A Useful Synthon for Sulphur Heterocycles; I. The Synthesis of Thiocoumarins

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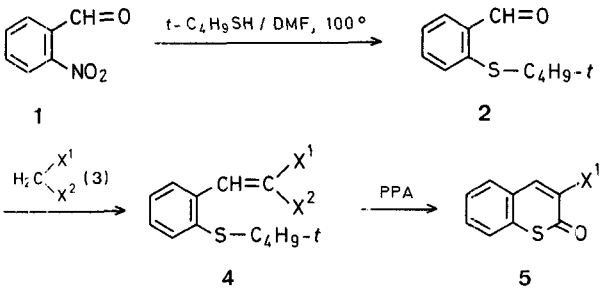
Despite much effort, general routes to thiocoumarins **5** are tedious and multistage processes giving only poor yields. Most methods depend upon the unstable *o*-mercaptobenzaldehyde or, for example, *o*-mercaptocinnamic acid, both of which require several step syntheses[1-8]. We herein report on a stable, readily available synthon, 2-*t*-butylthiobenzaldehyde (**2**) and on its conversion into a wide variety of thiocoumarins (see Schema **A** and Tables). The wider application of this synthon to give, for example, benzisothiazoles and benzothiophens is also considered[9]. 2-*t*-Butylthiobenzaldehyde (**2**) is thus prepared from *o*-nitrobenzaldehyde (**1**) in 96% yield, see procedure.



3,4	X^1	X^2	5	X^1
a	COOH/H	COOH	a	H
b	COOH	CN	b	H
c	$CO-NH_2$	CN	c	$CO-NH_2$
d	CN	CN	d	$CO-NH_2$
e	$COOC_2H_5$	CN	e	$COOC_2H_5$
f	$CO-C_6H_5$	CN	f	$CO-C_6H_5$
g	$-N=C(C_6H_5)-O-C(=O)-$		g	$N-C(H)(=O)-C_6H_5$
h	C_6H_5	COOH	h	C_6H_5
i	C_6H_5	CN	i	C_6H_5
j		CN	j	

Scheme **A**

The aldehyde **2** readily condenses with a variety of activated methylene derivatives **3** containing either an acid or nitrile group, suitable for subsequent cyclisation to the thiocoumarin. The products **4** are recorded in Table 1. It is clear that a nitrile group as the precursor to the thiocoumarin carbonyl function is preferable since (a) the condensations with aldehyde **2** occur more readily and in higher yield; (b) the cyclisation of the resulting styrenes proceeds much more readily and in higher yield, probably due to the correct geometry of the cyanostyrene (e. g. **4i**) as opposed to the cinnamic acid (e. g. **4h**) (86% at 100°, and 21% at 240°, respectively); and (c) work-up of the reaction mixture from cyclisation of the nitrile is more convenient in most cases. The initially formed product from cyclisation of the nitriles (possibly the imine) is soluble in the diluted polyphosphoric acid allowing ether extraction of side-products, followed by liberation of the thiocoumarin by reflux or basification of the acidic solution.

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Table 1. 2-t-Butylthiostyrenes **4a–j** from Aldehyde **2** and Methylene Compounds **3a–j**

