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Reaction of 2-Hydroxyacetophenones with Thionyl Chloride in the Presence of a Catalytic Amount of Pyridine[1)]

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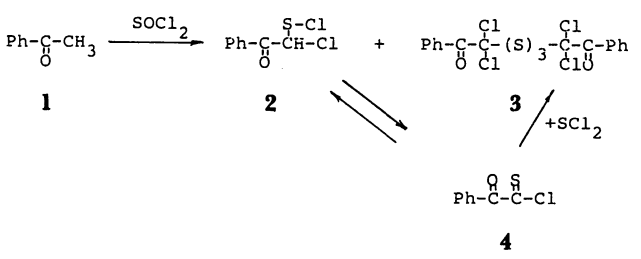
Reaction of 2-hydroxyacetophenone (**5**) with excess thionyl chloride in the presence of a catalytic amount of pyridine at room temperature afforded a thiirane **6**, while 2-hydroxy-4-methoxyacetophenone (**7**) furnished **8** when subjected to almost identical conditions. The products were characterized by microanalyses data and spectroscopic techniques including the mass spectroscopy. Plausible mechanisms for the conversions have been proposed in the light of available literature.

Thionyl chloride is routinely used as a chlorinating agent for many different substrate types.[2)] The course of the reaction of active methylene compounds with thionyl chloride seems unpredictable and so-called abnormal products have been reported in many cases[3)] often without further detailed investigations. The reaction of acetophenone (**1**) with $SOCl_2$ in the presence of a catalytic amount of pyridine furnishes **2** and **3**.[4,5)] The mechanism proposed for this reaction involves the intermediacy of α-oxobenzenethionyl chloride (**4**). However, the literature reveals that there is controversy over the existence of **4**[4,5)] and that little is known about the chemistry of related compounds with adjacent C=O and C=S functions.

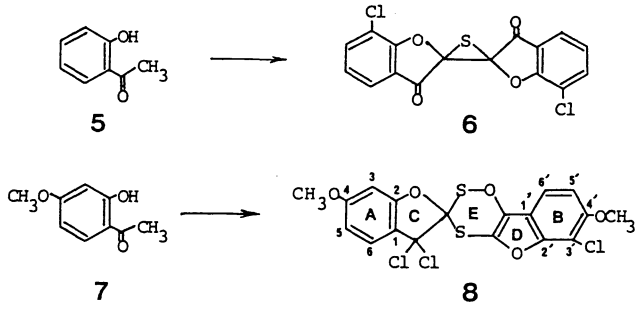


1 **2** **3** **4**

We have investigated the reaction of some 2-hydroxyacetophenones with excess of thionyl chloride in the presence of a catalytic amount of pyridine in an attempt to obtain cyclic α-oxothiocarboxylic esters with the aim to further the available information on the reaction intermediates and also to explore the synthetic potential of the products. We wish to report our results in this manuscript.

Results and Discussion

The reaction of 2-hydroxyacetophenone (**5**) with excess of thionyl chloride in the presence of a catalytic amount of pyridine at room temperature afforded a red gummy mass which was subjected to column chromatography. Elution with petroleum ether–benzene (1:1) yielded **6**. Further elution of the column with more polar solvents gave a gummy mixture which could not be resolved even on repeated column chromatography. When 2-hydroxy-4-methoxyacetophenone (**7**) was treated with excess $SOCl_2$, under almost identical conditions, also a red gummy mass was obtained which was subjected to column chromatography. Elution of the column with petroleum ether–benzene (4:1) furnished a white solid which was crystallized from petroleum ether–benzene to give white crystals of **8**. Attempts to resolve the complex tar obtained on further elution with more polar solvents were not successful. The structures of **6** and **8** were established with the help of microanalyses and spectroscopic data.



