

MANNICH REACTIONS OF INDOLES WITH DICHLOROMETHANE AND SECONDARY AMINES UNDER HIGH PRESSURE

Kiyoshi Matsumoto^{*a}, Takane Uchida^b, Shiro Hashimoto^c, Yukie Yonezawa^b, Hirokazu Iida^a, Akikazu Kakehi^d, and Shinichi Otani^c

a Graduate School of Human and Environmental Studies, Kyoto University, Kyoto 606-01, Japan

b Faculty of Education, Fukui University, Fukui 910, Japan

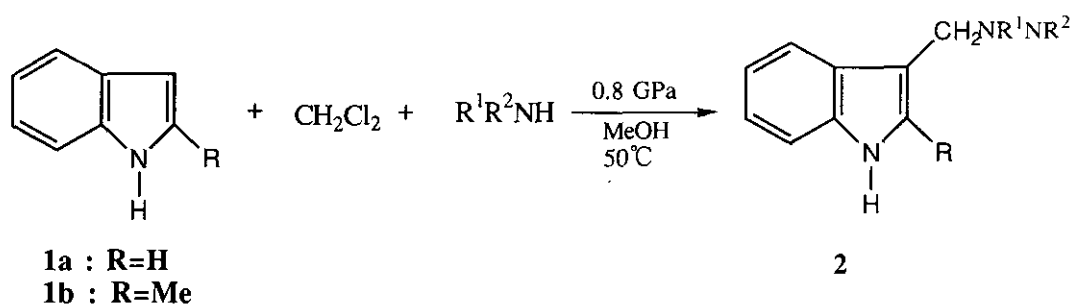
c Faculty of Integrated Human Studies, Kyoto University, Kyoto 606, Japan

d Faculty of Engineering, Shinshu University, Nagano 380, Japan

Abstract—Mannich reactions of indole with dichloromethane and secondary amines gave the corresponding Mannich bases in moderate to good yields, while 2-methylindole afforded only low yields of the Mannich bases. Some limitations were observed in the cases of hindered amines and 2-phenylindole.

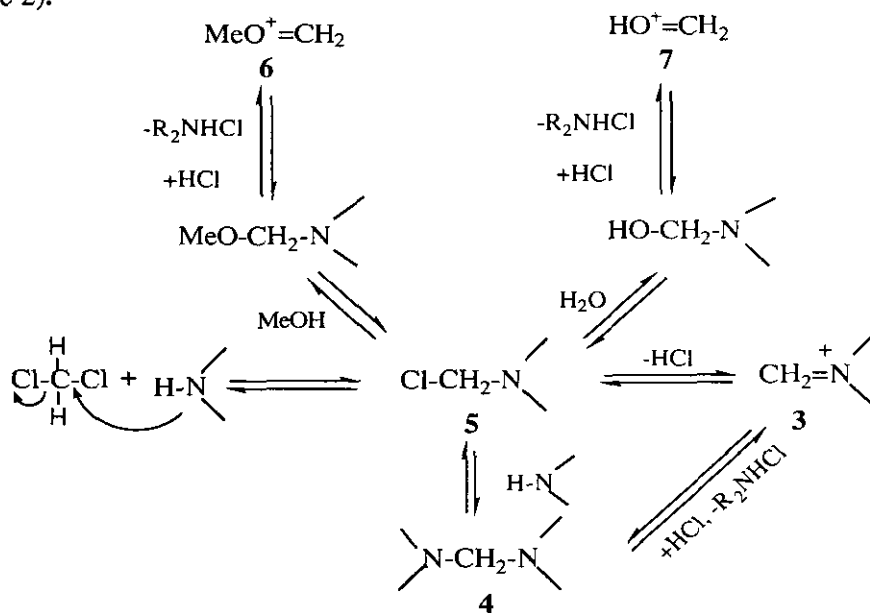
The Mannich can be used to yield a variety of amino methyl derivatives (Mannich bases) which have many synthetic and pharmacological applications.¹ The reaction is general for most aldehydes and ketones that have at least one enolizable hydrogen. In a context of our studies on possible transformations using CH_2Cl_2 as a C1 synthon,² Mannich reaction of several indoles with CH_2Cl_2 and secondary amines was investigated since aminomethylindoles, i.e. gramine and its analogs, are of interest in connection with their biological activities (Scheme 1).¹

In a typical example, a mixture of indole (**1a**) (5 mmol), amine (15 mmol) and dichloromethane (10 mmol) was diluted with methanol in an 8 ml polytetrafluoroethylene tube and compressed to 0.8 GPa and heated to *ca.* 50°C for the stated time (Table 1).



