CHEMISTRY LETTERS, pp. 1095-1098, 1977. Published by the Chemical Society of Japan

REACTIONS OF THIOL ESTERS WITH HALOGENS AND SOME N-HALO AND O-HALO COMPOUNDS

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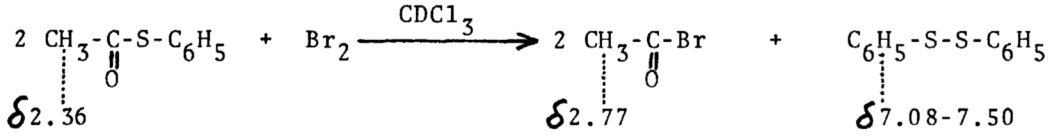
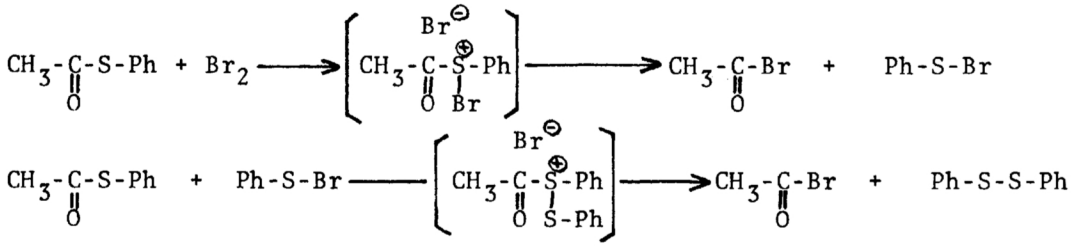
S-Phenyl thioacetate (1) quantitatively reacted with 1/2 mole of bromine(or chlorine), yielding acetyl bromide (or chloride) and phenyl disulfide. With iodine, 1 formed a complex, which reacted with an alcohol (MeOH, Me_3CCH_2OH, $PhCH_2OH$), forming the corresponding ester; a catalytic amount of iodine was sufficient for this trans-esterification. 1 reacted quantitatively with 1-chlorobenzotriazole. The reaction of 1 with t-butyl hypochlorite yielded t-butyl acetate (70%) and acetyl chloride(30 %).

The chemistry of thiol esters is of considerable interest especially in connection with the important role of acylated Coenzyme A (R-CO-S-CoA) in living systems. Differences between the reactivities of thiol esters and ordinary esters have been pointed out,[1] but the reactions of thiol esters have not fully been explored yet. We have investigated reactions of thiol esters with halogens and some N-halo and O-halo compounds, and wish to describe the results.

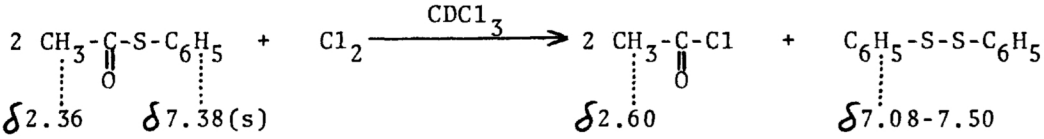
When S-phenyl thioacetate (1)(0.13 mmol) and bromine (0.065 mmol) were mixed in $CDCl_3$(0.4 ml) at room temperature, the NMR spectrum showed that 1 was almost instantaneously and quantitatively converted to acetyl bromide and phenyl disulfide.



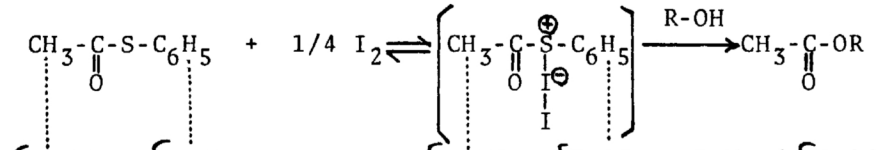
The fact that 1 mole of bromine reacted with 2 moles of 1 suggests that the following steps are probably involved.



When chlorine gas was bubbled through a $CDCl_3$ solution (0.4 ml) of 1 (0.13 mmol) for 5 minutes, the NMR spectrum showed that 1 was quantitatively converted to acetyl chloride and phenyl disulfide.



However, when iodine (0.065 mmol) and 1 (0.13 mmol) were mixed in $CDCl_3$ (0.5 ml), the NMR spectrum showed that no apparent reaction was taking place, although the phenyl absorption was slightly shifted to lower field. When the mixture was allowed to stand in an NMR tube for 8 days at 34°, all the 1 was hydrolyzed by moisture in the tube and converted to acetic acid (δ 2.10). This suggests the formation of an intermediate which readily reacts with nucleophiles. When an alcohol (0.60 mmol) was added to a mixture of 1 (0.20 mmol) and iodine (0.05 mmol) in $CDCl_3$ (0.5 ml), transesterification proceeded, yielding the corresponding alkoxy ester. These results suggest the formation of the iodine-thiolester complex shown below.



