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Control of product distribution in the domino metathesis reactions of *N*-alkynyl 2-azabicyclo[2.2.1]hept-5-en-3-ones. A convenient synthesis of functionalized γ-lactams and indolizidinones

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Dedicated to Profs. Manuel Lora-Tamayo and Antonio González González. In Memoriam

Abstract—In this report we describe the domino metathesis of *N*-alkynyl-2-aza-3-oxo-[2.2.1]hept-5-enes. The distribution of products of the domino processes of ROM–CM or ROM–RCM–CM depends on the starting material and on the catalyst used. A sequence of metathesis events has been proposed to account for these results. The procedure can be of use for the synthesis of lactams and indolizidinones.

The sequential transformation of the alkenes obtained in metathesis reactions[1] (domino process) constitutes an attractive application of this synthetic method, in particular in the case of bicyclic and other strained systems.[2] In the case of [2.2.1]bicyclic alkenes, the ring opening metathesis (ROM)–cross metathesis (CM) and ROM–CM–ring closing metathesis (RCM) sequences have been considered for norbornene,[3] 7-oxanorbornene,[4] and 2-azanorbornene[5] derivatives (Fig. 1).

Despite the synthetic potential of these processes, to the best of our knowledge the domino metathesis in *N*-alkynyl bicyclic compounds has not yet been considered.[6] In this way, the metathetical reactions of

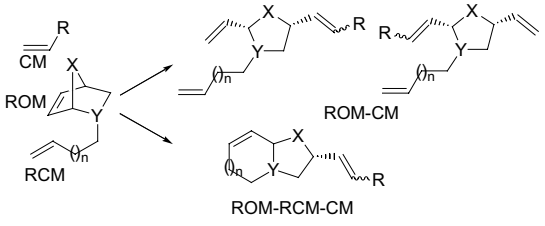
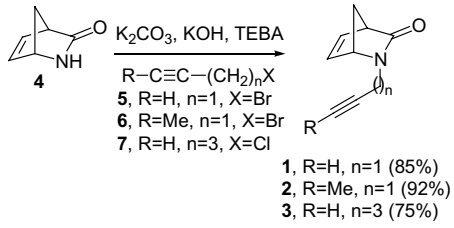


Figure 1.



Scheme 1.

compounds **1**–**3** (Scheme 1) with ethylene using catalysts **A** and **B** (Fig. 2)[7] have been studied and constitute the objective of the present report.

Compounds **1**–**3** were prepared by the reaction of lactam **4** with the appropriate halide[8,9] (Scheme 1).

The reactions of compounds **1**–**3** with ethylene (1 atm) in the presence of the ruthenium catalysts **A** or **B** afforded

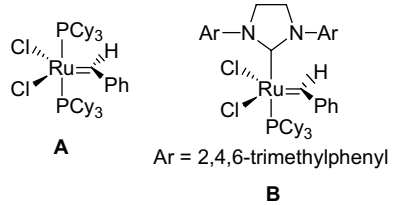


Figure 2.

Keywords: Metathesis; Azabicyclic; Lactams; Indolizidinones.
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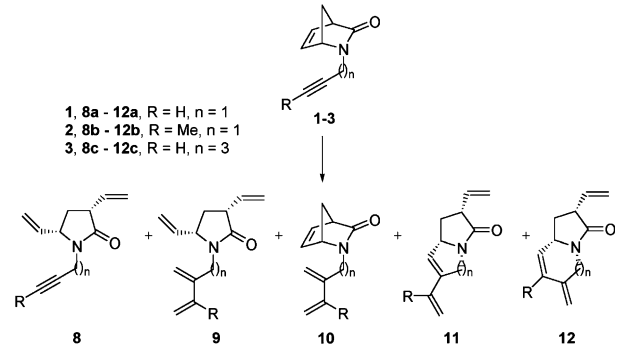


Scheme 2.

Table 1. Metathesis reactions of compounds **1**–**3** with ethylene[a]

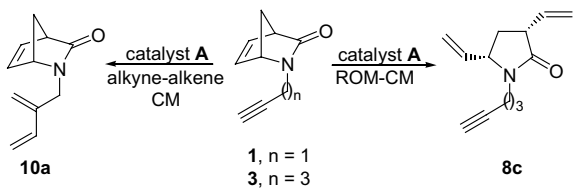
No	**1**–**3**	Catalyst	*t* (h)	Product distribution[b]				
				8	**9**	**10**	**11**	**12**
1	**1**	**A**	15	—	25	60	—	—
2	**2**	**A**	15	25	15	20	—	—
3	**3**	**A**	15	50	30	17	—	—
4	**1**	**B**	5	—	—	—	—	98
5	**2**	**B**	5	—	80	—	15	—
6	**3**	**B**	5	—	98	—	—	—

[a] Sealed tube, 1 atm ethylene, CH_2Cl_2, reflux, 10% catalyst.
[b] Isolated yield.

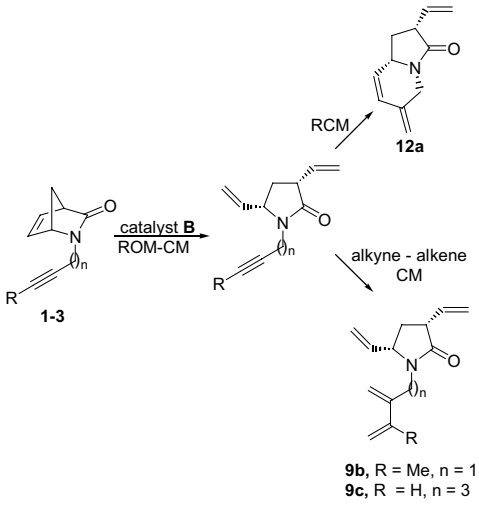
compounds **8**–**12** in variable amounts depending on the structure of the starting materials and the reaction conditions (Scheme 2, Table 1).

