Improved Procedure for the Preparation of 3,4-Dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ones

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Treatment of 2,2-dimethyl-2*H*-1-benzopyrans **5** with a *m*-chloroperoxybenzoic acid-trifluoroacetic acid mixture and subsequent short path bulb to bulb vacuum distillation of the crude 3,4-hydroxyesters **6** formed afforded title compounds in good yields. Suppression of trifluoroacetic acid was required when using 2,2-dimethyl-2*H*-1-benzopyrans with electron donating substituents such as precocenes, as starting compounds.

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Introduction.

In the context of our ongoing research on the chemistry and insect antijuvenile hormone activities of precocenes and related compounds [1-3], we became interested in the study of 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ones **1**. These compounds can be envisaged as tautomers of 3-hydroxyprecocenes, although it has been pointed out that the keto-enol equilibrium is mainly shifted to the side of the carbonyl form [4].

A preliminary literature search revealed a paucity of synthetic methods for preparation of these benzopyran-3-ones. Bubel and Tischenko [5] described the preparation of 4-methyl substituted analogues, in moderate yields, by condensation of phenols with mesityl oxide in the presence of boron trifluoride, followed by cyclization of the intermediate 2-hydroxyaldehyde by treatment with polyphosphoric acid.

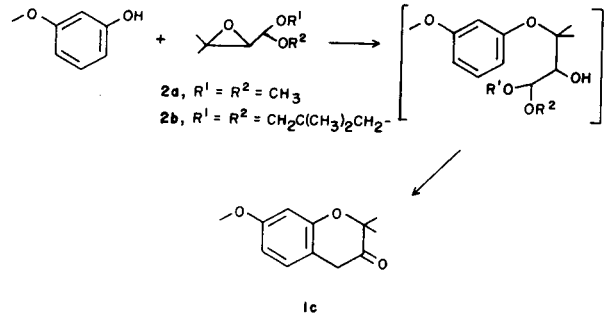
On the other hand, dehydration of 3,4-dihydro-3,4-dihydroxy-2*H*-1-benzopyrans by reaction with copper sulfate at 200° [6] or, alternatively, with *p*-toluenesulphonic acid in boiling benzene, at very short reaction times to avoid the dimer formation, has been reported to give moderate yields of 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-one (**1a**) and its 7-methoxy derivative **1c** [7]. Finally, Anastasis and Brown [7] have also described an essentially equivalent synthesis of the unsubstituted parent compound by treatment of the corresponding epoxide with a catalytic quantity of boron trifluoride etherate in dry benzene.

In the present communication, we summarize our efforts to develop a simple method for general application in the preparation of different types of 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ones **1** required as models in our studies on insect antijuvenile hormone activity relationships.

Results and Discussion.

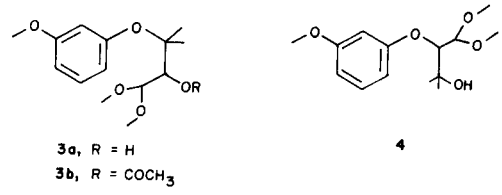
As depicted in Figure 1, the first approach that we attempted was patterned according to the procedure of the above Russian authors, by reacting 3-methoxyphenol with

Figure 1



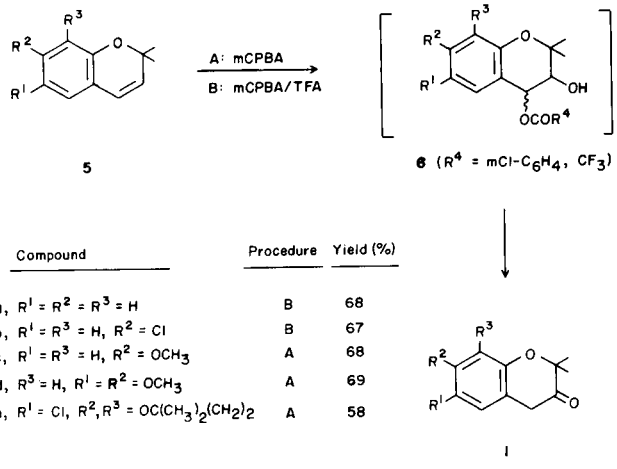
an appropriate synthon, such as an acetal of epoxyaldehyde **2**, in the presence of acid catalysts. It was anticipated that the putative secondary alcohol intermediate might be further cyclized to the desired benzopyran-3-one **1c** under these reaction conditions. However, all our attempts in this direction failed to give any conclusive results.

