Tetrahedron Vol. 48, No. 35, pp. 7265-7274, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

A Convenient Preparation of Symmetrical and Unsymmetrical 1,2-Diketones: Application to Fluorinated Phenytoin Synthesis

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(*Received in UK* 26 *June* 1992)

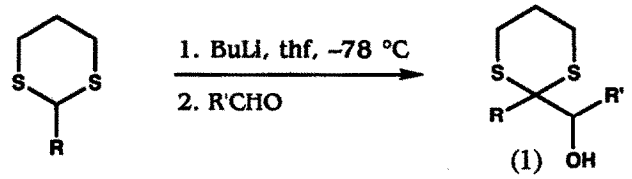
Abstract: 1,2-Diketones are efficiently produced in two steps by reaction of aldehydes with anions derived from 2-substituted dithianes followed by treatment of the resulting alcohols with NBS in aqueous acetone; phenytoin derivatives were prepared from these diketones by a standard method involving treatment with urea and potassium hydroxide under reflux.

In connection with our investigations into the effects of fluorination on drug metabolism we wished to synthesize from simple readily available starting materials a series of fluorinated aromatic 1,2-diketones as precursors to fluorinated derivatives of phenytoin useful for the study of metabolism-dependent toxicity.[1] Over the last twenty years a number of methods of synthesis of both aromatic and aliphatic 1,2-diketones has appeared in the literature.[2] These methods commonly fall into one of two categories: the oxidative insertion of the carbonyl group or groups; and the generation and acylation of a masked acyl anion equivalent. The more recent approaches include the use of an ethanediamide as a 1,2-diketo synthon,[3] the acylation of acyllithium reagents[4] and of anions derived from α-silyloxy alkyl phosphonates,[5] and *via* double insertion of isocyanides into alkyl halides.[6] However, many of the available methods are unattractive due either to limited generality, experimental difficulties, or limited availability of necessary starting materials.

Masked acyl anions form one of the most important groups of synthons for organic synthesis and have been the subject of much research. One of the most effective synthons for an acyl anion equivalent so far discovered is the 1,3-dithiane grouping first introduced by Corey. 1,3-Dithianes have proved to be of great synthetic utility due to ease of handling and wide applicability; indeed, 1,2-diketones have been produced from acyl dithianes by hydrolysis, and α-hydroxyketones have been prepared by treatment of the anions with aldehydes followed by mercury (II) hydrolysis.[7] This procedure was successful for benzoin in our hands, but is unsatisfactory for acyl dithiane substrates. This approach to diketone synthesis has the advantage that in the case of the unsymmetrical 1,2-diketone series no crossed product can be obtained, a problem often associated with the classical benzoin condensation. However, limitations do exist with these methods; for example, double addition of the nucleophile has been reported as a source of byproducts unless a large excess of the ester is used,[8] and deprotonation of ester rather than nucleophilic addition may also occur. Yields may also be limited by product deprotonation.[8,9] We reasoned that use of aldehydic electrophiles should resolve these

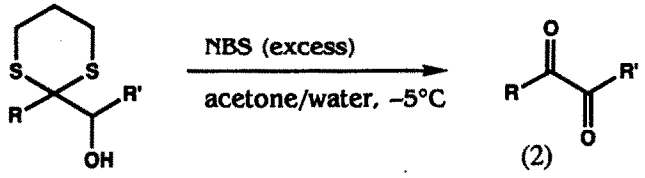
problems provided that a suitably efficient oxidation/hydrolysis pathway to 1,2-diketones could be found.

The commercially available 2-phenyl-1,3-dithiane was chosen as a convenient building block from which a series of unsymmetrically substituted diketones could be produced. Generation of the lithiated species from 2-phenyl-1,3-dithiane was easily accomplished by deprotonation with butyl lithium; condensation of the anion with the various monofluorobenzaldehydes gave the corresponding alcohols (1) in excellent yields. Similarly, a series of symmetrically substituted alcohols was produced by deprotonation of a range of fluorophenyl-1,3-dithianes and condensation of these anions with the matching fluorobenzaldehydes (Scheme 1, Table 1).



Scheme 1

We had initially envisaged that, following oxidation of these alcohols to the corresponding ketones, the dithiane group could be hydrolyzed to give the diketones. However, this two-step process proved unnecessary. Our previous experience of acyl dithiane chemistry[10] had taught us that hydrolysis of the 1,3-dithiane group in these molecules is particularly facile using *N*-bromosuccinimide in aqueous acetone,[7] a reagent also known to oxidize secondary alcohols.[11] We were pleased to find that under appropriate conditions a separate oxidation step was not required, the alcohols being rapidly and completely oxidized with concomitant hydrolysis to furnish the diketones in pleasing isolated yields (Scheme 2, Table 1).



