INTRODUCTION OF *NUCLEOPHILES* OR ETHYL GROUP TO THE INDOLE NUCLEUS THROUGH NUCLEOPHILIC SUBSTITUTION AND/OR RADICAL REACTIONS OF 1-METHOXYINDOLE-3- AND -2-CARBOXALDEHYDE[1]

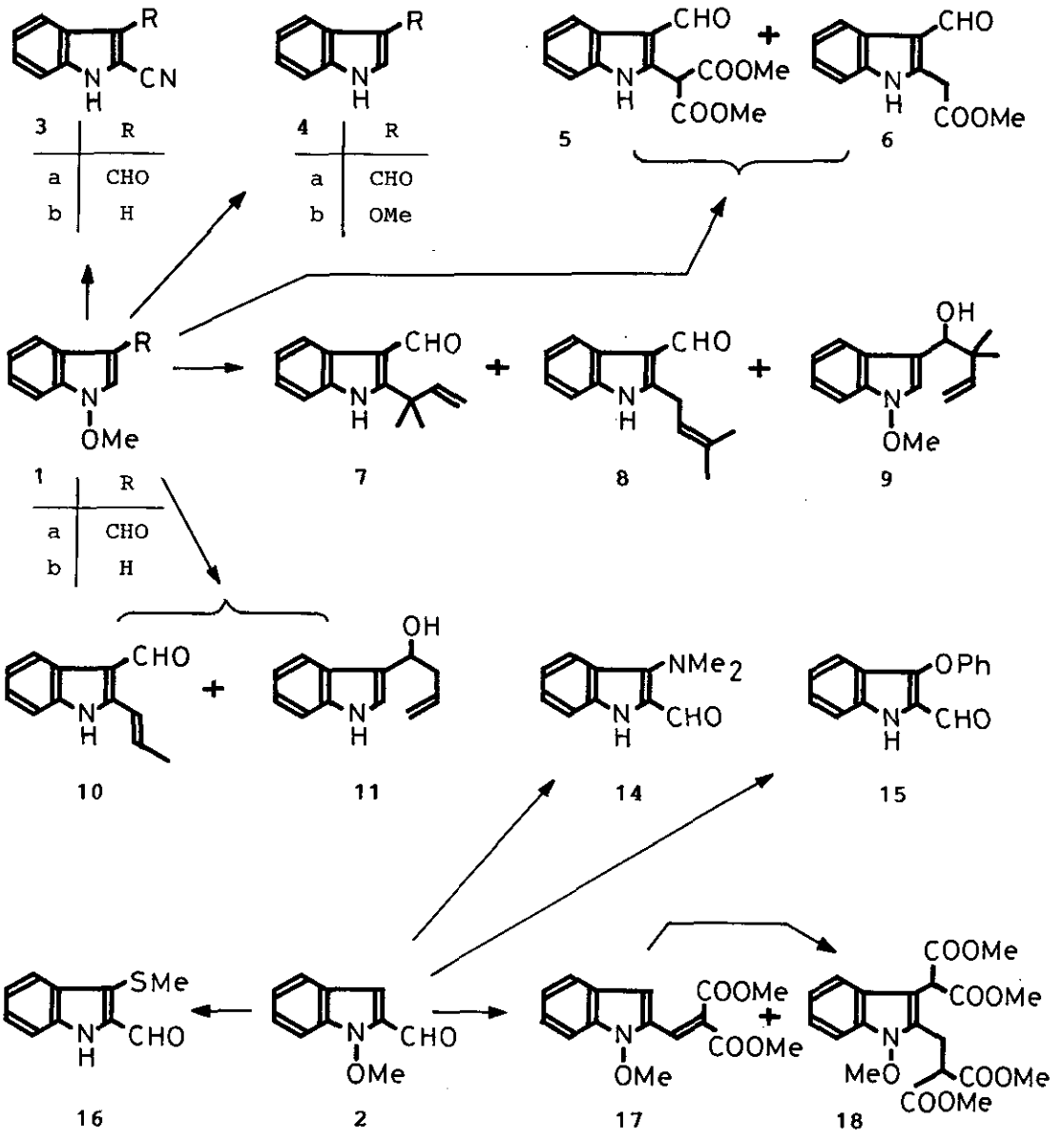
Fumio Yamada, Yoshikazu Fukui, Daisuke Shinmyo, and Masanori Somei*
Faculty of Pharmaceutical Sciences, Kanazawa University
13-1 Takara-machi, Kanazawa 920, Japan

Abstract—1-Methoxyindole-3- and -2-carboxaldehyde were found to undergo nucleophilic substitution and radical reactions resulting in the introduction of nucleophiles and/or ethyl group at the 2- or 3-position.

