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SYNTHESIS OF SULFUR-CONTAINING HETEROCYCLES USING THIONYL CHLORIDE OR SULFUR CHLORIDES

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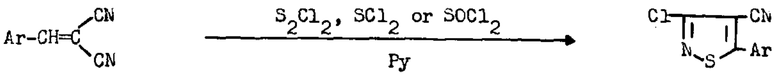
We have reported a new and simple method for isothiazole ring formation using thionyl chloride or sulfur chlorides.(1) This method was found thereafter to be applicable to various types of compounds, and it is our purpose of this communication to report a new approach to the general preparation of sulfur-containing heterocycles such as isothiazoles, benzo[b]thiophenes and thiophenes.

Reaction of benzylidenemalononitriles(1) with sulfur chlorides or thionyl chloride in the presence of pyridine led to formation of 5-aryl-3-chloro-4-isothiazolecarbonitriles(2) shown in Table 1.(2) In a typical experiment a mixture of benzylidenemalononitrile (1.0 mole), pyridine (0.2 mole) and sulfur monochloride (3.0 moles) was heated at 140 - 150° for 5 - 6 hours and poured into ice water. The precipitated material which was collected by filtration was dissolved in hot ethanol to remove insoluble gummy sulfur. The supernatant gave 3-chloro-5-phenyl-4-isothiazolecarbonitrile(2a), which could be converted to the known 3-methyoxy-5-phenyl-4-isothiazolecarbonitrile(3) with sodium methoxide.



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3 a: R=R'=Cl, bp 95-96°/33mm, yield 31%
b: R=CH_3,R'=Cl, bp 103-104°/26mm, yield 27%

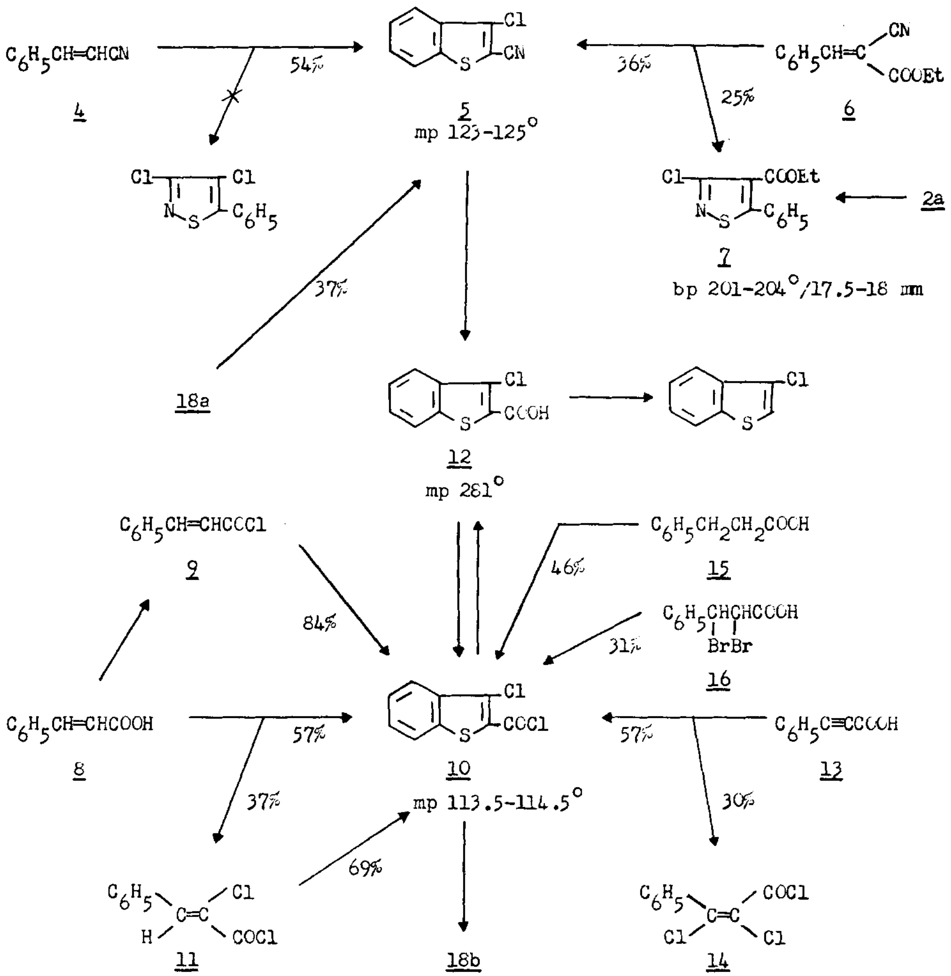
Table 1. 5-Aryl-3-chloroisothiazolecarbonitriles (2)

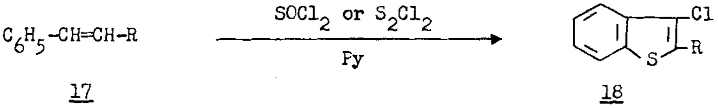
Compounds	Reagent	Yield(%)	M.p. (°C)	λ_{max}^{EtOH} mμ(ε)
2a, Ar=C_6H_5	S_2Cl_2	80	85-86	281 (15000)
	SCl_2	73		
	$SOCl_2$	43		
2b, Ar=p-Cl-C_6H_4	S_2Cl_2	72	119	285 (16000)
	SCl_2	70		
2c, Ar=o-Cl-C_6H_4	S_2Cl_2	73	97-98	270.5 (11500)
	SCl_2	58		
2d, Ar=2,6-diCl-C_6H_3	S_2Cl_2	73	140-141	268 (9500)
	SCl_2	56		
	$SOCl_2$	38		

