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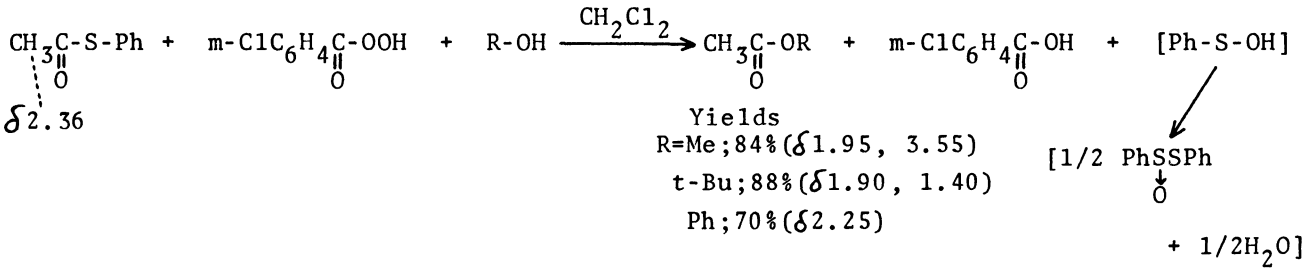
FACILE ACYLATION OF NUCLEOPHILES WITH OXIDIZING AGENT-THIOL ESTER PAIRS

Hiroshi MINATO*, Hiroshi KODAMA, Takashi MIURA, and Michio KOBAYASHI
Department of Chemistry, Tokyo Metropolitan University, Setagaya, Tokyo 158

Thiol esters (MeCO-SPh, 2,4,6-$Me_3C_6H_2CO$-SMe, p-$MeC_6H_4SO_2$-SMe) were found to function as good acylating agents for nucleophiles(MeOH, t-BuOH, PhOH, $PhNH_2$, Cl^-, Br^-) when mixed with oxidizing agents (m-$ClC_6H_4CO_3H$, N-bromosuccinimide) in CH_2Cl_2 solution. Thiol esters and NBS appear to form a sulfurane as the reactive intermediate.

The thiol group of Coenzyme A exhibits unique reactivity in living systems, and the acylated Coenzyme A (R-CO-S-CoA) functions as a very efficient acylating agent at ordinary temperatures with the aid of enzymes. However, common thiolesters cannot function as efficient acylating agents in the absence of enzymes. Recently Takagi et al. reported that upon UV irradiation lipoic acid and acetaldehyde reacted yielding 8-acetylthio-6-mercapto-octanoic acid,[1] which readily lost its 8-acetyl group by the attack of methanol when it was mixed with iodine in methanol.[2] We have been interested in the possibility of using common thiolesters as acylating agents with the aid of some suitable oxidizing agents, and wish to report the results of our investigation.

When S-phenyl thioacetate (1) (0.13 mmol) was mixed with methanol (0.26 mmol) in CH_2Cl_2 (0.4 ml) and then m-chloroperbenzoic acid (2) (0.13 mmol) was added, 1 was smoothly converted to methyl acetate at 34° (the yields as determined by PMR: 0.64 and 0.84 mol/mol of 1 after 3 hr and 24 hr, respectively). Acetic acid was found as a by-product (δ 2.10; 0.16 mol/mol 1, after 24 hr), presumably formed by the reaction of water with the reactive intermediate produced from 1 and 2.

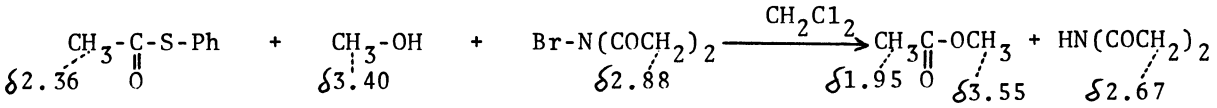


The intermediate is probably acetyl phenyl sulfoxide (CH_3-CO-S(→O)-Ph), but its presence was not detectable by PMR analysis. Probably it was rapidly consumed as it was formed. It appears that the oxidation step is slow and the acylation step is fast. The amount of benzenesulfenic acid was not determined, because sulfenic acids are known to undergo bimolecular condensation forming water and RS(→O)SR,[3]

