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REGIOSELECTIVE MANNICH REACTION OF PHENOLS UNDER HIGH PRESSURE USING DICHLOROMETHANE AS C1 UNIT#

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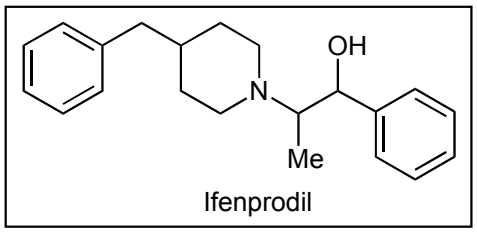
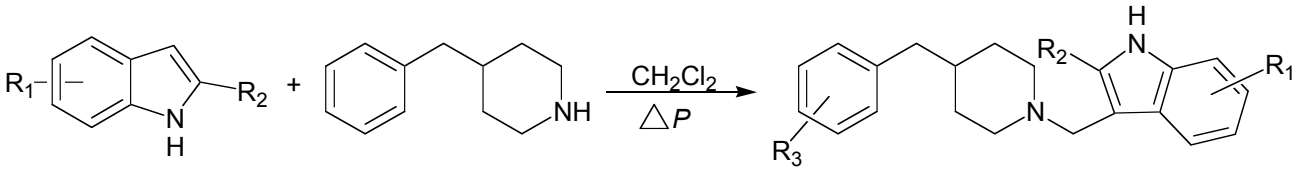
Abstract – Regioselectivity in Mannich reaction of 4-, 3-, and 2-substituted phenols with typical heterocyclic amines are investigated under reaction conditions developed by us. Phenol and 4-alkyl, and 4-chlorophenols in the title reaction predominantly gave the corresponding 2-(aminomethyl)phenols, while 4-methoxyphenol afforded, in addition to the mono(aminomethyl)phenols, a considerable amount of the bis adducts. Peculiarly enough, 3-methylphenol with amines afforded 3-methyl-4-(aminomethyl)phenols whereas 2-methylphenol produced 2-methyl-6-(aminomethyl)phenols.

The Mannich reaction 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. More recently, an asymmetric version of Mannich reactions promoted both by metal-based and metal-free asymmetric catalysts has attracted much attention and has been developed because the chiral Mannich bases often have served as useful intermediates in the synthesis of diverse biologically intriguing compounds such as alkaloids.[2,3] However, there are only few examples of Mannich reactions with phenols, particularly with respect to regiospecific aspects of the reaction. Recently, a series of tridentate ligands, *N*-benzyl-2-(2-hydroxyphenyl)glycines were prepared by the Mannich reactions of *p*-substituted phenols.[4,5] As a matter of course, when the two *ortho* positions of the phenol were blocked, as in the case of 2,6-dimethylphenol, the corresponding *p*-substituted compounds were formed.

One of the authors invented a novel and new method for Mannich reaction of simple aldehydes and ketones employing CH_2Cl_2 as a C1 Unit.[6] This methodology was also amenable to indoles that can be used to develop Ifenprodil analogues (typical examples of cerebral infarction aftereffects treatment medicines) as shown in Scheme 1.[7] Below, we briefly report the results of regioselectivitiy in the title Mannich reaction.



Ifenprodil



Scheme 1

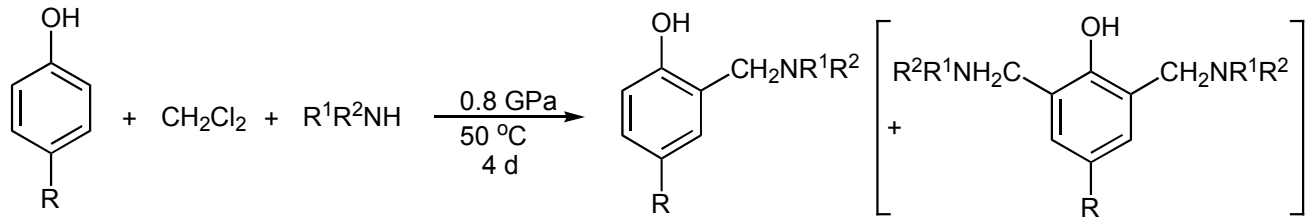
In a typical example, a mixture of phenol (5 mmol), amine (15 mmol) and dichloromethane (10 mmol) was diluted with methanol in an 8 mL polytetrafluoroethylene tube and compressed to 0.8 GPa and heated to ca. 50 °C for 4-8 days. The reaction conditions were optimized in the previous reported reactions so that either 0.8 GPa or 0.6 GPa at 50 °C proved to be for choice of best, including the substrate and reagents mol ratios.[6,7]

