A NOVEL SYNTHESIS OF 2,2'-BISINDOLE AND ITS APPLICATION FOR THE SYNTHESIS OF INDOLO[2,3-*a*]CARBAZOLE DERIVATIVES[1]

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Abstract —— A novel oxidative coupling method of 2-lithio-1-methoxyindole was developed resulting in the formation of 2,2'-bis(1-methoxyindole) (**6**). Catalytic hydrogenation of **6** produced 2,2'-bisindole (**9**). Diels-Alder reaction of **9** with dienophiles afforded indolo[2,3-*a*]carbazole derivatives.

Rebeccamycin (**1**),[2a] staurosporin,[2b] BE-13793C (**2**),[2c] tjipanazoles,[2d] and 6-cyano-5-methoxy-12-methylindolo[2,3-*a*]carbazole[2e] are interesting antibiotics,[2f] having indolo[2,3-*a*]carbazole[2g] as a common skeleton. Their multimodality of biological action such as potent antitumor activity and/or inhibition of protein kinase C or topoisomerase, and so on[2] have attracted much attention on their synthesis.[2] In this communication, we report a simple synthetic method of 2,2'-bisindole[3] and its application for the synthesis of indolo[2,3-*a*]carbazole derivatives in only *four steps* from 2,3-dihydroindole (**3**).

I. Preparation of 2,2'-bis(1-methoxyindole) and 2,2'-bisindole

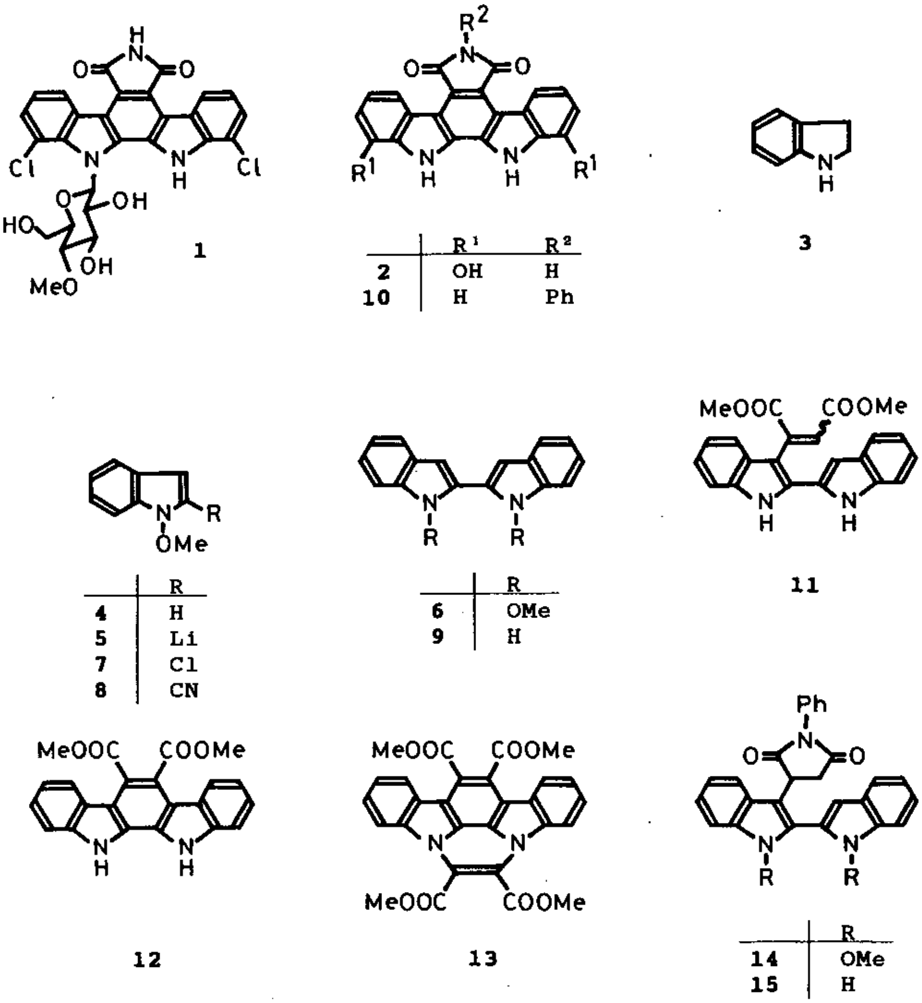
In the previous paper,[4] we have reported that 1-methoxyindole (**4**) is a versatile synthetic building block due to its ready availability[5] from **3** and regioselective formation of 2-lithio-1-methoxyindole (**5**, Figure 1).

Table I. Preparation of 2,2'-Bis(1-methoxyindole) (**6**) from 1-Methoxyindole (**4**)

Run	$CuSO_4$•	Reaction Conditions		Yield (%) of	
	(mol eq.)	Additives	Time (h)	**6**	Recovery
1	1	—	1	13	52
2	1	O_2	1	27	44
3	3	O_2	1	8	61
4	0.5	O_2	1	29	42
5	1	O_2 and ultra sound	1	34	20
6	0.22	〃	0.5	42	24
7	0.5	〃	1	54	8

• Used after drying $CuSO_4 \cdot 5H_2O$ *in vacuo* at 280°C for 1 h.

