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

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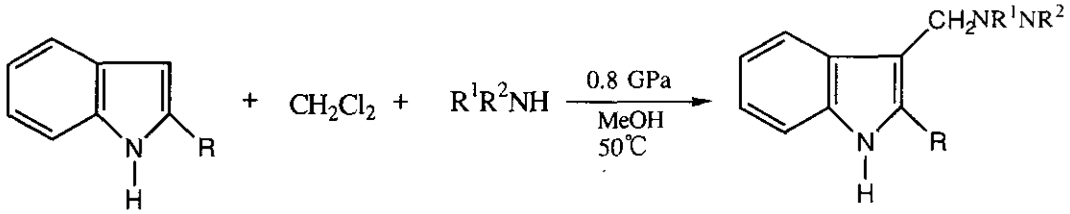
Abstract-Mannich reactions of indole with dichloromethane and secondary amines gave the corresponding Mannich bases in moderate to good yields, while 2-methylindole afforded only low yields of the Mannich bases. Some limitations were observed in the cases of hindered amines and 2-phenylindole.

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).

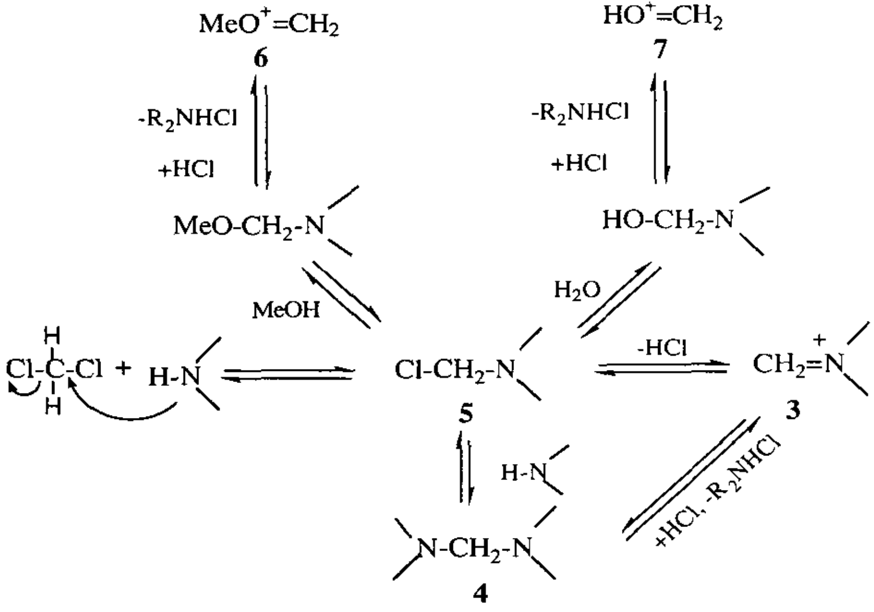


1a : R=H
1b : R=Me

2

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).



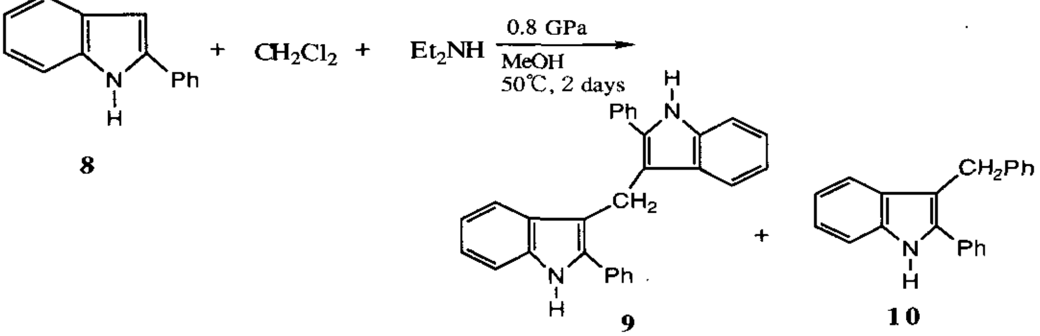
Scheme 2

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	$-CH_2CH_2OCH_2CH_2-$		4	24[d]	122–123
H	$-CH_2CH_2SCH_2CH_2-$		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

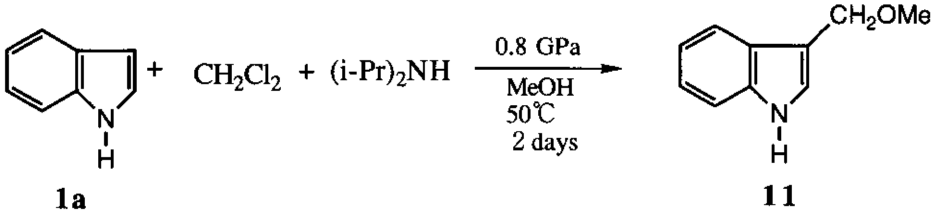
a Reaction conditions were not optimized. Satisfactory elemental analyses were obtained for all the compounds.
b Lit.[3] mp124°C.
c Lit.[4] mp 126–128°C.
d Obtained as hydrochloride salt. The structure was confirmed by the X-ray analysis.