As representative heterocyclic amines, pyrrolidine, piperidine, morpholine, and thiomorpholine were employed. The results of a variety of 4-substituted phenols with cyclic amines are summarized in Table 1. Firstly, reaction of phenol (**1a**) with amines (**2a-d**) underwent regiospecific 2-aminomethylation to afford chemo- and regioselectively the corresponding mono(aminomethyl) analogues (**3ab**-**3ad**) albeit in low yields. *It should be noted that the conventional Mannich reaction using formaldehyde generally gave the 2,6-bis(aminomethyl) derivatives.*[1]

In the case of 4-methylphenol (**1b**) with amines (**2a**-**c**), higher yields of the corresponding mono(aminomethyl) analogues (**3ba**-**3bc**) were obtained probably because of + I effect of methyl group. The reaction with thiomorphorine (**2d**) gave also the desired product (**4bd**: 60%) along with the bis(aminomethyl) product in 11 %. The reaction of *t*-butylphenol (**1c**) with **2a-b** analogously reacted in almost similar regioselective fashion.

In contrast, the activated 4-methoxyphenol (**1d**) afforded the mono(aminomethyl)phenols (**3da**-**3dd**) along with a considerable amount of the bis(aminomethyl)phenols, being in agreement with the known reactivity-selectivity principle.[8]

4-Chlorophenols (**1e**) also smoothly underwent reaction to give predominantly the corresponding (aminomethyl)phenols (**3ea**-**3ed**) rather than the bis(aminomethyl)phenols.



1a: R=H
1b: R=Me
1c: R=*t*-Bu
1d: R=MeO
1e: R=Cl

2a: pyrrolidine
2b: piperidine
2c: morpholine
2d: thiomorpholine

3aa - **3ed** **4aa** - **4ed**

Scheme 2

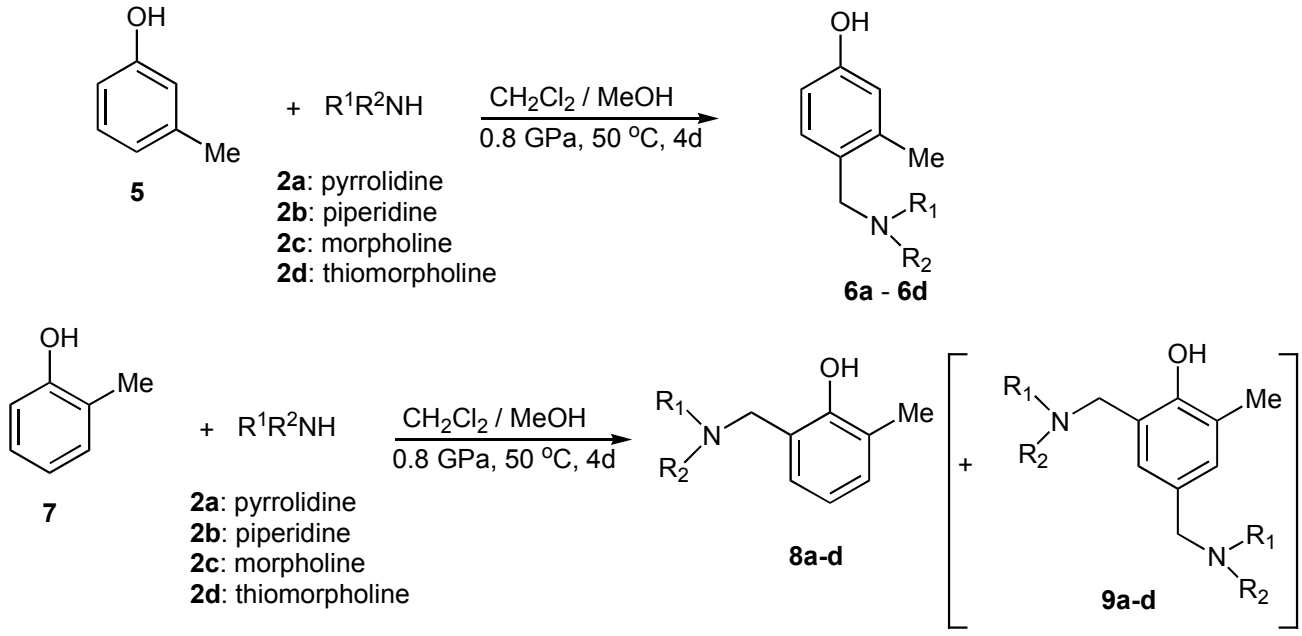
Table 1. Mannich bases (**3aa**-**4ed**) from *p*-substituted phenols (**1a**-**e**), dichloromethane, and amines (**2a**-**d**)[a]

