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SYNTHESES OF THE NITROGEN-CONTAINING HETEROCYCLES THROUGH THE REACTIONS OF ACTIVATED AMIDES AND OTHER ACTIVATED SPECIES

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The reactions of activated carboxamides, sulfonamides and substituted aromatic compounds to afford the N-containing heterocycles are described.

Stable weak organic bases can be convertible to the reactive species towards nucleophile in some cases when they are subjected to alkylation[1a,b], oxidation, halogenation or acylation. Activation through metal complex formation has also been reported. Reactivity modulation of weak organic bases and the reactions of the resulting activated species have been studied in general in this laboratory.

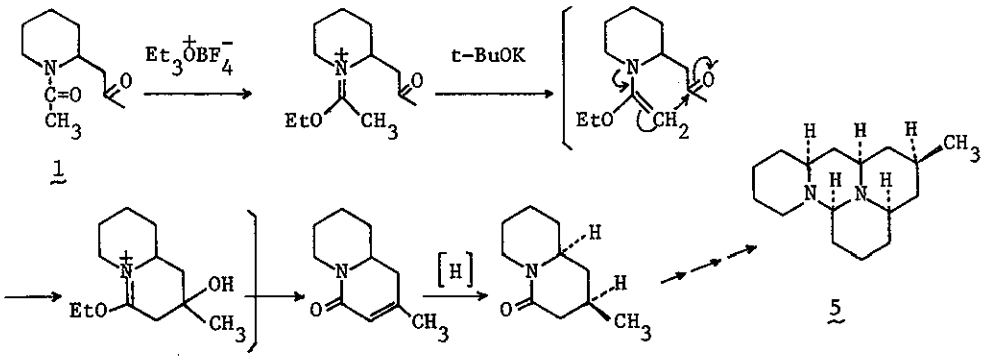
The present paper deals in particular with the synthesis of N-containing heterocycles using these activated species.

1. The reactions of amide acetals with nucleophiles.

The activation of carboxamides by O-alkylation and the reactions of the

resulting iminoethers with nucleophile have been fully investigated by many workers. We have also successfully utilized this method for the conversion of 3,3-disubstituted oxindoles to the 3,3-disubstituted indoline derivatives via the iminoether[2].

Meanwhile, we also found that O-alkylated salts or amide acetals liberated in situ the crresponding ethoxyenamines under the reaction condition and thus reacted with electrophiles to give the amides substituted at the β-position of nitrogen[3]. Here, the application of this method to the natural product synthesis is described[4].



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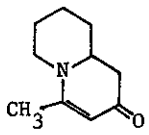
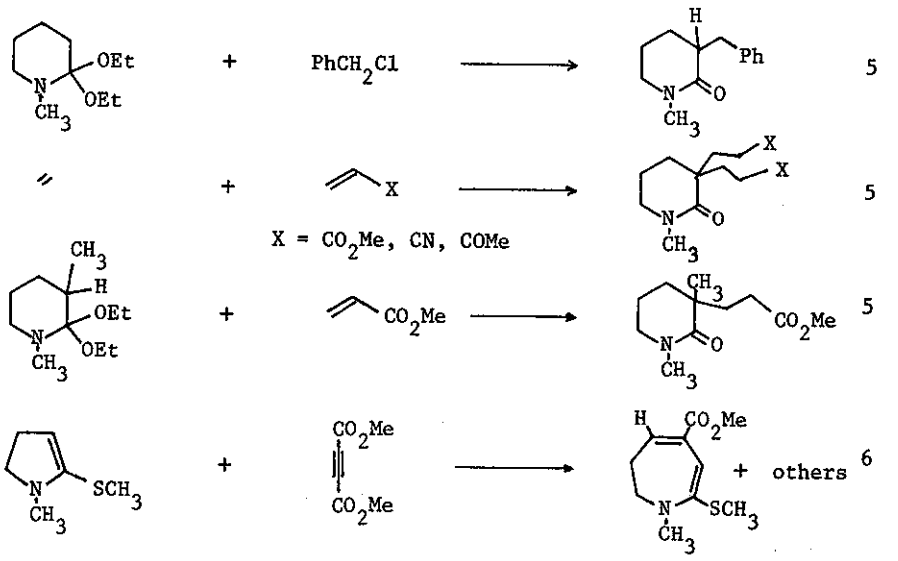
The cyclic compound(2) was prepared in fair yield from 1 by alkylation with Meerwein reagent followed by t-BuOK treatment. The aluminium t-butoxide treatment of 1 afforded only the isomeric product(3).