Reagent 3	Solvent and base	Reaction conditions temp./time	Product	Yield [%]	m.p. (solvent) or b.p./torr	I.R. (nujol) ν_{max} [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$ and/or DMSO-d_6) δ [ppm]	Molecular formula[a]
3a	$C_2H_5OH/C_5H_5N/C_5H_{11}N$	reflux/21 h	**4a**	97	185–186° (C_2H_5OH)	1680 (CO); 1640 (C=C); 785 (*ortho*)	1.24 (s, *t*-C_4H_9); 6.45 (d, CH—COOH); 8.43 (d, —CH); 7.86 (m, H-6); 7.3–7.7 (m, 4H); $J = 16$ Hz	$C_{13}H_{16}O_2S$ (236.2)
3b	$H_2O/NaOH$	80°/0.5 h	**4b**	69	177–178° (toluene/PE)	2255 (CN); 1705 (CO); 1608 (C=C); 770 (*ortho*)	1.27 (s, *t*-C_4H_9); 6.81 (OH); 7.5–7.8 (m, 3H); 8.20 (dd, H-6); 9.00 (s, =CH)	$C_{14}H_{15}NO_2$ (261.3)
3c	$C_2H_5OH/NaOC_2H_5$	20°/0.1 h	**4c**	58	188.5–190.5° (toluene)	2245 (CN); 1695 (CO); 3450, 3340 (NH_2); 770 (*ortho*)	1.27 (s, *t*-C_4H_9); 7.45–7.8 (m, 5H); 8.15 (dd, H-6); 9.00 (s, =CH)	$C_{14}H_{16}N_2OS$ (260.3)
3d	$C_2H_5OH/NaOC_2H_5$	20°/0.25 h	**4d**	76	142–144°/0.15	2250 (CN); 1375 (*t*-C_4H_9); 1685 (C=C); 765 (*ortho*)	1.27 (s, *t*-C_4H_9); 6.40 (m, 3H); 7.87 (dd, H-6); 8.41 (s, =CH)	$C_{14}H_{14}N_2S$ (242.3)
3e	$C_2H_5OH/NaOC_2H_5$	20°/1.5 h	**4e**	84	192–194°/0.6 (54–55° (PE))	2245 (CN); 1730 (CO); 1610; 780; 760	1.30 (s, *t*-C_4H_9); 1.40 (t, CH_3); 4.40 (q, CH_2); 7.4–7.8 (m, 3H); 8.30 (dd, H-6); 9.13 (s, =CH)	$C_{16}H_{19}NO_2S$ (289.3)
3f	$C_2H_5OH/NaOC_2H_5$	20°/0.5 h	**4f**	81	109–110° (toluene/PE)	2250 (CN), 1665 (CO), 800; 762; 710; 675	1.10 (s, *t*-C_4H_9); 8.25 (m, H-6); 7.5–8.0 (m, 8H); 8.68 (s, =CH)	$C_{20}H_{19}NOS$ (321.4)
3g	$Ac_2O/NaOAc$	100°/2 h	**4g**	45	148–149° (acetone/H_2O)	1795 (CO); 775; 708	1.30 (s, *t*-C_4H_9); 7.3–7.8 (m, 6H); 8.15 (dd, 2H, *ortho*-C_6H_4); 8.30 (s, =CH); 9.00 (dd, H-6)	$C_{20}H_{19}NO_2S$ (337.4)
3h	$Ac_2O/N(C_2H_5)_3$	reflux/1.5 h	**4h**	57	187–188° (toluene/PE)	1680 (CO); 1265; 715	1.30 (s, *t*-C_4H_9); 6.7–7.4 (m, 9H); 7.57 (dd, H-6); 8.43 (s, =CH)	$C_{19}H_{20}O_2S$ (312.4)
3i	$C_2H_5OH/NaOC_2H_5$	reflux/–[b]	**4i**	86	103–105° (PE)	2245 (CN); 780; 770; 710	1.27 (s, *t*-C_4H_9); 7.3–7.8 (m, 8H); 8.18 (dd, H-6); 8.39 (s, =CH)	$C_{19}H_{19}NS$ (293.4)
3j	$C_2H_5OH/NaOC_2H_5$	20°/0.25 h	**4j**	89	70–71° (PE)	2240 (CN); 780	1.25 (s, *t*-C_4H_9); 7.38 (m, 4H); 7.59 (m, d-thienyl); 8.15 (dd, H-6); 8.30 (s, =CH)	$C_{17}H_{17}NS_2$ (299.3)

[a] All products gave satisfactory microanalyses (C ±0.45%, H ±0.16%, N ±0.12%).

[b] Mixture is heated to reflux and immediately allowed to cool.

2-t-Butylthiobenzaldehyde (2):

A mixture of *o*-nitrobenzaldehyde (**1**; 20.0 g), potassium carbonate (20 g), *t*-butyl thiol (25 ml), and dimethylformamide (25 ml) is heated at 100° for 30 h, cooled and poured into water (500 ml). The product is extracted with ether and the extract washed successively with water (4 × 500 ml), 2% sodium hydroxide solution (5 × 200 ml), and then water. The dried (magnesium sulphate) solution is evaporated and the residue distilled first at atmospheric pressure to remove residual *t*-butyl thiol and then at low pressure to give the product as a pale yellow oil; yield: 24.65 g (96%); b.p. 80–82°/0.05 torr.

