Tetrahedron Letters,Vol.28,No.43,pp 5195-5198,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A ROUTE TO FUNCTIONALISED 1,5-DICARBONYL SYSTEMS VIA HETERODIENE CYCLOADDITIONS OF A 2-ACYL-2-ENOIC ACID

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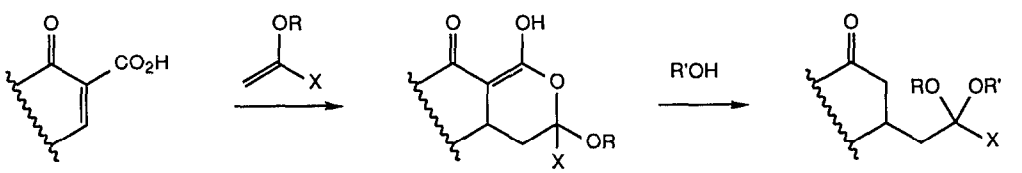
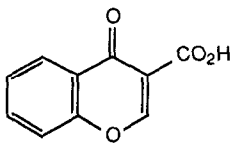
Summary: Chromone-3-carboxylic acid **1** undergoes heterodiene cycloadditions to alkoxyalkenes **2**, producing novel pyrans which on treatment with alkanols or water decompose into functionalised 1,5-dicarbonyl systems **6** - **11**, the sequence being potentially general for 2-acyl-2-enoic acids.

Recent results have shown that an electron-withdrawing group in the α-position of an α,β-unsaturated carbonyl compound significantly enhances its ability to function as a 4π (heterodiene) component in [4π + 2π] cycloadditions to electron-rich alkenes, and substrates incorporating this feature often react at room temperature or below with useful levels of stereoselection and tolerance to sensitive functionality.[1,2] We now report a new, potentially general application of this phenomenon in which the heterodiene is, somewhat unusually, an enoic acid, which undergoes the net decarboxylative conjugate addition shown in Scheme 1 to give functionalised 1,5-dicarbonyl systems. The sequence is notable for its ease of operation, both steps occurring without catalysis under mild and essentially neutral conditions, and is used here to prepare a variety of chroman-4-ones, which are useful in synthesis because of the widespread natural occurrence of biologically active chroman derivatives.[3]



SCHEME 1

The results of a series of heterodiene cycloadditions of chromone-3-carboxylic acid **1**[4] to alkoxyalkenes are summarised in Table 1. When treated at room temperature for 7 days with an excess of ethoxyethene **2a**, the acid **1** gave a mixture containing the formal *endo* and *exo* cycloadducts **3a** and **4a**. The mixture was readily analysed by 300 MHz ^{1}H n.m.r. spectroscopy, the spectra of the cycloadducts being almost identical to those of analogous systems obtained in similar fashion from 3-acylchromones.[2] Integration of diagnostic signals due to **3a** [δ 5.13 (4a-H)] and **4a** [δ 5.44 (3-H)] indicated that the *endo* isomer was predominant (ratio **3a**:**4a** *ca.* 3:1).[5]



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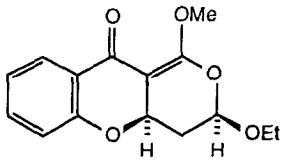

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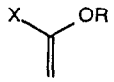

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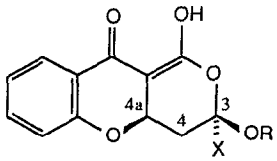

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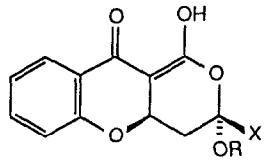

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	R	X
a	Et	H
b	Me	Me
c	Me	OMe

TABLE 1 FORMATION OF HETERODIENE CYCLOADDUCTS FROM THE ACID **1**

Dienophile	Time (days)	Products[6]	Ratio 3:4†	Yield of 3 (%)
2a	7	**3a** + **4a**	3:1	62
2b	3	**3b** + **4b**	4:1	69
2c	-‡	**3c**	-	95

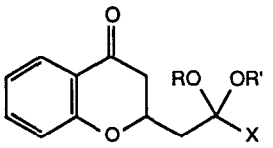
Procedure: A solution of the acid **1** in dichloromethane (4 ml/mmol) was stirred with the dienophile (20 equivalents) at room temperature until the starting material was no longer detectable by t.l.c. The volatiles were removed *in vacuo* and, after examination of the mixture by 300 MHz ^{1}H n.m.r. spectroscopy,[5] the major product was isolated by crystallisation.

