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REACTIONS OF 2-THENYL CHLORIDE AND 5-CHLORO-2-THENYL CHLORIDE

T. L. CAIRNS and B. C. McKUSICK

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In the course of a general investigation of thiophene chemistry, the reactions of 2-thenyl chloride (1) and 5-chloro-2-thenyl chloride (2, 3) were studied. The chlorine of 2-thenyl chloride is readily replaced by nucleophilic reagents, and in this way tri-2-thenylamine and 2-thenyl propionate, benzoate, ethylxanthate, and amyl ether were prepared. Similarly, 5-chloro-2-thenyl chloride was converted to the corresponding acetate, ethylxanthate, thiocyanate, ethyl ether, N-substituted-ε-caprolactam, and cyanide. The cyanide[1] was subsequently hydrolyzed to 5-chloro-2-thiopheneacetic acid *via* an imido ester hydrochloride.

2-Thenyl chloride is similar in properties to its analog, benzyl chloride, but it shows important differences. It is more prone to solvolysis in the presence of bases so that substances such as alcohols are often undesirable reaction media for 2-thenyl chloride. Thus, 2-thenyl chloride reacted with sodium cyanide in aqueous ethanol to give a mixture of ethyl 2-thenyl ether (25% yield) and 2-thenyl cyanide (32% yield); under the same conditions, benzyl chloride is known to give a high yield of benzyl cyanide uncontaminated by ethyl benzyl ether (9). It seems to be more readily attacked by nucleophilic reagents than is benzyl chloride. For example, when one mole of sodium amoxide in amyl alcohol was added to a mixture of one mole each of benzyl chloride and 2-thenyl chloride, the product, a mixture of amyl benzyl ether and amyl 2-thenyl ether, contained 78 mole-per cent of the latter.

The preparation and properties of 2-thenyl alcohol were studied briefly. Although it can be prepared from 2-thiophenecarboxaldehyde by reduction with lithium aluminum hydride, this method is inferior to that of Emerson and Patrick (13). The reduction procedure is of more value when applied to 2-acetylthiophene; it gives a good yield of α-(2-thienyl)ethanol and is probably the best laboratory synthesis of this alcohol, which is of interest because it is easily dehydrated to the polymerizable ethene, 2-vinylthiophene (7, 11, 12, 14). An attempt to prepare α-(2-thienyl)ethanol by hydrogenation of 2-acetylthiophene led instead to α-(2-tetrahydrothienyl)ethanol in low yield.

EXPERIMENTAL

Physical constants and analytical data of many of the new compounds are listed in Table I.

Thenyl chlorides. A slight modification of the chloromethylation procedures given in the literature (1, 16) was used. The best yield (50%) of 2-thenyl chloride (1), n_D^{25} 1.5630, was

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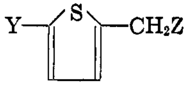
[1] Note added in proof: Ford, Prescott, and Colingsworth, *J. Am. Chem. Sos.*, **72**, 2109 (1950), described this cyanide and the acid, amide, and methyl ester derived from it in a paper which appeared after this paper had been accepted for publication.

obtained at −5° to −10°. The optimum temperature for preparing 5-chloro-2-thenyl chloride (2, 3) was 45°; yield 85%; b.p. 95–96° (15 mm.); n_D^{25} 1.5722; d_4^{25} 1.385.

Thenyl esters. 5-Chloro-2-thenyl acetate was prepared by adding 134 g. of 5-chloro-2-thenyl chloride dropwise to a stirred solution of 118 g. of potassium acetate in 240 ml. of acetic acid at 100°. After an hour at 100°, the mixture was cooled to 25°, diluted with 500 ml. of water, and extracted with ether. The extract was washed with water and 10% sodium carbonate solution before being dried over magnesium sulfate and distilled. 2-Thenyl propionate was prepared similarly. 2-Thenyl benzoate was obtained by stirring and refluxing a solution of 144 g. of sodium benzoate in 220 ml. of water with 49 g. of 2-thenyl chloride for one hour; 2-thenyl alcohol (6.0 g.) was a by-product.

