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Intramolecular Diels−Alder and Tandem Intramolecular Diels−Alder/1,3-Dipolar Cycloaddition Reactions of 1,3,4-Oxadiazoles

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In exploration of a new synthetic approach to the vinca alkaloids[1] based on the cycloaddition reactions of electron-deficient heterocyclic azadienes,[2] we report herein the first examples of intramolecular Diels−Alder and tandem intramolecular Diels−Alder/1,3-dipolar cycloaddition reactions[3] of 1,3,4-oxadiazoles. Limited reports of the cycloaddition reactions of electron-deficient and typically symmetrical 1,3,4-oxadiazoles (**1**, R = $\mathrm{CF_3}$, $\mathrm{SO_2Et}$, $\mathrm{CO_2Me}$) have been detailed (Figure 1).[4−10] In these studies of Vasilíev,[4] Sauer,[5] Seitz,[6] and most recently Warrener,[7,8] the 1,3,4-oxadiazoles were found to behave as electron-deficient azadienes in inverse electron demand Diels−Alder reactions although most examples disclosed have employed strained dienophiles. Reactions of olefinic dienophiles proceed through an initial [4 + 2] cycloadduct that loses N_2[11] to generate a carbonyl ylid which further reacts with the olefin in a 1,3-dipolar cycloaddition (Figure 1). The initial 1:1 adducts are not observed, and the second 1,3-dipolar cycloaddition is more facile than the initial Diels−Alder reaction which limits the reaction to the generation of symmetrical 2:1 cycloadducts. However, its implementation in tandem intramolecular cycloadditions could expand the range of oxadiazoles that participate in the reaction cascade, extend their use to unsymmetrical dienophiles and oxadiazoles, control the cycloaddition regioselectivity, and increase the utility of tandem Diels−Alder/1,3-dipolar cycloaddition reactions of such heterocyclic azadienes.

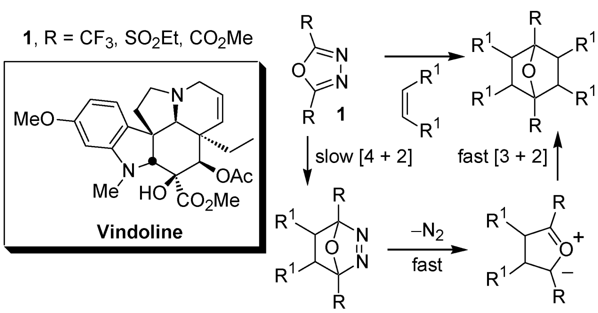
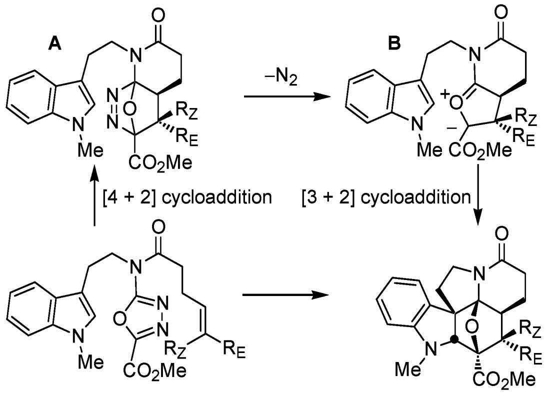


Figure 1.

Scheme 1



1a, R = H	*o*-$\mathrm{Cl_2C_6H_4}$, 180 °C, 3 h	87% **1b**
	or µwave 250 °C, 30 min	70%
(*E*)-**2a**, R_E = Me	*o*-$\mathrm{Cl_2C_6H_4}$, 180 °C, 24 h	65% **2b**
(*E*)-**3a**, R_E = $\mathrm{CH_2OTBS}$	*o*-$\mathrm{Cl_2C_6H_4}$, 180 °C, 24 h	86% **3b**
(*E*)-**4a**, R_E = Ph	*o*-$\mathrm{Cl_2C_6H_4}$, 175 °C, 14 h	61% **4b**
	or TIPB,[a] 230 °C, 5 h	60%
(*E*)-**5a**, R_E = OBn	TIPB,[a] 230 °C, 19 h	88% **5b**
(*Z*)-**6a**, R_Z = OBn	TIPB,[a] 230 °C, 38 h	41% **6b**
(*E*)-**7a**, R_E = $\mathrm{CO_2Me}$	TIPB,[a] 230 °C, 46 h	71% **7b**
(*Z*)-**8a**, R_Z = $\mathrm{CO_2Me}$	TIPB,[a] 230 °C, 60 h	62% **8b**
(*E*)-**9a**, R_E = CN	TIPB,[a] 230 °C, 22 h	79% **9b**
	o-$\mathrm{Cl_2C_6H_4}$, 170 °C, 144 h	76%
(*Z*)-**10a**, R_Z = CN	TIPB,[a] 230 °C, 22 h	74% **10b**
(*E*)-**11a**, R_E = Ts	TIPB,[a] 230 °C, >72–96 h	no reaction

[a] TIPB = triisopropylbenzene.