† Approximate value, as determined by integration of the ^{1}H n.m.r. spectrum of the mixture.

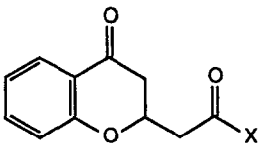
‡ Using 1.5 equivalents of the dienophile, the reaction was complete within 15 minutes at room temperature.

Crystallisation of the mixture gave the pure cycloadduct **3a**, which could be methylated with ethereal diazomethane to obtain the derivative **5**[6] in 95% yield. Cycloaddition of the acid **1** to 2-methoxypropene **2b** was somewhat faster, and produced a mixture of the adducts **3b** and **4b** from which the pure *endo* isomer **3b** was obtained by crystallisation. Reaction of the acid **1** with 1,1-dimethoxyethene **2c**[7] was rapid and exothermic, producing the unstable ortholactone **3c** within 15 minutes at room temperature.

The cycloadducts **3** underwent decarboxylation on treatment with alkanols or water (Table 2). Thus treatment of **3a** with ethanol resulted in the quantitative formation of the acetal **6**, while similar treatment with methanol gave the mixed acetal **7** as a pair of diastereoisomers (ratio *ca.* 9:1 by ^{1}H n.m.r. spectroscopy). Heating the cycloadduct **3a** in aqueous tetrahydrofuran gave the unstable aldehyde **8**. Similarly, treatment of the adduct **3b** with methanol or water furnished the ketal **9** or the dione **10** respectively. The cycloadduct **3c** was extremely labile, being transformed into the ester **11** (83%) on attempted chromatography over silica gel.



	R	X	R'
6	Et	H	Et
7	Et	H	Me
9	Me	Me	Me



	X
8	H
10	Me
11	OMe

TABLE 2 DECARBOXYLATION OF HETERODIENE CYCLOADDUCTS 3

Cycloadduct	R'OH	Product[6]	Isolated Yield (%)
3a	EtOH	6	100
3a	MeOH	7	100
3a	H_2O†	8	98
3b	MeOH	9	100
3b	H_2O†	10	92
3c	-‡	11	83

Procedure: A solution of the cycloadduct in the alkanol R'OH was heated under gentle reflux until the starting material was no longer detectable by t.l.c. The volatiles were removed *in vacuo* to obtain the product.

† The cycloadduct in THF - water (14:1) was heated under reflux for 16 h, and the product isolated as above.

‡ The cycloadduct was hydrolysed during flash chromatography over silica gel, eluting with dichloromethane.

The ability of chromone-3-carboxylic acid **1** to participate in heterodiene cycloadditions is presumably due to the favourable combination of its high electrophilicity with intramolecular hydrogen bonding between the carboxyl hydrogen and the chromone carbonyl group, which effectively locks the heterodiene unit into the s-*cis* configuration required for cycloaddition,[8] and the reaction may be general for 2-acylated and other 2-acceptor substituted enoic acids with a preference for the same arrangement. The susceptibility of the cycloadducts to alcoholysis is unsurprising in view of their acylal character, although the degree of diastereoselectivity in the formation of **7** is intriguing.[9] This and other aspects of the above chemistry are currently under investigation.

We thank the S.E.R.C. and Glaxo Group Research, Greenford, for a C.A.S.E. studentship.

REFERENCES

1 For examples, see M. Maier and R.R. Schmidt, *Justus Liebigs Ann. Chem.*, 1985, 2261; L.F. Tietze and E. Voss, *Tetrahedron Lett.*, 1986, **27**, 6181; and references cited therein.

2 S.T. Saengchantara and T.W. Wallace, *J. Chem. Soc., Perkin Trans. 1*, 1986, 789.

3 For reviews, see F.M. Dean, 'Naturally Occurring Oxygen Ring Compounds,' Butterworths, London, 1963; 'Chromenes, Chromanones and Chromones,' ed. G.P. Ellis, Wiley, New York, 1977; G.P. Ellis and I.M. Lockhart, 'Chromans and Tocopherols,' Wiley, New York, 1981; S.T. Saengchantara and T.W. Wallace, *Nat. Prod. Rep.*, 1986, **3**, 465.