5 **6** **7** **8**

Compound **6** analyzing for $C_{16}H_6Cl_2O_4S$ gave a positive Beilstein test indicating the presence of halogen. The presence of chlorine in **6** was clearly shown by the isotopic clusters in the mass spectrum and confirmed by microanalysis. Its IR spectrum displayed bands at 1725 (five membered ketone) and 690 (C–Cl). The ^1H NMR spectrum exhibited only the signals for aromatic protons as a multiplet in the region δ 7.00—8.00 displaying the 1,2,3-trisubstituted nature of the aromatic rings. The actual structure could only be elucidated by taking into account the mass fragmentation pattern of **6**. The mass spectrum did not exhibit the molecular ion peak expected at *m/z* 364, however, the peak with the highest mass to charge ratio was recorded at *m/z* 332 along with the isotopic peaks at *m/z* 334 and 336 whose relative intensities supported the presence of two chlorine atoms in this fragment. The formation of this fragment can be explained by the elimination of sulfur from the molecular ion (Chart 1). The most

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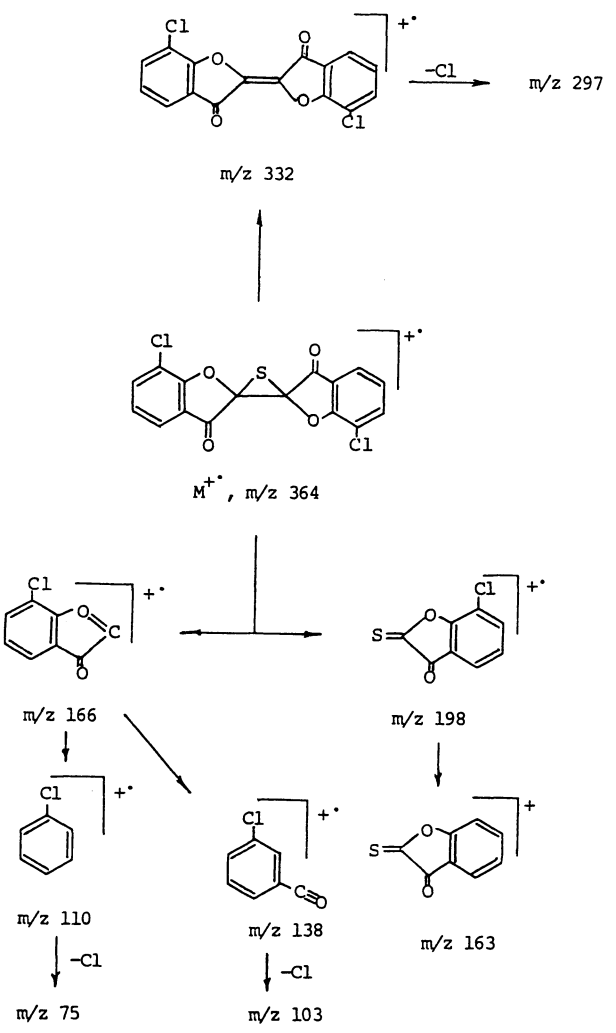
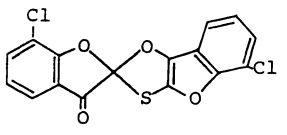


Chart 1.

diagnostic fragmentation was the fission of the molecule into two fragments recorded at *m/z* 166 (base peak) and 198 (11.52) accompanied by the isotopic peaks at *m/z* 168 (33.00) and 200 (3.84), respectively. The loss of chlorine from the ion at *m/z* 198 can give an ion at *m/z* 163, while the fragments at m/z 103, 110, and 138 can be derived either directly from the molecular ion or from the fragments with *m/z* 166 and 198. The position of the chlorine in the aromatic rings was located with the help of NMR data and taking into account the mechanistic considerations. On the basis of above discussion, two possibilities can be drawn, either a thiirane **6** or a 1,3-oxathiole **9**. The absence of an enol ether band in the IR spectrum, characteristic of 1,3-oxathiole skeleton,[6] helped in eliminating this possibility. The compound was, therefore, characterized as thiirane **6**.



