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Synthesis and Diels–Alder Reactions of 4-Vinylimidazoles

Carl J. Lovely,* Hongwang Du, and H. V. Rasika Dias[†]

Department of Chemistry and Biochemistry, The University of Texas at Arlington, Arlington, Texas 76019

lovely@uta.edu

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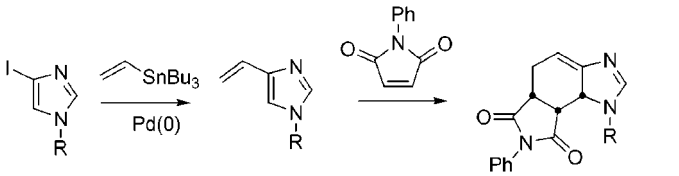
ABSTRACT



R = Tr, MOM, Ts, SO_2NMe_2

The synthesis of several 4-vinylimidazoles via Stille cross-coupling reactions of the corresponding protected 4-iodoimidazoles with tributylvinylstannane is described. These heterocyclic dienes are shown to be effective partners in the Diels–Alder reaction, providing adducts in good yield and exhibiting useful levels of isomer selectivity and stereoselectivity (*endo/exo*).

Recently, Scheuer, and Kinnel disclosed the isolation and structural elucidation of palau'amine **1** and related congeners.[1] In their report they suggested that the biosynthesis of palau'amine may involve a Diels−Alder (DA) reaction of vinylimidazole **2** with dehydrophakellin **3**, followed by a chloronium ion initiated 1,2-alkyl shift (Figure 1).[1] We became interested in exploring a biomimetic approach to palau'amine utilizing a DA/ring contraction sequence for the construction of the densely functionalized cyclopentyl ring found in **1** (Figure 1).[2] However, prior to investigating the feasibility of this approach, it was necessary to establish whether the precursor enamine **4** or congeners could be prepared effectively. Literature precedent was not especially encouraging in this respect.

While the ability of various vinylheterocycles to function as both 2π- and 4π-components in the DA reaction has been reported, there exist, to the best of our knowledge, only three

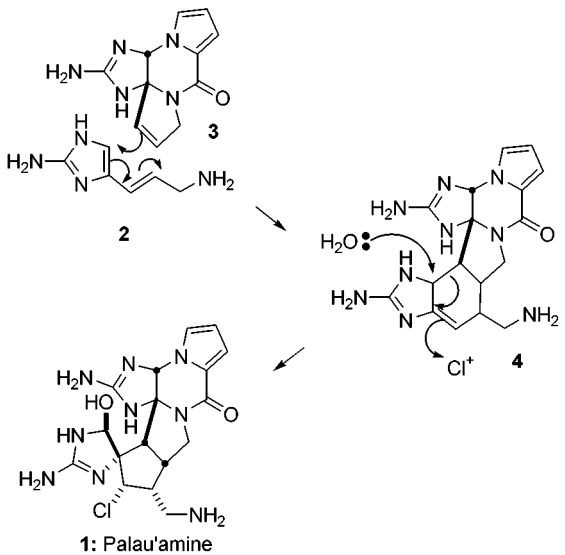


Figure 1. Proposed biosynthesis of palau'amine.

reports describing the DA behavior of 4- or 5-vinylimidazoles.[3] Walters and Lee reported that 5-vinylimidazoles

[†] Address correspondence regarding the X-ray structure reported in this paper to this author. E-mail: dias@uta.edu.

(1) Kinnel, R.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281.

(2) For synthetic approaches to palau'amine and related molecules, see: (a) Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *112*, 8793. (b) Overman, L. E.; Rogers, B. N.; Tellow, J. E.; Trenkle, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7159. (c) Dilley, A. S.; Romo, D. *Org. Lett.*, submitted for publication.

