Enyne ring-closing metathesis on heteroaromatic cations†

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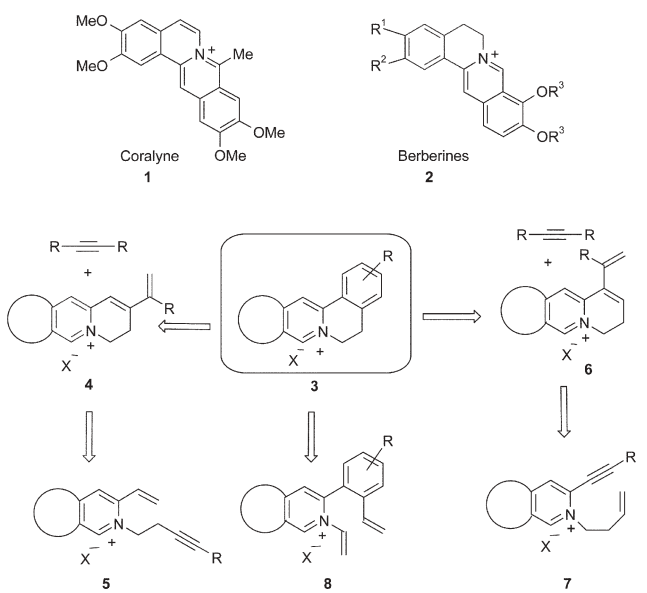
Cationic heteroaromatic enynes have been employed as substrates in enyne ring-closing metathesis, under an atmosphere of ethylene and using the Hoveyda–Grubbs catalyst, for the first time; the reaction affords new 1-vinyl- and 2-vinyl-substituted 3,4-dihydroquinolizinium salts, useful precursors for biologically relevant cations based on the quinolinizium system.

Azinium and azolium cations are easily obtained by alkylation of the corresponding azine and azole heterocycles. However, the synthesis and functionalization of quinolizinium cations, the representative system of heteroaromatic cations based on a bridgehead quaternary nitrogen, has remained relatively unexplored.[1] Recently, we reported the first example of a diene ring-closing metathesis (RCM) process involving heteroaromatic cations.[2,3] This process represents a unified approach to dihydroquinolizinium and related cations by RCM of *N*-alkenyl-α-vinyl-azinium salts. This strategy, although very efficient for the synthesis of some quinolizinium and related systems, is not feasible for the preparation of fused benzo- and dibenzo-systems such as **3** (Scheme 1). For this class of cations, which represent the heterocyclic core of cationic alkaloids such as coralyne **1**[4] and berberines **2**,[5] we envisaged a diene RCM process from the appropriate azinium salts **8**. However, an efficient synthesis of these precursors and the subsequent RCM reaction have to date proved to be an elusive goal in our hands. An alternative route to benzo- and naphthoquinolizinium systems was envisaged that involved a sequential enyne RCM[6,7] and Diels–Alder reaction, as shown in Scheme 1.

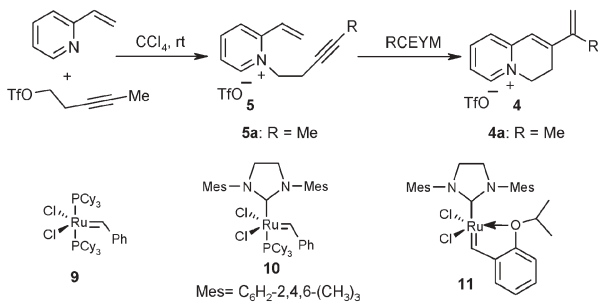


Scheme 1

In this communication, we report a new approach to 1- and 2-vinyl-substituted 3,4-dihydroquinolizinium cations by a ring closing enyne metathesis (RCEYM) reaction from appropriately substituted pyridinium substrates.

On the basis of our previous results on diene RCM, we initiated our studies by testing the N-alkylation of commercially available 2-vinylpyridine with 3-pentynyl triflate. The reaction was carried out in carbon tetrachloride, at room temperature, and gave the desired enyne **5a** in 77% yield. An extensive study of the reaction was required to find suitable conditions for a successful metathesis reaction of **5a** (Scheme 2).

