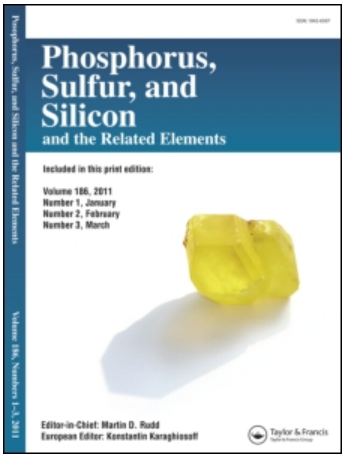

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HALOSUBSTITUTED 1,4-OXATHIOCINES. PREPARATION FROM THIOPHENE S,C-YLIDES AND STUDIES OF THERMAL REACTIVITY

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HALOSUBSTITUTED 1,4-OXATHIOCINES. PREPARATION FROM THIOPHENE S,C-YLIDES AND STUDIES OF THERMAL REACTIVITY

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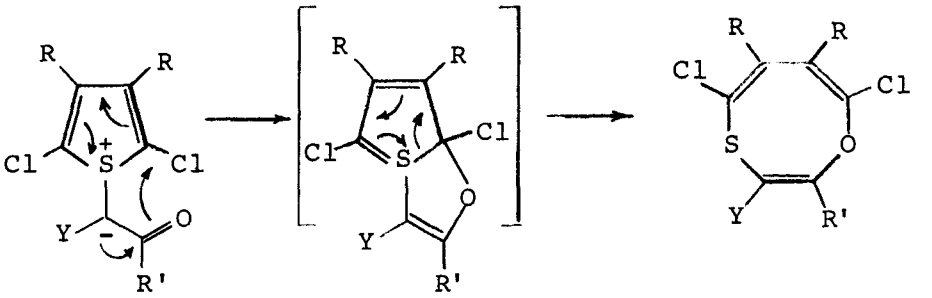
The reaction between tri- and tetrasubstituted thiophenes and diazocarbonyl compounds gave in most cases the corresponding 1,4-oxathiocines directly, without isolation of the intermediate C-S ylides. Two oxathiocines underwent thermal fragmentation leading to sulfur extrusion and the formation of tetrasubstituted phenols. A mechanism for the fragmentation is proposed and discussed.

Key words: Thiophene-S,C-ylides; oxathiocines; thermal fragmentation

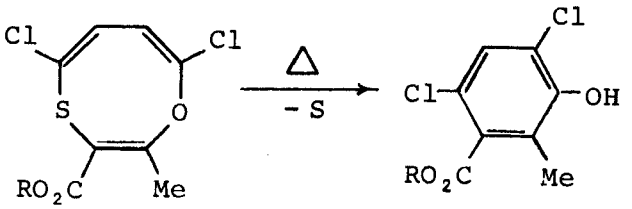
We have recently reported[1] on a smooth thermal rearrangement of halothiophene S,C-ylides (1) to 1,4-oxathiocines (2) (Scheme I), opening synthetic route to those hetero analogues of a 10π annulene system. We have observed, however, that oxathiocines (2) may not always represent the final reaction products, but they can, in some cases, undergo further transformation. That subsequent thermal reaction involves sulfur extrusion, accompanied by ring contraction, and a new type of 1,2-chlorine migration, resulting in the formation of a polysubstituted benzene derivative (3) (Scheme II).

In this work we studied the effect of substituents present in a starting thiophene molecule on the formation of the corresponding S,C-ylides, their rearrangements



(1) (2)

Scheme 1



(2) (3)

Scheme 2

TABLE I

Substituted thiophenes[a]

