BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 41 2954—2959 (1968)

1,3-Dipolar Cycloaddition Reaction of Thiophenecarbonitrile *N*-Oxides with Various Dipolarophiles

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(Received February 29, 1968)

Thiophene-2-carbonitrile *N*-oxide (I) and 5-chlorothiophene-2-carbonitrile *N*-oxide (II) were synthesized by the chlorination of corresponding aldoxime with nitrosyl chloride. These compounds gave Δ^2-isoxazolines and isoxazoles through 1,3-dipolar cycloaddition reaction with compounds having double or triple bond as dipolarophiles. In the cycloaddition reaction, II was less reactive than I. This would be explained by stability of II owing to electron-withdrawing ability of chlorine atom at 5-position in the thiophene ring. Furoxans, the dimers of the nitrile *N*-oxide, were formed from these 1,3-dipoles in the absence of dipolarophile.

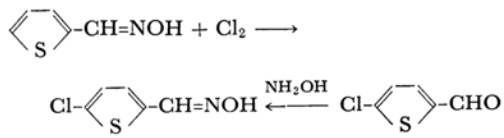
Many kinds of aromatic and aliphatic carbonitrile *N*-oxides and their reactions have been known.[1-7] We have also reported the 1,3-dipolar cycloaddition reaction as an elementary reaction of polymer formation.[8] However, neither synthesis of thiophenecarbonitrile *N*-oxides nor 1,3-dipolar cycloaddition reaction with them have ever been reported up to date. In the present study, synthesis of thiophene- and 5-chlorothiophene-2-carbonitrile *N*-oxides and their reactions with dipolarophile have been studied. Although thiophene-2-carbonitrile *N*-oxide and 5-chlorothiophene-2-carbonitrile *N*-oxide themselves could not be isolated, thiophene- and 5-chlorothiophene-2-carbohydroxamoyl chlorides reacted with dipolarophiles in the presence of triethylamine to give the products which would be expected from the corresponding carbonitrile *N*-oxides and dipolarophiles. The details will be described below.

Results and Discussion

I. Synthesis of Thiophene- and 5-Chlorothiophene-2-carbohydroxamoyl Chlorides. For a synthesis of hydroxamoyl chloride, the reaction of aldoxime with chlorine has generally been utilized.[5-8]

$$\mathrm{R\text{-}CH{=}NOH + Cl_2 \rightarrow R\text{-}\overset{\displaystyle Cl}{\overset{|}{C}}{=}NOH + HCl}$$

When thiophenecarboxaldoxime was subjected to such a chlorination procedure, the product obtained was not hydroxamoyl chloride but 5-chlorothiophene-2-carboxaldoxime resulted through chlorination of thiophene nuclei. The product was identical with the one prepared from 5-chlorothiophene-2-carboxaldehyde and hydroxylamine.



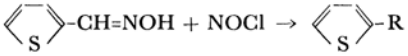
Accordingly, this reaction is inadequate to the preparation of thiophenecarbohydroxamoyl chloride.

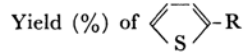
The reaction of aldoxime with nitrosyl chloride has been reported by Rheinbolt[9] as an another method of preparing hydroxamoyl chloride.

When the cooled ether solution of nitrosyl chloride was added to the cooled ether solution of thiophene-2-carboxaldoxime, precipitates were formed immediately and then disappeared slowly with evolution of gas on standing the reaction mixture at a low temperature. After the precipitates were dissolved completely and the evolution of gas stopped, hydroxamoyl chloride was obtained from the reaction mixture. If the precipitate was kept in chloroform-benzene at room temperature for a long period, thiophene-2-carbonamide was obtained. On contact with air, the precipitate decomposed slowly to give thiophene-2-carboxaldehyde and thiophene-2-carbonitrile. The results of the reaction of thiophenecarboxaldoxime with nitrosyl chloride are summarized in Table 1.