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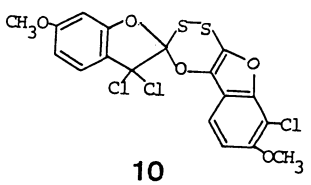
Compound **8** analyzing for $C_{18}H_{11}Cl_3O_5S_2$ also gave a positive Beilstein test. The presence of chlorine was confirmed by microanalysis and mass spectral data. Its IR spectrum displayed bands at 1610 (C=C), 1230 (enol ether), and 690 (C–Cl). The NMR spectrum proved comparatively more useful and clearly showed the presence of a chlorine in one of the aromatic rings. Two ortho-coupled doublets (J=9 Hz), each for one proton, at δ 7.44 and 7.80 were attributed to the protons at C-6 and C-6′, respectively. A high-field singlet at 6.54 ppm for one proton was due to C-3 proton. The signal for the C-5 and C-5′ protons merged and appeared as a multiplet centered at δ 6.75. Though the two methoxyl groups have slightly different environment, their signals appeared as a broad singlet at δ 3.80. The actual structure was, however, elucidated with the help of mass fragmentation pattern of **8** (Chart 2). The molecular ion peak could not be recorded in this case also and the peak at *m/z* 441 was the one with the highest mass to charge ratio accompanied by isotopic peaks at *m/z* 443 and 445, whose relative intensities showed the presence of two chlorine in this fragment. The formation of this fragment can be explained by the loss of a chlorine atom from the molecular ion. The most diagnostic peaks were those resulting by the retro-Diels–Alder fission of the ring E recorded at *m/z* 213 and 228. Another significant peak at *m/z* 214 was attributed to the doubly charged ion formed by the loss of sulfur monoxide from the $M^{+\cdot}$. The fragments derived from this ion were recorded at *m/z* 323, 358, 378, and 393. The above data grossly confirms the structure **8**. There are however few points which should be mentioned here. The assignment of chlorine on the ring A rather than on ring B is fully supported by the mass fragmentation pattern. Compound **10** was also taken into consideration. The possibility was however ruled out because there are few peaks which can only be explained by the loss of SO from the $M^{+\cdot}$ and this is not possible from **10**.



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The reaction of active methylene compounds with $SOCl_2$ proceeds either by *O*- or *C*-sulfinylation. *O*-Sulfinylation of carbonyl compounds leads to either *gem*-dichlorides[7] or α-monochloro ketones, while *C*-sulfinylation gives rise to α-chlorosulfinyl ketones. These products may then undergo further transformations to give a variety of products. The formation of **6**