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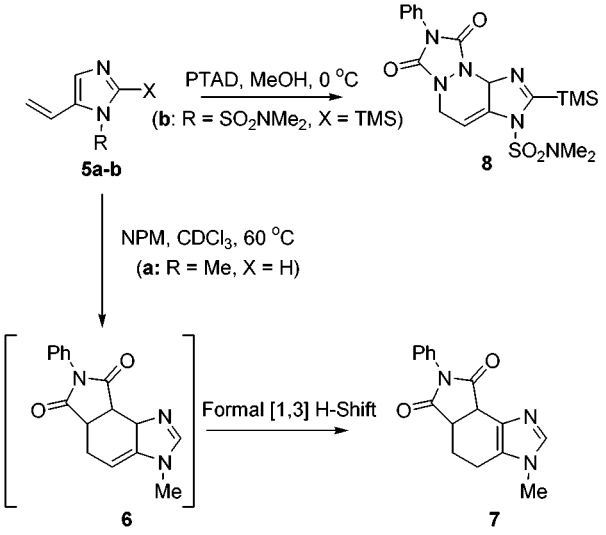
behave as 4π-components, e.g., **5a** reacting with *N*-phenylmaleimide (NPM) to produce **7** via the DA adduct **6** in moderate yield (Scheme 1).[4] More recently, Koomen and co-workers have shown that a 2-silyl-substituted 5-vinylimidazole **5b** undergoes a DA reaction with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) to produce the enamine **8** (Scheme 1).[5] Kosaka et al. reported that electron-deficient 4-vinylimidazoles can participate as 2π-components with reactive dienes such as cyclopentadiene.[6] In each case, the studies were of limited scope with respect to both the dienes and dienophiles. Furthermore, calculations performed by Walters indicated that DA reactions with 5-vinylimidazoles would be expected to proceed with little or no stereo- or regioselectivity.[6] In this communication, we wish to describe the synthesis and preliminary investigation of the DA behavior of several 4-vinylimidazoles.[7]

Scheme 1



In designing approaches to these dienes, a synthetic scheme was required that allowed for the utmost flexibility in order to evaluate the influence of substitution (at N1, C2, and on the vinyl group), in addition to being amenable to eventual extension to a solid phase format. The approach outlined below in Figure 2 appeared to meet these criteria. Thus, introduction of the vinyl group would rely on a Stille (or related) cross-coupling reaction with a protected 4-iodoimidazole **11**. The N1-substituted imidazole would be prepared by regioselective protection of 4(5)-iodoimidazole **12**, which in turn would originate from 2,4,5-triiodoimidazole by partial reductive deiodination.[8]

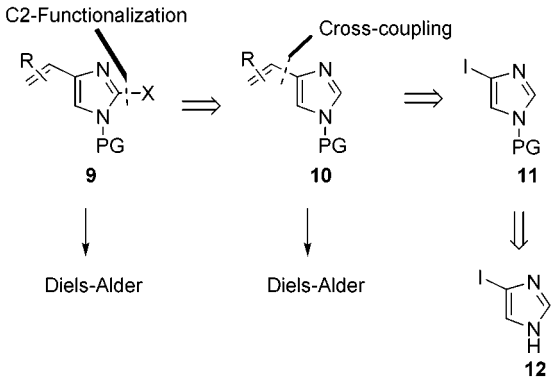


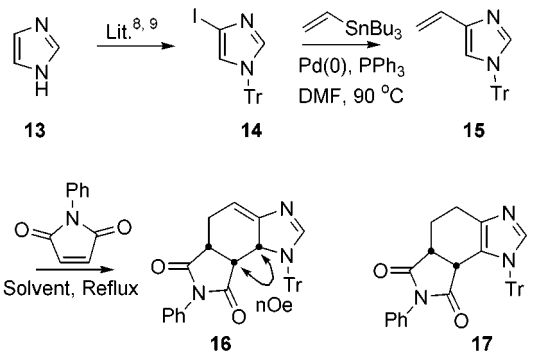
Figure 2. Proposed assembly of diverse 4-vinylimidazoles.

Our studies commenced with the synthesis of 4(5)-iodoimidazole according to literature procedures via polyiodination of imidazole and reductive deiodination with Na_2SO_3 in refluxing aqueous ethanol, providing the product in good overall yield.[8] Protection of N1 was accomplished with trityl chloride following the procedure of Kirk to afford imidazole **14**.[9] The protected iodoimidazole underwent efficient Stille cross-coupling with the tributyl(vinyl)stannane to provide the corresponding vinylimidazole in good yield (80−90%).[10,11] With the 4-vinylimidazole in hand, its ability to engage in the Diels−Alder reaction was evaluated. For this initial investigation, *N*-phenylmaleimide (NPM) was utilized as the dienophile.