1) R. Huisgen, R. Grashey and J. Sauer, "The Chemistry of Alkenes," Interscience Publishers, New York, N. Y. (1964), p. 806. R. Huisgen, *Angew. Chem.*, **75**, 604 (1963); R. Huisgen, *ibid.*, **75**, 742 (1963).
2) C. Grudmann, *Angew. Chem.*, **75**, 450 (1963).
3) H. Wieland, *Ber.*, **40**, 418 (1907); H. Wieland, L. Semper and E. Gmelin, *Ann.*, **367**, 61 (1909).
4) G. S. Skinner, *J. Am. Chem. Soc.*, **46**, 734 (1924).
5) O. Piloty and H. Steinkock, *Ber.*, **35**, 3114 (1902).
6) A. Werner, *ibid.*, **27**, 2846 (1894).
7) R. H. Wiley and B. J. Wakefield, *J. Org. Chem.*, **25**, 546 (1960).
8) Y. Iwakura, M. Akiyama and K. Nagakubo, This Bulletin, **37**, 767 (1964).
9) H. Rheinbolt, *Ann.*, **451**, 161 (1927).

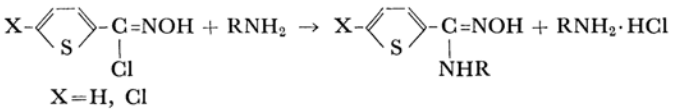
Table 1. Reaction products between nitrosyl chloride and thiophene-2-carboxaldoxime



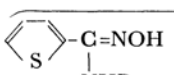
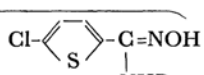
React. temp. (°C)	Reaction time (hr)		Yield (%) of 				
	Stir	Stand	R=-$CONH_2$	-CN	-CHO	-CH=NOH·HCl	-C(Cl)=NOH
0— 5	1.5	0	trace		53.4[b]	15.0	0[a]
−5— 0	3.0	0	0		23.0[b]	54.5	19.3
−10—−5	21.5	28	0	0	30.0	23.3	42.1
−15—−10	25.0	30	0	0	5.5	22.3	65.2

a) Starting material of aldoxime was recovered.
b) Combined yield of nitrile and aldehyde. They could not be separated because of their similar boiling points (nitrile; 196°C, aldehyde; 198°C).

Table 2. Results of reaction of thiophene- and 5-chlorothiophene-2-cabohydroxamoyl chlorides with amine

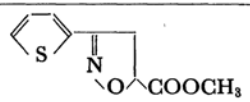
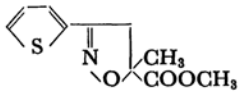
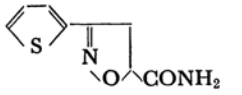
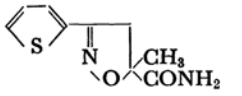
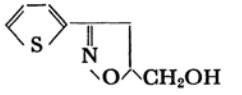
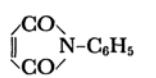
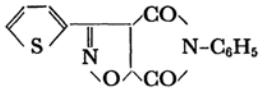
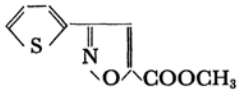
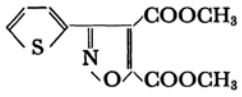
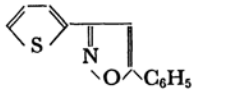


X=H, Cl

RNH_2	Product: 					Product: Cl- 				
	Mp (°C)	Yield (%)	Anal. (Calcd), % C	H	N	Mp (°C)	Yield (%)	Anal. (Calcd), % C	H	N
Aniline	90—93	74.5	60.75 (60.54	5.36 4.61	13.65 12.84)	132—134	70	52.21 (52.08	3.58 3.59	10.89 11.09)
p-Toluidine	170 (d)	67.0	62.18 (62.06	5.38 5.21	12.02 12.06)					
Triethylamine*	112—114 (d)	96.5	48.46 (48.01	2.41 2.42	10.99 11.20)	157—159 (d)	100	38.52 (37.46	1.76 1.26	8.58 8.78)

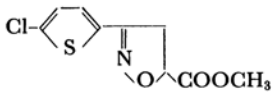
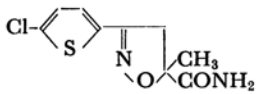
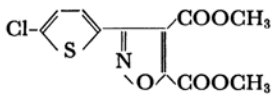
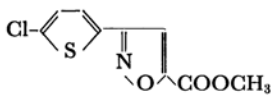
* In these cases, the products were furoxans, and their physical and analytical data are listed.

