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A New Investigation of Mannich Reaction

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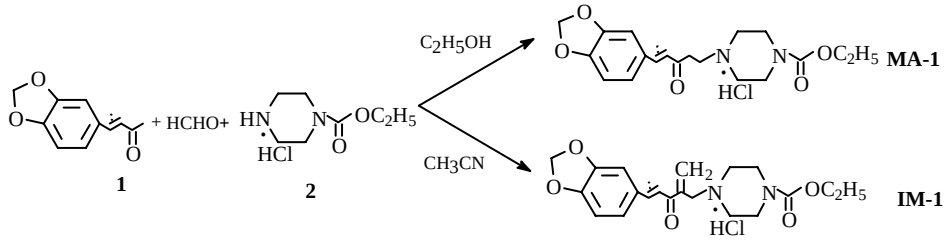
Abstract: During the synthesis of the derivatives of styryl ketonic Mannich bases, a side -product IM,other than the normal Mannich base MA, is obtained. Mannich reaction is further studied and the formation mechanism of product IM is postulated and discussed on the basis of deuterium labelling.

Keywords: Mannich reaction, side-product, styryl ketonic Mannich bases, mechanism.

Mannich reaction is widely used for the synthesis of many kinds of compounds[1]. In the synthesis of the derivatives of styryl ketonic Mannich bases, a one-pot method is used, in which ketone, secondary-amine hydrochloride, paraformaldehyde are refluxed together in alcohol[2,3]. In most cases the normal Mannich product **MA** is obtained. But when certain amine is used as the reactant, a side-product IM, instead of MA is obtained. MS and ^{1}HNMR data indicate that compound IM is a new type of Mannich base which has a terminal double bond at α-position of the ketone group. The result of pharmacological screening showed that **IM** was a better anticancer agent than corresponding normal product **MA**. Therefore the reaction is further investigated for extending the range of this type of reaction.



1 **2**

Using the same reactants **1** and **2**, we compared several conditions for investigation of the formation of compound **IM**. The results showed that the acidity, concentration of the ketone and amine, solvent type are the crucial factors as shown in the **Table 1,2,3**.

Acidity: After trying several pH values, we found that pH 4.5 - 5.0 was the most favorable acidity for the formation of **IM.** If the pH≤4.5 the mixture of **MA-I** and

IM-1 was obtained. If the pH was lowerd to 3.0, the only normal Mannich base was obtained. If the pH was higher then 6, the formation of both **MA** and **IM** was restrained (**Table 1**).

Table 1 The effects of pH on the orientation of Mannich reaction*

No.	1	2	3	4	5	6	7
PH	<1.0	1.5-2.0	2.5-3.0	3.5-4.0	4.5-5.0	5.5-6.0	>6.0
Product	MA-1	MA-1	MA-1	MA-1, IM-1	IM-1	IM-1	MA-1,IM-1
yield%**	64	67	55	18, 32	48	40	4, 5

*the solvent is alcohol; the ketone is 1 mmol and C=0.15 mol/L; temperature is 90℃; reaction time is 20 hrs;
** isolated by recrystallization

Concentration: In the same reaction condition, when the concentration of the ketone and amine were 0.1~0.15 mol/L. **MA-1** was the main product, while the concentration of the ketone and amine were 0.6 mol/L. The only product was **IM-1.** (**Table 2**).

Table 2 The effects of concentration on the orientation of Mannich reaction

No	1	2	3	4	5
Conc.(mol / L)	0.1	0.15	0.2	0.3	0.6
main product	MA-1	MA-1	MA-1, IM-1	MA-1,IM-1	IM-1
Yield**	71	57	42, 15	17, 40	64

*the solvent is alcohol; pH=2.5-3.0; temperature is 90℃, reaction time is 20 hr.
** Isolated by recrystallization

Solvent type: Fixing other reaction conditions, we changed the solvent of reaction and found, that in alcohol the most product was **MA-1**, but it was contaminated with **IM-1** and difficult to separated. Then we tried other solvents such as $ClCH_2CH_2Cl$, THF and CH_3CN, *etc.* Among these CH_3CN was found to be the most ideal solvent for the formation of product **IM**. (**Table 3**).