In continuing work on verifying our "1-hydroxyindole hypotheses",[2] we discovered that pyrrolo[2,3-*b*]indoles[2] were generally formed in the intramolecular nucleophilic substitution reactions of 1-hydroxytryptophan and 1-hydroxytryptamine derivatives.[3] Now, we have newly observed that the formation of C-C bond at the 2- or 3-*position of 1-methoxyindole-3-carboxal*dehyde (**1a**) occurs readily by the displacement of 1-methoxy group followed by intermolecular attack with nucleophiles[2,4] and/or radicalic reagents, as predicted. Nucleophilic substitution reactions also occurred in the case of 1-methoxyindole-2-carboxaldehyde[5] (**2**).

Treatment of **1a** with potassium cyanide (KCN) in *N,N*-dimethylformamide (DMF) and water at 75~80°C produced 2-cyanoindole-3-carboxaldehyde (**3a**) in 98% yield (Scheme 1). Under the same reaction conditions, indole-3-carboxaldehyde (**4a**) afforded complete recovery of starting material (**4a**), suggesting that **3a** was produced through the nucleophilic substitution reaction. While,

Scheme 1[9]



the reaction of 1-methoxyindole (**1b**) itself with KCN in DMF and water at reflux for 15 h afforded, to our surprise, 0.3% yield of 3-methoxyindole (**4b**) regardless of its quite instability under these reaction conditions, together with 2-cyanoindole (**3b**) and recovery of **1b** in 2 and 48% yields, respectively. These results indicate that the formyl group of **1a** plays a role in enhancing the reactivity of 2-position, nevertheless the presence is not necessary for the nucleophilic substitution reactions. When sodium dimethyl malonate was selected as a nucleophile, **1a** afforded dimethyl 2-(3-formylindol-2-yl)malonate (**5**) and methyl 2-(3-formylindol-2-yl)acetate (**6**) in 26 and 46% yields, respectively.

It should be noted that the reaction of **1a** with (3,3-dimethylallyl)trimethylsilane in the presence of tetrabutylammonium fluoride in tetrahydrofuran at room temperature gave the expected 2-(1,1-dimethylallyl)indole-3-carboxaldehyde (**7**), 2-(3,3-dimethylallyl)indole-3-carboxaldehyde (**8**), and α-(1,1-dimethylallyl)-1-methoxyindole-3-methanol (**9**) in 12, 7, and 14 % yields, respectively, together with 38% yield of recovery. Similar reaction of **1a** with allyltrimethylsilane afforded (*E*)-2-(1-propen-1-yl)indole-3-carboxaldehyde (**10**) and α-allyl-1-methoxyindole-3-methanol (**11**) in 23 and 28% yields, respectively. All attempts to transform **11** to **10** *via* Cope rearrangement and concomitant oxidation were unsuccessful.

Our hypotheses[2] for introduction of prenyl group to the indole nucleus led us to examine the reaction of **1a** with sodium 3-methyl-2-buten-1-olate in 3-methyl-2-buten-1-ol, resulting in the generation of the predicted 3-(1,1-dimethylallyl)-2-oxindole (**12**)[6] in 41% yield (Scheme 2). While, the same reaction carried out in DMF at room temperature produced inseparable mixture of 3-formyl-3-(1,1-dimethylallyl)-2-oxindole (**13**) and **12** (54 and 22% yields, respectively, based on 500 MHz ^{1}H-nmr spectrum), and by the treatment with refluxing methanol the mixture was quantitatively converted to **12**. Therefore, without isolation procedure of the mixture, **12** was obtained in 75% yield in one pot operation from **1a**. The mechanism depicted in

Scheme 2[9]

