NUCLEOPHILIC SUBSTITUTION REACTIONS ON INDOLE NUCLEUS: SYNTHESES OF 2-SUBSTITUTED INDOLE-3-CARBOXALDEHYDES[1]

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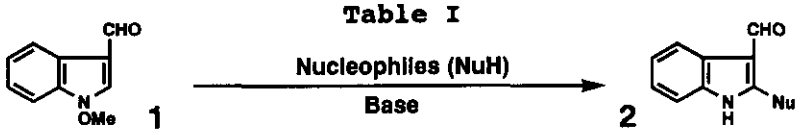
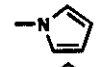
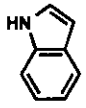
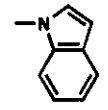
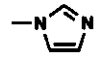
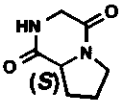
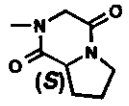
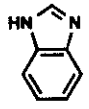
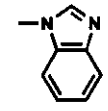
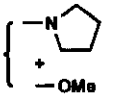
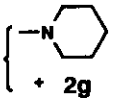
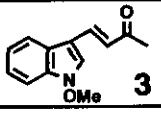
Abstract——1-Methoxyindole-3-carboxaldehyde is found to be a versatile substrate for the nucleophilic substitution reactions, culminating in the formation of 2-substituted indole-3-carboxaldehydes.

Nucleophilic substitution reactions are not familiar in the indole chemistry.[2,3] We predicted[3] that 1-hydroxyindoles should undergo nucleophilic substitution reactions, and disclosed[3] the expected reactions to occur. Quite recently, Moody and co-workers[4] reported that 1-substituted 2-chloroindole-3-carboxaldehyde reacted with nucleophiles. Indole-chromium carbonyl complexes are also known[5] 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 (8a*S*)-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

Table I



Entry	NuH	Base	Solvent	Reaction Temp.	Reaction Time (h)	Results[9] 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		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	$-CH_2COMe$	2i 48
11	$MeCOCH_2COOMe$	NaOMe	MeOH	75°C	2	$-CH_2COOMe$	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 observation[7] 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).

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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;[3b] **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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