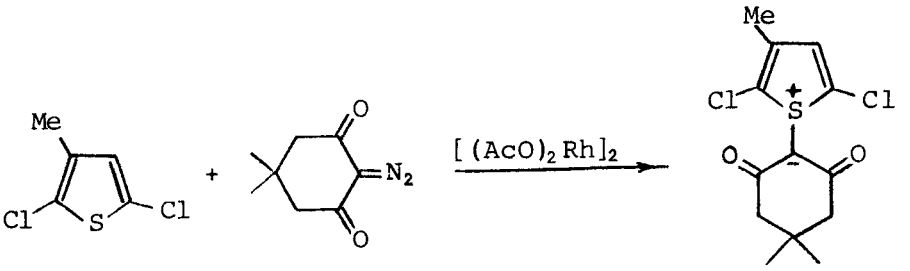
R_1 R_2 R_3 R_4	Ref.	Yield (%)	M.p./°C(b.p./°C/mm)	NMR (δ) ^1H	NMR (δ) ^{13}C
Cl Br H Cl	2	52	50-60/10 (lit.[3] 89-92/11)	6.73	109.32; 124.00; 127.62; 128.21
Cl Me H Cl	3	57	59-60/2 (lit.,[3] 44/1)	2.11(3H); 6.59(1H)	11.77; 120.10; 123.72; 126.05; 132.37
Cl Cl H NO_2	4	43	53-54 (from pet. ether) (lit.,[4] 54-55)	7.23	124.86; 127.80; 132.95; 146.57
Br Br H Br	2	76	95-100/10 (lit.,[2] 120/15)	6.87	110.61; 112.07; 113.56; 132.25
Me Br Br Me	2	89	42-44 (Kügelrohr dist) (lit.,[3] 44-46)	2.38	15.75; 15.81; 111.70; 131.44
I I H I	5	34	86 (from EtOH) (lit.,[5] 82-88)	7.04	78.72; 87.63; 94.25; 144.12

[a] Groups R_1, R_2, R_3, R_4 represent substituents in position 2, 3, 4, and 5, respectively.

to systems (2), and, finally, the susceptibility of the latter products to the fragmentation presented in Scheme II.

RESULTS AND DISCUSSION

Six tri- or tetra-substituted thiophenes were synthesized according to literature procedures (Table I), and have been treated with diazocompounds derived from

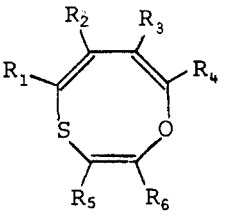


(1a)

Scheme 3

TABLE II

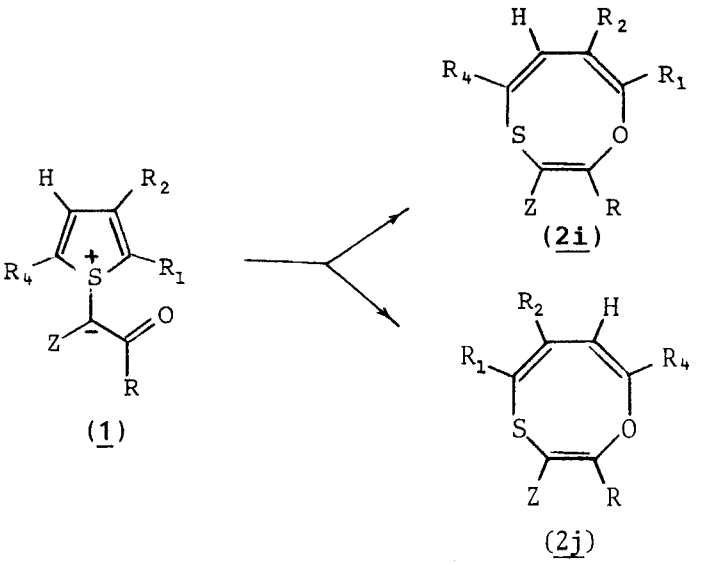
Substituted 1,4-oxathiocines



(2)

(2)[a]	R_1	R_2	R_3	R_4	R_5	R_6	Yield (%)	Reaction time and temperature
a	Cl	H	H	Cl	$CO_2{}^tBu$	Me	23	5 days; RT
a'	Cl	H	H	Cl	CO_2Et	Me	53	20 h; RT
b	Cl	Me	H	Cl	CO_2Et	Me	72	7 days; RT
c	Cl	Me	H	Cl	$CO_2{}^tBu$	Me	43	5 days; RT
d	Cl	Me	H	Cl	$C(O)CH_2CMe_2CH_2$		26	60 h; 65°C
e	Cl	Br	H	Cl	CO_2Et	Me	50	16 h; 70°C
f	Cl	Br	H	Cl	$C(O)CH_2CMe_2CH_2$		23	15 h; 80°C
g	Br	Br	H	Br	CO_2Et	Me	45	14 h; RT
h	Br	Br	H	Br	$C(O)CH_2CMe_2CH_2$		42	29 h; 80°C

[a] Relative position of groups R_5, R_6 with respect to groups R_1, R_2, R_3, R_4, has not been determined see Discussion).



