HETEROCYCLES, Vol. 60, No. 1, 2003, pp. 1 - 7
Received, 12th August, 2002, Accepted, 13th November, 2002, Published online, 15th November, 2002

REGIOSELECTIVE SYNTHESIS OF 1-BENZYL- AND 1-METHYL-4-VINYLIMIDAZOLE AND THEIR REACTIONS WITH *N*-PHENYLMALEIMIDE

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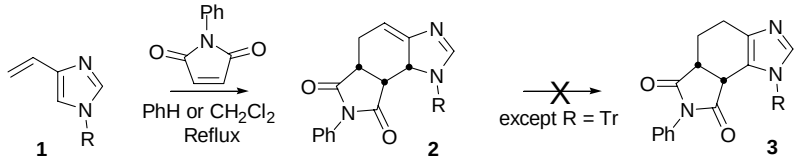
Abstract-The regioselective synthesis of 1-benzyl- and 1-methyl-4-vinylimidazole from 4,5-diiodoimidazole is described. Their Diels-Alder reactions with *N*-phenylmaleimide provide a variety of adducts, including the anticipated enamine and the corresponding aromatized isomer. However, additional products including ene adducts, a bis Diels-Alder adduct and oxidation products were isolated.

Without question, the Diels-Alder reaction is one of the most powerful synthetic transformations available to organic chemists as a result of the broad substrate scope and the generally predictable regio- and stereochemical course of this transformation.[1] Despite extensive research in this area, the application of the Diels-Alder reaction to imidazole derivatives has yet to receive significant attention.[2,3] Recently, we became interested in the application of the Diels-Alder reaction to 4-vinylimidazoles as a potentially efficient means to prepare a number of imidazole containing natural products and analogs. As part of this effort, our group has reported the preparation and Diels-Alder reactions of 4-vinylimidazoles possessing electron deficient substituents on N1 (Scheme 1).[4] These studies demonstrated that these dienes engage in the Diels-Alder reaction to provide the enamine (**2**) in good yield, without isomerizing to the thermodynamically more stable aromatic system (**3**), and as a single stereoisomer (*endo*). The ability to isolate these enamines was attributed to the conjugation present in the product, the reduction of the electron density on the imidazole N1 (R = Ts, MOM, SO_2NMe_2), and the reduction in steric compression between the N1 protecting group and the pyrrole ring (R = Tr) compared to the aromatic form.[4] As a continuation of these studies, we now describe the regioselective preparation and more complex reactivity of 4-vinylimidazoles with electron donating substituents on N1 (R = Bn, Me).



Scheme 1

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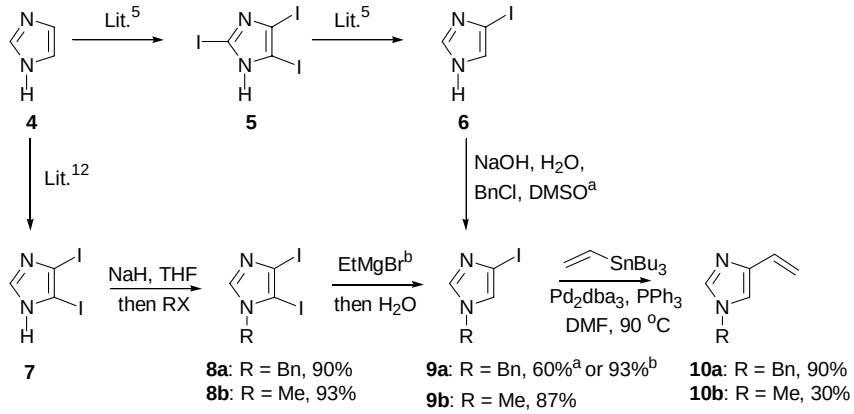
Prior to the studies reported in this paper only non-regiocontrolled approaches to these vinylimidazole had been reported. It was our intent to utilize 4-iodoimidazoles as precursors to these vinylimidazoles and employ transition metal cross-coupling reactions to introduce the vinyl group. The motivation for this approach lies in the divergency that can be obtained through the use of various cross-coupling partners. In order to effect this approach, a regioselective synthesis of 1-alkyl-4-iodoimidazoles was required. Although literature precedent was not particularly encouraging with regard to chemoselectivity, we initially explored the alkylation of 4(5)-iodoimidazole (**6**).[5] Our studies commenced with the synthesis of **6**, which was prepared according to literature procedures *via* polyiodination and reductive deiodination (Scheme 2).[5] Protection of N1 was accomplished by application of Pilarski's procedure for imidazole alkylation, thus treatment of **6** with benzyl chloride and aqueous NaOH in DMSO provided a mixture of the 4- and 5-iodoimidazoles in good overall yield.[6] This reaction was not chemoselective and a *ca*. 2:1 mixture of the two isomers (4- vs. 5-) was formed during the course of this reaction. Although the two regioisomers could be separated with reasonable efficiency by chromatography, the chemoselectivity of this alkylation reaction with BnCl suggested that attempts to react 4(5)-iodoimidazole with other small alkylating agents, e.g., MeI, would be less selective and in addition may lead to inseparable mixtures of 4- and 5-substituted imidazoles, therefore, an alternate route was developed.[7] Utilization of a symmetrical substrate, such as 4,5-diiodoimidazole, would circumvent the problem of regioisomer formation during the alkylation step, however the chemoselective removal of the 5-iodo substituent then became an issue. However, it is well-known that polyhalogenated imidazoles undergo halogen-metal exchange (Br/I→Li or Br/I→MgX) in a specific sequence under the appropriate conditions, i.e., C2>C5>C4, this ample precedence encouraged us to employ this approach.[5,8-11] Thus, 4,5-diiodoimidazole (**7**) was treated with NaH and then reacted with BnCl, or MeI to provide the corresponding protected imidazoles (**8a-b**) in excellent yields.[12] The 4,5-diiodoimidazoles were then treated with 1.1 eq. of EtMgBr in THF, after

