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New Reactions of Vinylindoles as Heterocyclic Dienes with 4-Phenyl-1,2,4-triazoline-3,5-dione: Non-Concerted *versus* Concerted Processes**

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Abstract. The reactions of some 3-vinylindoles and one 2-vinylindole with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) were investigated. In dependence on the structure of the vinylindole, the experimental results revealed the occurrence in some cases of a non-concerted step to furnish *Michael*-type adducts and in other cases of a probably concerted *Diels-Alder* reaction to furnish novel pyridazino[*b*]indoles, respectively. In one particular case, PTAD-catalysed dimerisation of the 3-vinylindole took place.

Introduction

Indoles with azo or hydrazo functions integrated into the cyclic system have attained great importance in the preparative development of pharmacologically active lead substances [1] [2]. For the syntheses of compounds of these types, the regio- and stereocontrolled functionalisation and/or [*b*] anellation of 2- and 3-vinylindoles with highly reactive azo-dienophiles or azoenophiles have meanwhile been successfully developed [1–5]. In the present preliminary communication, we report on further new results from the reactions of some selected 3- and 2-vinylindoles with the highly electrophilic dienophile 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD). Triazoline-diones have frequently been used as dienophiles for the introduction of N functionalities and represent one of the most reactive dienophile systems known to date [6] [7].

Results and Discussion

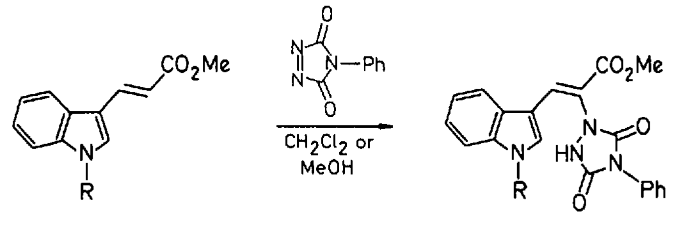
Our present results provide the first convincing experimental evidence for the occurrence in vinylindole chemistry of concerted (*e.g.* frontier orbital-controlled) and non-concerted (*e.g.* polarity-controlled) processes [8] in dependence on the structure of the vinyl-indole investigated and on the reaction conditions employed. On the basis of the frontier-orbital theory, the hypothesis that, in cases of high energy differences between HOMO(diene) – LUMO(dienophile) and HOMO(dienophile) – LUMO(diene), a two-step mechanism would be favoured [8] over a concerted process is generally accepted. On the other hand, *Diels-Alder* reactions with the electrophilic PTAD demonstrate [7] that this assumption should not be applied universally. However, in spite of the relatively low-lying E(LUMO) of PTAD ($E = -1.823$ eV according to our own MNDO calculations), non-concerted mechanisms also have to be taken into consideration; this has been reported in [7].

The methyl indol-3-ylacrylates **1a** and **1b** react with PTAD both under kinetic and under thermodynamic control (toluene, CH_2Cl_2, r.t., 2 d; CH_2Cl_2, –75°, 6 h) to furnish exclusively the *Michael*-type adducts **2a** and **2b** (m.p. 225° and 211°, respectively) with (Z)-configuration (*Scheme 1*). A primarily expected *Diels-Alder* adduct could not be detected analytically. The formation of products **2** can be described formally as proceeding through the prototropic shift-stabilised, zwitterionic intermediate of a non-concerted *Diels-Alder* reaction [9]. This simple N–C bond formation process between the reactants is probably a consequence of the highly polarised electronic structure of the 'push-pull' moiety in **1** (as is indicated by ^{13}C-NMR spectroscopic data) [10] and of the strongly electrophilic nature of PTAD.

In the reaction of PTAD with the highly reactive 3-(prop-1-enyl)indole **1c** [10], a formally PTAD-catalysed dimerisation takes place. Apart from the production of polymers, the only compound formed that could be isolated was the anellated urazole **5** (CH_2Cl_2, –75°, 1 h; 20°, 2 h; m.p. 282°). The reaction sequence is assumed to start with a regioselective electrophilic addition of PTAD to the electron-rich vinyl function of **1c** [10] to give the probable 1,4-dipolar intermediate **3** [9] (*Scheme 2*). The stabilisation process *via* prototropic shift to yield the *Michael*-type adduct is too slow in this case. The intermediate **3** is, instead, assumed to be captured initially by a further molecule of **1c** [10] (which has a higher nucleophilicity when compared with **1a**) more rapidly. Then, the resulting intermediate **4** undergoes regio- and stereoselective cyclisation in accordance with *Baldwin*'s rules [11] to furnish only a single diastereoisomer **5** (according to HPLC). In spite of the application of an (E/Z)-mixture of **1c**, the product configuration indicates that first of all the (E)-isomer of **1c** is involved in the cyclisation sequence for steric reasons.

