Synthesis of 3-Aryl-1,4-benzoxathianes: Application to the Preparation of a Sweet Compound

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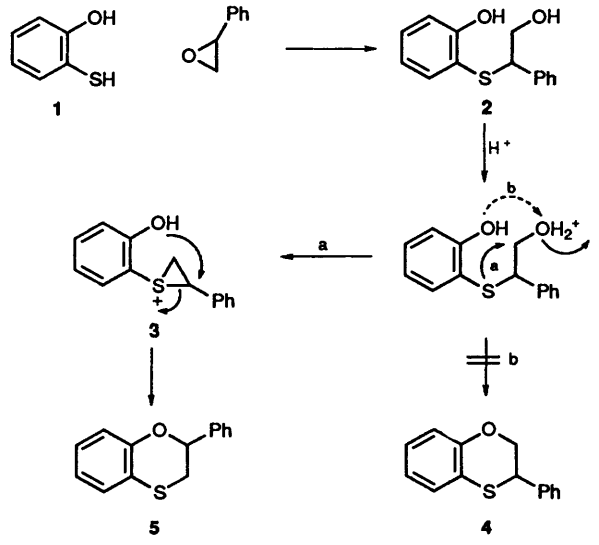
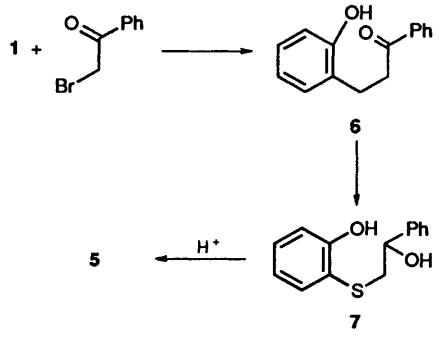
Attempts to prepare 3-phenyl-1,4-benzoxathiane by acid-catalysed ring-closure of 2-(2-hydroxyphenylthio)-2-phenylethanol gave instead 2-phenyl-1,4-benzoxathiane, *via* a rearrangement probably involving an episulfonium ion. The first synthesis of 3-aryl-1,4-benzoxathianes was obtained by *N*-bromosuccinimide-promoted oxidative rearrangement of 1,3-oxathiolanes derived from cyclohexanone. The application of this route to the synthesis of 3-(3-hydroxy-4-methoxyphenyl)-1,4-benzoxathiane, a compound *ca.* 2000 times as sweet as sucrose, is reported.

A large number of organic compounds containing the 3-hydroxy-4-methoxyphenyl (isovanillyl) moiety taste sweet.[1] Among those, the most interesting ones are bicyclic heterocycles, *e.g.* dihydroisocoumarins, 1,3- and 1,4-benzodioxanes, with the isovanillyl ring as a substituent of the heterocyclic ring.[2] Recent work from this laboratory[3] has shown that substitution of sulfur for oxygen in the ring which contains the hetero atom increases or, at least, maintains the sweetness potency. In order to complete a study of structure–taste relationship, we needed to measure the sweetness potency of 3-(3-hydroxy-4-methoxyphenyl)-1,4-benzoxathiane **11**. Perusal of the literature indicated that no 3-aryl-1,4-benzoxathiane has been prepared so far. At first, a simple way of preparing the required compound **11** appeared to be by an extension of a synthetic procedure already used for the synthesis of the corresponding 1,4-benzodioxanes.[4] The preparation of the model compound 3-phenyl-1,4-benzoxathiane **4** was, therefore, undertaken accordingly (see Scheme 1). The reaction of 2-



