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A NEW AND SIMPLE SYNTHESIS OF 1-HYDROXYINDOLE DERIVATIVES¹

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Abstract ————— A new and straightforward simple synthesis method for 1-hydroxyindole derivatives is developed.

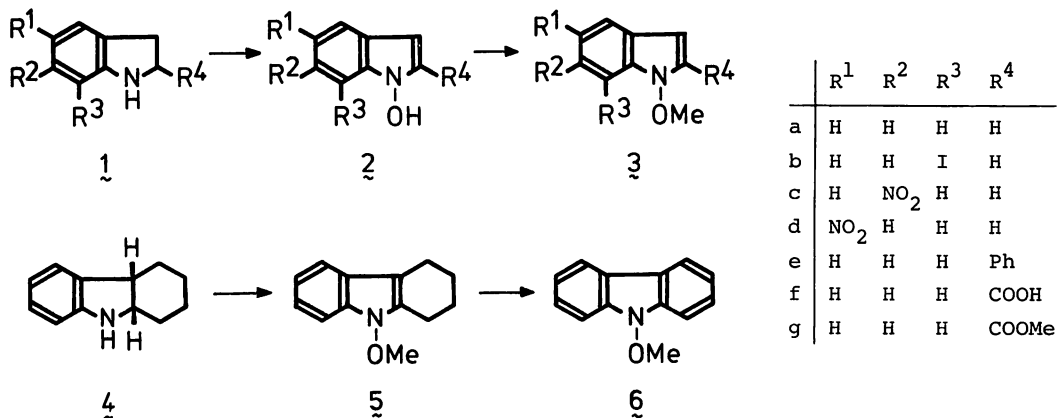
Since the appearance of pioneering papers by Acheson and co-workers,² reporting the synthesis of 1-methoxyindole (3a), we have been much interested in the chemistry of 1-hydroxyindoles, because the presence of 1-methoxyindoles as natural products³ prompted us to imagine that the corresponding unstable 1-hydroxyindoles are actually present in plants and microorganisms and play an important role *in vivo*.⁴ Based on these ideas,⁴ we have so far elaborated a convenient one pot synthesis method^{5d,f} for 3a and applied it for preparing various 1-hydroxyindoles,⁵ 1-methoxypimprinine,⁶ 1-methoxyindole-3-acetonitrile,⁶ (+)-paniculidine B,⁷ and (+)-1-methoxy-6,7-secoagroclavine.^{5f} However, utilization of an expensive N,N-dimethylformamide dimethyl acetal and anhydrous reaction conditions for the preparation of 1-hydroxyindoles are still cumbersome problems to be improved. We now succeeded in developing a new inexpensive synthesis method for 1-hydroxy- and 1-methoxyindoles, which works in the presence of water (H₂O) in one pot reaction from the corresponding 2,3-dihydroindoles. Oxidation of 2,3-dihydroindole (1a) was examined with 30% aqueous hydrogen peroxide in methanol-H₂O (10:1, v/v) at room temperature for 30 min in the presence of an oxidizing reagent, such as sodium tungstate,⁸ sodium phosphotungstate, sodium molybdate, oxone, and sodium metavanadate. The formation of 1-hydroxyindole (2a) in the reaction mixture was clearly detected by thin layer chromatography. We know that 1-hydroxyindole (2a) is quite unstable, but once 2a is converted to 1-methoxyindole (3a), its stability is increased to the extent which makes storage at room temperature possible for six years without any detectable decomposition under protection of light. Therefore, without isolation of the unstable 2a, we added an excess of ethereal diazomethane to the above mentioned reaction mixture, resulting in the forma-

Table I. Preparation of 1-Methoxyindole (3a) from 2,3-Dihydroindole (1a)

