

NUCLEOPHILIC SUBSTITUTION REACTIONS ON INDOLE NUCLEUS:
SYNTHESES OF 2-SUBSTITUTED INDOLE-3-CARBOXALDEHYDES¹

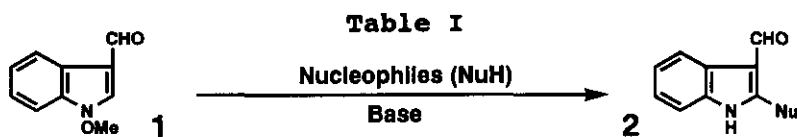
Fumio Yamada, Daisuke Shinmyo, and Masanori Somei*

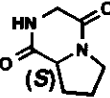
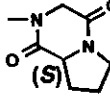
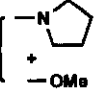
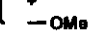
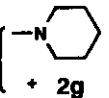
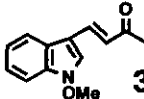
Faculty of Pharmaceutical Sciences, Kanazawa University,
13-1 Takara-machi, Kanazawa 920, Japan

Abstract—1-Methoxyindole-3-carboxaldehyde is found to be a versatile substrate for the nucleophilic substitution reactions, culminating in the formation of 2-substituted indole-3-carboxaldehydes.

Nucleophilic substitution reactions are not familiar in the indole chemistry.^{2,3} We predicted³ that 1-hydroxyindoles should undergo nucleophilic substitution reactions, and disclosed³ the expected reactions to occur. Quite recently, Moody and co-workers⁴ reported that 1-substituted 2-chloroindole-3-carboxaldehyde reacted with nucleophiles. Indole-chromium carbonyl complexes are also known⁵ to react with nucleophiles. In our continuing project^{1b,3,6} aimed at simple syntheses of indole alkaloids, we now found that readily available 1-methoxyindole-3-carboxaldehyde^{3a-c,7} (1) is a versatile substrate for the nucleophilic substitution reactions, producing 2-substituted indole-3-carboxaldehydes (2).

The reactions of 1 with nitrogen containing heterocycles were examined in the presence of NaH in DMF at room temperature and the results are summarized in Table I. As can be seen from the Table, nucleophiles, such as pyrrole, indole, imidazole, and (8aS)-octahydropyrrolo[1,2-a]pyrazine-1,4-dione, afforded the expected products (2a-d) in excellent to good yields (Entries 1-4). The reaction rate of benzimidazole was slow and even



Entry	NuH	Base	Solvent	Reaction Temp.	Reaction Time (h)	Results ^a	
						Nu	Yield (%)
1		NaH	DMF	r.t.*	3		2a 99
2		NaH	DMF	r.t.	24		2b 95
3		NaH	DMF	r.t.	48		2c 81
4		NaH	DMF	r.t.	6		2d 63
5		NaH	DMF	r.t.	120		2e 30
6		NaH	DMF	r.t.	6	 + 	2f 71 2g 24
7		NaH	DMF	r.t.	6	 + 2g	2h 26 64
8		NaH	DMF	r.t.	20	2g	79
9	—	NaH	DMF	r.t.	17	2g	78
10	MeCOMe	KH	THF	r.t.	2	—CH ₂ COMe	2i 48
11	MeCOCH ₂ COOMe	NaOMe	MeOH	75°C	2	—CH ₂ COOMe	2j 38
12	MeCOMe	2N-NaOH	MeOH	r.t.	6		3 96

*r.t. = room temperature

after 5 days, starting material was recovered as the major product (62%) together with a 30% yield of the desired product (2e) (Entry 5).

The reactions of 1 with sodium salts of alicyclic amines are interesting to note. Although 2f and 2h were obtained in the respective reactions with pyrrolidine and piperidine, a significant amount of 2-methoxyindole-3-carboxaldehyde (2g) was generated in both cases (Entries 6,7). In the reaction of *N*-formylpiperazine, the desired product was not formed at all, instead 2g was isolated in 79% yield (Entry 8). Formation of 2g might be explained by the initial reductive cleavage of N-OMe bond in 1 with NaH to liberate indole-3-carboxaldehyde and NaOMe. Once NaOMe is generated, it attacks the second molecule of 1 giving 2g and NaOMe, which in turn attacks the third molecule of 1, and recycling of the processes leads to complete formation of 2g. In order to examine this explanation, treatment of 1 with NaH in DMF was attempted resulting in the formation of 2g as a sole isolable product in 78% yield (Entry 9).

The reaction of 1 with acetone and KH in anhydrous THF produced exclusively 2i in 48% yield (Entry 10). Whereas, treatment of 1 with methyl acetoacetate and NaOMe in refluxing MeOH afforded 2j in 38% yield together with a 24% yield of recovered 1, and formation of 2i could not be detected (Entry 11). These results are quite interesting compared with the previous observation⁷ that 1 afforded 4-(1-methoxyindol-3-yl)-3-buten-2-one (3) in 96% yield by the reaction with acetone and 2N-NaOH in MeOH (Entry 12).

ACKNOWLEDGMENT

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 9. All new compounds gave satisfactory spectral and elemental analysis data. 2a) mp 264-266°C (decomp.); 2b) mp 259-260°C; 2c) mp 231-233°C; 2d) mp 280-282°C (decomp.); 2e) mp 231-233°C; 2f) mp 343°C (decomp.); 2g) mp 251-252°C; 2h) mp 262-263°C (decomp.); 2i) mp 133-135°C; 2j) mp 127-128°C; 3) mp 79-81°C.⁸

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