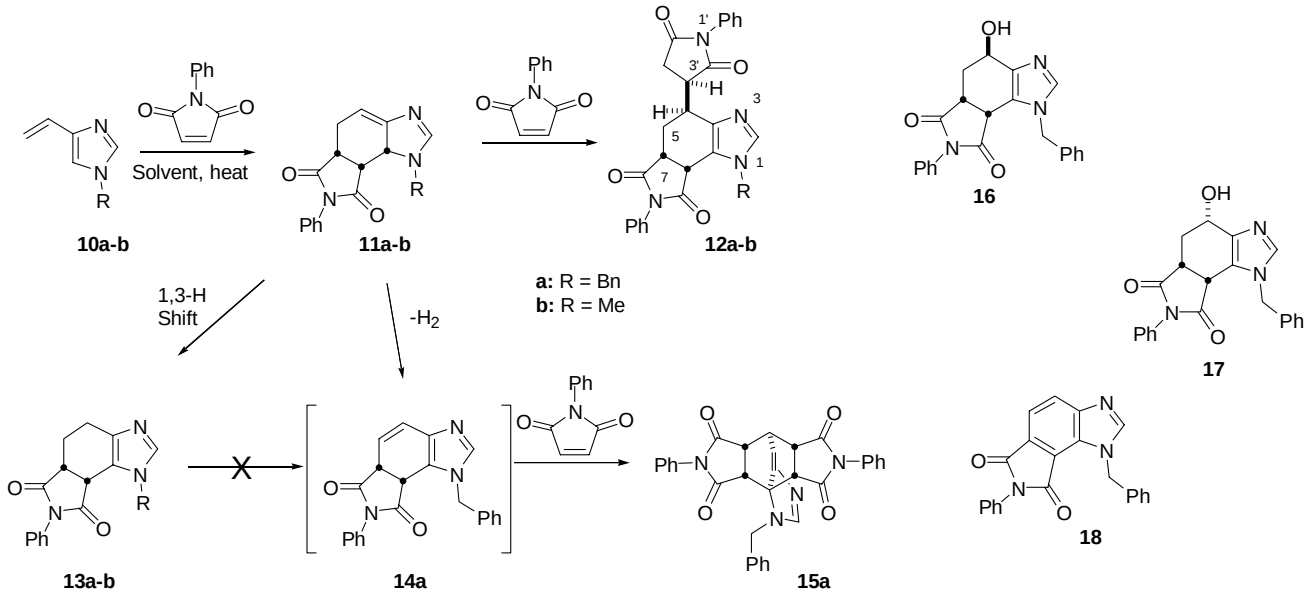


Scheme 2

iodine-magnesium exchange, the resulting Grignards were quenched with water. In each case analysis of ^{1}H-NMR spectra of the crude products indicated the formation of a single iodoimidazole. After purification and analysis through NOE experiments, it was clear that the iodide at C5 had been removed

selectively providing **9a** or **9b**, in accord with expectation. With the 4-iodoimidazoles (**9a-b**) in hand, they were subjected to Stille reactions with tributylvinyltin to provide the corresponding 4-vinylimidazoles (**10a-b**) in moderate to good yield.[13-15]

