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A Unified Approach to Quinolizinium Cations and Related Systems by Ring-Closing Metathesis†

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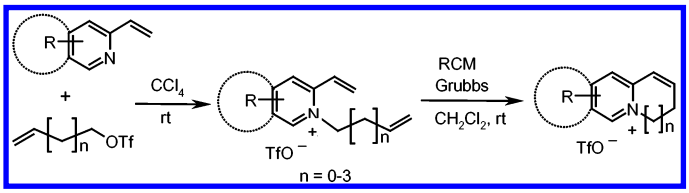
ABSTRACT



The first example of an olefin ring-closing metathesis reaction on cationic heteroaromatic systems is described. Dihydroquinolizinium cations and a variety of related cationic systems are synthesized in an efficient approach from *N*-alkenyl α-vinyl azinium salts using Grubbs' catalysts.

Quinolizinium-type cations,[1] a class of heteroaromatic compounds in which the cationic nature of the system is produced by the presence of a bridgehead quaternary nitrogen, are one of the three classes of charged heterocycles, the other two being azinium and azolium salts. These compounds have attracted attention in fields as diverse as natural products,[2] fluorescent dyes,[3] antitumoral compounds,[4] DNA intercalators,[5] and topoisomerase[6] and telomerase[7] inhibitors and, more recently, as NLO[8] and ionic liquids.[9]

While azinium and azolium cations are easily obtained by alkylation of the corresponding heterocycles, the synthesis and functionalization of quinolizinium cations has remained relatively unexplored.[10] Recently, we reported a general method for the introduction of C-substituents into the quinolizium system based on palladium-catalyzed C−C bond formation.[11] In this communication, we report preliminary results from an efficient olefin ring-closing metathesis (RCM)[12] approach to differently substituted 3,4-dihydroquinolizinium cations and related systems. This strategy represents the first example of a RCM process involving

† Dedicated to Prof. José Elguero on the occasion of his 70th birthday.

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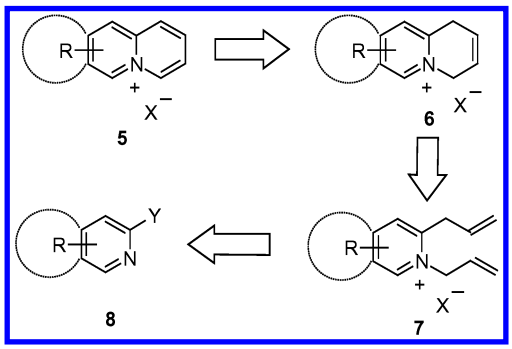
heteroaromatic cations[13] and cationic interconversion (azinium to quinolizinium).

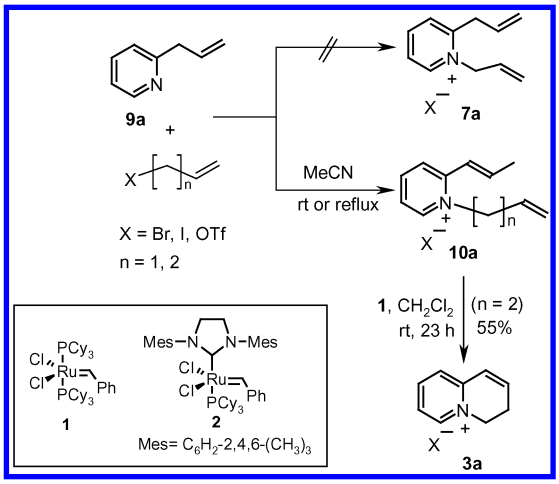
In our strategy for the synthesis of the quinolizinium system **5**, we envisaged that the dihydroquinolizium intermediate **6** could be easily obtained by a ring-closing metathesis (RCM) process from the key intermediate **7**, which would be accessible from the 2-haloazine **8** (Scheme 1).

Scheme 1



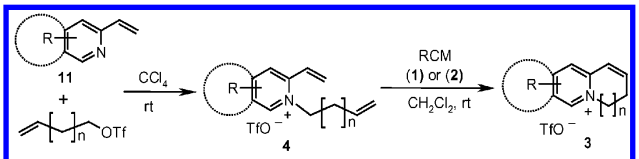
Initial model studies with 2-(2′-propenyl)pyridine **9a** showed that N-alkylation with either allyl iodide or allyl bromide produced not the expected pyridium salt **7a** but the more stable isomer **10a**, as result of double-bond migration. Double-bond isomerization also occurred when N-alkylation was attempted with allyl- and homoallyltriflates. Aryl and heteroaryl vinyl substrates have been used in RCM processes.[14] Thus, when the diolefinic compound **10a** was subjected to RCM conditions with Grubbs' catalyst **1**[15] (10 mol %), the dihydroquinolizium system **3a** was successfully formed in 55% yield (Scheme 2).

