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AN IMPROVED SYNTHESIS OF SUBSTITUTED BENZO[*b*]THIOPHEN-2-CARBOXYLIC ACIDS AND RELATED ACIDS

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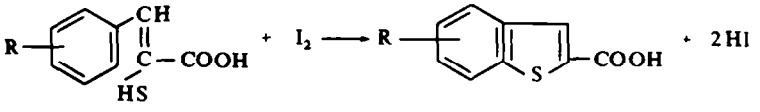
Abstract—The oxidative cyclization of β-aryl-α-mercaptoacrylic acids with chlorine in dry carbon tetrachloride rapidly gives the corresponding benzo[*b*]thiophen-2-carboxylic acids in high yield. This process is a considerable improvement on processes previously reported. The purity of the crude β-aryl-α-mercaptoacrylic acids can be determined by titration with iodine in ethanol and thus the crude intermediates can be cyclized without further purification by use of the calculated amount of chlorine.

CONSIDERABLE attention has recently been paid to the synthesis of benzo[*b*]thiophen derivatives as bio-isosteres[1,2] of pharmacologically active indole derivatives. One of the most widely used routes to the benzo[*b*]thiophen-2-carboxylic acids often used as intermediates in these syntheses, has been the oxidative cyclization of appropriately substituted β-aryl-α-mercaptoacrylic acids, first reported by Campaigne and Cline.[3] The reaction has usually been carried out by heating the β-aryl-α-mercaptoacrylic acid with an excess of iodine in a large volume of dry dioxan for 12 to 24 hr. Then either the solvent was partly removed under reduced pressure and the reaction mixture was diluted with water,[4] or the reaction mixture was directly diluted with a large volume of



water,[3] and the very crude product was isolated by a rather tedious process, after destruction of the excess of iodine with sodium bisulphite. We found both the isolation and the working-up wasteful of time and materials so we sought an improvement in the synthesis. We have now found that the reaction of one molar proportion of chlorine in carbon tetrachloride for a few minutes at room temperature with certain β-aryl-α-mercaptoacrylic acids in carbon tetrachloride, benzene or dioxan gives cleanly and in high yield the corresponding benzo[*b*]thiophen-2-carboxylic acids. The β-styryl acid similarly gives 5-phenylthiophen-2-carboxylic acid. The method has made accessible a number of hitherto unknown substituted benzo[*b*]thiophen-2-carboxylic acids.

The β-aryl-α-mercaptoacrylic acids (I) could be prepared satisfactorily from the related 5-arylidene rhodanines (II), despite the fact that there is considerable confusion in the literature concerning the m.ps of 5-arylidene rhodanines and the related β-aryl-α-mercaptoacrylic acids. The 5-arylidene rhodanines listed in Table 1 were prepared (80–95%) by boiling a solution of the appropriate aldehyde or ketone with rhodanine in

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TABLE 1. 5-ARYLIDENE RHODANINES (II)[a]

Ar	R	M.p. Found	M.p. Lit.	Found (%) C	H	N	S	Required
PhCH:CH	H	223–224°	223–224°[5]	—	—	—	—	—
o-MeO·C_6H_4	Me	149–151	—	54·1	4·05	5·5	24·4	*b*
m-MeO·C_6H_4	Me	169–170	169–170[6]	—	—	—	—	—
p-MeO·C_6H_4	Me	170–171	—	54·5	4·0	5·4	24·5	*b*
o-MeO·C_6H_4	H	251(*d*)	250(*d*)[7] 198–200[8]	52·4	3·8	5·4	25·2	*c*
m-MeO·C_6H_4	H	232	165–170[8] 229–230[9]	52·6	3·5	5·7	25·1	*c*
p-MeO·C_6H_4	H	250–251	207–208[8] 230–232[10] 249–254[11]	52·5	3·6	5·9	25·5	*c*
3.4-$(MeO)_2C_6H_3$	H	232	232[5]	—	—	—	—	—

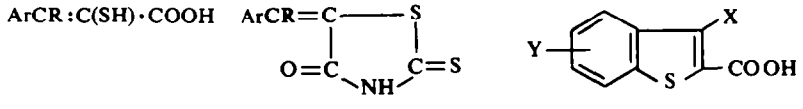
[a] Crystallized from ethanol in yellow or orange-yellow needles.
[b] $C_{12}H_{11}NO_2S_2$ requires C, 54·3; H, 4·2; N, 5·3; S, 24·2%.
[c] $C_{11}H_9NO_2S_2$ required C, 52·6; H, 3·6; N, 5·6; S, 25·5%.
[d] With decomposition.

