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[4+2] Versus [2+2] Cycloadditions with 1-Ethoxyethene and Heterocyclic Aldehydes; Formation of Vinyl Compounds

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***Abstract**: Inverse electron demand Diels-Alder reactions of ethoxyethene with heterocyclic aldehydes afforded a mixture of cycloadducts and vinyl compounds resulting from a competing [2+2] pathway.*

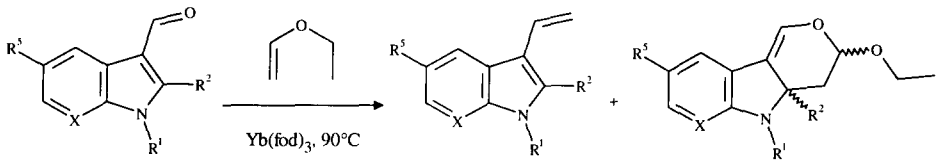
The reactions of electron rich dienophiles with π-electron deficient N-heteroaromatics are a well-established synthetic tool illustrated by Inverse electron demand (LUMO diene controlled) Diels-Alder reactions (IEDDA).[1-10] Electron withdrawing substituents in the diene, Lewis acids catalysts and high pressure considerably accelerate these [4+2] cycloadition reactions; recently the use of lanthanide reagents as catalysts for IEDDA has been reported.[5, 7, 11] 1-Oxa-1,3-butadienes reacted with enol ethers to give dihydropyrans which can be easily converted into carbohydrates in a straightforward manner[14] or into substituted pyridines[11,13]. We have recently reported[11] the synthesis of δ-carbolines using the reactivity towards hydroxylamine of the dihydropyran obtained in the IEDDA of 1-acetyl-2-benzylidene-1,2-dihydroindol-3-one with 1-ethoxyethene; we have also extended this procedure to the 7-aza analogues.

Wallace[15] has recently reported on the IEDDA reactions of 4-oxo-4*H*-1-benzopyran-3-carboxaldehydes with 1-ethoxyethene which produced only the expected 3-ethoxy-4,4a-dihydropyrano[4,3-*b*]benzopyran-10-ones as a mixture of diastereomers endo/exo.

In order to prepare heterocyclic intermediates in an ongoing research on cardiovascular drugs we reacted 1-ethoxyethene with heterocyclic aldehydes **1a-g** and **4h-m**. The reactions were performed at 90°C, during 2 or 3 days, in sealed tube with $Yb(fod)_3$ as catalyst (10%) using 1-ethoxyethene in large excess[21]. To our surprise the cycloadducts were accompanied by vinyl compounds resulting from a formal methylenation of the starting aldehyde. It is the first time, to our knowledge, that such a behavior has been reported in IEDDA reactions. The vinyl compounds were in some cases the major products of the reaction.

In the indoles series (Scheme 1), the best yields of transformation into vinyl compounds **2** were obtained with **1a**, **1b**, **1c**, **1e**; the substitution in 2-position greatly decreased the yield as in **1d**. The 3-formyl-7-azaindole **1b** was of similar reactivity to the 3-formylindole **1a**. The replacement of electron-withdrawing substituents in 1-position by a methyl group (compound **1g**) considerably lowered the yield since we recovered a 75% yield from the starting material.

A formyl group in 2-position as in 1-sulfonyl-2-formylindole greatly decreased the reactivity as only a 7% yield of 1-sulfonyl-2-vinylindole was obtained; replacement of the formyl group by a keto group as in 3-acetyl-1-sulfonylindole was unproductive.