Initial studies were conducted largely with the synthetic target vindoline in mind. Thus, the substrates bear a tethered indole to trap the in situ generated carbonyl ylid analogous to that in the work of Padwa.[12] Comparison of the relative ease of tandem [4 + 2]/[3 + 2] cycloadditions of substrates **1**−**11a** is consistent with the cascade being initiated by an inverse electron demand Diels−Alder reaction, and each is followed by loss of N_2 and an effective 1,3-dipolar cycloaddition with the tethered indole providing the cycloadducts in excellent conversions (Scheme 1). Although the reaction appears most facile when initiated by an inverse electron demand Diels−Alder reaction, even unactivated or electron-deficient tethered dienophiles participate effectively with the (*E*)-dienophiles typically being more reactive. In each case, a single diastereomer is produced in which the relative stereochemistry is set by a combination of (1) the dienophile geometry and (2) exclusive indole *endo* [3 + 2] cycloaddition sterically directed to the α-face of the 1,3-dipole by the fused lactam as first observed by Padwa.[12] Further alkene substitution does not alter this remarkable diastereoselectivity, although it does typically slow the cycloaddition cascade (**1** > **2** or **12**, **3** ≫ **13**), Schemes 1 and 2. Notably, the trisubstituted enol ethers **14**−**17** (vs **5** and **6**) constitute exceptions to this generalization. They are more reactive or remain suitably reactive to participate in the cycloaddition cascade with the *E*-isomers exhibiting a more pronounced reactivity (e.g., **16** vs **17**), presumably attributable to *endo* versus a slower *exo* [4 + 2] cycloaddition. Impressively, the tandem cycloadditions construct three new rings with formation of four new C−C bonds and set all six stereocenters about the central six-membered ring in a single step without trace of a second diastereomer. Important for our

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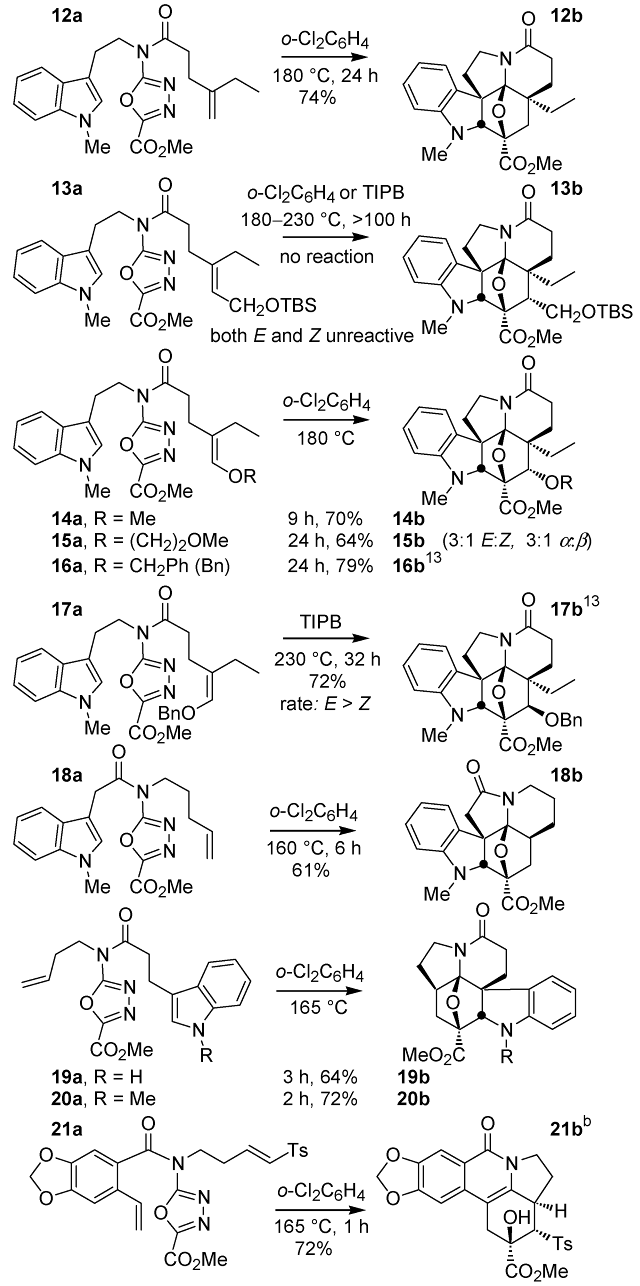
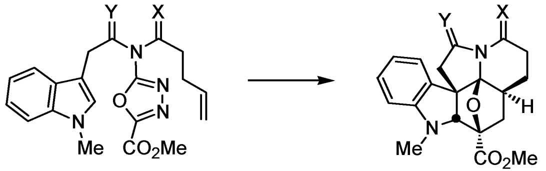
Scheme 2 [a]



