COMMUNICATION

Cyclisations of benzenesulfenyl chloride adducts with conjugated silyloxyenones: a new stereoselective reaction in the synthesis of 4,5-dihydrofuran-3(2*H*)-ones

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Adducts, generated *in situ* from *E*-α′-trialkylsilyloxy-α,β-unsaturated ketones with benzenesulfenyl chloride, cyclise in the presence of dry silica or zinc bromide to produce phenylsulfanyl substituted 4,5-dihydrofuran-3(2*H*)-ones with high stereoselectivity; oxidative elimination of the phenylsulfanyl group completes a new route to furan-3(2*H*)-ones.

Introduction

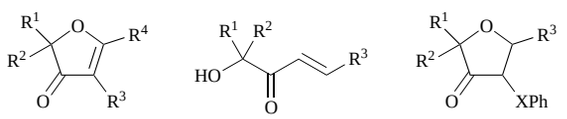
Furan-3(2*H*)ones **1**, their 4,5-dihydro derivatives, and structures containing furanone related sub-units are of widespread interest. Many of these compounds occur naturally, and they often possess novel structures and exhibit diverse biological activities. Furanones such as furaneol,[1] geiparvarin,[2] ascofuranone,[3] chilenones A and B,[4] jatrophone[5] and the eremantholides[6] are well known. Other furanone based structures, in particular breynolide[7] and phyllanthosin,[8] continue to attract attention and the structure of phoeniceroside, a novel bis-furanone, has been established.[9]

Several new methods for the synthesis of furan-3-(2*H*)-ones and their derivatives have been reported recently. These include the base-catalysed condensation of α-bromo ketones with aromatic aldehydes,[10] stereoselective cyclisations of unsaturated acyl selenides under free radical conditions[11] and catalytic intramolecular C–H insertion reactions of α-diazo-β-keto esters.[12] A stereoselective route to dihydrofuran-3(2*H*)-ones from chiral aldehydes and lithiomethoxyallene has been developed[13] and addition reactions of the lithium dienolate of 2,5-dimethylfuran-3(2*H*)-one with unsaturated compounds provides a novel route to bicyclic furanones.[14] Caesium fluoride catalysed condensation of keto ester derivatives represents the most recent development in the synthesis of furan-3(2*H*)-ones.[15]

Cyclisations of olefinic alcohols with electrophilic sulfur and selenium reagents remains a popular and versatile technique for the stereoselective synthesis of tetrahydrofurans and related compounds.[16] We anticipated that this protocol could be employed in a new route to furan-3(2*H*)-ones, also. Thus, cyclisation of a conjugated hydroxyenone **2**[17] or a derivative would lead to the substituted dihydrofuranone **3**. Elimination of the sulfur or selenium moiety, *via* the corresponding oxide—a process which would require preferential access to a *trans*-4,5-dihydrofuranone, *e.g.* **5**—would complete a new route to furan-3(2*H*)-ones from readily available starting materials. This approach has been successful in our hands and the results of the first phase of our study are described herein.

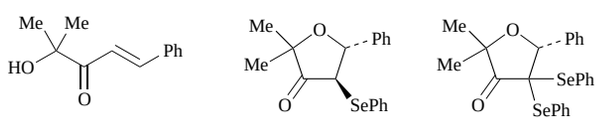
Results and discussion

Cyclisation of the hydroxyenone **4** was investigated initially. Reaction of this substrate with benzene-sulfenyl or -selenenyl chloride, in the presence of various basic reagents such as tri-



1 **2** **3**

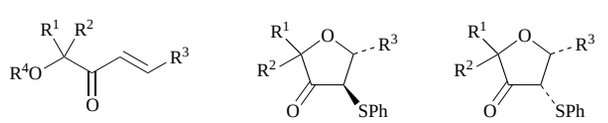
a $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = Ph$
b $R^1 = R^2 = Me$, $R^3 = SPh$, $R^4 = Ph$
c $R^1 = R^2 = Me$, $R^3 = I$, $R^4 = Ph$



4 **5** **6**

ethylamine or anhydrous sodium carbonate, gave complex mixtures of products. However, exposure of **4** to a combination of *N*-phenylselenophthalimide (N-PSP) and freshly fused zinc bromide (5 mol%), in dichloromethane, gave the furanone **5** (a labile oil) in 24% yield. Use of camphor-10-sulfonic acid as a catalyst produced **5** in similar yield (30%). Small quantities (10–15%) of a compound identified as the bis-selenide **6** were isolated from these reactions, also.

