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NEW REACTIONS OF 2-VINYLINDOLES WITH AZODIENOPHILES: DIELS-ALDER REACTION VERSUS MICHAEL-TYPE ADDITION

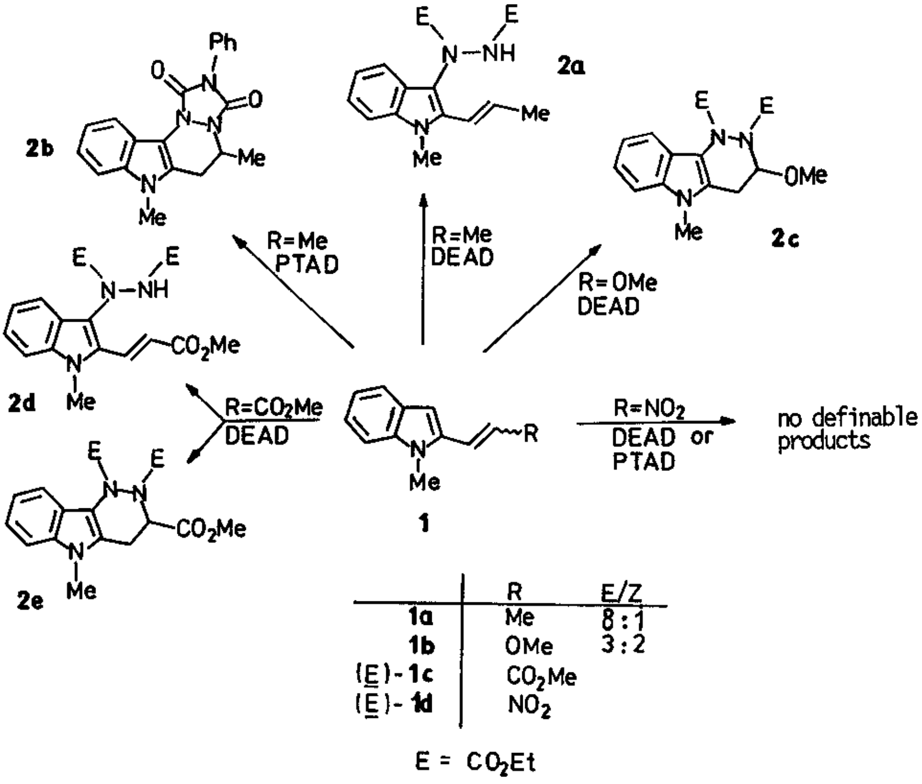
Ulf Pindur* and Myung-Hwa Kim

Department of Chemistry and Pharmacy, University of Mainz, Saarstrasse
21, D-6500 Mainz 1, Federal Republic of Germany

Abstract —— The reactions of donor- and acceptor-substituted 2-vinylindoles with azodienophiles such as, for example, diethyl azodicarboxylate (DEAD) and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) have been examined. Whereas DEAD gives rise to both Diels-Alder and Michael adducts, PTAD reacts preferentially to give novel cycloadducts with pyridazinoindole-type structures.

Selectively functionalized 2- and 3-vinylindoles represent 4π-reaction components and are thus synthetically attractive building blocks for the regio- and stereocontrolled construction of annellated indoles as well as of indole and carbazole alkaloids[1-5]. Whereas Diels-Alder reactions with 3-vinylindoles have been preparatively exploited for the synthesis of pharmacologically interesting lead structures by others[4] and by us[1-3,5], comprehensive studies on the synthetic potential and limitations of [4+2]-cycloadditions with 2-vinylindoles are still lacking. The main reason for this is that 2-vinylindoles are preparatively not so simply and economically accessible as the 3-vinylindoles[2,6]. In the present paper, and in continuation of our investigations on cycloadditions with vinylheterocycles[5], we report on new reactions of the 2-vinylindoles **1a-e** bearing selected donor or acceptor substituents on the vinyl group with diethyl azodicarboxylate (DEAD) and with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD).

