# Preparation of 1-hydroxyindole derivatives and a new route to 2-substituted indoles


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# PREPARATION OF 1-HYDROXYINDOLE DERIVATIVES AND A NEW ROUTE TO 2-SUBSTITUTED INDOLES[1]

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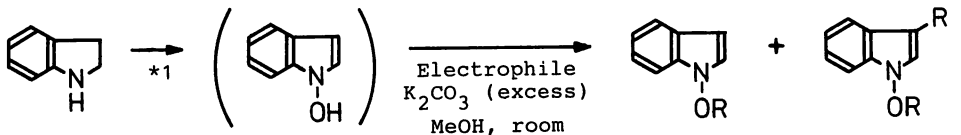
Abstract——An easy handling method of 1-hydroxyindole is developed. Based on the method, preparation and reaction of 1-hydroxyindole derivatives are investigated. A new regioselective lithiation of 1-methoxyindole and its application for the synthesis of 2-substituted indoles are also reported.

We have reported a convenient synthetic method for 1-hydroxyindoles[2] and its application for the total syntheses of 9-methoxycarbazole-3-carboxaldehyde and methoxybrassinin.[2f] In this communication, we wish to describe preparations of various 1-hydroxyindole derivatives, their reactions, and a versatile synthetic method for 2-substituted indoles based on a ready lithiation at the 2-position of 1-methoxyindole.

## I. Preparation of various 1-hydroxyindole derivatives

Although 1-hydroxyindole (2) has not been isolated because of its extremely unstable nature, we can easily obtain the aqueous methanol (MeOH) solution of 2 by the oxidation of 2,3-dihydroindole (1) in MeOH with a catalytic amount of sodium tungstate and 30% hydrogen peroxide as reported previously.[2e] Since 1-hydroxy group of 2 is acidic, addition of various alkylating reagents to the methanol solution of 2 in the presence of potassium carbonate ($K_2CO_3$) produced various 1-hydroxyindole derivatives (3a-g) as expected and the results are summarized in Table I. When benzyl bromide, (E)-cinnamyl bromide, or prenyl bromide is used as an alkylating reagent, formation of 4e-g was observed together with 3e-g. It is interesting to note that the compounds (4e-g) could not be produced by the reactions of the corresponding 3e-g with the respective alkylating reagent.

Table I. Preparation of Various 1-Hydroxyindole Derivatives

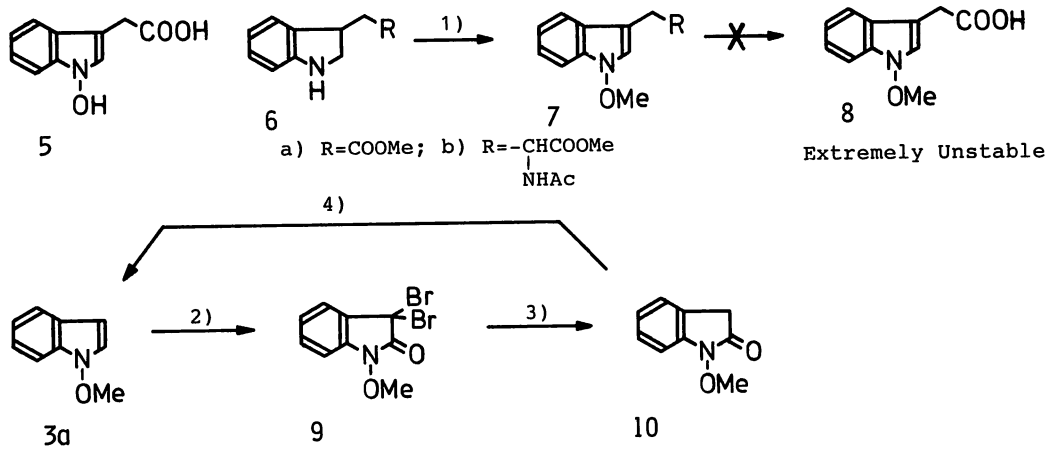



| Run | Electrophile | R | Yield (%) of 3 | 4 |
|---|---|---|---|---|
| 1 | $Me_2SO_4$ | a) Me | 51 | 0 |
| 2 | MeI | a) Me | 13 | 0 |
| 3 | $CH_2$=$CHCH_2Br$ | b) $CH_2$=$CHCH_2$ | 45 | 0 |
| 4 | TsCl | c) Ts | 14 | 0 |
| 5 | $Me(CH_2)_4CH_2I$ | d) $Me(CH_2)_4CH_2$ | 4 | 0 |
| 6 | $PhCH_2Br$ | e) $PhCH_2$ | 47 | 5 |
| 7 | (E)-PhCH=$CHCH_2Br$ | f) (E)-PhCH=$CHCH_2$ | 25 | 10 |
| 8 | $Me_2C$=$CHCH_2Br$ | g) $Me_2C$=$CHCH_2$ | 7 | 3 |
| 9 | t-$BuMe_2SiCl$ *2 | h) t-$BuMe_2Si$ | 47 | 0 |
| 10 | PhCOCl *2 | i) PhCO | 49 | 0 |