Table 3. 1,3-Dipolar cycloaddition products (1)

Dipolarophile	Product	Recrystallization solvent	Mp (°C)	Yield (%)	Anal. (Calcd), % C	H	N
$CH_2=CHCOOCH_3$			(Oil)[a]	80.7[c]			
$CH_2=C(CH_3)COOCH_3$			(Oil)[a]	81.0[c]			
$CH_2=CHCONH_2$		Benzene	160—162	59.0	49.22 (48.98	4.16 4.11	14.32 14.28)
$CH_2=C(CH_3)CONH_2$		Benzene	160	56.7	50.71 (51.42	5.13 4.80	13.36 13.33)
$CH_2=CHCH_2OH$		Ligroin	97—98	54.5	52.63 (52.46	4.63 4.95	7.42 7.65)
		Benzene + Ligroin	170—171	86.5	60.18 (60.40	3.45 3.38	8.97 9.36)
$HC\equiv CCOOCH_3$		Ligroin	100—101	54.0	51.98 (51.68	3.22 3.37	6.64 6.70)
$CH_3OCOC\equiv CCOOCH_3$		Ligroin	55—56	42.0	49.77 (49.44	3.05 3.40	5.13 5.24)
$HC\equiv C-C_6H_5$		Ligroin	106—107[b]	43.0	69.06 (68.72	3.76 3.99	6.08 6.17)

a) Identified as the corresponding amides derived by treating them with aqueous ammonia solution.
b) Furoxan as a by-product was formed. c) Raw yield.

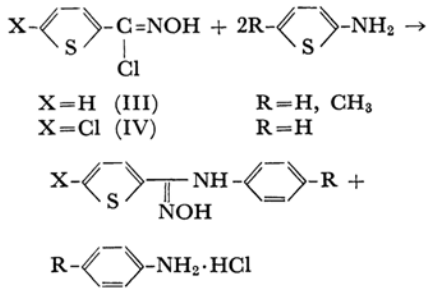
Table 4. 1,3-Dipolar cycloaddition products (2)

Dipolarophile	Products	Recrystallization solvent	Mp (°C)	Yield (%)	Anal. (Calcd), % C	H	N
$CH_2=CHCOOCH_3$		Ligroin	102—103	40.3[a]	44.39 (44.01	3.66 3.28	5.65 5.70)
$CH_2=C(CH_3)CONH_2$		Benzene	182—183	45.0[a]	44.62 (44.18	4.10 3.71	11.43 11.45)
$CH_3OCOC\equiv CCOOCH_3$		Ligroin	81	23.7[a]	43.95 (43.80	2.96 2.67	4.50 4.65)
$HC\equiv CCOOCH_3$		Ligroin	141—142	29.7[a]	44.69 (44.37	2.79 2.48	5.65 5.75)

a) Furoxan as a by-product was formed.

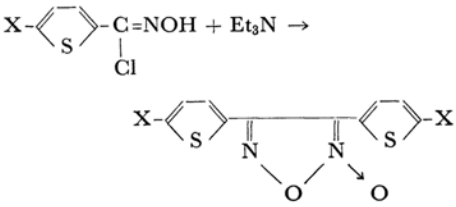
II. Reaction of Thiophene- and 5-Chlorothiophene-2-carbohydroxamoyl Chlorides.

II-1. Reaction with Amines. The amidoxime derivatives were obtained by the reaction of hydroxamoyl chloride with aniline or *p*-toluidine.