From these results we deduced that, when using catalyst **A** in the case of compounds **1** and **3**, which only differ in the length of the lateral alkyne chain, two single but different metathetical processes are dominant (Scheme 3): (i) in the case of **1**, the intermolecular alkyne–alkene metathesis (compound **10a**, entry 1) is the dominant metathetical event, and (ii) in the case of **3**, the ROM–CM (compound **8c**, entry 3) is the predominant path. Under similar reaction conditions compound **2**, which differs from **1** in the nature of the R substituent of the alkyne moiety, a mixture of the different reaction products was obtained (entry 2).

On the other hand, by using **B** as the catalyst (Scheme 4), compound **1** afforded the domino ROM–CM–RCM product **12a** in high yield (entry 4), whereas **3** gave rise to product **9c** (entry 6), which is the result of the simultaneous ROM–CM of the alkene moiety together with the CM of the alkyne. Under these reaction conditions compound **2** behaved similarly to **3**, giving rise to **9b** (entry 5) as the major reaction product.



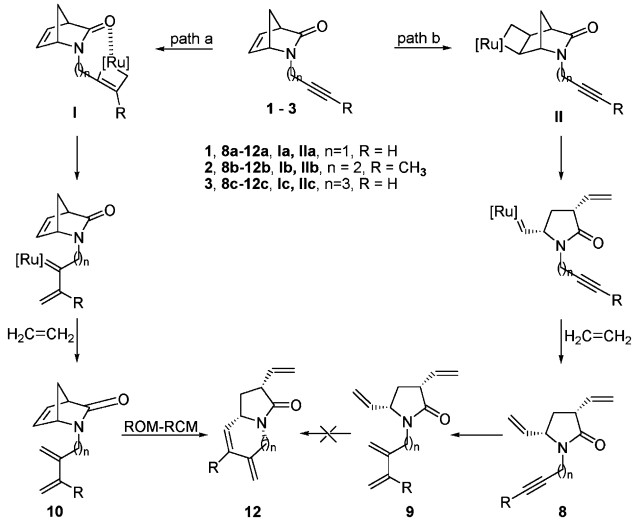
Scheme 3.



Scheme 4.

The overall comparison of these results deserves some comments (Scheme 5). In the case of alkyne–alkene cross metathesis with catalyst **A**, the reaction starts at the triple bond.[10] Formation of the metallacyclobutene on the triple bond[11] competes with formation of the related metallacyclobutane on the endocyclic double bond. In the case of compound **1**, coordination of the catalyst with the carbonyl group may favor metallacyclobutene formation (intermediate **Ia**, path a).[1a] However, in the case of compound **2** steric effects due to the presence of the terminal CH_3 group may counterbalance coordinative effects, thus giving rise to a random distribution of reaction products. Finally, in the case of compound **3** (path b) the distance between the triple bond and the carbonyl group hinders the operation of stabilizing interactions by chelation on the lateral chain, and therefore, the initial formation of the metallacyclobutane (intermediate **IIc**) predominates over metallacyclobutene formation (intermediate **Ic**).

It should be pointed out that the new functionalization present in **10a** and **8c** opens the possibility for meta-



Scheme 5.

thesis-Diels–Alder reaction sequences that have been proved to be an interesting and economical bond forming method.[12]

On the other hand, the use of the more active[13] catalyst **B** allowed a convenient synthesis of the functionalized indolizidinone[14] **12a** from compound **1** (Table 1, entry 4). The previously observed formation of **10a** as the major product using **A** as catalyst (Table 1, entry 1) appears to indicate that **10a** is the most important intermediate for the formation of **12a**: after formation of **10a**, ROM followed by RCM affords **12a** (Scheme 5).

Again making use of catalyst **B**, when a methyl group was attached to the alkyne moiety (compound **2**) or when a three-carbon methylene chain separated the two reactive centers (compound **3**), pyrrolidinones[15] **9b**,**c** were the most important products (Table 1, entries 5 and 6). Steric (compound **2**) and entropic (compound **3**) factors appear to be the origin of the failure of the CM or RCM reaction to give **12b** and **12c**, respectively. It should be pointed out that, according to our previous comments, compounds **9b**,**c** should be formed in these cases from **IIb**,**c** via ROM–CM (Scheme 5, path b) followed by alkyne–alkene CM.

With respect to quinolizidines **11**, these compounds were formed in very poor yields in all the cases considered. The well known kinetic preference for the formation of five membered ring systems[14] should be overcome by the higher steric effects associated with the '1,1-disubstituted' double bond of the dienic system. Only in the case of **11b**, with the same degree of substitution in both double bonds, is this kinetic preference partially manifested.[16]

In summary, in this report the domino metathesis reactions of *N*-alkynyl-2-aza-3-oxo-[2.2.1]hept-5-enes are described. In order to account for the observed distribution of products, a sequence of metathesis events has been proposed. The synthetic utility of the process was also emphasized.

Acknowledgements

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