1a-g **2a-g** **3a-g**

	X	R^1	R^2	R^5	Yield (%) **2***	Yield (%) **3**	Ratio endo / exo	Recovered **1** (%)
1a	CH	SO_2Ph	H	H	56	15	68 / 32	10
1b	N	SO_2Ph	H	H	28	36	65 / 35	10
1c	CH	$COCH_3$	H	H	32	-	-	40
1d	CH	$COCH_3$	CH_3	H	10	-	-	75
1e	CH	SO_2Ph	H	CH_3O	51	21	50 / 50	25
1f	CH	SO_2Ph	H	Br	5	30	50 / 50	60
1g	CH	CH_3	H	H	-	-	-	100

* Isolated yield of chromatographically homogeneous, spectroscopically pure products.

Scheme 1

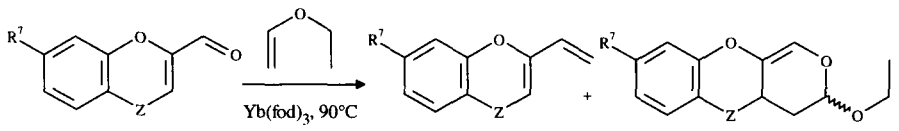
In the 1,4-benzodioxine series (Scheme 2), the yields were much higher and the reactivity was increased (2-18h of reaction) with a high endo selectivity for the cycloadducts **6l,m** which were preponderant over the vinyl compound **5l,m**.

In the 1,4-benzoxazines series (Scheme 2), the situation was more contrasted due to the low stability of the starting aldehydes **4h-k**. Compound **4j** afforded only the vinyl compound **5j** (18h of reaction) and **4i** gave only the isolated cycloadduct **6i** (after 3 days).

We have attempted to explain the formation of the vinyl compound. The treatment of an isolated mixture of diastereomers such as **3a** with 1-ethoxyethene and $Yb(fod)_3$ did not afford the vinyl product **2a**, which means that two different pathways were involved in the formation of the cycloadducts and the vinyl products. We postulated a competing [2+ 2] cycloaddition between the 1-ethoxyethene and the heterocyclic aldehydes **1,4**; the reaction of electron-rich olefin such as 1-ethoxyethene has been reported [16] to afford cyclobutane adducts but only with very electron-poor olefins like tetracyanoethene.

On the other hand, photochemical cycloaddition on the 2-3 bond of 1-acetylindole has been described with alkenes.[17,18] We found no influence of light on the outcome of the reaction. Deformylation process with formation of an activated form of the 1-sulfonylindole has been rejected due to the unproductive results obtained by reacting 1-sulfonylindole and 1-ethoxyethene in the same experimental conditions. Migignac[19] has reported the formation of acrylic acid ethyl ester derivatives by reaction of ketones with a

substituted 1-ethoxypropyne in presence of $TiCl_4$, via a cyclic intermediate resulting from a [2+2] cycloaddition.



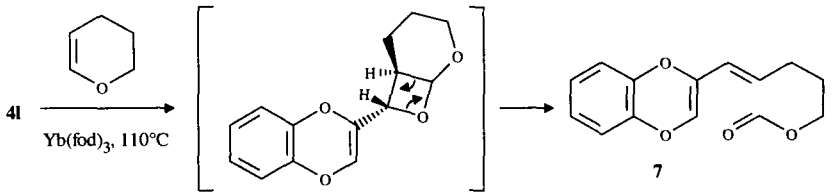
4h-m **5h-m** **6h-m**

	Z	R^7	Yield (%) **5***	Yield (%) **6**	Ratio endo / exo	Recovered **4** (%)
4h	NH	H	-	15	100 / 0	-
4i	NCH_3	H	-	20	100 / 0	40
4j	$NCOCH_3$	H	45	-	-	-
4k	NBoc	H	23	9	100 / 0	-
4l	O	H	19	47	100 / 0	10
4m	O	CH_3O	39	60	100 / 0	-

* Isolated yield of chromatographically homogeneous, spectroscopically pure products.

Scheme 2

We reacted 2,3-dihydropyran, which was less reactive than 1-ethoxyethene, with the reactive 1,4-benzodioxine aldehyde **4l** in order to obtain a substituted ethylenic derivative and so to gain information on the mechanism. We succeeded in isolating the unsaturated formate **7** which may be the result of a [2+ 2] cycloaddition giving an oxetane, followed by a cyclic rearrangement generating the ethylenic bond (*E* isomer) together with the formate ester.



