The chemistry of 3-[bis(methylthio)methylene]-5-phenyl-2(3H) furanone

G Sudhakar Reddy, Parvathi Neelkantan & D S Iyengar*
Indian Institute of Chemical Technology, Hyderabad 500 007, India

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The α-oxoketene s,s-acetals undergo regioselective functionalisation and this potential has been utilised extensively for the construction of several heterocyclic systems1,2. Essentially they may be considered as α,β-unsaturated ketones with fully substituted β-carbon and the chemoselective addition of nucleophiles to the system has been proved to be of good synthetic utility.

In continuation of our interest on α-arylidene Δ⁵⁻ butenolides, we have investigated the reaction of α-[bis(methylthio)methylene]furanes with different nucleophiles to get an insight into the behaviour of the α-oxoketene dithioacetal functionality present in the system. Interest in this system i.e. di(methylthio)methylene butenolide 1, is in view of the presence of two electrophilic centres, the lactone carbonyl and the exocyclic double bond. While it has been shown that the addition of nucleophile to α-arylidene butenolides leads to products derived from the initial carbonyl addition, in the case of acyclic α-oxoketene s,s-acetals, displacement of methylmercaptan group occurs by addition-elimination process. If the arylidene group is replaced by a bis(methylthio)methylene group, it would provide another site for a nucleophilic attack. The results of the present investigation on the reactions of nucleophile with 1 is depicted in Scheme I.

α-[Bis (methylthio) methylene]-γ-phenyl-Δ⁵⁻ butenolide 1 on reaction with aromatic amine, i.e., aniline, gave a mixture of pyrrole derivative 2 and the furan 3 in the ratio of 40:60, the overall yield being 80%. The compounds were identified on the basis of ¹H NMR and mass spectral data. The furan derivative 3 had a singlet at δ 2.65 for one s-methyl group whereas the pyrrole 2, exhibited two separate singlets at δ 2.56 and 2.65 for two s-methyl groups. Formation of the products 2 and 3 may be visualised as arising from the initial attack of aniline on the lactone carbonyl giving the anilide intermediate which can undergo cyclocondensation in two different ways shown in Scheme II.

Compound 1 was unaffected when treated with 2-aminopyridine in refluxing methanol or toluene. However, on heating the reactants without any solvent afforded the furan carboxamide 4 to the extent of 40% as the major product. On similar conditions 1 reacted with 1-phenylethylamine to give the respective furan derivative 5 as the major product in 50% yield.

Treatment of 1 with triethylamine in methanol resulted in the formation of 4-oxo-2-bis(methylthio)methylene benzenebutanoic acid methyl ester 6. This may be considered as TEA induced methanolysis of compound 1. Hydrazine hydrate reacted with compound 6 to give the pyrazidine derivative 7 which is also obtained by direct treatment of 1 with hydrazine hydrate3. 2-Aminopyridine when reacted with 6 did not give any addition product but behaved as a base effecting enolisation of compound 6 and resulted in the formation of furan acid ester 9.

Formation of 9 was also observed when 1 was refluxed with an alkali in methyl alcohol or by direct esterification of acid 10. The methylester 6 underwent reduction with sodium borohydride to give the alcohol ester which has spontaneously cyclised to γ-butyrolactone derivative 8. The same could also be obtained in a single pot reaction from Δ⁵⁻ butenolide 1 on treatment with sodium borohydride in methyl alcohol in presence of triethylamine. While attempting the epoxidation of compound 1 with MCPBA, the disulfoxide 11 was obtained.
In conclusion it is observed that nucleophilic reactions on compound 1 is initiated at the lactone carbonyl, followed by cyclocondensation, either by retaining the bis(thiomethyl) moiety or by the displacement of thiomethoxide depending upon the nucleophilicity of the attacking reagent.

**Experimental Section**

Melting points were determined on mettler FP51 instrument and are uncorrected. IR spectra were recorded on Perkin-Elmer model 2833 spectrometer and the values are in cm⁻¹. ¹H NMR spectra were recorded on Varian Gemini 200 MHz, solvent used was CDCl₃ and the values are expressed on δ. Mass spectra were recorded on V.G. 7070H mass spectrometer.

