7.24 (d, 1H, $J = 7.7$ Hz), 7.62 (d, 2H, $J = 8.2$ Hz). ^{13}C NMR (C_6D_6, 60 °C) δ (ppm): 20.3, 21.0, 42.9, 46.8, 53.1, 106.1, 109.5, 115.4, 118.8, 119.9, 120.2, 121.6, 127.3, 128.4, 129.5, 129.9, 131.5, 134.5, 137.7, 139.1, 143.1. IR (KBr) ν 1600, 1340, 1160 cm^{-1}. MS (ESI) m/z 391 (M+H). Anal. Calcd for $C_{23}H_{22}N_2O_2S$: C, 70.74; H, 5.68; N, 7.17. Found: C, 70.99; H, 5.89; N, 7.08.
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10. Synthesis of **15**: to a solution of **7** (0.150 g, 0.543 mmol) in anhydrous toluene (30 mL), 7 mg (0.011 mmol) of Grubbs **C** complex were added every 24 h during 3 days while stirring at 80 °C. The reaction mixture was filtered off through a Celite pad and washed with dry toluene (20 mL). The solvent was removed under reduced pressure and the residue purified by column chromatography (hexane–EtOAc 49:1) giving **15** (0.101 g, 67%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.16 (t, 2H, $J = 6.8$ Hz), 4.22 (t, 2H, $J = 6.8$ Hz), 4.82 (d, 2H, $J = 5.5$ Hz), 5.61–5.69 (m, 1H), 6.14 (d, 1H, $J = 2.7$ Hz), 6.65 (d, 1H, $J = 11.0$ Hz), 6.70 (d, 1H, $J = 2.7$ Hz), 7.11 (td, 1H, $J_1 = 7.7$ Hz, $J_2 = 1.1$ Hz), 7.18 (td, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.1$ Hz), 7.34 (d, 1H, $J = 8.2$ Hz), 7.51 (d, 1H, $J = 7.7$ Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.4, 44.0, 45.2, 103.0, 107.4, 109.3, 116.1, 116.5, 117.8, 119.6, 121.0, 121.7, 127.5, 127.6, 128.3, 130.0, 137.2. IR (neat) ν 1620, 1600 cm^{-1}. MS (APCI), m/z: 247 $[M+H]^+$. Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 82,72; H, 5.67; N, 11.48.