LITHIATION OF 3-DIMETHYLAMINOMETHYL- AND 3-DIMETHYLAMINOETHYL-1-METHOXYINDOLE DERIVATIVES[1]

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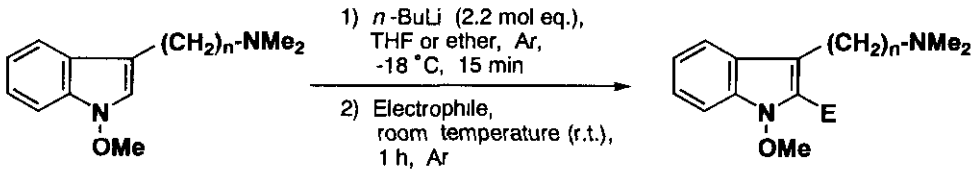
Abstract----Lithiation of 3-dimethylaminomethyl- and 3-dimethylaminoethyl-1-methoxyindole occurred regioselectively at the 2-position. 2-Substituted 3-dimethylaminomethyl-1-methoxyindoles were lithiated at the 4-position.

We have disclosed that alkoxy group at the 1-position of indole nucleus promotes regioselective lithiation at the 2-position.[2] We can expect that if the directing group were introduced additionally at the 3-position, lithiation would take place much easier and afford multi-functionalized indoles by subsequent reactions with electrophiles. We now wish to report the results of the lithiation of 3-dimethylaminomethyl-[3,4] (**1**) and 3-dimethylaminoethyl-1-methoxyindole[5] (**2**, lespedamine[5b]) derivatives.

Lithiation of **1** in THF (or ether) with *n*-BuLi (1.1 mol eq.) at -18°C occurred exclusively at the 2-position. Even when an excess amount of *n*-BuLi was used, extra lithiation at the 4- or 7-position was not observed. Subsequent reactions of the 2-indolyllithium with DMF, dimethyl disulfide, diphenyl disulfide, di-*sec*-butyl disulfide, TMS chloride, and trimethyltin chloride produced the corresponding 2-substituted indoles (**3a-f**) in excellent yields (Table I, Entries 1-6).

An indole alkaloid, lespedamine[5] (**2**), was also lithiated readily and trapping of the 2-indolyllithium with DMF and TMS chloride afforded **3g** and

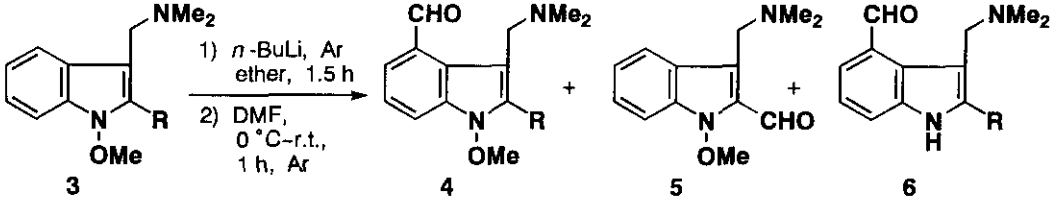
Table I[7]



1 : n = 1; **2** : n = 2 (lespedamine). **3**

Entry	Starting Material	Electrophile	E		Yield (%) of **3**
1	**1**	DMF	**a**	-CHO	96
2	**1**	TMSCl	**b**	-TMS	91
3	**1**	$(Ph\text{-}S)_2$	**c**	-SPh	97
4	**1**	$(Me\text{-}S)_2$	**d**	-SMe	96
5	**1**	$(sec\text{-}Bu\text{-}S)_2$	**e**	-S-*sec*-Bu	99
6	**1**	Me_3SnCl	**f**	$-SnMe_3$	96
7	**2**	DMF	**g**	-CHO	91
8	**2**	TMSCl	**h**	-TMS	86

Table II[7]