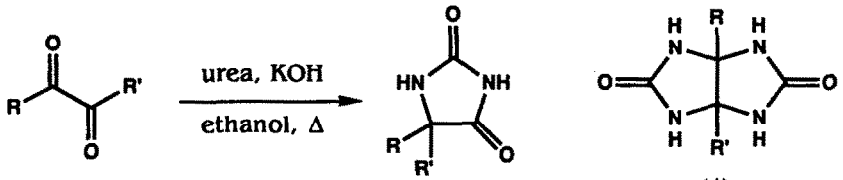
Scheme 2

Table 1. Preparation of 1,2-Diketones

Dithiane	Aldehyde	Alcohol(1)/%	Diketone(2)/%
2-Phenyl	Benzaldehyde	93	71
2-Phenyl	2-Fluorobenzaldehyde	67	68
2-Phenyl	3-Fluorobenzaldehyde	84	72
2-Phenyl	4-Fluorobenzaldehyde	75	87
2-(2-Fluorophenyl)	2-Fluorobenzaldehyde	76	74
2-(3-Fluorophenyl)	3-Fluorobenzaldehyde	60	82
2-(4-Fluorophenyl)	4-Fluorobenzaldehyde	89	85
2-Phenyl	Propionaldehyde	85	85
2-Phenyl	Butyraldehyde	59	54

To assess the general utility of this scheme, several alkyl aldehydes were also used as electrophiles. We found that the intermediate alcohols produced in this way did indeed undergo one-pot oxidation and hydrolysis to furnish the desired diketones (Table 1). Since many substituted benzaldehydes and alkyl aldehydes are readily available, this simple procedure is applicable the synthesis of a wide range of 1,2-diketones.

Conversion of the diketones into substituted phenytoin derivatives (3) was carried out by the standard benzilic acid rearrangement method,[12] involving treatment with urea and potassium hydroxide under reflux in ethanolic solution (Scheme 3, Table 2). Good yields of the desired products were obtained. In most cases a small quantity of the expected glycoluril byproduct (4) was also observed, and was minimized by using a ratio of benzil to urea close to 1:1. It has been reported that the glycoluril species is the exclusive product of the reaction between benzil and urea under acidic conditions.[13]



(3) (4)

Scheme 3

Table 2. Preparation of Phenytoin Derivatives

Diketone substituents		Yield/%
Phenyl	Phenyl	66
Phenyl	2-Fluorophenyl	58
Phenyl	3-Fluorophenyl	70
Phenyl	4-Fluorophenyl	54
2-Fluorophenyl	2-Fluorophenyl	49
3-Fluorophenyl	3-Fluorophenyl	70
4-Fluorophenyl	4-Fluorophenyl	83

The three unsymmetrical derivatives appear to be the first examples of unsymmetrical phenytoin analogues prepared by the benzilic acid rearrangement,[14] perhaps due to a lack of appropriate methods for synthesis of the necessary diketone intermediates. The method described herein should provide a suitable alternative.

EXPERIMENTAL SECTION

General experimental details

Petroleum ether (b.p. 40-60 °C and b.p. 60-80 °C) was distilled prior to use. Dichloromethane was dried by distillation from calcium hydride. Tetrahydrofuran was dried by distillation from the sodium–benzophenone ketyl radical.

Commercially available reagents were used as supplied unless otherwise stated. Commercial solutions of n-butyl lithium were stored at –20 °C; the reagent was dispensed by syringe under argon and standardized by the method of Gilman. Reactions requiring

rigorously anhydrous conditions were carried out in glassware which had been dried for several hours at 150-200 °C. Reactions were maintained in an atmosphere of argon or nitrogen and reagents and solvents introduced *via* syringe or using cannula techniques, through a septum cap.

Flash column chromatography was carried out on Merck 9385 Kieselgel 60 (230-400 mesh), using hand bellows or an air-line to apply pressure to the column. Thin layer chromatography was carried out on glass- or aluminium-backed plates coated with a 0.25 mm layer of silica gel 60H containing fluorescer; compounds were visualized by u.v. irradiation or by spraying with ethanolic dodecamolybdophosphoric acid or aqueous potassium permanganate followed by charring where appropriate.

Infrared spectra were recorded in the range 4000–600 cm^{-1} using a Perkin Elmer 883 spectrophotometer and were calibrated against the 1602 cm^{-1} absorption of polystyrene. Solid samples were run as Nujol mulls or in solution, and liquids as thin films. ^1H Nuclear magnetic resonance spectra were recorded using Bruker AC200 (200 MHz) or AMX400 (400 MHz) spectrometers. All spectra were recorded using deuteriochloroform solutions and tetramethylsilane as internal standard. Mass spectra were recorded on VG Micromass 7070E or VG Tritech TS250 instruments.

Melting points were determined on a Kofler Hotbench apparatus. Microanalyses were carried out by the Department of Chemistry microanalytical service.

