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Ring opening of cyclobutabenzofuranones with TMSI: Facile formation of benzoxepinenones

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Abstract

Cyclobutabenzofuranones (**1–4**) undergo regioselective ring opening with TMSI to furnish the benzoxepinenones (**6–9**), respectively. The furanone (**5**), however, remained unaffected, suggesting the necessity of an additional stabilising group for the generated cationic intermediate for the reaction to proceed.

Key words: Cyclobutabenzofuranones, TMSI, benzoxepinenones.

1. Introduction

In recent years cyclobutanones have emerged as versatile synthetic intermediates on account of their ready accessibility and high reactivity[1]. In the case of electrophile-induced transformations, reaction with trimethylsilyliodide (TMSI) has proven[2] to be particularly useful, furnishing β-iodoketones through a regioselective ring opening. When the cyclobutanone is fused to another ring, this reaction provides an interesting ring homologation. In this paper, we report on the TMSI-induced ring opening of cyclobutabenzofuranones to lead to benzoxepinenones (Scheme 1). The cyclobutabenzofuranones (**1–5**) were investigated. We have earlier described the synthesis of the cyclobutabenzofuranones (**1–3**)[3,4]. The cyclobutabenzofuranones (**4–5**) were also similarly synthesized through intramolecular ketene–alkene cycloaddition of the corresponding *o*-styrylphenoxy acetic acids. Alkylation of 2-(2-hydroxyphenyl)propan-2-ol with ethyl α-bromoacetate in the presence of anhydrous potassium carbonate furnished the phenoxy ester (**11**) in good yield. This was subjected to dehydration using phosphorus oxychloride and the product hydrolysed to afford the desired *o*-styrylphenoxy acetic acid (**13**). Similarly, alkylation of 2-vinyl-5-methylphenol with ethyl α-bromopropionate followed by hydrolysis of the product furnished the *o*-styrylphenoxy acetic acid (**16**). These acids on heating with *p*-toluenesulfonyl chloride and triethylamine in benzene underwent intramolecular ketene–alkene cycloaddition to provide the cyclobutabenzofuranones (**4–5**), respectively, in good yields (Scheme 2 and 3).

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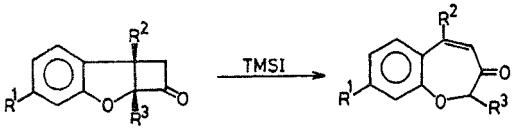
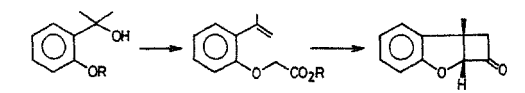


1 : $R^1=R^2=R^3=Me$
2 : $R^1=R^2=Me$, $R^3=H$
3 : $R^1=H$, $R^2=R^3=Me$
4 : $R^1=R^3=H$, $R^2=Me$
5 : $R^1=R^3=Me$, $R^2=H$

6 : $R^1=R^2=R^3=Me$
7 : $R^1=R^2=Me$, $R^3=H$
8 : $R^1=H$, $R^2=R^3=Me$
9 : $R^1=R^3=H$, $R^2=Me$

SCHEME 1.

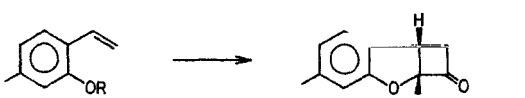


10 : R=H
11 : $R=CH_2CO_2Et$

12 : R=Et
13 : R=H

4

SCHEME 2.



14 : R=H
15 : $R=CH(Me)CO_2Et$
16 : $R=CH(Me)CO_2H$

5

SCHEME 3.

We had previously demonstrated[3] the application of cyclobutabenzofuranone (**1**) in a synthesis of marine sesquiterpenes and further explored[4] the chemistry of (**1–3**) in aphotochemical ring expansion. In our continuing programme towards exploring the utility of these cyclobutanones in synthesis, it was felt appropriate to investigate the strong electrophile TMSI-induced transformation of these. In the event, interaction of (**1**) with an *in situ*-generated TMSI in carbon tetrachloride in the presence of mercury as catalyst furnished the benzoxepinenone (**6**) in 60% yield as the only isolated product after chromatography. The structure was arrived at from spectral data and additionally confirmed from comparison with an authentic sample[5]. Interestingly, no trace of any iodoketone was observed. Similarly, the cyclobutabenzofuranones (**2–4**) also afforded the corresponding benzoxepinenones (**7–9**), respectively, in