Scheme 1

mercaptophenol **1** with styrene epoxide in the presence of a base catalyst gave the expected sulfide **2** *via* the attack of the nucleophilic thiol at the more reactive benzylic carbon, as already reported for other cases.[5] The assignment of structure **2** was established by ^{1}H NMR analysis, the spectral data reported[5] being compared for both isomers derived from thiophenol. However, ring closure with an acid ion exchanger as a catalyst unexpectedly afforded 2-phenyl-1,4-benzoxathiane **5** rather than **4**. The structure **5** is supported by the ^{1}H NMR spectrum of the product, in particular by the highfield chemical shift of 2-H. However, in order to further confirm the structural assignment, **5** was obtained by an independent synthesis (Scheme 2). Alkylation of **1** with bromoacetophenone, followed

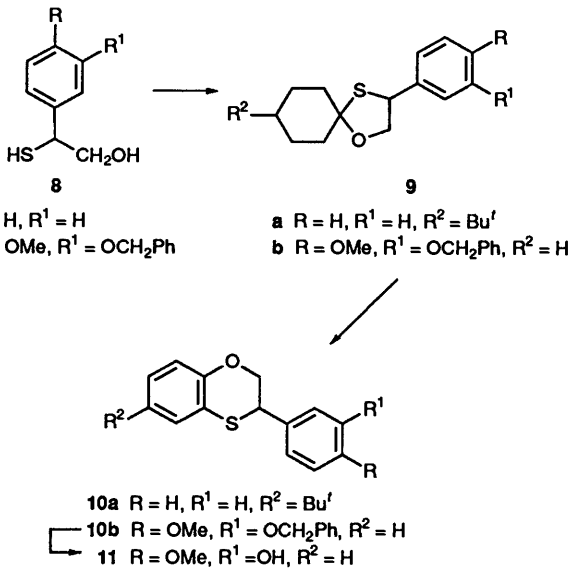


Scheme 2

by $NaBH_4$ reduction to diol **7** and acid-catalyzed ring closure of the latter provided **5** (9% overall yield). That compound **5** was obtained instead of **4** in the former sequence of reactions may be tentatively explained in terms of the formation of an intermediate episulfonium ion **3** (Scheme 1). Such a hypothesis is supported by examples of very similar processes reported in the literature.[5,6]

In order to overcome the difficulty, we envisaged that 3-aryl-1,4-benzoxathianes could be obtained by the oxidative rearrangement of cyclohexanone-derived 1,3-oxathiolanes. In fact, 1,4-benzodithianes and 1,4-benzothiazines have been obtained in good yield by some of us by rearrangement of cyclohexanone 1,3-thiolanes[7] or 1,3-azathiolanes,[8] respectively.

The feasibility of this type of synthesis was tested on the oxathiolane **9a** obtained from 4-*tert*-butylcyclohexanone and 2-mercapto-2-phenylethanol **8a** (Scheme 3). The latter was prepared[9] by $LiAlH_4$ reduction of the xanthate ester, obtained in turn, from 2-bromophenylacetic acid and potassium *O*-ethyl xanthate. The oxidative rearrangement was successfully performed by using *N*-bromosuccinimide rather than bromine, which minimized the formation of brominated products. As



Scheme 3

expected, the reaction led in good yield, to a 4:1 mixture of 6-*tert*-butyl-3-phenyl-1,4-benzoxathiane **10a** and of a derivative of **10a** with a bromine atom in the aromatic ring. However, treatment of the crude mixture with BuLi in tetrahydrofuran (THF), as already described for the benzodithiane series,[7] gave complete reductive dehalogenation, so that the yield of **10a** reached 68%. These results represent the first synthesis of a 3-aryl-1,4-benzoxathiane.

The application of the same synthetic scheme to target compound **11** required, however, some modifications because of the presence of the OH group on the aromatic ring. The appropriate mercaptoethanol **8b** was obtained from 3-hydroxy-4-methoxymandelic acid by a sequence involving selective esterification, benzylation of the phenolic OH, and thiolation *via* a Mitsunobu reaction with Ph_3P/diethyl azodicarboxylate (DEAD)/zinc dimethyldithiocarbamate (Ziram),[10] followed by $LiAlH_4$ reduction. The oxathiolane **9b** was obtained in almost quantitative yield, and the oxidative rearrangement, followed by BuLi treatment of the crude product, afforded the protected 1,4-benzoxathiane **10b** in 45% yield. After unsuccessful attempts at the deprotection of benzylic groups by catalytic hydrogenation, selective cleavage of the benzyloxy *vs.* the methoxy group was achieved with $SnCl_4$,[11] and provided **11** in 41% yield. The failure of hydrogenation may be due to the presence of sulfur in **9**.