3

The piperidone(4), prepared from 2 by catalytic hydrogenation, was used as a key intermediate in the synthesis of (±)-dihydrodeoxyepiallocernuine(5).

The cyclic amide acetals were also found to react with various nucleophiles. The typical examples are shown below.



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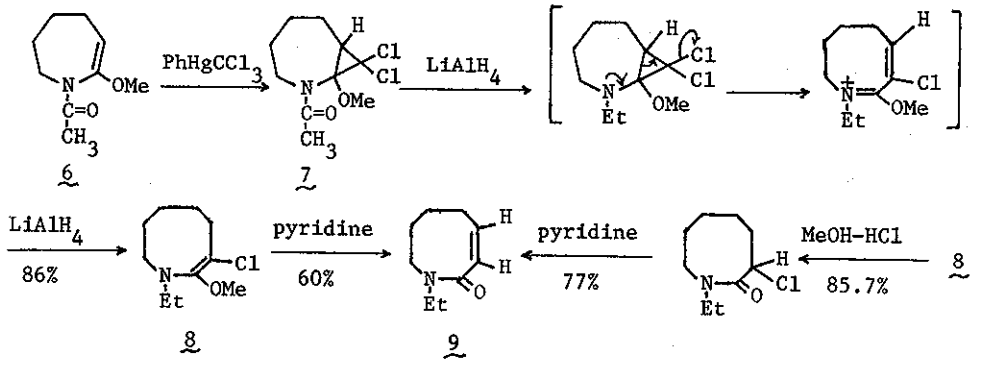
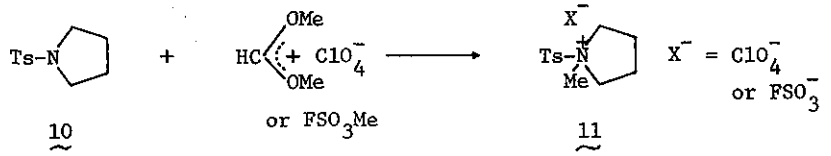
Then, the stepwise ring enlargement of lactams was investigated[7]. The N-masked methoxyenamine(6)[8] was chosen as an active species. When 6 was allowed to react with $PhHgCCl_3$, the adduct(7) was obtained in 23% yield along with the recovered starting material (46%). Ring enlargement took place when 7 was treated with $LiAlH_4$ to give 8, which was converted either by pyridine treatment or hydrolysis with MeOH-HCl followed by pyridine treatment to the unsaturated eight-membered lactam(9).



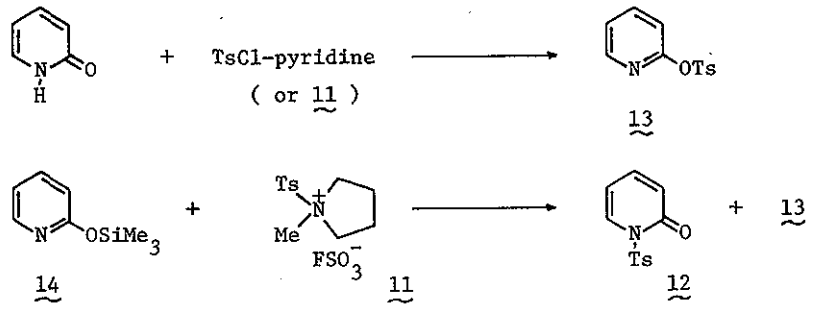
2. The reaction of activated sulfonamide.