Phenol	Amine	Pressure (GPa)	[Temp] (°C)	Time (day)	Product	Yield (%)[b]	Mp (°C)[c]
1a	**2a**	0.6	[50]	4	**3aa**	14	oil[9]
1a	**2b**	0.6	[50]	4	**3ab**	17	32-33 [lit., 30-32][10]
1a	**2c**	0.8	[rt]	3	**3ac**	25	93-94 [lit., 90][11]
1a	**2d**	0.8	[rt]	3	**3ad**	19	117-118[12]
1b	**2a**	0.5	[50]	4	**3ba**	48	62-63[12]
1b	**2b**	0.5	[50]	4	**3bb**	47	56-57 [lit., 45][13]
1b	**2c**	0.5	[50]	4	**3bc**	32	55-57[14]
1b	**2d**	0.6	[50]	4	**3bd (4bd)**	60 (11)	87-88[12] (116.5-117)
1c	**2a**	0.8	[50]	4	**3ca**	56	oil
1c	**2b**	0.8	[50]	4	**3cb**	62	50 [lit., 46-47][15]
1c	**2c**	0.8	[50]	4	**3cc (4cc)**	63 (7)	59.5 [lit., 76-78][15] (127-127.5)
1c	**2d**	0.8	[50]	4	**3cd (4cd)**	60 (11)	87-88 [85-87][16] (116.5-117)
1d	**2a**	0.8	[50]	4	**3da (4da)**	12 (36)	oil (oil)
1d	**2b**	0.8	[50]	4	**3db (4db)**	53 (21)	oil[18] (oil)
1d	**2c**	0.8	[50]	4	**3dc (4dc)**	20 (20)	oil[17] (87-88)
1d	**2d**	0.8	[50]	4	**3dd (4dd)**	47 (29)	105.5-106.5 [102-104][18] (syrup)
1e	**2a**	0.8	[50]	4	**3ea (4ea)**	49 (15)	74-75[19] (oil)
1e	**2b**	0.8	[50]	4	**3eb**	35	55-56 [lit., 57][20]
1e	**2c**	0.8	[50]	4	**3ec (4ec)**	36 (18)	73-74[21] (oil)
1e	**2d**	0.8	[50]	4	**3ed (4ed)**	73 (10)	131-133 [lit., 127-129][22] (120-121)

[a] Satisfactory spectroscopic and elemental analyses were obtained for all compounds.
[b] Isolated yield. Parenthesis shows the yields of the bis(aminomethyl) derivatives.
[c] Parenthesis shows mp of the bis(aminomethyl) derivatives.

The regioselective trends of the results are qualitatively in agreement with those of classical conventional S_EAr reactions because the 4 position is already blocked by a functional group.

3-Methylphenol (**5**), which is not blocked at *para*-position, also underwent smooth reaction to afford the corresponding 4-(aminomethyl)-3-methylphenol (**6**) in moderate isolated yields as summarized in Table 2. No di(aminomethyl) analogues were not detected. The *para*-regioselectiviy is apparently ascribed to +M effect of OH group.