However, treatment of the silyl ether **7a** with benzeneselenenyl chloride in dichloromethane, at ambient temperature for 24 h, yielded **5** (isolated following dry flash chromatography on silica gel using 1 : 9 ethyl acetate–light petroleum as eluent) in 84% yield (ν_{CO} 1750 cm^{-1}; δ_H 3.63 (H-4) and 4.87 (H-5), $J_{4,5}$ = 10 Hz). Oxidative elimination of the phenylselanyl moiety in a freshly purified sample of **5** ($NaIO_4$ in methanol–water at room temperature for 2 h, then heat at 50 °C for 4 h) gave the furanone **1a** (bullatenone), a natural product, in 70% yield.



7 **8** **9**

a $R^1 = R^2 = Me$, $R^3 = Ph$, $R^4 = SiMe_3$
b $R^1 = R^2 = Me$, $R^3 = 3,4\text{-}(MeO)_2C_6H_3$, $R^4 = SiMe_3$
c $R^1,R^2 = -(CH_2)_5-$, $R^3 = Ph$, $R^4 = SiMe_3$
d $R^1 = R^2 = Me$, $R^3 = \alpha$-naphthyl, $R^4 = SiMe_3$
e $R^1 = Me$, $R^2 = Et$, $R^3 = Ph$, $R^4 = SiMe_3$
f $R^1 = Me$, $R^2 = \alpha$-naphthyl, $R^3 = Ph$, $R^4 = SiMe_3$
g $R^1 = R^2 = Me$, $R^3 = Pr^i$, $R^4 = Si(Bu^t)Me_2$
h $R^1,R^2 = -(CH_2)_5-$, $R^3 = heptyl$, $R^4 = SiEt_3$
i $R^1 = R^2 = Me$, $R^3 = CH_2CH_2Ph$, $R^4 = CH_2OCH_2Ph$
j $R^1 = Me$, $R^2 = PhSCH_2CH_2$, $R^3 = Ph$, $R^4 = SiMe_3$

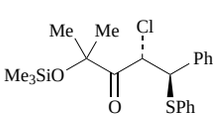
Attempts to extend this methodology to the synthesis of other aryl-substituted furan-3(2*H*)-ones were surprisingly

Table 1 Preparation of furanones **8** and **9**

Enone	Furanones[a]	Yield (%)	Ratio **8**:**9**
7a	**8a** + **9a**	70	95:5
7b	**8b** + **9b**	60	93:7
7c	**8c** + **9c**	69	93:7
7d	**8d** + **9d**	78	97:3
7e	**8e**[b] + **9e**	55	96:4
7f	**8f**[c] + **9f**	63	92:8
7g	**8g** + **9g**	74	94:6
7h	**8h** + **9h**	76	98:2
7i	**8i** + **9i**	79	90:10
7j	**8j**[d] + **9j**	45	95:5

[a] All compounds are racemic. [b] Isomer ratio, 8:3. [c] Isomer ratio, 1:4. [d] Isomer ratio, 1:3.

unsuccessful and gave extremely disappointing yields of cyclisation products. Our attention was then directed to the corresponding reactions of the enone derivatives **7** with benzenesulfenyl chloride. Much greater success was enjoyed in this part of the investigation which produced a new, highly stereoselective, sulfur mediated route to phenylsulfanyl-substituted 4,5-dihydrofuran-3(2*H*)-ones. Unlike the situation encountered with the selenenyl reagent, addition of a slight excess of benzenesulfenyl chloride to a solution of enone **7a** in dichloromethane did not produce the expected dihydrofuranone directly. Instead a yellow oil, identified as a mixture of regioisomeric β-chloro sulfides **10** and **11**, was obtained (ν_{CO} 1720 cm^{-1},



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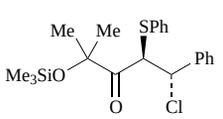

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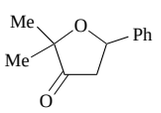

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δ_H 5.5–5.6). Radial chromatography of the mixture on silica gel produced a new product—a mixture of the stereoisomeric furanones **8a** and **9a** in 70% yield, overall. A similar result was obtained by adding dry silica gel[18] to a solution of the chloro sulfides, generated *in situ* from the sulfenyl chloride and **7a**. This protocol was then adopted as a general procedure for the cyclisation of a range of other aryl-substituted silyloxyenones (Table 1).