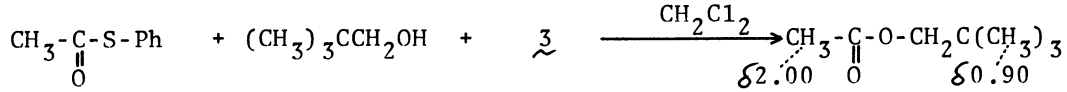
which tends to be further disproportionated to RSO_2-SR and RSSR.[4]

In an attempt to find a more efficient oxidizing agent, use of N-bromosuccinimide (3) was examined. Takagi et al.[2] described that among numerous oxidants examined only I_2, Br_2, and 3 were effective for the oxidation of their 8-acetylthiooctanoic acid. Kumamoto and Mukaiyama reported that the oxidation of thiolesters with 3 in CCl_4 yielded acyl sulfoxide which reacted with nucleophiles.[5]

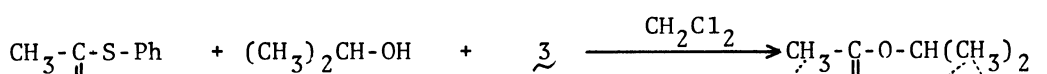
When 1 (0.13 mmol) and methanol (0.13 mmol) was dissolved in CH_2Cl_2 (0.4 ml), and 3 (0.13 mmol) was added, it was found that 1 was quantitatively converted to methyl acetate in 1 hr. The results of the reactions with several nucleophiles are summarized below.



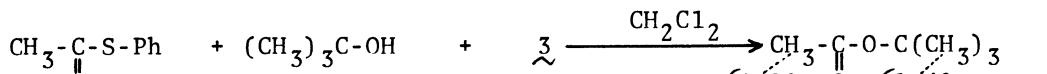
0.13 mmol 0.13 mmol 0.13 mmol 1 hr 1.00 mol/mol 1



0.13 mmol 0.13 mmol 0.13 mmol 3 hr 0.80 mol/mol 1

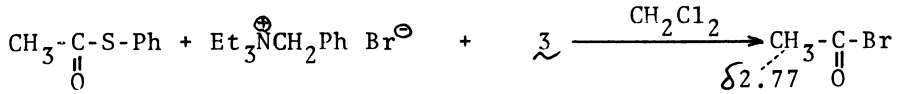


0.13 mmol 0.13 mmol 0.13 mmol 3 hr 0.70 mol/mol 1

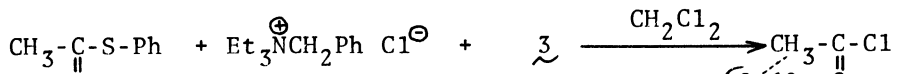


0.13 mmol 0.13 mmol 0.13 mmol 3 hr 0.70 mol/mol 1

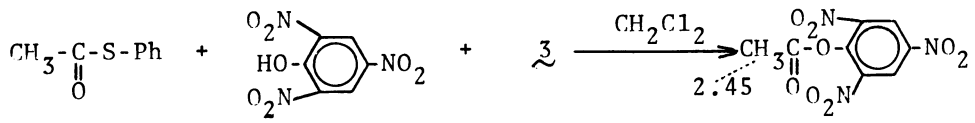
0.13 mmol 0.26 mmol 0.156 mmol 3 hr 1.00 mol/mol 1



0.099 mmol 0.28 mmol 0.16 mmol 24 hr 0.53 mol/mol 1



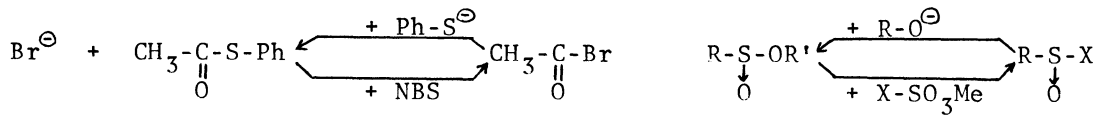
6.37 mmol 25.5 mmol 12.7 mmol 24 hr 0.43 mol/mol 1



