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The Use of Vinyl Imidazoles as Diels-Alder Dienes

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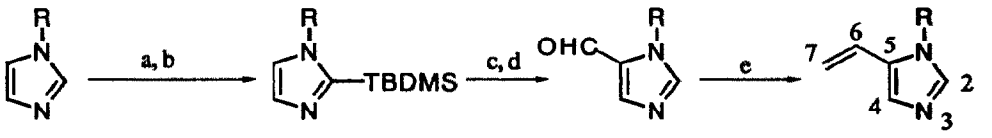
Abstract: The first use of a vinylimidazole as a Diels-Alder diene is reported. Semiempirical calculations are used to characterize 1-methyl-5-vinylimidazole as an electron-rich diene.

The preparation and utility of benzimidazole, purine, and caffeine derivatives is well-documented.[1] We envisioned that a general approach to the 5,6-fused ring systems related to these compounds could be effected by the Diels-Alder reaction of appropriately substituted 5-vinylimidazoles.[2] While this type of reactivity has been observed for the related vinyl-substituted furan,[3] pyrrole,[4] pyrazole,[5] isoxazole,[6] and indole[7] systems, the [4+2]-cycloaddition of vinylimidazoles as the diene component in the Diels-Alder reaction has not yet been documented. With the rich potential for this type of transformation in mind, we have begun an investigation of the synthesis and subsequent Diels-Alder reaction of substituted vinylimidazoles. Herein we report the first successful implementation of this methodology in the case of 5-vinyl imidazoles.

Imidazoles are known to react with dieneophiles to give cycloadducts across the 2,5 positions of the heterocyclic ring.[8] It was recently shown that 4-vinyl imidazoles with electron-withdrawing alkenyl substituents could react as dienophiles in [4+2] cycloadditions with simple dienes.[9] In order to establish that 1-protected-5-vinylimidazoles would participate as dienes in the Diels-Alder reaction, we prepared the vinyl imidazole derivatives **4a** and **4b** using simple modifications of syntheses reported in the literature (Scheme I).[10] In both cases, the appropriately protected imidazole (**1a** or **1b**) was deprotonated (*n*-BuLi/hexanes, 0 °C) and the resulting anion trapped with *tert*-butyldimethylsilyl chloride (TBDMSCl) to give the 1,2-protected imidazoles **2a** and **2b**. Formylation of imidazoles **2a** and **2b** was accomplished using another equivalent of n-BuLi followed by quenching of the reaction solution with dimethylformamide (DMF).[11] Desilylation with *n*-tetrabutylammonium fluoride (TBAF) in THF afforded the 5-formyl imidazoles **3a** and **3b**.[12] The requisite unsaturation was introduced using Wittig methylenation (LDA, $[Ph_3PCH_3]^+Br^-$) which gave the 1-methyl (**4a**) and 1-methoxymethyl (**4b**) 5-vinyl imidazoles in 64 and 80% yields, respectively from **2a** and **2b**.



1a-b **2a-b** **3a-b** **4a-b**

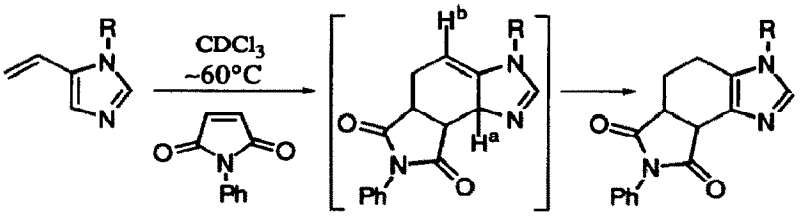
a) R=CH_3 b) R=CH_2OCH_3

a) *n*-BuLi b) TBDMSCl c) *n*-BuLi, DMF d) TBAF e) LDA/$[Ph_3PCH_3]^+Br^-$

Scheme I

The 5-ethenyl-1-methylimidazole (**4a**) was stirred at ~60 °C in $CDCl_3$ solution in the presence of one mole equivalent of *N*-phenylmaleimide (Scheme II). Monitoring of the reaction mixture by NMR over a 24 h period revealed the consumption of the two starting materials and the successive formation of two new products. After ~3.5 hours, ^1H NMR showed the reaction mixture to contain a 1.3:1 ratio of starting vinyl imidazole **4a** and what has been identified as enamine **5a**. Loss of the aromaticity of the imidazole ring