R	Yield, Time Needed for Reaction
R=Me (δ 2.04; 3.68)	100% (4.2 hr)
R=Me_3CCH_2 (δ 2.02; 0.9, 3.77)	94% (126 hr)
R=$PhCH_2$ (δ 2.00; 5.04)	70% (65 hr)
R=Et (δ 2.02; 1.26(t), 4.12(q))	100% (19 hr)

The benzenethiol formed was slowly oxidized with iodine and the oxygen in the air, and both benzenethiol and phenyl disulfide were found as products.

With neopentyl alcohol, the reaction was very slow and 94% complete only after 6 days. If the reaction involves a bulky iodine-thiolester complex, the slow reaction with neopentyl alcohol is understandable. In the case of benzyl alcohol, the iodine added as the catalyst was slowly reduced by benzyl alcohol (and benzenethiol), and when benzyl acetate was formed in a 70% yield, the solution became colorless and the reaction stopped, with 30% of 1 remaining.

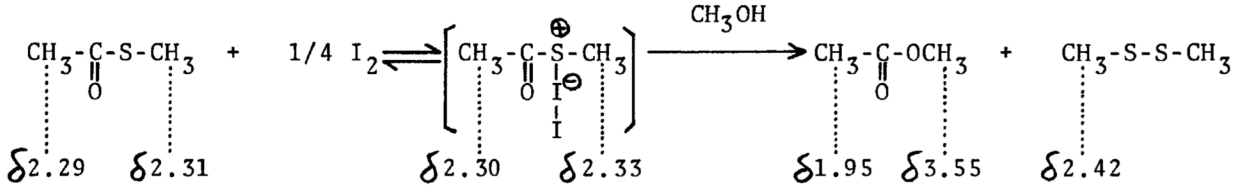
The assumption of the formation of the iodine-thiolester complex is supported by the studies on the formation of similar complexes from iodine and alkyl sulfides. The structure of a charge-transfer complex, $(PhCH_2)_2S^{\oplus}-I^{\ominus}-I$, from benzyl sulfide and iodine has been established by X-ray diffraction analyses.[2]

Iodine functions as a catalyst, and only 0.125 mole iodine per mole of 1 effectively catalyzes this transesterification. When I_2/1/MeOH was 0.125/1/3, the yield of methyl acetate was 51 (2.2 hr), 83 (4.5 hr), and 100% (5.5 hr), and when I_2/1/MeOH was 0.25/1/3, the yield of methyl acetate was 42 (1.5 hr), 98 (2.7 hr), and 100% (4.2 hr).

When t-butyl alcohol was mixed with 1 and iodine in a similar manner, the only change observable in the NMR spectrum was a steady decrease of the t-butyl absorption, which completely disappeared in 6 days. Apparently t-butyl alcohol

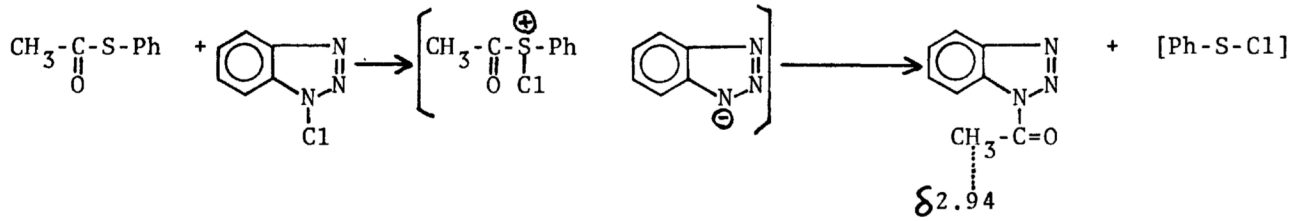
was converted to volatile isobutylene. Iodine is known to catalyze dehydration of diacetone alcohol to mesityl oxide.[3]

In a similar manner S-methyl thioacetate was treated with 1/4 mole of iodine and 3 moles of methanol; methyl acetate was formed in an 89% yield after 8.5 hr.

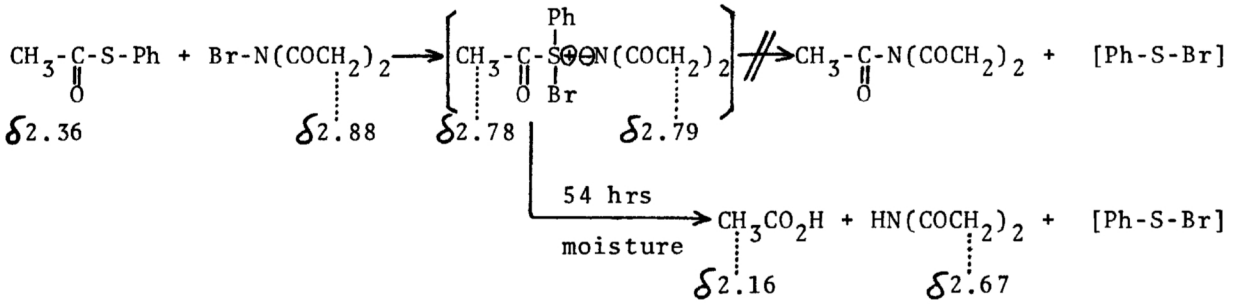


The reactions of thiol esters with several N-halo and O-halo compounds were also investigated. The reaction with N-bromosuccinimide was described previously,[4] which resulted in the formation of a bromosulfonium succinimide.