2-Phenyl-1,3-dithiane

Hydrogen chloride gas was bubbled through a solution of benzaldehyde (6.24 g, 59 mmol) and 1,3-propanedithiol (6.5 g, 60 mmol) in dichloromethane (100 ml) at 4 °C until the solution became saturated (approx 5 mins). Stirring was continued at 4 °C for 1 hour before allowing the reaction to warm to 25 °C. The solution was washed successively with water (2 x 50 ml), 10% aqueous potassium hydroxide (3 x 50 ml) and water (2 x 50 ml). The dichloromethane solution was dried ($MgSO_4$) and evaporated to yield an off-white solid; one recrystallization from methanol gave 2-phenyl-1,3-dithiane as a white crystalline solid (8.43 g, 73%), m.p. 67-68 °C; δ_H(200 MHz, $CDCl_3$) 1.8-2.0 (1H, m), 2.05-2.2 (1H, m), 2.8-3.1 (4H, m), 5.1 (1H, s), 7.25-7.35 (3H, m) and 7.5-7.6 (2H, m); *m/z* (EI) 196 (M^+).

2-(2-Fluorophenyl)-1,3-dithiane

A mixture of 1,3-propanedithiol (3.63 g, 3.40 ml, 33 mmol) and 2-fluorobenzaldehyde (4.09 g, 2.85 ml, 33 mmol) in dichloromethane (100 ml), treated as above, gave 2-(2-fluorophenyl)-1,3-dithiane (5.40 g, 77%) as an off-white solid, m.p. 74-75 °C (Found: C, 55.90; H, 5.16. $C_{10}H_{11}S_2F$ requires C, 56.04; H, 5.17%); δ_H(200 MHz, $CDCl_3$) 1.8-2.0 (1H, m), 2.05-2.2 (1H, m), 2.8-3.1 (4H, m), 5.1 (1H, s), 7.0-7.4 (3H, m) and 7.6 (1H, t, *J* 6 Hz); *m/z* (EI) 214 (M^+).

2-(3-Fluorophenyl)-1,3-dithiane

A mixture of 1,3-propanedithiol (5.13 g, 4.80 ml, 47.5 mmol) and 3-fluorobenzaldehyde (5.88 g, 3.95 ml, 47.5 mmol) in dichloromethane (100ml), treated as above, gave 2-(3-fluorophenyl)-1,3-dithiane (8.55 g, 84%) as an oily solid; δ_H(200 MHz, $CDCl_3$) 1.8-2.05 (1H, m), 2.1-2.3 (1H, m), 2.9-3.15 (4H, m), 5.2 (1H, s), 6.9-7.0 (1H, m) and 7.2-7.4 (3H, m); *m/z* (EI) 214 (M^+).

2-(4-Fluorophenyl)-1,3-dithiane

A mixture of 1,3-propanedithiol (4.81 g, 4.50 ml, 44.5 mmol) and 4-fluorobenzaldehyde (5.57 g, 3.90 ml, 44.5 mmol) in dichloromethane (100ml), treated as above, gave 2-(4-fluorophenyl)-1,3-dithiane (7.20 g, 76%) as a white solid, m.p. 106-108

°C (Found: C, 55.83; H, 5.15. $C_{10}H_{11}S_2F$ requires C, 56.04; H, 5.17%); δ_H(200 MHz, $CDCl_3$) 1.8-2.0 (1H, m), 2.05-2.2 (1H, m), 2.8-3.1 (4H, m), 5.1 (1H, s), 6.9-7.1 (2H, m) and 7.4-7.5 (2H, m); *m/z* (EI) 214 (M^+).

2-(α-Hydroxybenzyl)-2-phenyl-1,3-dithiane

To a solution of 2-phenyl-1,3-dithiane (2.90 g, 14.8 mmol) in thf (70 ml) was added a solution of n-butyllithium in hexane (1.1 equiv.) at –78 °C, and the mixture was stirred at –78 °C for 2 hours. To the resulting anion was added benzaldehyde (1.61 g, 1.55 ml, 15.25 mmol) at –78 °C, and the reaction allowed to reach room temperature overnight. The reaction mixture was poured onto saturated ammonium chloride solution and dichloromethane (20 ml) added. The dichloromethane layer was separated and the aqueous layer extracted with dichloromethane (3 x 50 ml). The organic fractions were combined, dried ($MgSO_4$), and the solvent removed to yield a yellow oil which was purified by flash column chromatography using 10% ethyl acetate/petroleum ether to give the product as a white solid (4.15 g, 93%); m.p. 118-119 °C (Found: C, 67.73; H, 6.02. $C_{17}H_{18}S_2O$ requires C, 67.50; H, 5.99%); ν_{max}/cm^{-1} 3455; δ_H(200 MHz, $CDCl_3$) 1.8-2.0 (2H, m), 2.6-2.8 (4H, m), 3.0 (1H, d, *J* 5 Hz), 5.0 (1H, d, *J* 5 Hz), 6.85-6.95 (2H, m), 7.1-7.4 (4H, m) and 7.65-7.75 (2H, m); *m/z* (EI) 302 (M^+).

