Research Article

Cycloaddition Reaction of Ethyl Thioacetate and the Dienamine Derived from Pummerer's Ketone

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The objective of this work is to study the regio- and stereochemistry of the cycloadducts obtained from the treatment of ethyl thioacetate and the dienamine derived from Pummerer's ketone.

1. Introduction

The use of Bunte salt (1), for example, the ethyl ester as precursors of thioaldehydes, for example, ethyl thioacetate, was described by the German chemist Hans Bunte [1, 2]. This early work employed symmetrical dienes as trapping agents, the one exception being thebaine.

Kirby and coworkers [3–8] reported the formation of ethyl thioacetate (3) from sulphonyl chloride (2) by elimination of hydrogen chloride with triethylamine. The thioaldehyde was trapped by a variety of 1,3-dienes such as 2,3-dimethylbutadiene (4), cyclohexadiene (5), anthracene (6a), 9,10-anthracene (6b), and thebaine (7). The cycloadducts of the corresponding dienes (8), (9), (10), and (11) were obtained in high yields, as it is shown in Scheme 1.

The major thebaine cycloadduct (11) was found to be unstable. When it was heated under reflux in toluene for 8 h, it was converted in high yield into the isomer (12) indicating that the cycloadduct (11) had been formed under kinetic control.

Y. Watanabe and T. Skakibara [9] treated 1,4-diacetoxy-1,3-butadiene (13) with ethyl thioacetate (3) derived in situ from thioglycolate [10], and obtained an inseparable mixture of threo- and erythro-isomers in 68% yield Scheme 2.

Recently, we reported [11] that treatment of the transient thioaldehyde (3) with unsymmetrical diene 1-methoxy-1,3-cyclohexadiene (15) gave the cycloadducts (16) and (17) in good yield in an endo : exo ratio of 4 : 1, Scheme 3.

The aim of the present study is to extend and explore the regiochemistry and stereochemistry of the reaction of ethyl thioacetate (3) with unsymmetrical diene, which is the dienamine (19) derived from Pummerer's ketone.

2. Results and Discussion

2.1. Cycloaddition Reaction of Ethyl Thioacetate and the Dienamine Derived from Pummerer's Ketone. With the aim of extending the study of thioacetate ester reactions with unsymmetrical conjugated dienes, a diene substituted in the 2-H position with an amino group was selected. The compound chosen was the dienamine (19) prepared [12] from the readily accessible enone, Pummerer's ketone (18) (Scheme 4).

The dienamine was formed as oil, from the ketone and pyrrolidine in methanol, as described in reference [12], and used immediately without purification. The Bunte salt (1) was treated with triethylamine in ethanol-benzene in the presence of 1 mol equivalent of the dienamine (19) and calcium chloride dihydrate for 3 days. Then the mixture was worked up under acidic conditions, which could be hydrolysed to the enamine (20) to give the cycloadduct (21) as a gum in 20% yield (Scheme 5). The yield of this product was increased to 40% by using 3 mol equivalents of the Bunte salt (1) for 4 days. Purification of the adduct (21) was carried on preparative silica t. l. c. plates.

TABLE 1: 200 MHz ^1H N.M.R spectrum of the cycloadduct (21).

Protons	δ P.P.m.	Coupling constants (Hz)
7	6.93	ddq, j8.2, 1.9 and 0.6
9	6.86	dP, j1,9 and 0.6
6	6.61	dm, j8.2 and <0.4
4a	4.86	dd, j4.0 and 0,7
OCH ₂ CH ₃	4.21	q, j7.2
de 11	4.11	dd, j2.9 and 1.3
4	3.35	d, j4.0
1	2.92	qd, j3.1 and 0.8
2 β	2.57	dd, j19.8 and 3.1
8-Me	2.26	S, with fine splitting
2 α	1.97	ddd, j19.8, 3.3 and 1.3
9b-CH ₃	1.63	S
OCH ₂ CH ₃	1.28	t, j7.2

TABLE 2: Nuclear overhauser difference NOE (CDCl₃; 200 MHz) of the cycloadduct (21).

