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[4 + 2]-Cycloaddition with Inverse Electron Demand: Reaction of 3-Vinylindoles with Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate**

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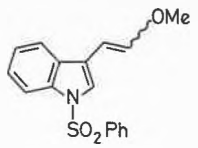
Abstract: The 1′-substituted 3-vinylindoles **1a** and **1b** react locoselectively with the tetrazine **2** to form the corresponding 1,4-dihydro-1,2-diazines. The 2′-methoxy-substituted compound **1c** yields the 4-(indol-3-yl)-substituted 1,2-diazine **5** on reaction with the tetrazine **2**. The reactions proceed through [4 + 2]-cycloaddition, [4 + 2]-cycloreversion, and, in the case of the reaction of **1c**, an additional elimination of methanol.



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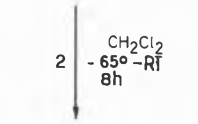

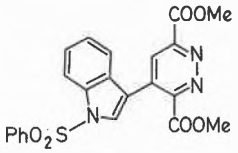

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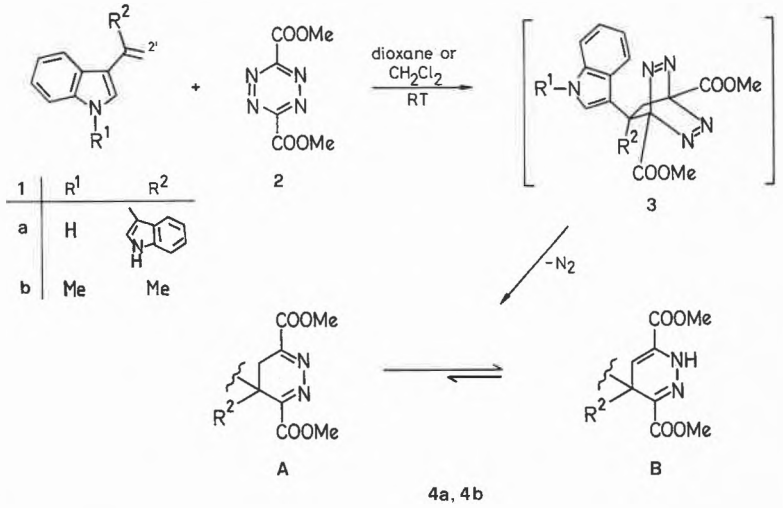
As 4π-electron systems, vinylindoles are preparatively interesting synthons for the anellation of the indole skeleton and for the preparation of numerous natural products[1,2], for which the Diels-Alder reaction plays a predominant role in the synthetic concept[3]. As a result of their pronounced π-donor reactivity, it is also to be expected that, after a [4 + 2]-cycloaddition with inverse electron demand, they will react with electron-poor dienes[4–6]. In continuation of our studies to expand the synthetic potential of this class of indoles for the preparation of novel anellated heterocycles and carbazole alkaloids, we have now investigated the reactions of some selected 3-vinylindoles **1** with the tetrazine **2**[6].

It is already known that electron-rich, benzo-condensed heterocycles react with the s-*cis*-fixed azadiene system of **2** to give anellated products of the pyridazine series[4]. For example, *N*-methylindole undergoes reaction at its 2,3-double bond with **2** to form a chinolino[3,4-*c*]pyridazine derivative[4]. We have now found that **2** has a higher preference for reaction at the exocyclic vinyl functions of **1a** and **1b**. The reaction proceeds through the cycloadduct **3**, which is not isolable due to the high angular strain, (step 1: [4 + 2]-cycloaddition, step 2: [4 + 2]-cycloreversion[5,7]) and subsequent elimination of nitrogen to give the indol-3-yl-substituted 1,4-dihydro-1,2-diazines **4a** and **4b**, which are capable of



tautomerization. According to a 400 MHz ^{1}H-NMR spectroscopic analysis, the equilibrium is shifted completely to the right (structure **B**). The locoselectivity of the reaction course is completely in accord with that observed for the reactions of styrene and its derivatives with compound **2**[5].

The azadiene **2** also undergoes cycloaddition to the vinyl function of (*E*/*Z*)-**1c**. The 4-(indol-3-yl)-1,2-diazine **5** is the only stable product formed in this reaction. From a mechanistic viewpoint, [4 + 2]-cycloaddition, [4 + 2]-cycloreversion, and elimination of methanol take place. The driving force to the 6π-heteroaromatic product is most probably the gain of the energy of aromatization (see also ref.[5]). The clear locochemistry of the reactions described here prompted us to study further cycloaddition reactions with inverse electron demand of variably functionalized vinyl heterocycles. It can be expected that use of this principle will open new routes to heterocyclic substituted pyridazines.