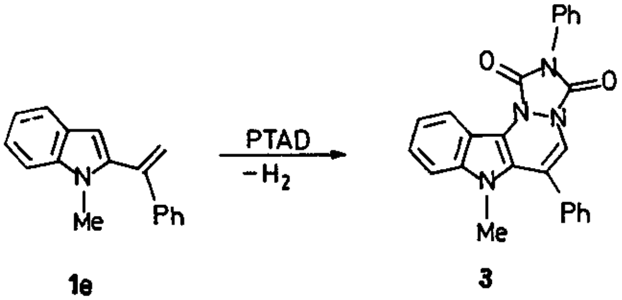
Compounds **1a-d** were prepared by a known procedure (Wittig reaction or aldol addition)[7] from N-methylindole-2-carboxaldehyde and compound **1e** was prepared according to Ref.[8] whereby some details of the reported procedure were modified by us[9]. The azodienophiles are generally recognized as being highly reactive and, in the present work, exhibit an alternation between Diels-Alder reaction versus Michael addition. DEAD reacts with (E/Z)-**1a** (8:1) to give exclusively the (E)-Michael adduct **2a** (12% yield); a (Z)-Michael adduct was not detected (tlc monitoring of the reaction), presumably as a result of steric effects. The particularly electron-rich (E/Z)-methyl enol ether **1b** (3:2) reacts to give exclusively the cycloadduct **2c** (20% yield) with a pyridazinoindole structure via a [1,3]-H shift. Reaction of the pure (E)-methyl indole-2-acrylate **1c** results in the formation of both the Michael adduct **2d** (7% yield) and the Diels-Alder product **2e** (27% yield). In the 2'-substituted 2-vinylindole series **1a-d**, the highly reactive PTAD reacted only with **1a** to give a defined product (**2b**; 32% yield) in spite of numerous variations of the reaction conditions. The product **2b** is the result of a Diels-Alder reaction. In the reaction of PTAD with (E)-N-methyl-2-(2-nitrovinyl)-indole (**1d**) no identifiable reaction product was formed as a result of electronic deactivation (marked decrease in the HOMO energy of the diene moiety)[10].



	R	E/Z
1a	Me	8:1
1b	OMe	3:2
(E)-**1c**	CO_2Me	
(E)-**1d**	NO_2	

E = CO_2Et

We have also exemplarily tested the reaction behavior of 1'-substituted 2-vinylindoles such as, for example, **1e** towards azodienophiles. In this context, the first reactions of 1'-substituted 2-vinylindoles with PTAD were described recently[11]. It was reported that, at 20 °C in acetone, Michael adducts were always obtained. We have now found that, of the series of azodienophiles, **1e** reacts only with the more reactive PTAD. In addition to small amounts of polymers, the only isolable reaction product was the dehydrogenated [4+2]-cycloadduct **3** (30% yield of crude product; reaction conditions: CH_2Cl_2, 40 °C, 3 days). PTAD thus reacts here both as a dienophile and as an oxidizing agent (urazole was also isolated from the reaction mixture). Under these conditions, a Michael adduct - as reported in Ref.[11] - was detected in trace amounts only by tlc. Steric hindrance resulting from structural restraints to the achievement of the s-cis-conformation in the [4+2]-transition state is assumed to be responsible for the principle sluggishness of **1e** and other 1'-substituted 2-vinylindoles in Diels-Alder reactions (low yields of [4+2]-cycloadducts).



For the example of the reaction of **1a** with PTAD, we have followed the time course of the reaction by ^{1}H-nmr spectroscopy. The measurements performed at 0, 20, and 60 °C in CD_2Cl_2 gave no evidence for the occurrence of a betaine (or diradical) intermediate or a diazetidine. In addition, attempts to trap a possible intermediate by reaction with CD_3OD gave no indications of new products other than **2b**[12]. We thus assume that a concerted mechanism is in operation.

The constitutions and conformations of the new products **2a-e** and **3** were confirmed by their ^{1}H- and ^{13}C-nmr spectra (selective decoupling, NOE, INDOR, and J-modulated spin-echo experiments).

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Büchi SMP 20 apparatus and are not corrected. The nmr spectra were recorded on a Bruker WM 400 spectrometer with TMS as internal standard (δ, ppm). The EI mass spectra were obtained using a Varian MAT 711 instrument. Elemental analyses were performed with a Carlo Erba Strumentazione apparatus. Flash chromatography was performed on Merck silica gel (0.040-0.063 mm).

The 2-vinylindoles **1a**, **1b**, and **1d** were prepared by a modification of the procedure of Ref.[7]; **1a** was obtained as an 8:1 E/Z-mixture and **1b** as a 3:2 E/Z-mixture in yields of 79 and 31%, respectively; **1d** was obtained as the pure E-stereoisomer. The 2-vinylindole 1e was prepared by a slight modification of the procedure of Ref.[8] and obtained in 70% yield[9]. The yields of the crude products **2** and **3** (tlc analysis) were considerably higher than those of the pure isolated products used for the analytical investigations described. All reactions were run in highly pure, anhydrous solvents under inert gas atmospheres.

