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A CONVENIENT SYNTHESIS OF 3-SUBSTITUTED-5,5-DIMETHYL-TETRAHYDRO-2-BENZOPYRAN-8-ONES THROUGH HETERO-DIELS-ALDER REACTION

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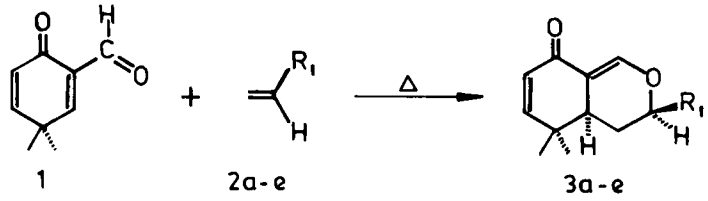
ABSTRACT: 2-Formyl-4,4-dimethylcyclohexa-2,5-dien-1-one undergoes hetero-Diels-Alder reactions with electron-rich olefins to yield 3-substituted-5,5-dimethyl-3,4,4a,5-tetrahydro-8H-2-benzopyrane-8-ones. The endo addition is favoured.

Hetero-Diels-Alder reactions of α,β-unsaturated carbonyl compounds as heterodiene are well-known and require severe experimental conditions[1]. The introduction of electron withdrawing groups at the α-position of the α,β-unsaturated carbonyl compounds would be expected to lower LUMO energy level and therefore increase the reactivity of such a heterodiene in the Diels-Alder reaction with inverse electron demand[2,3]. Recently we[4] and others[5] reported the synthetic utility of 2-formyl-4,4-

dimethylcyclohexa-2,5-dien-1-one[6] **(1)**, towards construction of decalones via Diels-Alder reaction with variety of conjugated dienes. We report herein the stereoselective hetero-Diels-Alder reactions of **1** with electron-rich olefins **2a-e** to yield 3-substituted-5,5-dimethyl-3,4-4a,5-tetrahydro-8H-2-benzopyran-8-ones, **(3a-e)**.

The toluene solution of **1** and excess of ethyl vinyl ether **2a** was heated in the presence of small amount of hydroquinone for 24 h at 55°C in a sealed tube. Evaporation of solvent followed by silica gel column chromatographic purification of the residue furnished 98% yield of hetero-Diels-Alder adduct, 3-ethoxy-3,4,4a,5-tetrahydro-5,5-dimethyl-8H-2-benzopyran-8-one, **(3a)**. In the ^{1}H-NMR spectrum of **3a**, C_3-H appeared at δ 5.0 with coupling constants $J_{3,4}$ = 1.8, 9.7 Hz thereby indicating the axial position for H-3[7]. Further structural proof for compound **3a** was obtained from ^{13}C-NMR spectral assignments. On the other hand, olefins **2b-e** failed to react with **1** in refluxing toluene solution. However, when the toluene solution of olefins **2b-e** and **1** containing small amount of hydroquinone was heated at 160°C in a sealed tube, corresponding endo Diels-Alder adducts **3b-e** were

Table 1: Synthesis of Benzopyranones, **3a-e**



1 2a-e 3a-e

2a R_1 = OEt
2b R_1 = OAc
2c R_1 = Ph(4'-OMe)
2d R_1 = Ph(3',4'-OMe_2)
2e R_1 = Ph(3',4',5'-OMe_3)

Product	R^1	Mole ratio 1:2	Time (h)	Temp. (°C)	Yield[a] (%)	mp[b] (°C)
3a	OEt	1:20	24	55	98	72-84
3b	OAC	1:20	24	160	25	101-103
3c	Ph-OMe,4'	1:2	1.5	160	59	130-131
3d	Ph-OMe_2,3',4'	1:2	2	160	66	120-122
3e	Ph-OMe_3,3',4',5'	1:2	24	160	84	171-173

[a] Yield of isolated pure product, satisfactory microanalysis obtained: C ± 0.34, H ± 0.12

[b] Uncorrected

obtained in moderate to good yields (Table 1). This is the first report of hetero-Diels-Alder reactions of 2-acylcycloalk-2-en-1-one with geminal substituents at γ-carbon atom[7,8]. The advantage of having these geminal substituents at γ-carbon atom is that they prevent the tautomerization and hence permit the reaction of **1** with relatively less reactive olefins such as **2b-e** to be carried out under drastic conditions.