Figure 2



Conversely, when sodium 3-methoxyphenolate was reacted with **2a** in hexamethylphosphoramide at 150° [8], a low yield (12%) of a 2:1 isomeric mixture of alcohols **3a** and **4** was isolated (Figure 2). This mixture could not be resolved by the usual chromatographic procedures, but its selective acetylation to secondary acetate **3b** was achieved by treatment with acetic anhydride in pyridine. Effective cyclization of **3a**, though, was not observed by treatment with a variety of acid catalysts. The above results were not improved when **2a** was replaced by a more stable acetal such as **2b**.

Figure 3



5

6 (R^4 = mCl-C_6H_4, CF_3)

Compound	Procedure	Yield (%)
Ia, $R^1 = R^2 = R^3 = H$	B	68
Ib, $R^1 = R^3 = H$, $R^2 = Cl$	B	67
Ic, $R^1 = R^3 = H$, $R^2 = OCH_3$	A	68
Id, $R^3 = H$, $R^1 = R^2 = OCH_3$	A	69
Ie, $R^1 = Cl$, $R^2, R^3 = OC(CH_3)_2(CH_2)_2$	A	58

1

An alternative procedure was suggested by previous observations from this and other laboratories in the direct epoxidation of activated 2*H*-1-benzopyrans, such as natural precocenes, by treatment with *m*-chloroperoxybenzoic acid. Under these conditions, formation of *cis* and *trans* mixtures of hydroxyester derivatives was nearly quantitative [9,10].

It was anticipated that heating these ester mixtures in the presence of *m*-chlorobenzoic acid, originated *in situ* from ester cleavage, might lead to the formation of benzopyran-3-ones **1**. In fact this proved to be the case. As shown in Figure 3, good yields of benzopyran-3-ones **1c-e** were obtained when crude mixtures of hydroxyesters **6c-e**, prepared by treatment of the corresponding 2*H*-1-benzopyrans **5** with *m*-chloroperoxybenzoic acid, were subjected to short path bulb to bulb distillation at 0.1-0.2 torr.

However, this procedure promoted extensive decomposition of the intermediate hydroxyesters with concomitant formation of the corresponding benzoypran-3-ones in very low yields (10%), when applied to 2*H*-1-benzopyrans **5a,b** without electron donating substituents at C-7. This failure was attributed to dissimilarities in the reactivity at C-4 of both types of compounds, induced by the presence or absence of activating groups at C-7. These differences in reactivity at that site are important in facilitating the departure of the ester group in the thermal elimination process.

Finally, this drawback was overcome by addition of trifluoroacetic acid in the epoxidation reaction. The presence of this acid promotes formation of hydroxytrifluoroacetates that are better leaving groups than the corresponding *m*-chlorobenzoates, making possible also in this case the preparation of benzopyran-3-ones in good yields (*cf.* Figure 3), when the distillation was carried out at 19-20 torr to counterbalance the higher volatility of fluorinated esters. It is worthy of note that this modified procedure led to extensive polymerization and decreased yields of benzopyran-3-ones when applied to 2*H*-1-benzopyrans **5c-e**, as anticipated from the easy dimerization in the treatment of these benzopyrans with strong acids.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus and are uncorrected. The ir spectra were obtained with a Perkin Elmer 399B instrument. The ^1H nmr spectra were recorded on a Bruker WP 80 SY spectrometer operating at 80.13 MHz in the Fourier transform mode; all chemical shifts are given in ppm downfield from internal tetramethylsilane for solutions in deuteriochloroform at normal temperature probe (32°). Gas chromatography-mass spectra were determined on a Hewlett-Packard 5995 B instrument, using a 25 m OV-101 capillary column. Elemental analyses were performed with a 1106 Carlo Erba instrument.

2-Acetoxy-3-(3-methoxy)phenoxy-3-methylbutanal Dimethyl Acetal (**3b**) and 3-Hydroxy-2-(2-methoxy)phenoxy-3-methylbutanal Dimethyl Acetal (**4**).