caused the *N*-methyl group of this first product (**5a**) to be shifted upfield 0.60 ppm (^{1}H NMR) relative to the starting material in which the *N*-methyl appeared at δ 3.59. On the basis of selective decoupling experiments the multiplets at δ 4.81 and δ 4.52 in this crude spectrum were assigned to the allylic (H^a) and alkenyl (H^b) protons in intermediate **5a**. After the full 24 h reaction period none of **5a** remained. The ^{1}H NMR spectrum showed evidence of only the rearomatized tetrahydrobenzimidazole **6a** which was isolated in 41% yield and fully characterized.[13]



a) R =CH_3 b) R =CH_2OCH_3

Scheme II

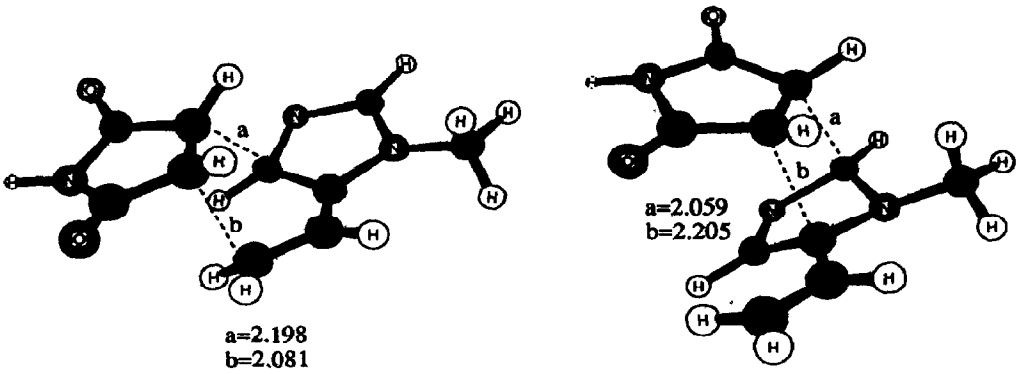
Reaction of the 5-ethenyl-1-methoxymethylimidazole (**4b**) with *N*-phenylmaleimide in $CDCl_3$ proceeded more sluggishly than the previous reaction (Scheme II). After 26.5 h at ~60 °C the reaction mixture contained a 1:3 ratio of the starting vinyl imidazole and what was assigned as cycloadduct **5b**. Only after 50 h did the second product begin to appear, and even after 6 days at ~60 °C the reaction had not yet gone to completion. Work-up of the reaction at this time gave only a 14% yield of the desired product **6b**. The enamine **5b** which had been observed in solution was apparently unstable to chromatography and could not be recovered. However, addition of *p*-toluenesulfonic acid (*p*-TsOH) to the initial reaction mixture was found to facilitate *in situ* isomerization of **5b** to the final product. In the presence of a catalytic amount of *p*-TsOH, only a trace amount of intermediate **5b** was observed (^{1}H NMR) in the reaction mixture after 5 h at ~60 °C. Thereafter, only the starting materials and the aromatic product **6b** were observed as the reaction progressed over 70 h, at which point the desired product (**6b**) could be isolated in 41% yield by standard work-up and chromatography.[14]

In order to help us better characterize the cycloaddition reactions of this new class of dienes, we calculated the HOMO and LUMO energies of 1-methyl-5-vinyl-imidazole **4a** using the PM3 semiempirical method (Table 1) as implemented in SPARTAN 3.0.[15] The HOMO energy of **4a** confirms that it is an electron-rich diene (cf. 1,3-dimethoxybutadiene: HOMO=-8.73235 eV, LUMO=0.29557) while the orbital coefficients suggest that reactions of polarized dieneophiles with **4a** should not be regioselective.[16] Additionally, we computed the transition structures for all four possibilities of the reaction of maleimide with both diene moieties of **4a**; dienes (C_4-C_5-C_6-C_7) and (C_2-C_3-C_4-C_5) (Figure 1). As was anticipated, the lowest energy transition structures were those found for reaction of the dieneophile with the exocyclic diene (C_4-C_5-C_6-C_7).[17] In these cases there was very little preference between the endo- (H_f=26.592 kcals/mol) and exo-modes **7** of cycloaddition (H_f=26.237 kcals/mol) at the PM3 level. Transition structures for the reaction of the dieneophile with the endocyclic (C_2-C_3-C_4-C_5) diene were both approximately 4 kcals/mol higher in energy than the comparable exocyclic diene cases. The endo-mode of cycloaddition **8** (H_f=30.251 kcals/mol) was slightly favored in this case *versus* the exo-mode (H_f=31.643 kcals/mol).

Table 1. The HOMO and LUMO Energies and Orbital Coefficients of 1-Methyl-5-Vinylimidazole **4a**.

	Energy (eV)	2[a]	3	4	5	6	7
LUMO	0.01708	-0.38895	0.08551	0.37973	-0.38452	-0.37236	0.50881
HOMO	-8.88828	0.47232	0.1980	**-0.44217**	-0.52012	0.27082	**0.44468**

a=atom number, **4a**.