R_1, R_4 = Cl, Br

R_2 = Me, Br

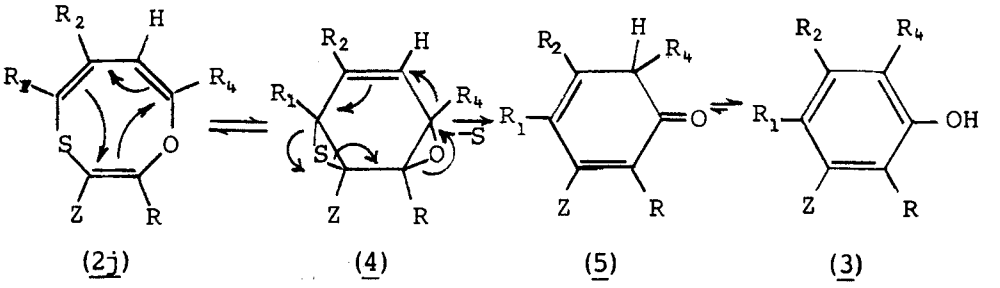
Scheme 4

ethyl diazoacetoacetate,[6] t-butyl diazoacetoacetate,[7] and diazodimedone,[8] in the presence of rhodium acetate.[9] Three of the thiophene derivatives (2,3-dichloro-5-nitro; 2,5-dimethyl-3,4-dibromo; 2,3,5-triiodo) failed to react with any of the diazocompounds, probably as a result of steric and/or electronic effects of the substituents in positions 2 and 5. The only ylide (**1**), stable enough to be isolated and characterized without spontaneous isomerization to the corresponding (**2**), was the product obtained from 2,5-dichloro-4-methylthiophene and diazodimedone (**1a**) (Scheme III). When (**1a**) was thermally converted into the corresponding oxathiocine, structural transformations: thiophene → (**1a**) → oxathiocine could be easily followed by the changes in the NMR spectra of the species involved. For example, the C(3)H atom in the starting thiophene (δ 6.59) undergoes deshielding upon conversion to the ylide (δ 6.84), reflecting the increase in the electronegativity of sulfur atom; rearrangement to the oxathiocine results in strong shielding (δ 5.27) as a consequence of the loss of aromatic character. Similarly, ^{13}C NMR spectroscopy demonstrated that the strongly shielded ylidic carbon in (**1a**) (δ 76.71) is dramatically deshielded (δ 113.90) when it becomes the C(3) atom of the oxathiocine ring. The nearly equivalent carbonyl carbons in (**1a**) (δ 190.10, 193.49) are converted into electronically different (δ 168.31, 198.09) atoms in (**2d**).

The oxathiocines (**2**), prepared (with the exception of the ylide **1a**) directly from the ylide precursors, are listed in Table II. The structure of products (**2a**)–(**2h**) was determined by NMR (^1H and ^{13}C) and IR spectroscopy, mass spectrometry, and elemental analysis. The obtained compounds (**2**) were then tested for their thermal reactivity, according to the equation shown in Scheme II for **2a**, **a'**. For the 1,4-oxathiocines derived from a trisubstituted thiophene, the ability to undergo thermal fragmentation should be determined by the regioselectivity of the formation