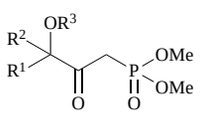
The furanone structure of the product resulting from cyclisation of **7a** was supported by a characteristic infrared absorption at 1760 cm^{-1}, and by conversion into the furanone **12** by reaction with triphenyltin hydride–AIBN in refluxing toluene. Examination of the ^{1}H NMR spectrum of the product mixture (**8a** + **9a**) clearly indicated that the reaction had proceeded in a highly stereoselective manner with the *trans*-isomer **8a** predominating by a factor of at least 19:1 (Table 1).† Careful rechromatography of the mixture produced a pure sample of **8a** whose proton NMR spectrum showed a pair of doublets (J 10.2 Hz) at δ 3.53 and 4.87 for the furanone H-4 and H-5 protons, respectively. The *trans*-stereochemistry was further supported by ^{1}H NOE difference spectra of the compound. Thus, irradiation of the methyl group singlet at δ 1.0 produced a significant enhancement of the furanone C-5 proton resonance only. Likewise, irradiation of the other methyl resonance at δ 1.43 resulted in a similar enhancement of the C-4 proton signal. Repeated chromatography of a mixture of **8a** and **9a** from a large-scale reaction, gave a clean sample of the novel *cis*-isomer **9a**. A pair of doublets (J 4.9 Hz) at δ 3.90 and 5.52 for the H-4 and H-5 protons respectively, were observed in the ^{1}H NMR spectrum of **9a**. The compound was labile and readily equilibrated with the *trans*-isomer under various conditions.

† Long term contact of the isomer mixture with silica gel in dichloromethane or potassium carbonate in methanol produced no change in the *trans*:*cis* ratio.

Several other *E*-aryl-substituted silyloxyenones (obtained by aldol condensation of various hydroxy ketones with arenecarbaldehydes in ethanolic KOH,[19] followed by silylation under standard conditions), including the cyclohexyl derivative **7c**, could be converted into the corresponding furanones in good yields and with high *trans*:*cis* selectivity. Enones **7e** and **7f** produced the corresponding furanones **8e** + **9e** and **8f** + **9f**, each as a mixture of diastereoisomers which could not be separated.

Extension of the chemistry to substrates derived from aliphatic hydroxyenones was then addressed. Trimethylsilyl ethers were not employed as substrates in these reactions because other O-protected hydroxyenones were more readily available. The ketophosphonates **13**, required as intermediates in the synthesis of the enones *via* Horner–Wadsworth–Emmons condensations with aldehydes, were difficult to prepare as their trimethylsilyl ethers. For example, reaction of methyl 2-trimethylsilyloxyisobutyrate, in THF, with dimethyl lithiomethylphosphonate, did not produce the corresponding ketophosphonate **13** (R^3 = $SiMe_3$) in satisfactory yield. Consequently, other trialkylsilyl or benzyloxymethyl ethers of the ketophosphonates were necessary for the preparation of enones **7g**–**i**. These were isolated as the *E*-isomers following reaction of the phosphonates and appropriate aldehydes with lithium chloride and triethylamine in acetonitrile (Masamune–Roush conditions[20]), at room temperature, for three to five days.

Silica gel failed to induce cyclisation of the enone–sulfenyl chloride adducts in these cases. Use of fused zinc bromide in sub-stoichiometric quantities (usually 25 mol%) was successful however, and produced the 5-alkyl-substituted furanones in an efficient and highly stereoselective manner from the hydroxyenone precursors. Cyclisations of enone **7i**, which contains a cheap benzyloxymethyl (BOM) O-protecting group, were troublesome on a large scale (>5 mmol) due to problems in removing BOM-derived residues from the furanone product.



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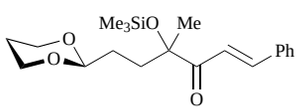

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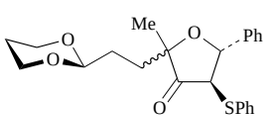

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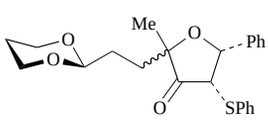

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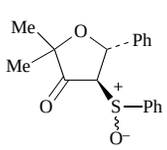

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Cyclisation of the functionalised enone **7j** proceeded in moderate yield and produced a mixture of the isomeric furanones **8j** and **9j**, each as a pair of diastereoisomers. Likewise, the 1,3-dioxane-derived substrate[21] **14** gave the furanones **15** and **16** (ratio 97:3) in 38% yield, overall.

