

INTRODUCTION OF NUCLEOPHILES OR ETHYL GROUP TO THE INDOLE NUCLEUS THROUGH NUCLEOPHILIC SUBSTITUTION AND/OR RADICAL REACTIONS OF 1-METHOXYINDOLE-3- AND -2-CARBOX-ALDEHYDE¹

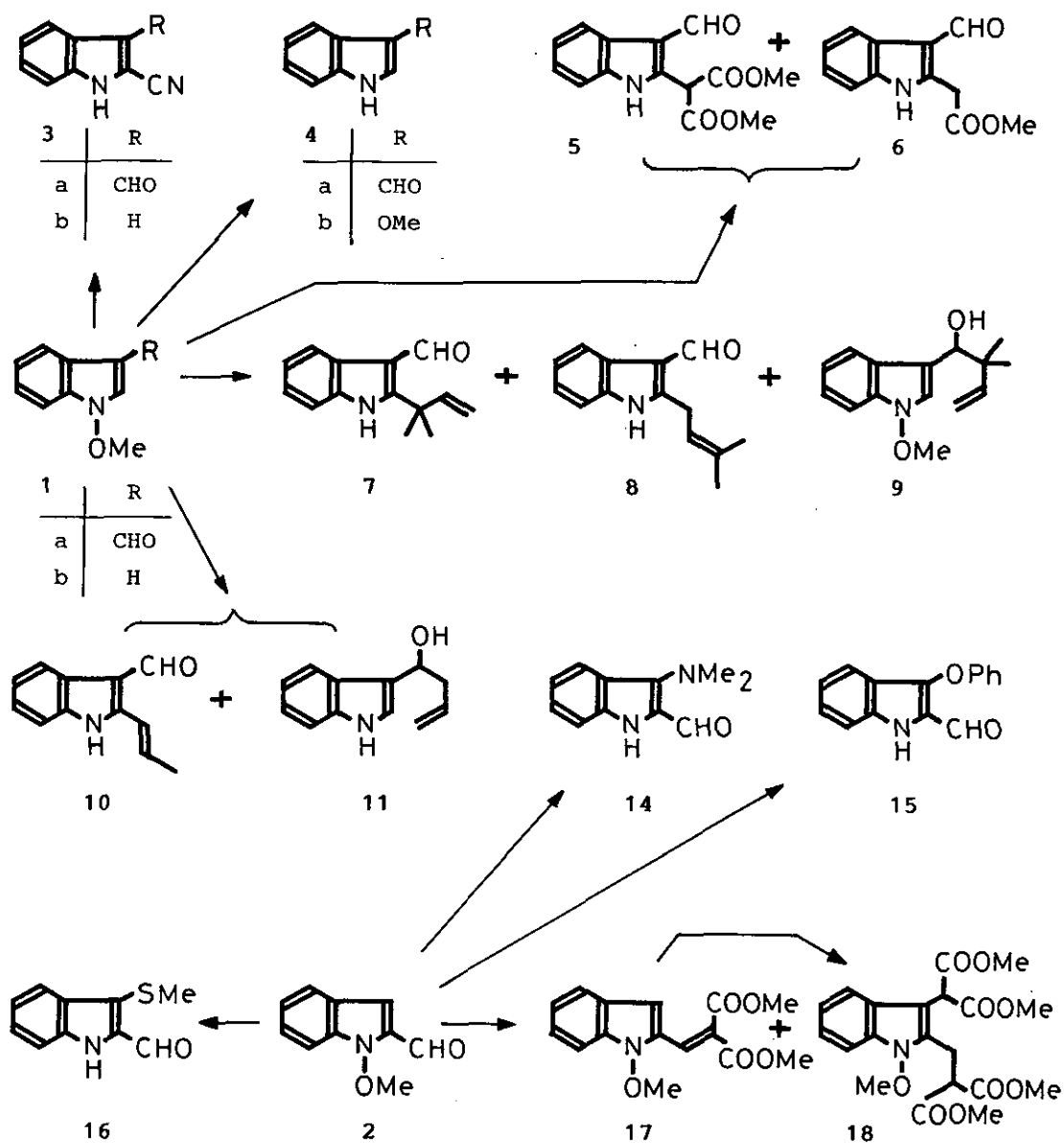
Fumio Yamada, Yoshikazu Fukui, Daisuke Shinmyo, and Masanori Somei*

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*]indoles² 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-carboxaldehyde (**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-carboxaldehyde⁵ (**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 1⁹

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 hypotheses² 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 ¹H-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

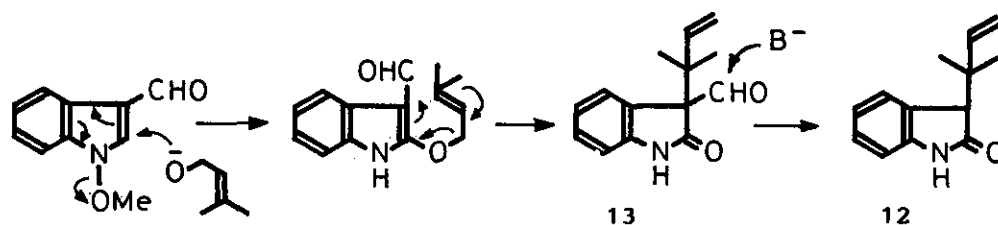
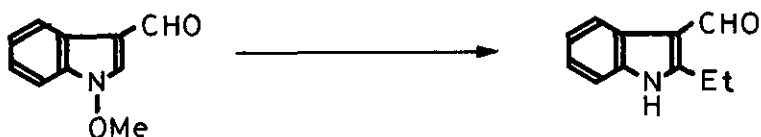
Scheme 2⁹

Table I. Preparation of 2-Ethylindole-3-carboxaldehyde from
1-Methoxyindole-3-carboxaldehyde⁹



Run	BEt ₃ (mol. eq.)	Reaction Conditions			Yield (%) of	
		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

1. Dedicated to Prof. E. C. Taylor on the occasion of his 70th birthday.
This is partly reported, Book of Abstracts, "The 23rd Congress of Heterocyclic Chemistry", Nagoya, Oct., 1992, p. 157. This report is Part 63 of a series entitled "The Chemistry of Indoles". Part 62: K. Nakagawa, N. Aoki, H. Mukaiyama, and M. Somei, *Heterocycles*, 1992, **34**, 2269.
2. a) M. Somei, T. Kawasaki, Y. Fukui, F. Yamada, T. Kobayashi, H. Aoyama, and D. Shinmyo, *Heterocycles*, 1992, **34**, 1887 and references cited therein. b) Review: M. Somei, *Yuki Gosei Kagaku Kyokai Shi*, 1991, **49**, 205.
3. M. Somei, T. Kawasaki, K. Shimizu, Y. Fukui, and T. Ohta, *Chem. Pharm. Bull.*, 1991, **39**, 1905.
4. a) T. Kawasaki, A. Kodama, T. Nishida, K. Shimizu, and M. Somei, *Heterocycles*, 1991, **32**, 221. b) Photo rearrangement of 1-methoxyindole: M. Somei and M. Natsume, *Tetrahedron Lett.*, 1973, 2451.
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.
7. W. J. Greenlee and P. C. Srinivasan, U. S. Patent 5,124,327 (1992) [*Chem. Abstr.*, 1992, **117**, 124478r].
8. A. Suzuki, *Yuki Gosei Kagaku Kyokai Shi*, 1971, **29**, 995.
9. Satisfactory spectroscopic and elemental analyses or high resolution mass spectral data have been obtained for all new compounds.

Received, 13th November, 1992