The 3-vinylindole **1d**, which is sterically less hindered and less polarised at the vinyl group, reacted with PTAD under kinetic control (in CH_2Cl_2 or pure MeOH, –75°, 20 min) to produce the cycloadduct **6** (m.p. 211°) in almost quantitative yield (*Scheme 3*). The *Diels-Alder* reaction was so rapid that a potential intermediate could not be detected by analytical methods (TLC, UV, NMR) nor even be trapped in pure MeOH as the solvent at –75°. Hence, we postulate

Scheme 1



1	R
a	Me
b	SO_2Ph

2a (40%)
2b (90%)

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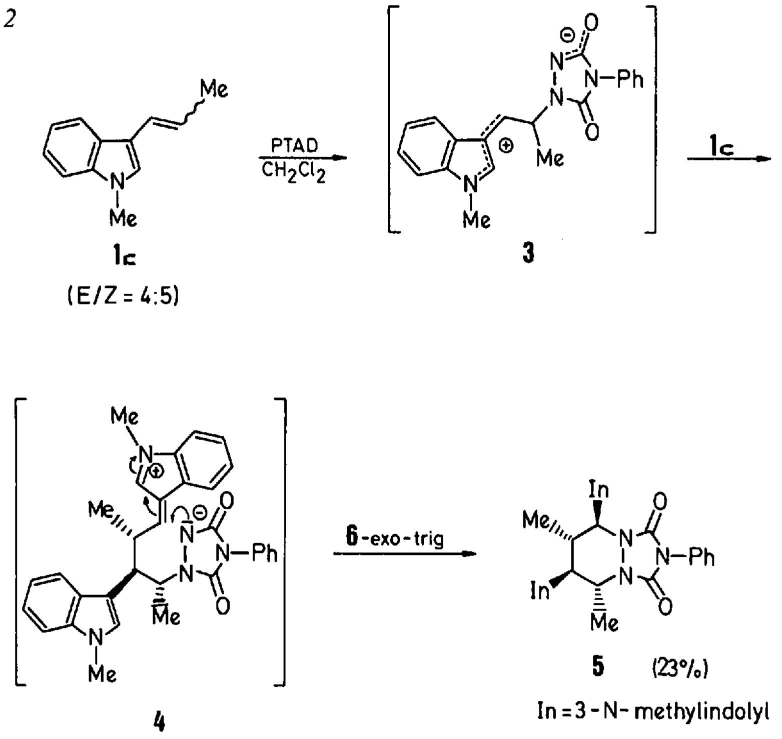
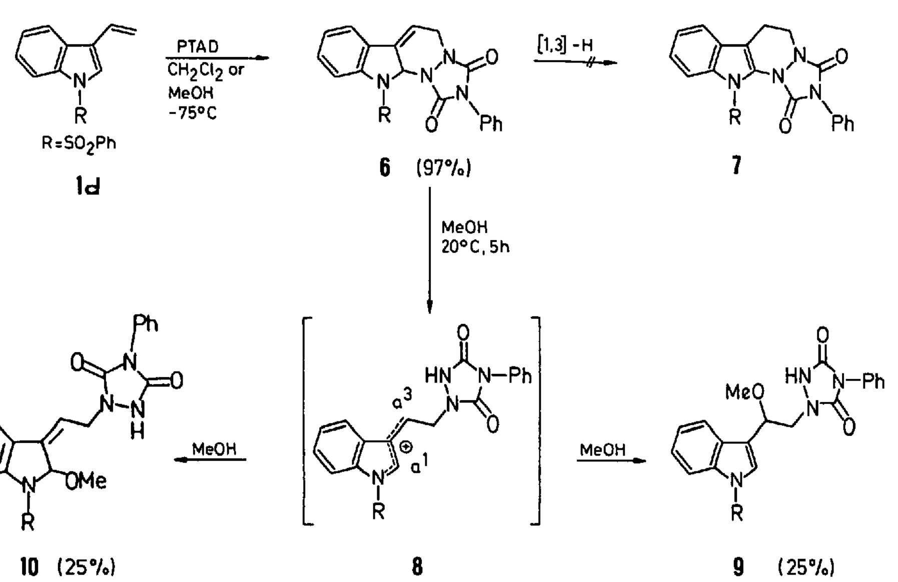
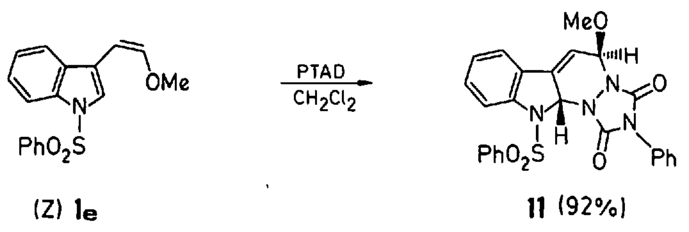
Scheme 2