Irradiated protons	δ	1-H	2B-H	2A-H	4-H	4a-H	6-H	7-H	8-Me	9-H	9b-Me	11-H	OCH ₂ CH ₃	OCH ₂ CH ₃
1-H	2.92	-74.75	2.06	1.62	0.09	0.17	0.14	0.53	0.03	4.54	1.47	4.78	0.64	0.45
2B-H	2.57	2.72	-56.59	21.16	0.26	0.26	0.32	0.23	0.31	0.67	-0.3	-0.03	0.24	0.13
2A-H	1.97	1.99	20.95	-62.44	0.26	-0.01	0.16	0.09	-0.71	-0.13	-0.15	0.29	0.51	0.29
4-H	3.35	-0.03	0.08	0.26	-65.22	6.1	0.08	0.07	0.07	0.08	-0.12	-0.06	0.17	0.12
4a-H	4.86	0.08	0.12	0.22	7.98	-83.16	0.2	0.12	0.36	0.06	2.71	0.06	0.56	0.09
8-Me	2.26	0.01	0.09	-0.52	0.09	0.38	0.21	7.02	-262.8	6.98	0.1	0.06	0.16	0.32
9b-Me	1.63	4.37	0.34	0.59	-0.43	11.28	0.57	0.31	0.8	4.68	-224.96	18.83	0.96	0.40
11-H	4.11	5.62	-0.24	0.30	0.36	0.91	0.07	-0.27	0.19	0.14	6.73	-76.67	-7.37	0.52
OCH ₂ CH ₃	4.21	0.40	0.17	0.35	0.13	0.26	0.09	0.22	0.30	0.05	0.57	-6.58	-150.13	4.98
OCH ₂ CH ₃	1.28	0.13	0.07	0.27	0.09	0.12	0.12	0.30	0.26	0.13	0.04	0.28	4.56	-232.28

SCHEME 1

The molecular formula of the cycloadduct (5) was identified by accurate mass measurement. The fragmentation patterns are discussed in (Table 3). The presence of the carbonyl groups was confirmed by i. r. spectroscopy; a strong band at $\bar{\nu}$ 1730 cm^{-1} was attributed to both carbonyl groups. The structure of the adduct (21), with the exception of stereochemistry, was assigned on the basis of the ^1H n.m.r. spectrum. The 90 MHz spectrum distinguishes between the 2 possible regioisomers (21) and (22) as shown in Scheme 6.

The 4a-H signal, δ 4.86 (d, j 4.0 Hz), is easily recognized by its low field position, similar to that of the corresponding signal, δ 4.65, in Pummerer's ketone (18), arising from deshielding by the inductive effect of oxygen. This allows identification of the signal for 4-H, δ 3.35 (d, j 4Hz), since no other signals have this splitting. The fact that this signal is a clean

doublet discounts structure (22), since 4-H would be coupled with 11-H. It was not possible to establish the stereochemistry (i.e., with of 4, racemic, diastereoisomers (21) is, assuming that the cis ring fusion of Pummerer's ketone is maintained) from the 90 MHz spectrum (Scheme 7).

However, the 200 MHz spectrum and the nuclear overhauser (n.o.e) studied (Tables 1 and 2) established the structure (21) unambiguously. The structure (21) can be distinguished from (21a) by the long-range "W" coupling, J 1.3 Hz, between H-11 and 2 α -H. This coupling would not be expected in the isomer (21a). Importantly, this is supported by n.o.e experiments. Thus, irradiation at δ 4.11 (11-H) increased the intensity of the singlet centered at δ 1.63 (9b-Me). Conversely, the doublet at δ 4.11 (11-H) increased in intensity when the methyl group, δ 1.63 was irradiated.

SCHEME 2

SCHEME 3

SCHEME 4

SCHEME 5

SCHEME 6

SCHEME 7

SCHEME 8

These observations establish the relative stereochemistry at the centers 11, 1, and 9b and also confirm the regiochemistry.

When the cycloadduct (21) was hydrolysed with 1.03 M sodium hydroxide in tetrahydrofuran at room temperature the acid (23) was obtained as a gum in 83% yield (Scheme 8).

The molecular formula, $C_{16}H_{16}O_4S$, was determined by accurate mass measurements as shown in Table 4. The i. r. spectrum showed a broad, strong band at $\bar{\nu}$ 1730 cm^{-1} , arising from the ketonic and carboxylic carbonyl groups. The 1H n.m.r. spectra of the ester (21) and the acid (23) were closely similar, apart from the replacement of ethoxyl signals by a broad hydroxyl signal, which disappeared upon exchange with deuterium oxide.

It was hoped that a crystalline product, suitable for combustion analysis, would be obtained. However, so far the acid (23) has resisted crystallization.

