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Synthesis of fused bicyclic imidazoles by ring-closing metathesis

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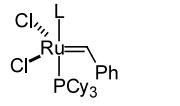
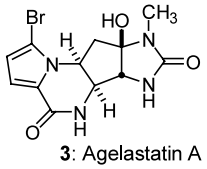
Abstract—The preparation of a number of dienylimidazole via chemoselective metal–halogen exchange and their utility in ring-closing metathesis is described. Essentially all regioisomeric permutations participate in metathesis with the notable exception of 4-vinyl-5-allylimidazoles, provided that the imidazole N3 atom is protonated.

Olefin metathesis has continued to evolve over the past few years as an extremely useful transformation in organic synthesis.[1] The development of robust and commercially available transition metal catalysts (e.g. **1** and **2**, inter alia) has permitted a thorough investigation of the scope and limitations of this reaction. Of the various modes of olefin metathesis, the intramolecular variant (ring-closing metathesis (RCM)) has received a significant amount of attention with this reaction being employed for the construction of numerous carbocyclic and heterocyclic systems. However, despite this activity, there appear to be no reports of the application of this transformation to imidazole containing systems, although hydantoins[2] and very recently 2-amino-5-imidazolones[3] have been investigated. As a continuation of our program to develop methods for the elaboration of simple imidazoles,[4] we now wish to report our studies on the RCM reactions of imidazole derivatives.



1: L = PCy_3
2: L = 1,3-Mes_2Im



3: Agelastatin A

At the outset of this work there were two issues of concern regarding the viability of metathesis reactions involving imidazoles. In particular was the possibility of imidazole ligation through donation of the N3-lone pair to the transition metal, either potentially rendering the complex catalytically inert or attenuating the reactivity.[5] The second issue related to the possibility of the formation of stable carbene complexes with vinylimidazoles similar to that observed by the Grubbs' group with *N*-vinylimidazole in some early work on ruthenium alkylidene complexes.[6,7] Conceivably the use of electron-withdrawing substituents on the imidazole might alleviate the first problem, whereas the validity of the second issue could only be established experimentally.

Our studies commenced with the preparation of diene **6** which was to serve as a precursor to allylic alcohol (**8a**) which was required as a key intermediate en route to the oroidin-derived marine alkaloid, agelastatin A (**3**).[8,9] The known dimethylsulfamoyl protected diiodoimidazole (**4**) served as the starting material for the preparation of **6**.[10] Thus treatment of **4** with EtMgBr followed by reaction with *N*-methyl-*N*-2-pyridylformamide provided the corresponding aldehyde (**5**) in 70% yield.[10,11] Stille cross-coupling of **5** with tributylvinylstannane, followed by treatment with CH_2=CHMgBr gave **6**. With this alcohol in hand it was treated with Grubbs' first generation catalyst **1** in CH_2Cl_2 at reflux, disappointingly however, no metathesis products were obtained. Only methyl and ethyl ketone products, resulting from fragmentation and rearrangement, were obtained in low yields.[12] Since these types of reaction pathways have been observed with allylic alcohols previously, the alcohol was protected as the TBS ether and reevaluated in the RCM reaction with the same catalyst but to no avail. It has been reported that the newer second-generation Grubbs' catalyst (**2**) can offer improved performance over **1** in both reactivity and functional group tolerance.[13] However, on reacting **6** or **7** with **2** no evidence for cyclization was obtained. As mentioned above, one

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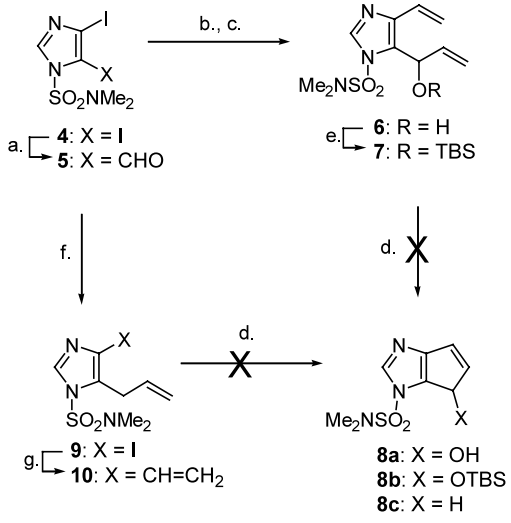
of the potential problems with imidazole substrates in metathesis reactions is the possibility of ligation via N3 with the ruthenium alkylidene, rendering the catalyst inactive. Thus attempts were made to circumvent this issue by protonating the offending nitrogen by treating the metathesis substrates (**6** or **7**) with *p*-TsOH prior to introduction of **1** or **2**. Unfortunately this also did not lead to successful metathesis, rather allylic transposition occurred. To prevent this rearrangement, a substrate lacking the hydroxy group (i.e. **8c**) was prepared from **4** via metallation (I→MgX), transmetallation (MgX→Cu) and then allylation to provide **9** (Scheme 1, Table 1, entry 1).[14] Stille cross coupling of **9** with tributylvinylstannane gave the required metathesis substrate (**10**) which unfortunately did not cyclize on exposure to either **1** or **2** as the free base or as the imidazolium salt.

