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NOVEL ROUTE TO FUSED NITROGEN HETEROCYCLES BY OLEFIN METATHESIS

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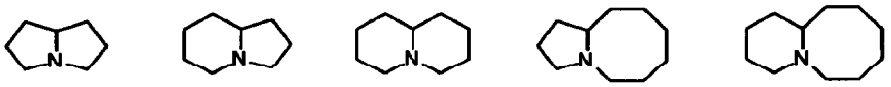
Abstract. A novel technique for the efficient synthesis of fused nitrogen heterocycles has been developed that features the molybdenum alkylidene-catalyzed metathesis of α,ω-dienes containing a nitrogen atom in the chain linking the two olefinic functional groups. The starting materials may be readily prepared in three steps from succinimide and glutarimide *via* sequential Mitsunobu alkylation, sodium borohydride reduction, and addition of a vinyl cuprate to an *N*-acyliminium salt generated *in situ*.

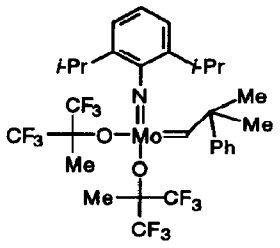
Fused nitrogen heterocyclic systems bearing a nitrogen atom at one of the bridgehead positions constitute structural subunits that are common to a diverse array of alkaloid natural products. A number of biologically important alkaloids contain the pyrrolizidine, indolizidine, quinolizidine ring systems **1**-**3**, respectively.[1] The pyrrolidinoazocine and the piperidinoazocine ring systems **4** and **5** may either be found in alkaloids or serve as intermediates in their synthesis.[2] Consequently, the invention and development of general techniques for the construction of such systems represents a major challenge in the arena of alkaloid synthesis.



1 **2** **3** **4** **5**

In conjunction with our work directed toward the asymmetric synthesis of manzamine A, we had occasion to explore new strategies for the synthesis of functionalized pyrrolidinoazocines, since this ring system is a structural component of this complex alkaloid.[3] After considering a variety of options, we were attracted to recent reports of Grubbs, who made the exciting discovery that simple, unsaturated oxygen and nitrogen heterocycles could be formed by the olefin metathesis of a series of α,ω-dienes using molybdenum and ruthenium alkylidene complexes.[4] We discovered that the molybdenum carbene complex {$PhMe_2CCH$=Mo=N-[2,6-(i-Pr)$_2C_6H_3$][$OCMe(CF_3)_2]_2$} (**6**)[5]

may be exploited to catalyze the ring closing metathesis of a highly functionalized substrate to deliver an advanced intermediate in our novel approach to manzamine A.[3b] Consequent to this success, we were intrigued by the possibility that transition metal alkylidene-catalyzed ring-closing olefin metathesis might be more generally applied to the problem of constructing fused nitrogen heterocycles. The reduction of this idea to practice constitutes the substance of the present account.



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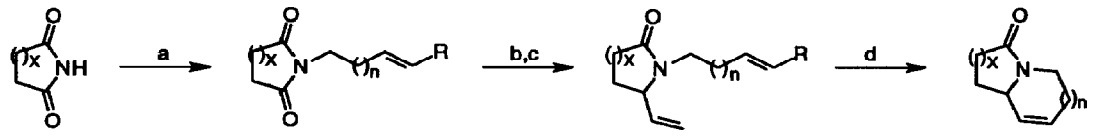
In order to explore the scope and limitations of the cyclizations of α,ω-dienes *via* molybdenum alkylidene-catalyzed metathesis, a series of such dienes were prepared from succinimide (**7**) and glutarimide (**8**) according to the sequence of reactions outlined in Scheme 1. Thus, alkylation of **7** and **8** with a series of unsaturated alcohols under Mitsunobu conditions[6] furnished the corresponding imides **9a-d** and **10b-d** in 70-90% yields.[7] Hydride reduction of these imides in the aqueous ethanol in the presence of acid then gave intermediate ethoxy amides[8] that were treated directly with lithium divinylcuprate in the presence of BF_3·OEt_2 to give the cyclization substrates **11a-d** and **12b-d** (30–40% unoptimized overall yield) by addition to an *N*-acyl iminium salt generated *in situ*.[9]

Scheme 1



7: x = 1
8: x = 2

9a-d: x = 1
10b-d: x = 2

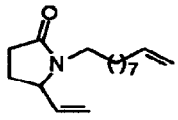
11a-d: x = 1
12b-d: x = 2

13a-d: x = 1
14b-d: x = 2

Series a: n = 0, R = Me
b: n = 1, R = H
c: n = 2, R = H
d: n = 3, R = H

(a) $RCH{=}CH(CH_2)_{n+1}OH$, PPh_3, DEAD, THF, RT, 24 h. (b) $NaBH_4$, HCl, EtOH, - 5 °C, 1 h.
(c) BF_3·OEt_2, Et_2O, -70 °C, 5 min; $(CH_2{=}CH)_2CuLi$, - 70 °C, 20 min.
(d) $PhMe_2CCH{=}Mo{=}N[2,6\text{-}(i\text{-}Pr)_2C_6H_3][OCMe(CF_3)_2]_2$, PhH, RT or 50 °C.

When the α,ω-dienes **11a-c** and **12b,c** (0.01–0.02 M in dry, degassed benzene) were stirred with the molybdenum catalyst **6** (10 mol%) at room temperature, facile ring-closing metathesis ensued to give the corresponding bicyclics **13a-c** and **14b,c** in 80–90% yields. The dienes **11d** and **12d** underwent cyclization to provide the medium ring products **13d** and **14d** in 65–75% yields, but these reactions required heating at 50 °C and the addition of a second portion of **6** (10 mol%) after 3 h to effect completion of the reaction. The possibility of forming larger rings by metathesis of the 1,13-diene **15** was also briefly examined, but under even highly dilute reaction conditions in which **15** (0.01 M in benzene) was slowly added to a solution of catalyst **6** (5 mL of 0.004 M in benzene) by a syringe pump, only dimeric products of the general structure **16** were isolated; none of the desired fused bicyclic product **17** could be detected. We are exploring the feasibility of inducing macrocyclizations of more constrained α,ω-dienes to expand the scope of this catalytic ring forming process.



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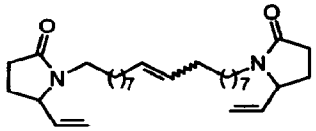

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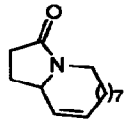

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In summary, we have established the feasibility of constructing pyrrolizidines, indolizidines, quinolizidines, pyrrolidinoazocines, and piperidinoazocines via a novel molybdenum-catalyzed olefin metathesis. Applications of this general strategy for the formation of these fused nitrogen heterocyclic systems to challenging problems in alkaloid synthesis are currently underway in our laboratory.

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