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HIGH-PRESSURE DIELS-ALDER REACTIONS OF 2-METHYLTHIO- AND 2-ACETOXYFURAN. AN EFFICIENT ENTRY TO 4-HYDROXYCYCLOHEXANONES[1]

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Abstract — Diels-Alder reactions of 2-methylthio- and 2-acetoxyfuran were performed at 15 kbar and room temperature. The adducts were proved to be a useful precursor of 4-hydroxycyclohexanones.

Our recent efforts have been focused on the synthetic application of high-pressure technique to several kinds of Diels-Alder reactions. In this communication, we wish to report i) the successful Diels-Alder reactions of 2-methylthio- and 2-acetoxyfuran at high-pressure and ii) the conversion of the adducts to 4-hydroxycyclohexanones.

In connection with our interest in the synthesis of epoxydon (1)[3] and glyoxalase I inhibitor (2),[4] we envisaged a Scheme I strategy to construct the 4-hydroxycyclohexanone derivatives. Recently, however, Koizumi et al. have reported that the total synthesis of 2 by using similar approach.[5] This result prompts us to report our preliminary findings in this field.

Under conventional conditions, 2-methylthio- and 2-acetoxyfurans react only with reactive dienophiles such as maleic anhydride.[6, 7] When the reaction was performed at 15 kbar and room temperature, we

Scheme I.

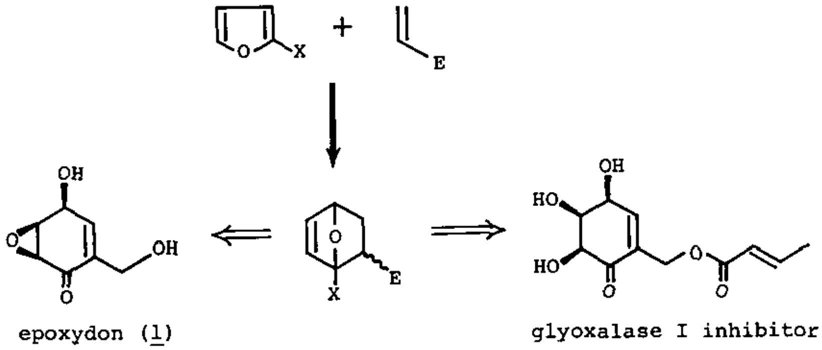
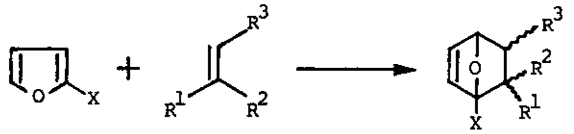


Table 1. Diels-Alder reactions of 2-methylthio- and 2-acetoxyfuran[a]



3a: X = SMe
b: X = OAc

run	3	R^1	R^2	R^3	time, h	yield, %[b]	endo/exo ratio[c]
1	a	COOMe	H	H	8	64	2 : 1
2	a	CN	H	H	8	53	2 : 1
3	a	$COCH_3$	H	H	8	(85)	2 : 1
4	a	CHO	H	H	8	polymerization	
5	a	Cl	CN	H	6	(90)[d]	1 : 0
6	a	OAc	CN	H	22	(50)[d]	1 : 0
7	a	COOMe	H	COOMe	8	40	1 : 0
8	b	Cl	CN	H	8	~100	1 : 0
9	b	COOMe	H	H	41	71	1.3 : 1
10	b	CN	H	H	69	~100	1.2 : 1
11	b	CHO	H	H	8	>90	1.2 : 1
12	b	CHO	H	H	72[e]	57	1 : 2
13	b	$COCH_3$	H	H	8	>90	1.3 : 1
14	b	COCl	H	H	96[f]	(>90)	1 : 1
15	b	COOMe	H	COOMe	8	54	1 : 0

[a] Reactions were carried out in CH_2Cl_2 at 15 kbar and room temperature unless otherwise noted. General procedure for high-pressure reactions is described in our previous reports.

[b] Isolated yields after purification by preparative tlc at 0 °C or SiO_2 column chromatography.

[c] Determined by nmr.

[d] These adducts were highly unstable and considerably decomposed during isolation procedures.

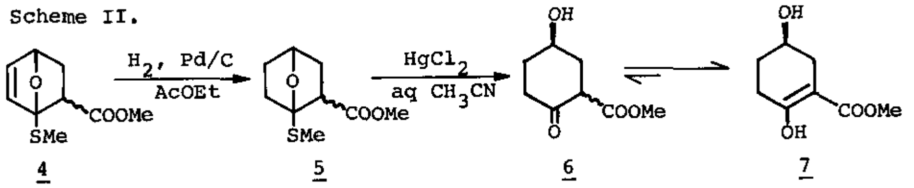
[e] At atmospheric pressure without solvent.