We were concerned that the failure of these substrates to undergo metathesis might arise from the formation of stable metallacarbenes as had been observed previously with *N*-vinylimidazole, therefore, we decided to investigate diallyl systems in which the ring nitrogens can no longer interact with the alkene. Access to such substrates required only minor modifications of the sequence previously employed. Thus, metallation of **9** (I→MgX), transmetallation (MgX→Cu) and allylation provided the diallyl substrate (**11**, Table 1, entry 1). When this was subjected to metathesis with **1**, no evidence for cyclization was observed, formation and metathesis of the imidazolium salt was unsuccessful. On the other hand, metathesis of **11** with **2** led to successful cyclization, albeit in 22% yield. However, on preparation (1.1 equiv. *p*-TsOH) and metathesis of the imidazolium ion from **11**, the dihydrobenzimidazole (**12**) was obtained in 77% yield. With the identification of suitable conditions we set out to identify the scope and limitations of this transformation around the imidazole nucleus. Initially, the effect of substitution on the 4-allyl moiety was investigated. Thus the methallyl substituted derivative (**13**, Table 1, entry 2) and the allylic alcohol (**15**, Table 1, entry 3) were prepared and evaluated. Each substrate participated in the metathesis reaction with reasonable efficiency. The methallyl substrate provided the non-conjugated dibenzimidazoles (**14**), the structure of which was confirmed through an X-ray analysis of the product (Fig. 1). As can be seen in Table 1 (entry 3), the allylic alcohol provides benzimidazole (**16**), in which the initial product undergoes elimination of water.



Scheme 1. *Reagents and conditions*: (a) EtMgBr, CH_2Cl_2, then 2-PyN(CHO)Me, 70%; (b) CH_2=CHSnBu$_3$, Pd_2dba_3, PPh_3, DMF, 90°C, 97%; (c) CH_2=CHMgBr, THF, 56%; (d) 5–50 mol% **1** or **2**, CH_2Cl_2, reflux; (e) TBSCl, DMF, imidazole, 84%; (f) see Table 1 (g); CH_2=CHSnBu$_3$, Pd_2dba_3, PPh_3, DMF, 90°C, 99%.

One of the key variables investigated was the necessity for an electron-withdrawing N1-substituent, accordingly the benzyl-protected analog was prepared. Starting from the benzyl 4,5-diiodo derivative (**17**),[4b] two sequential metallation and substitution reactions provided the required substrate (**19**, Table 1, entry 4). After protonation with *p*-TsOH and introduction of the ruthenium carbene **2**, we were delighted to find that this substrate participated in metathesis to provide the corresponding cyclized product (**20**) in 87% yield. The methallyl-substituted derivative (**21**, Table 1, entry 5) was prepared and it engaged in metathesis very efficiently to provide **22**, the identity of which was confirmed by X-ray analysis (Fig. 2). As a result of these observations, the implication was that essentially any mode of linkage around the imidazole nucleus should be amenable to metathesis. Accordingly, substrates linked at other positions were prepared and investigated. The *N*-allyl systems (**24**, **26**, **31**) were constructed by *N*-allylation of 4,5-diiodoimidazole or 2,4,5-tribromoimidazole15 and then metallation and electrophilic trapping with allyl bromide (**24** and **31**, Table 1, entries 6 and 9) or acetaldehyde (dehydration then provided the allyl–vinyl system, **26**, Table 1, entry 7). Intriguingly, all of these substrates participated in metathesis after protonation and introduction of the catalyst, even **26**. This latter result (Table 1, entry 7) is particularly striking given that the corresponding 4,5-linked congener did not provide the cyclic product. At this point, we have no definitive explanation for this observation, although steric effects through the 4-iodo substituent may be important since its removal from **26** provides a substrate (**27**, Table 1, entry 8) that participates in metathesis but with reduced efficiency (Scheme 2).

