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Novel domino reactions in β-carbolines with triple bonded dienophiles

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ABSTRACT

Vinylpyrrolo-[2,1-*a*]-β-carbolines **1** give different products upon reaction with dienophiles. With dimethyl acetylenedicarboxylate (DMAD), a novel domino process takes place, involving Michael attack and rearrangement, affording complex polycycles like **3**, **4**, and **5**. Diels–Alder cycloadditions are favored in the presence of Lewis acids and are the only reactions with dimethyl maleate. When 3-butyn-2-one is used as dienophile, a Stevens rearrangement is observed giving product **9**.

The tetrahydro-β-carboline system is present in numerous naturally occurring alkaloids, many of which display useful and interesting biological activities like mutagenic properties, significant anti-tumor and anti-HIV activities, and inhibition of topoisomerase I.[1] Among the most widely used methods to build these kinds of compounds are the classical Pictet–Spengler cyclization,[2] the Bischler–Napieralski reaction,[3] and certain coupling reactions catalyzed by palladium complexes.[4] In particular, vinyl-substituted tetrahydro-1*H*-β-carbolines are of prime importance for the construction of β-carboline-containing compounds.[5] 1-Vinyl moieties can be introduced through the Pictet–Spengler condensation, the Bischler–Napieralski condensation/reduction sequence, or catalytic cyclization of *N,O*-acetals.[5,6]

Previous work in our laboratories[7] established the efficacy of employing ring-closing metathesis (RCM)[8] reactions for the construction of fused nitrogen heterocycles such as **1a–b** from suitable substituted 1-vinyl-β-carbolines. The combination of RCM with other cyclization processes such as Diels–Alder is a powerful synthetic tool that we and others have used in synthesis of complex molecules.[9] Once we had achieved the construction of vinylpyrrolo-[2,1-*a*]-β-carbolines via enyne metathesis reactions, we addressed the [4+2] cycloadditions of these compounds with several dienophiles. Our aim was the synthesis of the structures of alkaloids like those of the geissospermum group.[10]

Thus, we reacted compound **1a** with dimethyl acetylene dicarboxylate (DMAD) in toluene, observing total conversion of the starting material into two new products after 3 days of stirring at rt (conditions A, Table 1). None of the products were the expected [4+2] cycloadducts. After convenient NMR studies, we assigned them to structures **4a** and **5a**, the latter being an unstable compound which decomposed in hours at rt (Scheme 1). This result showed that a rearrangement process had taken place involving the formation of intermediate charged species. Thus, we changed the solvent to a more polar one. With THF no divinyl compound **5a** was detected and the isolated yield of **4a** increased to 42%. In this reaction, we obtained an 11% yield of pyrrole **2a**, which comes from the oxidation of starting material, and we detected a Diels–Alder product in the crude mixture, which could not be completely purified (conditions B). The best yield in **4a** was achieved in DCM reaching 56% with isolation of 17% of **5a** and 5% of **2a** (conditions C). On the other hand, the reaction of **1a** with DMAD in refluxing THF gave a new product, **3a**, jointly with a small amount of **2a** and traces of **7**. Compound **3a**, isolated in 46% yield, was an isomer of **4a** that was assigned to its *E* isomer (conditions D).

Next, we combined the enyne RCM reaction used for the synthesis of **1a** with the rearrangement process observed above in a *one-pot* fashion (conditions E). Thus, reaction of **8** with 5% of **Ru[II]** Grubbs' catalyst and addition of DMAD after completion of the metathesis gave compound **4a** in 41% along with a small amount of **2a**. In addition, 8% of the metathesis product **1a** was recovered. The presence of the ruthenium species in this case hardly affects the result of the reaction, slightly favoring the oxidation of **1a** into **2a**.