$C_{11}H_{14}OS$	calc.	C 68.02	H 7.27
(194.2)	found	68.31	7.50

M.S.: *m/e* = 194 (M^+, 20%); 138 ($M^+ - C_4H_8$, 100%); 137 (43%); 110 (20%); 109 (27%); 104 (30%).

I.R. (liquid film): ν_{max} = 1698 (CO); 1385, 1375 (*t*-C_4H_9); 722 cm^{-1} (*o*-disubst.).

^{1}H-N.M.R. ($CDCl_3$): δ = 10.86 (s, CHO); 8.00 (m, H-6); 7.60 (m, 3H); 1.32 ppm (s, *t*-C_4H_9).

Preparation of 2-*t*-Butylthiostyrenes (4a–j):

2-t-Butylthiocinnamic acid (**4a**): A mixture of 2-*t*-butylthiobenzaldehyde (**2**; 1.60 g), malonic acid (1.71 g), pyridine (3.5 ml), piperidine (10 drops), and ethanol (2 ml) is heated on a boiling water bath for 21 h, then evaporated to dryness. The residue is recrystallised from ethanol to give the product **4a**; yield: 1.89 g (97%).

α-Cyano-2-t-butylthiocinnamic acid (**4b**): Cyanoacetic acid (1.60 g) is neutralised with 4 molar sodium hydroxide solution and extra alkali (1 ml) is added together with the aldehyde (1.94 g) and water to give a volume of 10 ml. The mixture is heated and stirred at 80° for 0.5 h and then cooled, acidified to congo red (pH 2), filtered, and the product recrystallised.

α-Substituted cinnamonitriles (**4c–4f** *and* **4i**): To the aldehyde (**2**; 1.94 g, 0.01 mol) and nitrile (**3**; X^1 = CN, X^2 = $CONH_2$, CN, $COOC_2H_5$, C_6H_5CO or C_6H_5; 0.01 mol) in ethanol (5 ml) is added with stirring sodium ethoxide in ethanol (0.6 ml, 20% w/v) and the mixture stirred as in Table 1. Addition of water liberates the product **4** which is filtered (solids) or extracted (liquids).

2-Phenyl-4-(2-t-butylthiophenylmethylene)-oxazol-5-one (**4g**): The aldehyde (**2**); (1.94 g), hippuric acid (2.0 g), and anhydrous sodium acetate (0.84 g) are dissolved in acetic anhydride (3.2 g) at 110° and then the mixture is heated on the water bath for 2 h, followed by

Table 2. Thiocoumarins **5** from 2-t-Butylthiostyrenes **4a–j**

Substrate	Reaction conditions temp./time/workup	Product	Yield [%]	m.p. (solvent) or b.p./torr	Molecular formula[a] or Lit. m.p. or b.p.	I.R. (nujol) ν_{max} [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$ and/or DMSO-d_6) δ [ppm]
4a	100°/1.5 h/A	**5a**	70	79–80°[b]	Lit.[1] 80–80.5°	1668 (CO); 825; 762; 735	6.48 (d, H-3); 7.76 (d, H-4); 7.60 (~d, H-5); 7.42 (br. s, 3H); J_{34} = 11 Hz
4b	100°/2 h/B	**5b**	100	203–204° (C_2H_5OH)	$C_{10}H_6O_3S$ (206.2)	1740 (CO); 1605; 790; 773; 765; 735	5.10 (s, OH); 7.5–7.70 (m, 3H); 7.95 (dd, H-5); 8.73 (s, H-4)
4c	100°/0.8 h/C	**5c**	90	249–250°	Lit.[10] 246°	3415; 3180; (NH_2); 1705 (CO);	8.00 (br, NH_2); 7.75 (m, 3H); 8.15
4d	100°/0.5 h/C	**5c**	81	(toluene)		762; 730	(d, H-5); 8.86 (s, H-4)
4e	100°/0.8 h/D	**5e**	54[c]	218–220°/1.5	$C_{12}H_{10}O_3S$ (234.2)	1715 ($COOC_2H_5$); 1640 (CO); 1280; 1215; 1015; 755	1.39 (t, CH_3); 4.40 (q, CH_2); 7.46 (m, 3H); 7.70 (m, H-5); 8.36 (s, H-4)
4f	100°/0.8 h/B	**5f**	44	152–153°[d]	Lit.[4] 154°	1665; 1620 (CO's); 1225; 800; 755; 740; 720; 690; 685	8.36 (s, H-4); 7.5–8.1 (m, 9H)
4g	60°/1.5 h/A	**5g**	61	144.5–145.5° (toluene/PE)	$C_{16}H_{11}NO_2S$ (281.3)	3410 (NH); 1685 (CO); 1615; 770; 722; 715	7.3–7.9 (m, 9H); 9.03 (s, NH); 9.10 (s, H-4)
4h	240°/1 h/A	**5h**	21	112–113°[b]	$C_{15}H_{10}OS$ (238.2)	1630 (CO); 762; 740; 710; 700	7.65 (s, H-4); 7.2–7.6 (m, 3H)
4i	100°/0.8 h/B	**5h**	86				
4j	100°/0.5 h/B	**5j**	37	177–179° (PE)	$C_{13}H_8OS_2$ (244.2)	1625 (CO); 1590; 1380; 790; 750	7.2–7.5 (m, 5H); 7.67 (d, H-5); 7.93 (m, 1H); 7.96 (s, H-4)

