Tetrahedron Letters,Vol.23,No.11,pp 1147-1150,1982 0040-4039/82/111147-04$03.00/0
Printed in Great Britain

DIELS-ALDER REACTIONS OF MALONDIALDEHYDE DERIVATIVES WITH REVERSED ELECTRON DEMAND; AN EASY APPROACH TO STRUCTURALLY UNIQUE CARBOHYDRATES AND COMPOUNDS OF THE THROMBOXANE TYPE

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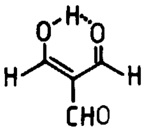
Summary 2-Formyl-malondialdehyde (1) reacts at 22°C in a type of Diels-Alder reaction with reversed electron demand with the enol-ethers (18) - (21) and (23) - (25) within a few hours to give the dihydropyrans (2) - (9) and (12) - (17). Thio-enol-ethers may also be employed in this cycloaddition.

α,β-unsaturated aldehydes can be converted to dihydropyrans using enol-ethers at 160-180°C in a Diels-Alder reaction with reversed electron demand.[1] Malondialdehydes should also be capable of such a reaction via the enol form, although higher temperatures may be necessary, since the energy of the LUMO and hence the free energy of activation are raised by the donor substituent on C-3 of the α,β-unsaturated aldehyde.[2] Such reactions had not previously been observed, because malondialdehyde is thermally labile.

We recently showed that the introduction of an acceptor-group on C-2 of an α,β-unsaturated carbonyl-system appreciably reduced the energies of the LUMO's, so that Diels-Alder reactions could even be carried out at 20°C with such systems.[3]

We have now observed a similar phenomenon with malondialdehyde; thus 2-formylmalondialdehyde[4] (triformylmethane) (1) reacts already at 20°C with the enol-ethers (18) - (21) and (23) - (25) giving the dihydropyrans (2) - (9) and (12) - (17) in good to very good yields.[5] Thio-enol-ethers may also be employed in this cycloaddition; the dihydropyrans (10) and (11) are formed from (1) and (22). However the reaction times are here longer, and the yields smaller.

The cycloadditions are regioselective, and with respect to the configuration of the enol-ether employed also stereoselective. However the reaction always produces two diastereomers in different yields. It appears that it may



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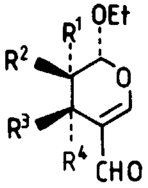
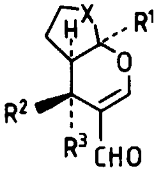
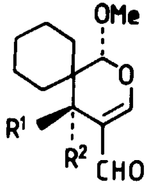


	R^1	R^2	R^3	R^4
2	H	H	H	OH
3	H	H	OH	H
4	Me	H	H	OH
5	Me	H	OH	H
6	H	Me	H	OH
7	H	Me	OH	H

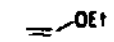
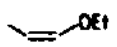
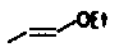
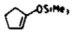
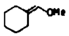


	R^1	R^2	R^3	X
8	H	H	OH	O
9	H	OH	H	O
10	H	H	OH	S
11	H	OH	H	S
12	OMe	H	OH	CH_2
13	OMe	OH	H	CH_2
14	$OSiMe_3$	H	OH	CH_2
15	$OSiMe_3$	OH	H	CH_2



	R^1	R^2
16	H	OH
17	OH	H

Table I. Cycloaddition of triformylmethane (1) and enolethers (18 - 25)

educts (1) and		products	ratio of isomers	yield, % (isolated)	reaction time h (22 °C)	m.p., °C	
	(18)	(2) and (3)	4:5	65	24	-	-
	(19)	(4) and (5)	3:1	85	5	51	-
	(20)	(6) and (7)	1:7	70	5	-	57
	(21)	(8) and (9)	1:4	73	2	-	117
	(22)	(10) and (11)	1:3	30	200	135	146
	(23)	(12) and (13)	1:3	80	1	50(dec)	50(dec)
	(24)	(14) and (15)	1:6	63	8 (5 °C)	-	-
	(25)	(16) and (17)	2:3	95	15	107	108

procede via either an *endo* or an *exo*-transition-state. It is not quite clear whether the free aldehyde group or the carbonyl group fixed by a hydrogen bond reacts. However energy considerations and product analyses indicate that the fixed carbonyl group reacts. The constitution and relative configuration[6] of the resulting adducts was assigned on the basis of the ^1H-NMR spectra. However an unambigous assignment was not possible for the annellated compounds (<u>12</u>) - (<u>15</u>). For this reason a single-crystal X-ray analysis was performed for (<u>13</u>).