Thus convenient synthesis of benzopyranones **3a-e** has been achieved. It is norteworthy that sesquiterpenoids ricciocarpin A and ricciocarpin B having the same skeleton as adduct **3** are recently found to occur naturally[9].

EXPERIMENTAL[10]

General Procedure for the Hetero-Diels-Alder Reaction of 1-Formyl-4,4-dimethyl-cyclohexa-2,5-dien-1-one (1) with olefins 2a-e (details given in table 1)

A solution of compound **1** (150 mg, 1 mmole) and olefin **2** in toluene (5 ml) containing hydroquinone (5 mg, 0.045 mmole) was heated in a sealed tube at temperature and for the period mentioned in table 1. After cooling the reaction mixture the excess of solvent was distilled in vacuo and the residue was

chromatographed on silica gel (100-200 mesh) to furnish cycloadducts **3a-e**, crystallised from ethyl acetate-ether (68-80°C).

3-Ethoxy-5,5-dimethyl-3,4,4a,5-tetrahydro-8H-2-benzopyran-8-one **(3a)** :

IR: ν_{max} 1665 cm^{-1} (conjugated >C=0); ^1H NMR: δ 0.95, 1.16 (s, 3H each, 2 x C_5-CH_3), 1.27 (t, 3H, J = 7.0, OCH_2CH_3); 1.81 (dt, 1H, J = 9.7, 12.5, 12.5, H-4), 2.07 (ddd, 1H, J = 1.8, 5.9, 12.5, H-4), 2.77 (ddd, 1H, J = 2.0, 5.9, 12.5, H-4a), 3.64, 4.03 (dq, 1H each, J = 7.0, 9.3, OCH_2CH_3), 5.00 (dd, 1H, J = 1.8, 9.7, H-3), 5.94 (d, 1H, J = 10.2, H-7), 6.65 (d, 1H, J= 10.2, H-7), 6.65 (d, 1H, J = 10.2, H-6), 7.56 (d, 1H, J = 2.0, H-1).

^{13}C NMR: δ 185.79 (s, C-8), 158.35 (d, C-6), 151.87 (d, C-1), 127.67 (d, C-7), 111.88 (s, C-8a), 101.12 (d, C-3), 64.83 (t, OCH_2CH_3), 39.58 (d, C-4a), 35.00 (s, C-5), 28.84 (t, C-4), 26.34, 21.96 (q, 2 x C_5-CH_3), 14.81 (q, OCH_2CH_3).

3-Acetoxy-5,5-dimethyl-3,4,4a,5-tetrahydro-8H-2-benzopyran-8-one **(3b)** :

IR: ν_{max} 1760 and 1665 cm^{-1} (ester and conjugated >C=0 respectively): ^1H NMR: δ 0.98, 1.19 (s, 3H each,

2 x C_5-CH_3), 1.92 (dt, 1H, J = 10.1, 12.5, 12.5, H-4), 2.11 (ddd, 1H, J = 2.6, 5.9, 12.5, H-4), 2.16 (s, 3H, $OCOCH_3$), 2.85 (ddd, 1H, J = 2.2, 5.9, 12.5, H-4a), 5.97 (d, 1H, J = 10.2, H-7), 6.17 (dd, 1H, J = 2.6, 10.1, H-3), 6.68 (d, 1H, J = 2.2, H-6), 7.52 (d, 1H, J = 2.2, H-1).