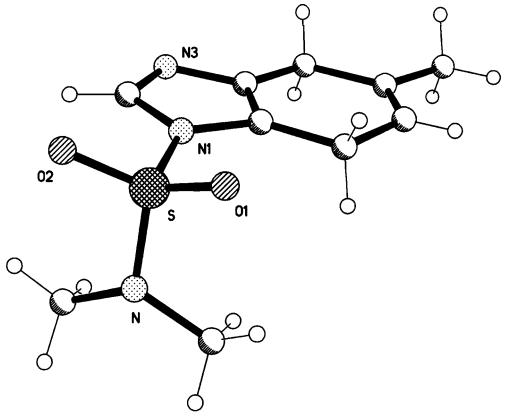
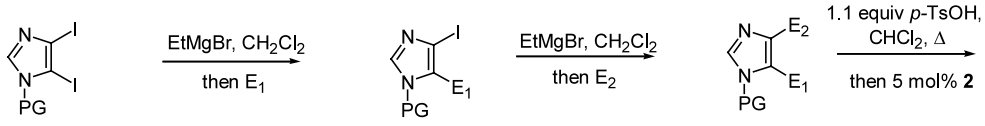
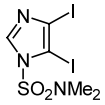
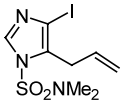
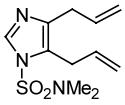
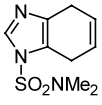
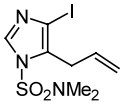
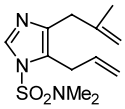
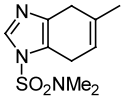
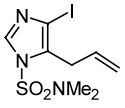
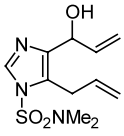
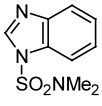
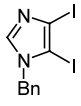
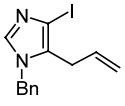
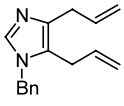
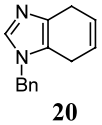
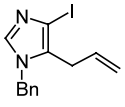
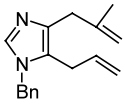
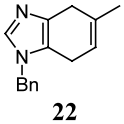
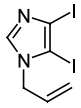
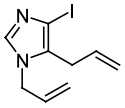
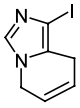
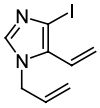
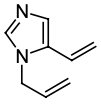
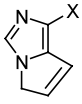
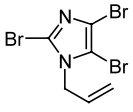
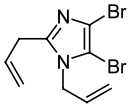
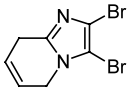


Figure 1. X-Ray crystal structure of RCM product **14**.



Scheme 2.

Table 1.

Entry	Substrate #	Reagents[16] (Yield/%)	Product	Reagents (Yield/%)	Product	Conditions[17] (Yield/%)	Product
1	 **4**	CuCN.2LiCl then allyl bromide (96)	 **9**	CuCN.2LiCl then allyl bromide (60)	 **11**	r.t., 12 h (77)	 **12**
2			 **9**	CuCN.2LiCl then methallyl chloride (66)	 **13**	r.t., 2 h (81)	 **14**
3			 **9**	CH_2=CHCHO (49)	 **15**	r.t., 1.5 h (45)	 **16**
4	 **17**	CuCN.2LiCl then allyl bromide (77)	 **18**	CuCN.2LiCl then allyl bromide (58)	 **19**	reflux, 1 h (87)	 **20**
5			 **18**	CuCN.2LiCl then methallyl chloride (70)	 **21**	reflux, 3 h (82)	 **22**
6	 **23**	CuCN.2LiCl then allyl bromide (72)	 **24**			r.t., 2 h (90)	 **25**
7 8		CH_3CHO then $CuSO_4$, xylenes, reflux (7)	 **26**	H_2O (56)	 **27**	X = I, r.t., 3 h (53) X = H, r.t. 12 h (32)	 **28**: X = I **29**: X = H
9	 **30**	CuCN.2LiCl then allyl bromide (76)	 **31**			r.t., 12 h (78)	 **32**

In summary, efficient syntheses of a number of dienyl imidazoles have been developed that rely on chemoselective metallation–electrophile capture sequences. These substrates participate in RCM reactions with Grubbs' second generation ruthenium carbene catalysts provided that the imidazole N3 atom is protonated. Apparently, only 4,5-allyl vinyl systems do not participate in the metathesis reaction. Further extensions and application of this transformation to natural product total syntheses are under way and will be reported in due course.