[f] At atmospheric pressure in the presence of a few drops of propylene oxide. See also ref. 10.

found the reaction with a variety of dienophiles smoothly proceeded almost regioselectively to yield the expected ortho-adducts. The results are summarized in Table 1.[8] Interestingly, 2-acetoxyfuran reacted with acrolein and acryloyl chloride even at atmospheric pressure (runs 12 and 14).[9, 10] These results encouraged us to proceed with the further transformations.

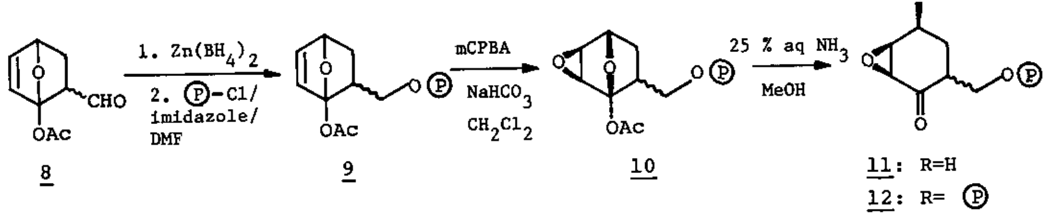
As shown in Scheme II, hydrogenation of the adduct 4 followed by treatment with mercuric salt gave

Scheme II.



4-hydroxycyclohexanone 6 in almost quantitative yield.[11] Judging from the nmr spectral result, 6 is an equilibrium mixture of keto- and enol-tautomers.[12] Extension of this methodology to 8 was next examined (Scheme III).[13] Selective reduction of aldehyde with $Zn(BH_4)_2$ followed by protection

Scheme III. (Ⓟ = $SiMe_2Bu^t$)



afforded 9 in 60 % overall yield. Epoxidation of 9 with m-chloroperbenzoic acid in the presence of $NaHCO_3$ gave the desired exo-epoxides 10 in 83 % yield. The conversion of 10 to 11 was rather troublesome and the use of common reagents (e.g., K_2CO_3/aq MeOH; NaOMe/MeOH; Et_3N/MeOH) resulted in a complex mixture probably due to the base-sensitive structure of 11. Fortunately, however, treatment of 10 with aq NH_3 (3 equiv.) in MeOH smoothly proceeded to afford 11 in 70 % yield. The product contains a complete stereochemistry for the synthesis of 1 and its structure was unambiguously confirmed by 400 MHz nmr measurement. The remained problem is the introduction of double bond on 11. Unfortunately, all attempts to construct the enone function on 11 or the corresponding bis-silyl ether 12 under a variety of conditions [LDA/PhSeCl then H_2O_2; LDA/Me_3SiCl then $Pd(OAc)_2/CH_3CN$; DDQ/C_6H_6, reflux; $PdCl_2$-$Pd(OAc)_2$/aq dioxane, 85 °C; SeO_2/t-BuOH, reflux] were fruitless.

Although an attempt for the total synthesis of 1 was unsuccessful at present stage, we believe the above mentioned procedure will provide a useful route to various 4-hydroxycyclohexanone derivatives.