Compound **11** was tasted in comparison with 3% (w/v) aqueous sucrose as reported in a previous paper.[2c] Since a 15 mg dm^{-3} solution of **11** gave the same sweet sensation as a standard solution, it can be considered approximately 2000 times as sweet as sucrose. It is at least 3 times as sweet as the corresponding 2-isovanillyl isomer,[2] thus confirming the observation that replacement of oxygen by sulfur in the sequence Aryl-X-CH-isovanillyl (where X = O or S) generally leads to an improvement in the sweetness potency.

The results reported here extend the scope of the oxidative rearrangement of cyclohexanone 1,3-dihetero ketals, which provides a simple method of synthesis of some benzoheterocycles.

Experimental

M.p.s are uncorrected. NMR spectra were recorded on a Bruker WP80 instrument at 80 MHz in $CDCl_3$ using tetramethylsilane as internal standard and are expressed in δ (p.p.m.). *J* Values are given in Hz. Mass spectra were recorded on a Finnigan TSQ70 spectrometer equipped with an ICIS data system.

Flash column chromatography was performed on silica gel 60 (Merck, 0.040–0.063 nm). Tetrahydrofuran (THF) and diethyl ether were distilled from sodium–benzophenone immediately before use.

2-(2-*Hydroxyphenylthio*)-2-*phenylethanol* **2**.—A stirred solution of 2-mercaptophenol **1** (0.1 g, 0.79 mmol) and potassium carbonate (0.109 g, 0.79 mmol) in water (0.8 cm^3) was treated under nitrogen with styrene epoxide (0.09 cm^3, 0.79 mmol) for 2 h at room temperature. The mixture was then treated with dil. HCl and extracted with ethyl acetate. The extract was dried and evaporated to provide a residue which was chromatographed with hexane–ethyl acetate (7:3) as eluent to give **2** as an oil (0.15 g, 77%); δ_H 3.9–4.2 (2 H, AB of ABX, CH_2), 3.9–4.1 (1 H, X of ABX, CH) and 1.55 (2 H, OH); *m/z* (%) 246 (28), 215 (10), 126 (18), 103 (100), 91 (75) and 77 (38).

2-(2-*Hydroxyphenylthio*)-1-*phenylethanone* **6**.—A suspension of NaH (80% in paraffin oil; 0.237 g, 7.93 mmol) in dry toluene (10 cm^3) was treated with **1** (1 g, 7.93 mmol) and refluxed 15 min. After addition of α-bromoacetophenone (1.58 g, 7.93 mmol), the mixture was refluxed for 15 h under nitrogen and then cooled, acidified with dil. HCl and extracted with ethyl acetate. The extract was washed with satd. aqueous $NaHCO_3$, dried and evaporated to provide a residue which was chromatographed with hexane–ethyl acetate (8:3) as eluent to give **6** as an oil (0.3 g, 16%); δ_H 4.2 (2 H, s, CH_2), 1.55 (1 H, OH) and 6.8–8.0 (9 H, ArH).

2-(2-*Hydroxyphenylthio*)-1-*phenylethanol* **7**.—A solution of compound **6** (0.11 g, 0.45 mmol) in dry ethanol (15 cm^3) was treated with $NaBH_4$ (0.017 g, 0.45 mmol) and the mixture stirred for 30 min. The mixture was then evaporated and the residue taken up in water and the solution treated with 0.1 mol dm^{-3} HCl. The mixture was extracted with ethyl acetate and the extract evaporated to give a quantitative yield of **7**; δ_H 2.9–3.1 (2 H, AB of ABX, CH_2), 4.6–4.8 (1 H, X of ABX, CH), 1.55 (1 H, OH) and 6.7–7.6 (9 H, ArH); *m/z* (%) 246 (6), 228 (8), 140 (100), 125 (11), 107 (33) and 97 (15).