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Table 1

Cond.	Reaction conditions						Products (ratio in crude/yield % pure product)											
	R	DMAD	Temp	Solv.	Time	Other	**1**		**2**		**3**		**4**		**5**		**6**		**7**	
							Ratio	Yield	Ratio	Yield	Ratio	Yield	Ratio	Yield	Ratio	Yield	Ratio	Yield	Ratio	Yield
A	H	2.0	rt	Tol	3d	–	–	–	–	–	–	–	1	33	1	24	–	–	–	–
B	H	2.0	rt	THF	3d	–	–	–	1	11	–	–	3	42	–	–	–	–	1	n.i.[a]
C	H	2.0	rt	DCM	1d	–	–	–	2	5	–	–	11	56	5	17	–	–	1	n.i.
D	H	2.0	Δ	THF	2d	–	–	–	3	16	5	46	–	–	–	–	–	–	1	n.i.
E	H	2.0	60	Tol	4d + 5h	**[Ru]-II** 5%	4	8	1	n.i.	–	–	12	41	–	–	–	–	–	–
F	H	3.0	−20 to rt	Tol	16h	BF_3 1.5	2	10	–	–	3	27					2	13	1	n.i.
G	H	2.0	−78 to rt	DCM	7d	$SnCl_4$ 1.5	–	–	–	–	–	–	–	–	–	–	2	27	1	13[b]
C	Me	2.0	rt	DCM	2d	–	–	–	1	n.i.	–	–	16	52	3	8	–	–	–	–

[a] n.i.: not isolated.
[b] As a mixture containing **6**.

The formation of **3a**, **4a**, and **5a** is explained in Scheme 2. Recently, Voskressenky described a rearrangement of β- and γ-carbolines in the presence of DMAD that gave azocines upon reaction with carbon 11b.[11] The reaction begins with the nucleophilic attack to the DMAD that behaves as a Michael acceptor, and subsequent reaction of the species **A** with carbon α to the nitrogen at the carboline system. This transformation required the presence of methanol to stabilize the intermediate. In our case, the process would start in the same way and, after the formation of **A**, an intramolecular attack of this intermediate either to carbon 6a (path a) or to carbon 1 (path b) would give, respectively, compounds **4** and **5**. The formation of compound **3** only occurs under refluxing conditions or in the presence of a Lewis acid (vide infra). Thus, we assume that it comes from the isomerization of **4**, which is primarily formed in the reaction.

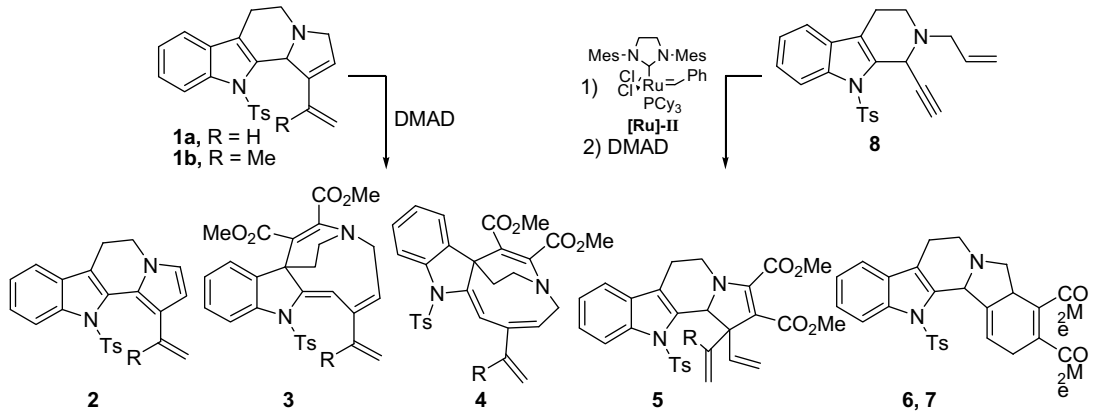
With these results in hand, we carried out the same reactions in the presence of a Lewis acid to avoid the nucleophilic attack of the β-carboline nitrogen, thus favoring the Diels–Alder process. With BF_3, the crude reaction mixture showed a 2:1 ratio of Diels–Alder adducts and product **3a** (conditions F). With $SnCl_4$, the formation of **3a** was avoided and both [4+2] adducts **6** and **7** were formed in 2:1 ratio (conditions G). Adduct **6** was isolated in 27% yield, while **7** was obtained unpurified with **6**. The stereochemical assignment of these two adducts was made with NOE experiments and was further supported by an X-ray analysis of **6** (see Supplementary data).