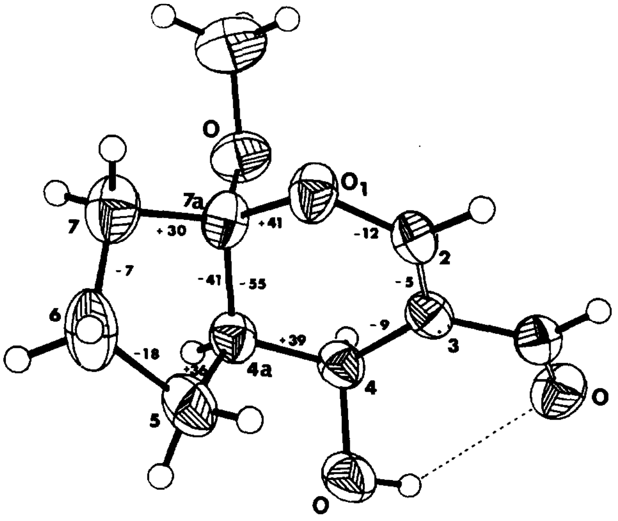


Figure 1. Molecular structure of the Diels-Alder adduct (<u>13</u>), showing its relative configuration, ring torsion angles and 50% thermal ellipsoids.

Crystals of (<u>13</u>) are monoclinic, space group $P2_1/n$, with four molecules in a cell of dimensions a = 12.799(5), b = 5.977(5), c = 13.083(6) Å, β = 104.36(5)°. The structure was solved by multisolution direct methods and refined with anisotropic C and O and isotropic riding H to R = 0.068, R_w = 0.063 for 933 unique reflections with $F>4\sigma(F)$ measured on a Stoe-Siemens 4-circle diffractometer with MoK_α radiation. The hydroxyl H was located in a difference Fourier and refined independently; it makes an intramolecular hydrogen bond (H...O = 2.33 Å) to the carbonyl oxygen.[7]

The procedure which has been described here makes the synthesis of structurally unique carbohydrates and compounds of the thromboxane type feasible.

This work was supported by the Fonds der Chemischen Industrie.

References and Notes

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2. R. Sustmann, *Pure Appl. Chem.* 40, 569 (1975); K.N. Houk and R.W. Stozier, *J. Am. Chem. Soc.* 95, 4094 (1973); see also J. Flemming: *Grenzorbitale und Reaktionen organischer Verbindungen.* Verlag Chemie, Weinheim 1979.

3. L.-F. Tietze, G. v. Kiedrowski, K. Harms, W. Clegg and G.M. Sheldrick, *Angew. Chem.* 92, 130 (1980); *Angew. Chem., Int. Ed. Engl.* 19, 134 (1980). L.-F. Tietze and G. v. Kiedrowski, *Tetrahedron Letters* (1981) 219; L.-F. Tietze, G. v. Kiedrowski and B. Berger, *Angew. Chem.*, in press.

4. Z. Arnold, *Coll. Czech. Chem. Commun.*, 26, 3051 (1961).

5. General specification for the reaction of triformylmethane (1) with enol-ethers: 1.1 to 1.7 mole-equivalents of the enol-ether are added to a stirred suspension of 100 mg (100 mmol) triformylmethane (1) (freshly sublimed and ground) in 5 ml of a water- and oxygen-free benzene-dichloromethane mixture (10:1). After complete reaction of (1) (DC) the solvent and (if necessary) excess enol-ether are evaporated *in vacuo* and the residue separated by chromatography on silica-gel.

6. (4): ^{1}H-NMR (CDCl$_3$): δ = 1.22 (t, J = 7 Hz; 3 H, CH$_3$), 1.23 (d, J = 7.5 Hz; 3 H, CH$_3$), 2.00 (m, 1 H, 3-H), 2.82 (d, J = 11 Hz; 1 H, OH), 3.75 (mc, 2 H, CH$_2$), 4.34 (dd, J = 11,4.5 Hz; 1 H, 4-H; after H/D-exchange: d, J = 4.5 Hz), 5.18 (dd, J = 2.5, 1 Hz; 1 H, 2-H), 7.21 (s, 1 H, 6-H), 9.40 (s, 1 H, CHO).
   (5): ^{1}H-NMR (CDCl$_3$): δ = 1.20 (d, J = 7 Hz; 3 H, CH$_3$), 1.25 (t, J = 7 Hz; 3 H, CH$_3$), 2.06 (m, 1 H, 3-H), 3.50 (s, 1 H, OH), 4.25 (mc, 2 H, CH$_2$), 4.42 (d, J = 6.5 Hz; 1 H, 4-H), 5.15 (d, J = 2.5 Hz; 1 H, 2-H), 7.22 (s, 1 H, 6-H), 9.32 (s, 1 H, CHO).

7. The profile-fitting procedure of W. Clegg, *Acta Cryst.*, A37, 22 (1981) was employed for data collection; all other calculations were performed using a Data General Eclipse mini-computer and programs written by G.M.S.

(Received in Germany 29 December 1981)