*1. 2,3-Dihydroindole (0.1 mmol), $Na_2WO_4 \cdot 2H_2O$ (0.2 mol eq.), 30% $H_2O_2$ (10 mol eq.) were used in MeOH.[2e]

*2. Benzene solution of 2 was used.

Scheme 1




1) i: $Na_2WO_4 \cdot 2H_2O$, 30%$H_2O_2$; ii: $CH_2N_2$; 2) NBS, t-BuOH; 3) Zn-AcOH; 4) $LiAlH_4$

The benzene solution of 2 could be obtained by adding benzene and water to the above methanol solution of 2, followed by the separation of an organic layer and drying over sodium sulfate. Treating this benzene solution of 2 with either t-butyldimethylsilyl chloride or benzoyl chloride in the presence of $K_2CO_3$, 1-t-butyldimethylsilyloxy- (3h) and 1-benzoyloxyindole (3i) were prepared in 47% and 49% yields, respectively. On the other hand, oxidation of 1 with m-chloroperbenzoic acid in methylene chloride generated the methylene chloride solution of 2 and addition of an ethereal diazomethane afforded 1-methoxyindole (3a) in 51% yield.

Thus, we established that unstable 2 could be easily handled as methanol, benzene, and methylene chloride solutions without any special precautions in the presence of air.

Based on these findings, preparation of 1-hydroxyindole-3-acetic acid (5), being imagined to be a metabolite of auxin,[3] was attempted (Scheme 1). Thus, methyl 2,3-dihydroindole-3-acetate (6a) was converted to methyl 1-methoxyindole-3-acetate (7a) in 55% yield. Subsequent alkaline hydrolysis of 7a produced an extremely unstable product, presumed to be 1-methoxyindole-3-acetic acid (8), which rapidly collapsed to many products. This result suggests that 5 would be a quite unstable compound. Similarly, Nb-acetyl-1-methoxytryptophan methyl ester (7b) was produced in 63% yield from the corresponding 6b.

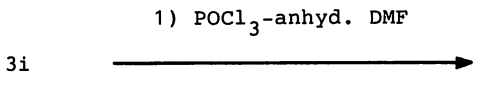
II. Reactions of 1-hydroxyindole derivatives

Bromination of 3a with N-bromosuccinimide afforded 3,3-dibromo-1-methoxy-2-oxindole (9) in 60% yield (Scheme 1). Subsequent treatment of 9 with zinc in acetic acid produced 1-methoxy-2-oxindole[4] (10) in 65% yield. Since 10 could be reduced to 3a, interconversion method between 3a and 10 was established.

Although Vilsmeier-Haack reaction of 1-tosyloxyindole (3c) produced a 67% yield of 2-chloroindole-3-carboxaldehyde[5] (12) as a sole product, 1-t-butyldimethylsilyloxyindole (3h) produced 12 and 1-hydroxyindole-3-carboxaldehyde[6] (11) in 32% and 39% yields, respectively (Scheme 2). On the other hand, Vilsmeier-Haack reaction of 1-benzoyloxyindole (3i) afforded 11 and 12 in varied yields depending on the reaction conditions and the results are shown in Table II. As can be seen from the Table II, long reaction time and an excess amount of phosphorus oxychloride prefer the formation of 12 to 11. Taking into consideration that Vilsmeier-Haack reaction of 3a produced 91% yield of 1-methoxyindole-3-carboxaldehyde[2d,6] (13), these results are explained by the mechanism proposed in Scheme 2, where better leaving group and excess amount of reagent force the reaction to the right at the irrevers-