Finally, compound **1b** gave, under conditions C, a mixture of divinyl compounds **5b** and **4b**. The latter product could be crystallized and submitted to X-ray diffraction analysis. This was used to confirm the structure of **3a** and **4a**. An ORTEP drawing is shown in Figure 1.

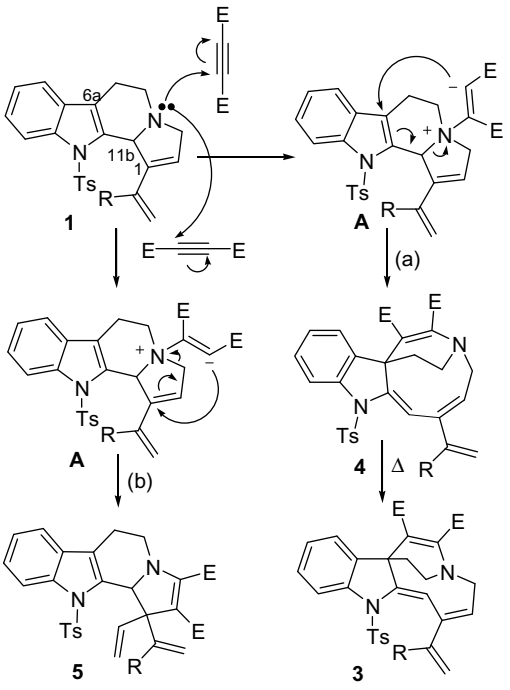
The rearrangement reaction was next effected with other dienophiles. Thus, compound **1a** was reacted with 3-butyn-2-one in conditions C (Table 1). The only reaction product was assigned to structure **9** (53%). This product is the result of the quenching of the intermediate **B**, due to the presence of acidic protons in the media and subsequent Stevens rearrangement.[12] This is a [1,2] rearrangement of ammonium salts via ammonium ylides that normally needs the presence of a strong base. In our case, the stabilization of the negative charge in ylide **C** makes it possible for the process to take place in our reaction conditions. On the other hand, the reaction of **1a** in the same conditions with dimethyl maleate gave a mixture of the four possible Diels–Alder adducts. The two major isomers, **10** and **11,** were isolated in 42% and 14% yields, respectively, and their stereochemical assignment was made by NOE experiments (Scheme 3).

Finally, we studied the reaction of 2-allyl-1-vinyl-β-carboline **12** with DMAD under conditions C. This substrate gave a mixture of products **13** and **14** in 1:3 ratio, **13** being an unstable product. These products come, respectively, from the same rearrangement reaction. The intermediate **D** reacts either with carbon 6a (path a, Scheme 4) or with the vinyl moiety at carbon 1 (path b). The latter process was not observed with previous substrates possibly because of conformational restraints of those compounds.

In conclusion, a novel rearrangement process of vinyl β-carbolines is shown. Upon convenient choice of reaction conditions and reactants, these compounds give a Michael type addition followed by nucleophilic attack to one unsaturated carbon which leads to new polycycles with high increase in skeletal complexity. Alternatively, Stevens rearrangement or Diels–Alder cycloadditions can be carried out. The complete study on the scope and limitations of these reactions and further applications in natural alkaloid syntheses is underway in our laboratory.