Scheme 1

As shown in Table 1, indole (**1a**) with amines gave the corresponding Mannich bases (**2b**) in moderate to excellent yields, though the reaction conditions were not optimized, whereas 2-methylindole (**1b**) produced only low yields of the products. This is presumably due to steric hindrance by 2-methyl group. The Mannich reaction is believed to involve, in acidic medium, an electrophilic imminium ion (**3**), whereas in basic medium, the reactant is postulated to be bisaminomethane (**4**).¹ Indeed, the formation of bisaminomethanes from dichloromethane and secondary amines was reported previously by us.⁵ Thus, under the present reaction conditions (amine : 15 mmol, dichloromethane : 10 mmol), the reactive species is probably imminium ion (**3**) (Scheme 2).



Scheme 2

Table 1. Mannich bases (2) from indoles, dichloromethane, and amines^a

R	R1	R2	Reaction Time (d)	Yield (%)	mp (°C)
H	Et	Et	2	68	103–104 ^b
H	–(CH ₂) ₄ –		4	62	118–119
H	–(CH ₂) ₅ –		2	50	160–161 ^c
H	–CH ₂ CH ₂ OCH ₂ CH ₂ –		4	24 ^d	122–123
H	–CH ₂ CH ₂ SCH ₂ CH ₂ –		4	80 ^d	191–192(decomp.)
H	Me	Cyclohexyl	4	98	152–153
H	H	PhCH ₂	4	17	95–97
Me	Et	Et	2	18	90–92
Me	–(CH ₂) ₅ –		2	7	105–106

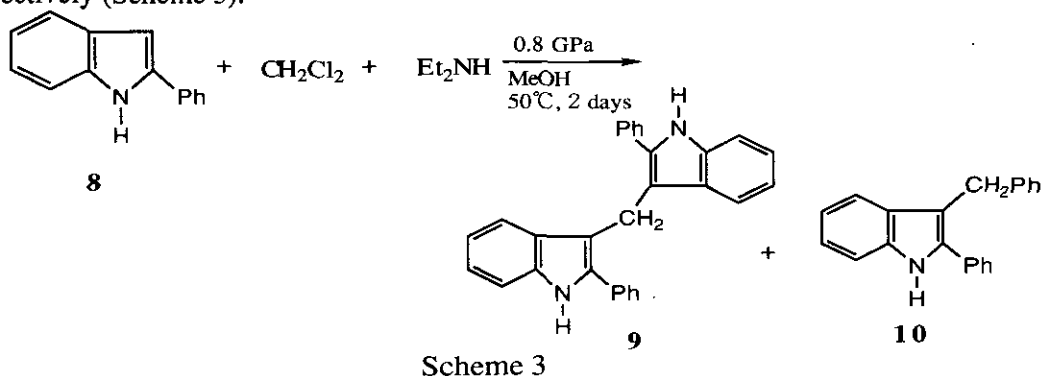
a Reaction conditions were not optimized. Satisfactory elemental analyses were obtained for all the compounds.

b Lit.³ mp 124°C.

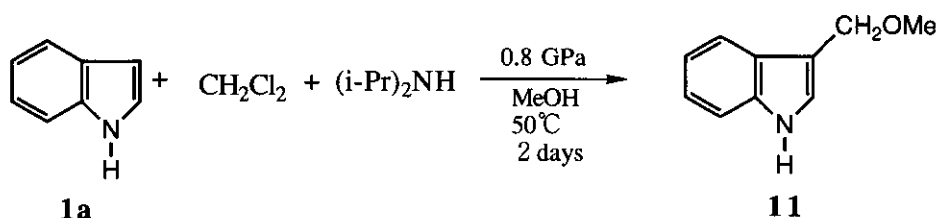
c Lit.⁴ mp 126–128°C.

d Obtained as hydrochloride salt. The structure was confirmed by the X-ray analysis.

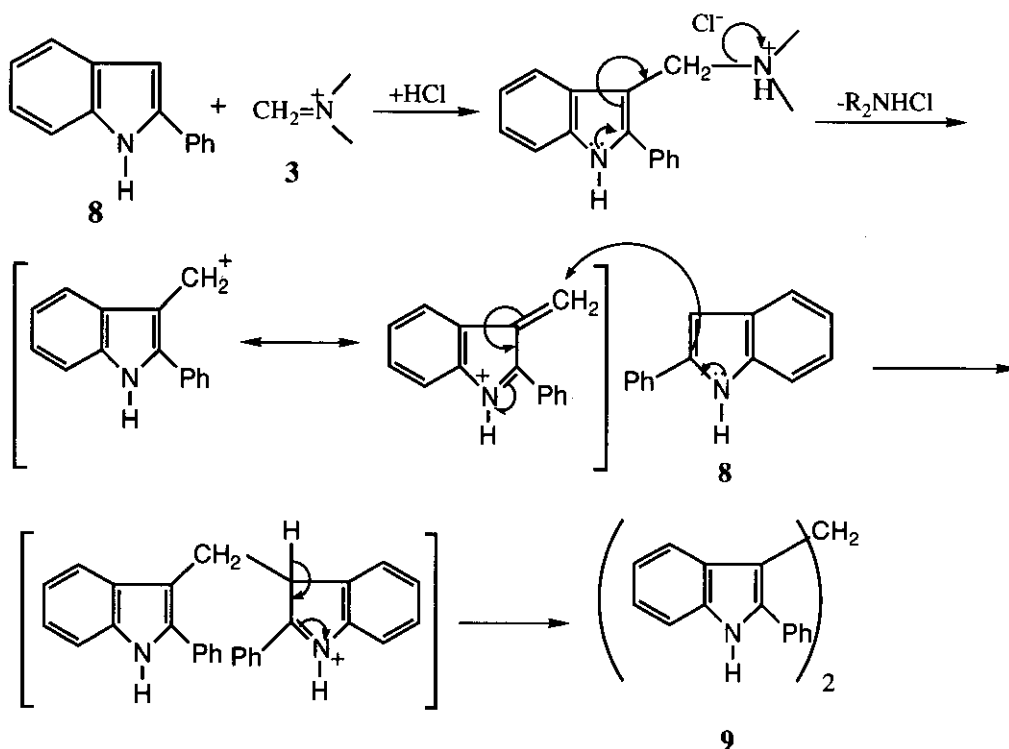
In contrast with **1**, the reaction of 2-phenylindole (**8**) with diethylamine and dichloromethane under similar conditions did not afford the corresponding Mannich bases, but bis(2-phenylindolyl)methane (**9**)⁶ and 2-phenyl-3-hydroxymethylindole (**10**)⁷ in 8 and 3% yields, respectively (Scheme 3).