A 1:1.3 mixture of 4-vinylimidazole **15** and NPM in benzene was heated at reflux for 30 h. Examination of the ^{1}H NMR spectrum of the crude reaction mixture indicated that two major products had formed in addition to a few minor products. The resulting major adducts were conveniently separated by flash column chromatography to provide enamine **16** and imidazole **17** in 60% and 3% yield, respectively. The stereochemistry of the enamine was determined via NOESY experiments to be that derived from an *endo* transition state. In an attempt to increase the overall yield of the reaction and reduce the reaction time, the reaction was repeated under essentially identical conditions except with 2.5 equiv of NPM. This modification was only partially successful; although the reaction time was reduced and the yield of the reaction was increased incrementally, the ratio of the enamine **16** to the aromatic adduct **17** decreased from 20:1 to 8:1. The effect of solvent on the isomer ratio was evaluated by employing a variety of solvents in the reaction. Thus, a 1:2.5 mixture of **15** and NPM were heated in the

(3) Sepulveda-Arques, J.; Abarca-Gonzalez, B.; Medio-Simon, M. *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: San Diego, 1995; Vol. 63, p 339.
(4) Walters, M. A.; Lee, M. D. *Tetrahedron Lett.* **1994**, *35*, 8307.
(5) Deghati, P. Y. F.; Wanner, M. J.; Koomen, G.-J. *Tetrahedron Lett.* **1998**, *39*, 4561.
(6) Kosaka, K.; Maruyama, K.; Nakamura, H.; Ikeda, M. *J. Heterocycl. Chem.* **1991**, *28*, 1941.
(7) For studies relating to Diels−Alder reactions of 2-vinylimidazoles, see: (a) Abarca-Gonzalez, B.; Jones, R. A.; Medio-Simon, M.; Quilez-Pardo, J.; Sepulveda-Arques, J.; Zaballos-Garcia, E. *Synth. Commun.* **1990**, *20*, 321. (b) Rothenburg, A. S.; Daulplaise, D. L.; Panzer, H. P. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 560.
(8) Iddon, B.; Lim, B. L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 735.
(9) Kirk, K. L. *J. Heterocycl. Chem.* **1985**, *22*, 57.
(10) (a) Cliff, M. D.; Pyne, S. G. *J. Org. Chem.* **1995**, *60*, 2378. (b) Cliff, M. D.; Pyne, S. G. *J. Org. Chem.* **1997**, *62*, 1023. (c) Cliff, M. D.; Pyne, S. G. *Tetrahedron* **1996**, *52*, 13703.
(11) (a) Altman, J.; Wilchek, M. *J. Heterocycl. Chem.* **1988**, *25*, 915. (b) Kokosa, J. M.; Szafasz, R. A.; Tagupa, E. *J. Org. Chem.* **1983**, *48*, 3605.

Scheme 2



indicated solvent at reflux until all of the vinylimidazole was consumed (TLC analysis), the yields of the isolated products are given in Table 1. It is clear from entries 1 and 2 that

Table 1. Solvent Dependence of Isolated Product Yield

entry	solvent (reaction time/h)	enamine **16**	imidazole **17**
1	xylene (1)[a]	0	0
2	toluene (3)[a]	52	8
3	benzene (12)[a]	63	8
4	benzene (30)[b]	60	3
5	chloroform (24)[a]	84	0
6	dichloromethane (24)[a]	52	0

[a] A solution containing 1.0 equiv of **15** and 2.5 equiv of NPM in the indicated solvent (3 mL) was heated at reflux for the indicated time. [b] 1.3 equiv of NPM was employed.