In the studies previously reported by our group, the Diels-Alder reactions were conducted in either CH_2Cl_2 or benzene at reflux and so for comparative purposes, these same solvents were employed in this work.[4] Generally, a 1:2.5 mixture of the 4-vinylimidazole (**10a** or **10b**) and *N*-phenylmaleimide (NPM) in the appropriate solvent was heated in a sealed tube at the indicated temperature in the Table. The outcome of these reactions is discussed below.



Scheme 3

Table: Yields and Product Distribution for the Reactions of 4-Vinylimidazoles (**10a-b**) with *N*-Phenylmaleimide

Entry	R[a]		Solvent	Temp/°C	Time/h	**11**/%	**12**/%	**13**/%	**15**/%
1	Bn	**10a**	CH_2Cl_2	50	14	80[b]	9	-	-
2	Bn	**10a**	CH_2Cl_2	50	10	88	-	-	-
3	Bn	**10a**	CH_2Cl_2	50	18[c]	-	-	80	-
4	Bn	**10a**	PhH	90	21[d]	-	18	18	28
5	Bn	**10a**	PhH	90	21[e]	-	-	75	-
6	Bn	**10a**	PhH	90	21[f]	-	19	74	-
7	Bn	**10a**	PhH	90	21[g]	-	-	32	19
8	Me	**10b**	CH_2Cl_2	50	3.5	-	21	39[h]	-
9	Me	**10b**	CH_2Cl_2	50	24	-	36	21	
10	Me	**10b**	CH_2Cl_2	50	13	-	-	76	-
11	Me	**10b**	PhH	90	6[d]	-	15	46	-

(a). A solution containing 1.0 eq. of **10a-b** and 2.5 eq. of *N*-phenylmaleimide in PhH or CH_2Cl_2 was heated at the indicated temperature for the indicated time. (b). Contaminated with a few percent of the aromatized product. (c) 30 mol% *p*-TsOH (d). The reactions in benzene were allowed to proceed until all of the enamine had been consumed. This was done to assist product isolation. (e). The reaction was run in the presence of catechol (30 mol%). (f). The reaction was run in the presence of BHT (30 mol%). (g) Oxygen was bubbled through the reaction prior to heating. (h) Overall yield from **10b** after treatment of the "purified" enamine with *p*-TsOH.

1-Benzyl-4-vinylimidazole: Examination of the ^{1}H-NMR spectrum of the crude reaction mixture of the experiments performed in CH_2Cl_2 indicated that two new products had formed (Table, Entry 1). The resulting adducts were separated by column chromatography to provide the enamine (**11a**) and ene product (**12a**) in 80% and 9% yield respectively (Scheme 3). In contrast to the enamines prepared previously (**2**, Scheme 1), **11a** was much less stable to silica gel, on purification, even with Et_3N treated silica gel, a small amount of isomerization to the aromatized product (**13a**) was observed. Although it should be pointed out that none of this aromatized product was observed by TLC during the reaction, or in the ^{1}H-NMR spectrum of the crude product. A NOESY experiment was performed on the Diels-Alder adduct (**11a**) and it was clear from this spectrum that the addition had occurred *via* an *endo* transition state. The second product (**12a**) isolated from this reaction, is assumed to arise from an ene reaction between **11a** and excess NPM.[16] It was subsequently discovered that if the reaction was not allowed to quite go to completion, then only the enamine and trace amounts of the ene product were formed (TLC analysis). Concentration and trituration of the crude product allowed the isolation of the pure enamine in 88% yield (Table, Entry 2). It also proved possible to isolate the aromatic product as the sole product when the reaction was conducted in the presence of 30 mol% *p*-TsOH (Table, Entry 3). A ^{1}H NMR spectrum of the crude material from this reaction indicated that the only product was **13a**. When the reaction was repeated in benzene a different set of products was obtained, this was partly due to the fact that the reaction was allowed to run until the enamine (**11a**) had been consumed (Table, Entry 4).[17] Under these conditions, three compounds were isolated. The aromatized adduct (**13a**) was isolated in 18% yield along with a comparable quantity of the ene product (**12a**), however the major product, isolated in 28% yield, was a compound that had incorporated two moles of NPM. It was clear from the NMR spectral data that this compound was not an isomeric ene product. Subsequently, X-Ray analysis of this material revealed that this adduct had a completely different origin, it was in fact a bis Diels-Alder adduct (**15a**, Figure 1). This compound results from the cycloaddition of NPM to vinylimidazole (**14a**) that arises from oxidation of the initial adduct (**11a**).[18,19] Control experiments indicate that the enamine undergoes oxidation, since the reaction of **13a** with NPM does not produce the bis adduct, but resubmission of **11a** to the reaction conditions leads to the formation of **15a**. Further support for this conclusion was obtained by heating a sample of **11a** under conditions utilized for the Diels-Alder reaction except in the absence of NPM leading to the formation of the aromatic adduct (**13a**, 58%), vinylimidazole (**14a**, 9%), and a trace of the fully aromatized adduct (**18**, 3%). Surprisingly, in addition to these three products, alcohols (**16** and **17**) were isolated as an inseparable 2:1 mixture of stereoisomers in 20% yield. The isolation of