[a] All products gave satisfactory microanalyses (C ±0.39%, H ±0.39%, N ±0.06%).

[b] Purified by column chromatography, $SiO_2/CHCl_3$.

[c] When the diluted reaction mixture was refluxed for 4 h, the acid **5b** was obtained (86%).

[d] Direct from reaction mixture.

addition of ethanol (4 ml) at 95°. The cooled solution is extracted with ether and the dried extract evaporated to yield the crude product.

α-Phenyl-2-t-butylthiocinnamic acid (**4h**): The aldehyde (**2**; 1.94 g), phenylacetic acid (2.0 g), triethylamine (2.0 g), and acetic anhydride (5 ml) are heated under reflux for 1.5 h, water is added at 90°, and the cooled mixture is filtered to give the product.

Preparation of Thiocoumarins 5; General Procedure:

The styrene (**4**; 1.0 g) in polyphosphoric acid (~40 g) is heated as shown in Table 2, when the mixture is cooled and diluted with water. The products are isolated by one of the following procedures:

Method A: The product is extracted with chloroform and purified by elution through a column of silica with chloroform.

Method B: The solution is extracted once with ether and the extract discarded. The aqueous phase is diluted to 700 ml and refluxed for 4 h, cooled, filtered, and the product dried and recrystallised.

Method C: The solution is neutralised at 20–30° with 4 molar sodium hydroxide solution and filtered. The product is washed with water and dried in a vacuum dessicator.

Method D: The pH of the solution is adjusted to pH 5.5 using 4 molar aqueous sodium hydroxide and then the mixture is boiled (1.5 h), cooled, and the product ether extracted.

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[1] C. Chmelewsky, P. Friedländer, *Ber. Dtsch. Chem. Ges.* **46**, 1903 (1913).

[2] H. Simonis, A. Elias, *Ber. Dtsch. Chem. Ges.* **49**, 763 (1916).

[3] H. W. Zimmer, J. M. Holbert, *U.S. Patent* 3287459 (1966); *C.A.* **66**, 46331 (1967).

[4] G. Herberty, H. Wamhoff, F. Korte, *Z. Naturforsch.* [b] **23**, 312 (1968).

[5] A. Ricci, *Ann. Chim. (Rome)* **48**, 985 (1958).

[6] A. Ricci, A. Martani, *Ann. Chim. (Rome)* **53**, 588 (1963).

[7] A. Ruwet, M. Renson, *Bull. Soc. Chim. Belg.* **77**, 465 (1968); **78**, 449 (1969).

[8] W. D. Cotterill, C. J. France, R. Livingstone, J. R. Atkinson, *J. Chem. Soc. Perkin Trans. 1* **1972**, 817.

[9] O. Meth-Cohn, B. Tarnowski, *Synthesis* **1978**, 58.

[10] H. D. Brown, *U.S. Patent*, 3278547 (1966); *C.A.* **65**, 18593 (1966).

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