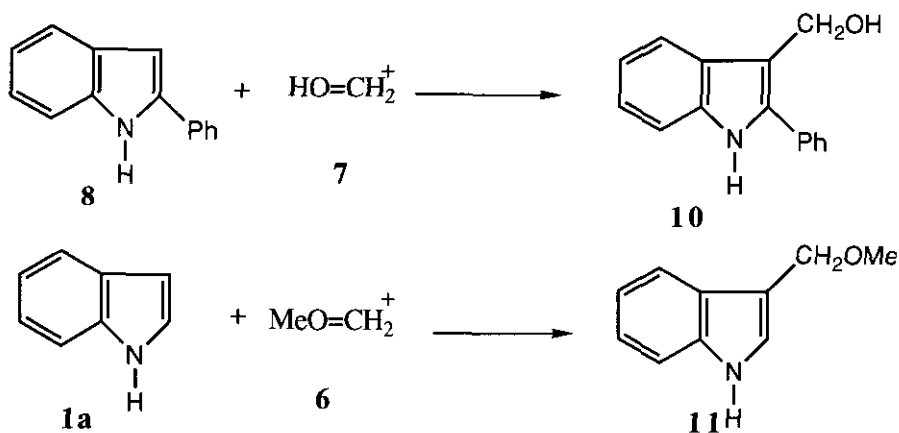
When highly congested secondary amines such as di-isopropylamine and dicyclohexylamine were used in the reactions with **1**, only isolable compound was 3-methoxymethylindole (**11**)⁸ in 10 and 11 % yields, respectively (Scheme 4). The formations for these compounds involve presumably the reaction steps as depicted in Scheme 5 and 6.



Scheme 4



Scheme 5



Scheme 6

ACKNOWLEDGMENT

This work was supported in part by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan (Nos. 04303003 and 04453023). The authors are also grateful to the Ministry of Education, Science, and Culture, Japan for purchasing the high-field NMR instruments by the cost of special installation (1992).

REFERENCES

1. M. Tramontini and L. Angiolini, *Tetrahedron*, 1990, **46**, 1791; M. Tramontini L. Angiolini, and N. Ghedini, *Polymer*, 1988, **29**, 771; M. Tramontini, *Synthesis*, 1973, 703; B. B. Thompson, *J. Pharm. Sci.*, 1968, **57**, 715; F. F. Blick, *Org. React.*, 1942, **1**, 303.
2. K. Matsumoto, *Ang. Chem., Int. Ed. Engl.*, 1982, **21**, 922.
3. H. Kuhn and O. Stein, *Ber.*, 1937, **70**, 567.
4. R. E. Orth, J. W. Bennett, O.-N. Ma, and L. Young, *J. Pharm. Sci.*, 1968, **57**, 1814.
5. K. Matsumoto, S. Hashimoto, Y. Ikemi, and S. Otani, *Heterocycles*, 1984, **22**, 1417.
6. mp 184-186°C; ^1H -nmr(CDCl_3) δ 4.56(s, 2H), 6.7-7.6(m, 18H), 7.98(s, 2H).
7. mp 103°C; ^1H -nmr(CDCl_3) δ 1.57(s, 1H), 4.94(s, 2H), 7.1-7.8(m, 9H), 8.2(br s, 1H).
8. mp 96-97°C; ^1H -nmr(CDCl_3) δ 3.39(s, 3H), 4.68(s, 2H), 6.9-7.3(d, $J=6.8$ Hz, 1H), 7.71(d, $J=8.3$ Hz, 1H), 8.1(br s, 1H).

Received, 10th May, 1993