Synthesis of oxygen and nitrogen heterocycles via stabilized carbocations and ring closing metathesis.

Doodeman, R.

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SUMMARY

SYNTHESIS OF OXYGEN EN NITROGEN HETEROCYCLES
VIA STABILIZED CARBOCATIONS AND RING-CLOSING METATHESIS

The construction of C-C-bonds is one of the most important reactions in organic synthesis. A powerful method to make these bonds is the addition of carbon nucleophiles to N-acyliminium ions. Already for a long period, there has been significant interest in our group for this type of transformation and valuable insight has been gained in inter- and intramolecular reactions. Together with addition reactions to the related, but somewhat less intensively studied oxycarbenium ions, they form an important access to new, substituted heterocycles. Another versatile C-C-bond forming reaction, which has attracted widespread attention in recent years, is the ring-closing olefin metathesis reaction. Olefin metathesis is a process in which carbon-carbon double bonds are redistributed in the presence of metal-carbene complexes. Major advances in catalyst design in the last few years gave access to many new applications and transformations. This thesis describes the combination of carbocationic chemistry and ring-closing metathesis, two versatile methods which offer a powerful entry into the construction of new, biologically interesting compounds.

In Chapter 1, an introduction into the chemistry of N-acyliminium- and oxycarbenium ions and into ring-closing metathesis is presented. Chapter 2 describes the synthesis of several 2-substituted 2H-chromenes. The general strategy is outlined in Scheme 1, in which the core skeleton is constructed first using ring-closing metathesis (RCM), followed by introduction of different substituents at the 2-position via an oxycarbenium ion intermediate.

Scheme 1

Vinylphenols 1 were obtained by a standard Wittig reaction from the corresponding commercially available aldehydes or ketones. These phenols were reacted with two alkoxy-
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1,2-propadienes under Pd-catalyzed reaction conditions to arrive at the allylic acetals 2. Benzyloxy-1,2-propadiene (R'' = Bn) appeared to react significantly faster and under milder conditions than methoxy-1,2-propadiene (R'' = Me), also resulting in higher yields. These diolefins were subjected to ring-closing metathesis conditions to yield the chromene core skeleton 3. In this reaction, the imidazol-2-ylidene-substituted Ru-catalyst proved to be superior over the conventional Grubbs’ catalyst. Introduction of various nucleophiles at the 2-position via the strongly colored and aromatic 1-benzopyrylium ion 4 proceeded uneventfully to yield the desired products 5.

Chapter 3 deals with the synthesis of 4,5-disubstituted trans-fused bicyclic lactams. Starting from isopropoxylactam 6, which was obtained enantiomerically pure via an enzymatic route, Michael addition with several derivatives of dimethyl malonate afforded lactams 7 with complete trans-selectivity (Scheme 2). Alternatively, the unsaturated substituent at C-4 could be introduced via a cuprate addition of alkenyllithium species to arrive at lactams 8 without the two ester groups. Subsequent removal of the acetyl group using pyrrolidine afforded the N-acyliminium ion precursors. This time, the N-acyliminium reaction was used to introduce the second alkene or an acetylenic moiety, in order to be able to perform ring-closing metathesis. Thus, these N,O-acetals were reacted with three different nucleophiles, i.e. allyltrimethylsilane, allenylmethyltrimethylsilane and allenyltributyltin to afford diene 9, triene 10 and enyne 15, respectively, all containing the trans-configuration in the 5-membered ring.

Scheme 2

The following ene-ene ring-closing metathesis reactions of 9 and 10 furnished the desired trans-fused bicyclic lactams 11 and 12. Interestingly, 7-membered rings were formed
most readily, followed by the 8- and the 12-membered rings. Unfortunately, the synthesis of the 9- and 10-membered ring could not be accomplished. In addition, the reactions of the substrates with the two ester groups were higher yielding, probably because of the preferred conformation for ring-closing metathesis. It was also observed that only the least substituted double bond of the diene reacted in the metathesis reaction. The same influence of the ring size on the ring closure could be seen in the enyne metathesis of 9. The trans-fused 7-membered ring bicycle 13 (n = 1) was formed, although the reaction needed three days at 70 °C to go to completion, but all efforts to obtain the 8- and 10-membered ring failed. Besides, attempts to form trienes 14 on reaction of the acetylene with the diene failed. Reversal of the position of the olefin and acetylene (e.g. 15) had a positive effect on the reaction speed. The trans-fused bicyclic lactam 16 (n = 1) was formed much faster than 13 and also the 8-membered ring (n = 2) could be isolated.

In Chapter 4, the efforts to arrive at bridged azabicyclic systems are described. The initial approach started with commercially available succinimide 17 and glutarimide 18. Introduction of the first olefinic moiety via N-alkylation using NaH and alkenyl bromides, partial reduction of the imide to the ethoxylactam and finally C-alkylation using LHMDS and alkenyl bromides afforded diolefins 19 (Scheme 3). Unfortunately, all attempts to cyclize these compounds failed. Only once, a small amount of compound 20 could be isolated, but this result was not reproducible. In addition, the cyclizations of N-alkylated diolefins 22 proved to be difficult. Only the 13-membered ring bicycle 23 could be obtained in a reproducible fashion.

Scheme 3

Because it proved to be difficult to cyclize dienes with one of the alkenes connected to nitrogen, we turned our attention to ring systems with the nitrogen atom adjacent to the bridgehead position. Ethoxylactam 24 was chosen as the starting compound (Scheme 4). Alkylation using LDA and allyl bromide and protection of the hydroxy functionality
provided the N-acyliminium ion precursor 25. This was reacted with BF₃·OEt₂ and allyltrimethylsilane to give 26. Reaction of this diene with catalyst C gave cyclization to bridged bicyclic lactam 27.

**Scheme 4**

Finally, in Chapter 4, the synthesis of azabicyclo[4.1.1]alk-3-enes with a bridging nitrogen atom is described (Scheme 5). Starting from succinimide 17 and glutarimide 18, the first allyl group was introduced in a one-pot procedure. Substitution at nitrogen with a tosyl, tert-butoxycarbonyl and methoxycarbonyl group, followed by partial reduction of the lactam with NaBH₄ and PPTS in methanol yielded N,O-acetals 28. These were reacted in an N-acyliminium ion reaction with different nucleophiles to arrive at diolefins 29 and triolefins 30, in which the 6-membered ring gave a higher cis/trans-ratio than the corresponding 5-membered ring and the methoxycarbonyl group gave a better ratio than the tosyl group. The last step was the ring-closing metathesis reaction of the cis-precursors, which afforded the desired azabicyclo[4.2.1]non-3-enes 31 and azabicyclo[4.3.1]dec-3-enes 32. In these reactions, the 6-membered ring gave higher yields than its 5-membered ring counterpart. Structures of type 31 and 32 are interesting because of their appearance in natural products with important biological activity, such as cocaine.

**Scheme 5**