1,2-Bis(ethoxycarbonyl)-1-[1-methyl-2-(*E*-1-propenyl)-indol-3-yl]-hydrazine (2a). 1-Methyl-2-(1-propenyl)-indole (1a) (1.03 g, 6 mmol) was dissolved in 20 ml of toluene, the solution was treated with DEAD (1.40 g, 8 mmol) and a spatula tip of hydroquinone, and the mixture was stirred at 50 °C for 52 h. The solvent was then evaporated under vacuum, the residue was extracted with dichloromethane, and the extract dried with calcium chloride. The product was purified by flash chromatography with petroleum ether/ethyl acetate (6.5:3.5) as eluent. Pale yellow crystals were obtained; yield: 0.25 g (12%); mp 107 °C (dichloromethane, petroleum ether); ir (KBr): 3380-3210 (NH), 1770-1680 cm^{-1} (2 CO); ^1H-nmr ($CDCl_3$): 1.18-1.33 (2 br t, dynamic effect, 6 H, 2 $COOCH_2C\underline{H}_3$), 1.70 (dd, $^3\underline{J}$ = 6.8 Hz, 3 H, $=CH-C\underline{H}_3$), 3.60 (s, 3 H, NCH_3), 4.11-4.19 (br q, dynamic effect, 4 H, 2 $COOC\underline{H}_2CH_3$), 6.14 (dq, $^3\underline{J}$ = 6.8 Hz and 11.2 Hz, 1 H, $CH=C\underline{H}-CH_3$), 6.33 (d, $^3\underline{J}$ = 11.2 Hz, 1 H, $C\underline{H}=CH-CH_3$), 6.95-6.97 (br s, 1 H, NH, exchangeable with D_2O), 7.13 (t, 1 H, 6-H), 7.20 (t, 1 H, 5-H), 7.27 (d, $^3\underline{J}$ = 8 Hz, 1 H, 7-H), 7.74 (br d, 1 H, 4-H); ^{13}C-nmr ($CDCl_3$): 14.36 and 14.48 (2 $CH_2\underline{C}H_3$), 15.27 (CH_3), 30.10 (NCH_3), 61.88 and 62.69 (2 CH_2), 109.16, 118.31, 119.08, 120.05, 121.91, 134.44 (CH), 115.90, 123.80, 131.20, 135.40 (quaternary C), 154.90 and 167.10 (2 CO); EI-ms: *m/z* = 345 (M^+, 34%), 183 (100%). Anal. Calcd. for $C_{18}H_{23}N_3O_4$ (345.40): C, 62.57; H, 6.71; N, 12.17. Found: C, 62.53; H, 6.56; N, 12.12.

5,7-Dimethyl-2-phenyl-4,5,6,12-tetrahydroindolo[2,3-*c*][1,2,4]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (2b). 1-Methyl-2-(1-propenyl)-indole (1a) (0.855 g, 5 mmol) was dissolved in 10 ml of toluene and a solution of PTAD (0.876 g, 5 mmol) in 20 ml of toluene plus 3 ml of dichloromethane was added slowly from a pipette. The mixture was then stirred at 20 °C for 1 h, the solvent was removed, and the residue was dissolved in dichloromethane/acetone. The product was purified by flash chromatography using petroleum ether/ethyl acetate (5:5) as eluent. Colorless crystals were obtained; yield: 0.55 g (32%); mp 205 °C (petroleum ether); ir (KBr): 1760-1700 cm^{-1} (2 CO); ^1H-nmr (CD_2Cl_2): 1.36 (d, $^3\underline{J}$ = 6.6 Hz, 3 H, 5-CH_3), 2.86 (dd, $^2\underline{J}$ = 16.1 Hz, 1 H, 6-H), 3.55 (dd, $^2\underline{J}$ = 16.1 Hz, $^3\underline{J}$ = 6.3 Hz, 1 H, 6-H), 3.68 (s, 3 H, NCH_3), 4.96 (m, 1 H, 5-H), 7.07-7.62 (m, 8 H, 2-N-Ph and 8-, 9-, 10-H), 8.52 (d, $^3\underline{J}$ = 7.9 Hz, 1 H, 11-H); EI-ms: *m/z* = 346 (M^+, 100%). Anal. Calcd. for $C_{20}H_{18}N_4O_2$ (346.39): C, 69.36; H, 5.20; N, 16.18. Found: C, 69.94; H, 5.44; N, 16.80.