4 P.J. Cremins, S.T. Saengchantara, and T.W. Wallace, *Tetrahedron*, 1987, **43**, 3075.

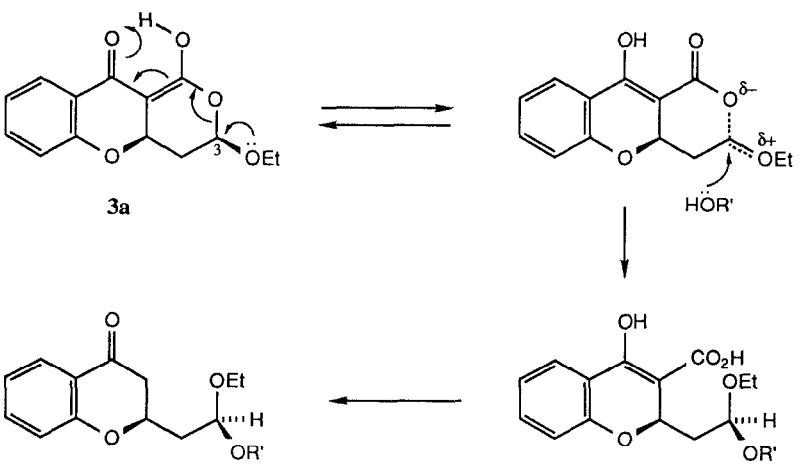
5 N.m.r. data (δ_H, 300 MHz, $CDCl_3$): **3a**, 2.28 (1 H, ddd, *J* 9.8, 10.8, 13.0 Hz, 4β-H), 2.63 (1 H, ddd, *J* 2.3, 5.7, 13.0 Hz, 4α-H), 5.13 (1 H, dd, *J* 5.7, 10.8 Hz, 4a-H), 5.28 (1 H, dd, *J* 2.3, 9.8 Hz, 3-H), 12.48 (1 H, s, OH); **4a**, 2.23 (1 H, ddd, *J* 2.4, 11.3, 13.0 Hz, 4β-H), 2.58 (1 H, ddd, *J* 2.4, 5.8, 13.0 Hz, 4α-H), 5.30 (1 H, dd, *J* 5.8, 11.3 Hz, 4a-H), 5.44 (1 H, t, *J* 2.4 Hz, 3-H), 12.50 (1 H, s, OH); **3b**, 2.42 (1 H, dd, *J* 7.0, 13.5 Hz, 4β-H), 2.46 (1 H, dd, *J* 8.7, 13.5 Hz, 4α-H), 3.43 (3 H, s, OMe), 5.08 (1 H, dd, *J* 7.0, 8.7 Hz, 4a-H), 12.46 (1 H, s, OH); **4b**, 2.12 (1 H, dd, *J* 11.1, 12.9 Hz, 4β-H), 2.59 (1 H, dd, *J* 5.9, 12.9 Hz, 4α-H), 3.32 (3 H, s, OMe), 5.21 (1 H, dd, *J* 5.9, 11.1 Hz, 4a-H), 12.52 (1 H, s, OH); **3c**, 2.33 (1 H, dd, *J* 10.9, 12.7 Hz, 4β-H), 2.7 (1 H, dd, *J* 6.0, 12.7 Hz, 4α-H), 3.35 (3 H, s, OMe), 3.47 (3 H, s, OMe), 5.11 (1 H, dd, *J* 6.0, 10.9 Hz, 4a-H), 12.35 (1 H, s, OH).

6 All new compounds gave satisfactory spectroscopic and microanalytical or high resolution m.s. data. Melting point °C (solvent): **3a**, 104 - 105 (ether - petroleum); **3b**, 96.5 - 97.5 (ether - petroleum); **3c**, 92 - 94 (ether - petroleum); **5**, 126 - 128 (ethyl acetate - petroleum 100 - 120 °C); **10**, 52 - 53 (ether - petroleum); **6**, **7**, **8**, **9**, and **11** are oils. 'Petroleum' refers to the fraction of b.p. 40 - 60 °C.

7 E.J. Corey, J.D. Bass, R. LeMahieu, and R.B. Mitra, *J. Am. Chem. Soc.*, 1964, **86**, 5570.

8 The degree of concertedness of these cycloadditions has not yet been established. The expectation that the *exo* (minor) isomer would be the thermodynamically more stable cycloadduct of each pair (due to the anomeric effect) has been confirmed *via* equilibration experiments.

9 A possible explanation is shown in Scheme 2. Polarisation of the 2,3-bond (arrows), which may be assisted *via* protonation of the carbonyl group by a second molecule of **3a**, leads to attack by the alcohol at C-3, producing a β-ketoacid which decarboxylates to generate the observed product. Assuming the implied preference for attack with inversion, the major product with methanol should be the isomer **7a**. When the attacking species is water the product is a hemiacetal **12**, which decomposes to the aldehyde **8**.



7a R' = Me
12 R' = H

SCHEME 2

(Received in UK 11 August 1987)