3-Methoxyphenol (0.139 g, 1.1 mmoles) was added under dry nitrogen atmosphere and vigorous stirring to a suspension of sodium hydride (0.024 g, 1 mmole) in hexamethylphosphoramide (10 ml). When gaseous evolution had ceased, epoxyacetal **2a** [11] (0.144 g, 1 mmole) was added and the mixture was stirred at 150° until glc monitoring revealed the disappearance of **2a** (20 hours). The crude reaction mixture was allowed to cool, diluted with water (10 ml) and extracted with benzene (3 × 30 ml). The combined organic extracts were washed with water, brine and dried over magnesium sulphate. The residue obtained after solvent removal was purified by flash column chromatography [12] (silica gel; hexane:ethyl acetate/2:1), affording 0.052 g (12% overall yield) of a mixture of alcohols **3a** and **4** (2:1 isomeric ratio), which could not be further separated by conventional chromatographic means.

A solution of this mixture (0.010 g, 0.04 mmole) in pyridine (3 ml), was treated with acetic anhydride (1 ml) and the crude reaction mixture was stirred 4 hours at room temperature until completion (glc monitoring). The residue obtained after removal of volatile components was purified by preparative tlc (silica gel; hexane:ethyl acetate/6:1) to afford pure acetate **3b** (0.006 g, R_f 0.25) and pure alcohol **4** (0.004 g, R_f 0.12).

Compound **3b**.

This compound had ir (carbon tetrachloride): 2995, 2940, 2830, 1745, 1600, 1485, 1235, 1145, 965 and 695 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.30 (s, 6H, CH_3), 2.15 (s, 3H, CH_3CO), 3.40 (s, 3H, CH_3O), 3.51 (s, 3H, CH_3O), 3.78 (s, 3H, CH_3O), 4.67 (d, 1H, J = 5 Hz, H-1), 5.14 (d, 1H, J = 5 Hz, H-2) and 6.40-7.30 (4H, ArH); ms: 165 (M^+-147, 9), 75 (100).

Anal. Calcd. for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.40; H, 7.49.

Compound **4**.

This compound had ir (carbon tetrachloride): 3540, 3500-3150 (br), 2930, 2830, 1600, 1490, 1380, 1200, 1150, 1080, 1050 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.31 (s, 6H, CH_3), 3.38 (s, 3H, CH_3O), 3.49 (s, 3H, CH_3O), 3.78 (s, 3H, CH_3O), 4.10 (d, 1H, J = 8 Hz, H-2), 4.50 (d, 1H, J = 8 Hz, H-1) and 6.40-7.30 (4H, ArH); ms: 270 (M^+ < 2), 75 (100).

Anal. Calcd. for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.05; H, 8.23.

2*H*-1-Benzopyrans **5a-d** [13] were prepared by using reported procedures: for **5a** and **5b** [14], and for **5c** and **5d** [15].

9,10-Dihydro-6-chloro-2,2,8,8-tetramethyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*']dipyran (**5e**).

This compound was prepared from 4-chlororesorcinol in 45% overall yield by using a procedure developed in this laboratory [2]. Compound **5e** had mp 77-79°; ir (carbon tetrachloride): 3030, 2990, 2940, 1640, 1610, 1470, 1435, 1205, 1160, 1125 and 890 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.34 (s, 6H, CH_3), 1.41 (s, 6H, CH_3), 1.78 (t, 2H, J = 7.2 Hz, CH_2), 2.68 (t, 2H, J = 7.2 Hz, CH_2), 5.48 (d, 1H, J = 10 Hz, CH=), 6.22 (d, 1H,

J = 10 Hz, CH=) and 6.87 (s, 1H, ArH); ms: 294 (M^+, 18), 279 (100).

Anal. Calcd. for $C_{16}H_{19}ClO_3$: C, 68.95; H, 6.87; Cl, 12.72. Found: C, 68.69; H, 7.05; Cl, 12.60.

3,4-Dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ones (**1**). Procedure A.

m-Chloroperoxybenzoic acid (2 mmoles) was added to a solution of the corresponding 2*H*-1-benzopyran **5c-e** (1 mmole) in chloroform (15 ml) and the mixture was stirred for 10 minutes at room temperature (tlc monitoring). Then the crude reaction mixture was washed with a 1:1/10% sodium sulphite:saturated sodium bicarbonate solution, water, brine and dried over magnesium sulphate. The crude mixture of *cis* and *trans*-hydroxyesters **6** obtained after solvent removal was subjected to a careful vacuum (0.1-0.2 torr) bulb to bulb distillation to afford a distillate which contained a mixture of *m*-chlorobenzoic acid and the expected benzopyran-3-one **1c-e**. The distillate was diluted with diethyl ether (25 ml) and the solution was washed with saturated sodium carbonate solution, brine and dried over magnesium sulphate. The residue obtained after solvent removal was purified by filtration through a short silica gel column, eluting with hexane:diethyl ether/8:1, to yield pure ketone **1c-e**.

