Novel Dienes from α-Ylidene and α-Alkoxylidene Lactones. Useful Intermediates for the Synthesis of Benzofurans

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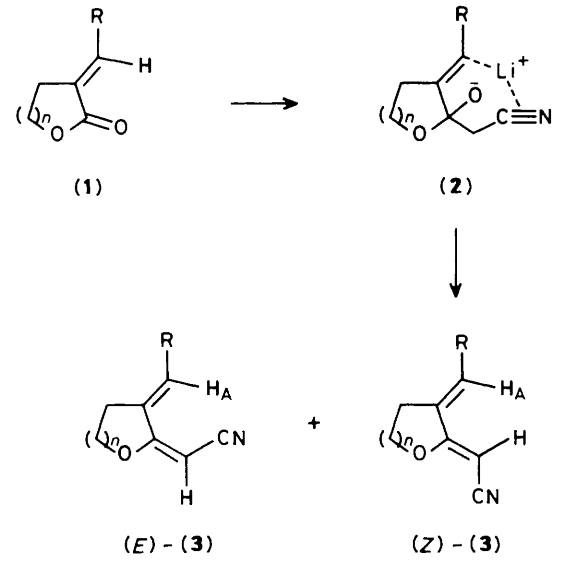
Novel dienes, formed by reaction of α-ylidene and α-alkoxylidene lactones with the lithium salt of acetonitrile, are readily converted into benzofuran precursors by a highly regioselective (and in the case of the former derivatives) a highly stereoselective Diels–Alder reaction.

The Diels–Alder reaction is one of the most useful reactions in synthetic organic chemistry.[1] Consequently, improvements which increase the efficiency or enlarge its applicability are always desirable,[2] and the discovery of novel dienes is important in this respect.

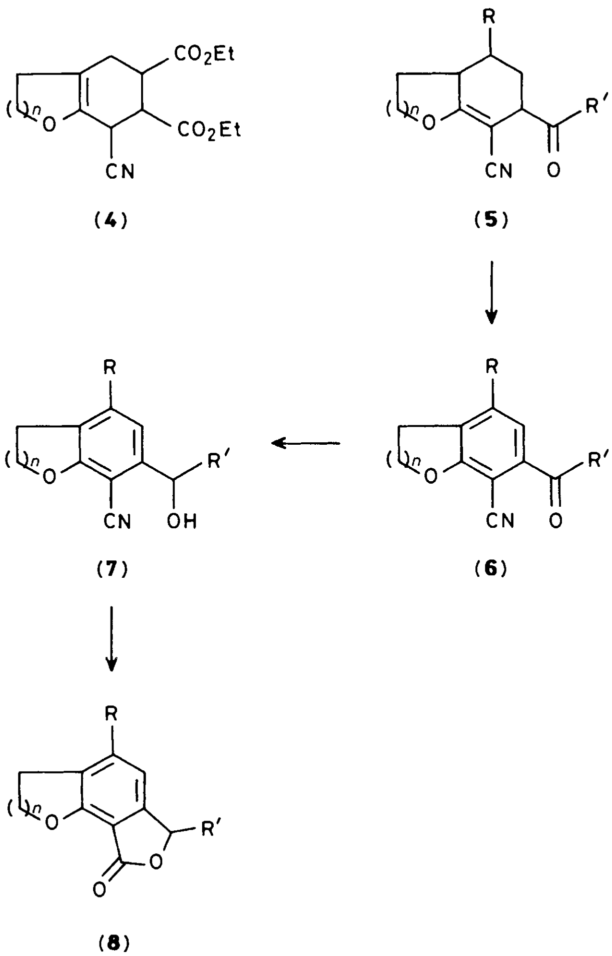
In the course of our studies directed towards the synthesis of spiro-dilactones we had occasion to explore the chemistry of carbanion additions to the enone system of α-methylene lactones.[3] Herein, we describe the results of our studies in which α-ylidene and α-alkoxylidene lactones were treated with the lithium anion of acetonitrile. In a typical run, n-butyl-lithium (45 mmol) was added dropwise to a stirred solution of acetonitrile (45 mmol) in dry tetrahydrofuran (THF) (100 ml) at −78 °C and in an atmosphere of nitrogen.

Table 1.

	Diene	(3)	Cycloadduct (5)			% Yield	M.p. (b.p.)
	n	R	*n*	R	R′	overall from (**1**)	/°C
a	1	H	1	H	Me	30	154
b	1	Et	1	Et	Me	34	164
c	1	Ph	1	Ph	Me	23	110.5
d	2	Ph	2	Ph	Me	25	158
e	1	OMe	1	OMe	Me	33	(52—54/1 Torr)
f	1	OEt	1	OEt	Me	40	(34—36/0.2 Torr)



Scheme 1



α-Methylene lactone (**1**; *n* = 1, R = H, 35 mmol) in dry THF (20 ml) was added dropwise to this solution and the mixture stirred at −78 °C for 3 hours before being quenched with 6 M HCl. Removal of the organic phase and extraction of the aqueous phase with dichloromethane yielded neither of the expected products, *viz.*, the γ-hydroxyketone,[4] nor the 1,4-addition product,[5] but instead afforded the (*Z*)- and (*E*)-isomers of the novel diene, 2-cyanomethylidene-3-methylenetetrahydrofuran (**3a**) which were separated by dry column chromatography on Kieselgel. The assignment of the (*Z*)-configuration to the major product was supported by the chemical shift of H_A at δ 5.72; the comparable proton in the minor product came to resonance downfield at δ 6.38. A number of these dienes were prepared, see Table 1.