In the α,β-ethylenic aldehydes **1,4**, the presence of one or two heteroatoms O, N, partially counterbalance the effect of the withdrawing aldehyde group and decrease the rate of a 4π participation in a $LUMO_{diene}$-controlled Diels-Alder reaction and so allowed reaction by another pathway. We are currently investigating these reactions in order to increase the selectivity and the yields towards the formation of the ethylenic compounds.

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21. Typical procedure: Compound **1a** (0.5 mmol) was dissolved in 1-ethoxyethene (2 ml) in presence of $Yb(fod)_3$ (0.05 mmol) and heated in a sealed tube at 90°C during 2 days; after evaporation of the solvent the mixture was chromatographed on a silica gel column using petroleum ether / CH_2Cl_2 (75 / 25, v / v) as eluent. Compound **2a** was the first eluted compound and then, diastereomers **3a**; compound **2a** was identical to an authentic sample[20] , oil; IR (Film) ν = 1170 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 5.31 (d, 1H, H_{eth}, J = 11.0 Hz), 5.75 (d, 1H, H_{eth}, J = 17.6 Hz), 6.72 (dd, 1H, H_{eth}, J = 11.0, 17.6 Hz), 7.20 - 7.33 (m, 2H, H_{arom}), 7.36 - 7.43 (m, 2H, H_{arom}), 7.49 (m, 1H, H_{arom}), 7.56 (s, 1H, H_2), 7.70 (d, 1H, H_{arom}, J = 7.4 Hz), 7.84 (d, 2H, H_{arom}, J = 8.1 Hz), 7.96 (d, 1H, H_{arom}, J = 7.4 Hz), M.S. (C.I.,NH_3): m/z 284 (M^++1); compound **3a** (endo); mp: 124 - 126°C; IR (KBr) ν = 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 1.27 (t, 3H, CH_3, J = 7.4 Hz), 2.18 (m, 1H, CHH), 3.00 (ddd, 1H, CHH, J = 2.9, 5.2, 12.5 Hz), 3.56 - 3.70 (m, 1H, OCHH), 3.90 - 4.04 (m, 1H, OCHH), 4.58 (ddd, 1H, CHØ, J = 2.9, 5.2, 10.2 Hz), 5.31 (dd, 1H, OCHOEt, J = 2.9, 10.2 Hz), 6.69 (d, 1H, H_{eth}, J = 2.9 Hz), 6.94 (m, 1H, H_{arom}), 7.06 - 7.14 (m, 2H, H_{arom}), 7.46 (m, 2H, H_{arom}), 7.57 (m, 1H, H_{arom}), 7.65 (m, 1H, H_{arom}), 7.84 (m, 2H, H_{arom}); compound **3a** (exo); Oil; IR (Film) ν = 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 1.20 (t, 3H, CH_3, J = 7.4 Hz), 1.96 (ddd, 1H, CHH, J = 2.9, 11.8, 12.5 Hz), 2.94 (ddd, 1H, CHH, J = 1.5, 5.2, 12.5 Hz), 3.53 - 3.65 (m, 1H, OCHH), 3.76 - 3.88 (m, 1H, OCHH), 4.55 (ddd, 1H, CHØ, J = 2.9, 5.2, 11.8 Hz), 5.17 (m, 1H, OCHOEt), 6.61 (d, 1H, H_{eth}, J = 2.9 Hz), 6.92 (m, 1H, H_{arom}), 7.06 - 7.16 (m, 2H, H_{arom}), 7.44 (m, 2H, H_{arom}), 7.54 (m, 1H, H_{arom}), 7.71 (m, 1H, H_{arom}), 7.84 (m, 2H, H_{arom}).

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