TABLE I

THENYL COMPOUNDS



Y	Z	BOILING POINT[g]		M.P. OR n_D^{25}	d_4^{25}	YIELD %	FORMULA	ANALYSIS, % Carbon		Hydrogen	
		°C.	MM.					Calc'd	Found	Calc'd	Found
H	$OCOC_2H_5$	108–110	18	1.5112	1.135	65	$C_8H_{10}O_2S$	56.4	56.3	5.9	6.2
H	$OCOC_6H_5$	134–135	0.9	58–59°[a]		60	$C_{12}H_{10}O_2S$	66.0	65.8	4.6	4.6
H	OC_5H_{11}-*n*	104–105	13	1.4922	0.9844	69	$C_{10}H_{16}SO$	65.2	64.8	8.8	9.0
H	$SCSOC_2H_5$	120–127	0.4	1.6157	1.239	84	$C_8H_{10}OS_3$	38.0	38.6	3.6	3.6
Cl	$OCOCH_3$	130–132	24	1.5249	1.285	86	$C_7H_7ClO_2S$	44.1	44.2[b]	3.7	3.9
Cl	OC_2H_5	81–82	6	1.5183	1.1757	47	C_7H_9ClOS	47.6	48.2	5.1	5.3
Cl	$SCSOC_2H_5$	145–147	1.4	1.6188	1.328	77	$C_8H_9ClOS_3$	38.0	38.6[c]	3.6	3.6
Cl	SCN	121–123	1.4	1.6242	1.379	75	$C_6H_4ClNS_2$	38.0	38.2	2.1	2.2
Cl	CN	117–119	7	1.5551	1.3144	39	C_6H_4ClNS	45.7	45.8	2.6	2.7
Cl	$CONH_2$			121–122°[d]		6	C_6H_6ClNOS	41.0	41.4	3.4	3.7
Cl	CO_2CH_3	67–72	0.5	1.5301		29	$C_7H_7ClO_2S$	44.1	44.9	3.7	4.3
Cl	CO_2H	115–112	0.5	65.5–66°[e]		64	$C_6H_5ClO_2S$	40.8	40.9	2.9	3.1
Cl	$\underbrace{N(CH_2)_5C}{=}O$			71–73.5°[a]		40	$C_{11}H_{14}ClNOS$	54.2	54.4[f]	5.8	5.9

[a] Recrystallized from hexane.

[b] Sap. equiv.: Calc'd, 191; Found, 191.

[c] Chlorine: Calc'd, 14.0; Found, 14.65.

[d] Recrystallized from benzene.

[e] Recrystallized from cyclohexane.

[f] Chlorine, nitrogen, sulfur: Calc'd, 14.6, 5.8, 13.1; Found, 14.6, 5.5, 12.7.

[g] Distillations were through a six-inch, indented, Claisen-type head.

Alkaline hydrolysis of 5-chloro-2-thenyl acetate gave 5-chloro-2-thenyl alcohol. Aqueous permanganate at 10° oxidized the alcohol to 5-chloro-2-thiophenecarboxylic acid, m.p. and mixture m.p. 150–151° (8). 5-Chloro-2-thenyl alcohol soon splits out water with formation of *bis*-(5-chloro-2-thenyl) ether (13) unless stored over solid potassium carbonate. The alcohol has been prepared before (13) but not analyzed.

Anal. Calc'd for C_5H_5ClOS: Cl, 23.9. Found: Cl, 24.2.

Ethylxanthates. Carbon disulfide (107 g.) was added with cooling to a solution of 50 g. of sodium hydroxide in 50 ml. of water and 500 ml. of 95% ethanol. The solution was stirred and gently refluxed as 150 g. of 2-thenyl chloride was added over a period of 15 minutes. The mixture was refluxed 45 minutes, cooled, and poured into water. The xanthate was extracted with ether. Distillation gave 206 g. of yellow 2-thenyl ethylxanthate. 5-Chloro-2-thenyl ethylxanthate was prepared similarly.

5-Chloro-2-thenyl thiocyanate. A solution of 87.5 g. of potassium thiocyanate in 50 ml. of water and 220 ml. of acetone was stirred and refluxed while 100 g. of 5-chloro-2-thenyl chloride was added over a period of 30 minutes. Heating was continued for three hours, the mixture was poured into 750 ml. of water, and the product was taken up in ether and distilled. The thiocyanate is a skin irritant.

Thenyl ethers. To prepare amyl 2-thenyl ether, 20 g. of 2-thenyl chloride was added to a solution of 3.8 g. of sodium in 75 ml. of *n*-amyl alcohol and the mixture was heated at 100° for an hour. Water and ether were added and the organic layer was separated and distilled. 5-Chloro-2-thenyl ethyl ether was prepared similarly.