0.13 mmol 0.13 mmol 0.13 mmol 3 hr 1.00 mol/mol 1

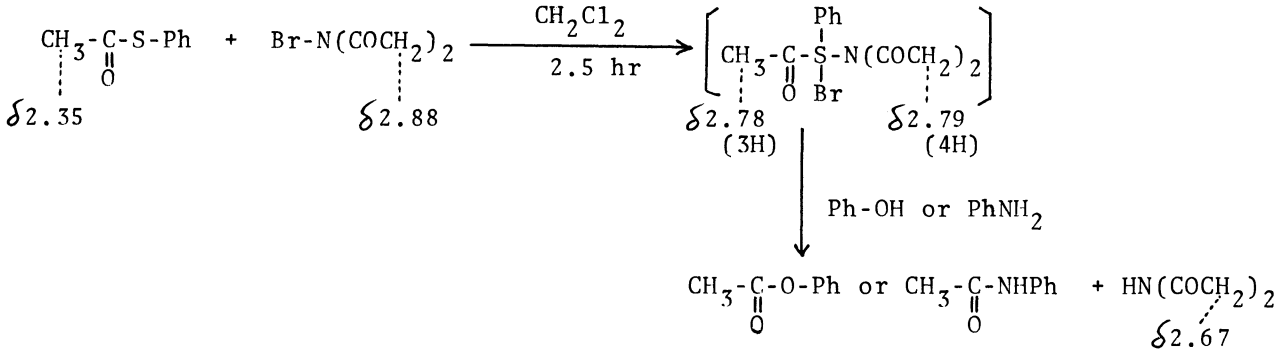
It is of interest that such poor nucleophiles as chloride and bromide ions are acetylated at room temperature by the thiol ester-NBS pair. Acyl halides usually react readily with alcohols and thiols, forming esters and thiol esters. The results described here presents the process which is essentially the reversal of the esterification, forming acyl halides from thiol esters. Conversion of esters

to acyl halides in a single step has not been reported in the literature. As a little different example, we have reported the conversion of sulfinate esters (R-S(→O)-OR') to sulfinyl halides (R-S(→O)-X) by the reactions with $X\text{-}SO_3CH_3$ (X = F, Cl).[6]

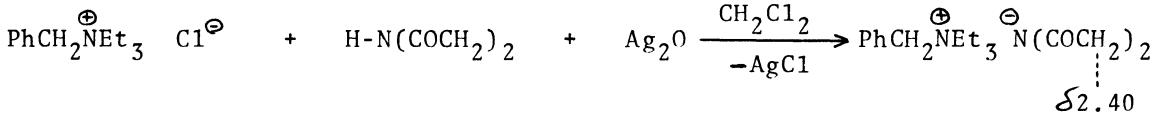


It is also of a considerable interest that such a strong acid as picric acid is readily acetylated at room temperature.

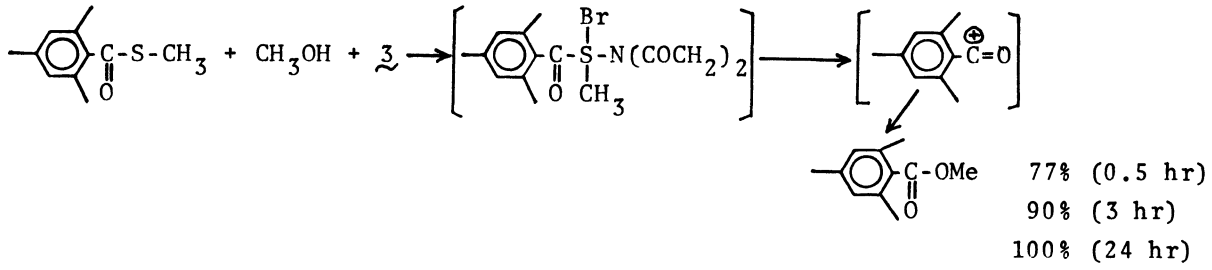
When 3 was added to a CH_2Cl_2 solution of 1 and phenol (or p-nitrophenol), the phenol was not acetylated, but brominated by 3. Therefore, phenol was acetylated by a different manner. When a mixture of 1 (0.13 mmol) and 3 (0.13 mmol) in CH_2Cl_2 (0.4 ml) was allowed to stand for 2.5 hr at 34°, its PMR spectrum showed that 1 and 3 reacted quantitatively, forming an intermediate (δ2.78, 3H; δ2.79, 4H).