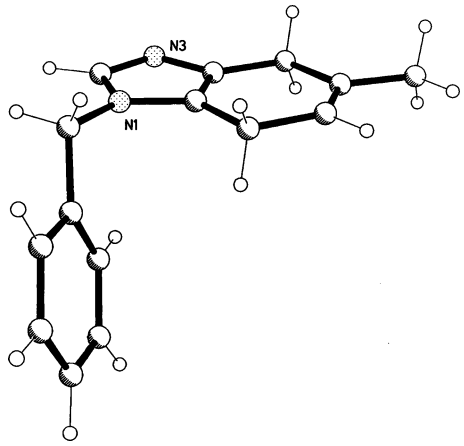


Figure 2. X-Ray structure of RCM product **22**.

Acknowledgements

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16. **General procedure**: An ethereal solution of EtMgBr (3 M, 14.3 mL, 42.9 mmol) was added dropwise to a magnetically stirred solution of **17** (16.00 g, 39.9 mmol) in CH_2Cl_2 (160 mL) at room temparature. After stirring at room temperature for 30 min, a THF solution of CuCN·2LiCl (1 M, 39.0 mL, 39.9 mmol) was added, followed by cooling to −30°C. Allyl bromide (3.67 mL, 42.6 mmol) was added by syringe and then the reaction mixture was warmed to 0°C and stirred for 4 h. The reaction was quenched by the addition of half saturated aqueous NH_4Cl containing 2% concentrated NH_3 and stirring for 20 min. The resulting blue solution was extracted with CH_2Cl_2 (×2), the combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (SiO_2, hexane/EtOAc, 1:1) to afford **17** (9.67 g, 77%) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.22$ (ddd, 2H, $J = 1.5$, 1.8, 5.9 Hz), 4.93 (ddt, 1H, $J = 1.5$, 1.8, 17.2 Hz), 5.04 (ddt, 1H, $J = 1.5$, 1.5, 10.3 Hz), 5.06 (s, 2H), 5.70 (ddt, 1H, $J = 5.9$, 10.3, 17.2 Hz), 7.02–7.06 (m, 2H), 7.27–7.35 (m, 3H), 7.45 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 29.1$, 49.6, 85.2, 116.9, 127.0, 128.4, 129.2, 131.5, 133.5, 135.5, 139.4; IR ($CHCl_3$, cm^{-1}): 3080, 3031, 2978, 2906, 1638, 1486, 1230, 1163, 976, 919, 722; EIMS (m/z): 65, 148, 275 (100%), 303, 324 (M^+), 325 (M^++1); Anal. calcd for $C_{13}H_{13}IN_2$: C, 48.17; H, 4.04; N, 8.64. Found: C, 48.03; H, 4.27; N, 8.73.
17. **General procedure**: Diallyl imidazole **19** (300 mg, 1.26 mmol) and *p*-TsOH (264 mg, 1.39 mmol) were dissolved in CH_2Cl_2 (12.6 mL) and heated at reflux for 30 min. After cooling to room temperature Grubbs' catalyst (**2**, 53 mg, 0.062 mmol) was added and then the mixture was heated to reflux for 60 min. After cooling to room temperature, the solvent was removed by rotary evaporation and aqueous $NaHCO_3$ solution was added to the residue. After the addition of solid K_2CO_3 to make the solution basic, that organic components were extracted with CH_2Cl_2. The organic solution was dried ($MgSO_4$) and concentrated to afford the crude product, which was purified by flash chromatography (SiO_2, hexane/EtOAc, 1:4) to afford **20** (230 mg, 87%) as a colorless solid. Mp: 140.0–140.5°C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.06$ (m, 2H), 3.32 (m, 2H), 5.01 (s, 2H), 5.72 (m, 1H), 5.89 (m, 1H), 7.04–7.08 (m, 2H), 7.24–7.33 (m, 3H), 7.46 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 23.0$, 26.7, 48.7, 122.1, 125.9, 126.9, 128.1, 129.0, 134.5, 136.1, 136.5; IR (KBr, cm^{-1}): 3089, 3030, 2871, 2835, 1651, 1594, 1493, 1438, 1364, 1234, 1178, 951, 900, 826, 736, 680, 456; EIMS (m/z): 65, 91, 119, 172, 210 (M^+), 211 (M^++1, 100%). Anal. calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.73; H, 6.71; N, 12.97.