TABLE 2. β-ARYL-α-MERCAPTOACRYLIC ACIDS (I)

Ar	R	M.p. Found	M.p. Lit	Found (%) C	H	S	Required (%) C	H	S	Notes
PhCH:CH	H	155–156°	148–151°[5,a] 149[16]	64·0	4·6	15·3	64·1	4·9	15·5	*b, c*
o-MeO·C_6H_4	Me	128–129	—	59·0	5·4	14·1	59·0	5·4	14·3	*d*
m-MeO·C_6H_4	Me	166–168	*e*	58·6	5·3	14·3	59·0	5·4	14·3	*d*
p-MeO·C_6H_4	Me	138–139	—	58·9	5·5	14·25	59·0	5·4	14·3	*d*
o-MeO·C_6H_4	H	133–135	133–135[7] 138–141[8]	56·9	4·4	15·0	57·2	4·8	15·3	*f*
m-MeO·C_6H_4	H	98–100	97·5–100[8] 98–99[10]	57·1	4·5	15·4	57·2	4·8	15·3	*f*
p-MeO·C_6H_4	H	177–178	171–172·5[8] 172[17] 178[10]	57·5	4·6	15·1	57·2	4·8	15·3	*g*
3.4-$(MeO)_2C_6H_3$	H	171–172	171–172[5] 179[12] 182[18]	55·2	5·4	13·6	55·0	5·0	13·4	*h*

[a] M.P. of a crude amorphous product.
[b] Thick orange needles from benzene.
[c] $C_{11}H_{10}O_4S$ required *M*. 206. *M* (mass spectrum) 206.
[d] Colourless or pale yellow flakes from cyclohexane.
[e] M.p. not recorded.[6]
[f] Recrystallized from benzene.
[g] Recrystallized from toluene.
[h] Recrystallized from methanol.

benzene containing ammonium acetate and glacial acetic acid. The mixture was heated for 15 min to 6 hr, depending on the aldehyde or ketone used, with continuous removal of water by means of a Dean–Stark trap. Details are given in Table 1, which also includes some results of previous workers for comparison.



I II III

The 5-arylidene rhodanines were hydrolysed with 15% aqueous caustic soda on the steam bath[12] for 20 min to give the corresponding β-aryl-α-mercaptoacrylic acids (Table 2).

TABLE 3. BENZO[*b*]THIOPHEN-2-CARBOXYLIC ACIDS (III)[a]

X	Y	Yield (%) Found	Yield (%) Lit.[b]	M.p. Found	M.p. Lit.	Found (%) C	Found (%) H	Found (%) S	Notes	PMR spectrum[c] τ-value	PMR spectrum[c] Assignment
Me	4-OMe	74	—	247–248°	—	59·2	4·8	14·0	*e, f*	2·75 *q*	H-7
										3·04 *m*	H-5 & H-6
Me	5-OMe	75	—	250–251	—	59·1	4·5	14·1	*e, f*	2·17 *d*[g]	H-7
										2·60 *d*	H-4
										2·83 *q*	H-6
Me	6-OMe	75	—	248–249	—	59·5	4·4	14·1	*e, f*	2·19 *d*[h]	H-4
										2·52 *d*	H-7
										2·90 *q*	H-5
H	5-OMe	60	40[16]	214–216	215–216[15]	57·5	3·8	15·5	*i, j*	1·96 *d*[k]	H-3
										2·14 *q*	H-7
										2·48 *d*	H-4
										2·84 *q*	H-6
H	5,6-(OMe)$_2$	75	25[3]	260–261	260–261[3]	55·1	4·1	13·3	*l, n*	2·03 *s*	H-3
										2·47 *s*	H-7
										2·53 *s*	H-4

[a] *M* (mass spectrum) was correct.

[b] Prepared by Campaigne and Cline's cyclization with iodine.[3]

[c] Measurements were made with CD_3·CO·CD_3 as solvent. by using a J.E.O.L. instrument operating at 100 MHz. Aromatic proton signals only are reported.

[e] $C_{11}H_{10}O_3S$ required C. 59·5; H. 4·5; S. 14·4%.

[f] Colourless flakes from methanol.

[g] $J_{4,6}$ 2·5 Hz. $J_{6,7}$ 9 Hz.

[h] $J_{4,5}$ 9 Hz. $J_{5,7}$ 2·5 Hz.

[i] Calc. for $C_{10}H_8O_3S$; C. 57·7; H. 3·9; S. 15·4%.

[j] Silvery flakes from acetic acid.

[k] $J_{3,7}$ 0·5 Hz. $J_{4,6}$ 2·5 Hz. $J_{6,7}$ 9 Hz. (*d*=doublet. *m*=multiplet. *q*=quartet. *s*=singlet).