3-(4'-Methoxyphenyl)-5,5-dimethyl-3,4,4a,5-tetrahydro-8H-2-benzopyran-8-one (3c):

IR: ν_{max} 1660 cm^{-1} (conjugated >C=0) ; ^1H NMR: δ 0.98, 1.18, (s, 3H each, 2 x C_5-CH_3), 1.91 (dt, 1H, J = 11.4, 11.4, 13.5, H-4), 2.08 (ddd, 1H, J = 2.0, 5.9, 13.5, H-4), 2.89 (ddd, 1H, J = 2.0, 5.9, 11.4, H-4a), 3.82 (s, 3H, OCH_3), 4.97 (dd, 1H, J = 2.0, 11.4, H-3), 5.99 (d, 1H, J = 10.3, H-7), 6.68 (d, 1H, J = 10.3, H-6), 6.93 (d, 2H, J = 8.7, H-3', H-5'), 7.31 (d, 2H, J = 8.7, H-2', H-6'), 7.79 (d, 1H, J = 2.0, H-1).

^{13}C NMR: δ 186.36 (s, C-8), 159.54 (s, C-4'),158.58 (d, C-6), 154.57 (d, C-1), 127.94 (d, C-7), 131.96 (s, C-1'), 127.20 (d, C-2' and C-6'), 113.89 (d, C-3' and 5'), 112.35 (s, C-8a), 78.57 (d, C-3), 55.15 (q, OCH_3), 40.95 (d, C-4a), 35.17 (s, C-5), 31.18 (t, C-4), 26.57, 22.15 (q, 2 x C_5-CH_3).

3(3',4'-Dimethoxyphenyl)-5,5-dimethyl-3,4,4a,5-tetrahydro-8H-2-benzopyran-8-one (3d) :

IR: ν_{max} 1660 cm^{-1} (conjugated >C=0); ^{1}H NMR: δ 0.99, (s, 3H each, 2 x C_5-CH_3), 1.92 (dt, 1H, J = 11.5, 11.5, 13.5, H-4), 2.09 (ddd, 1H, J = 1.8, .5.7, 13.5, H-4), 2.89, (ddd, 1H, J = 1.8, 5.7, 11.5, H-4a), 3.89, 3.92 (s, 3H each, 2 x OCH_3), 4.94 (dd, 1H, J = 1.8, 11.5, H-3), 5.99, (d, 1H, J = 10.1, H-7), 6.68 (d, 1H, J = 10.1, H-6), 6.90 (m, 3H, H-5', H-6'), 7.79 (d, 1H, J = 1.8, H-1).

3-(3',4',5'-Trimethoxyphenyl)-5-5-dimethyl-3,4,4a,5-tetrahydro-8H-2-benzopyrane-8-one (3e):

IR: ν_{max} 1660 cm^{-1} (conjugated >C=0) ; ^{1}H NMR : δ0.99, 1.20 (s, 3H each, 2 x C_5-CH_3), 1.87 (dt, 1H, J = 11.5, 11.5, 13.5, H-4), 2.11 (ddd, 1H, J = 1.7, 5.9, 13.5, H-4), 2.90 (ddd, 1H, J = 1.9, 5.9, 11.5, H-4a), 3.85 (s, 3H, OCH_3), 3.90 (s, 6H, 2 x OMe), 4.89 (dd, 1H, J = 1.7, 11.5, H-3), 5.99 (d, 1H, J = 10.3, H-7), 6.58 (s, 2H, H-2', H-5'), 6.90 (d, 1H, J = 10.3, H-6); 7.78 (d, 1H, J = 1.9, H-1).

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10. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75.4 MHz respectively with Varian XL-300 in $CDCl_3$ using TMS as internal standard, J values are given in Hz. Mass spectra were recorded with Shimadzu GC

MS-QP 1000 spectrometer at 70 ev. IR spectra were recorded with a Perkin Elmer 681 spectrometer. The microanalysis was done on Carlo Erba Strumentazione 1106 elemental analyser.

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