[a] Relative stereochemistry determined by ^{1}H NMR NOE's. [b] Relative stereochemistry determined by X-ray, ref 14.

projected application, the closure of **17** incorporates and sets all six stereocenters characteristic of vindoline in a single operation including three contiguous and four total quaternary centers.[13,14]

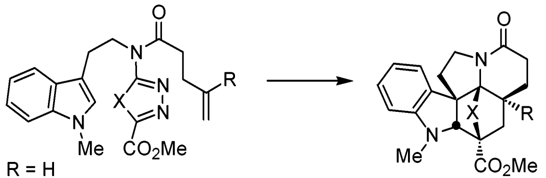
As anticipated, initiation of the cycloaddition cascade occurs more rapidly with tethered Diels−Alder closure to provide a five- versus six-membered fused ring (**19** and **20** vs **18**), although it is notable that even the latter closures occur with a facility that exceeds typical unactivated alkene intramolecular Diels−Alder reactions. The complementary substitution of the oxadiazole reinforces a preferred [4 + 2] and [3 + 2] cycloaddition regioselectivity that is consonant with use in a synthesis of vindoline, and it further stabilizes the intermediate carbonyl ylid 1,3-dipole relative to **1**. However, it does constitute a less electron-deficient oxadiazole than those previously examined.[4−8] This loss of intrinsic reactivity for the initial [4 + 2] cycloaddition, which is marginal even for the parent oxadiazole **1** (Figure 1, R = CO_2Me),[9] is compensated for by its use in an intramolecular Diels−Alder reaction. Even here, N-acylation of the oxadiazole C2 amino group is required for sufficient [4 + 2] cycloaddition reactivity, and there is little distinction whether it is incorporated into the dienophile or dipolarophile tether (eq 1). Analogous to prior observations,[4−8] the corresponding 1,3,4-thiadiazoles **23** and **24** were significantly less reactive than the oxadiazoles (eq 2).



(1)

1a, X = O, Y = H_2	o-$Cl_2C_6H_4$, 180 °C, 3 h	87% **1b**
18a, X = H_2, Y = O	o-$Cl_2C_6H_4$, 160 °C, 6 h	61% **18b**
22a, X = Y = H_2	o-$Cl_2C_6H_4$ or TIPB, 160–230 °C, ≥24 h	no reaction

- N-acylation (EWG) accelerates reaction

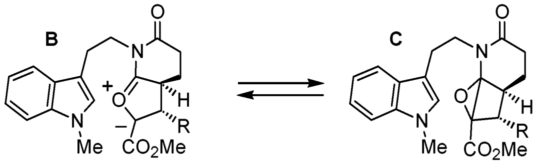


(2)

R = H		
1a, X = O	o-$Cl_2C_6H_4$, 180 °C, 3 h	87% **1b**
23a, X = S	TIPB, 230 °C, >48 h	no reaction
R = Et		
12a, X = O	o-$Cl_2C_6H_4$, 180 °C, 24 h	74% **12b**
24a, X = S	o-$Cl_2C_6H_4$, 180 °C or TIPB, 230 °C, 24 h	no reaction