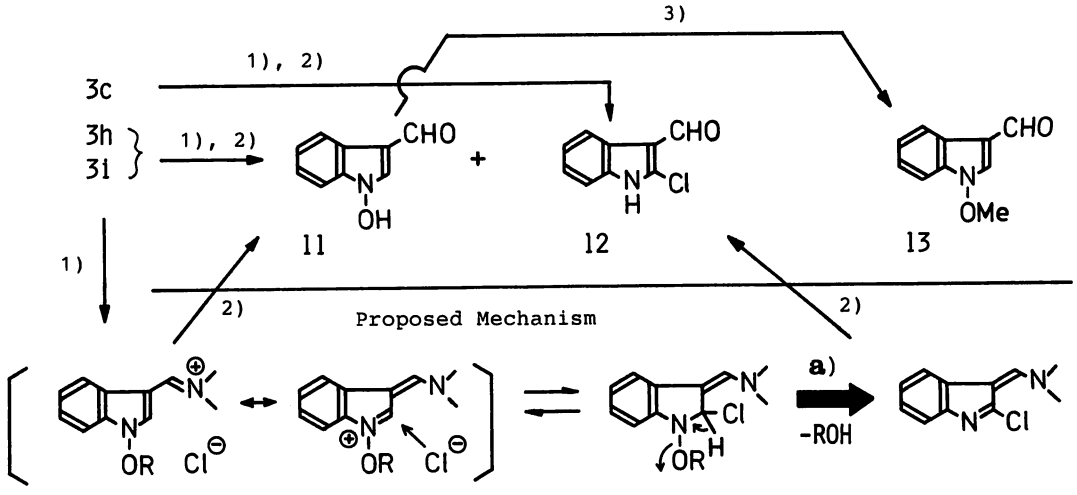
ible step a) culminating in the better yield of 12. Treatment of 11 with an ethereal diazomethane afforded 13 in 93% yield.

Table II. Preparation of 1-Hydroxyindole-3-carboxaldehyde




| Run | $POCl_3$ (mol eq.) | Reaction Time (h) | Yield (%) of 11 | 12 |
|---|---|---|---|---|
| 1 | 3 | 47 | 0 | 98 |
| 2 | 3 | 11 | 0 | 90 |
| 3 | 2.5 | 3 | 36 | 55 |
| 4 | 2 | 3 | 57 | 14 |

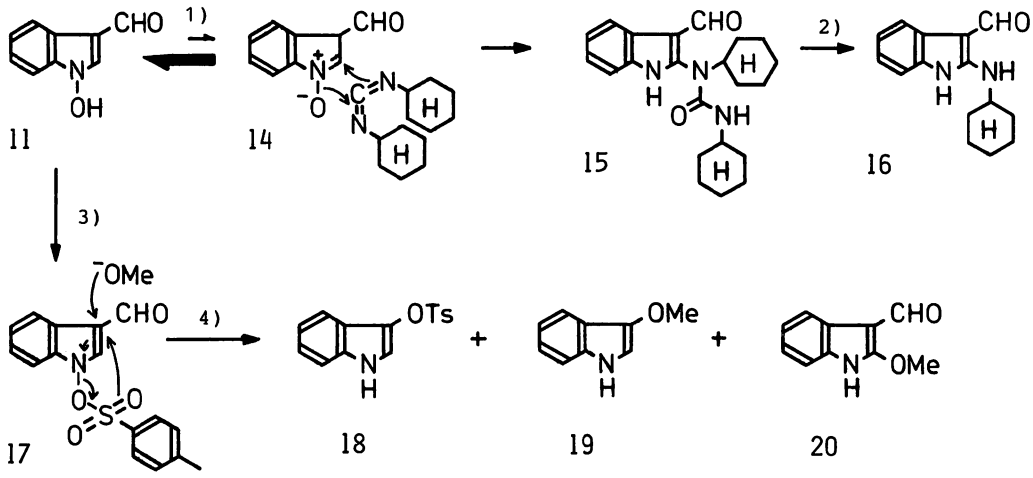
Scheme 2




1) $POCl_3$-anhyd. DMF; 2) NaOH-$H_2O$; 3) $CH_2N_2$

The reaction of 11 with 1,3-dicyclohexylcarbodiimide (DCC) in the presence of triethylamine produced 83% yield of N,N'-dicyclohexyl-N-(3-formylindol-2-yl)urea (15), which was then converted to 2-cyclohexylaminoindole-3-carboxaldehyde (16) in 37% yield upon treatment with aq. sodium hydroxide (Scheme 3). The formation of (15) may be explained by the [2+3] cycloaddition reaction of DCC with the nitrone (14), supposed to exist as a tautomer of 11. On the other hand, treatment of 11