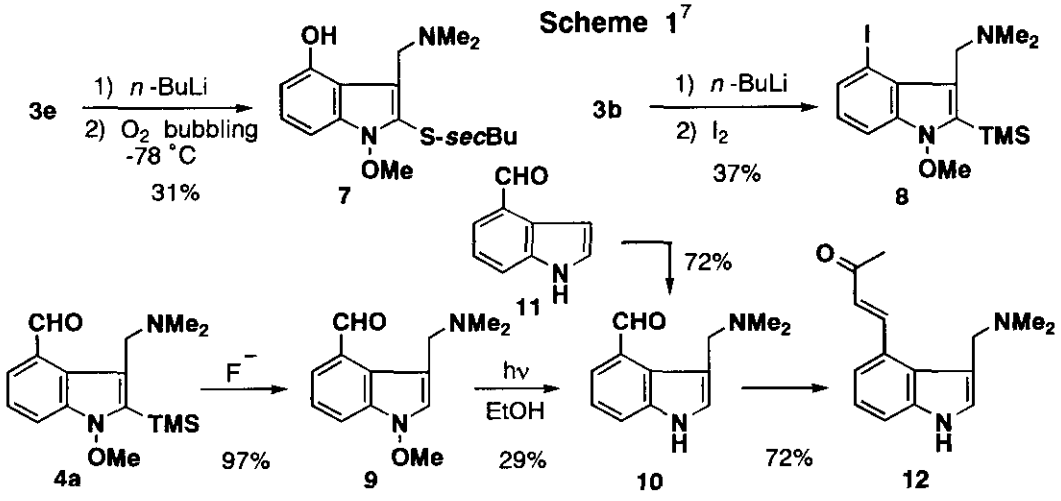
Entry	Starting Material	Lithiation Condition *n*-BuLi (mol eq.)	Reaction Temp. (°C)	R	Yield (%) of **4**	**5**	**6**
1	**3b**	3.1	reflux	a) TMS	70	14	0
2	**3c**	1.7	reflux	b) SPh	67	0	6
3	**3d**	3.0	20	c) SMe	43	13	0
4	**3e**	3.0	reflux	d) S-*sec*-Bu*	67	0	0

* Reaction time with DMF was 15 min. Formation of **7** was observed in 10% yield.

3h, respectively (Entries 7 and 8).

With suitably functionalized 1-methoxyindole derivatives (**3b-e**, **3h**) in hand, we next attempted to lithiate them at the 4-position, expecting that the bulky 2-substituent would force the dimethylamino group to the direction of the 4-position. In fact, as long as THF was used as a solvent, we could not realize the lithiation at the 4-position of **3b-e**. We found finally that when the solvent was ether, the desired lithiation took place and the results are shown in Table II. For example, treatment of the lithiated solution of **3b** with DMF afforded 4-formyl (**4a**) and 2-formyl (**5a**) derivatives in 70 and 14% yields, respectively (Entry 1). Under similar reaction conditions, **3c-e** produced 4-formylindoles (**4b-d**) as major product (Entries 2-4). While, trapping of the lithiated solution with molecular oxygen or iodine produced 4-hydroxy or 4-iodo compound, respectively, and typical examples are shown in Scheme 1.

Scheme 1[7]



It is interesting to note that all our attempts to lithiate **3h** at the 4-position were unsuccessful under various reaction conditions (using *t*-, *sec*-, or *n*-BuLi; THF or ether; at -78°C to refluxing).

The structures of the products were determined unequivocally. Thus treatment of **4a** with $(n\text{-Bu})_4N^+F^-$ afforded **9** in 97% yield. Subsequent uv irradiation or Raney nickel reduction of **9** produced **10**, which was identical with the authentic sample prepared by Mannich reaction of indole-4-carboxaldehyde[6] (**11**). Similarly, all compounds (**4b-d**) were derived to **10** by the reduction with Raney nickel, though in varied yields.

Since we have already succeeded in the syntheses of ergot alkaloids *via* **10** through aldol condensation product (**12**),[6] this constitutes an alternate synthetic route for the alkaloids based on 1-methoxyindole chemistry.

ACKNOWLEDGMENT

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7. All new compounds gave satisfactory spectral and elemental analysis for crystals or high resolution mass spectral data for oil. **3a-h**: oil; **4a**: mp 86.5-87.5°C; **4b**) mp 117.0-118.0°C; **4c**) mp 68.5-69.0°C; **4d**, **5**, **6**, **7**, and **8**: oil; **9**) mp 94.0-95.0°C.

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