The competitive reaction of benzyl chloride and 2-thenyl chloride with sodium amoxide. A solution of 23.0 g. (1.00 g.-atom) of sodium in 490 ml. of amyl alcohol was added to a well-stirred solution of 132.6 g. (1.00 mole) of 2-thenyl chloride and 126.6 g. (1.00 mole) of benzyl chloride in 250 ml. of amyl alcohol at 65–70°. The mixture was stirred at 95–100° for 45 minutes, cooled to room temperature, and stirred with 400 ml. of water to dissolve sodium chloride. The organic layer was distilled. The main fraction, b.p. 127–129° (26 mm.), n_D^{25} 1.4906, weighed 181 g. From its sulfur content (13.7%) it was, on a mole basis, 78% amyl 2-thenyl ether and only 22% amyl benzyl ether (4).

Tri-2-thenylamine. 2-Thenyl chloride (182 g.) was added to 600 ml. of well-stirred liquid ammonia over a period of 20 minutes. The mixture stood at room temperature for 16 hours to allow the ammonia to evaporate. Then 700 ml. of 10% sodium hydroxide and 400 ml. of ether were added to the residue. The ether layer was separated and heated on a steam-bath to remove the ether. A solid mass remained; it weighed 117 g. and was no longer completely soluble in ether. Ether extraction effected the separation of 85 g. of pasty solid from insoluble matter. The pasty solid was pressed on a clay plate to remove 2-thenylamine, di-2-thenylamine, and other oils. Subsequent crystallization from hexane gave 45 g. (32% yield) of tri-2-thenylamine, m.p. 67–69°. After several recrystallizations it melted at 70.5–71°.

Anal. Calc'd for $C_{15}H_{15}NS_3$: C, 59.0; H, 4.95; N, 4.6.
Found: C, 58.7; H, 5.2; N, 4.6.

N-(5-Chloro-2-thenyl)-ε-caprolactam.[2] The N-sodio derivative of ε-caprolactam was prepared by adding 9.6 g. of sodium hydride in small portions with stirring to 45.2 g. of ε-caprolactam in 300 ml. of dry xylene. A solution of 66.8 g. of 5-chloro-2-thenyl chloride in 50 ml. of xylene was added dropwise and the mixture was refluxed five hours. Sodium chloride and xylene were removed by filtration and distillation *in vacuo*, respectively, and the crystalline residue was extracted with 650 ml. of boiling hexane. Cooling the hexane solution caused 46 g. of crude N-(5-chloro-2-thenyl)-ε-caprolactam to separate. This after recrystallization from hexane weighed 38.5 g.

5-Chloro-2-thiopheneacetonitrile. Fifty grams of 5-chloro-2-thenyl chloride was added in a period of 15 minutes to a stirred solution of 29 g. of potassium cyanide in 30 ml. of water at 105°. After 45 minutes of heating and stirring, the mixture was cooled, ether, water, and diatomaceous earth were added, the mixture was filtered to remove resin, and the ether layer was distilled; yield 39%.

Under six other sets of conditions, including the use of xylene or aqueous acetone as the reaction medium, even lower yields of nitrile were obtained. In some cases considerable *bis*-(5-chloro-2-thenyl) ether (13) was formed.

5-Chloro-2-thiopheneacetamide and methyl 5-chloro-2-thiopheneacetate. Hydrogen chloride was passed into a mixture of 6.7 g. of methanol and 31.5 g. of 5-chloro-2-thiopheneacetonitrile at 0–5° until 8.0 g. (10% excess) had been absorbed. Dry ether (55 ml.) was added. The mixture was held at 0° for six hours and then filtered to remove 15.0 g. of crude imido ester hydrochloride. The hydrochloride was heated at 100° with 50 ml. of water. This caused

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[2] Prepared by Dr. R. E. Benson.

oil mixed with 2.0 g. (6% yield) of a solid, 5-chloro-2-thiopheneacetamide, to separate. Distillation of the oil gave 4.4 g. of methyl 5-chloro-2-thiopheneacetate. An additional 6.7 g. (total yield, 29%) was obtained from the ether solution from which the imido ester hydrochloride had been filtered by saturating it with hydrogen chloride and then pouring it into ice-water. Analysis indicated that the ester was slightly impure.