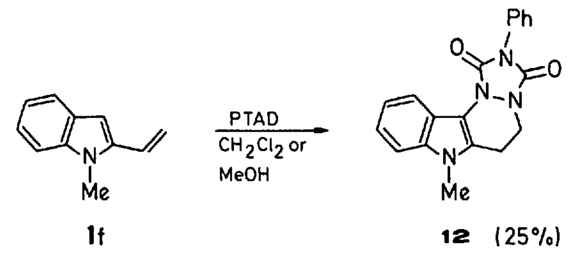
Scheme 3



Scheme 4



Scheme 5



for this particular reaction a concerted mechanism involving a ($HOMO_{diene} - LUMO_{dienophile}$)-controlled [$4_\pi + 2_\pi$] step [10] [12]. However, the isolated cycloadduct **6**, which does not experience stabilisation *via* a formal [1,3]-prototropic shift to form a tetracyclic indole compound **7** (as shown by temperature-dependent ^{1}H-NMR spectroscopy) [13], does not possess sufficient stability to exist in nucleophilic protic solvents (such as MeOH) at r.t. On the other hand, in aprotic polar solvents (such as DMSO), **7** is extremely stable and remains unchanged for several days at r.t. In MeOH at 20°, compound **6** was cleaved at the aminal moiety within *ca.* 5 h to form the two solvolysis products **9** and **10** (m.p. 163° and 143°, respectively); the cleavage involves the 1,4-dipolar intermediate as a^1 and a^3 reagent [9] [14], most probably in the protonated form **8**. The driving force for this reaction is probably the gain of 'indolisation' energy achieved by the formation of **9** and, in addition, the formation of a stable secondary lactam.

It is generally accepted that the product configuration in *Diels-Alder* reactions can be a useful probe for predicting the reaction mechanism (two-step *vs.* one-step process) [8]. Thus, for example, the (*Z*)-methoxypropenyl-substituted indole **1e** reacted very rapidly and stereoselectively (no other isomer was detected) with PTAD to yield the [4 + 2] cycloadduct **11** (*Scheme 4*; CH_2Cl_2, −75°, 10 min; m.p. 171°). The configuration of the tested 3-vinylindole **1e** was retained in the transition state. Hence, we assume a concerted process for this reaction.

In analogy with compound **6**, the MeO-substituted cycloadduct **11** is also unstable in MeOH at r.t. (TLC monitoring of reaction) but definable reaction products could not be isolated. We have been able to perform an X-ray structure analysis of **11** (*Fig. 1*) and the configurational predictions based on ^{1}H-NMR measurements were unambiguously confirmed. In addition, the geometry of the five-ring anellated 1,2-diazine reveals a kinetically controlled *Diels-Alder* reaction *via* an *endo*-transition state. This *endo*-transition state should be energetically favoured by secondary frontier-orbital overlap [8].

The reaction of the (*E*)-isomer of **1e** with PTAD is, on the other hand, more complex and we have not yet been able to characterise any products.