The mechanism postulated for the formation of such dienes is outlined in Scheme 1. The reaction is basically an aldol-type condensation, but we suggest that the initial preference for cyclic hemiacetal formation over the open keto form is almost certainly due to the additional stabilization of the alkoxide anion (**2**) by lithium chelation with the π-electrons of the nitrile function and of the *exo*-methylene double bond. This property will be associated with the small size and highly polarizing power of the lithium cation which enables it to be held in a cage by the aforementioned substituents. This postulate is supported by our inability to form dienes using anions other than those of nitriles, while attempts to repeat the reaction with the sodium or potassium salts of acetonitrile also failed. The formation of *exo*-enol ethers from the reaction of lactones with lithium enolates has been reported previously.[6]

The cyano-substituted dienes produced in this manner were subsequently employed in a number of Diels–Alder reactions; thus (**3a**) afforded (**4**) when refluxed with diethyl fumarate. Surprisingly, when methyl vinyl ketone was the dienophile, reaction with each of the dienes (**3a**—**d**) yielded a single regioisomer (**5a**—**d**) in which the double bond had shifted into conjugation with the cyano group. Typically, assignment of (**5a**) was performed on the basis of its n.m.r. spectra.† The presence of the complex multiplet at δ 3.8—4.6, assigned to the protons on C(2), indicated that the double bond had moved into conjugation with the cyano group, since only the presence of a chiral centre at C(3a) would account for this

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† Compound (**5a**): ^{1}H n.m.r. ($CDCl_3$) 1.1—2.9 (m, 7H), 2.23 (s, 3H), 3.25—3.4 (m, 1H), and 3.8—4.6 (m, 2H); ^{13}C n.m.r. ($CDCl_3$) 23.74 (t), 24.59 (t), 29.08 (q), 30.66 (t), 40.25 (d), 46.99 (d), 72.31 (t), 75.40 (s), 117.54 (s), 174.97 (s), and 207.51 (s).

All new compounds gave satisfactory elemental analysis.

observation, while the position of the carbonyl carbon at δ 207.51 ruled out the possibility of an α,β-unsaturated ketone structure. The ^{13}C n.m.r. spectrum, showing only 11 carbon resonances, indicated that the product was diastereoisomerically pure. On the other hand the adducts from 2-cyanomethylidene-3-alkoxylidenetetrahydrofurans (**3e,f**) displayed two sets of chemical shift non-equivalent lines in the ^{13}C n.m.r., indicative of the presence of diastereoisomers. In all these adducts (**5a—f**) the carbon atoms of the double bond came to resonance at δ 174.97 and 75.04, at positions comparable with the signals obtained for the same carbon atoms in the starting diene (δ 170.84 and 63.44 respectively), with the large difference in chemical shift between the two carbon atoms being attributed to the polarization of the double bond by the CN group. By comparison, the signals for the carbon atoms of the double bond in (**4**) appeared at δ 143.76 and 108.55.

The observed alteration of the chemical shifts of (**5**) on addition of the shift reagent Pr(fod)$_3$ (fod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionate) supported a structure in which the nitrile and carbonyl groups were '*ortho*' to each other, and this was confirmed by the conversion of these cycloadducts into the corresponding lactones (**8**). Thus, *N*-bromosuccinimide-promoted aromatization of (**5**) followed by sodium borohydride reduction of the product (**6**), and subsequent quenching of the reaction mixture (**7**) with anhydrous methanolic hydrochloric acid, yielded the dihydrobenzofuranolactones (**8**).[‡] Extended Hückel calculations[7] carried out on the dienes support the observed regiochemistry of their Diels–Alder reactions.

Similar reactions occurred when ethyl vinyl ketone and methylacrylate were employed as dienophiles, an indication that the present method for the synthesis of compounds of the type (**6**) should have wide applicability for the construction of a wide variety of benzofurans, and subsequently furano- and pyrano-coumarins.

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[‡] *Selected spectroscopic data:* (**8a**), $\nu_{max.}$ 1760 cm^{-1}; ^{1}H n.m.r. (CDCl$_3$) 1.5 (d, 3H, J 2 Hz), 3.17 (t, 2H, J 8.5 Hz), 4.73 (t, 2H, J 8.5 Hz), 5.42 (q, 1H, J 2 Hz), 6.76 (d, 1H, J 4 Hz), and 7.63 (d, 1H, J 4 Hz).