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CLEAVAGE OF THE ETHYLENETHIOACETAL GROUPS IN THE NITROGEN CONTAINING HETEROCYCLES[1)]

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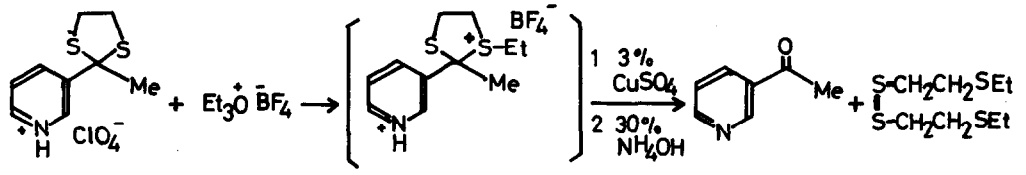
In the previous paper[2)], we reported that bis-sulfonium salts obtained by the alkylation of the ethylenethioacetals with two molar equivalents of Meerwein Reagent($Et_3O^+BF_4^-$) were smoothly hydrolyzed affording the corresponding aldehydes or ketones in high yields. On the other hand, mono-sulfonium salts obtained by use of a molar equivalent of the reagent give substantial amounts of unexpected by-products on hydrolysis. This difficulty could be overcome by trapping the thereby liberated mercaptan by ambident methods. This modified procedure was found to be particulary effictive on the hydrolysis of the ethylenthioacetal groups in the nitrogen containing heterocycles[3)], which will be discussed in the present report.

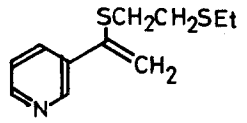
It is easily conceivable that the nitrogen atoms in these compounds should be protected from being alkylated by $Et_3O^+BF_4^-$ treatment. Protonation is well suited for this purpose because it is known to occur much more easily on the nitrogen than on the sulfur atom in comparison with alkylation[4)]. In fact, only



1 2 3

the S-monoethylated salt(2) was obtained as a crystalline salt when 3-acetylpyridine ethylenethioacetal perchlorate(1) was reacted at room temperature with

two molar equivalents of $Et_3O^+BF_4^-$ in CH_2Cl_2 for four days. The N,S-bis-sulfonium salt(2) thus obtained was hydrolyzed with 3% $CuSO_4$ solution, followed by basification with 30% NH_4OH according to the procedure recommended in the previous paper[2] to yield 3-acetyl pyridine(3)(95%) and the disulfide(4)(73%), as was expected. On the other hand, direct hydrolysis of 1 with 10% NaOH afforded the vinyl sulfide(5) as a main product. In the same way, the amino ketone(6)[5] was obtained from the corresponding perchlorate(7) via the N,S-bis-salt(8a) in the yield of 88%. In this case, however, prolonged refluxing of the reaction mixture was required for the completion of alkylation.



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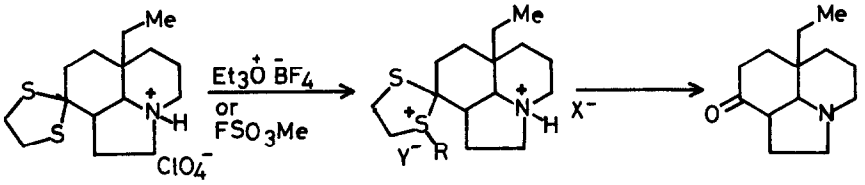


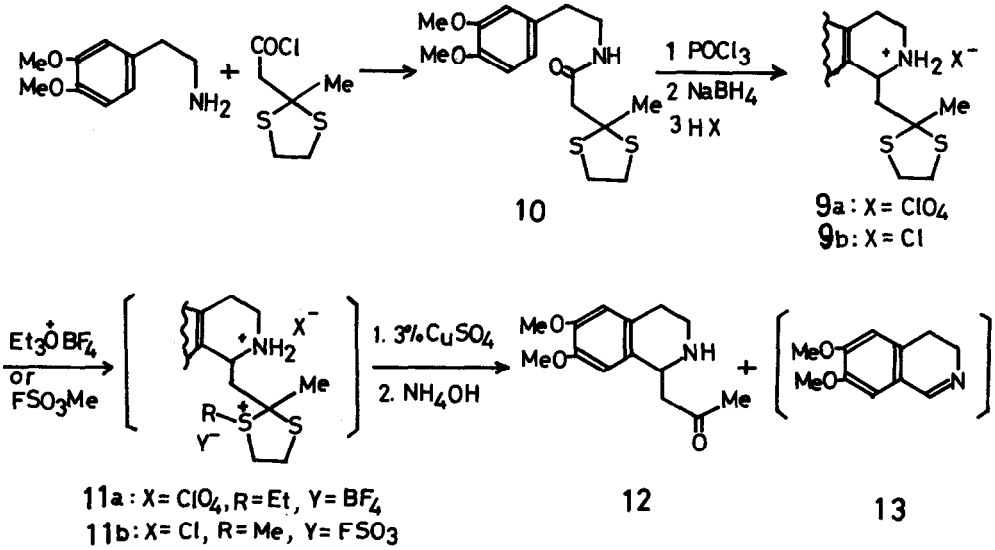
7 8a : X= ClO_4, R= Et, Y= BF_4 6

8b: X= ClO_4, R= Me, Y= FSO_3

It is noteworthy that S-alkylations of 1 and 7 proceed quite slowly as mentioned above whereas bis-sulfonium salts are formed readily on the alkylation of the ethylenethioacetal groups in the compounds containing no cationic center. Therefore, when the substrate is rather unstable, some decomposition may occur during the alkylation. Actually, formation of the by-product*1 was observed while the N-protonated dihydroisoquinoline derivative(9a)*2 was being refluxed with an excess of $Et_3O^+BF_4^-$ in CH_2Cl_2. This undesirable side reaction could be avoided by use of methyl fluorosulfonate(FSO_3CH_3)[6], a still more effective alkylating reagent than $Et_3O^+BF_4^-$. Thus, 9b*3 was dissolved in a large excess of FSO_3CH_3 and stirred at room temperature for three days. After the evaporation of FSO_3CH_3 and the same work-up as above, the pure amino ketone(12)[7] was obtained in a satisfactory yield(78.5%). Methylation of 7 with FSO_3CH_3 also proceeded at room temperature within two days and the subsequent hydrolysis of

the resultant fluorosulfonate(8b) afforded the ketone(6) in high yield, which gave an another example of the facile cleavage of this type of thioacetals with FSO_3CH_3.

The present method would be applicable on the synthetic studies of alkaloids or nitrogen containing heterocycles.



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*1 The structure of this compound has been tentatively assigned as 13.

*2 The compound(9) was prepared many years ago by cyclization of the amide(10) with $POCl_3$ followed by successive $NaBH_4$ reduction and N-protonation with an aim of the synthesis of emetine(S. Sugasawa and T. Oishi, unpublished work). The authors are grateful to Professor Emeritus Shigehiko Sugasawa, Tokyo University, for his interest throughout this work and for his permission of the publication of the studies originally attempted by him. At that time, an attempt for the cleavage of the ethylenethioacetal groups in isoquinoline derivatives with $HgCl_2$ was unsuccessful because insoluble donor-acceptor complex of the amino group with $HgCl_2$ was precipitated out from the reaction mixture immediately after the reactants were mixed.

*3 Initially, it was assumed that the ammonium chloride(9b) would partly be in equillibrium with the corresponding free base under the alkylation condition and the N-alkylated product would eventually be accumulated. However, it became apparent from the present experiment that the hydrochloride moiety of 9b was stable enough and remained unchanged during the reaction.

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