Scheme 1. Reaction of compounds **1** with DMAD under different conditions and RCM-rearrangement domino reaction of **8.**



Scheme 2. Mechanistic proposal for the rearrangement of **1** into **3**, **4**, and **5.**

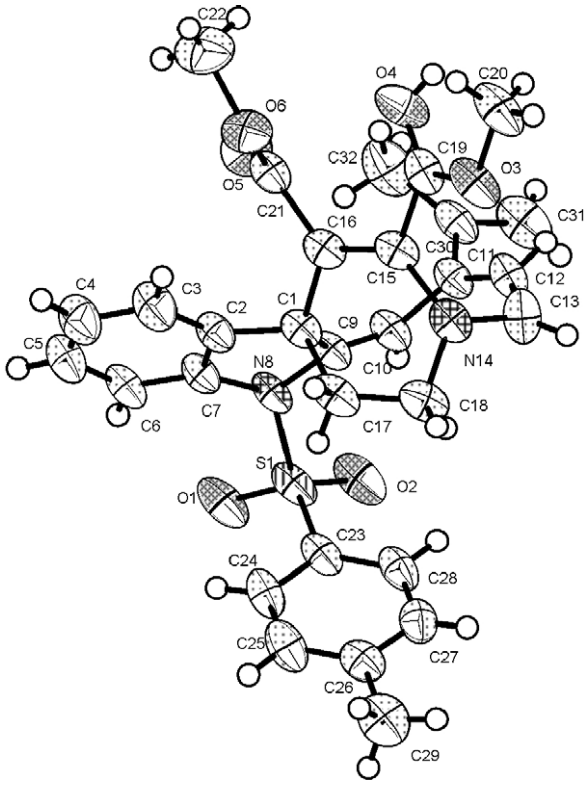
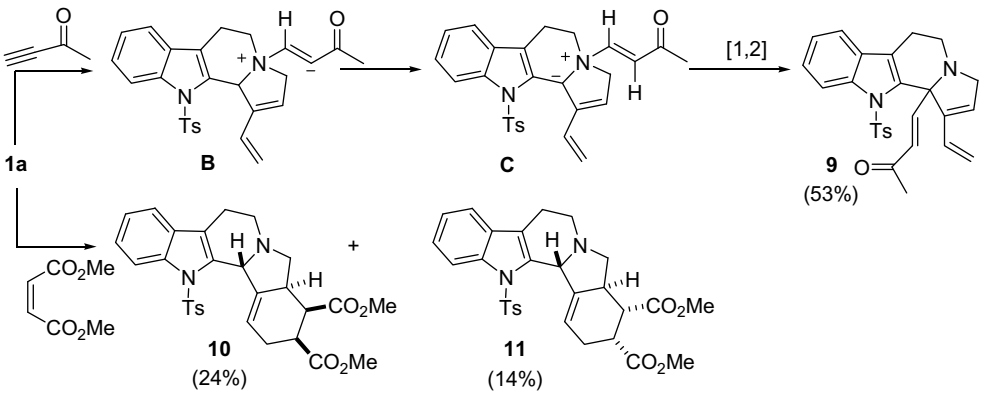
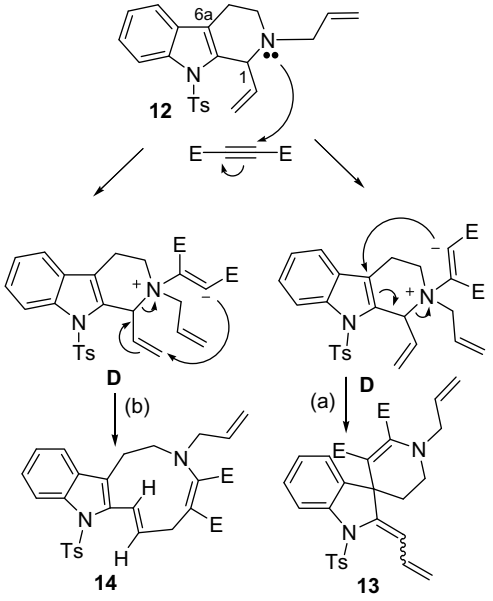


Figure 1. ORTEP diagram for compound **4b**.



Scheme 3. Reactions of **1a** with 3-butyn-2-one and dimethyl maleate.



Scheme 4. Reaction of **12**.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and spectroscopic data and spectra for new compounds as well as CIF files for structures **4b** and **6**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.025.

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