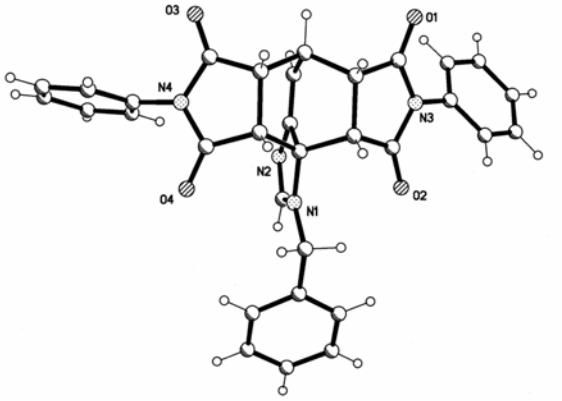


Figure 1: X-Ray Structure of **15a**

oxygenated products suggested that dissolved oxygen in the reaction solvent was the source of these alcohols, and so the reactions were conducted in the presence of anti-oxidants (catechol or butylatedhydroxytoluene - BHT). In the presence of 30 mol% of catechol only the aromatized product was obtained (Table, Entry 5), whereas when the reaction of **10a** was performed in the presence of 30 mol% of BHT, the aromatized product and the ene adduct were obtained (Table, Entry 6). To further probe this issue, the reaction was repeated after bubbling oxygen through the solvent under otherwise standard conditions for the cycloaddition (Table, Entry 7), on purification of the crude reaction mixture, the bis Diels-Alder adduct (**15a**) is obtained in 19% yield, along with the aromatic compound (**13a**, 32%). In addition to these adducts, a mixture of the alcohols (**16** and **17**) was obtained as a 2:1 mixture of stereoisomers in 28% yield that presumably results from the oxidation of **11a**.

1-Methyl-4-vinylimidazole: Similar experiments were performed with this diene in both CH_2Cl_2 and benzene as reaction solvents. In CH_2Cl_2 two compounds were observed in the ^1H NMR spectrum of the crude product, the *endo* enamine (**11b**)[20] and the ene product (**12b**, **11b**:**12b** = 3:1). In this case, the enamine was extremely sensitive to purification on silica gel, proving difficult to obtain in pure form and so it was converted to the aromatic isomer (**13b**) in 57% yield (39% overall) by treatment with *p*-TsOH for the purpose of characterization.[21] Crystals suitable for analysis by X-Ray crystallography were obtained from the ene product (**12b**) in this case (Figure 2). Not only did this analysis provide the relative stereochemistry of the C3'-stereocenter, it confirmed the regiochemistry of the 4-vinylimidazole (**10b**) and suggested that the Diels-Alder product has the indicated *endo* stereochemistry. The additional steps could be circumvented by allowing the reaction to proceed for 24 h, at which time **11b** was completely consumed (Table, Entry 9), or by performing the reaction in the presence of *p*-TsOH (Table, Entry 10). In benzene, the ene and aromatized adducts were isolated in 15% and 46% yield respectively. Although the reaction was allowed to run until all of the enamine was consumed, no bis Diels-Alder adduct was isolated in this case. We attempted to obtain **11b** free from contamination with the aromatized product by running the reaction to less than completion, analogous to the benzyl case described above. However in this instance, it did not prove possible to isolate the enamine by trituration.

