Cycloadditions of 3-Methoxyfuran with Mono-activated Dienophiles; Application to the Synthesis of (±)-Avenaciolides

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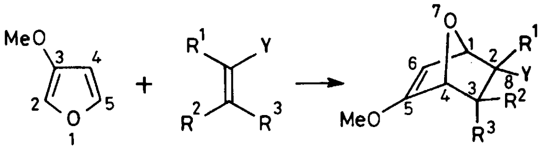
Summary Cycloadditions of 3-methoxyfuran (**1**) with several mono-activated dienophiles gave the *endo* adducts stereoselectively under the usual conditions in satisfactory yields; two of the adducts were transformed into potential intermediates (**7a**) and (**7b**) for the synthesis of (±)-avenaciolide and (±)-isoavenaciolide, respectively.

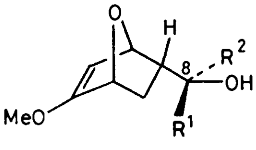
Cycloadditions of furan with mono-activated dienophiles usually take place slowly (several weeks) and non-stereoselectively in low yields[1] and give *ca.* 1 : 1 mixtures of the *endo* and *exo* adducts, even under high pressure conditions which give satisfactory yields (*ca.* 55%).[2] We demonstrate here the novel reactivity of 3-methoxyfuran (**1**) in its stereoselective cycloadditions with dienophiles, and describe its application to the synthesis of (±)-avenaciolides.



(1) dienophile adduct

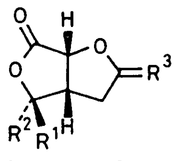
(2) $R^1=R^2=R^3=H, Y=COC_8H_{17}$

(3) $R^1=R^2=R^3=H, Y=CHO$



(4a) $R^1=C_8H_{17}, R^2=H$

(4b) $R^1=H, R^2=C_8H_{17}$



(5a) $R^1=C_8H_{17}, R^2=H, R^3=$ ▬H, •••CO$_2$Me

(5b) $R^1=H, R^2=C_8H_{17}, R^3=$ ▬H, •••CO$_2$Me

(6a) $R^1=C_8H_{17}, R^2=H, R^3=H, OCOMe$

(6b) $R^1=H, R^2=C_8H_{17}, R^3=H, OCOMe$

(7a) $R^1=C_8H_{17}, R^2=H, R^3=O$

(7b) $R^1=H, R^2=C_8H_{17}, R^3=O$

The results summarized in the Table of the reactions of (**1**)† with typical dienophiles indicate that, except in one instance (run 10), the cycloadditions proceeded smoothly and with high stereoselectivity under mild conditions within several days, giving the *endo* adducts in satisfactory yields (40—100%).‡ The enhanced reactivity and predominant formation of the *endo* isomers not only are expected from calculated values§ of HOMO energies, π-electron densities[3] at C-2, and dipole moments in the furans, but also may be rationalized in terms of the overlap of π-orbitals at electron-rich (C-6) and electron-deficient (C-8) atoms as well as the Coulomb interaction between the two atoms in the cycloadducts. We have applied this method to the synthesis of (±)-avenaciolides.

Table. Cycloadditions of (**1**) with dienophiles.[a]

	Dienophile					Adduct	
Run	R^1	R^2	R^3	Y	Time	Yield[b] /%	*Endo*:*Exo*[c]
1	H	H	H	CO_2Me	2 d	66	10:0
2	H	H	H	CO_2Me	6 h[d]	94	10:0
3	H	H	H	COMe	2 d	100	10:0
4	H	H	H	$COC_{18}H_{17}$	3 d	100	10:0
5	H	H	H	CHO	7 d[e]	86	10:0[f]
6	H	H	H	CN	2 d	66	4:1
7	Cl	H	H	CN	2 d	77	10:0[g]
8	H	Me	H	COMe	12 d	49	10:0
9	Me	H	H	COMe	10 d	36	10:0[h]
10	H	Me	Me	COMe	2 d	0	

[a] All reactions were carried out at 20 °C in ethereal homogeneous solutions containing 4 M concentrations of both the reactants under atmospheric pressure, unless otherwise stated. [b] Crude yields. [c] The configurations and ratios of the *endo* and *exo* adducts were estimated by ^1H n.m.r. spectroscopy. [d] Performed at 15 kbar pressure (1 bar = 10^5 Pa). [e] Performed at 0 °C. [f] The product was isolated as its hydride reduction product and identified by spectral data. [g] The product was reduced (Zn–Cu couple, EtOH, reflux, 2 h) to give predominantly the *endo* adduct of run 6; the *endo* configuration was assigned only tentatively. [h] The *endo* configuration was tentatively assigned.