**Reaction of α-[bis(methylthio)methylene]-γ-phenyl-Δ²γ-butenolide¹ 1 with aniline.** To the solution of α-[bis(methylthio)methylene]-γ-phenyl-Δ²γ-butenolide (1, 0.264 g, 1 mmole) in toluene (20 mL), aniline (0.093 g, 1 mmole) was added at room
temperature and the contents were refluxed for 3 hrs. Solvent was removed under reduced pressure and the residue was purified by passing over silica gel column using hexane: ethylacetate (95:5) as eluent to obtain the pyrrole derivative 2 in 32% yield (0.108 g). On increasing the polarity of the eluting solvent with hexane-ethylacetate (80:20) the furan derivative 3 was obtained in 48% yield (0.148 g).

3-[Bis(methylthio)methylene]-1, 5-diphenyl pyrrole-2(3H)-one 2. m.p. 147°C; IR: 1690 (s), 1520 cm⁻¹. ¹H NMR: δ 2.56 (s, 3H), 2.65 (s, 3H), 6.32 (s, 1H), 7.03-7.33 (m, 10H). Mass (m/z): 339 (M⁺, base peak). HRMS for C₁₉H₁₈N₂O₂S: Calcd.: 339.075; Found: 339.076.

2-Methylthio-5-phenyl-3-(N-Phenylformamido)-furan 3: m.p. 132°C; IR: 1635, 1600, 1530 cm⁻¹. ¹H NMR: δ 2.65 (s, 3H), 7.1-7.72 (m, 11H), 9.20 (s, 1H). Mass (m/z): 309 (M⁺), 217 (base peak). HRMS for C₁₉H₁₉N₂O₂: Calcd.: 309.082; Found: 309.083.

Reaction of α-[bis(methylthio)methylene]-γ-phenyl-Δ³-butenolide 1 with 2-amino pyridine 4. A mixture of compound 1 (0.264 g) and 2-amino-pyridine (0.094 g) was heated at 85°C for 30 min. After 30 min the reaction mixture was extracted in ethylacetate (25 mL). The organic layer was concentrated and the residue was purified over silica gel column using hexane-ethylacetate (80:20) as eluent and the compound 4, 2-methylthio-5-phenyl-furan-3-N-(2'-pyridyl) carbamoxide, was obtained in 40% (0.124 g) yield, m.p. 130°C; IR: 1630, 1600, 1500 cm⁻¹. ¹H NMR: δ 2.7 (s, 3H), 7.0-7.1 (m, 1H), 7.2 (s, 1H), 7.25-7.8 (m, 6H), 8.25-8.45 (m, 2H), 9.6-9.8 (br-NH). FAB Mass (m/z): 311, 263 (M⁺-SCH₃). HRMS for C₁₉H₁₉N₂O₂S: Calcd.: 310.123; Found: 310.125.

2-Methylthio-5-phenyl-furan-3 (1'-phenyl) ethyl carbamoxide 5. A mixture of compound 1 (0.264 g) and 1-phenylethylamine was heated at 100°C for 30 min. Afterwards the reaction mixture was extracted in ethylacetate (25 mL). The organic layer was concentrated and the residue was purified over silica gel column using hexane-ethylacetate (80:20) as eluent and the compound 5 was obtained in 45% (0.148 g) yield, m.p. 152°C; IR: 1640, 1600, 1550 cm⁻¹. ¹H NMR: 1.55-1.65 (d, 3H, J=6 Hz), 2.6 (s, 3H), 5.3-5.5 (m, 1H), 7 (s, 1H), 7.25-7.8 (m, 11H). Mass (m/z): 337 (M⁺), 190, base peak [M-C₆H₅CH(CH₃)-N=C=O]. HRMS for C₂₀H₁₉N₂O₂S: Calcd.: 337.113; Found: 337.112.

4-Oxo-2 [bis(methylthio) methylene] benzenebutanoic acid methyl ester 6. To the solution of α-[bis (methylthio) methylene]-γ-phenyl-Δ³-butenolide (1, 0.264 g, 1 mmole) in methyl alcohol (20 mL) TEA (0.101 g, 1 mmole) was added and the reaction mixture was stirred at room temperature (30°C). The reaction was monitored by TLC. After 1 hr solvent was removed under reduced pressure and the residue was extracted with ethylacetate (2x25 mL). The combined organic layer was successively washed with dilute hydrochloric acid (20 mL) followed by water (2x20 mL). The organic layer was dried over sodium sulphate, concentrated and purified over silica gel column using hexane: ethylacetate (9:1) as eluent and the acyclic ester 4 was obtained in 96% (0.284 g) yield (semi-solid); IR: 1720, 1530 cm⁻¹. ¹H NMR: δ 2.35 (s, 3H), 2.45 (s, 3H), 3.75 (s, 3H), 4.48 (s, 2H), 7.42-7.6 (m, 3H), 7.95-8.05 (m, 2H); Mass (m/z): 296, 264, 248, 236, 105 (base peak); HRMS for C₁₉H₁₇O₃S: Calcd.: 296.054; Found: 296.055.