Procedure B.

m-Chloroperoxybenzoic acid (2 mmoles) and trifluoroacetic acid (1.5 mmoles) were added to a solution of the corresponding 2*H*-1-benzopyran **5a,b** (1 mmole) in chloroform. Then the crude reaction mixture was subjected to the same procedure above described with the exception that bulb to bulb distillation was carried out under a pressure of 19-20 torr.

3,4-Dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-one (**1a**).

Starting from 2*H*-1-benzopyran **5a**, this compound was isolated in 68% yield (Procedure B), mp 34-35°; ir (carbon tetrachloride): 3025, 1980, 1730, 1590, 1490, 1460, 1380, 1360, 1260, 1235, 1170, 1145 and 960 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.40 (s, 6H, CH_3), 3.59 (s, 2H, CH_2) and 6.90-7.40 (4H, ArH).

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 74.98; H, 6.86. Found; C, 75.19; H, 6.97.

3,4-Dihydro-7-chloro-2,2-dimethyl-2*H*-1-benzopyran-3-one (**1b**).

Starting from 2*H*-1-benzopyran **5b**, this compound was isolated in 67% yield (Procedure B), mp 36-38°; ir (carbon tetrachloride): 2980, 1730, 1605, 1580, 1485, 1415, 1380, 1360, 1240, 1170, 1075, 970 and 875 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.40 (s, 6H, CH_3), 3.55 (s, 2H, CH_2) and 7.01 (s, 3H, ArH).

Anal. Calcd. for $C_{11}H_{11}ClO_2$: C, 63.02; H, 5.29; Cl, 16.43. Found; C, 63.14; H, 5.48; Cl, 16.48.

3,4-Dihydro-7-methoxy-2,2-dimethyl-2*H*-1-benzopyran-3-one (**1c**).

Starting from precocene I (**5c**), this compound was isolated as an oil in 68% yield (Procedure A); ir (carbon tetrachloride): 2980, 2840, 1730, 1620, 1590, 1505, 1445, 1380, 1360, 1205, 1260, 1010, 985 and 840 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.41 (s, 6H, CH_3), 3.53 (s, 2H, CH_2), 3.78 (s, 3H, CH_3O), 6.56 (d, 1H, J = 2.3 Hz, H-8), 6.60 (dd, 1H, J_1 = 8 Hz, J_2 = 2.3 Hz, H-6) and 6.98 (d, 1H, J = 8 Hz, H-5).

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found; C, 69.81; H, 6.88.

3,4-Dihydro-6,7-dimethoxy-2,2-dimethyl-2*H*-1-benzopyran-3-one (**1d**).

Starting from precocene II (**5d**), this compound was isolated as an oil in 69% yield (Procedure A); ir (carbon tetrachloride): 2940, 2830, 1725, 1615, 1510, 1450, 1380, 1360, 1230, 1200, 1125, 1010 and 950 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.42 (s, 6H, CH_3), 3.53 (s, 2H, CH_2), 3.86 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O) and 6.58 (s, 2H, ArH).

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found; C, 66.22; H, 7.07.

3,4,9,10-Tetrahydro-6-chloro-2,2,8,8-tetramethyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*']dipyran-3-one (**1e**).

Starting from benzodipyran **5e**, this compound was isolated in 58% yield (Procedure A), mp 145°; ir (carbon tetrachloride): 2980, 2940, 1730, 1615, 1585, 1465, 1385, 1380, 1215, 1160, 1125 and 920 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.37 (s, 6H, CH_3), 1.40 (s, 6H, CH_3), 1.81 (t, 2H, J = 6.7 Hz, CH_2), 2.72 (t, 2H, J = 6.7 Hz, CH_2), 3.48 (s, 2H, CH_2CO) and 6.93 (s, 1H, ArH).

Anal. Calcd. for $C_{16}H_{19}ClO_3$: C, 65.42; H, 6.52; Cl, 11.73. Found; C, 65.54; H, 6.59; Cl, 11.83.

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