

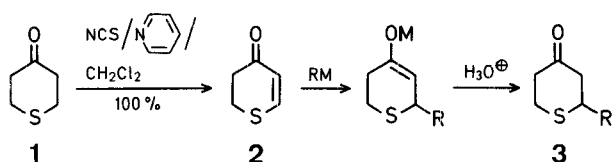
The Synthesis of 2-Substituted Thian-4-ones using Organocuprates

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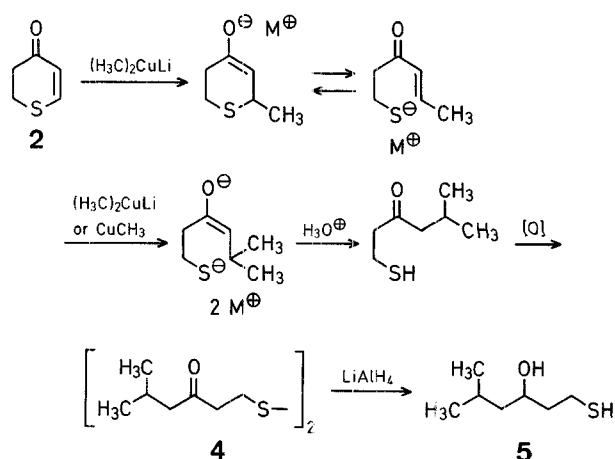
Substituted thian-4-ones are useful synthetic intermediates², but to prepare them by the conventional Dieckmann cyclisation approach³ is time-consuming and low-yielding. A three-stage route from thian-4-one (**1**) itself to 2-substituted derivatives (**3**) has recently been disclosed², in which the ketone is protected as the dioxolane, *N*-chlorosuccinimide is used to chlorinate position 2, and reaction with a Grignard reagent (RMgBr) followed by acid work-up gives **3**. We report an alternative, higher-yielding procedure for carrying out this conversion.

2,3-Dihydrothian-4-one (**2**) is available in quantitative yield from **1** by the use of *N*-chlorosuccinimide and pyridine in dichloromethane⁴. We were interested in using **2** in organometallic (RM) conjugate addition reactions to form 2-substituted thian-4-ones (**3**) after quenching of the intermediate enolate.



Organocuprates are generally the reagents of choice for conjugate addition reactions⁵, and so **2** was first treated with lithium dimethylcuprate. However, when the reaction was carried out with only 1.1 molar equivalents of lithium dimethylcuprate in diethyl ether at 0 °C, the major product (38%) was the disulphide **4**, which presumably arises by ring-opening of the enolate followed by further reaction with organocuprate.

Further proof of the disulphide structure was obtained by reduction of **4** with lithium aluminium hydride to give 1-mercapto-5-methylhexan-3-ol (**5**).



The conversion of β -alkylthio- α,β -unsaturated carbonyl compounds into β,β -dialkylketones by a similar process is well documented⁶. Varying the ratio of the reactants had little effect, but lowering the temperature did lead to some of the desired product. However, we eventually found that the best way to convert **2** to **3** is to use the mixed cuprate^{7,8} reagent $\text{LiCu(R)C}\equiv\text{C}-\text{C}_3\text{H}_7-n$ (**6**) at -78°C . A variety of 2-substituted thian-4-ones was prepared using this procedure (see Table).

2-Butylthian-4-one (**3b**; R = C₄H₉); Typical Procedure:

Dry hexamethylphosphorous triamide (1.71 g, 0.0105 mol) is added to a slurry of dry pentynylcopper (0.68 g, 0.0052 mol) in dry ether (12 ml) and the mixture is stirred at room temperature under nitrogen until it becomes homogeneous (10 min). The solution is then cooled to -78°C and a solution of butyllithium in hexane (4.4 ml of 1.20 molar solution; 0.0052 mol) added dropwise. The resulting orange solution is stirred for 15 min at -78°C and **2** (0.50 g, 0.00438 mol) in dry ether (10 ml) is added over 15 min. The mixture is kept at -78°C under nitrogen for 1.75 h, and then ice-cold 10% aqueous ammonium sulphate solution (100 ml) is added with vigorous stirring. After allowing the mixture to warm up, it is extracted with ether (3 \times 100 ml), the ether extracts are washed with ice-cold 2% v/v sulphuric acid (2 \times 100 ml), and the precipitated copper salts are filtered off using celite. The filtrate is washed with aqueous sodium hydrogen carbonate solution (2 \times 100 ml), the solution dried with magnesium sulphate, and the solvent evaporated.