5-Chloro-2-thiopheneacetic acid. 5-Chloro-2-thiopheneacetonitrile was not easily hydrolyzed by acid, and alkaline hydrolysis converted it to tar. However, 5-chloro-2-thiopheneacetic acid was readily obtained by refluxing 5-chloro-2-thiopheneacetamide or, better, methyl 5-chloro-2-thiopheneacetate with 10% aqueous sodium hydroxide for 15 minutes.

2-Thenyl alcohol (13, 15, 17, 18, 19). 2-Thiophenecarboxaldehyde was prepared as described by Dunn, Waugh, and Dittmer (5). The intermediate salt of 2-thenyl chloride with hexamethylenetetramine, not previously analyzed, melted at 189–190°.

Anal. Calc'd for $C_{11}H_{17}ClN_4S$: C, 48.4; H, 6.3.
Found: C, 48.2; H, 6.3.

The Nystrom-Brown method of reduction (6) was used. Twenty grams of 90% lithium aluminum hydride was stirred in 600 ml. of boiling ether for three hours. The reaction flask was immersed in cold water and 170 g. of 2-thiophenecarboxaldehyde was added over a period of three hours at such a rate that gentle refluxing occurred. Then 150 ml. of 12 *N* hydrochloric acid in 500 ml. of water was added to the mixture at 10–20° with stirring. The ether layer was separated, washed with water and aqueous sodium carbonate, dried over magnesium sulfate, and distilled over 0.5 g. of potassium carbonate. The yield of 2-thenyl alcohol, b.p. 101–102° (16 mm.), n_D^{25} 1.5593, was 129 g. (75%). It gave a negative test with 2,4-dinitrophenylhydrazine. Oxidation with aqueous permanganate at 10° gave 2-thiophenecarboxylic acid, m.p. and mixture m.p. 125–126° (8), in 20% yield.

Except for slight discoloration, 2-thenyl alcohol was unaffected by being held under nitrogen in a 225°-bath for 15 hours. At 200° a small amount of oxalic acid converted it to an orange resin; some formaldehyde, detected by odor, was formed in the process. Orange resins were also obtained at 25° under the influence of sulfuric acid, phosphoric acid or stannic chloride. 2-Thenyl alcohol gradually dehydrates to 2-thenyl ether (13) unless stored over potassium carbonate; one such unstabilized sample contained 15% 2-thenyl ether and 18% higher-boiling material after two years at 25°. Similar dehydration occurs when 2% by weight of 12 *N* hydrochloric acid is dissolved in 2-thenyl alcohol and the solution allowed to stand 24 hours at 25°.

Reduction of 2-acetylthiophene. A. By lithium aluminum hydride. Under the conditions used above for the reduction of 2-thiophenecarboxaldehyde, α-(2-thienyl)ethanol (7, 10, 11, 14) was obtained in 75% yield; b.p. 83° (8 mm.); m.p. 20–21°; n_D^{25} 1.5429. Its phenylurethan (14) melted at 84.5–85.5°.

B. By hydrogen. A solution of 126 g. (1.00 mole) of 2-acetylthiophene (Socony-Vacuum Oil Co.; n_D^{25} 1.5629) and 50 ml. of absolute ethanol was hydrogenated for six hours at 150° and a pressure of 2000–2800 lbs./sq. in. in the presence of 3.0 g. of ruthenium dioxide. An uptake corresponding to 0.7 mole of hydrogen was observed. Distillation gave 100 g. of material of b.p. 68–69° (4 mm.); n_D^{25} 1.5552. Eight grams of the distillate was mixed with 4.0 g. of phenyl isocyanate and 3 drops of pyridine and the mixture was allowed to stand for two days at 25°. Removal of material volatile at 100° (0.5 mm.) left 2.0 g. of oil from which, by treatment with hexane, 0.44 g. of the *phenylurethan of α-(2-tetrahydrothienyl)-ethanol* was isolated. It melted at 80.5–81° after several crystallizations from chloroform-hexane mixtures. A mixture with the phenylurethan of α-(2-thienyl)ethanol melted at 60–74°.

Anal. Calc'd for $C_{13}H_{17}NO_2S$: C, 62.1; H, 6.8; N, 5.6.
Found: C, 62.2; H, 6.75; N, 5.7.

Evidently a low yield of α-(2-tetrahydrothienyl)ethanol, and little or no α-(2-thienyl)-ethanol, was formed by this method.

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SUMMARY

2-Thenyl chloride and 5-chloro-2-thenyl chloride have been converted to corresponding esters, ethers, ethylxanthates, cyanides, and other similar compounds.

Wilmington, Delaware

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