Diethyl 3-Methoxy-5-methyl-1,2,3,4-tetrahydroindolo[3,2-*c*]pyridazine-1,2-dicarboxylate (2c). 1-Methyl-2-(2-methoxyvinyl)-indole (1b) (0.579 g, 3.1 mmol) was dissolved in 20 ml of toluene, the solution was treated with DEAD (0.539 g, 3.1 mmol) and a spatula tip of hydroquinone, and the mixture was stirred at 20 °C for 2 h. The solvent was then removed under vacuum, the residue was treated with water, and extracted with diethyl ether. The product was purified by flash chromatography using petroleum ether/ethyl acetate (6:4) as eluent. Colorless crystals were obtained; yield: 0.22 g (20%); mp 125 °C (dichloromethane/diethyl ether); ir (KBr): 2940-2830 (CH), 1740-1690 cm^{-1} (2 CO); ^1H-nmr (acetone-$\underline{d}_6$): 1.18-1.31 (br t, dynamic process, 6 H, 2 $COOCH_2C\underline{H}_3$), 2.95 (d, $^2\underline{J}$ = 17.4 Hz, 1 H, 4-H), 3.25 (dd, $^2\underline{J}$ = 17.4 Hz, $^3\underline{J}$ = 6.1 Hz, 1 H, 4-H), 3.51 (s, 3 H, OCH$_3$), 3.62 (s, 3 H, NCH$_3$), 4.05-4.27 (br q, dynamic process, 4 H, 2 COOC$\underline{H}_2$CH$_3$), 5.81 (br d, 1 H, 3-H), 7.03-7.09 (br t, 1 H, 7-H), 7.11 (t, $^3\underline{J}$ = 8.5 Hz, 1 H, 8-H), 7.34 (d, $^3\underline{J}$ = 8.5 Hz, 1 H, 6-H), 7.59-7.71 (br d, 1 H, 9-H); ^{13}C-nmr (CDCl$_3$): 14.34 and 14.40 (2 CH$_2\underline{C}$H$_3$), 29.21 (NCH$_3$), 57.59 (OCH$_3$), 27.60 (4-C), 62.50 (2 COO$\underline{C}$H$_2$CH$_3$), 82.62 (3-C), 108.60, 119.31, 121.35 (CH), 114.54, 120.89, 123.01, 135.10 (quaternary C), 155.29 and 160.19 (2 CO); EI-ms: *m/z* = 361 (M$^+$, 65%), 288 (100%). Anal. Calcd. for $C_{18}H_{23}N_3O_5$ (361.40): C, 59.80; H, 6.41; N, 11.63. Found C, 59.83; H, 6.21; N, 11.66.

1,2-Bis(ethoxycarbonyl)-1-[1-methyl-2-(*E*-2-methoxycarbonylvinyl)-indol-3-yl]-hydrazine (2d). Methyl 3-(1-methyl-2-indolyl)-propenoate (**1c**) (0.645 g, 3 mmol) was dissolved in 20 ml of toluene, a solution of DEAD (1.045 g, 6 mmol) in 20 ml of toluene was added dropwise, and the mixture was stirred at 76 °C for 16 h. The solvent was then removed under vacuum and the residue was purified by flash chromatography using petroleum ether/ethyl acetate (6:4) as eluent. Orange-yellow crystals were obtained; yield: 0.08 g (7%); mp 185 °C (petroleum ether); ir (KBr): 3340-3220 (NH), 3040-2860 (CH), 1770-1650 cm^{-1} (2 CO): ^{1}H-nmr (CDCl$_3$): 1.13-1.33 (2 br t, dynamic process, 6 H, 2 COOCH$_2$C$\underline{H}_3$), 3.81 (s, 3 H, NCH$_3$), 3.82 (s, 3 H, COOCH$_3$), 4.09-4.18 (br q, dynamic process, 4 H, 2 COOC$\underline{H}_2$CH$_3$), 6.43 (d, $^3\underline{J}$ = 16.0 Hz, 1H, C$\underline{H}$=CH-COOCH$_3$), 7.13-7.31 (m, 4 H, 5-, 6-, 7-H; and NH, exchangeable with D$_2$O), 7.81 (d, $^3\underline{J}$ = 16.0 Hz, 2 H, =C$\underline{H}$-COOCH$_3$ and 4-H); ^{13}C-nmr (CDCl$_3$): 14.37 and 14.46 (2 CH$_2\underline{C}$H$_3$), 30.97 (NCH$_3$), 51.81 (OCH$_3$), 63.22 (2 $\underline{C}$H$_2$CH$_3$), 109.66, 119.66, 119.91, 121.00, 124.53, 131.02 (CH), 120.33, 123.51, 129.75, 137.16 (quaternary C), 156.13 and 167.24 (2 CO); EI-ms: *m/z*: = 389 (M$^+$, 96%), 197 (100%). Anal. Calcd. for $C_{19}H_{23}N_3O_6$ (389.41): C, 58.60; H, 5.95; N, 10.79. Found: C, 58.24; H, 6.33; N, 10.55.