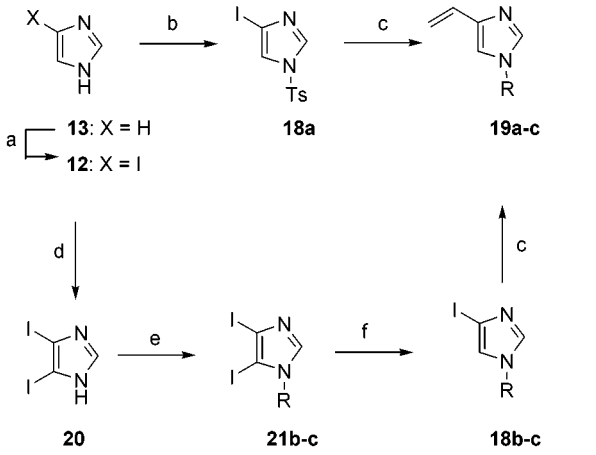
these cycloadducts are thermally sensitive as evidenced by the diminished yields in higher boiling solvents.[12] In the lower boiling chlorinated solvents (entries 5 and 6) the overall yields are good, as are the isomer selectivities. These latter reactions appeared to proceed more cleanly than those carried out in higher boiling solvents. Also evident from these results is the preference for the initial DA adduct **16** in all cases examined. The ability to isolate the enamine adduct **16** was encouraging for the eventual application of this approach to the total synthesis of palau'amine. Despite these results, the trityl-protecting group was not viewed as being ideal in subsequent transformations as a result of its steric bulk.[13] However, it was thought that these enamines might be stabilized electronically by the incorporation of electron-withdrawing substituents on nitrogen, thereby reducing the ability of the N1 lone pair to provide a driving force for aromatization.

A variety of electron-deficient protecting groups were selected that exhibited different electronic and steric demands (Table 2). The protected 4-iodoimidazoles **18a**−**c** were

(12) It is believed that this is due to the lability of the trityl-protecting group at elevated temperature.

(13) In addition, attempts to engage this diene with activated acyclic dieneophiles have been unsuccessful in large part as a result of steric hindrance.

Scheme 3[a]



[a] Reagents and conditions: (a) ref 8; (b) ref 10a; (c) Pd_2dba_3, Ph_3P, $Bu_3SnCH{=}CH_2$, DMF, 90 °C; (d) ref 16; (e) NaH, THF, MOMCl or Me_2NSO_2Cl; (f) EtMgBr, THF, then H_2O.

prepared in one of two ways. In the case of the tosyl substituent, the 4-iodoimidazole **18a** is known and can be prepared by sulfonylation of 4(5)-iodoimidazole in good yield and with good regioselectivity (Scheme 2).[10a] We have demonstrated that smaller protecting groups can be introduced via alkylation and then reduction of 4,5-diiodoimidazole.[14] Thus, 4,5-diiodoimidazole was treated with NaH and then reacted with MOMCl or Me_2NSO_2Cl to provide the corresponding protected imidazoles in excellent yields.[15,16] Treatment with 1.1 equiv of EtMgBr followed by reaction with water led to the reductive removal of the 5-iodo substituent.[17,18] The protected 4-iodoimidazoles were subjected to Stille cross-coupling, providing the corresponding vinylimidazoles in good yield (Table 2).[19]

Table 2. Yields for the Preparation of Vinylimidazoles **19a**−**c**

R		**21** (%)	**18** (%)	**19** (%)
Ts	**a**		69	92
MOM	**b**	89	90	52
SO_2NMe_2	**c**	62	54	79

Each of the vinylimidazoles **19a**−**c** was subjected to DA reactions with NPM in either benzene or dichloromethane.

(14) Du, H.; Lovely, C. J.; Dias, H. V. R. *Tetrahedron Lett.*, manuscript in preparation.

(15) The introduction of the dimethylsulfamoyl group can be problematic with respect to the regioselectivity when 4(5)-iodoimidazole is used; therefore it was prepared in an analogous fashion to the MOM-protected derivative. See: Bhagavatula, L.; Premchandran, R. H.; Plata, D. J.; King, S. A.; Morton, H. E. *Heterocycles* **2000**, *53*, 729.

(16) Carver, D. S.; Lindell, S. D.; Saville-Stones, E. A. *Tetrahedron* **1997**, *53*, 14481.

(17) Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618.

(18) The identity of this regioisomer was confirmed through an NOE experiment.

(19) Janin, Y. L.; Aubertin, A.-M.; Chiaroni, A.; Riche, C.; Monneret, C.; Bisagni, E.; Grierson, D. S. *Tetrahedron* **1996**, *52*, 15157.

