THE INTRODUCTION OF METHOXY GROUP TO THE AROMATIC RING OF HETEROAROMATIC SYSTEMS ; A MODEL STUDY FOR THE INTRODUCTION OF METHOXY GROUP TO THE 5-POSITION OF 3,3-DISUBSTITUTED INDOLINE ALKALOIDS

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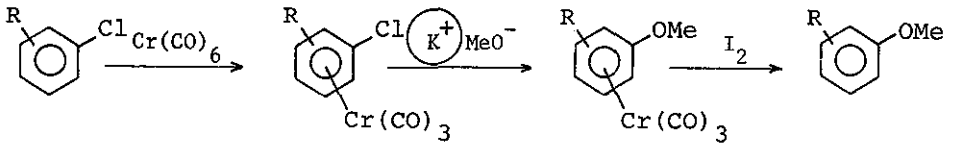
Introduction of methoxy group to the 5-position of 3,3-disubstituted indoline derivative was achieved by the substitution of chlorine of the corresponding 5-chloroindoline with methoxy group, substitution being assisted by chromium tricarbonyl complex formation and by the use of "naked" methoxide anion.

In nature, there are many oxindole, indole and 3,3-disubstituted indoline alkaloids bearing mono-, di- and trimethoxy groups on the aromatic ring. However, synthesis of these alkaloids has not progressed so far. Particularly, synthesis of alkaloids having two or three methoxy groups has not been reported yet. In most of the previous synthesis of such alkaloids, indole derivatives having oxygen function at the desired position are used as a starting material. For example, 5-methoxyindole was used in the synthesis of iboga alkaloids[1] and 6-benzyloxy- and 6-methoxyindoles were used in the syntheses of reserpine[2] and vindoline[3], respectively.

We intended the introduction of methoxy group to the aromatic ring after the fundamental skeleton of the alkaloids had been constructed. For this purpose, it is necessary to develope a mild method which is feasible in the presence of other functional groups in the same molecule. Chlorination followed by nucleophilic substitution of chlorine by methoxide anion will be the method of choice if an excellent means for replacing chlorine by methoxide anion is developed. It has been well established that nucleophilic substitution of chlorine in chlorobenzene by methoxide anion is extremely facilitated by chromium tricarbonyl complex(CTC-complex) formation[4,5]. We thought that the above method is quite promising for our purpose because CTC-complex formation can be carried out in the presence of other functional groups such as amino, hydroxyl or ester groups in the same molecule under a neutral condition. However, the substitution reaction should proceed even in the presence of other electron-donating groups on the same aromatic ring for being applied to the natural product synthesis. In fact, when π-(o-chloroanisole)chromium tricarbonyl(CTC-o-chloroanisole), a typical CTC-chlorobenzene derivative bearing electron-donating group, was refluxed for 24 hr with potassium methoxide in methanol, the reaction did not take place at all. This difficulty is considered to be associated with the rather weak nucleophilicity of methoxide anion since Semmelhack[5] have recently reported that when a nucleophile is sufficiently effective, even a hydrogen atom of CTC-benzene can be replaced by that particular nucleophiles. Thus, the so-called "naked" methoxide anion[6] reported to have high reactivity was used in place of simple methoxide anion and found that the substitution of chlorine of CTC-chlorobenzene bearing various electron-donating groups(alkyl, methoxy and dimethylamino) by "naked" methoxide anion proceeded surprisingly smoothly under mild conditions affording the corresponding CTC-anisole derivatives[7]. The removal of

chromium tricarbonyl moiety can readily be achieved by simple irradiation[8] or oxidation by iodine[5,7] or ceric ammonium nitrate[9]. The overall reaction is illustrated as follows.

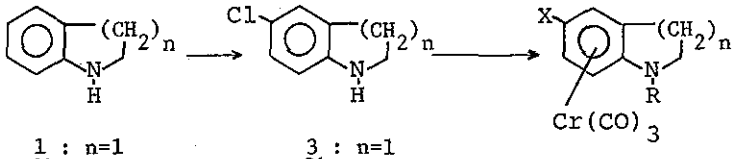


R = Me, OMe, NMe_2

K^+ : K^+ trapped by 18-crown-6

Now, we examined whether the present method is applicable to heteroaromatic systems. As a simple model experiment, introduction of a methoxy group into tetrahydroquinoline and indoline was investigated. It has been reported that chlorination of N-acetyl-1,2,3,4-tetrahydroquinoline with sulfuryl chloride followed by deacetylation with acid affords 6-chloro-1,2,3,4-tetrahydroquinoline (4)[10]. In the same way, 5-chloroindoline(3)[bp 83-4°/3.5torr(Lit.[11] 132-5°/20 torr)] was obtained in 77% yield from indoline(1). When 6-chloro-1,2,3,4-tetrahydroquinoline(4) was refluxed with 2 eq of chromium hexacarbonyl in diglyme-cyclohexane(1:1) at 125° for 53 hr in an atmosphere of nitrogen[4a,12], the corresponding CTC-complex(6a) was obtained as yellow crystal[mp 121-2°] in 50% yield. The starting material unemployed was recovered cleanly by extraction with dilute hydrochloric acid from the reaction mixture[85% yield, calculated from the consumed starting material(4)]. In the same way, CTC-5-chloroindoline(5a)[mp 107-8°] was obtained in 68% yield[84% yield, calculated from the consumed chloroindoline(3)]. These complexes are insoluble in 10%-HCl, which shows that the basicity of amino groups is extremely decreased by complex formation. On the other hand, base-catalyzed hydrogen abstraction from secondary amines was found to take place readily.