4-[Bis (methylthio) methyl]-6-phenyl-3 (2H)pyridazinone 7. To the solution of 4-oxo-2-[bis(methylthio)methylene]-benzene butanoic acid methyl ester (6, 0.296 g, 1 mmole) in methanol (20 mL), hydrazine hydrate (0.05 g, 1 mmole) was added at room temperature and the mixture was refluxed for 8 hr. The solvent was removed under reduced pressure and taken in ethylacetate. The combined organic layer was washed thoroughly with water (3x20 mL), dried over sodium sulphate concentrated and purified by passing over silica gel column using hexane: ethylacetate (80:20) as eluent in 80-90% yield, m.p. 224°C; IR: 3300-3400 (br), 1680 cm⁻¹. ¹H NMR: δ 2.1 (s, 6H), 5.2 (s, 1H), 7.1 (s, 1H), 7.6 (s, 6H), 12.3 (brs, 1H, exchangeable with D₂O); Mass (m/z): 278 (M⁺).

3-[Bis (methylthio)methylene]dihydro-5-phenyl-2 (3H)-furanone 8. To the solution of α-[bis(methylthio)methylene]-γ-phenyl-Δ³-butenolide (0.264 g, 1 mmole) in methyl alcohol (20 mL), triethylamine (0.10 g, 1 mmole) was added and the contents were stirred at r.t. for 30 min. Sodium borohydride (0.057 g, 1.5 mmole) was added to it and the mixture was stirred at room temperature for additional 30 min and finally refluxed for 1 hr. Solvent was removed under
reduced pressure and the residue was taken in ethylacetate (20 mL). The organic layer was washed with water (2×20 mL), dried over sodium sulphate, concentrated and the product 3[bis(methylthio)methylene]dihydro-5-phenyl-2(3H)-furanone 8 was isolated by passing over silica gel column using hexane-ethyl acetate (95:5) as eluent in 90% yield (0.239 g) (viscous liquid); IR: 1740, 1560 cm⁻¹; ¹H NMR: δ 2.38 (s, 3H), 2.42 (s, 3H), 2.82-2.95 (dd, 1H, J=8.5, 18 Hz), 3.37-3.50 (dd, 1H, J=8.5, 18 Hz), 5.33-5.41 (dd, 1H, J=8.6, 6.0 Hz), 7.16-7.37 (m, 5H); Mass (m/z): 266 (M⁺, base peak); HRMS for C₁₅H₁₄O₂S₁: Calcd.: 266.043; Found: 266.043.

2-Methylthio-5-phenyl-furan-3-carboxylic acid methyl ester 9. To the solution of α-[bis(methylthio)methylene]-γ-phenyl-Δ⁵β-butenolide s,s-dioxide 11. To the solution of α-[bis(methylthio)methylene]-γ-phenyl-Δ⁵β-butenolide (0.264 g, 1 mmole) in dichloromethane (20 mL), m-CPBA (0.688 g, 2 mmole) was added at room temperature and the mixture was stirred at room temperature for 30 min. Solvent was removed under reduced pressure and the residue was taken in ethyl acetate (20 mL). The organic layer was washed with saturated sodium bicarbonate solution (20 mL) followed by water (2×20 mL). The organic layer was dried over Na₂SO₄, concentrated and the residue was purified by passing over silica gel column using hexane-ethylacetate (20:80) as eluent. The disulfide 11 was isolated in 90% yield (0.266 g), m.p. 185°C; IR: 1740, 1540 cm⁻¹; ¹H NMR: δ 3.15 (s, 3H), 3.25 (s, 3H), 7.3 (s, 1H), 7.6 (m, 3H), 7.9 (m, 2H); Mass (m/z): 296, 281, 202, 186, 158, 105 (base peak). HRMS for C₁₅H₁₁O₂S₂: Calcd.: 296.017; Found: 296.017.

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References