of the oxathiocine itself (Scheme IV). The proposed mechanism for the fragmentation of (**2**) is presented in Scheme V. There are two essential features in the collapse of the intermediate (**4**), postulated in the mechanistic sequence. Firstly, it is believed that sulfur extrusion involves a chelotropic process of the cleavage of both C—S bonds, promoted by the π electrons shift from the adjacent vinyl group. In that sense, the reaction can be viewed as an analogy of the known[10] desulfurization of allyl disulfide, promoted by triphenylphosphine, and resulting in the formation of allyl sulfide with one substituent undergoing allylic rearrangement in the course of the reaction. The fission of the S—C(Z) bond in (**4**) provides the necessary nucleophilic assistance for the rearrangement of the α-haloepoxide function. In a structurally related system, reaction between α-acetoxy oxiranes and carbon nucleophiles involves the attack at β-position and expulsion of acetate ion.[11] Thermal isomerization of α-chloro oxiranes to α-chloroketones, studied extensively by McDonald et al.,[12] was shown to involve the *intramolecular* 1,2 chlorine migration. Since the aromatization of the initially produced keto form (**5**) to product (**3**) involves the tautomeric process, the reaction should be possible only for substrates (**2**) carrying a hydrogen atom in position 7 (**2**, R_3=H).

We have found that the thermal fragmentation of the oxathiocines to substituted benzenes occurred in two cases, that is only for substrates with the unsubstituted positions 6 *and* 7 (Scheme II, R=Et, ^{t}Bu). No benzene derivatives were formed when the oxathiocine ring had only one unsubstituted carbon atom (**2b–h**). This result suggests that the initial nucleophilic addition of the oxygen atom to the thiophene α-carbon atom (first step in Scheme I) takes place with high regioselectivity, yielding the oxathiocine product corresponding to structure **2i** (Scheme IV). It is unlikely that the origin of the regioselectivity is only electronic in nature, since it was observed when substituent R_2 was bromine, as well as methyl group. The geometry of the ylides (**1**) almost certainly involves the β-dicarbonyl plane twisted with respect to the plane of the ring, with the restricted rotation about the C—S ylidic bond.[13] The approach of the oxygen atom to carbon-2 (formation of the O—C bond) should be expected to release the torsional strain between the chlorine atom at C(2) and the C(3) R_2 group. Moreover, this regioselectivity leads to the intermediate with the R_2 group located at the terminal of the conjugated π system, and both, alkyl groups and halogens are known[14] to stabilise the adjacent carbon—carbon double bond.



Scheme 5

The oxathiocine unsubstituted at positions 6 and 7, but derived from diazodimedone,[1] also could not be degraded to the aromatic product (**3**). The cyclohexenone ring, fused to the oxathiocine skeleton, restricts probably in this case the flexibility of the latter system, necessary for the sulfur extrusion and the ring contraction step. We have demonstrated therefore that the thermal rearrangements of thiophene C—S ylides (easily prepared from thiophenes and diazocarbonyl substrates) represents a convenient route to some substituted 1,4-oxathiocines (**2**), but the fragmentation of the eight-membered ring products to elemental sulfur and substituted benzenes is limited to only specific patterns of substitution.

EXPERIMENTAL

Melting points were recorded on a Reichert hot-stage apparatus and a Reichert hot-stage microscope, and are uncorrected. IR spectra were recorded on a Perkin-Elmer 883 spectrometer as liquid films or Nujol mulls. Mass spectra were recorded using a Varian MAT '88 spectrometer or MAT Finnigan 90. Spectra of halogeno compounds indicate only the major peak of the clusters of isotopic peaks. NMR (^1H and ^{13}C) spectra were recorded in $CDCl_3$ on Bruker AM 300 or WM 500 instruments, and the chemical shifts are given relative to TMS. Silica gel (Merck, Kieselgel 60) was used for column chromatography. TLC was conducted using Merck Kieselgel 60F-254 plates; for the preparative TLC Merck Kieselgel 60F-254, 200 × 200 × 2 mm plates were used. Petroleum ether refers to the fraction of b.p. 60–80°C. A laboratory sonication bath was used for sonication experiments.

