A Simplified Procedure for the Preparation of 2-Alkoxycarbonyl-5-aryl-4-cyano-3-hydroxy-3-phenyltetrahydrothiophenes

Satoshi Kambe*, Koji Saito

Oyama Technical College, Oyama-shi, Tochigi, 323, Japan

Akio Sakurai

The Institute of Physical and Chemical Research, Wako-shi, Saitama, 351, Japan

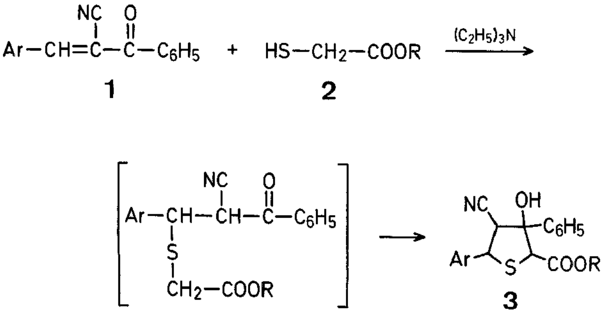
Hiroshi Midorikawa

Department of Domestic Science, Showa Women's University, Tokyo, 154, Japan

Recently, as a part of our synthetic studies using α,β-unsaturated nitriles[1,2,3], the one-step synthesis of 7*H*-thiazolo[3,2-*a*]pyridine derivatives from α-cyanocinnamic esters and mercaptoacetic esters in the presence of triethylamine was reported[4]. On the other hand, it has been well known that the formation of the thioether group by the addition of a thiol to an olefin can be utilized to carry out a Dieckmann synthesis of a 3-oxotetrahydrothiophene from an α-mercapto ester and α,β-unsaturated nitrile[5,6,7].

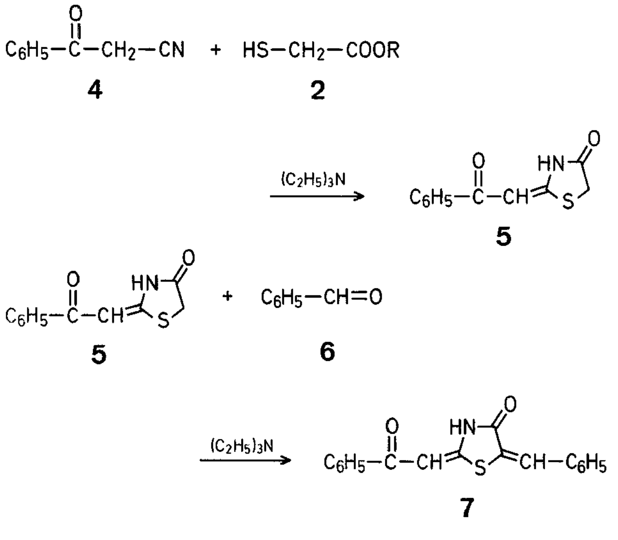
In the present communication, we report a facile synthesis for the title compounds **3** through the Michael addition of mercaptoacetic esters **2** to benzylidenebenzoylacetonitriles **1** in the presence of triethylamine without isolation of intermediate thioethers.

The reaction of **1** with **2** was carried out in a suitable alcohol containing triethylamine, direct synthesis of 7*H*-thiazolo[3,2-*a*]pyridine or 3-oxotetrahydrothiophene derivatives being expected. However, an unexpected colorless crystalline product was obtained upon the treatment of **1a** with **2a** in methanol containing triethylamine (Method A). Microanalytical and spectroscopic data confirmed it to be 4-cyano-3-hydroxy-2-methoxycarbonyl-3,5-diphenyltetrahydrothiophene (**3a**). Reactions of other benzylidenebenzoylacetonitriles **1** with **2** also gave similar tetrahydrothiophene derivatives. However, the substituent effect was obscure in this case. Furthermore, **3** was also obtained in poor yield by the condensation of benzoylacetonitrile with aromatic aldehydes and **2** in the presence of triethylamine (Method B).