2-(α-Hydroxy-2-fluorobenzyl)-2-phenyl-1,3-dithiane

To the anion prepared from 2-phenyl-1,3-dithiane (5.0 g, 25.5 mmol) as described above was added 2-fluorobenzaldehyde (3.15 g, 2.71 ml, 26.3 mmol) at –78 °C. After reaching room temperature overnight, the reaction mixture was worked up as described above to give a yellow oil which was purified by column chromatography (10% ethyl acetate/petroleum ether) to give the product as a white solid (5.5 g, 67%); m.p. 93-95 °C (Found: C, 63.80; H, 5.33. $C_{17}H_{17}S_2FO$ requires C, 63.72; H, 5.35%); ν_{max}/cm^{-1} 3454; δ_H(200 MHz, $CDCl_3$) 1.8-2.0 (2H, m), 2.6-2.8 (4H, m), 3.05 (1H, d, *J* 5 Hz), 5.4 (1H, d, *J* 5 Hz), 6.8-7.2 (3H, m), 7.1-7.2 (4H, m) and 7.65-7.75 (2H, m); *m/z* (EI) 320 (M^+).

2-(α-Hydroxy-3-fluorobenzyl)-2-phenyl-1,3-dithiane

To the anion prepared from 2-phenyl-1,3-dithiane (2.0 g, 10.2 mmol) as described above was added 3-fluorobenzaldehyde (1.29 g, 1.10 ml, 10.75 mmol) at –78 °C. After reaching room temperature overnight the reaction mixture was worked up as described above to give a yellow oil which was purified by column chromatography (10% ethyl acetate/petroleum ether) to give the product as a white solid (2.75 g, 84%); m.p. 88-90 °C (Found: C, 63.90; H, 5.37. $C_{17}H_{17}S_2FO$ requires C, 63.72; H, 5.35%); ν_{max}/cm^{-1} 3449; δ_H(200 MHz, $CDCl_3$) 1.8-2.0 (2H, m), 2.6-2.8 (4H, m), 3.0 (1H, d, *J* 5 Hz), 5.0 (1H, d, *J* 5 Hz), 6.55-6.7 (2H, m), 6.85-6.95 (1H, m), 7.1-7.2 (1H, m), 7.4-7.5 (3H, m) and 7.65-7.75 (2H, m); *m/z* (EI) 320 (M^+).

2-(α-Hydroxy-4-fluorobenzyl)-2-phenyl-1,3-dithiane

To the anion prepared from 2-phenyl-1,3-dithiane (2.0 g, 10.2 mmol) as described above was added 4-fluorobenzaldehyde (1.27 g, 1.10 ml, 10.54 mmol) at –78 °C. After reaching room temperature overnight, the reaction mixture was worked up as described above to give a yellow oil which was purified by column chromatography (10% ethyl acetate/petroleum ether) to give the product as a white solid (2.45 g, 75%); m.p. 134-135 °C (Found: C, 63.77; H, 5.37. $C_{17}H_{17}S_2FO$ requires C, 63.72; H, 5.35%); ν_{max}/cm^{-1} 3447; δ_H(200 MHz, $CDCl_3$) 1.8-2.0 (2H, m), 2.6-2.8 (4H, m), 3.1 (1H, d, *J* 4 Hz), 5.0 (1H, d, *J* 4 Hz), 6.8-6.85 (4H, m), 7.2-7.3 (3H, m) and 7.65-7.75 (2H, m); *m/z* (EI) 320 (M^+).

2-(2-Fluorophenyl)-2-(α-hydroxy-2-fluorobenzyl)-1,3-dithiane

To the anion prepared from 2-(2-fluorophenyl)-1,3-dithiane (3.05 g, 14.2 mmol) as described above was added 2-fluorobenzaldehyde (1.77 g, 1.50 ml, 14.75 mmol) at –78 °C. After reaching room temperature overnight, the reaction mixture was worked up as described above to give a yellow oil which was purified by column chromatography (10% ethyl acetate/petroleum ether) to give the product as a white solid (3.64 g, 76%); m.p. 92-94 °C (Found: C, 60.60; H, 4.78. $C_{17}H_{16}S_2F_2O$ requires C, 60.32; H, 4.76%); ν_{max}/cm^{-1} 3515; δ_H(200 MHz, $CDCl_3$) 1.8-2.0 (2H, m), 2.6-2.8 (4H, m), 3.2 (1H, d, *J* 5 Hz), 5.8 (1H, d, *J* 5 Hz) and 6.7-7.6 (8H, m); *m/z* (EI) 338 (M^+).