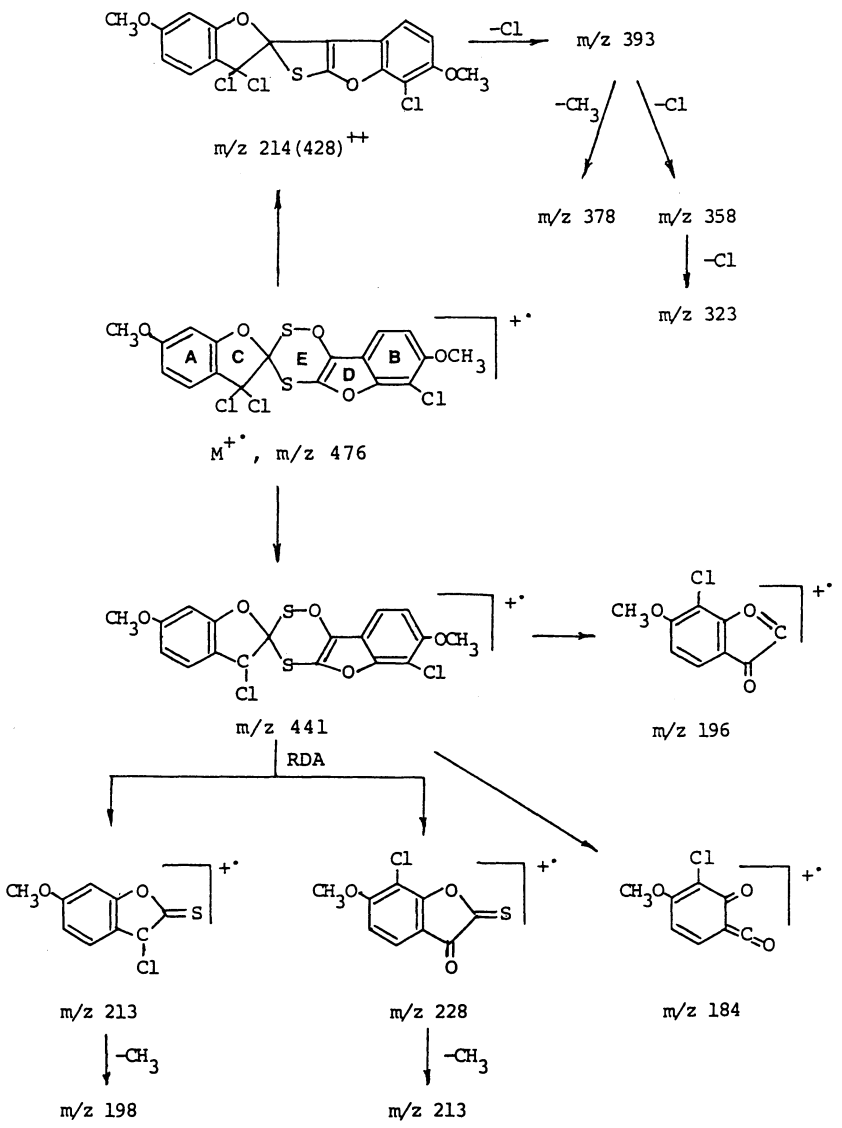
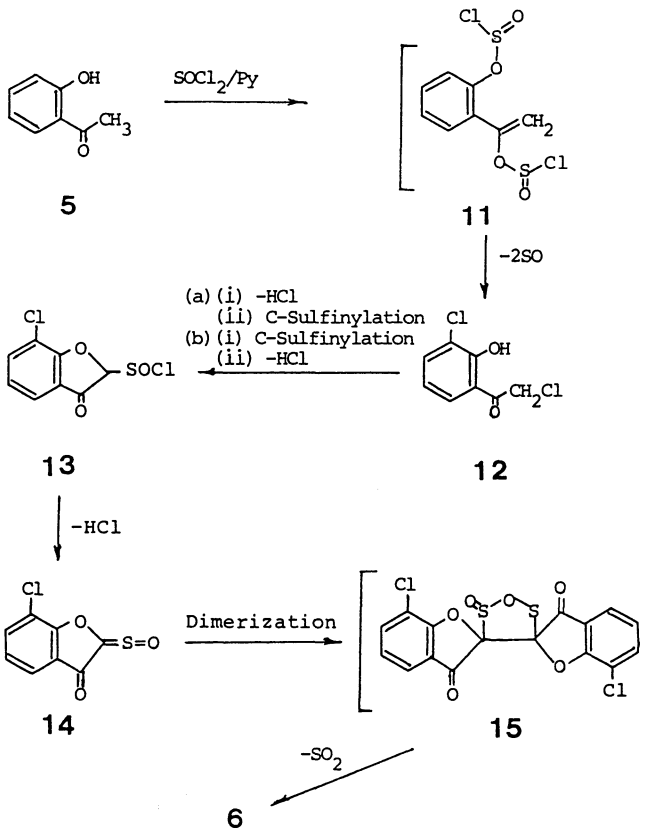


Chart 2.