[l] Calc. for $C_{11}H_{10}O_4S$; C. 55·5; H. 4·2; S. 13·5%.

[n] Colourless feathery needles from methanol. 5-Phenylthiophen-2-carboxylic acid (90%. lit.[3] 61%). m.p. 186–187° (lit.[6] 187–188°) was crystallized from benzene as colourless needles (Found: C. 64·5; H. 4·2; S. 15·6. Calc. for $C_{11}H_8O_2S$; C. 64·7; H. 3·9; S. 15·7%).

Since the β-aryl-α-mercaptoacrylic acids are notoriously difficult to purify by recrystallization,[10] we looked for a convenient method of estimating them in the crude reaction mixture. These acids are easily oxidized to the corresponding disulphides by iodine and this method has been used preparatively.[5, 13, 14] We found that this oxidation is very rapid and almost quantitative in ethanol, so that it can be used to estimate the mercapto-acids. For this purpose a solution of the mercapto-acid in ethanol was treated with an excess of standard ethanolic iodine, and after 5 min the excess of iodine was back titrated with standard thiosulphate.

The mercaptoacrylic acids (I) in dry carbon tetrachloride, benzene or dioxan were cyclized oxidatively by treatment with 1 molar proportion of chlorine in dry carbon tetrachloride at room temperature. The orange-yellow colour observed immediately after the reagents were mixed soon faded, and hydrogen chloride was evolved. The product was isolated either by filtering off the solid that separated, or by removal of the solvent under reduced pressure and recrystallization of the residue. The crude dry mercaptoacrylic acids could be satisfactorily cyclized in this way provided that the amounts of the reactants were calculated on the basis of the titrations described above. The properties of the products are given in Table 3. Unfortunately, attempted cyclization of β-*o*-methoxy- and β-*p*-methoxy-phenyl-α-mercaptoacrylic acid gave material from which none of the required acid could be isolated. Campaigne and Kreighbaum[15] also failed to cyclize β-*p*-methoxy- and β-2,3-dimethoxy-phenyl-α-mercaptoacrylic acid.

EXPERIMENTAL

5-(3-Methoxy-α-methylbenzylidene)rhodanine —*m*-Methoxyacetophenone (75 g, 0·5 mole) was added to a boiling solution of rhodanine (66·5 g, 0·5 mole) in benzene (500 ml) containing ammonium acetate (4 g) and glacial acetic acid (12 ml). A Dean–Stark trap was used to collect the water (10 ml) liberated during the first 2 hr of the reaction. Benzene (100 ml) was then distilled from the reaction mixture and the resulting solution was boiled for a further 2 hr and then cooled. The product (106 g, 80%) crystallized out as a mass of yellow needles and was collected, washed with water, then with a little ethanol and dried. It was recrystallized from ethanol and had m.p. 169–170° (lit.[6] 169–170°).

Cinnamaldehyde reacted similarly with rhodanine but required only 20 min to give cinnamylidene rhodanine (90%). Details of this and other products prepared similarly are given in Table 1.

β-Aryl-α-mercaptoacrylic acids

The 5-arylidene rhodanines were hydrolysed with aqueous sodium hydroxide (15%, w/v) on a steam bath for 20 min as described by Julian and Sturgis.[12] The yields and details of the products are given in Table 2.

Estimation of the purity of the crude β-aryl-α-mercaptoacrylic acids

Enough of the crude dry acid was dissolved in ethanol to give an approximately 0·1M solution. An excess of 0·1N ethanolic iodine was added and the mixture was kept for 5 min at room temperature. The excess of iodine was then titrated with 0·1N sodium thiosulphate solution with starch as indicator. Since 1 ml of 0·1N iodine solution was consumed by each 0·0001 mole of mercaptoacrylic acid, the purity of the crude acid could be determined.

3-Methyl-5-methoxybenzo[b]thiophen-2-carboxylic acid

A solution of chlorine (0·71 g, 0·01 mole) in dry carbon tetrachloride (25 ml) was added to a solution of β-(3-methoxyphenyl)-β-methyl-α-mercaptoacrylic acid (2·24 g, 0·01 mole) in dry carbon tetrachloride (20 ml). An orange colour was immediately produced, but it soon faded, and a yellow solid was precipitated with the simultaneous evolution of hydrogen chloride. After 30 min, the solid was filtered off, the solution was concentrated under reduced pressure to half its original volume and the solid produced

was collected. The total product (1·75 g, 75%) crystallized from methanol in colourless flakes, m.p. 214–216° (lit.[16] 215–216°). In other experiments dry dioxan or dry benzene was used to dissolve the mercaptoacrylic acid. Occasionally it was necessary to remove all the solvent under reduced pressure and to crystallize the residue. Details of the products are given in Table 3.

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