The I.R. spectra of **3** showed the existence of OH (3432–3345 cm^{-1}), CN (2250–2220 cm^{-1}), and C=O groups (1725–1692 cm^{-1}). However, the carbonyl group of **3g** (Ar = C_6H_5, R = C_2H_5) showed a doublet absorption for C=O (1740 and 1721 cm^{-1}) which is probably attributable to the Fermi resonance or stereoisomerism.

In contrast with the above Method A, when benzoylacetonitrile (**4**) was used instead of **1**, the reaction led to the formation of 2-benzoylmethylene-4-oxotetrahydrothiazole (**5**). The product **5** reacted with benzaldehyde (**6**) in the presence of triethylamine to give 5-benzylidene-2-benzoylmethylene-4-oxotetrahydrothiazole (**7**).



2-Alkoxycarbonyl-5-aryl-4-cyano-3-hydroxy-3-phenyltetrahydrothiophenes 3; General Procedures:

Method A: A mixture of the benzylidenebenzoylacetonitriles **1** (0.01 mol) and the mercaptoacetic esters **2** (0.01 mol) in a suitable alcohol (5 ml) containing triethylamine (1.01 g, 0.01 mol) is heated under reflux with stirring for 5 h. The colorless crystals which deposit during the reaction are isolated by suction, washed with water and a suitable alcohol, and recrystallized from acetone.

Method B: A mixture of benzoylacetonitrile (**4**; 1.45 g, 0.01 mol), an aromatic aldehyde (0.01 mol) and the mercaptoacetic esters **2** (0.01 mol) in a suitable alcohol (5 ml) containing triethylamine (1.01 g, 0.01 mol) is heated under reflux for 6 h. Work-up is as described under Method A.

Reaction solvent and washings: **3a–3f**; methanol, **3g–3l**; ethanol.

2-Benzoylmethylene-4-oxotetrahydrothiazole (5):

A solution of benzoylacetonitrile (**4**; 1.45 g, 0.01 mol) and ethyl mercaptoacetate (**2a**; 1.20 g, 0.01 mol) in ethanol (5 ml) containing triethylamine (1.01 g, 0.01 mol) is heated under reflux for 2 h. After cooling, the resultant precipitate is isolated by suction and recrystallized from tetrahydrofuran/ethanol; yield: 1.2 g (54%); m.p. 215–216 °C.

$C_{11}H_9NO_2S$	calc.	C 60.27	H 4.14	N 6.39	S 14.60
(219.2)	found	60.35	4.14	6.43	14.53

I.R. (Nujol): ν = 3200; 1725; 1700 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 3.78 (s, 2H, —CH$_2$—); 6.77 (s, 1H, =CH—); 7.4–8.0 (m, 5H$_{arom}$); 11.40–12.45 ppm (br, 1H, —NH—).

5-Benzylidene-2-benzoylmethylene-4-oxotetrahydrothiazole (7):

A mixture of benzoylmethylene-4-oxotetrahydrothiazole (**5**; 1.09 g, 0.005 mol) and benzaldehyde (**6**; 0.53 g, 0.005 mol) in ethanol (5 ml) containing triethylamine (0.50 g, 0.005 mol) is heated under reflux for 7 h. The yellow crystals which precipitate during the reaction are isolated by suction, washed with water and ethanol, and recrystallized from tetrahydrofuran/ethanol; yield: 1.1 g (71%); m.p. 189–190 °C.

0039-7881/80/1032-0839 $ 03.00

Table. 2-Alkoxycarbonyl-5-aryl-4-cyano-3-hydroxyl-3-phenyltetrahydrothiophenes **3**