In each case the enamine adduct was readily obtained as the sole isolable product in either of the two solvents. The principle differences between the two solvent systems were the shorter reaction times in the higher boiling solvent and the cleaner reactions in dichloromethane. In contrast to the trityl-protected enamine adduct **16** described above, the Ts-protected enamine **22a** was amenable to analysis by X-ray crystallography (Figure 3). The crystal structure clearly

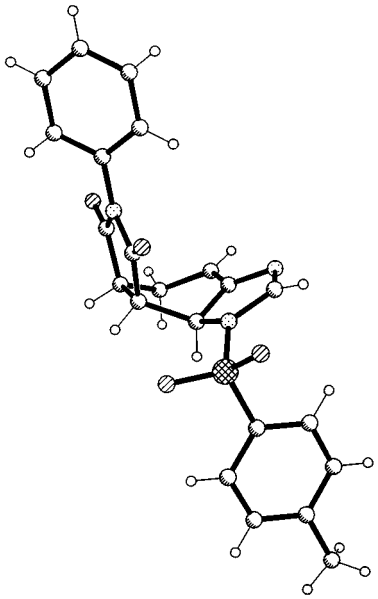


Figure 3. X-ray crystal structure of enamine **22a**.

reveals that the C8a and C8b hydrogen atoms were syn to one another, indicating that the adduct had formed through an *endo* transition state. The fact that the ^{1}H NMR spectra for all of the enamine adducts bear a striking resemblance to one another suggests that they all arise via an *endo* transition state.[20,21] Clearly the ability to isolate stable

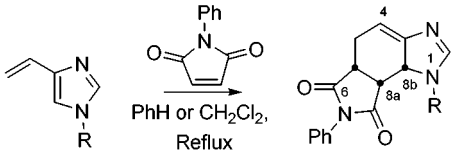
Table 3. Yields for the Cycloaddition Reactions[a]

entry	R		solvent[a]	time (h)	yield (%)
1	Ts	**a**	PhH	27	80
			CH_2Cl_2	48	89
2	MOM	**b**	PhH	2.5	70
			CH_2Cl_2	17	86
3	SO_2NMe_2	**c**	PhH	9	93
			CH_2Cl_2	48	94

[a] A solution containing 1.0 equiv of **19a**−**c** and 2.5 equiv of NPM in the indicated solvent (3 mL) was heated at reflux for the indicated time.

enamine adducts with 4-vinylimidazoles on reaction with NPM and not with 5-vinylimidazoles warrants comment. It is believed that there are several factors that contribute to these observations. First, the enamine adduct is conjugated in this instance, whereas with the isomeric 5-vinylimidazoles it is not. Second, with the bulky trityl-protecting group, it is presumed that there is significant barrier to aromatization due to increasing steric compression in the aromatic isomer (Scheme 2, cf. **16** vs **17**). Third, electron-deficient protecting groups can stabilize the enamine by reducing the electron density on nitrogen (N1), thereby alleviating the driving force for aromatization.[22] This is particularly noteworthy with the MOM-protecting group (Scheme 4, **19c** → **22c**) where in Walters' work, only the aromatized compound was isolated in low yield.[23]

Scheme 4



In summary, we have demonstrated that 4-vinylimidazoles can be prepared in an efficient manner and that they are effective dienes in the Diels−Alder reaction. Stable Diels−Alder adducts are isolated from this reaction independent of the nature of the N-substituent, this is in stark contrast with the isomeric 5-vinylimidazoles. We are currently investigating the scope of this reaction with respect to dienophiles, imidazole substitution patterns and its application in natural product total synthesis.[15] The results of these studies will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all of the new compounds. The X-ray data for compound **22a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) NOESY experiments were used to support this supposition, and these experiments revealed cross-peaks due to an NOE between C8a and C8b in both **22b** and **22c**.

(21) The trace formation of *exo* adducts cannot be excluded. Although there are traces of other components produced in these reactions, we have not isolated any other products from the reaction mixtures. See ref 14.

(22) We have found with electron-donating substituents on N1 that the enamines have an enhanced tendency to aromatize, although the enamine can be isolated. In addition, these enamines are prone to further reactions, see ref 14.

(23) It should be pointed out that in Walters' work, under conditions similar to ours ($CDCl_3$, 60 °C), 16% of the aromatized benzimidazole was obtained. However, the addition of *p*-TsOH increased this yield to 41%.