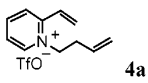
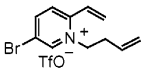
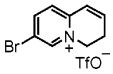
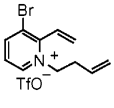
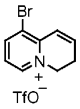
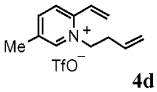
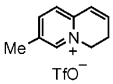
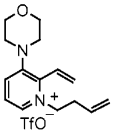
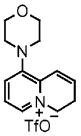
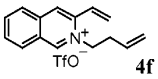
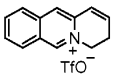
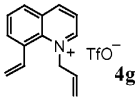
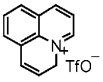
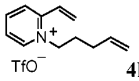
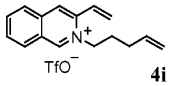
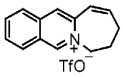
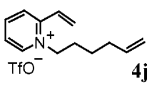
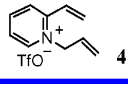
Scheme 2



Having obtained this initial result, 2-vinylpyridines[16] **11** clearly seemed to be the more promising starting azines for transformation into the appropriate *N*-(3-butenyl) 2-vinylpyridinium substrates, which would in turn react selectively under RCM conditions to give the expected dihydroquinolizium cations **3**. This idea was tested by preparing 1-(3′-butenyl)-2-vinylpyridium salt **4a** by N-alkylation of the corresponding substituted 2-vinylpyridine with 3-butenyltriflate. It was found that **4a** underwent the RCM process

Table 1. Dihydroquinolizium Cations and Related Cationic Systems by Ring-Closing Metathesis



entry	substrate	RCM product[a]	yield (%)[b]
1	 **4a**	 **3a**	83[c]
2	 **4b**	 **3b**	80
3	 **4c**	 **3c**	80
4	 **4d**	 **3d**	82
5	 **4e**	 **3e**	85
6	 **4f**	 **3f**	75
7	 **4g**	 **3g**	79
8	 **4h**	 **3h**	88[d]
9	 **4i**	 **3i**	94[d]
10	 **4j**	 **3j**	54[d]
11	 **4k**	 **3k**	-

[a] Reactions were carried out using 5 mol % catalyst **2** at room temperature in CH_2Cl_2. [b] Isolated yield. [c] Performed with 2 mol % catalyst **1** at room temperature. [d] High dilution (0.005 M).

on using either catalyst **1** (5 mol %) or **2**[17] (5 mol %) for 1 h at room temperature in dichloromethane and that the reactions gave good yields (Table 1, entry 1).

Differently substituted dihydroquinolizinium salts **3b**−**e** were obtained in a straightforward route starting from substituted 2-bromopyridines (Table 1, entries 2−5), with isolated yields of up to 80% in the RCM step. In a similar way, substrates **4f** and **4g** were obtained from 3-bromo isoquinoline (Table 1, entry 6) and 8-bromoquinoline (Table 1, entry 7). These intermediates then gave 3,4-dihydropyridoisoquinolinium **3f** and 3*H*-pyridoquinolinium **3g** in 75 and 79% yields, respectively. These results show that the RCM reaction works very efficiently on charged systems and provides a general protocol for the preparation of the dihydroquinolizinium system. Furthermore, the quinolizium system can also be obtained since oxidation of **3** afforded **5** in good yields.[18]

The scope of this method was further expanded to seven- (Table 1, entries 8 and 9) and eight-membered rings (entry 10). Unlike the formation of the six-membered system, RCM is only successful with catalyst **2** (5 mol %), but yields of between 6 and 46% were obtained when the reaction was carried out at 0.1 M concentration. Under these conditions, self-metathesis salts were formed in the reaction, and these made the isolation of RCM products extremely difficult. A simple modification of the reaction conditions working at higher dilution (0.005 M) allowed compounds **3h** and **3i** to be obtained in excellent yield (88 and 94%, entries 8 and 9) and **3j** in acceptable yield (54%, entry 10). As shown by the results in Table 1, the one notable limitation of the RCM was found in the formation of the indolizinium system **3k**. Attempts to produce the RCM on **4k** using catalysts **1** and **2** and Hoveyda−Grubbs catalyst[19] in dichloromethane at room-temperature failed. Neither the salt **3k** nor the most stable neutral compound indolizine could be isolated from the complex reaction mixtures obtained. Variations in the reaction conditions, including a change of the solvent (DMF) and/or temperature (50 °C), were also unsuccessful.

In conclusion, the above results show that RCM is a viable reaction on *N*-alkenyl-α-vinylazinium salts. The reactions afford a variety of heteroaromatic cations, including dihydroquinolizium and pyridoisoquinolinium, -quinolinium, -azepinylium, and -azocinylium, in good overall yield from readily available starting materials. This approach should allow access to biologically relevant cations based on the quinolizium system.

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Supporting Information Available: Experimental procedures and characterization data for compounds **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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