2-(3-Fluorophenyl)-2-(α-hydroxy-3-fluorobenzyl)-1,3-dithiane

To the anion prepared from 2-(3-fluorophenyl)-1,3-dithiane (3.60 g, 16.8 mmol) as described above was added 3-fluorobenzaldehyde (2.08 g, 1.78 ml, 17.35 mmol) at –78 °C. After reaching room temperature overnight, the reaction mixture was worked up as described above to give a yellow oil which was purified by column chromatography (10% ethyl acetate/petroleum ether) to give the product as a white solid (3.40 g, 60%); m.p. 99-101 °C (Found: C, 60.46; H, 4.74. $C_{17}H_{16}S_2F_2O$ requires C, 60.32; H, 4.76%); ν_{max}/cm^{-1} 3453; δ_H(200 MHz, $CDCl_3$) 1.85-2.0 (2H, m), 2.6-2.85 (4H, m), 3.1 (1H, d, *J* 5 Hz), 5.0 (1H, d, *J* 5 Hz), 6.55-6.7 (2H, m), 6.95-7.15 (3H, m), 7.25-7.35 (1H, m) and 7.4-7.5 (2H, m); *m/z* (EI) 338 (M^+).

2-(4-Fluorophenyl)-2-(α-hydroxy-4-fluorobenzyl)-1,3-dithiane

To the anion prepared from 2-(4-fluorophenyl)-1,3-dithiane (3.98 g, 18.6 mmol) as described above was added 4-fluorobenzaldehyde (2.30 g, 2.00 ml, 19.1 mmol) at –78 °C. After reaching room temperature overnight, the reaction mixture was worked up as described above to give a yellow oil which was purified by column chromatography (10% ethyl acetate/petroleum ether) to give the product as a white solid (5.57 g, 89%); m.p. 132-134 °C (Found: C, 60.21; H, 4.78. $C_{17}H_{16}S_2F_2O$ requires C, 60.32; H, 4.76%); ν_{max}/cm^{-1} 3478; δ_H(200 MHz, $CDCl_3$) 1.8-2.0 (2H, m), 2.6-2.8 (4H, m), 3.2 (1H, d, *J* 5 Hz), 5.0 (1H, d, *J* 5 Hz), 6.85 (4H, d, *J* 7 Hz), 7.00 (2H, t, *J* 7 Hz) and 7.6-7.7 (2H, m); *m/z* (EI) 338 (M^+).

2-(1-Hydroxypropyl)-2-phenyl-1,3-dithiane

To the anion prepared from 2-phenyl-1,3-dithiane (1.00 g, 5.1 mmol) as described above was added propionaldehyde (0.30 g, 0.37 ml, 5.20 mmol) at –78 °C. After reaching room temperature overnight, the reaction mixture was worked up as described above to give a yellow oil which was purified by column chromatography (10% ethyl acetate/petroleum ether) to give the product as a white solid (1.10 g, 85%); m.p. 75-76 °C (Found: C, 61.20; H, 7.12. $C_{13}H_{18}S_2O$ requires C, 61.38; H, 7.13%); ν_{max}/cm^{-1} 3483; δ_H(200 MHz, $CDCl_3$) 0.9 (3H, t, *J* 7 Hz), 1.1-1.15 (1H, m), 1.5-1.6 (1H, m), 1.9-2.0 (2H, m), 2.15 (1H, br s), 2.65-2.8 (4H, m), 3.75 (1H, d, J 1.5 Hz), 7.25-7.45 (3H, m) and 7.95-8.05 (2H, m); *m/z* (EI) 254 (M^+).

2-(1-Hydroxybutyl)-2-phenyl-1,3-dithiane

To the anion prepared from 2-phenyl-1,3-dithiane (1.00 g, 5.1 mmol) as described above was added butyraldehyde (0.37 g, 0.46 ml, 5.14 mmol) at –78 °C. After reaching room temperature overnight, the reaction mixture was worked up as described above to give a yellow oil which was purified by column chromatography (10% ethyl acetate/petroleum ether) to give the product as a clear oil (810 mg, 59%); ν_{max}/cm^{-1}

3463; δ_H(200 MHz, $CDCl_3$) 0.85 (3H, t, *J* 8 Hz), 1.1-1.3 (2H, m), 1.35-1.55 (2H, m), 1.85-2.0 (3H, m), 2.7-2.8 (4H, m), 3.8-3.85 (1H, m), 7.2-7.3 (1H, m), 7.3-7.4 (1H, m) and 7.8-7.9 (2H, m); *m/z* (EI) 268 (M^+).