In contrast to the several described reactions of PTAD with 3-vinylindoles, 2-vinylindoles react with PTAD to produce extremely stable [4 + 2] cycloadducts [4]. In continuation of these investigations, we have now examined the corresponding reactions of the sterically less hindered 2-vinylindole **1f** [10]. In addition to the formation of polymers, when performed in CH_2Cl_2 or MeOH, cycloadduct **12** (CH_2Cl_2, −75°, 20 min; m.p. 201°) was formed (*Scheme 5*). We have not been able to detect any potential intermediate by the available analytical methods.

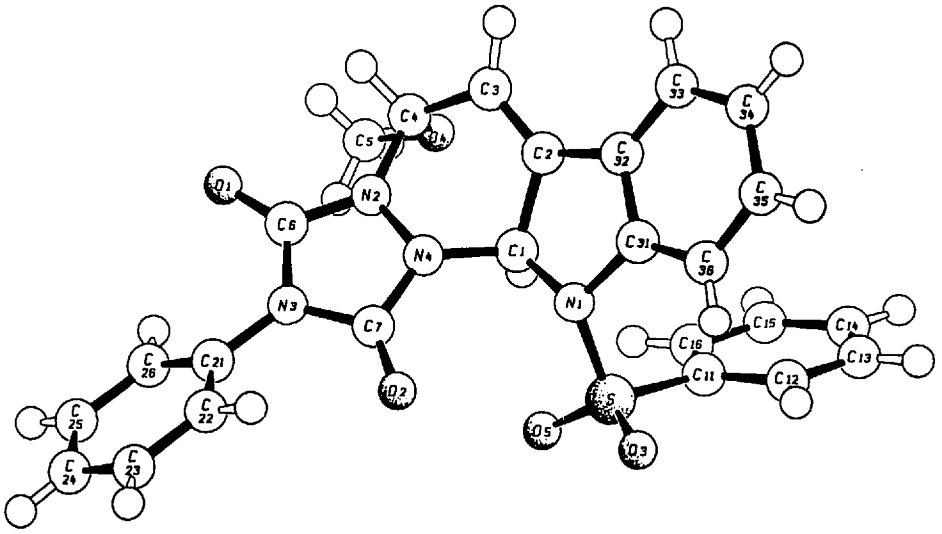


Fig. 1. Schakal *plot of the molecular structure of* **11** (space group: $P2_1/c$, $Z = 4$) [15]

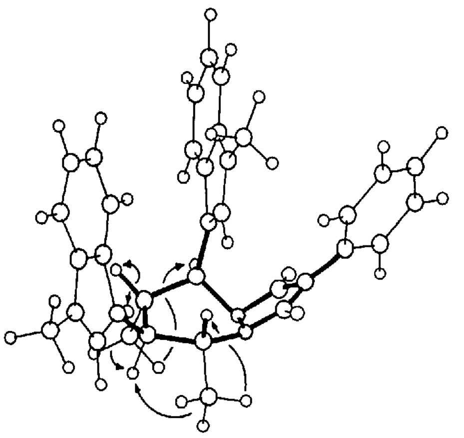


Fig. 2. *Energy-minimised molecular structure of* **5** (molecular modeling force field programme *Alchemy II*^{TM}) *also illustrating some of the diagnostically relevant* ^1H, ^1H-*NOE's detected at 400 MHz*. The bicyclic ring system and the β-orientated bonds arising from the bicyclic system are shown as thickened lines for improved clarity.

Therefore, for this reaction we assume a ($HOMO_{diene} - LUMO_{dienophile}$)-controlled cycloaddition *via* a concerted step.

The constitutions and relative configurations of the described products were elucidated, mainly with the help of high-resolution NMR spectroscopic methods [16].

The diagnostically relevant ^{1}H, ^{1}H-NOE's are shown in *Fig. 2* for **5** which possesses four stereocentres.

In summary, the new results presented above demonstrate for the first time the broad reactivity pattern obtainable by means of concerted *vs.* non-concerted mechanisms for the reactions of some selected vinylindoles with PTAD. The results reflect throughout the common reactivity pattern of PTAD towards 1,3-butadienes very well [7], whereby, depending on the diene structure, either simple electrophilic addition or concerted $[4_\pi + 2_\pi]$ cycloadditions processes are involved.