Figure 1



Now, we wish to report a new oxidative coupling reaction of **5** with anhydrous cupric sulfate ($CuSO_4$). Thus, *n*-butyllithium (1 mol eq.) was added to **4** (1.714 g) in anhydrous tetrahydrofuran under argon atmosphere at -18 °C (ice-NaCl cooling bath). Treatment of the resultant yellow solution of **5** with anhydrous $CuSO_4$ under oxygen atmosphere with ultra-sound stirring at 0°C produced 2,2'-bis(1-methoxyindole) (**6**, 919 mg, 54%), and the results are summarized in Table I. As can be seen from the Table, the presence of oxygen (compare run 2 with 1) and ultra-sound (run 5 with 2) were essential for improving the yield of **6**. Quantity of $CuSO_4$ had a significant effect on the coupling yield, and 0.5 mol eq. was found to be recommendable (runs 4 and 7). Finally, we could obtain **6** in 54% yield, in addition to **4**, with an excellent reproducibility under the reaction conditions of run 7. Although cupric chloride[6] and cuprous cyanide were examined as a coupling reagent under various reaction conditions, the yield of **6** was poorer (6~38%) than that with anhydrous $CuSO_4$, and a significant amount of either 2-chloro- (**7**, 4~21%) or 2-cyano-1-methoxyindole (**8**, 3~10%) was produced as a by-product, respectively.

Catalytic hydrogenation of **6** with 10% Pd/C under atmospheric hydrogen at room temperature for 6 h afforded 2,2'-bisindole[3] (**9**) in 79% yield.

II. Preparation of indolo[2,3-*a*]carbazole derivatives

With suitable building block **9** in hand, we next examined its Diels-Alder reaction.[2g] Treatment of **9** with *N*-phenylmaleimide in *o*-dichlorobenzene at reflux afforded 17% yield of 6-phenylindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione (**10**). In the same reaction using a catalytic amount of 10% Pd/C, the yield of **10** was improved to 30%. The reaction of **9** with dimethyl acetylenedicarboxylate in the presence of 10% Pd/C in xylene at reflux produced **11** and **12** in 37 and 9% yields, respectively, while the reaction in *o*-dichlorobenzene at reflux afforded **12** in 36% yield in addition to 17% yield of unknown 2:1 adduct (**13**, deduced based on spectral data). Treatment of **12** with aniline at reflux for 18 h afforded **10** in 48% yield together with 49% yield of recovery.

On the other hand, the reaction of **6** with *N*-phenylmaleimide in the presence of boron trifluoride etherate at room temperature afforded 68% yield of Michael adduct (**14**). Subsequent treatment of **14** with 10% Pd/C in xylene at reflux produced **10** and 1,1'-demethoxy Michael adduct (**15**) in 32% and 14 % yields, respectively. Treatment of **15** with 10% Pd/C in xylene at reflux also afforded **10** in 42% yield.

Although optimum reaction conditions are not made, we could develop a simple four step synthetic method of indolo[2,3-*a*]carbazole derivatives from **3**. Application of the newly found coupling reaction with $CuSO_4$ to various organometallics, and Diels-Alder reaction of **6** and **9** with dienophiles are currently in progress.

REFERENCES AND NOTES

1. This is partly reported, Book of Abstracts, "The 17th Symposium on Progress in Organic Reactions and Syntheses", Fukuoka, Nov. 1991, p. 206. This report is Part 59 of a series entitled "The Chemistry of Indole". Part 58: M. Somei, K. Kobayashi, K. Shimizu, and T. Kawasaki, *Heterocycles*, 1992, **33**, 77.
2. a) D. E. Nettleton, T. W. Doyle, B. Krishnan, G. K. Matsumoto, and J. Clardy, *Tetrahedron Lett.*, 1985, **26**, 4011; K. S. Lam, D. R. Schroeder, J. M. Veitch, J. A. Matson, and S. Forenza, *J. Antibiot.*, 1991, **44**, 934. b) A. Fukusaki, N. Hashiba, T. Matsumoto, A. Hirano, Y. Iwai, and S. Omura, *J. Chem. Soc., Chem. Commun.*, 1978, 800. c) K. Kojiri, H. Kondo, T. Yoshinari, H. Arakawa, S. Nakajima, F. Satoh, K. Kawamura, A. Okura, H. Suda, and M. Okanishi, *J. Antibiot.*, 1991, **44**, 723. d) R. Bonjouklian, T. A. Smitka, L. E. Doolin, R. M. Molloy, M. Debono, S. A. Shaffer, R. E. Moore, J. B. Stewart, and G. M. L. Patterson, *Tetrahedron*, 1991, **47**, 7739. e) G. Knubel, L. K. Larsen, R. E. Moore, I. A. Levine, and G. M. L. Patterson, *J. Antibiot.*, 1990, **43**, 1236. f) S. Akinaga, K. Gomi, M. Morimoto, T. Tamaoki, and M. Okabe, *Cancer Res.*, 1991, **51**, 4888. g) J. Bergman, "Studies in Natural Products Chemistry", Volume 1, ed. by Atta-ur-Rahman, Elsvier, 1988, pp. 3-30. See also references cited in the above literatures.
3. J. Bergman and N. Eklund, *Tetrahedron*, 1980, **36**, 1439. J. Bergman, B. Egestad, and N. Eklund, *Tetrahedron Lett.*, 1978, 3147.
4. T. Kawasaki, A. Kodama, T. Nishida, K. Shimizu, and M. Somei, *Heterocycles*, 1991, **32**, 221.
5. M. Somei, *Yuki Gosei Kagaku Kyokai Shi*, 1991, **49**, 205; M. Somei and T. Kawasaki, *Heterocycles*, 1989, **29**, 1251.
6. T. Kauffmann, *Angew. Chem.*, 1974, **86**, 321.

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