Oxidation of the sulfide **8a** was problematic with reagents such as MCPBA or H_2O_2. Upon reaction with a Davis oxaziridine (*N*-phenylsulfonyl-2-phenyloxaziridine) in chloroform at room temperature for 11 days, **8a** was converted into the sulfanylfuranone **1b** (51%) while oxidation with tetrabutylammonium periodate in the same solvent (40 °C, 50 h) gave a mixture of **1b** (35%) and the novel iodofuranone **1c** (14%), mp 110–112 °C; ν_{CO} 1690 cm^{-1}; δ_C 23.5, 64.3, 87.1, 128.5, 128.65, 128.9, 132.7, 179.5 and 203.6.

Magnesium monoperoxyphthalate (MMPP) under phase-transfer conditions (dichloromethane–water–benzyltriethylammonium chloride) produced the sulfoxide **17**, in 62% yield, as a mixture of diastereoisomers. Thermolysis of the mixture (toluene reflux, 72 h) yielded furanone **1a** in 73% yield. Alternatively, compound **8a** could be converted directly into **1a** (65% yield) at reflux in the same solvent containing a five-fold excess of TBA–Oxone as the oxidising agent.[22]

Further work on the use of compounds **8** in the synthesis of other furanones, including 4-hydroxyfuran-3(2*H*)-ones is in progress.

Experimental

trans-4-Phenylsulfanyl-2,2-dimethyl-5-(4-methoxyphenyl)-4,5-dihydrofuran-3(2*H*)-one

Benzenesulfenyl chloride (513 mg, 3.55 mmol), in dry dichloromethane (10 ml), was added dropwise under a nitrogen atmosphere to a solution of 1-(4-methoxyphenyl)-4-methyl-4-(trimethylsilyloxy)pent-1-en-3-one (980 mg, 3.55 mmol) in the same solvent (10 ml). The solution was stirred at room temperature for 15 h and silica gel 60 (2 g; Merck 7747), which had been heated at 150 °C under vacuum (<1 mmHg) for 12 h, was then added. The resulting mixture was stirred for a further 3 h, and then the insoluble material was isolated by filtration through a sintered glass funnel and washed with dichloromethane (2 × 10 ml). Evaporation of the combined filtrate and washings gave a white solid which was recrystallised twice from dichloromethane–heptane to yield the *furanone* (740 mg, 64%) as a white microcrystalline solid, mp 102–103 °C (Found: C, 69.35; H, 6.4; S, 10.0. $C_{19}H_{20}O_3S$ requires: C, 69.5; H, 6.1; S, 9.8%); ν_{max}(KBr)/cm^{-1} 3000, 1760, 1600, 1520, 1470, 1445, 1375, 1310, 1250, 1160, 1080, 1040, 825, 750, 700; δ_H(270 MHz, $CDCl_3$, *J*/Hz) 0.98 (3 H, s), 1.40 (3 H, s), 3.56 (1 H, d, *J* 10), 3.81 (3 H, s), 4.80 (1 H, d, *J* 10), 6.73–7.53 (9 H, m); δ_C(67.5 MHz) 21.2, 24.5, 55.3, 58.5, 78.3, 81.1, 114.1, 127.9, 128.7, 129.0, 130.7, 131.4, 134.6, 159.9, 213.4.

2,2-Dimethyl-5-phenylfuran-3(2*H*)-one

Solid TBA–Oxone (5.1 g, 5 mmol) was added to a solution of furanone **8a** (0.298 g, 1 mmol) in dry toluene (30 ml). The mixture was refluxed for 72 h, then cooled and the upper toluene layer decanted from the lower thick oily residue which was subsequently washed with toluene (2 × 10 ml). The combined toluene layer and extracts were washed with water (3 × 15 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Radial chromatography of the resulting light brown solid, using ethyl acetate–hexane (1:9) as eluent gave the *furanone* **1a** (0.112 g, 65%) as a white solid, mp 65–67 °C (lit.,[23] 67.5–68.5 °C).

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