yields ranging between 40 and 50%. The observed regioselectivity of ring opening of these cyclobutabenzofuranones is in keeping with the observations of Miller[2] but different from that encountered in the acid-catalysed ring opening of a cyclobutaindenone[6]. In contrast to (**1**–**4**), the cyclobutabenzofuranone (**5**) was recovered unchanged under the reaction conditions. It would seem that the presence of a methyl group to provide additional stability to the generated cationic intermediate prior to proton elimination is necessary for the reaction to proceed. A similar requirement of a methyl group for a facile intramolecular acylation in the starting *o*-styrylphenoxy acetic acids had previously been encountered[5].

2. Experimental

2.1. General

All the compounds described herein possessing asymmetric carbons are racemates. All reactions were carried out under N_2. Melting points and boiling points are uncorrected and melting points were taken in an open capillary in a sulfuric acid bath. Solvents and reagents were reagent-grade materials and were further purified by conventional methods. Petroleum refers to the fraction of bp 60–80°C and light petroleum refers to the fraction of bp 40–60°C. The purity of the products was routinely checked by TLC. Preparative TLC was performed with silica gel $60H_{254}$ (E. Merck) plates of 1-mm thickness. Na_2SO_4 was used to dry organic extracts.

The IR spectra are for $CHCl_3$ solutions. ^1H NMR spectra were recorded at 60 MHz in CCl_4 solutions, unless otherwise stated. Peak positions are indicated in ppm downfield from internal TMS in δ units.

2.2. cis 2a,7b-Dihydro-7b-methylcyclobuta[b]benzofuran-2(1H)-one (**4**)

A mixture of 2-(2-hydroxyphenyl)propan-2-ol (**10**) (prepared in 90% yield from addition of CH_3MgI to 2-hydroxyacetophenone) (2.27 g, 14.9 mmol), ethyl α-bromoacetate (2.4 g, 14.9 mmol), anhydrous potassium carbonate (2.06 g, 14.9 mmol) and a pinch of potassium iodide in dry acetone (60 ml) was heated under reflux with stirring for 12 h. It was then concentrated to one third of the volume, diluted with water and extracted with ether. The combined ethereal layer was washed with cold aqueous sodium hydroxide solution (1.25 N) and water, dried and concentrated. The residue was passed down a column of silica gel and eluted with petroleum to afford the alkylated product (**11**) (2.69 g, 76%).

^1H NMR δ 1.25(t, J=6 Hz, 3H), 1.51(s, 6H), 4.21(q, J=6 Hz, 2H), 4.51(s, 2H), 6.95(m, 4H). This was subjected to dehydration without further purification.

To a cooled (0°C) and stirred solution of the above alkylated product (2.9 g) in dry pyridine (10 ml), phosphorus oxychloride (1.2 ml) was added and stirring continued at room temperature for 24 h. The reaction mixture was then diluted with cold water and extracted with ether. The ethereal extract was washed with water and dried. Removal of ether furnished an oil which showed expected spectral feature. ^1H NMR δ 1.21(t, J=6 Hz, 3H), 2.12(s, 3H), 4.14(q, J=6 Hz, 2H), 4.49(s, 2H), 5.63(br s, 2H), 6.85(m, 4H) and was directly hydrolysed.

A mixture of the above ester (**12**) (1.07 g) in methanol (10 ml) and aqueous potassium hydroxide solution (5 ml, 5N) was stirred at room temperature for 24 h. It was then diluted with water, acidified with cold dilute hydrochloric acid (6N) and extracted with ether. The combined ethereal layer was washed with saturated brine and water, dried and concentrated to afford the desired acid (**13**) as a crystalline solid (860 mg, 92%). Crystallised from ether–light petroleum, mp 95–96°C. ^{1}H NMR ($CDCl_3$): δ 2.19(s, 3H), 4.72(s, 2H), 5.19(m, 2H), 7.12(m, 4H), 7.59(br s, 1H). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.73; H, 6.29; Found: C, 68.35; H, 6.24.

Intramolecular ketene alkene cycloaddition of the above acid (760 mg) *via* the reported[3] procedure furnished the cyclobutabenzofuranone (**4**) as an oil (560 mg, 81%), bp 86–88°C (0.2 mm Hg). IR 1785 cm^{-1}. ^{1}H NMR δ 1.63(s, 3H), 2.21(m, 2H), 5.21(m, 1H), 7.03(m, 4H). Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79; Found: C, 76.17; H, 5.85.