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-hyroxymethylindole (**10**)[7] in 8 and 3% yields, respectively (Scheme 3).

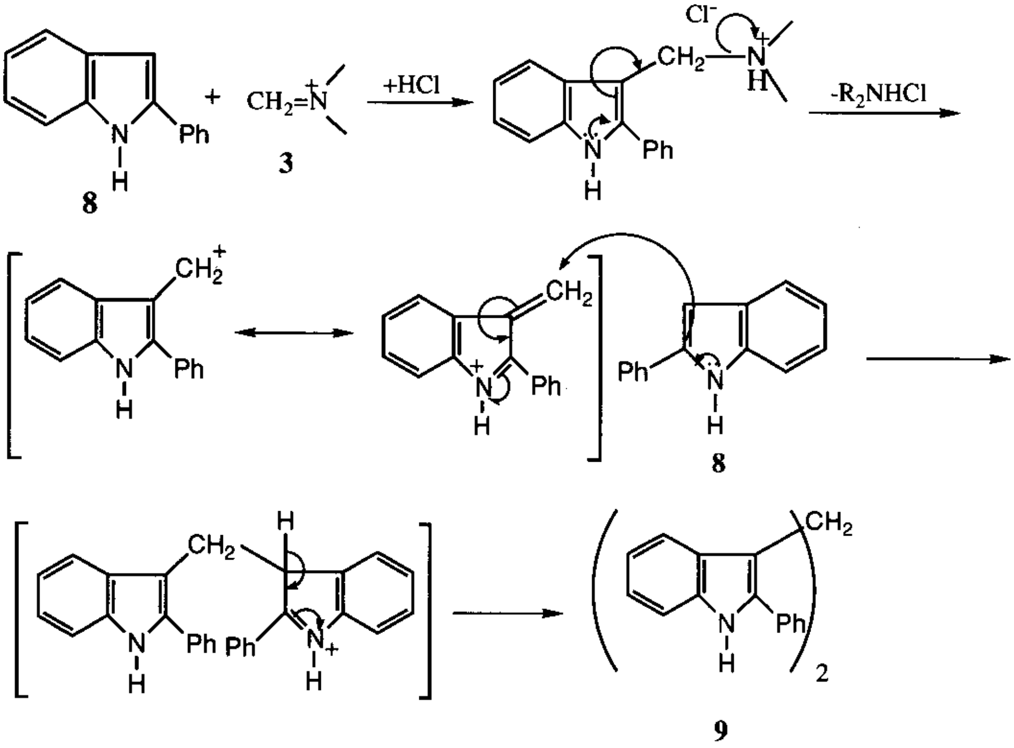


Scheme 3

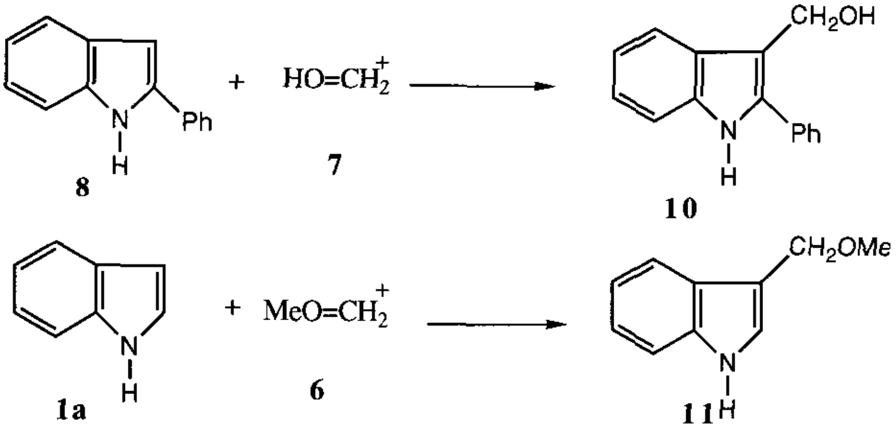
When highly congested secondary amines such as di-isopropylamine and dicyclohexylamine were used in the reactions with **1**, only isolable compound was 3-methoxymethylindole (**11**)[8] in 10 and 11 % yields, respectively (Scheme 4). The formations for these compounds involve presumably the reaction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



Scheme 4



Scheme 5



Scheme 6

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6. mp 184-186°C; ^{1}H-nmr($CDCl_3$) δ 4.56(s, 2H), 6.7-7.6(m, 18H), 7.98(s, 2H).
7. mp 103°C; ^{1}H-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; ^{1}H-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).

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