Table 1 shows the results obtained in this search for optimal conditions for the preparation of 2-propenyl-3,4-dihydroquinolizinium compound **4a**. In general, polymerization is the main process using Grubbs' catalysts **9**[8] and **10**[9] in dichloromethane at room temperature[10] (Table 1, entries 1, 2 and 4) and the RCEYM reaction is favored by dilution (Table 1, entry 5). Under an



Scheme 2

Table 1 Results for the metathesis of **5a**

Entry	Catalyst	Conditions	Yield **4a** (%)[a]
1	**9** (5%)	CH_2Cl_2, rt, 0.1 M	—[b]
2	**10** (5%)	CH_2Cl_2, rt, 0.1 M	—[b]
3	**10** (5%)	CH_2Cl_2, 0 °C, 0.1 M	—[c]
4	**10** (15%)	CH_2Cl_2, rt, 0.01 M	—[b]
5	**10** (5%)	CH_2Cl_2, rt, 0.003 M	5
6	**10** (5%)	CH_2Cl_2, $CH_2{=}CH_2$, rt, 0.001 M	37
7	**10** (5%)	CH_2Cl_2, $CH_2{=}CH_2$, reflux, 0.005 M	48
8	**11** (5%)	CH_2Cl_2, $CH_2{=}CH_2$, reflux, 0.001 M	66
9	**11** (5%)	$ClCH_2CH_2Cl$, $CH_2{=}CH_2$, reflux, 0.001 M	83
10	**10** (5%)	$ClCH_2CH_2Cl$, $CH_2{=}CH_2$, reflux, 0.001 M	66
11	**9** (5%)	$ClCH_2CH_2Cl$, $CH_2{=}CH_2$, reflux, 0.001 M	—[c]

[a] Isolated yield. [b] Polymerization products. [c] No reaction.

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atmosphere of ethylene[11] the polymerization process is minimized but the cross metathesis (CM) product[12] between **5a** and ethylene is formed as a by-product[13] in significant yields (10–32%) depending on the dilution and reaction temperature (Table 1, entries 6 and 7).

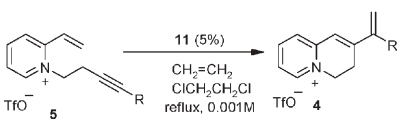
The Hoveyda–Grubbs catalyst **11**[14] was found to be the most efficient catalyst when used in a higher boiling point solvent such as dichloroethane (Table 1, entry 9). Under these conditions the 2-propenyl-3,4-dihydroquinolizinium salt **4a** was isolated in 83% yield. Results of the metathesis of **5a** catalyzed by **9** and **10** under the optimized conditions found for **11** gave a lower conversion when using **10** (Table 1, entry 10) or resulted in the failure of the metathesis reaction with **9** (Table 1, entry 11).

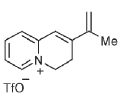
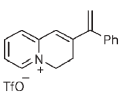
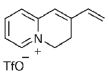
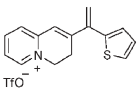
A good yield (81%) was also achieved for the styrylquinolizinium derivative **4b** (Table 2, entry 2) but the yield decreased to 38% when the metathesis reaction was applied to the 1-(3-butynyl)-2-vinylpyridinium salt **5c** (Table 2, entry 3). All attempts to isolate the 2-(1-thienylethynyl)-3,4-dihydroquinolizinium salt **4d** failed (Table 2, entry 4), likely due to the low stability of this salt under the reaction conditions. On the other hand, substitution on the vinyl moiety in substrates **5** resulted in failure of the RCEYM reaction and formation of cross-metathesis products[15] between the alkyne and ethylene.

Although recent mechanistic[16] studies show that the accelerating effect of ethylene in RCEYM is best explained by the well-known ene-then-yne cycle, in this case, the isolation of trienes **12** and their subsequent conversion into the RCEYM products **4**[13] strongly supports the case that the reaction of substrates **5** is initiated on the alkynyl moiety (yne-then-ene) (Scheme 3).

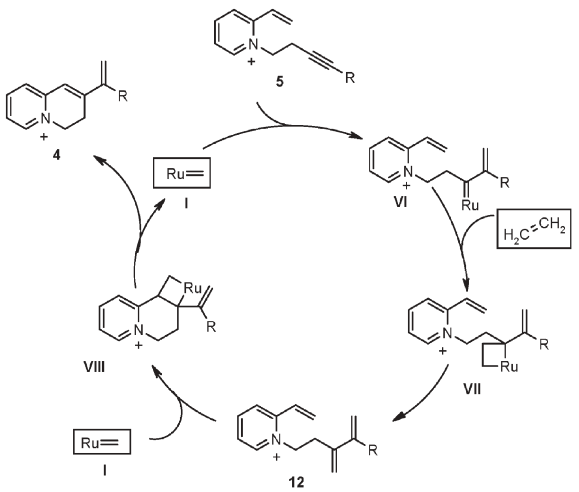
The metathesis reaction on pyridinium substrates **7** was easier and more efficient than in **5**. Thus, when the optimal conditions found for **4a** were applied to the pyridinium enyne **7a**, prepared by *N*-alkylation of 2-propynylpyridine with 3-butenyl triflate,[17] the metathesis product **6a** was obtained in an 86% yield (Table 3, entry 1). The results summarized in Table 3 illustrate the scope of the

Table 2 2-Vinyl-3,4-dihydroquinolizinium cations **4** by enyne ring-closing metathesis



Entry	Substrate		RCEYM product		Yield (%)[a]
1	R = Me	**5a**		**4a**	83
2	R = Ph	**5b**		**4b**	81
3	R = H	**5c**		**4c**	38
4	R = 	**5d**		**4d**	—

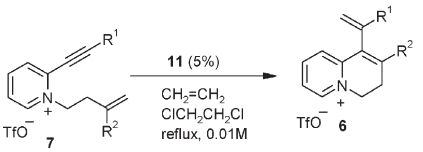
[a] Isolated yield.