Dibenzoyl (benzil)

A solution of 2-(α-hydroxybenzyl)-2-phenyl-1,3-dithiane (89 mg, 0.29 mmol) in acetone was added dropwise over a period of 20 minutes to a solution of *N*-bromosuccinimide (900 mg 5.05 mmol) in 3% water/acetone (30 ml) at 5 °C. The mixture was stirred and allowed to reach room temperature over 30 minutes, then poured onto a saturated aqueous sodium sulphite solution (20 ml) and dichloromethane (20 ml). After stirring for 10 minutes, the organic layer was separated, washed with water (2 x 25 ml) and dried ($MgSO_4$). The solvent was removed to yield the diketone as a yellow oil which was purified by column chromatography (dichloromethane) to yield the product as a yellow solid (43 mg, 71%); m.p 94-96 °C; ν_{max}/cm^{-1} 1660 and 1678; δ_H(200 MHz, $CDCl_3$) 7.45-7.55 (4H, m), 7.65-7.75 (2H, m) and 7.9-8.0 (4H, m); *m/z* (EI) 210 (M^+)

2-Fluorodibenzoyl (2-fluorobenzil)

A solution of 2-(α-hydroxy-2-fluorobenzyl)-2-phenyl-1,3-dithiane (1.06 g, 3.31 mmol) in acetone was added dropwise to a solution of *N*-bromosuccinimide (10.0 g 56.17 mmol) in 3% water/acetone at 5 °C as described above. Work up as described above gave the diketone as a yellow oil which was purified by column chromatography to give the product as a yellow solid (513 mg, 68%); m.p. 63-64 °C (Found: C, 74.07; H, 3.94. $C_{14}H_9O_2F$ requires C, 73.67; H, 3.97%); ν_{max}/cm^{-1} 1684; δ_H(200 MHz, $CDCl_3$) 7.15 (1H, ddd, *J* 1, 8 and 10 Hz), 7.35 (1H, dt, *J* 1 and 7.5 Hz), 7.55-7.75 (5H, m) and 7.95-8.1 (2H, m); *m/z* (EI) 228 (M^+).

3-Fluorodibenzoyl (3-fluorobenzil)

A solution of 2-(α-hydroxy-3-fluorobenzyl)-2-phenyl-1,3-dithiane (1.00 g, 3.10 mmol) in acetone was added dropwise to a solution of *N*-bromosuccinimide (10.0 g 56.17 mmol) in 3% water/acetone at 5 °C as described above. Work up as described above gave the diketone as a yellow oil which was purified by column chromatography to give the product as a yellow solid (510 mg, 72%); m.p. 102-104 °C (Found: C, 73.30; H, 3.94. $C_{14}H_9O_2F$ requires C, 73.67; H, 3.97%); ν_{max}/cm^{-1} 1675 and 1684; δ_H(200 MHz, $CDCl_3$) 6.95-7.2 (4H, m), 7.25-7.4 (3H, m) and 7.6-7.65 (2H, m); *m/z* (EI) 228 (M^+).

4-Fluorodibenzoyl (4-fluorobenzil)

A solution of 2-(α-hydroxy-4-fluorobenzyl)-2-phenyl-1,3-dithiane (950 mg, 2.96 mmol) in acetone was added dropwise to a solution of *N*-bromosuccinimide (10.0 g 56.17 mmol) in 3% water/acetone at 5 °C as described above. Work up as described above gave the diketone as a yellow oil which was purified by column chromatography to give the product as a yellow solid (585 mg, 87%); m.p. 118-120 °C (Found: C, 73.89; H, 3.95. $C_{14}H_9O_2F$ requires C, 73.67; H, 3.97%); ν_{max}/cm^{-1} 1667; δ_H(200 MHz, $CDCl_3$) 6.95-7.05 (2H, m), 7.25-7.35 (2H, m), 7.4-7.5 (1H, m) and 7.75-7.9 (4H, m); *m/z* (EI) 228 (M^+).

2,2'-Difluorodibenzoyl (2,2'-difluorobenzil)

A solution of 2-(2-fluorophenyl)-2-(α-hydroxy-2-fluorobenzyl)-1,3-dithiane (1.08 g, 3.20 mmol) in acetone was added dropwise to a solution of *N*-bromosuccinimide (10.0 g 56.17 mmol) in 3% water/acetone at 5 °C as described above. Work up as described above gave the diketone as a yellow oil which was purified by column chromatography to

give the product as an off-white solid (580 mg, 74%); m.p. 99-100 °C (Found: C, 68.30; H, 3.24. $C_{14}H_8O_2F_2$ requires C, 68.29; H, 3.27%); ν_{max}/cm^{-1} 1676; δ_H(200 MHz, $CDCl_3$) 7.1-7.2 (2H, m), 7.3-7.4 (2H, m), 7.6-7.75 (2H,m) and 8.05-8.15 (2H, m); *m/z* (EI) 246 (M^+).

3,3'-Difluorodibenzoyl (3,3'-difluorobenzil)

A solution of 2-(3-fluorophenyl)-2-(α-hydroxy-3-fluorobenzyl)-1,3-dithiane (980 mg, 2.89 mmol) in acetone was added dropwise to a solution of *N*-bromosuccinimide (10.0 g 56.17 mmol) in 3% water/acetone at 5 °C as described above. Work up as described above gave the diketone as a yellow oil which was purified by column chromatography to give the product as a yellow solid (580 mg, 82%); m.p. 108-110 °C (Found: C, 68.27; H, 3.25. $C_{14}H_8O_2F_2$ requires C, 68.29; H, 3.27%); ν_{max}/cm^{-1} 1676; δ_H(200 MHz, $CDCl_3$) 7.3-7.6 (4H, m) and 7.65-7.8 (4H, m); *m/z* (EI) 246 (M^+).