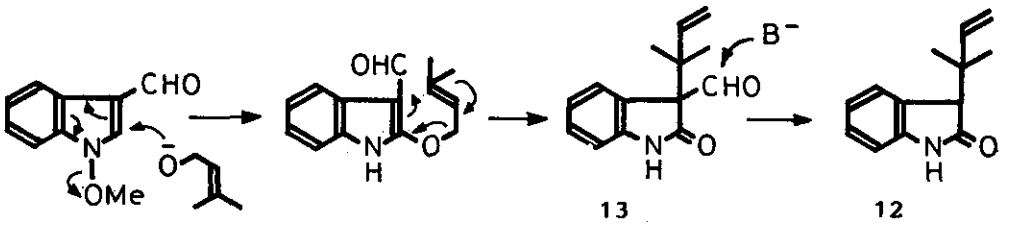
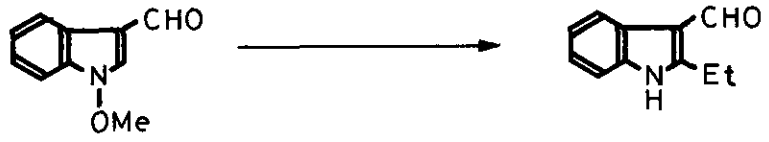


Table I. Preparation of 2-Ethylindole-3-carboxaldehyde from 1-Methoxyindole-3-carboxaldehyde[9]



	1a					**19** + **1a**	
Run	BEt_3	Reaction Conditions				Yield (%) of	
	(mol. eq.)	Atmosphere	Additives	Temp. (°C)	Time (h)	**19**	**1a**
1	1.1	Ar	-	22	2	23	69
2	2.5	Ar	-	20	3	44	49
3	7.0	Ar	-	20	3	38	31
4	2.5	Ar	-	reflux	3	38	38
5	2.5	Ar	AIBN	reflux	3	31	39
6	2.5	O_2	-	17	3	12	73

Scheme 2 could explain these results.

Nucleophilic substitution reactions were also observed in the case of **2**.[2] Thus, the reaction of **2** with dimethylamine in refluxing methanol, potassium phenoxide in refluxing *tert.* butanol, and sodium thiomethoxide in refluxing methanol, afforded 3-dimethylamino- (**14**), 3-phenoxy- (**15**), and 3-methylthioindole-2-carboxaldehydes (**16**) in 90, 44, and 73% yields, respectively (Scheme 1). Preparation of various derivatives of **16** is in progress aiming at HIV virus transcriptase inhibitors.[7] Interestingly, **2** did not undergo substitution reaction with sodium dimethyl malonate, instead aldol condensation and Michael addition reactions to the product (**17**) were observed, culminating in the formation of **17** and **18** in 44 and 21% yields, respectively. *Under similar reaction conditions, 17 reacted with sodium* dimethyl malonate to give **18** in 27% yield together with 40% yield of recovery (**17**).

On the other hand, the reaction of **1a** with triethylborane (Et_3B, 2.5 mol eq.) in benzene at room temperature produced 2-ethylindole-3-carboxaldehyde (**19**) in 44% yield together with 49% yield of recovery (**1a**) and the results are summarized in Table I. Changes in reaction conditions such as the amounts of Et_3B (runs 1~3), reaction temperature (run 4), addition of 2,2'-azobisisobutyronitrile (AIBN, run 5), or change in atmosphere from argon to dioxygen (run 6) could not improve the yield. In the similar reaction of indole-3-carboxaldehyde (**4a**) with Et_3B, the best yield of **19** was 7%. Since radicallic nature of Et_3B is well known,[8] radical reactions of 1-methoxyindoles are under investigation.

The current subject is whether the same type of reactions stated above occur in the case of 1-hydroxytryptophan and/or 1-hydroxytryptamine derivatives, and the results will be reported in due course. With the attempted and versatile building blocks (**6**, **7**, **8**, **12**, etc.) in hand, we are on the way towards total syntheses of various indole alkaloids.

REFERENCES AND NOTES

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5. The yield of **2** was improved to 98%. See reference 4a.
6. We have already succeeded in a synthesis of similar building block, 3-(1,1-dimethylpropargyl)-1-methoxy-2-oxindole: M. Somei, H. Sato, N. Komura, and C. Kaneko, *Heterocycles*, 1985, **23**, 1101.
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9. Satisfactory spectroscopic and elemental analyses or high resolution mass spectral data have been obtained for all new compounds.

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