Table 3 The effect of solvent type on the orientation of Mannich reaction*

	1	2	3	4
solvent	CH_3CH_2OH	$ClCH_2CH_2Cl$	THF	CH_3CN
product	**MA –1+ IM-1**	**MA-1，IM-1**	**IM-1**	**IM-1**
yield**	52, 7	16, 37	46	78

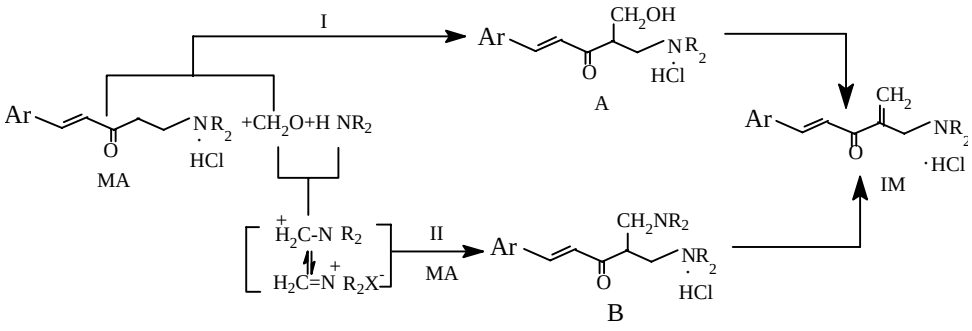
* pH = 4.5 - 5.0, concentration is 0.6 mol / L, temperature is 90℃, reaction time is 12 hr.
** isolated by recrystallization

That the reactivity of ketones for this type of reaction are different. Generally speaking, the ketones with the electron-drawing groups are more active than those with the electron-donating groups. Further work is in progress.

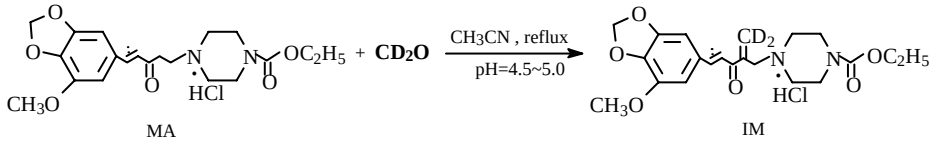
The normal Mannich product **MA** was usually formed at first as shown on the TLC. When the reaction time was prolonged, the amount of **MA** reduced and the product **IM** developed more and more. At the same time, other impurities also increased. So two

possible mechanisms for the formation of compound **IM** were proposed (**Scheme 1**). First, compound **IM** maybe formed by the further hydroxymethylation of the normal product **MA** and subsequent dehydration. Second, compound **IM** may be formed by the deamination of the diamine **B**.

Scheme 1 Plausible mechanisms of the formation of compound **IM**



We mixed the product **MA** with paraformaldehyde without the ammonium salt, the expected product **IM** was obtained. When deuterium labelled paraformaldehyde was used, the obtained compound **IM** was also deuterium labelled at the terminal methylene group, this result agreed with the first mechanism and proved the first mechanism to be possible.



α, β-Unsaturated ketone can be obtained by the deamination of normal Mannich bases[4]. Compound **MA** which has a carbonyl group and the α-protons which can reacted with paraformaldehyde and amine further to proceed the second Mannich reaction. Several methods have been tried to synthesize the diamine **B**, but only a small amout of **IM** was obtained instead of diamine **B.** This fact indecated, that the mechanism of formation of **IM** also could be considered through deamination of diamine **B**. Because of the diamine **B** was very unstable, so it was difficult to be defected.

MA-1: mp:191-19°C. ^{1}HNMR (DMSO-d_6, δppm): 1.21 (t, 3H, J = 7.2Hz, $COOCH_2CH_3$), 3.24-3.37 (m, 10H, $5NCH_2$), 4.09 (q, 2H, J = 7.2Hz, $COOCH_2CH_3$), 4.10 (s, 2H, $COCH_2$), 6.08 (s, 2H, OCH_2O), 6.76 (d, 1H, J = 16.2Hz, = CHCO), 6.96 (d, 1H, J = 8.1Hz, ArH), 7.21 (dd, 1H, J_1 = 7.2Hz, J_2 = 1.8Hz, ArH), 7.34 (d, 1H, J = 1.8Hz, ArH), 7.60 (d, 1H, J = 16.2Hz, CH=); MS (*m/z*): 360 (M^+, 22), 315 (2), 202 (68).
IM-1: mp:178-182°C. ^{1}HNMR (DMSO-d_6, δppm)**:** 1.20 (t, 3H, J = 7.2Hz, $COOCH_2CH_3$), 3.20-3.60 (m, 6H, $3CH_2N$), 3.80-4.16 (m, 6H, $2NCH_2$ + $COOCH_2CH_3$),

6.08 (s, 2H, OCH_2O), 6.70 (s, 1H, C = CH_{2f}), 6.96 (d, 1H, J = 7.2Hz, ArH), 7.03 (s, 1H, C = CH_{2g}), 7.27 (d, 1H, J = 7.2Hz, ArH), 7.60 (s, 3H, HC = CH + ArH); MS (*m/z*): 372 (M^+, 100), 355 (20), 299 (5), 216 (38); HRMS: 372.1689 (M^+, 100), 355.1643 (15), 327.1346 (3.6), 299.1376 (3.8), 216.0769 (29.1).

Acknowledgment

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