The formation of predominantly only one (21) of eight possible diastereoisomers requires comment. Vedejs et al. reported [13] a related cycloaddition reaction. They found that the thioaldehydes having electron-withdrawing groups (ZCHS; Z=CN, CO_2CH_3 , or $COCH_3$), generated from the phenacyl sulphides, could be trapped by 2-ethoxybutadiene to give Diels-Alder adducts. The compounds with sulphur attached to C (1) of the diene were found to be formed predominantly. This regiochemistry corresponds to that

observed in the reaction of thioacetate and the dienamine (19). The unusually high endo selectivity of the latter reaction could be due to the strong steric repulsion between the 9b-methyl and ester groups in the exo isomer. Finally, attack by the thioaldehyde on the dienamine (19) has occurred cis to the 9b-methyl group and 4a-hydrogen atom and trans to the larger 9b-aryl group and 4a-oxygen atom. The 200 MHz 1H n.m.r. spectrum showed weak signals that could represent another isomer, but otherwise the reaction was remarkably stereo- and region-selective.

3. Experimental

3.1. Preparation of 1-(4a,9b-Dihydro-8-9b-dimethyl-3-dibenzofuran-yl)Pyrrolidine (19). Following the steps developed in reference [12], pyrrolidine (0.85 mL) was added to a suspension of 4a,9b-dihydro-8,9b-dimethyl-dibenzo-furan-3(4H)-one, Pummerer's ketone (18) (0.5 g, 2.3 mmol) in methanol (12.5 mL), and the mixture was heated in a steam bath for 10 min. The resulting clear yellow solution was allowed to stand at room temperature for 1 h. After that, evaporated from the solution which resulted in a yellow syrupy residue which was redissolved in benzene and evaporated to dryness to yield the dienamine (19) (0.61 g, 98%) as a yellow syrupy. Found: m/z 267 (M, basepeak); ($\bar{\nu}$ $CHCl_3$) 1580 (weak band)

TABLE 3: Mass spectrum of Ethyl 1,2,3,4a,9b-hexahydro-8,9b-dimethyl-3-oxo-4,1-(epithiomethano)dibenzofuran-11-endo-carboxylate (21).

21				
Found	Calculated	% base peaks	Composition	Constitution
332,1079	332,1082	9,3	C ₁₈ H ₂₀ O ₄ S	M ⁺⁺
317,0842	317,0847	0,15	C ₁₇ H ₁₇ O ₄ S	M-CH ₃] ⁺
259,0796	259,0793	1,6	C ₁₅ H ₁₅ O ₂ S	M-C ₃ H ₅ O ₂] ⁺
257,0637	257,0637	0,7	C ₁₅ H ₁₃ O ₂ S	M-C ₃ H ₇ O ₂] ⁺
217,0679	217,0687	0,7	C ₁₃ H ₁₃ OS
159,0812	159,0810	100	C ₁₁ H ₁₁ O
146,0731	146,0732	7,7	C ₁₀ H ₁₀ O

and 1650 cm⁻¹ (strong band); δ (CDCl₃, 90 MHz) 1.36 (s, 9b-CH₃), 1.85 (m, 3'- and 4'-CH₂), 2.25 (s, 8-CH₃), 3.2 (m, 2'- and 5'-CH₂), 4.5–6.5 (bs, 4H), and 6.55–7.2 (m, aryl-H).

3.2. Preparation of the Cycloadduct 21 of Ethyl Thioxoacetate and 1-(4a,9b-Dihydro-8-9b-dimethyl-3-dibenzofuranyl) Pyrrolidine (19). The Bunte salt (3) (0.478 g, 2.05 mmol) and calcium chloride dihydrate (0.32 g, 2.05 mmol) were dissolved in ethanol (15 mL). Then dienamine (19) (0.457 g, 1.72 mmol) in benzene (15 mL) and triethyl-amine (0.218 g, 2.05 mmol) were added to the mixture of salts. The reaction mixture was stirred at room temperature for 3 days then was diluted with analar chloroform (40 mL) and water (30 mL). After that dilute (5%) hydrochloric acid was added until the calcium sulphite had dissolved and the mixture had become clear. The organic layer was washed successively with aqueous sodium hydrogen carbonate,