4,4'-Difluorodibenzoyl (4,4'-difluorobenzil)

A solution of 2-(4-fluorophenyl)-2-(α-hydroxy-4-fluorobenzyl)-1,3-dithiane (990 mg, 2.92 mmol) in acetone was added dropwise to a solution of *N*-bromosuccinimide (10.0 g 56.17 mmol) in 3% water/acetone at 5 °C as described above. Work up as described above gave the diketone as a yellow oil which was purified by column chromatography to give the product as a yellow solid (610 mg, 85%); m.p. 120-122 °C (Found: C, 68.38; H, 3.25. $C_{14}H_8O_2F_2$ requires C, 68.29; H, 3.27%); ν_{max}/cm^{-1} 1664; δ_H(200 MHz, $CDCl_3$) 7.15-7.3 (4H, m) and 7.95-8.1 (4H, m); *m/z* (EI) 246 (M^+).

1-Phenyl-1,2-butanedione

A solution of 2-(1-hydroxypropyl)-2-phenyl-1,3-dithiane (100 mg, 0.39 mmol) in acetone was added dropwise to a solution of *N*-bromosuccinimide (1.0 g 5.61 mmol) in 3% water/acetone at 5 °C as described above. Work up as described above gave the diketone as a yellow oil which was purified by column chromatography to give the product as a yellow oil (53.7 mg, 85%); ν_{max}/cm^{-1} 1695 and 1785; δ_H(200 MHz, $CDCl_3$) 1.25 (3H, t, *J* 8.5 Hz), 2.95 (2H, q, *J* 8.5 Hz), 7.5-7.7 (3H, m) and 7.95-8.0 (2H, m); *m/z* (EI) 162 (M^+).

1-Phenyl-1,2-pentanedione

A solution of 2-(1-hydroxybutyl)-2-phenyl-1,3-dithiane (100 mg, 0.37 mmol) in acetone was added dropwise to a solution of N-bromosuccinimide (1.0 g 5.61 mmol) in 3% water/acetone at 5 °C as described above. Work up as described above gave the product as a yellow oil which was purified by column chromatography to give the product as a yellow oil (35.3 mg, 54%); ν_{max}/cm^{-1} 1702 and 1779; δ_H(200 MHz, $CDCl_3$) 1.05 (3H, t, *J* 8.5 Hz), 1.75 (2H, q, *J* 8.5 Hz), 2.9 (2H, t, *J* 8.5 Hz), 7.5-7.7 (3H, m), 8.0-8.05 (2H, m); *m/z* (EI) 176 (M^+).

Benzoin

A solution of 2-(α-hydroxybenzyl)-2-phenyl-1,3-dithiane (90 mg, 0.30 mmol), mercury (II) chloride (198 mg, 0.73 mmol) and calcium carbonate (73 mg, 0.73 mmol) were dissolved in aqueous acetonitrile (15 ml) and heated under reflux for two hours. TLC analysis at this time showed the reaction to be complete. The reaction mixture was passed through a pad of celite which was washed thoroughly with dichloromethane. The pooled organic layers were washed with 2 M aqueous sodium acetate (20 ml), water (20 ml) and a saturated brine solution (20 ml), and the solvents removed to give a white

solid which was purified by column chromatography to give benzoin as a white solid (39 mg, 61%); m.p 132-134 °C; ν_{max}/cm^{-1} 3400 and 1969; δ_H(400 MHz, $CDCl_3$) 4.6 (1H, d, *J* 6 Hz), 6.0 (1H, d, *J* 6 Hz), 7.1-7.5 (8H, m) and 7.9-8.1 (2H, m); *m/z* (EI) 212 (M^+).

5,5-Diphenylhydantoin (phenytoin)

Benzil (2.00 g, 10 mmol), potassium hydroxide (2.00 g, 17.82 mmol) and urea (780 mg, 13 mmol) were dissolved in dry ethanol (40 ml) and stirred at 50-60 °C for two hours at which time TLC analysis indicated complete consumption of starting material. The reaction mixture was then poured onto an ice/water mixture (100 ml) and the solution filtered to remove a small quantity of 4,5-diphenyl-4,5-dihydroxy-2-imidazolone.The remaining red solution was acidified with 10 M hydrochloric acid to precipitate the product as a white solid which was removed by filtration, washed with water and dried over phosphorus pentoxide to give the product (1.66 g, 66%); ν_{max}/cm^{-1} 1729, 1763 and 3200; δ_H(200 MHz, $(CD_3)_2SO$) 7.3-7.5 (10 H, m), 9.4 (1H, s) and 11.0 (1H, br s); *m/z* (EI) 252 (M^+).