Product No.	Ar	R	Yield [%] by Method A	 B	m.p. [°C]	Molecular formula[a]	I.R. (nujol)[b] ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6)[c] δ [ppm]
3a	C_6H_5	CH_3	34	18	210–211°	$C_{19}H_{17}NO_3S$ (339.3)	3400; 2250; 1725	3.41 (s, 3H, CH_3); 4.17–4.30 (d, 1H, C$\underline{H}$—CH); 5.07–5.20 (d, 1H, CH—C$\underline{H}$); 5.07 (s, 1H, S—C$\underline{H}$—CO); 6.51 (s, 1H, OH); 7.1–8.0 (m, 10H_{arom})
3b	4-H_3C—C_6H_4	CH_3	27	14	215–216°	$C_{20}H_{19}NO_3S$ (353.4)	3362; 2222; 1710	2.33 (s, 3H, 4-$\underline{H}_3C$—C_6H_4); 3.50 (s, 3H, CH_3); 3.86–4.34 (d, 1H, C$\underline{H}$—CH); 4.90–5.38 (d, 1H, CH—C$\underline{H}$); 5.12 (s, 1H, S—C$\underline{H}$—CO); 6.54 (s, 1H, OH); 7.0–8.2 (m, 9H_{arom})
3c	4-H_3CO—C_6H_4	CH_3	30	19	218–219°	$C_{20}H_{19}NO_4S$ (369.4)	3381; 2240; 1710	3.96 (s, 3H, CH_3); 4.25 (s, 3H, 4-$\underline{H}_3CO$—C_6H_4); 4.40–4.60 (d, 1H, C$\underline{H}$—CH); 5.34–5.54 (d, 1H, CH—C$\underline{H}$); 5.56 (s, 1H, S—C$\underline{H}$—CO); 6.97 (s, 1H, OH); 7.3–8.5 (m, 9H_{arom})
3d	4-O_2N—C_6H_4	CH_3	15	6	215–216°	$C_{19}H_{16}N_2O_5S$ (384.3)	3345; 2220; 1710; 1520	3.50 (s, 3H, CH_3); 3.96–4.46 (d, 1H, C$\underline{H}$—CH); 4.96–5.46 (d, 1H, CH—C$\underline{H}$); 5.23 (s, 1H, S—C$\underline{H}$—CO); 6.60 (s, 1H, OH); 7.0–8.7 (m, 9H_{arom})
3e	4-Cl—C_6H_4	CH_3	22	11	217–218°	$C_{19}H_{16}ClNO_3S$ (373.8)	3400; 2240; 1710	3.49 (s, 3H, CH_3); 3.95–4.23 (d, 1H, C$\underline{H}$—CH); 4.90–5.18 (d, 1H, CH—C$\underline{H}$); 5.13 (s, 1H, S—C$\underline{H}$—CO); 7.2–8.4 (m, 9H_{arom})[d]
3f	2-Cl—C_6H_4	CH_3	12	4	219–220°	$C_{19}H_{16}ClNO_3S$ (373.8)	3380; 2220; 1715	3.49 (s, 3H, CH_3); 4.05–4.44 (d, 1H, C$\underline{H}$—CH); 5.33–5.77 (d, 1H, CH—C$\underline{H}$); 5.10 (s, 1H, S—C$\underline{H}$—CO); 6.67 (s, 1H, OH); 6.9–8.3 (m, 9H_{arom})
3g	C_6H_5	C_2H_5	33	17	202–203°	$C_{20}H_{19}NO_3S$ (353.4)	3432; 2224; 1740; 1721	0.82–1.04 (t, 3H, $CH_2C\underline{H}_3$); 3.8–4.2 (m, 3H, $C\underline{H}_2CH_3$, C$\underline{H}$—CH); 4.98–5.20 (d, 1H, CH—C$\underline{H}$); 5.07 (s, 1H, S—C$\underline{H}$—CO); 6.50 (s, 1H, OH); 7.2–7.9 (m, 10H_{arom})
3h	4-H_3C—C_6H_4	C_2H_5	29	18	199–200°	$C_{21}H_{21}NO_3S$ (367.4)	3400; 2240; 1705	0.80–1.16 (t, 3H, $CH_2C\underline{H}_3$); 2.33 (s, 3H, 4-$\underline{H}_3C$—C_6H_4); 3.9–4.3 (m, 3H, $C\underline{H}_2CH_3$, C$\underline{H}$—CH); 4.90–5.30 (d, 1H, CH—C$\underline{H}$); 5.15 (s, 1H, S—C$\underline{H}$—CO); 6.59 (s, 1H, OH); 7.1–8.0 (m, 9H_{arom})
3i	4-H_3CO—C_6H_4	C_2H_5	27	17	210–211°	$C_{21}H_{21}NO_4S$ (383.4)	3375; 2240; 1699	0.68–0.89 (t, 3H, $CH_2C\underline{H}_3$); 3.59 (s, 3H, 4-H_3CO—C_6H_4); 3.7–4.0 (m, 3H, $C\underline{H}_2CH_3$, C$\underline{H}$—CH); 3.99 (s, 1H, S—C$\underline{H}$—CO); 4.80–4.97 (d, 1H, CH—C$\underline{H}$); 6.32 (s, 1H, OH); 6.7–7.7 (m, 9H_{arom})
3j	4-O_2N—C_6H_4	C_2H_5	13	6	220–221°	$C_{20}H_{18}N_2O_5S$ (398.4)	3490; 2245; 1710; 1510	0.66–1.20 (t, 3H, $CH_2C\underline{H}_3$); 3.7–4.5 (m, 3H, $C\underline{H}_2CH_3$, C$\underline{H}$—CH); 5.04–5.50 (d, 1H, CH—C$\underline{H}$); 5.16 (s, 1H, S—C$\underline{H}$—CO); 6.34–6.80 (br, 1H, OH); 7.3–8.8 (m, 9H_{arom})
3k	4-Cl—C_6H_4	C_2H_5	23	15	209–210°	$C_{20}H_{18}ClNO_3S$ (387.8)	3425; 2230; 1710	0.96–1.23 (t, 3H, $CH_2C\underline{H}_3$); 3.8–4.3 (m, 3H, $C\underline{H}_2CH_3$, C$\underline{H}$—CH); 4.96–5.30 (d, 1H, CH—C$\underline{H}$); 5.16 (s, 1H, S—C$\underline{H}$—CO); 6.44–6.68 (br, 1H, OH); 7.2–8.4 (m, 9H_{arom})
3l	2-Cl—C_6H_4	C_2H_5	14	5	193–194°	$C_{20}H_{18}ClNO_3S$ (387.8)	3350; 2240; 1705	0.93–1.24 (t, 3H, $CH_2C\underline{H}_3$); 3.7–4.4 (m, 3H, $C\underline{H}_2CH_3$, C$\underline{H}$—CH); 5.13 (s, 1H, S—C$\underline{H}$—CO); 5.47–6.74 (d, 1H, CH—C$\underline{H}$); 6.54–6.80 (br, 1H, OH); 7.3–8.3 (m, 9H_{arom})