2-*Phenyl*-2,3-*dihydro*-1,4-*benzoxathiine* **5**.—(a) A solution of compound **2** (0.06 g, 0.24 mmol) in dry toluene (5 cm^3) was stirred with Amberlyst 15 (15 mg) for 4 h. After this it was filtered, dried and concentrated to give **5** as an oil (30 mg); δ_H 2.9–3.5 (2 H, AB of ABX, CH_2), 5.1–5.3 (1 H, X of ABX, CH) and 6.8–7.6 (9 H, ArH); *m/z* (%) 228 (68), 195 (15), 167 (29), 137 (62), 104 (100), 96 (88) and 77 (49).

(b) Compound **7** (0.08 g, 0.33 mmol) in dry toluene (5 cm^3) was heated for 3 h at 60 °C in the presence of Amberlyst 15 (44 mg) and then filtered and chromatographed through a short column to give **5** (0.04 g, 54%), identical with the compound obtained by procedure (a).

8-tert-*Butyl*-3-*phenyl*-1-*oxa*-4-*thiaspiro*[4.5]*decane* **9a**.—To a magnetically stirred solution of 4-*tert*-butylcyclohexanone (0.50 g, 3.24 mmol) and toluene-*p*-sulfonic acid monohydrate (0.2 g, 1.03 mmol) in acetic acid (2 cm^3) at room temperature, was added 2-mercapto-2-phenylethanol **8a** (0.5 g, 3.24 mmol) dissolved in the same solvent (1.5 cm^3). After 1.5 h the mixture was washed with 10% aq. sodium hydrogen carbonate and extracted with diethyl ether. The extract was washed with water until neutral, dried and evaporated. Chromatography (benzene) of the residue afforded a mixture of diastereoisomeric spirooxathiolanes **9a** (0.7 g, 74% yield) (Found: C, 74.5; H, 9.1. $C_{18}H_{26}OS$ requires C, 74.43; H, 9.02); δ_H 0.85 (9 H, s, Bu^t), 1.1–2.4 (9 H, m), 4.0 (1 H, m, CH-S), 4.1 (1 H, m, CH-O), 4.6 (1 H, m,

CHO), 7.15–7.35 (3 H, m, ArH) and 7.4 (2 H, d, *J* 8.3, ArH); *m/z* 290.

8-tert-*Butyl*-3-*phenyl*-2,3-*dihydro*-1,4-*benzoxathiine* **10a**.—To a solution of **9a** (0.70 g, 2.41 mmol) in anhydrous $CHCl_3$ (70 cm^3) was added *N*-bromosuccinimide (1.28 g, 7.23 mmol). After 30 min the mixture was washed with 10% aq. sodium hydrogen carbonate and then with water until neutral. The organic layer, after being dried and evaporated, gave a 4:1 (GC/MS) mixture (0.68 g) of **10a** and of a brominated derivative. The mixture was directly treated with BuLi (1.6 mol dm^{-3} solution in THF; 0.3 cm^3) under N_2 at −78 °C. After 2 h the reaction mixture was treated with saturated aq. NH_4Cl and extracted with ethyl ether. The extract was washed with water until neutral, dried (Na_2SO_4) and evaporated under reduced pressure to give pure **10a** (0.63 g, 68% yield) (Found: C, 76.1; H, 7.0. $C_{18}H_{20}OS$ requires C, 76.01; H, 7.09); δ_H 1.31 (9 H, s, Bu^t), 4.22 (1 H, m, CH-S), 4.53 (2 H, m, CH_2O), 6.89 (1 H, d, *J* 8.3, ArH), 7.08–7.14 (2 H, m, ArH) and 7.37–7.48 (5 H, m, ArH); *m/z* 284.