7, H_f=26.237 kcals/mol **8**, H_f=30.251 kcals/mol

Fig. 1. Transistion Structures for the Exo-Cycloaddition Mode of Diene(C_4-C_5-C_6-C_7) (**7**), and the Endo-Cycloaddition Mode of Diene(C_2-C_3-C_4-C_5) (**8**) with maleimide (PM3). Distances are in Angstroms; Black bonds represent bonds which were of order two in the ground state.

This work documents the first successful use of vinyl imidazoles as Diels-Alder dienes. Additionally, we have characterized 1-methyl-5-vinylimidazole as an electron-rich diene using semiempirical calculations. We are currently investigating the reaction of this diene and related vinyl imidazoles with unsymmetrically-substituted alkenes in an attempt to both corroborate our theoretical findings and to determine the scope and generality of this process.

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11. In a typical procedure 6.2 mL (15.5 mmol) *n*-BuLi (2.5 M in hexanes) was added to 3.08 g (15.3 mmol) 2-(*tert*-butyldimethyl)silyl-1-methylimidazole (**2a**) in THF (25 mL) at -78 °C, and the mixture warmed slowly to an ambient temperature. Four hours after the base was added, the reaction was cooled again to -78 °C for the addition of 1.2 mL (15.8 mmol) DMF. The reaction was quenched after 12 h by adding saturated ammonium chloride, and 2-(*tert*-butyldimethyl)silyl-5-formyl-1-methylimidazole (3.00 g, 88%) was obtained by standard workup.
12. The regiochemistry of this acylation was confirmed by comparison of the physical and spectroscopic properties of **6a** with those reported in the literature for 2-formyl-1-methylimidazole: Iversen, P. E.; Lund, H. *Acta. Chem. Scand.* **1966**, *20*, 2649-2657, and 5-formyl-1-methylimidazole Link, H.; Bernauer, K. *Helv. Chim. Acta.* **1972**, *55*, 1053-1062; Jones, R. G. *J. Am. Chem. Soc.* **1949**, *71*, 644-647; Matthews, H. R.; Rapoport, H. *J. Am. Chem. Soc.* **1973**, 2297-2303.
13. **(6a):*cis*-3,4,5,5a,6,7,8,8a-octahydro-6,8-dioxo-3-methyl-7-phenylpyrrolo[3,4-*e*]benzimidazole** (mp 109-112 °C); IR (neat) 2931, 1712, 1500, 1379, 1177, 910, 730 cm^{-1}; ^1H NMR δ 7.36 (m, 3H), 7.39 (s, 1H), 7.22 (m, 2H), 4.19 (d, 1H, J = 7.7 Hz), 3.51 (m, 1H), 3.50 (s, 3H), 2.58 (m, 3H), 1.95 (m, 1H); ^{13}C NMR δ 177.4, 174.7, 137.4, 131.8, 129.7, 128.7, 128.0, 126.7, 126.1, 41.3, 40.4, 30.8, 21.0, 16.8; MS *m/z* (rel intensity) 281 (M^+, 53), 207 (7), 161 (8), 133 (100), 119 (16), 92 (17), 65 (9), 51 (5); Exact mass calcd for $C_{16}H_{15}N_3O_2$ 281.1164, found 281.1162.
14. **(6b):*cis*-3,4,5,5a,6,7,8,8a-octahydro-6,8-dioxo-3-methoxymethyl-7-phenylpyrrolo[3,4-*e*] benzimidazole** IR (neat) 2936, 1711, 1499, 1382, 1179, 1102, 696 cm^{-1}; ^1H NMR δ 7.54 (s, 1H), 7.24 (m, 5H), 5.14 (m, 2H), 4.22 (d, 1H, J = 8.1 Hz), 3.53 (m, 1H), 3.25 (s, 3H), 2.60 (m, 3H), 2.00 (m, 1H); ^{13}C NMR δ 177.5, 174.8, 138.0, 132.0, 131.1, 129.1, 128.5, 126.9, 126.4, 75.9, 56.1, 41.4, 40.8, 21.4, 17.2; MS *m/z* (rel intensity) 311 (M^+, 65), 292 (28), 268 (25), 251 (18), 207 (33), 164 (100), 133 (46), 119 (86), 91 (27), 77 (30); Exact mass calcd for $C_{17}H_{17}N_3O_3$ 311.1270, found 311.1277.
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17. Transition structures were characterized by their one imaginary (negative) frequency. Animation of this frequency in SPARTAN 3.0 showed the motion of atoms to be consistent with the bond-forming process.

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