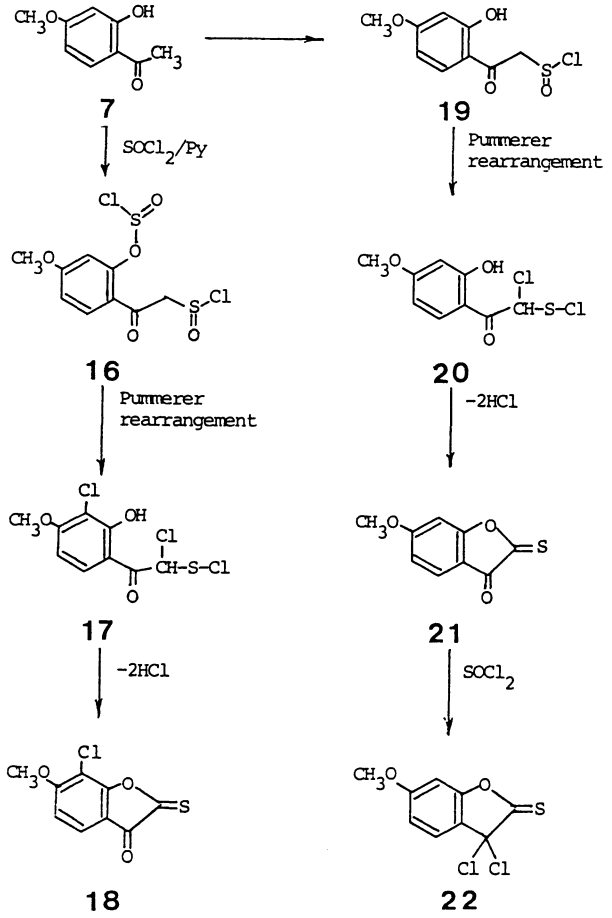
and **8** can be explained by a combination of these processes.

There are some reports on the formation of thiirane from active methylene compounds by the reaction with $SOCl_2$.[8] A plausible mechanism for the formation of **6** from **5** can be outlined as in Scheme 1, in analogy to the precedent examples. *O*-Sulfinylation of both the hydroxyl as well as carbonyl functions of **5** can lead to **11** which can yield **12** by Cl migration accompanied by the loss of sulfur monoxide. Compound **13** can be obtained from **12** either by route (a) or (b). The loss of HCl from **13** followed by dimerization accompanied by the loss of SO_2 may furnish thiirane **6**.[8] It is important to mention here that the chlorination of phenol with $SOCl_2$ has never been observed and there is only one recent report which describes the chlorination of an aromatic compound with $SOCl_2$.[9]

The mechanism for the formation of **8** is not very clear, however, a probable mechanism can be outlined as in Scheme 2. α-Chlorosulfenyl chlorides **17** and **20** can be obtained from sulfinyl chlorides **16** and **19**, respectively, by the Pummerer rearrangement.[10] α-Oxo thiocarboxylic esters **18** and **21** can be obtained from **17** and **20**, respectively, by the loss of two molecules of HCl. [4+2]Cyclodimerization of **18** and **22** can lead to **8**. Though the probability of conversion of $\rangle C{=}O$ to $\rangle CCl_2$ after the dimerization also exists, we think that in such a case [4+4] addition would have been more preferable. It is not clear why the other mode of cyclization which could give compound **10** was not preferred. Though the mechanism proposed is purely speculative, it is most appropriate in the light of available data. It is clear that the two substrates show different behavior towards the reagent and since there are many factors such as nature of the substrate, amount and



Scheme 1.



18 + 22 → 8

Scheme 2.

concentration of the reagent used, the order of addition, solvent and temperature, which affect the course of the reaction, it is difficult to explain the difference in their behavior at this stage.

In conclusion, the present manuscript describes the reaction of two 2-hydroxyacetophenones **5** and **6** with excess $SOCl_2$ in the presence of a catalytic amount of pyridine to furnish **6** and **8**, respectively. Though the yields are not high, the accomplishment of these complicated spiro skeleton in a single step from readily available starting materials is quite significant. The plausible mechanisms and their fragmentation patterns have been discussed. Nuclear chlorination with $SOCl_2$ of the aromatic systems has been observed which has only one precedence.

Experimental

All melting points were recorded on a Kofler microscopical hot stage and are uncorrected. Infrared spectra were obtained on a Pye Unicam SP3-100 spectrophotometer. Ultraviolet spectra measured on a Pye Unicam PU 8800 instrument. NMR spectra were recorded on a 60 MHz Varian A60D instrument using TMS as internal standard. Mass spectra were recorded with a JEOL JMS-D300 spectrometer at 70 eV.