When 1 (2 mmol) and 1-chlorobenzotriazole (2 mmol) were mixed in CH_2Cl_2 (10 ml) at -100° and then warmed up, its NMR spectrum showed that 1 had quantitatively been converted to 1-acetylbenzotriazole (identified by its mp (49-51°), IR spectrum, and comparison with an authentic sample).

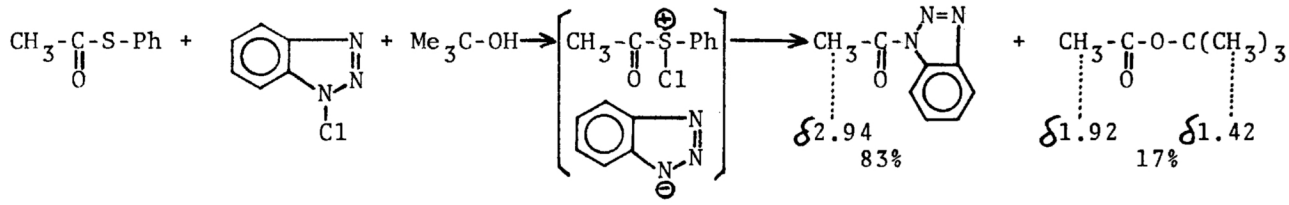


In the case of the reaction with N-bromosuccinimide, the bromosulfonium succinimide intermediate was stable for about 6 hr at 34°, and when allowed to stand at 34°, it was slowly decomposed by moisture (completely in 54 hr). The analysis of the products formed showed that succinimide anion reacted differently from benzotriazole anion and did not attack the activated acetyl group.

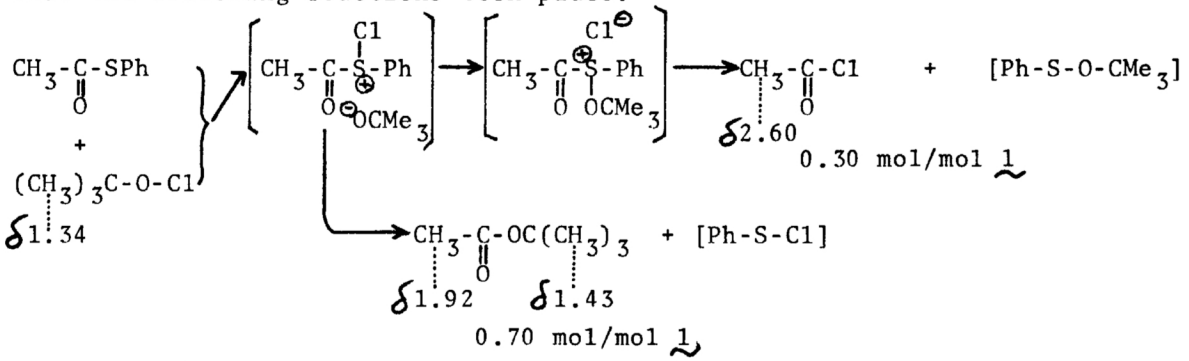


For conversion of sulfides to alkoxysulfonium (or dialkylaminosulfonium) ions, the treatment of sulfides with 1-chlorobenzotriazole or N-bromosuccinimide and then with ROH (or R_2NH) is a good method,[5-8] and for this conversion 1-chlorobenzotriazole is more reactive and gives better yields than N-bromosuccinimide. However, the above result suggests that 1-chlorobenzotriazole cannot be used for oxidative activation of thiol esters for the acylation of nucleophiles, although N-bromo-

succinimide proved to be a good activator for that purpose.[4] In fact, when 2 mmoles each of 1, 1-chlorobenzotriazole, and t-butyl alcohol were mixed at -100° and then warmed up to room temperature, the NMR spectrum showed that only 17% of 1 was used for acetylating t-butyl alcohol and 83% of 1 was used for acetylating benzotriazole.



When 1 (0.1 mmol) was mixed with t-butyl hypochlorite (0.3 mmol) in $CDCl_3$ (0.5 ml), 0.12 mmol of t-butyl hypochlorite was consumed, and the NMR spectrum indicated that the following reactions took place.



Both Ph-S-$OCMe_3$ and Ph-S-Cl are reactive compounds, and the products expected are t-butyl chloride and Ph-S(→O)-S-Ph; the latter is expected to disproportionate to Ph-SO_2-S-Ph and Ph-S-S-Ph. t-Butyl chloride (δ1.62) was found in a 27% yield.

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(Received August 1, 1977)