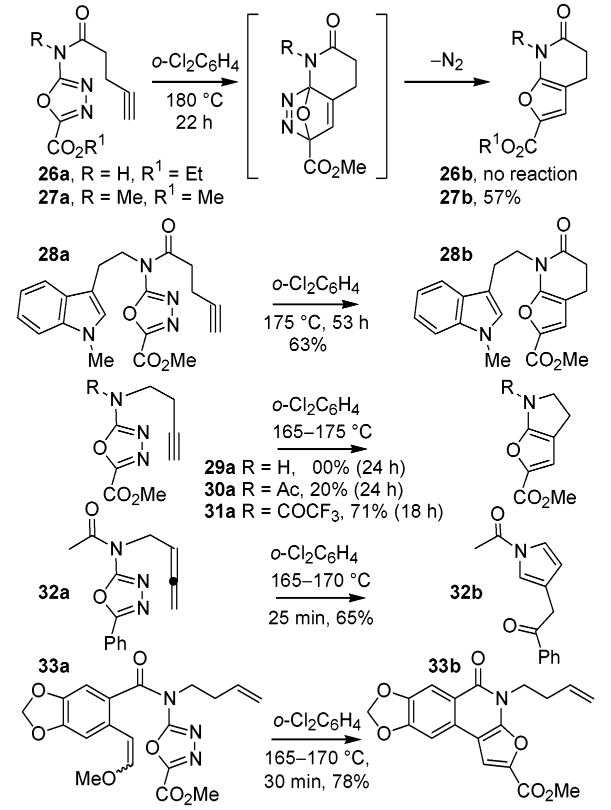
- oxadiazole > thiadiazole (>> NMe-triazole)[9]

Although prior studies of Warrener indicate that a cyclobutene epoxide (e.g., **C**, eq 3) need not be an intermediate in the reaction cascade,[8] we have made observations that suggest they may be reversible, transient intermediates in the slower thermal reactions. Thus, TLC monitoring or premature workup of the slower reactions in which the initial [4 + 2] cycloaddition appears to be much faster than the subsequent [3 + 2] cycloaddition (e.g., **17a**) allows detection or isolation of products resulting from only the first [4 + 2] cycloaddition reaction and subsequent loss of N_2.[15] However, when these reactions are taken to completion or run under more vigorous conditions, the yields increase and no intermediate cycloadduct is isolated, suggesting the generation of an intermediate (e.g., **C**) more stable than the 1,3-dipole **B** and its ultimate conversion to the final product. Although the potential intermediacy of **C** is immaterial to the reaction outcome, the observations that the disappearance of starting material does not necessarily coincide with the appearance of final product and that more vigorous, not less vigorous, reaction conditions typically improve conversions even with sensitive 1,3-dipoles (e.g., **16**/**17**) can be key to the successful implementation of the reaction cascade. Finally, although it is possible that an indole [4 + 2] cycloaddition initiates the reaction cascade, especially in those examples where closure would provide an entropically preferred fused five-membered ring, all attempts to detect such reactivity have not been successful. Thus,

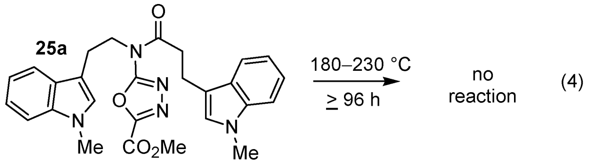


(3)

Scheme 3



(1) only intermediate products resulting from olefin [4 + 2] cycloaddition are detected if the reaction is prematurely worked up, (2) the substrate **25** containing an indole dienophile and dipolarophile failed to undergo reaction (eq 4), and (3) substrate **28** provided the product derived only from alkyne, not indole, [4 + 2] cycloaddition as detailed above.



• reaction initiated by olefin [4 + 2] cycloaddition

Whereas unactivated alkynes fail to react with oxadiazoles in intermolecular Diels−Alder reactions,[10] tethered alkynes cleanly provide furan [4 + 2] cycloadducts (Scheme 3). Like observations made in eq 1, the reactions of **29**−**31** improve with substitution of the C2 amine with progressively stronger electron-withdrawing groups. Similar products can also be obtained using alkyne equivalents (e.g., **33**) in the absence of an effective tethered [3 + 2] dipolarophile. In the case of **33**, the enhanced reactivity of the enol ether is sufficient to supersede the typical entropic preference for closure to provide a fused five- versus six-membered ring. Similarly, the unactivated alkyne [4 + 2] cycloaddition of **28** supersedes a potential indole [4 + 2] cycloaddition to cleanly provide the furan also overriding the entropic preference for closure to provide a five- versus six-membered ring. Finally, [4 + 2] reaction of allene **32** is much faster than that of the corresponding alkene or alkyne and is followed by an isomerization and elimination to provide a pyrrole. Analogous observations have been made in the cycloaddition reactions of tethered allenyl 1,2-diazines.[16]

Further exploration of the cascade cycloaddition reactions of 1,3,4-oxadiazoles and their applications are in progress and will be reported in due course.

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Supporting Information Available: Full experimental details for the preparation of **1a**−**33a** and **1b**−**33b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Stereochemical assignments for **16b** and **17b** have been confirmed by X-ray of the analogous products bearing an indole C6 methoxy substitutent.
(14) The X-ray crystal structure of **21b** has been deposited with the Cambridge Crystallographic Data Centre under the deposition number CCDC 186237.
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