5-(2-Fluorophenyl)-5-phenylhydantoin

This compound was prepared as described above using 2-fluorobenzil (250 mg, 1.1 mmol), potassium hydroxide (183 mg, 3.25 mmol) and urea (65 mg, 1.08 mmol) dissolved in dry ethanol (10 ml). Work up as described above gave the product as a yellow solid (171 mg, 58%) (Found: C, 66.68; H, 4.11; N, 10.47. $C_{15}H_{11}O_2N_2F$ requires C, 66.67; H,4.07; N, 10.35%); ν_{max}/cm^{-1} 1718, 1760 and 3190; δ_H(200 MHz, $(CD_3)_2SO$) 6.9 (3H, t, *J* 7.5 Hz), 7.1-7.4 (3H, m), 7.4-7.6 (5 H m), 9.2 (1H, s) and 11.3 (1H, br s); *m/z* (EI) 270 (M^+).

5-(3-Fluorophenyl)-5-phenylhydantoin

This compound was prepared as described above using 3-fluorobenzil (250 mg, 1.1 mmol), potassium hydroxide (183 mg, 3.25 mmol) and urea (65 mg, 1.08 mmol). Work up as described above gave the product as a yellow solid (207 mg, 70%) (Found: C, 66.68; H, 4.11; N, 10.47. $C_{15}H_{11}O_2N_2F$ requires C, 66.74; H, 4.13; N, 10.42%); ν_{max}/cm^{-1} 1722, 1750 and 3205; δ_H(200 MHz, $(CD_3)_2SO$) 7.1-7.6 (9 H, m), 9.4 (1H, s) and 11.3 (1H, br s); *m/z* (EI) 270 (M^+).

5-(4-Fluorophenyl)-5-phenylhydantoin

This compound was prepared as described above using 4-fluorobenzil (250 mg, 1.1 mmol), potassium hydroxide (183 mg, 3.25 mmol) and urea (65 mg, 1.08 mmol). Work up as described above gave the product as a yellow solid (160 mg, 54%) (Found: C, 66.60; H, 4.09; N, 10.31. $C_{15}H_{11}O_2N_2F$ requires C, 66.67; H, 4.07; N, 10.35%); ν_{max}/cm^{-1} 1728, 1762 and 3198; δ_H(400 MHz, $(CD_3)_2SO$) 6.75-6.85 (2 H m), 6.9-7.0 (7H, m), 8.9 (1H, s) and 11.0 (1H, br s); *m/z* (EI) 270 (M^+).

5,5-bis-(2-Fluorophenyl)-hydantoin

This compound was prepared as described above using 2,2'-difluorobenzil (245 mg, 0.99 mmol), potassium hydroxide (183 mg, 3.25 mmol) and urea (65 mg, 1.08 mmol). Work up as described above gave the product as a yellow solid (140 mg, 49%) (Found: C, 62.54; H, 3.44; N, 9.70. $C_{15}H_{11}O_2N_2F_2$ requires C, 62.50; H, 3.47; N, 9.72%); ν_{max}/cm^{-1} 1725, 1758 and 3210; δ_H(200 MHz, $(CD_3)_2SO$) 7.3-7.4 (6H, m), 7.5-7.6 (2 H m), 9.1 (1H, s) and 11.2 (1H, br s); *m/z* (EI) 288 (M^+).

5,5-bis-(3-Fluorophenyl)-hydantoin

This compound was prepared as described above using 3,3'-difluorobenzil (244 mg, 0.99 mmol), potassium hydroxide (183 mg, 3.25 mmol) and urea (65 mg, 1.08 mmol). Work up as described above gave the product as a yellow solid (198 mg, 70%) (Found: C, 62.54; H, 3.45; N, 9.73. $C_{15}H_{11}O_2N_2F_2$ requires C, 62.50; H, 3.47; N, 9.72%); ν_{max}/cm^{-1} 1726, 1764 and 3183; δ_H(200 MHz, $(CD_3)_2SO$) 7.1-7.35 (6H, m), 7.4-7.6 (2H m), 9.5 (1H, s) and 11.3 (1H, br s); *m/z* (EI) 288 (M^+).

5,5-bis-(4-Fluorophenyl)-hydantoin

This compound was prepared as described above using 4,4'-difluorobenzil (267 mg, 1.08 mmol), potassium hydroxide (183 mg, 3.25 mmol) and urea (65 mg, 1.08 mmol). Work up as described above gave the product as a yellow solid (259 mg, 83%) (Found: C, 62.47; H, 3.50; N, 9.55. $C_{15}H_{11}O_2N_2F_2$ requires C, 62.50; H, 3.47; N, 9.72%); ν_{max}/cm^{-1} 1725, 1781 and 3199; δ_H(200 MHz, $(CD_3)_2SO$) 7.2-7.6 (8 H m), 9.4 (1H, s) and 11.3 (1H, br s); *m/z* (EI) 288 (M^+).

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