The energies of the HOMO's of the 3-vinylindoles used here are in the range −7.0 to −7.2 eV[8]. It can thus safely be assumed that these cycloadditions take place under $HOMO_{dienophile}/LUMO_{enophile}$ control[9] as the energy separation of the frontier orbitals in the transition state is about 6 eV (E_{LUMO} of **2**: −1.11 eV[10]). The locochemistry at the 1-aminobutadiene structural unit of **1** can be deduced from the high π-electron density and from the large HOMO-coefficient at C-2′ of the vinyl function[11].

The new cycloadducts described here were separated using flash chromatography[12] and were obtained in analytically pure form after recrystallization. The structural analytical data are in accord with the proposed constitutions. The 1,3-H coupling of the vinyl proton with the NH group observed in the 400 MHz ^{1}H-NMR spectrum of compound **4** is especially informative (^4J = 2.18 and 2.20 Hz for **4a**, **4b** (**B**), Table 1).

Typical Procedure for Cycloaddition of 3-Vinylindoles with Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate (reaction of **1a** with **2**): 0.92 g (4.6 mmol) **2**[13] were added to a solution of 1.0 g (3.9 mmol) **1a**[14] in 25 mL dioxane under nitrogen atmosphere at room temperature. The reaction started immediately with formation of N_2 gas. After a reaction time of 10 min the mixture was poured into ice water and was then extracted fivefold with 20 mL dichloromethane. The organic layer was dried over $CaCl_2$ and evaporated in

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Table 1. Cycloadducts **4a**, **4b**, and **5**.

Product	Yield [%][a]	*m.p.* [°C][b]	Molecular Formula[c]	^{1}H-NMR ($CDCl_3$)[d] δ [ppm]	MS (70 eV)[e] *m/z* (rel. int. %)
4a	86	165 (petrol ether/ ethyl acetate)	$C_{24}H_{20}N_4O_4$ (428.15)	3.49 (s, 3H, $COOCH_3$), 3.71 (s, 3H, $COOCH_3$), 6.41 (d, ^4J = 2.18 Hz, 1H, dihydrodiazine C5-H), 6.90 (s, 1H, indole C2-H), 6.92 (s, 1H, indole C2-H), 7.00 (pt, 2H, indole C5-H or C6-H), 7.15 (pt, 2H, indole C5-H or C6-H), 7.31 (d, ^3J = 7.98 Hz, 2H, indole C4-H or C7-H), 7.51 (d, ^3J = 7.93 Hz, 2H, indole C4-H or C7-H), 8.19 (bs, 2H, indole NH), 8.47 (d, $^4J \approx 2$ Hz, 1H, dihydrodiazine NH). Measured at 200 MHz.	428 (1), 43 (100)
4b	67	179 (ethyl acetate)	$C_{18}H_{19}N_3O_4$ (341.14)	1.94 (s, 3H, CH_3), 3.58 (s, 3H, NCH_3), 3.75 (s, 3H, $COOCH_3$), 3.76 (s, 3H, $COOCH_3$), 5.61 (d, ^4J = 2.21 Hz, 1H, dihydrodiazine C5-H), 6.93 (s, 1H, indole C2-H), 7.05 (pt, 1H, indole C5-H or C6-H), 7.19 (pt, 1H, indole C5-H or C6-H), 7.28 (d, ^3J = 8.23 Hz, 1H, indole C4-H or C7-H), 7.46 (d, ^3J = 8.05 Hz, 1H, indole C4-H or C7-H), 8.33 (bs, 1H, ^4J-coupling not resolved, NH). Measured at 400 MHz.	341 (9), 282 (100)
5	45	207–209 (methanol)	$C_{22}H_{17}N_3O_6S$ (451.09)	3.79 (s, 3H, $COOCH_3$), 4.09 (s, 3H, $COOCH_3$), 7.31 (t, ^3J = 7.28 Hz, 1H, phenyl-H or indole-H), 7.41 (t, ^3J = 7.35 Hz, 1H, phenyl-H or indole-H), 7.48 (t, ^3J = 8.1 Hz, 2H, phenyl H3,4), 7.47 (d, ^3J = 8.0 Hz, 1H, phenyl-H or indole-H), 7.58 (t, ^3J = 7.45 Hz, 1H, phenyl-H or indole-H), 7.89 (s, 1H, indole C2-H), 7.93 (d, ^3J = 8.1 Hz, 2H, phenyl H2,6), 8.06 (d, ^3J = 8.37 Hz, 1H, phenyl-H or indole-H), 8.38 (s, 1H, diazine H5, no exchange with D_2O). Measured at 400 MHz.	451 (94), 77 (100)

[a] Yields of analytically pure isolated products. [b] Uncorrected. [c] Satisfactory microanalyses obtained. [d] Measured at 200 and 400 MHz using a Bruker AC 200 and 400 instrument. [e] Recorded with Varian MAT CH 7A mass spectrometer.

vacuum. The residue was solved in some toluene and separated by flash-chromatography[12] (silica gel 60, Merck, grain size 0.040–0.063 mm, eluent: petrol ether (40–60 °C)/ethyl acetate 6 + 4) and recrystallized from petrol ether (40–60 °C)/ethyl acetate (cf. Table 1).

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