Methyl 3-*Benzyloxy*-4-*methoxymandelate*.—A solution of methyl 3-hydroxy-4-methoxymandelate (2.96 g, 14 mmol) in butan-2-one (20 cm^3) was treated with K_2CO_3 (2.31 g, 16.7 mmol), benzyl bromide (1.67 cm^3, 14 mmol) and KI (116 mg, 0.7 mmol) and the mixture then refluxed for 3 h. The mixture was then filtered and evaporated and the residue chromatographed with hexane–ethyl acetate (1:1) to afford the title compound (3.16 g, 75%); m.p. 100 °C; δ_H 3.28 (1 H, d, *J* 6, OH), 3.70 (3 H, s, $ArOCH_3$), 3.90 (3 H, s, CO_2CH_3), 5.08 (1 H, d, *J* 6, C*H*OH), 5.15 (2 H, s, $ArCH_2$), 6.8–7.1 (3 H, ArH) and 7.2–7.5 (5 H, Ph).

2-(3-*Benzyloxy*-4-*methoxyphenyl*)-2-*mercaptoethanol* **8b**.—Diethyl azodicarboxylate (DEAD; 3.23 cm^3) was added to a solution of methyl 3-benzyloxy-4-methoxymandelate (3.14 g, 10.4 mmol), triphenylphosphine (5.45 g, 20.8 mmol), and zinc dimethyldithiocarbamate (Ziram) (1.59 g, 5.2 mmol) in toluene (30 cm^3). The mixture was kept under nitrogen at 0 °C for 4 h after which it was evaporated and the residue chromatographed with hexane–ethyl acetate (7:3), to give an inseparable mixture (4.16 g) of Ziram and methyl 2-(3-benzyloxy-4-methoxyphenyl)-2-dimethylthiocarbamoylthioacetate. An analytical sample obtained by preparative TLC has δ_H 3.5 (6 H, br s, 2 × NCH_3), 3.75 (3 H, s, CO_2CH_3), 3.9 (3 H, s, OCH_3), 5.18 (2 H, s, OCH_2Ph), 5.68 (1 H, s, CHS), 6.8–7.1 (3 H, m, ArH) and 7.2–7.5 (5 H, m, Ph); *m/z* (%) 405 (6), 285 (100), 257 (3), 225 (4), 193 (8), 165 (7), 151 (2) and 91 (27). The crude compound was dissolved in dry THF (15 cm^3) and added dropwise to a solution of $LiAlH_4$ in THF (1 mol dm^{-3}; 14.8 cm^3). After 90 min the mixture was quenched with ethyl acetate (3 cm^3) and treated with 6 mol dm^{-3} HCl until it reached pH 2. The precipitate was filtered off and the filtrate concentrated and extracted with dichloromethane. The extract was washed with brine, dried and evaporated and the residue chromatographed with hexane–ethyl acetate as eluent to give **8b** (1.58 g, 55%), m.p. 52 °C; δ_H 3.6–4.1 (3 H, m), 3.81 (3 H, s, OCH_3), 5.13 (2 H, s, $ArCH_2$), 6.8–6.9 (3 H, ArH) and 7.1–7.5 (5 H, Ph); *m/z* (%) 290 (83), 259 (29), 257 (26), 166 (39), 137 (32) and 91 (100).