Therefore, in order to achieve the desired substitution reaction, these nitrogens should be masked before "naked" methoxide anion treatment. Addition of 6a to a benzene suspension of 1.5 eq of potassium hydride and 0.25 eq of 18-crown-6 followed by benzyl bromide treatment at room temperature afforded the N-benzyl derivative(6b) in 91% yield after SiO_2 chromatography, which was treated with 4 eq of potassium methoxide in the presence of 0.5 eq of 18-crown-6. The reaction completed after only 3 hr at 70° and the corresponding methoxy derivative(6c) was obtained as an unstable yellow oil in 91% yield after purification. Subsequent oxidative cleavage of chromium tricarbonyl moiety by iodine in THF/10%-HCl afforded, within 30 min at room temperature, 6-methoxy-N-benzyl-1,2,3,4-tetrahydroquinoline(8)[hydrochloride: mp 187-8°(dec.), 90% yield]. Similarly, 5-methoxy-N-benzylindoline(7)[hydrochloride: mp 183-4° (dec.)] was obtained by N-protection(90%), substitution(92%) and iodine treatment(93%).

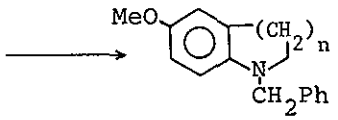


1 : n=1
2 : n=2

3 : n=1
4 : n=2

5a : n=1, X=Cl, R=H
b : n=1, X=Cl, R=CH_2Ph
c : n=1, X=OMe, R=CH_2Ph

6a : n=2, X=Cl, R=H
b : n=2, X=Cl, R=CH_2Ph
c : n=2, X=OMe, R=CH_2Ph

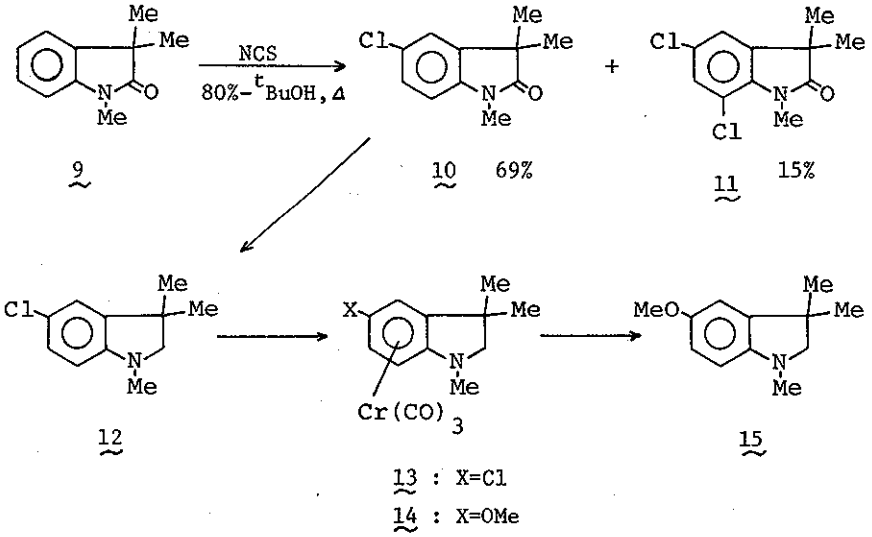


7 : n=1
8 : n=2

Then, introduction of methoxy group to 1,3,3-trimethyloxindole and indoline, model compounds of naturally occurring 3,3-disubstituted oxindole and indoline

alkaloids, was examined. Attempted formation of CTC-complex of 5-chloro-1,3,3-trimethyloxindole(10) prepared from 1,3,3-trimethyloxindole(9) by NCS chlorination failed even if 10 was refluxed for 2 days with excess of $Cr(CO)_6$ in diglyme-cyclohexane. However, the corresponding indoline(12) derived from 10 by $LiAlH_4$ reduction afforded the complex(13)[mp 132-3°] after 50 hr in the yield of 50%. Once the complex was formed, replacement of chlorine by "naked" methoxide anion took place quite smoothly to yield the CTC-methoxyindoline(14) [mp 90-1°, 93%]. The release of the corresponding free base(15)[picrate: mp 153-4°(dec.), hydrochloride: mp 198-9°(dec.)] also proceeded essentially in quantitative yield, establishing the practical way of introducing methoxy groups to the 5-position of complex 3,3-disubstituted indoline skeleton.

Applications of the present method to the synthesis of 6-methoxy-3,3-disubstituted indoline derivatives and 5-, 6- and 7-methoxy-2,3-disubstituted indole derivatives are now in progress.



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