

LITHIATION OF 3-DIMETHYLAMINOMETHYL- AND 3-DIMETHYLAMINO-  
ETHYL-1-METHOXYINDOLE DERIVATIVES<sup>1</sup>

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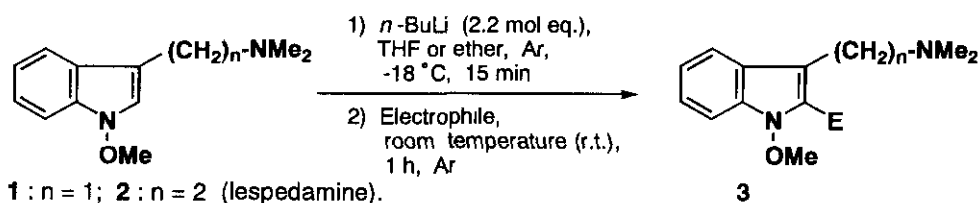
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*Abstract*----Lithiation of 3-dimethylaminomethyl- and 3-dimethylaminoethyl-1-methoxyindole occurred regioselectively at the 2-position. 2-Substituted 3-dimethylaminomethyl-1-methoxyindoles were lithiated at the 4-position.

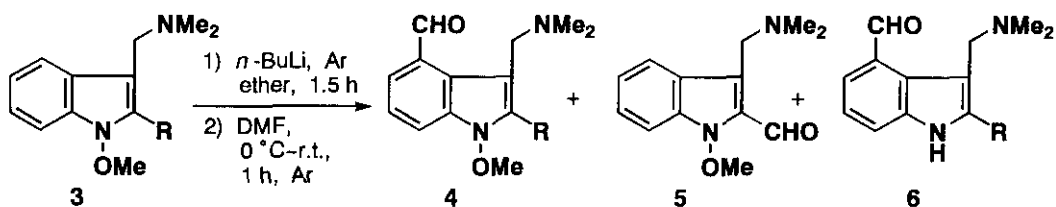
We have disclosed that alkoxy group at the 1-position of indole nucleus promotes regioselective lithiation at the 2-position.<sup>2</sup> We can expect that if the directing group were introduced additionally at the 3-position, lithiation would take place much easier and afford multi-functionalized indoles by subsequent reactions with electrophiles. We now wish to report the results of the lithiation of 3-dimethylaminomethyl-<sup>3,4</sup> (1) and 3-dimethylaminoethyl-1-methoxyindole<sup>5</sup> (2, lespedamine<sup>5b</sup>) 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<sup>5</sup> (2), was also lithiated readily and trapping of the 2-indolyllithium with DMF and TMS chloride afforded 3g and

Table I<sup>7</sup>

Entry	Starting Material	Electrophile	Yield (%) of E	3
1	1	DMF	a -CHO	96
2	1	TMSCl	b -TMS	91
3	1	(Ph-S) <sub>2</sub>	c -SPh	97
4	1	(Me-S) <sub>2</sub>	d -SMe	96
5	1	( <i>sec</i> -Bu-S) <sub>2</sub>	e -S- <i>sec</i> -Bu	99
6	1	Me <sub>3</sub> SnCl	f -SnMe <sub>3</sub>	96
7	2	DMF	g -CHO	91
8	2	TMSCl	h -TMS	86

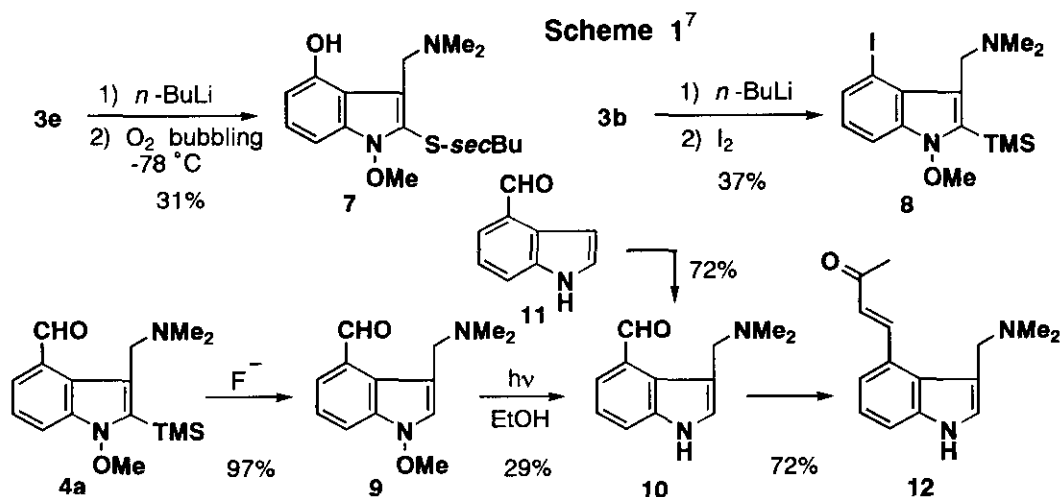
Table II<sup>7</sup>

Entry	Starting Material	Lithiation <i>n</i> -BuLi (mol eq.)	Condition Reaction Temp. (°C)	Yield (%) of R	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- <i>sec</i> -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.



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  $-78^\circ\text{C}$  to refluxing).

The structures of the products were determined unequivocally. Thus treatment of **4a** with  $(n\text{-Bu})_4\text{N}^+\text{F}^-$  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<sup>6</sup> (**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**),<sup>6</sup> this constitutes an alternate synthetic route for the alkaloids based on 1-methoxyindole chemistry.

#### ACKNOWLEDGMENT

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#### REFERENCES AND NOTES

1. Dedicated to Dr. A. Brossi on the occasion of his 70th birthday. This is partly reported, Abstracts of Papers, The 19th Symposium on Progress in Organic Reactions and Syntheses, Kanazawa, November, 1993, p. 115. This report is Part 69 of a series entitled "The Chemistry of Indoles". Part 68: F. Yamada, D. Shinmyo, and M. Somei, *Heterocycles*, 1994, **38**, 273.
2. a) M. Somei and T. Kobayashi, *Heterocycles*, 1992, **34**, 1295; T. Kawasaki, A. Kodama, T. Nishida, K. Shimizu, and M. Somei, *ibid.*, 1991, **32**, 221. b) Review: M. Somei, *Yuki Gosei Kagaku Kyokai Shi*, 1991, **49**, 205.
3. Prepared by Mannich reaction of 1-methoxyindole<sup>2b</sup> in 98% yield.
4. Related lithiation of 1-triisopropylsilyl-3-dimethylaminomethylindole: M. Iwao, *Heterocycles*, 1993, **36**, 29.
5. a) Readily available in five steps from methyl 2-nitrophenylacetate: M. Somei, H. Sato, and C. Kaneko, *Heterocycles*, 1983, **20**, 1797 and references cited therein. b) H. Morimoto and H. Oshio, *Liebigs Ann. Chem.*, 1965, **682**, 212.
6. Review: M. Somei, *Yuki Gosei Kagaku Kyokai Shi*, 1982, **40**, 387; M. Somei, *Advances in Pharmaceutical Sciences, The Research Foundation of Pharmaceutical Sciences*, 1985, **1**, 45; M. Somei, *Yakugaku Zasshi*, 1988, **108**, 361.
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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