Scheme 3



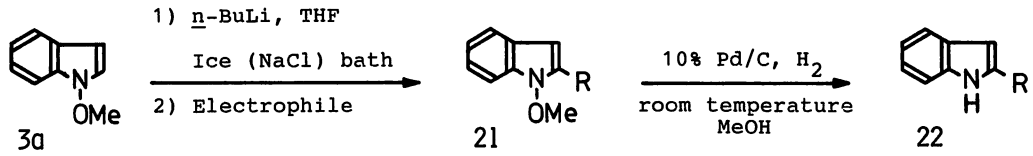

1) DCC, $Et_3N$, THF; 2) 20% NaOH-MeOH; 3) TsCl, pyridine; 4) NaOMe, MeOH

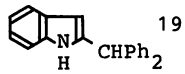
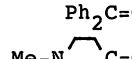
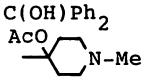
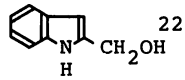
with tosyl chloride in pyridine produced 93% yield of unstable 1-tosyloxyindole-3-carboxaldehyde (17). Subsequent reaction of 17 with sodium methoxide in MeOH generated 3-tosyloxyindole (18), 3-methoxyindole (19), and 2-methoxyindole-3-carboxaldehyde (20) in 16%, 12%, and 8% yields, respectively. These results clearly exhibit that nucleophilic attack on the indole nucleus becomes feasible when a suitable leaving group is introduced into the 1-position. Attempts to introduce nucleophiles into the benzene part of indole nucleus are in progress.

III. A versatile lithiation method of 1-methoxyindole and its application for the syntheses of 2-substituted indoles

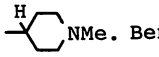
Various directing groups[7] which allow the regioselective lithiation of indole at the 2-position have been developed and widely used in indole synthesis. However, most of them could not be removed after functionalization at the 2-position. Although 1-benzenesulfonyl[7b] and 1-lithiocarboxylate[7d] groups are removable directing groups, they require low reaction temperatures (-76°C) and/or the extremely pyrophoric t-butyllithium. Now, we report that 1-methoxy group is an ideal directing group which permits ready lithiation and can be removed under mild reaction conditions. Thus, 1-methoxyindole (3a) was lithiated at the 2-position by the treatment with n-butyllithium in tetrahydrofuran (THF) in an ice and sodium chloride bath for 10 min. Subsequent addition of electrophiles in THF afforded the corresponding 2-substituted 1-methoxyindoles (21a-f) in good to excellent yields and the results

Table III. Regioselective Lithiation of 1-Methoxyindole at the 2-Position and the Syntheses of 2-Substituted Indoles




| Run | Electrophile | R | Yield (%) of 21 | Yield (%) of 22 + Other *Product* |
|---|---|---|---|---|
| 1 | $Me_2C=O$ | a) $C(OH)Me_2$ | 90 | 85 |
| 2 | $Ph_2C=O$ | b) $C(OH)Ph_2$ | 81 | 60 +  19 |
| 3 |  | c)  *1 | 68 | 97*2 |
| 4 | $Me_2NCHO$ | d) CHO | 63 | 62 +  22 |
| 5 | $(MeO)_2C=O$ | e) COOMe | 60 | 90 |
| 6 | $I_2$ | f) I | 73 | - |

*1. The product was isolated after acetylation with $Ac_2O$-pyridine.

*2. R= . Benzylic acetoxy group was completely removed.

are summarized in Table III.

Deprotection of 1-methoxy group was readily attained by the catalytic hydrogenation at room temperature and atmospheric pressure over 10% Pd/C. For example, reduction of 21a in MeOH produced 2-(1-hydroxy-1-methyl)- (22a), 2-(1-methoxy-1-methyl)-, and 2-(1-methyl)ethylindole in 85%, 7%, and 4% yields, respectively. Similarly, 21d gave 22d and indole-2-methanol in 62% and 22% yields, respectively. Other results are also included in Table III.

Now that 1-methoxyindoles become readily available, the syntheses of 2-substituted indoles, alkaloids, and their 1-methoxyindole derivatives are in progress based on the present lithiation method.

ACKNOWLEDGMENT

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6. R. M. Acheson, P. G. Hunt, D. M. Littlewood, B. A. Murrer, and H. E. Rosenberg, J. Chem. Soc., Perkin Trans. 1, 1978, 1117: Although Acheson and co-workers claimed the formation of 11 by Vilsmeier-Haack reaction of 1-acetoxyindole, their compound was orange red crystals (mp 146-150°C). Our sample (11) was pure and colorless prisms (mp 159-160°C, recrystallized from chloroform). Ir (KBr): 3096, 1605, 1513, 1384, 1308, 1237, 736 $cm^{-1}$. $^1$H-Nmr ($CD_3OD$) $\delta$ : 7.09-7.59 (3H, m), 7.94-8.22 (1H, m, 4-H), 8.13 (1H, s, 2-H), 9.76 (1H, s, CHO). Ms m/z: 161 ($M^+$). Anal. Calcd for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.05; H, 4.23; N, 8.79.
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