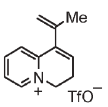
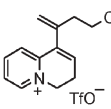
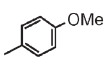
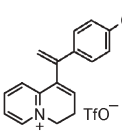
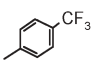
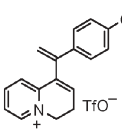
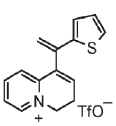
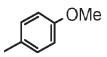
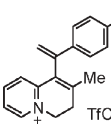


Scheme 3 Mechanism for the metathesis of enynes **5**.

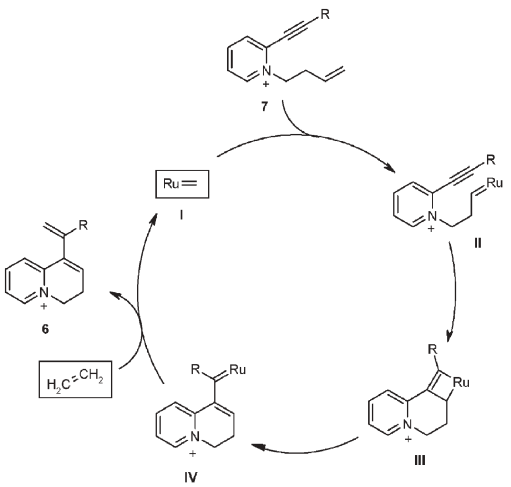
reaction to produce 1,2-disubstituted 3,4-dihydroquinolizinium salts, which is only affected by substitution on the alkene. Thus, 1-vinyl-substituted 3,4-dihydroquinolizinium salts **6b–e** were

Table 3 Vinyl-3,4-dihydroquinolizinium cations **6** by enyne ring-closing metathesis



Entry	Substrate	RCEYM product		Yield (%)[a]
1	R^1 = Me R^2 = H **7a**		**6a**	86
2	R^1 = CH_2CH_2OTBS R^2 = H **7b**		**6b**	93
3	R^1 =  R^2 = H **7c**		**6c**	90
4	R^1 =  R^2 = H **7d**		**6d**	87
5	R^1 =  R^2 = H **7e**		**6e**	94
6	R^1 =  R^2 = Me **7f**		**6f**	19

[a] Isolated yield



Scheme 4 Mechanism for the metathesis of enynes **6**.

obtained from the appropriate pyridinium enynes in isolated yields between 87–94% (Table 3, entries 2–5). Substitution on the alkene had a significant influence on the yield of the reaction, with the 1,2-disubstituted quinolizinium derivative **6f** being obtained in low yield (19%) (Table 3, entry 6).

It is worth noting that the success of this reaction also needs the presence of ethylene but it is less dependent on the dilution of the reaction mixture (0.01 M *vs.* 0.001 M). This result is probably related to the higher stability to polymerization of both the enyne **7** and the resulting 1-propenyl-3,4-dihydroquinolizinium **6** when compared to **5** and **4**, respectively. Experiments with different compounds **7** showed that in the absence of ethylene the conversion is very poor. This result supports that for substrates **7** the metathesis under Mori's conditions[11] is likely initiated on the alkene, with the role of ethylene being to promote the formation of the active complex methylidene ruthenium **I** (Scheme 4).

In conclusion, the enyne metathesis is a viable reaction on 2-vinyl- and 2-ethynylpyridinium salts. The reaction allowed the synthesis of unknown 1-vinyl- and 2-vinyl-substituted 3,4-dihydroquinolizinium salts and seems to be more general for the preparation of 1-substituted derivatives. This approach should allow an alternative access to biologically relevant cations based on the quinolinizium system.

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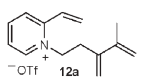
13 Compound **12a** is an isolable intermediate when the reaction is carried out at room temperature or 40 °C. Under the metathesis conditions this triene was quantitatively converted into **4a**



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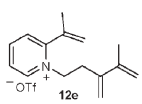
15 Compound **12e** was the only isolated product in 55% yield in the attempted metathesis of 2-(2-propenyl)-1-pent-3-ynylpyridinium triflate



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17 For the synthesis of enynes **7** see supplementary information†.