2,5-Dichloro-3-methylthiophenium (4',4'-dimethylcyclohexane-2',6'-dione)1'-S,C-ylide, **1a**. Diazodimedone[8] (2.5 g, 0.015 mol) was added portionwise at room temperature under the atmosphere of nitrogen to a mixture of 2,5-dichloro-3-methylthiophene (19.9 g, 0.12 mol) and tetrakis(acetato)-dirhodium(II) (5 mg). The mixture was stirred at room temperature for three days, dry hexane (20 mL) was added to dissolve the excess of thiophene, and the product was filtered off. The crude product (2.5 g, 54%) was purified by column chromatography. The initial elution with petroleum ether gave some unreacted thiophene; (**1a**) was obtained by elution with chloroform, 2.1 g (45%). M.p. 154°C (Kofler), 130°C (microscope). ν_{max}(nujol) 1713, 1640, 1599 cm^{-1}. δ_H 0.94 (6H, s, C(4')Me_2), 2.04 (3H, s, C(3)Me), 2.17 (2H, s, CH_2), 2.32 (2H, s, CH_2), 6.84 (1H, s, C(4)H). δ_c 15.14 (Me), 27.86 (2 × Me), 30.88 (C-4'), 51.34 (CH_2), 51.61 (CH_2), 76.71 (C-1'), 123.41, 129.90, 134.56, 141.54 (4 × C_{thioph}), 190.10, 193.49 (2 × CO). Anal. Calcd for $C_{13}H_{14}Cl_2O_2S$: C, 51.49; H, 4.65. Found: C, 51.19; H, 4.69%.

Preparation of 1,4-oxathiocines (**2**); *General procedure.* Diazocompound (1 mol-equiv.), substituted thiophene (8 mol-equiv.), and tetrakis(acetato)dirhodium(II) (1.1 mol-%) were mixed at room temperature, under sonification and in the atmosphere of dry nitrogen. The mixture was then kept at required temperature for the required period of time (see Table II), until TLC of the mixture indicated complete disappearance of the diazocompound. The reaction product was then purified by column chromatography, the excess of thiophene being isolated as first, less polar fraction, by elution with petroleum ether, and the products (**2**) by elution with petroleum ether/ether (1:1). Selected data used for identification of compounds (**2a**)–(**2h**) are presented in Table III.

Thermal fragmentation of (**2**). The solution of (**2**) in a selected solvent was heated under reflux until TLC showed disappearance of the substrate. After evaporation of the solvent under reduced pressure, the product was purified by preparative TLC using petroleum ether/ether (1:1) as eluting solvent.

2,4-Dichloro-5-ethoxycarbonyl-6-methylphenol (**3a**) was prepared from 2-methyl-3-ethoxycarbonyl-5,8-dichloro-1,4-oxathiocine[14] (0.18 g, 0.73 mmol) by heating the solution of (**2**) in chlorobenzene (20 ml) under reflux for 6 h. Yield 0.10 g (63%); m.p. 92–93°C (lit.[14] m.p. 92.5–93°C). δ_H 1.38 (3H, t, J_{HH} 5.0 Hz, Me of CO_2Et), 2.22 (3H, s, C(6)Me), 4.40 (2H, q, J_{HH} 5.0 Hz, CH_2 of CO_2Et), 7.21 (1H, s, C(3)H). δ_c 13.60 (Me), 14.12 (Me), 61.91 (CH_2), 120.84, 121.46, 124.64 (3 × C_{arom}), 126.48 (C(3)), 134.07 (C_{arom}), 148.59 (C(1)), 166.40 (CO).

2,4-Dichloro-5-tert-butoxycarbonyl-6-methylphenol (**3b**) was prepared from (**2a**) (0.07 g, 0.23 mmol) by heating its solution in toluene (20 ml) under reflux for 15 h. Yield 0.05 g (79%); m.p. 136–138°C (microscope). ν_{max} 1635 (CO) cm^{-1}. δ_H 1.60 (9H, s, ^{t}Bu), 2.24 (3H, s, C(6)Me), 7.20 (1H, s, C(3)H).