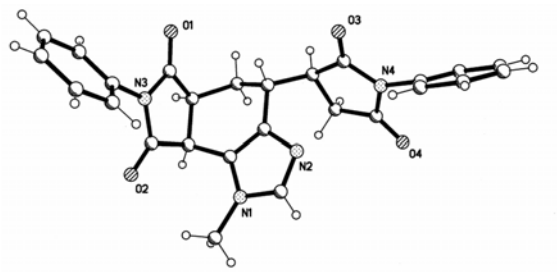


Figure 2: X-Ray Structure of **12b**

In summary, we have prepared 1-alkyl-4-vinylimidazoles in a regiodefined manner and these dienes participate in efficient Diels-Alder reactions. Under the appropriate reaction conditions, the initial enamine adduct can be obtained in good yield with a benzyl protecting group, although this enamine is

less stable than those which possess electron deficient substituents on N1.[4] Under more forcing conditions, benzene at reflux or prolonged reaction times, additional adducts are obtained that result from the incorporation of a second equivalent of NPM, either *via* an ene reaction or through an oxidation-Diels-Alder reaction sequence. These 2:1 adducts were not isolated in reactions involving more electron deficient 4-vinylimidazoles.[4] The methyl-substituted 4-vinylimidazole appears to be more reactive than the benzyl protected derivative, although it did not prove possible to isolate the pure enamine. The 4-regioisomers appear to be more reactive than the corresponding 5-regioisomer, and afford higher yields of the cycloadduct.[22] We are currently investigating the Diels-Alder chemistry of these and other 4-vinylimidazoles with other dienophiles and the application of these reactions to the synthesis of several imidazole containing natural products. These results will be reported in due course.

ACKNOWLEDGEMENTS

This work was supported by the Robert A. Welch Foundation (CJL: Grant Y-1362; HVRD: Grant Y-1289), the Texas Higher Education Coordinating Board-Advanced Research Program (003656-0004-1999), and The University of Texas at Arlington (Start-up Funds). The NSF (CHE-9601771) is thanked for partial funding of the purchase of a 500 MHz NMR spectrometer. Prof. Stephen Pyne (University of Wollongong, Australia) is gratefully acknowledged for advice regarding the reduction of compound **5**.

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16. The relative stereochemistry of the C3'-stereocenter has not been established unequivocally for **12a**. However, the similarity of the NMR spectra of **12a** with that of **12b**, for which the stereochemistry was determined *via* X-Ray crystallography, suggests that they possess similar relative stereochemistry. Further support for this assumption comes from an X-ray determination of a closely related ene product derived from a 2-methyl substituted benzyl protected 4-

vinylimidazole, which possessed the same relative stereochemistry as **12b**. H. Du, C.J. Lovely, and H.V.R. Dias unpublished results.
17. The reaction was allowed to proceed until all of the enamine had been converted into other products in order to simplify purification.
18. Noland has demonstrated that similar bis adducts can be obtained in the Diels-Alder reactions of 3-vinylindoles, although these substrates contained substituents, e.g., $-NO_2$, that either were readily eliminated ($-HNO_2$) or activate oxidation ($-H_2$) to provide the new diene. W. E Noland, M. J. Konkel, M. S. Tempesta, R. D. Cink, D. M. Powers, E. O. Schlemper, and C. L. Barnes, *J. Heterocycl. Chem*., 1993, **38**, 183. See also L Pfeuffer and U. Pindur, *Helv. Chem. Acta*, 1987, **70**, 1419.
19. This X-ray determination confirms the regiochemical assignment of the 4-vinylimidazole (**10a**).
20. The stereochemistry of this adduct was not determined experimentally, but inferred from the similarities of its ^{1}H NMR spectrum to that of other related enamines prepared in these laboratories, see ref. 4. Further support for the indicated stereochemistry comes from the X-Ray analysis of the ene adduct, which indicates that it is derived from reaction with the *endo* Diels-Alder adduct.
21. Our own observations regarding the isolation of this enamine are in accord with those reported by Walters and Lee for the corresponding 5-isomer. See ref. 2f.
22. We have performed comparable experiments with 1-methyl-5-vinylimidazole and have determined that these substrates are less reactive, requiring 9 h for complete consumption of starting material.