It has been reported from this laboratory that the sulfonamide(10) can be N-alkylated affording the salt(11)[9a,b], which selectively tosylates amino group in the presence of hydroxy group in the same molecule[9c].



10 11

In an expectation that when the nitrogen atom of pyridone was masked by tosylation the reactivity of pyridone would be modulated, the synthesis of N-tosylpyridone(12)[10a,b] was attempted. However, usual tosylation affords exclusively the O-tosylated product(13). On the other hand, when O-silylated compound(14) was allowed to react with 11, the desired 12 (46.3%) was obtained along with 13 (27.9%)[11]. This may be attributable to the weak nucleophilicity of a counter anion involved in 11. The reaction of 12 is now under investigation.

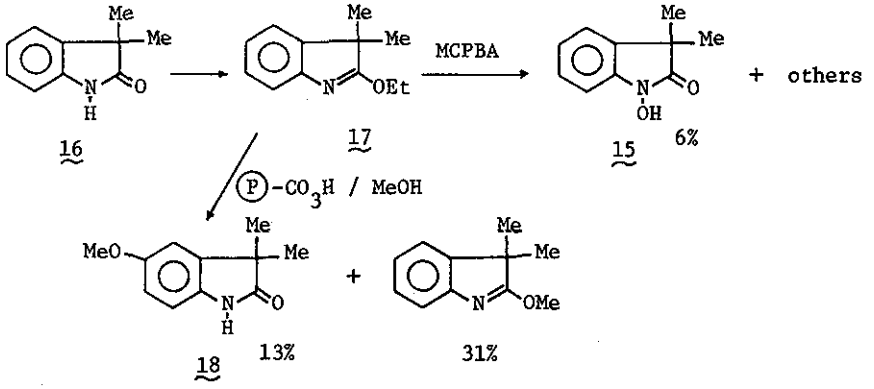


3. Introduction of hydroxy group into the aromatic rings of oxindoles or indolines.

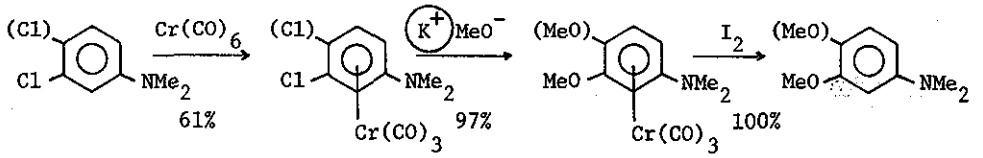
There are many natural oxindole or indoline bases bearing hydroxy groups in the aromatic ring. Usually, the syntheses of these alkaloids have been achieved starting with the simple oxindoles or indoles having these functional

groups from the beginning. We intended the introduction of hydroxy groups at the relatively later stage of the synthesis.

Gassman[12] has reported that N-hydroxyoxindole affords 5-methoxyoxindole(42%) and 7-TsO-oxindole(32%) by O-tosylation followed by MeOH treatment. However, preparation of N-hydroxyoxindoles from oxindoles has not been reported yet. Therefore, as a model system, synthesis of 15 from 16 was attempted. When iminoether(17) was oxidized with MCPBA, 15 was obtained only in 6% yield along with many others. However, when polymer-supported peracid[14] was employed, the desired rearranged product(18) was obtained directly.[13] The yield has not been optimized yet.



In addition, we recently succeeded in the enforced nucleophilic substitution reaction of π-(m,p-dimethylaminochlorobenzene)chromium tricarbonyl complex with "naked" methoxide ion[15]. Extention of this novel reaction to the indoline system is now in progress.



$\textcircled{K^+}$ = K^+ trapped by 18-crown-6

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