[a] The microanalyses were in satisfactory agreement with the calculated values (C ±0.40, H ±0.27, N ±0.23, S ±0.30).

[b] All I.R. spectra were measured with a Shimazdu I.R. spectrometer.

[c] All ^{1}H-N.M.R. spectra were measured with a JEOL JNM-MH-60 using TMS as internal standard.

[d] O$\underline{H}$: not located.

		C	H	N	S
$C_{18}H_{13}NO_2S$	calc.	70.35	4.26	4.56	10.41
(307.3)	found	70.52	4.46	4.73	10.37

I.R. (Nujol): ν = 3300; 1700 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 6.80 (s, 1H, =CH—CO—); 7.2–8.2 (m, 1H, =CH— and 10H_{arom}); 12.66–13.17 ppm (br, 1H, —NH—).

Received: May 27, 1980

---

* To whom correspondence should be addressed.

[1] S. Kambe et al., *Synthesis* **1977**, 841.

[2] S. Kambe et al., *Synthesis* **1979**, 287.

[3] S. Kambe et al., *Synthesis* **1980**, 366.

[4] S. Kambe et al., *Synthesis* **1977**, 839.

[5] B. R. Baker et al., *J. Org. Chem.* **12**, 135 (1947).

[6] D. Binder, P. Stanetty, *Synthesis* **1977**, 200.

[7] D. N. Reinhoudt et al., *Synthesis* **1978**, 368.