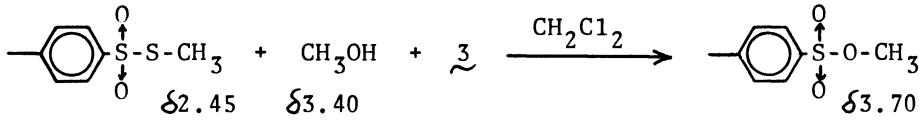
When phenol (0.26 mmol) or aniline (0.26 mmol) was added to the mixture, acetylation was complete in 0.5 hr, and phenyl acetate (0.93 mol/mol 1) or acetanilide (1.00 mol/mol 1) was formed. The structure of the intermediate is not certain, but the PMR absorptions of succinimide hydrogens (δ2.79) suggest that it is not an ion pair ($PhAcBrS^{\oplus}\,^{\ominus}N(COCH_2)_2$) but a sulfurane ($PhAcBrS\text{-}N(COCH_2)_2$). When benzyltriethylammonium succinimide was prepared in a CH_2Cl_2 solution, the succinimide anion absorbed at δ2.40.



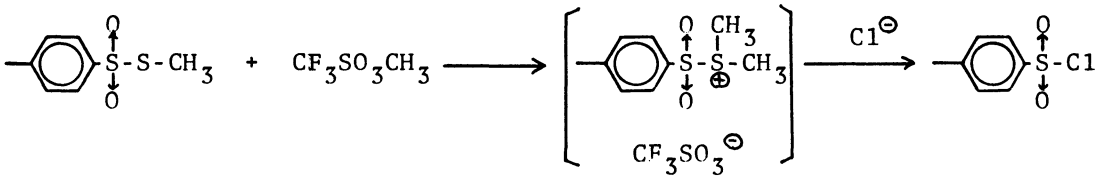
In an attempt to elucidate the mechanism of the reaction of the intermediate with nucleophiles, S-methyl thiomesitoate was treated with 3 and methanol. The reaction is expected to be slow if methanol attacks a sterically crowded intermediate. However, methanol was smoothly mesitoylated. This finding indicates that in this case the brominated intermediate decomposes, yielding another intermediate (mesitoyl cation), which rapidly reacts with methanol.



Possibility of sulfonylation by thiolsulfonate-oxidizing agent pair was examined. When S-methyl p-toluenethiosulfonate was treated with 3 and methanol, the methanol was sulfonylated.



Sulfonylation of nucleophiles was further examined by using another kind of oxidizing agents, namely methyl triflate. After a mixture of S-methyl p-toluenethiosulfonate (1.05 mmol) and methyl triflate (5.65 mmol) was allowed to stand without solvent in a sealed ampoule at room temperature for 10 days, the ampoule was opened and the remaining methyl triflate was removed under reduced pressure. When a nitromethane solution (2 ml) of benzyltriethylammonium chloride (1.86 mmol) was added, reaction took place instantaneously. The solution was concentrated, and chromatographic separation of the residue yielded p-toluenesulfonyl chloride (0.26 mol/mol of p-Ts-SMe used).



Thus, oxidizing agents-thiol ester pairs appear to function as efficient acylating agents at room temperature.

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