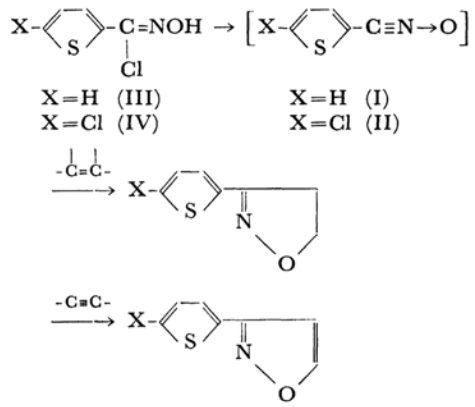
the presence of chlorine on 5-position in thiophene ring gave profound effect on the reaction of thiophenecarbohydroxamoyl chloride with amines. Thiophene-2-carbohydroxamoyl chloride reacted explosively with amines in the absence of solvent, but 5-chlorothiophene-2-carbohydroxamoyl chloride did not react unless it was heated. The influence of chlorine on 5-position to the reactivity was also observed in an aldoxime. When 5-chlorothiophene-2-carboxaldoxime was heated in an aqueous alkaline solution, it rearranged readily to 5-chlorothiophene-2-carbonamide, but thiophene-2-carboxaldoxime gave only alkali salt, and could be was recovered by treating the salt with acid.

Thiophenecarbohydroxamoyl chlorides gave furoxan in a quantitative yield in the presence of triethylamine.



The furoxan derived from 5-chlorothiophenecarbohydroxamoyl chloride was hardly soluble in usual organic solvents and was decomposed slowly above 100°C, whereas the furoxan derived from thiophenecarbohydroxamoyl chloride was more stable. Results are summarized in Table 2.

II-2. 1,3-Cycloaddition Reaction. When hydroxamoyl chloride was treated with triethylamine in the presence of alkenes or alkynes, it reacted with them preferentially. For example, 3-(2-thienyl)-4,6-dioxo-3a,4,5,6a-tetrahydro-6*H*-pyrrolo-[3,4-d]-isoxazole was obtained from thiophene-2-carbohydroxamoyl chloride and *N*-phenylmaleimide. It would be reasonable to consider that thiophenecarbohydroxamoyl chloride reacts with double bond or triple bond through nitrile *N*-oxide as an intermediate.



Results of 1,3-cycloaddition reaction are shown in Tables 3 and 4.

Allyl alcohol was less reactive upon hydroxamoyl chloride than maleimide. Such a result would be interpreted by following consideration accepted generally. 1,3-Dipolar cycloaddition reaction was enhanced by electron-withdrawing group in dipolarophile.[1] Further, a difference in the reactivity was observed between thiophene and 5-chlorothiophene derivative. Furoxan was obtained as a by-product in every reaction of 5-chlorothiophene derivative. Therefore, the reactivity of 5-chlorothiophenecarbohydroxamoyl chloride seems to be reduced by chlorine atom at 5-position. This might be explained by resonance effect of chlorine substituent.

Experimental

5-Chlorothiophene-2-carboxaldehyde. 5-Chlorothiophene-2-carboxaldehyde was prepared by Vilsmeier reaction[10] from 2-chlorothiophene, bp 105—107°C/19 mmHg (lit.[11] 100—105°C/18 mmHg).

Thiophene-2-carboxaldoximes. The oxime was prepared by treating 1 mol of thiophenecarboxaldehyde with 1.1 mol of hydroxylamine hydrochloride and 1.1 mol of sodium hydroxide in aqueous ethanol solution. Thiophene-2-carboxaldoxime was recrystallized from benzene, mp 136°C (lit.[12] 135—136°C). 5-Chlorothiophene-2-carboxaldoxime; mp 140°C (from EtOH) (lit.[11] 140°C).

Thiophenecarbohydroxamoyl chlorides. A solution of 19.7 g (0.155 mol) of the thiophene-2-carboxaldoxime in 250 m*l* of anhydrous ether was cooled below −10°C. Into the stirred solution was added a solution of 35 g (0.54 mol) of nitrosyl chloride in 180 m*l* of anhydrous ether in 30 min under dry nitrogen atmosphere. After the reaction mixture was allowed to stand at a temperature below −10°C for 5 hr, another 200 m*l* of anhydrous ether was added. Stirring and introducing nitrogen gas were continued until the evolution of hydrogen chloride stopped. It took about

10) "Org. Syntheses," Coll. Vol. IV, p. 915 (1963).
11) P. Fournari and J. P. Chane, *Bull. Soc. Chim. France*, **1963**, 479; *Chem. Abstr.*, **59**, 1570 (1963).
12) P. Grunanger and P. V. Finzi, *Gazz. Chim. Ital.*, **89**, 1771 (1959); *Chem. Abstr.*, **55**, 4480 (1961).

evolution of hydrogen chloride stopped. It took about 25 hr.