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8. Selected spectral data of the adducts. 4(endo-isomer): ir(neat), 1735 cm^{-1}; nmr(CDCl$_3$) δ 1.68 (1H, dd, J = 11, 4 Hz), 2.23(3H, s), 2.37(1H, ddd, J = 11, 9.5, 5 Hz), 3.04(1H, dd, J = 9.5, 4 Hz), 3.66(3H, s), 4.99(1H, dd, J = 5, 2 Hz), 6.15(1H, d, J = 6 Hz), 6.52(1H, dd, J = 6, 2 Hz). 4(exo-isomer): ir(neat), 1740 cm^{-1}; nmr(CDCl$_3$) δ 1.66(1H, dd, J = 11, 8 Hz), 2.18(3H, s), 2.44(1H, ddd, J = 11, 4.5, 4 Hz), 2.68(1H, dd, J = 8, 4 Hz), 3.75(3H, s), 5.12(1H, dd, J = 4.5, 1.8 Hz), 6.23(1H, d, J = 5.5 Hz), 6.50(1H, dd, J = 5.5, 1.8 Hz). 8(endo-isomer): ir(neat), 1750, 1725, 1325, 1260, 1240, 1210, 1170, 1065 cm^{-1}; nmr(CCl$_4$) δ 1.65(1H, dd, J = 11.5, 4 Hz), 2.16(3H, s), 2.34(1H, ddd, J = 11.5, 9, 4 Hz), 2.89(1H, dt, J = 9, 4 Hz), 4.84(1H, dd, J = 4, 1.5 Hz), 6.47(2H, d, J = 1.5 Hz), 9.30(1H, d, J = 4 Hz). 8(exo-isomer): ir(neat), 1760, 1730, 1245, 1210 cm^{-1}; nmr (CCl$_4$) δ 1.68(1H, dd, J = 12, 8 Hz), 2.12(3H, s), 2.32(1H, ddd, J = 12, 4.5, 3.5 Hz), 2.75(1H, dt, J = 8, 4.5 Hz), 4.95(1H, dd, J = 4.5, 2 Hz), 6.43(1H, dd, J = 6, 2 Hz), 6.53(1H, d, J = 6 Hz), 9.43 (1H, d, J = 4.5 Hz).
9. 2-Acetoxyfuran was carefully distilled from CaH$_2$ and freshly distilled one was used to get a good yield.
10. Cf. H. Kotsuki, K. Asao, and H. Ohnishi, *Bull. Chem. Soc. Jpn.*, 57, 3339(1984).
11. Direct treatment of 4 gave only methyl 2-(methylthio)benzoate.
12. Acetylation yielded a diacetate of 7 quantitatively: ir(neat) 1770, 1730, 1655 cm^{-1}; nmr(CCl$_4$) δ 1.8-2.7(6H, m), 1.98, 2.10, 3.64(each 3H, s), 4.99(1H, quintet, J = 5 Hz).
13. Spectral data of the products. 9(endo-isomer): ir(neat), 1770, 1260, 1220, 1185, 1170, 840, 780 cm^{-1}; nmr(CCl$_4$) δ 0.00(6H, s), 0.88(9H, s), 2.07(3H, s), 2.0-2.6(3H, m), 3.34(1H, dd, J = 11.5, 10 Hz), 3.42(1H, dd, J = 12.5, 10 Hz), 4.62(1H, dd, J = 5, 2 Hz), 6.24(1H, dd, J = 6, 2 Hz), 6.39(1H, d, J = 6 Hz). 9(exo-isomer): ir(neat), 1760, 1260, 1220,1120, 1065, 840, 780 cm^{-1}; nmr(CCl$_4$) δ 0.06(6H, s), 0.89(9H, s), 1.60(1H, dd, J = 5.5, 2.5 Hz), 2.09(3H, s), 2.0-2.4(2H, m), 3.43, 3.70(each 1H, dd, J = 10.5, 7.5 Hz), 4.68(1H, m), 6.32(1H, dd, J = 6, 2 Hz), 6.53(1H, d, J = 6 Hz). 10(endo-isomer): ir(neat), 1760, 1375, 1255, 1220, 1165, 1005, 840, 780 cm^{-1}; nmr(CCl$_4$) δ 0.05 (6H, s), 0.89(9H, s), 1.35(1H, dd, J = 11, 4.5 Hz), 2.11(3H, s), 2.1-2.6(2H, m), 3.20(1H, d, J = 3.5 Hz), 3.68(1H, dd, J = 3.5, 1 Hz), 3.75(2H, s), 4.19(1H, d, J = 5 Hz). 10(exo-isomer): mp 63-66 °C; ir(CHCl$_3$), 1755, 1255, 1120, 835 cm^{-1}; nmr(CDCl$_3$) δ 0.03(6H, s), 0.87(9H, s), 1.6-1.9(2H, m), 2.13(3H, s), 2.51(1H, ddt, J = 8, 7, 5 Hz), 3.36(1H, dd, J = 10, 7 Hz), 3.39(1H, d, J = 4 Hz), 3.66(1H, dd, J = 10, 7 Hz), 3.94(1H, d, J = 4 Hz), 4.34(1H, d, J = 4 Hz). 11(major product): ir (neat), 3440, 1710, 1255, 1110, 1090, 835, 790 cm^{-1}; nmr(400 MHz, CDCl$_3$) δ 0.01(6H, s), 0.84(9H, s), 1.84(1H, d, J = 7.8 Hz), 2.02(1H, dt, J = 12.2, 10 Hz), 2.04(1H, dt, J = 12.2, 6.1 Hz), 2.18 (1H, ddt, J = 10, 6.1, 3.9 Hz), 3.28, 3.61(each 1H, d, J = 4.2 Hz), 3.80(1H, dd, J = 9.7, 3.9 Hz), 3.84(1H, dd, J = 9.7, 6.1 Hz), 4.28(1H, ddd, J = 10, 7.8, 6.1 Hz).

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