Table. 2-Substituted Thian-4-ones **3a-e**

Product No.	R	Yield ^a [%]	Molecular formula ^b	I.R. (film) $\nu_{\text{C}=\text{O}}$ [cm ⁻¹]	¹ H-N.M.R. (CDCl ₃) δ [ppm]
3a	CH ₃	37	C ₆ H ₁₀ OS (130.0)	1711	1.30 (d, <i>J</i> = 7 Hz, 3H); 2.8 (m, 7H) ^c
3b	<i>n</i> -C ₄ H ₉	52	characterisation, see experimental	— ^c	1.00 (s, 9H); 2.4–3.5 (m, 7H)
3d	<i>t</i> -C ₄ H ₉	70 ^d	— ^c	1709	2.7–3.1 (m, 6H); 4.2 (m, 1H); 7.3 (s, 5H)
3e	C ₆ H ₅	44 ^f	C ₁₁ H ₁₂ OS (192.1)	1710 ^g	—
3f		28	C ₁₉ H ₃₀ O ₂ SSi (356.2)	1714	0.06 (s, 3H); 0.89 (s, 12H); 1.3 (m, 8H); 2.76 (m, 6H); 3.75 (m, 1H); 4.1 (m, 1H); 5.62 (m, 2H)

^a Yield of product isolated as an oil.

^b The microanalyses were in satisfactory agreement with the calculated values, C \pm 0.14, H \pm 0.14, S \pm 0.22.

^c In accord with data given in Ref.².

^d Semi-solid at room temperature, purified by sublimation at 25 °C/1 torr.

^e M.S.: *m/e* = 172.0919 (M⁺), calc. for C₆H₁₀OS: 172.0918.

^f Solid, m.p. 67–68 °C, Ref.² m.p. 72–74 °C.

^g Nujol mull.

Flash chromatography or preparative plate chromatography gives 2-butylthian-4-one (**3b**) as an oil; yield: 0.388 g (52%).

C ₉ H ₁₆ OS	calc.	C 62.79	H 9.30	S 18.60
(172.1)	found	62.86	9.30	18.38

I.R. (film): $\nu = 1713 \text{ cm}^{-1}$.

¹H-N.M.R. (CDCl₃): $\delta = 0.89$ (s, 3H); 1.44 (m, 6H); 2.2–3.5 ppm (m, 7H).

Bis[5-methyl-3-oxohexyl] Disulphide (**4**):

To a cold (0 °C) slurry of ultra-pure copper(I) iodide (0.93 g, 0.0049 mol) in dry ether (21 ml) is added 1.5 molar methyllithium solution in hexane (5.85 ml) over 15 min, followed by dropwise addition of 2,3-dihydrothiin-4-one (**2**; 0.50 g, 0.0044 mol) in cold, dry ether (10 ml). After 1 h, saturated ammonium chloride solution (100 ml) is added, and air bubbled through the solution for several hours. Extraction with ether (3 × 100 ml) is followed by rapid washing of the organic layer with cold 5% hydrochloric acid (100 ml), then 5% sodium hydrogen carbonate solution (2 × 100 ml), drying with magnesium sulphate, evaporation, and flash chromatography⁹ using 4:1 petroleum ether/ether gives **4**; yield: 0.24 g (38%).

C ₁₄ H ₂₆ O ₂ S ₂	calc.	C 57.93	H 8.97	S 22.07
(290.1)	found	58.36	9.01	21.81

M.S.: $m/e = 290.1$ (M^+), 145.

I.R. (film): $\nu = 1714$ (s) cm^{-1} .

¹H-N.M.R. (CDCl₃): $\delta = 0.93$ (d, $J = 6$ Hz, 6H); 2.29 (m, 3H); 2.82 ppm (s, 4H).

1-Mercapto-5-methylhexan-3-ol (**5**):

Reduction of **4** (0.37 g, 0.00127 mol) with lithium aluminium hydride (0.193 g, 0.00508 mol) in dry ether (20 ml) gives, after work up by extraction and preparative plate chromatography, **5**; yield: 0.29 g (78%).

C ₇ H ₁₆ OS	calc.	C 56.76	H 10.81	S 21.62
(148)	found	56.69	10.67	22.02

I.R. (film): $\nu = 3360, 2565 \text{ cm}^{-1}$.

¹H-N.M.R. (CDCl₃): $\delta = 0.90$ (d, $J = 6$ Hz, 6H); 1.2–1.9 (m, 5H); 1.99 (s, 1H, reduced with D₂O); 2.68 (m, 2H); 3.29 (t, $J = 7$ Hz, 1H); 3.82 ppm (d, 1H).

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² J. Davies, J. B. Jones, *J. Am. Chem. Soc.* **101**, 5405 (1979).

³ C. Barkenbuss, V. C. Midkiff, R. M. Newman, *J. Org. Chem.* **16**, 232 (1951).

⁴ C. H. Chen, G. A. Reynolds, J. H. Van Allen, *J. Org. Chem.* **42**, 2777 (1977).

⁵ G. H. Posner, *Org. React.* **19**, 1 (1972).

⁶ G. H. Posner, D. J. Brunelle, *J. Chem. Soc. Chem. Commun.* **1973**, 907.

⁷ E. J. Corey, D. J. Beames, *J. Am. Chem. Soc.* **94**, 7210 (1972).

⁸ Lithium alkyl(phenylthio)cuprate reagents (cf. G. F. Posner, D. J. Brunelle, L. Sinoway, *Synthesis* **1974**, 622) were tried but without success.

⁹ W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **43**, 2923 (1978).