After filtration of oxime hydrochloride, the solvent was removed under reduced pressure without heating, and light brown solid and small amount of oil were obtained. The solid was recrystallized from ligroin to give colorless crystals of thiophene-2-carbohydroxamoyl chloride (III), 11 g (44%), mp 102°C.

Found: C, 37.54; H, 2.81; N, 8.49%. Calcd for C_5H_4ClNOS: C, 37.17; H, 2.50; N, 8.67%.

The oily product was identified as thiophene-2-carboxaldehyde by IR.

In a similar way 5-chlorothiophene-2-carbohydroxamoyl chloride (IV) was prepared, mp 127—128°C (ligroin).

Found: C, 30.48; H, 1.75; N, 7.12%. Calcd for $C_5H_3Cl_2NOS$: C, 30.64; H, 1.54; N, 7.15%.

5-Chlorothiophene-2-carboxaldehyde was also detected by IR.

5-Chlorothiophene-2-carbonamide. In 20 m*l* of 0.1 N aqueous sodium hydroxide solution was dissolved 0.1 g of 5-chlorothiophene-2-carboxaldoxime, refluxed for 30 min and was allowed to stand overnight. The reaction mixture was evaporated under reduced pressure to give a solid mass. Extraction and recrystallization of this solid with benzene gave white needles, 5-chlorothiophene-2-carbonamide, mp 178°C (lit.[13] 179°C, 181°C). IR(KBr): –NH(3400, 3200 cm^{-1}), amide I (1685 cm^{-1}) and amide II (1600 cm^{-1}).

Reaction of III and IV with Aniline and *p*-Toluidine. To a solution of 0.5 g of III in 20 m*l* of anhydrous THF, 0.56 g of aniline (0.006 mol) was added dropwise, and white needles formed within a few minutes. The reaction mixture was refluxed for 2 hr and allowed to stand overnight. The needles deposited were filtered and the filtrate was evaporated *in vacuo* to give a solid mass, which was recrystallized from benzene - *n*-hexane to yield crystals, mp 90—93°C. The reaction of III with *p*-toluidine and of IV with aniline were conducted similarly.

Reaction of III and IV with Triethylamine. To a mixture of 20 m*l* of anhydrous THF and 0.5 g (0.003 mol) of III was added 0.4 g (0.004 mol; 30 mol% excess) of triethylamine at room temperature with stirring. The reaction mixture was allowed to stand for 2 days. The precipitate was filtered off and washed with anhydrous THF. Combined THF solution was evaporated *in vacuo* to afford white mass. Recrystallization from THF - benzene gave white powder of 2,2′-dithienylfuroxan, mp 112—114°C (dec.). This furoxan was soluble in THF, but hardly soluble in benzene, toluene, carbon tetrachloride, chloroform, methanol, ethanol, and water. The reaction of IV with triethylamine was conducted by the similar procedure as described above.

Reaction of III and IV with Various Dipolarophiles (1,3-Dipolar Cycloaddition Reaction). All of the reaction were conducted in anhydrous THF using triethylamine as a hydrogen chloride acceptor. In each reaction, 30 mol% excess amount of a dipolarophile was used. A typical example of the reaction is as follows. To a mixture of 10 m*l* of anhydrous THF, 0.5 g (0.003 mol) of III and 0.7 g (0.004 mol) of *N*-phenylmaleimide was added dropwise 0.5 g (0.0031 mol) of triethylamine at −5°C with stirring. Triethylamine hydrochloride formed immediately. The reaction mixture was allowed to stand overnight at room temperature. The triethylamine hydrochloride was filtered and washed with a large amount of anhydrous THF. The solid product was obtained by removing the solvent from the filtrate. Recrystallization three times from benzene gave 0.8 g (87%) of colorless needles, mp 170—171°C.

13) R. Graft, *Ann.*, **661**, 141 (1963); G. Kuhnhanss, *J. Prakt. Chem.*, **3**, 137 (1956).