TABLE III
Synthesis of 1,4-oxathiocines (2)

(2)	ν_{max} (cm^{-1})	m/z (%)	NMR ^1H	NMR ^{13}C	Analysis Found(%) C	Analysis (Required) H
(2a)	1713, 1627	-	1.45 (9H, s), 2.26 (3H, s), 5.80 (1H, d), 6.61 (1H, d)	21.2, 27.6, 27.8, 82.8, 108.9, 114.7, 125.6, 135.7, 137.7, 157.6, 163.8	47.34 (46.92)	4.88 (4.59)
(2a')	1720, 1620		1.29 (3H, t), 3.24 (3H, s), 4.22 (2H, q), 5.85 (1H, d), 6.67 (1H, d)	14.0, 21.6, 61.9, 107.4, 115.1, 125.3, 136.2, 137.4 159.4, 164.8		
(2b)	1720, 1605	261 (42), 232 (16), 216 (88), 61 (100)	1.32 (3H, t), 1.98 (3H, s), 2.34 (3H, s), 4.25 (2H, q), 6.00 (1H, s)	13.9, 18.8, 21.8, 61.7, 107.2, 118.1, 119.9, 133.5, 145.9, 158.4, 164.9	45.00 (45.06)	4.20 (4.13)
(2c)	1712, 1630	279 (25), 167 (36), 149 (100), 57 (83)	1.42 (9H, s) 1.67 (3H, s), 2.20 (3H, s), 5.91 (1H, s)	18.8, 21.4, 27.7, 82.3, 108.4, 118.2, 119.6, 133.6, 145.4, 156.3, 163.8	48.30 (48.51)	5.20 (5.02)
(2d)[a]	1678, 1638, 1600	268 (54), 212 (61), 184 (100)	1.16 (6H, s), 2.25 (3H, s), 2.42 (2H, s), 2.85 (2H, s), 5.27 (1H, s)	10.1, 28.6, 35.5, 38.1, 51.7, 113.9, 117.2, 119.0, 126.2, 153.8, 168.3, 198.1	49.84 (51.49)	4.05 (4.65)
(2e)	1721, 1599	-	1.28 (3H, t), 2.35 (3H, s), 4.23 (2H, q), 6.14 (1H, s)	13.7, 21.7, 61.8, 106.7, 118.3, 121.8, 128.9, 136.3, 138.4, 158.6, 163.9	33.63 (33.55)	2.51 (2.53)

Table 3 (cont.)

(2f)[b]	1684, 1600	-	1.08 (6H, s), 2.39 (2H, s), 2.53 (2H, s), 6.22 (1H, s)	27.7, 31.6, 45.4, 51.0, 112.8, 119.0, 123.2, 127.8, 136.2, 164.6, 194.1	40.52 (39.16)	3.31 (3.01)
(2g)	1720, 1602	-	1.26 (3H,t), 2.31 (3H, s), 4.19 (2H, q), 6.24 (1H, s)	13.7, 21.5, 61.6, 107.6, 110.5, 123.2, 125.9, 133.0, 142.9, 158.4, 163.8	27.19 (26.75)	2.06 (2.02)
(2h)[c]	1681	-	1.10 (6H, s), 2.40 (2H, s), 2.52 (2H, s), 6.33 (1H, s)	27.8, 31.7, 45.3, 51.1, 112.1, 113.7, 124.1, 125.7, 132.0, 164.5, 194.0	31.39 (31.40)	2.01 (2.42)

[a] M.p. ($MeOH/iPr_2O$) 151°C (dec., Kofler); 127-128°C (microscope)

[b] M.p. 130°C (Kofler); 127-136°C (microscope)

[c] M.p. 135°C (Kofler); 130-137°C (microscope)

δ_c 13.32 (Me), 28.09 (3 × Me), 83.31 ($\underline{C}Me_3$), 120.33, 121.77, 124.15, (3 × C_{arom}), 126.41 (C(3)), 135.18 (C_{arom}), 148.54 (C(1)), 165.49 (CO). MS m/z 276 (M^+, 20%), 220 (100), 203 (79), 174 (7). Anal. Calcd for $C_{12}H_{14}Cl_2O_3$: C, 52.38; H, 5.13. Found: C, 52.68; H, 5.55%.

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