Diethyl 3-Methoxycarbonyl-5-methyl-1,2,3,4-tetrahydroindolo[3,2-*c*]pyridazine-1,2-dicarboxylate (2e). This product was obtained in addition to **2d** by flash chromatography as colorless crystals; yield: 0.31 g (27%); mp 178 °C (petroleum ether); ir (KBr): 3020-2840 (CH), 1790-1660 cm^{-1} (2 CO); ^{1}H-nmr (CDCl$_3$): 1.35 (dt, dynamic process, 6 H, 2 COOCH$_2$C$\underline{H}_3$), 3.17 (d, $^2\underline{J}$ = 16.7 Hz, 1 H, 4-H), 3.24 (dd, $^2\underline{J}$ = 16.4 Hz, $^3\underline{J}$ = 7.5 Hz, 1 H, 4-H), 3.61 (s, 3 H, NCH$_3$), 3.71 (s, 3 H, COOCH$_3$), 4.20-4.41 (br q, dynamic process, 4 H, 2 COOC$\underline{H}_2$CH$_3$), 5.58 (br d, 1 H, 3-H), 7.06-7.27 (m, 3 H, 6-, 7-, 8-H), 7.71 (d, $^3\underline{J}$ = 7.7 Hz, 1 H, 9-H); EI-ms: *m/z* = 389 (M$^+$, 100%). Anal. Calcd. for $C_{19}H_{23}N_3O_6$ (389.41): C, 58.60; H, 5.95; N, 10.79. Found: C, 57.99; H, 6.26; N, 10.40.

2,6-Diphenyl-7-methyl-4,12-dihydroindolo[2,3-*c*][1,2,4]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (3). PTAD (0.35 g, 2 mmol) was dissolved in 5 ml of dichloromethane, a solution of 1-(1-methyl-2-indolyl)-1-phenylethene (**1e**) (0.38 g, 1.65 mmol) together with a spatula tip of hydroquinone in 15 ml of dichloromethane was added dropwise, and the resultant mixture was stirred at 40 °C for 3 days. The reaction solution was then washed three times with 20 ml portions of water, the dichloromethane phase was separated, and the solvent evaporated under mild conditions. The residue was purified by flash chromatography using petroleum ether/ethyl acetate (6:4) as eluent. Pale yellow crystals were obtained; yield: 0.08 g (12%); mp 230 °C (petroleum ether); ir (KBr): 1780-1660 cm^{-1} (CO); ^{1}H-nmr ($CDCl_3$): 3.24 (s, 3 H, NCH_3), 6.93 (s, 1 H, 5-H), 7.10-7.62 (m, 13 H, 2-N-Ph, 6-Ph, 8-, 9-, 10-H), 8.48 (td, ^3J = 8.2 Hz, ^4J = 0.9 Hz, 1 H, 11-H); ^{13}C-nmr ($CDCl_3$): 32.54 (NCH_3), sp^2-C: 109.47, 119.05, 121.19, 122.63, 123.60, 125.81, 128.40, 128.55, 128.78, 129.15, 129.20 (CH), 112.84, 116.73, 122.90. 131.29, 131.41, 134.27, (quaternary C), 143.10 and 144.90 (2 CO); EI-ms: m/z = 406 (M^+, 86%), 259 (100%). Anal. Calcd. for $C_{25}H_{18}N_4O_2$ (406.45): C, 73.86; H, 4.47; N, 13.76. Found: C, 73.21; H, 4.66; N, 13.46.

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