$ \begin{array}{c} \text{1a} \\ \text{Indole} \end{array} \xrightarrow[2) \text{Ethereal } \text{CH}_2\text{N}_2 \text{ (excess)}]{1) \text{Oxidizing Reagent} \\ \text{MeOH-H}_2\text{O (10:1, v/v)} \\ 30\% \text{ H}_2\text{O}_2, 30 \text{ min, stirring}} \begin{array}{c} \text{3a} \\ \text{1-Methoxyindole} \end{array} + \text{1a} + \text{Unknown Products} $						
Run	Oxidizing Reagent (mol eq.)	30% H ₂ O ₂ (mol eq.)	Reaction Temp. (°C)	Yield (%) of 3a	Yield (%) of 1a	
1	Na ₂ WO ₄ ·2H ₂ O, 0.1	1	13	15	21	
2	" "	3	18	35	5	
3	" "	10	17	50	0	
4	" 0.2	1	18	24	18	
5	" "	3	16	40	4	
6	" "	10	16	52	0	
7	" 1.0	1	18	14	28	
8	" "	3	18	5	3	
9	" "	10	16	0	0	
10	2Na ₂ O·P ₂ O ₅ ·12WO ₄ ·18H ₂ O, 0.2	1	14	26	29	
11	" "	3	15	41	11	
12	" "	10	15	58	0	
13	Na ₂ MoO ₄ ·2H ₂ O, 0.2	1	12	5	54	
14	" "	3	14	11	40	
15	" "	10	14	18	9	
16	NaVO ₃ , 0.2	1	16	0	44	
17	" "	3	20	0	54	
18	" "	10	16	0	0	
19	2KHSO ₅ ·KHSO ₄ ·K ₂ SO ₄ *1 (oxone) 1.1	0	19	11	0	+ indole, 17%

*1: This reaction was carried out for 10 min in acetone-H₂O (10:1, v/v).

Chart 1.



tion of 3a together with unknown products and the unreacted starting material. The results obtained under typical reaction conditions are summarized in Table I. Since the oxidation rate of oxone was faster than those of metal oxides, its reaction was carried out for 10 minutes (run 19). As can be seen from the Table, sodium tungstate and sodium phosphotungstate were found to be superior oxidizing catalyst to sodium molybdate and oxone. On the other hand, sodium metavanadate did not give the desired 3a at all. Under the reaction conditions described in the runs 3, 6, and 12, we can now prepare 3a in the range of 50-58% overall yield from 1a in one pot operation.

Using sodium tungstate under similar reaction conditions as described in the run 6, 1-methoxy-7-iodo- (3b, mp 35-35.5°C), 1-methoxy-6-nitro- (3c, mp 90-91°C), 1-methoxy-5-nitro- (3d, mp 89.5-90.5°C), and 1-methoxy-2-phenylindole (3e, mp 46-47°C) were also prepared from the corresponding 2,3-dihydroindoles (1b-e) in 26%, 60%, 49%, and 66% yields, respectively (Chart 1). When the methylation step was omitted in the case of 1e, 56% yield of 1-hydroxy-2-phenylindole (2e, mp 174-175°C) was obtained as stable compound, which was identical with the authentic sample prepared from benzoin oxime.⁹ Methylation of 2e by either ethereal diazomethane or methyl iodide and potassium hydroxide produced 3e in 86% or 64% yields, respectively. Similarly, oxidation of 4a, 9a-cis-1,2,3,4,4a,9a-hexahydrocarbazole (4) and subsequent methylation with ethereal diazomethane afforded 39% yield of 9-methoxy-1,2,3,4-tetrahydrocarbazole (5, oil). Oxidation of 5 with dichlorodicyanobenzoquinone (2 mol eq.) in benzene afforded 9-methoxycarbazole (6, mp 40-41°C) in 65% yield. Further efforts to convert 6 into alkaloid, 3-formyl-9-methoxycarbazole, are under way.

It should be noted that considerable oxidative decarboxylation was observed in the case of 2,3-dihydroindole-2-carboxylic acid (1f), resulting in the formation of 3a and the desired methyl 1-methoxyindole-2-carboxylate (3g, mp 40.5-41.5°C) in 48% and 12% yields, respectively. Application of this decarboxylation to amino acid derivatives is in progress.

The present simple synthesis method for 1-hydroxyindoles should open a new frontier of the chemistry of indole. Oxidation of 2-oxindoles is also under investigation.

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4. Our imagination is the following. The most electron rich part of indole nucleus is the nitrogen. Therefore, oxidation is reasonably considered to occur initially at the nitrogen in vivo, culminating in the formation of 1-hydroxyindoles. Although 1-hydroxyindoles are generally unstable in vitro, they might be stable in vivo, and genuine biologically active substances. Subsequent methylation of them produce 1-methoxyindole alkaloids.
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