Acrylonitrile and crotononitrile gave 3,4,5-trichloroisothiazole(3a) and 3,4-dichloro-5-methylisothiazole(3b), respectively, whereas cinnamonitrile(4) gave 3-chlorobenzo[b]thiophene-2-carbonitrile(5) instead of the expected 3,4-dichloro-5-phenylisothiazole by the reaction with sulfur monochloride. Ethyl benzylidenecyanoacetate(6) gave also 5 together with ethyl 3-chloro-5-phenyl-4-isothiazolecarboxylate(7) which was identical with 7 derived from 2a.

This finding prompted us to investigate the related compounds for the benzo[b]thiophene synthesis. Although a reaction of cinnamic acid(8) with thionyl chloride gave only cinnamoyl chloride(9), the reaction in the presence of pyridine afforded 3-chlorobenzo[b]thiophene-2-carbonyl chloride(10)(4) and α-chloro-*trans*-cinnamoyl chloride(11),(5) whereas the similar reaction with sulfur monochloride did not give any identified product. Compounds 9 and 11 were converted to 10 with both sulfur monochloride and thionyl chloride in the presence of pyridine. Hydrolysis of 5 and 10 gave 3-chlorobenzo[b]thiophene-2-carboxylic acid(12), which was decarboxylated by heating to the known 3-chlorobenzo[b]thiophene.(6)

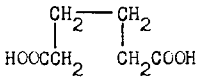
From 13, 15 and 16, 10 was also obtained by the action of thionyl chloride and pyridine. In the reaction of 13 with thionyl chloride and pyridine, α,β-dichloro-*cis*-cinnamoyl chloride (14)(10) was isolated from the filtrate of 10. In a similar way compounds 17a-c gave benzo[b]thiophene derivatives 18a-c, respectively. The aldehyde 18a could be converted to 5 in a usual way *via* the oxime. Styrene(17d) carrying no substituent on the β carbon gave 2,3-dichlorobenzo[b]thiophene(18d)(6) using thionyl chloride and pyridine.





a: R=CHO	a: R=CHO (7),	mp 104°, yield 30%
b: R=COOEt	b: R=COOEt (8),	mp 69-69.5°
c: R=C_6H_5	c: R=C_6H_5 (9),	mp 67-69°, yield 45%
d: R=H	d: R=Cl (6),	mp 54-55°, yield 41%

Three aliphatic acids 19, 20 and 21 were reacted with thionyl chloride and pyridine to form thiophene derivatives 22 (mp 45°, yield 63%),(11) 23 (bp 97-100°/25mm, 11%)(12) and 24 (16%),(13) respectively.



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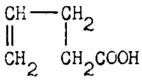

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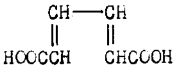

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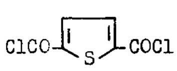

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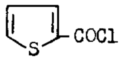

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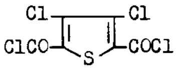

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References

1 a) T. Naito, S. Nakagawa J. Okumura, K. Takahashi and K. Kasai, Bull. Chem. Soc., Japan, 41, 957 (1968).

b) T. Naito, S. Nakagawa, J. Okumura, K. Takahashi, K. Masuko and Y. Narita, ibid, 41, 965 (1968).

c) J. Okumura, S. Nakagawa, K. Masuko and T. Naito, Abstracts of papers, the 88th annual meeting of Pharmaceutical Society of Japan (Tokyo, April 5-7, 1968), p.123.

d) S. Nakagawa, Y. Narita and T. Naito, ibid, p.124.

2 The structure of all products in this paper was established by elemental analysis, uv, ir and nmr spectra. The yield given here is that in a typical run when the reaction was carried out repeatedly.

3 R. U. Lemieux and R. G. Micetich, U. S. Patent, 3,311,611(1967); R. G. Micetich and R. Raap, J. Med. Chem., 11, 159 (1968).

4 Recently A. J. Krubsack and T. Higa have obtained 10 from 8 and 15 by the similar reaction (Tetrahedron Letters, 1968, 5149).

5 The acid, mp 137-138° ; P. Pfeiffer and G. Haefelin, Ber., 55, 1785 (1922), mp 139°.

6 A. H. Schlesinger and D. T. Mowry, J. Am. Chem. Soc., 73, 2614 (1951).

7 A. Ricci, D. Balucani and N. P. Buu-Hoi, J. Chem. Soc., 1967, 779.

8 Identified by gas chromatography with the authentic sample obtained from 10 and ethanol.

9 E. J. Geering, U. S. Patent, 3,278,552 (1966).

10 The acid, mp 120-120.5° ; T. Stoermer and P. Heymann, Ber., 46, 1256 (1913), mp 120-121°.

11 W. Ried and H. Mengler, Ann. Chem., 678, 113 (1964).

12 L. W. Jones and C. D. Hurd, J. Am. Chem. Soc., 43, 2444 (1921).

13 Isolated as the methyl ester, mp 168-169°.