3-(3-*Benzyloxy*-4-*methoxyphenyl*)-1-*oxa*-4-*thiaspiro*[4.5]-*decane* **9b**.—To a solution of **8b** (1.38 g, 4.76 mmol) in toluene (60 cm^3) were added cyclohexanone (0.49 cm^3) and toluene-*p*-sulfonic acid (72 mg, 0.38 mmol). The mixture was refluxed 2 h in a Soxhlet apparatus containing 4 Å molecular sieves, cooled and treated with aq. $NaHCO_3$. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined organic phase and extracts were dried and evaporated and the residue was recrystallized from cyclohexane to afford **9b** (1.66 g, 94%), m.p. 75 °C (Found: C, 71.0; H, 7.1. $C_{22}H_{26}O_3S$ requires C, 71.32; H, 7.07); δ_H 1.4–2.1 (10 H), 3.85 (3 H, *s*, OCH_3), 3.95 (1 H, dd, CHS), 4.30 (1 H, dd, CHO), 4.53 (1 H, *t*, CHO), 5.17 (2 H, s, $ArCH_2$), 6.78 (1 H, d, *J* 8, 5′-H), 6.89 (1 H, dd, *J* 8 and 2, 6′-H), 7.01 (1 H, d, *J* 2, 2′-H) and 7.2–7.5 (5 H, m, Ph); *m/z* (%) 370 (84), 272 (21), 181 (38), 165 (7), 153 (16), 121 (8) and 91 (100).

3-(3-*Benzyloxy*-4-*methoxyphenyl*)-2,3-*dihydro*-1,4-*benzoxathiine* **10b**.—*N*-Bromosuccinimide (2.14 g, 12 mmol) was added to a solution of **9b** (1.48 g, 4 mmol) in $CHCl_3$ (150 cm^3) previously eluted through neutral alumina. The mixture was stirred for 40 min under nitrogen and then extracted with 20% aq. $NaHCO_3$. The organic phase was washed with water, dried and evaporated. The residue was chromatographed with hexane–ethyl acetate (85:15) as eluent to give an oil (0.5 g) which, by GC/MS, appeared to be a mixture of **10b** (76%) and of a monobromo derivative (24%). The brominated compound has *m/z* (%) 444 (23), 442 (20), 353 (9), 272 (3) and 91 (100). This mixture was dissolved in dry THF (6 cm^3) and a solution of butyllithium in hexane (2.5 mol dm^{-3}; 0.14 cm^3) was added to it under nitrogen. Further portions of the BuLi solution were added (total 2.5 cm^3 in 5 h) to the mixture until GC monitoring indicated that the amount of the bromo derivative was reduced to < 5%. Satd. aq. NH_4Cl (4 cm^3) was added to the mixture which after evaporation and dilution with water was extracted with ethyl acetate. Work-up gave **10b** (0.4 g, 27%), m.p. 91 °C (Found: C, 72.1; H, 5.6. $C_{22}H_{20}O_3S$ requires C, 72.50; H, 5.53); δ_H 3.87 (3 H, s, OCH_3), 4.1–4.6 (3 H, ABX, $ArCHCH_2$), 5.15 (2 H, s, $ArCH_2$), 6.8–7.2 (3 H, ArH) and 7.2–7.5 (5 H, m, Ph); *m/z* (%) 364 (100), 273 (27), 227 (12) and 137 (24).

3-(3-*Hydroxy*-4-*methoxyphenyl*)-2,3-*dihydro*-1,4-*benzoxathiine* **11**.—A solution of **10b** (0.22 g, 0.6 mmol) in dry dichloromethane (15 cm^3) was treated under nitrogen with $SnCl_4$ (70 mm^3). After 20 h the mixture was poured into ice and treated with satd. aq. $NaHCO_3$ (3 cm^3). The organic phase was separated, dried and evaporated. Chromatography of the residue with hexane–ethyl acetate (7:3) as eluent gave **11** (67 mg, 41%), m.p. 82 °C (Found: C, 66.0; H, 5.2. $C_{15}H_{14}O_3S$ requires C, 65.67; H, 5.14); δ_H 3.90 (3 H, s, OCH_3), 4.2–4.6 (3 H, ABX, $ArCHCH_2$) and 6.8–7.2 (3 H, ArH); *m/z* (%) 274 (77), 241 (14), 150 (57), 137 (100) and 135 (42).

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