2.3. cis 2a,7b-Dihydro-2a,5-dimethylcyclobuta[b]benzofuran-2-(1H)-one(**5**)

Alkylation of 2-vinyl-5-methylphenol (1.8 g) with ethyl-α-bromo-propionate (2.42 g) in acetone in the presence of anhydrous potassium carbonate as for (**10**) furnished the alkylated ester (**15**) (2.27 g, 75%). ^{1}H NMR δ 1.23(t, J=6 Hz, 3H), 1.61(d, J=6 Hz, 3H), 2.29(s, 3H), 4.18(q, J=6 Hz, 2H), 4.69(q, J=6 Hz, 1H), 5.17(dd, A of ABX, J_{AX}=10 Hz, 1H), 5.62(dd, B of ABX, J_{BX}=18 Hz, 1H), 6.53(br s, 1H), 6.72(d, J=7 Hz, 1H), 7.08(m, X of ABX, J_{AB}=2 Hz, 1H), 7.36(d, J=8 Hz, 1H).

Without further purification this was hydrolysed as for (**12**) to afford the desired acid (**16**) in 70% yield as a crystalline solid, crystallised from ether–light petroleum mp 114–116°C. ^{1}H NMR ($CDCl_3$) δ 1.68(d, J=6 Hz, 3H), 2.32(s, 3H), 4.82(q, J=6 Hz, 1H), 5.19(dd, A of ABX, J_{AX}=10 Hz), 5.66(dd, B of ABX, J_{BX}=18 Hz), 6.62(br s, 1H), 6.84(d, J=8 Hz, 1H), 7.08(m, X of ABX, J_{AB}=2 Hz, 1H), 7.42(d, J=8 Hz, 1H), 8.23(br, 1H). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.9; H, 6.79; Found: C, 69.52; H, 6.49.

Intramolecular ketene–alkene cycloaddition of the above acid (**16**) as before afforded the cyclobutabenzofuranone (**5**) in 87% yield as a crystalline solid after chromatography over silica gel. Crystallised from light petroleum mp 74–75°C. IR 1785 cm^{-1}. ^{1}H NMR: δ 1.54(s, 3H), 2.27(s, 3H), 3.0–3.8(m, 3H), 6.54(br s, 1H), 6.63(s, 1H), 7.02(d, J=8 Hz, 1H). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43; Found: C, 76.78; H, 6.53.

2.4. General procedure for the reaction of cyclobutabenzofuranones with TMSI as illustrated for (1)

To a stirred solution of (**1**) (100 mg, 0.5 mmol) in carbon tetrachloride (4 ml), mercury (90 mg, 4 mmol) and anhydrous sodium iodide (240 mg, 1.6 mmol) were added followed by freshly distilled trimethylsilyl chloride (140 mg, 1.3 mmol) dropwise. The reaction mixture was stirred at room temperature for 1 h and then heated to reflux slowly for 6 h, cooled to room temperature and stirred overnight. It was then poured into aqueous sodium thiosulfate solution and extracted with ether. The

combined ethereal extract was washed with water, dried and concentrated. The residual oil was subjected to preparative TLC using 2% ethylacetate in petroleum. This afforded (**6**) as an oil (60 mg, 60%), identical (IR, ^{1}H NMR) with an authentic sample[5].

Similarly, cyclobutabenzofuranone (**2**) furnished the benzoxepinenone (**7**) in 50% yield bp 85–90°C (0.1 mm Hg). IR 1655 cm^{-1}. ^{1}H NMR: δ 2.33(br s, 6H), 4.33(s, 2H), 6.21(br s, 1H), 7.04(m, 3H). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.50; H, 6.43; Found: C, 76.88; H, 6.27.

Cyclobutabenzofuranone (**3**) gave rise to the benzoxepinenone (**8**) in 50% yield, identical with sample reported earlier[5]. Cyclobutabenzofuranone (**4**) afforded the benzoxepinenone (**9**) in 40% yield. bp 96–98°C (0.4 mm Hg). IR 1655 cm^{-1} ^{1}H NMR: δ 2.36(br s, 3H), 4.39(s, 2H), 6.33(s, 1H), 7.31(m, 4H). Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79; Found: C, 75.93; H, 5.60.

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