brine (10 mL), and water (20 mL), subsequently dried over (MgSO₄), and evaporated. The obtained residue (0.55 g) was chromatographed on a silica (HF₂₅₄) column. Elution with light petroleum-chloroform (1:1) gave a mixture (0.37 g) which was separated on silica t. l. c. plates developed several times with light petroleum-ether (7:3), to give ethyl 1,2,3,4a,9b-hexahydro-8,9b-dimethyl-3-oxo-4,1-(epithiomethano)dibenzofuran-11-endo-carboxylate (21) (100 mg, 18%). (Found: m/z 332.1079; C₁₈H₂₀O₄S requires M, 332.1077; $\bar{\mu}$ (CHCl₃) (strong band) 1730 cm⁻¹, δ (CDCl₃, 90 MHz) 1.28 (t, J7.0 Hz, OCH₂CH₃), 1.67 (s, 9b-CH₃) 2.26 (s, 8-CH₃), 1.97–2.57 (m, 2-CH₂), 2.92 (m, 1-H), 3.35 (d, J4.0 Hz, 4-H), 4.11 (m, 11-H), 4.21 (q, J7 Hz), 4.86 (d, J4.0 Hz, 4a-H), and 6.60–6.95 (m, 6-, 7-, and 9-H); δ (CDCl₃; 200 MHz) 1.28 (t, J7.2 Hz, OCH₂CH₃), 1.63 (s, 9b-CH₃), 1.97 (ddd, J19.8, 3, 3, and 1.3 Hz, 2 α -H), 2.26 (s with fine splitting, 8-CH₃), 2.57 (dd, J19.8 and 3.1 Hz, 2 β -H), 2.92 (qd, J3.1 and 0.8 Hz, 1-H), 3.35 (d, J4.0 Hz, 4-H), 4.11 (dd,

TABLE 4: Mass spectrum of 1,2,3,4a,9b-hexahydro-8,9b-dimethyl-3-oxo-4,1-(epithiomethano)dibenzofuran-11-endo-carboxylic acid (23).

23				
Found	Calculated	%	Composition	Constitution
304.0773	304.0769	7.6	C ₁₆ H ₁₆ O ₄ S	M ⁺⁺
215.0511	215.0521	0.7	C ₁₃ H ₁₁ OS	M-C ₃ H ₅ O ₃] ⁺⁺
214.0993	214.0994	2.1	C ₁₄ H ₁₄ O ₂
159.0809	159.0810	100	C ₁₁ H ₁₁ O
146.0727	146.0731	11.3	C ₁₀ H ₁₀ O

J2.9 and 1.3 Hz, 11-H), 4.21 (q, J7.2 Hz, OCH₂CH₃), 4.86 (dd, J4.0 and 0.7 Hz, 4a-H) 6.61 (dm, J8.2 and 0.4 Hz, 6-H), 6.86 (dp, J1.9 and 0.6 Hz, 9-H), and 6.93 (ddq, J8.2, 1.9 and 0.6 Hz, 7-H).

3.3. Preparation of the Cycloadduct Ketone 21 Using 3 mol Equivalents of the Bunte Salt. The Bunte salt (3) (0.743 g, 3.35 mmol) and calcium chloride dihydrate (0.493 g, 3.35 mmol) were dissolved in ethanol (15 mL). A mixture of the dienamine (19) (0.299 g, 1.12 mmol) and triethylamine (0.339 g, 3.35 mmol) was added to the salt mixture. The reaction mixture was stirred at room temperature for 4 days then was worked up and chromatographed as described before to give the ketone (21) (0.12 g, 33.4%). The ¹H n.m.r. spectrum was identical obtained by using 1 mol equivalent of the Bunte salt.

3.4. Hydrolysis of the Ester 21. 1.03 M sodium hydroxide (1 mL) was added to a solution of the ester (21) (40 mg, 0.12 mmol) in tetrahydrofuran (2 mL) and the mixture was stirred at room temperature overnight. After 24 h the solution

was concentrated with slight heating under reduced pressure. The resulting aqueous solution was concentrated, washed with ether (5 × 10 mL), then acidified with 5% hydrochloric acid (2 mL) and after extracted with ether (5 × 10 mL). The ethereal extracts were washed with brine (5 mL), dried (MgSO₄), and evaporated under reduced pressure with slight heating to give the acid (23) (30 mg, 83%) as an amorphous solid. (Found: m/z 304.0773; C₁₆H₁₆O₄S requires M, 304.0765); $\bar{\mu}$ (CHCl₃) 1730 cm⁻¹ (strong band); δ (CDCl₃, 90 MHz) 1.65 (s, 9b-CH₃), 2.26 (s, 8-CH₃), 1.80–2.90 (m, 2-CH₂), 2.95 (m, 1-H), 3.40 (d, J 4.0 Hz, 4-H), 4.19 (m, 11-H), 4.87 (d, J 4.0 Hz, 4a-H), 6.57–7.0 (m, 6-, 7- and 9-H), and 8.0 (bs, COOH).

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