Scheme 3

Table 2. Mannich bases (**6a-d, 8a-d, 9d**) from *m*- and *o*-methylphenols (**5**, **7**), dichloromethane, and amines (**2a-d**)[a]

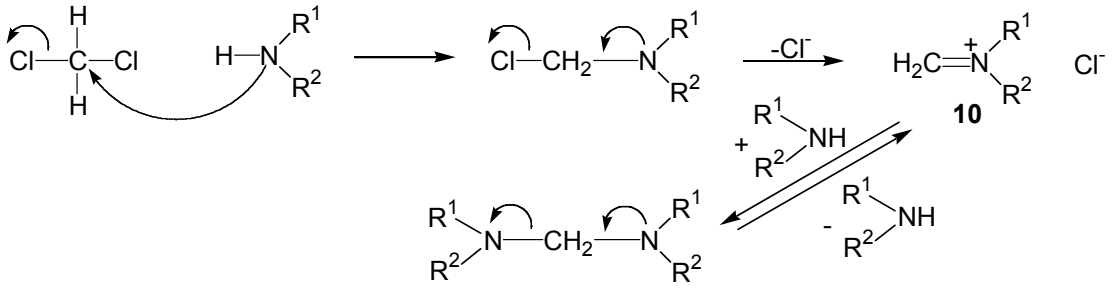
meta					*ortho*				
Phenol	Amine	Product	Yield (%)	Mp (°C)	Phenol	Amine	Product	Yield (%)[b]	Mp (°C)[c]
5	**2a**	**6a**	46	107-108[d, 23]	**7**	**2a**	**8a**	29	oil
5	**2b**	**6b**	16	oil[24]	**7**	**2b**	**8b**	25	oil[24]
5	**2c**	**6c**	27	oil	**7**	**2c**	**8c**	33	oil[25]
5	**2d**	**6d**	25	67.5-68.5[d]	**7**	**2d**	**8d (9d)**	30 (6)	76-77 (154.5-155.0)[d]

[a] Reaction conditions were 0.8 GPa, 50 °C and 4days. Satisfactory spectroscopic and elemental analyses were obtained for all compounds.
[b] Isolated yield. Parenthesis shows the yields of the bis(aminomethyl) analogues.
[c] Parenthesis shows mp of the bis(aminomethyl) analogues.
[d] The structure was established by an X-ray analysis.

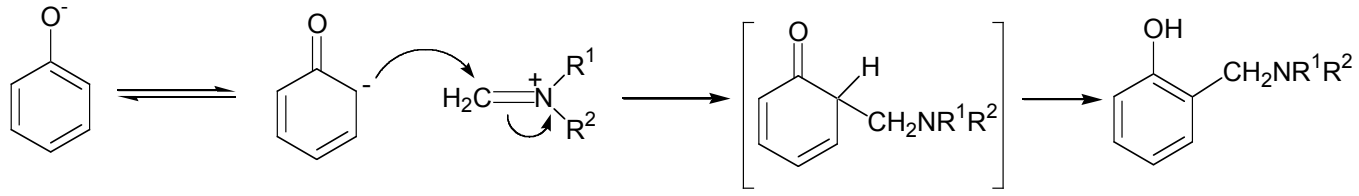
In contrast with this and very intriguingly enough, 2-methylphenol produced the 2-(aminomethyl)-6-methylphenol (**8**) in spite of strong +M effect of *para*-OH group together so-called with buttressing effect. Only in the case of thiomorphorine, the 1,3-dimethylamino-5-methylphenol was isolated in 6 % yield. The reason(s) for regiospecific aspects regarding 2-methylphenol and 3-methylphenol is (are) not yet clear.

It is generally thought that the Mannich reaction takes place by electrophilic attack of a methyleneimminium ion (**10**) which is presumably generated as depicted in Schemes 4 and 5.[1]

Further studies on applications of this methodology for synthetic applications to bidentate, tridentate and calixarene ligands as well as theoretical calculations of regioselectivities are envisaged.



Scheme 4



Scheme 5

Note added in proof: Effect of pressure on the yield.

Table 3. Mannich bases (**3ac** and **3bc**) from *p*-substituted phenols (**1a** or **1b**), dichloromethane, and **2c**

Phenol	Amine	Pressure (GPa)	[Temp] (^{o}C)	Time (day)	Product	Yield (%)
1a	**2c**	0.2	[rt]	3	**3ac**	No reactions
1a	**2c**	0.4	[rt]	3	**3ac**	13
1a	**2c**	0.8	[rt]	3	**3ac**	25
1b	**2c**	0.2	[rt]	3	**3bc**	No reactions
1b	**2c**	0.5	[50]	4	**3bc**	32

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This paper is dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

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