Reduction of the adduct (**2**), prepared from (**1**) and octyl vinyl ketone (run 4 in the Table), with lithium tri-t-butoxyaluminium hydride [tetrahydrofuran (THF), 0 °C, 1 h] produced only the corresponding (2*RS*,8*RS*)-alcohol (**4a**) (90%), while treatment of the adduct (**3**), prepared from (**1**) and acrolein (run 5), with octyl-lithium (THF, −30° C,

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† 3-Methoxyfuran (**1**) was easily prepared from commercially available 3-bromofuran by a two-step process (i, BuLi–I_2, ether; ii, NaOMe–CuO, MeOH, reflux, 24 h) in 55% yield; *cf.* J. Srogl, M. Janda, and I. Stibor, *Collect. Czech. Chem. Commun.*, 1970, **35**, 3478.

‡ All new compounds gave satisfactory spectral data.

§ The calculation was performed by the SCF MO Pariser–Parr–Pople method using the usual set of semi-empirical parameters for the resonance integrals and the Coulomb repulsion integrals: H. Baba, S. Suzuki, and T. Takemura, *J. Chem. Phys.*, 1969, **50**, 2078; S. Suzuki, T. Fujii, and T. Ishikawa, *J. Mol. Spectrosc.*, 1975, **57**, 490: energies of HOMO [furan −10·41 eV; (**1**) −9·68 eV], π-electron densities at C-2 [furan 1·081; (**1**) 1·162], and dipole moments [furan 2·00 D, *Y*-comp. −2·00 D; (**2**) 1·11 D, *X*-comp. −0·41 D, *Y*-comp. −1·04 D]. The latter moment lies nearly along the line connecting the C-2 and C-4 atoms.

6 h) afforded the isomeric (2*RS*,8*SR*)-alcohol (**4b**) as the sole isolable product (62%). The high stereoselectivity in the addition reactions may be accounted for by attack of the hydride reagent and the octyl anion from the less hindered side of the carbonyl compounds (**2**) and (**3**) which assume conformations with maximum overlap of the π-orbitals in question. Ozonolysis of (**4a**) and (**4b**) (MeOH, −78 °C) followed by Jones oxidation effected formation of the epimeric lactone esters (**5a**) (60%) and (**5b**) (40%) *via* their respective cyclic acetals. These esters, when hydrolysed (K_2CO_3–aq.MeOH, room temp., 12 h) and then oxidized [lead(IV) acetate, C_6H_6, reflux, 2 h], were converted into the lactone acetates (**6a**) and (**6b**) which, without further purification and on hydrolysis and subsequent Jones oxidation, gave two isomeric bis-lactones (**7a**), oil, (53%) and (**7b**), m.p. 79—81 °C, (22%), respectively. These compounds were identified as well known intermediates[4,5] in the syntheses of (±)-avenaciolide and (±)-isoavenaciolide, respectively.[6]

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[1] R. J. Ouellette, A. Rosenblum, and G. Booth, *J. Org. Chem.*, 1968, **33**, 4302; F. Kienzle, *Helv. Chim. Acta*, 1975, **58**, 1180.

[2] W. G. Dauben and H. O. Krabbenhoft, *J. Am. Chem. Soc.*, 1976, **98**, 1992; *cf.* J. Rimmelin, G. Jenner, and P. Rimmelin, *Bull. Soc. Chim. Fr.*, 1978, II-461.

[3] *Cf.* I. G. John and L. Radom, *J. Am. Chem. Soc.*, 1978, **100**, 3981.

[4] W. L. Parker and F. Johnson, *J. Am. Chem. Soc.*, 1969, **91**, 7208; *J. Org. Chem.*, 1973, **38**, 2489.

[5] K. Yamada, M. Kato, M. Iyoda, and Y. Hirata, *J. Chem. Soc., Chem. Commun.*, 1973, 499.

[6] For syntheses of avenaciolide and isoavenaciolide, see T. Sakai, H. Horikawa, and A. Takeda, *J. Org. Chem.*, 1980, **45**, 2039 and references cited therein; R. C. Anderson and B. Fraser-Reid, *Tetrahedron Lett.*, 1977, 2865 and references cited therein.