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[1] U. Pindur, L. Pfeuffer, M.-H. Kim, *Helv. Chim. Acta* **1989**, *72*, 65, and ref. cit. therein.

[2] U. Pindur, *Heterocycles* **1988**, *27*, 1253, and ref. cit. therein.

[3] U. Pindur, L. Pfeuffer, *Chimia* **1986**, *40*, 124.

[4] U. Pindur, M.-H. Kim, *Heterocycles* **1988**, *27*, 967.

[5] R. S. Sanchis-Llorca, J. Sepulveda-Arques, E. Zaballos-Garcia, R. A. Jones, *Heterocycles* **1987**, *26*, 401.

[6] D. L. Boger, S. M. Weinreb, 'Hetero *Diels-Alder* Methodology in Organic Synthesis', Academic Press, New York, 1987.

[7] For recent investigations on the mechanisms of *Diels-Alder* reactions of PTAD with 1,3-butadienes, see: F. Jensen, C.S. Foote, *J. Am. Chem. Soc.* **1987**, *109*, 6376.

[8] J. Sauer, R. Sustmann, *Angew. Chem.* **1980**, *92*, 733; *ibid. Int. Ed.* **1980**, *19*, 779; I. Fleming, 'Frontier Orbitals and Organic Reactions', Wiley, New York, 1976.

[9] It should be noted that the terms 'zwitterionic' and 'diradical', when used for describing intermediates, refer to the limiting *Lewis* structures, and that the actual intermediates can have varying degrees of zwitterionic or diradical character, depending on the specific system and experimental conditions. On the basis of the structures of the trapped products **9** and **10**, we prefer to view the intermediate in the present discussion as having a predominantly zwitterionic character.

[10] U. Pindur, L. Pfeuffer, *Monatsh. Chem.* **1989**, *120*, 27; U. Pindur, M.-H. Kim, M. Eitel, *Tetrahedron Lett.* **1990**, *31*, 1551.

[11] J.E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976**, 734.

[12] However, in spite of the equal yields of **6** as the single product formed under identical conditions, when the reaction was performed in MeOH or in CH_2Cl_2, which provides evidence in favour of a concerted reaction, an alternative, two-step process still cannot be ruled out. For example, the rapid reaction of **1d** with PTAD could give rise to a dipolar or a diradicaloid intermediate [7], which cyclised very rapidly under kinetic control to form **6** in both solvents at low temperatures whereas, in MeOH at higher temperatures and with longer reaction times, the formed intermediate gave rise mainly to the solvolysis products **9** and **10**.

[13] For the formally [1,3]-H shift, a higher energy barrier has to be overcome so that the heterolysis of **6** should be favoured in, for example, the good solvating and nucleophilic solvent MeOH.

[14] The first evidence for the occurrence of a 1,4-dipolar intermediate in the reaction of 1-phenyl-4-vinylpyrazole with PTAD was presented by J. Sepulveda-Arques, M. M. Simon, *Tetrahedron Lett.* **1985**, *26*, 6357.

[15] Full details of the X-ray structural analysis will be reported elsewhere: U. Pindur, M.-H. Kim, W. Massa, *Helv. Chim. Acta*, in preparation.

[16] All compounds gave satisfactory CHN microanalytical data (C ± 0.15, H ± 0.05, N ± 0.12) in agreement with M^+ peaks recorded in the 70-eV EI-MS. The established constitutions and relative configurations were elucidated mainly by combinations of NMR spectroscopic methods (400 MHz ^{1}H-NMR: NOE measurements, INDOR spectra, selective homo decoupling; 100.6-MHz ^{13}C-NMR: APT technique, DEPT experiments). The molar ratios of the reactants used were 1:1. The reaction mixtures were worked up by flash chromatography on *Merck* silica gel *60* (grain size: 0.040–0.063 mm, eluents: AcOEt, petroleum ether (40–60°). All reactions were performed in strictly pure solvents under Ar. For the preparations of the 2- and 3-vinylindoles, see: E. Akgün, U. Pindur, *Chimia* **1985**, *39*, 264; U. Pindur, L. Pfeuffer, *Monatsh. Chem.* **1989**, *120*, 157; M. Eitel, U. Pindur, *Synthesis* **1989**, 364.