Reaction of 2-Hydroxyacetophenone (5) with Thionyl Chloride in the Presence of a Catalytic Amount of Pyridine. 2-Hydroxyacetophenone (4.0 g, 29.4 mmol) was dissolved in thionyl chloride (52.5 g, 44.0 mmol) and a catalytic amount of pyridine (0.46 g, 0.58 mmol) was added. The contents were stirred at room temperature for 3 h. Excess $SOCl_2$ was removed at room temperature under reduced pressure to give a red gummy mass which was subjected to column chromatography over silica gel. Elution with petroleum ether–benzene (1:1) afforded a light pink solid, crystallized from $CHCl_3$–MeOH mixture to furnish white crystals of thiirane **6** (1.45 g, 27%), mp 160—162 °C; IR (KBr): ν_{max} 2940, 1725, 1610, 1590, 1470, 1450, 1320, 1295, 1215, 1190, 1140, 1100, 1060, 1000, 860, 830, 750, 730, 690, 640 cm^{-1}; UV (MeOH): λ_{max} 240, 290 nm; ^1H NMR ($CDCl_3$): δ=7.00—8.00 (m, Ar-H); MS (rel. int.): *m/z* 336 (4.01), 335 (3.68), 334 (21.76), 333 (3.05), 332 (33.27), 298 (1.94), 200 (3.84), 198 (11.52), 168 (33.00), 167 (2.50), 166 (100.00), 163 (18.21), 137 (10.30), 112 (8.90), 110 (35.32), 103 (18.45), 92 (15.00), 75 (40.35). Found: C, 52.52; H, 1.51; Cl, 19.18%. Calcd for $C_{16}H_6Cl_2O_4S$: C, 52.62; H, 1.66; Cl, 19.42%.

Reaction of 2-Hydroxy-4-methoxyacetophenone (7) with Thionyl Chloride in the Presence of a Catalytic Amount of Pyridine. To a solution of 2-hydroxy-4-methoxyacetophenone (3.0 g, 18 mmol) in thionyl chloride (32.26 g, 27.0 mmol) was added a small amount of pyridine (0.03 g,

0.36 mmol). The reaction mixture was stirred at room temperature for 3 h. Excess $SOCl_2$ was then removed at room temperature under reduced pressure to get a red gummy mass which was subjected to column chromatography over silica gel. Elution with petroleum ether–benzene (4:1) afforded a white solid which was crystallized from a mixture of petroleum ether–benzene to yield white crystals of **8** (1.46 g, 34%), mp 129—130 °C; IR (KBr): ν_{max} 2960, 1610, 1585, 1526, 1490, 1440, 1420, 1345, 1325, 1260, 1230, 1180, 1130, 1100, 1030, 1020, 975, 940, 930, 850, 830, 810, 785, 740, 690, 640, 620 cm^{-1}; ^1H NMR ($CDCl_3$): δ=3.80 (6H, s, 2×OMe), 6.54 (1H, s, H-3), 6.75 (2H, m, H-5,5′), 7.44 (1H, d, J=9 Hz, H-6), 7.80 (1H, d, J=9 Hz, H-6′); MS (rel. int.): m/z 445 (4.12), 443 (8.10), 441 (11.26), 397 (3.80), 395 (7.42), 394 (2.15), 393 (11.32), 382 (2.00), 380 (4.20), 378 (6.12), 360 (4.52), 359 (3.00), 358 (13.28), 324 (7.20), 323 (20.40), 230 (8.00), 229 (10.00), 228 (24.54), 216 (8.95), 215 (42.15), 214 (23.50), 213 (100.00), 198 (12.51), 196 (16.54), 184 (2.55), 150 (14.50). Found: C, 44.99; H, 2.17; Cl, 22.04%. Calcd for $C_{18}H_{11}Cl_3O_5S_2$: C, 45.25; H, 2.32; Cl, 22.26%.

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