Chem. Pharm. Bull. **42**(8) 1676—1678 (1994) Vol. 42, No. 8

A MODIFIED MANNICH REACTION USING 1,3-DIOXOLANE

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Mannich reaction of ketones using 1,3-dioxolane instead of formaldehyde, paraformaldehyde, or 1,3,5-trioxane afforded the corresponding Mannich bases in high yields. Under the same conditions the aminomethylation of aromatics did not proceed but the intramolecular aminomethylation, like a Pictet-Spengler type reaction, proceeded smoothly.

KEYWORDS Mannich reaction; aminomethylation; 1,3-dioxolane; formaldehyde; paraformaldehyde

Mannich reaction, aminomethylation, is one of the most important reactions in the field of organic synthesis. However, there are cases in which occurrence of side reactions and/or incompletion of reaction lowers yields of Mannich bases. We found that Mannich reaction of ketones using 1,3-dioxolane instead of formaldehyde, paraformaldehyde, or 1,3,5-trioxane gave the corresponding Mannich bases in extremely high yields. Now we report a modified Mannich reaction using 1,3-dioxolane.

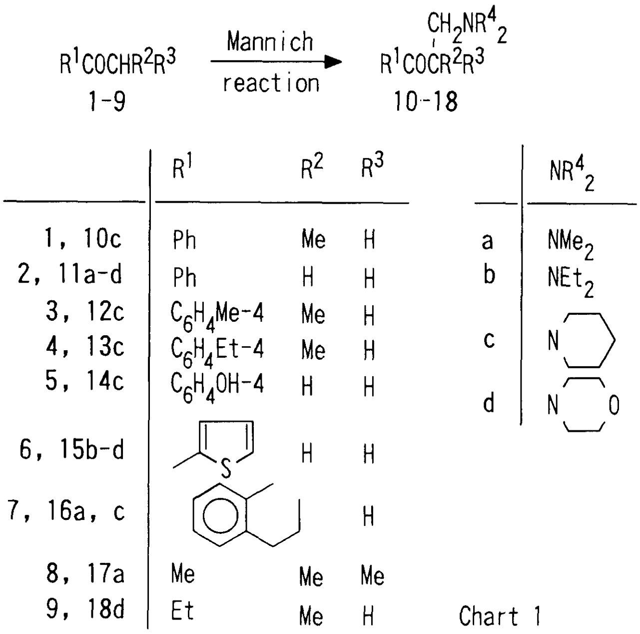


Chart 1

First, we carried out Mannich reaction of propiophenone (**1**), piperidine hydrochloride, and 1,3-dioxolane in the presence of 0.10 equimolar amount of concentrated hydrochloric acid (c-HCl) in several kinds of solvents. The results are summarized in Table I. The yields were determined by HPLC analysis to compare them exactly. By use of 1,3-dioxolane as solvent, the reaction proceeded smoothly to give the desired Mannich base (**10c**) in high yield (entry 6). The reactions in other solvent were not completed by heating even for 8 h, and consequently the yields were 53.1-74.5% (entries 1-5).

Table I. Solvent Effect in Modified Mannich Reactions of **1** and Piperidine Using 1,3-Dioxolane$^{a)}$

Entry	Solvent	Yield (%)$^{b)}$
1	MeOH	53.1
2	EtOH	74.5
3	Pr^{i}OH	74.4
4	1,4-dioxane	70.6
5	MeCN	71.0
6	1,3-dioxolane	95.5

a) A mixture of **1** (1.00 g), piperidine•HCl (1.2 eq), 1,3-dioxolane (2.0 eq), c-HCl (0.1 eq), and solvent (1.0 ml) was heated at 90 $^{\circ}$C (bath temperature) for 8 h. b) Maximum yields by HPLC analysis.

Secondly, in the presence of several kinds of acids, the Mannich reaction of **1**, piperidine salts, and 1,3-dioxolane was performed. The results are summarized in Table II. Addition of 0.05-0.10 equimolar amount of c-HCl or methanesulfonic acid advanced the reaction to give **10c** in high yield (entries 2, 3, 7, 8), while addition of 0.20-0.40 equimolar amount of c-HCl caused decomposition of **10c** into 2-methyl-3-oxo-3-phenylpropene (entries 4, 5). In the absence of c-HCl, the reaction did not proceed at all (entry 1), but in the case of methanesulfonic acid and p-toluenesulfonic acid the reactions proceeded to afford **10c** in 42.6 and 81.6% yields, respectively (entries 6, 9). Use of oxalic acid and acetic acid did not advance the reactions entirely.

We selected 1,3-dioxolane as solvent and 0.05-0.10 equimolar amount of c-HCl as an acidic catalyst in Mannich reaction using 1,3-dioxolane. Under these reaction conditions modified Mannich reactions were carried out, and their yields were compared with those of the known normal reactions using formaldehyde, paraformaldehyde, or 1,3,5-trioxane reported in the literature.[1-11]

The normal Mannich reaction was carried out according to the known method, and their yields were determined by HPLC analysis. The results are summarized in Table III.

Results of our modified Mannich reaction using 1,3-dioxolane are summarized in Table IV. All reactions gave the corresponding Mannich bases in high yields (82.2-99.8%), which were 8.9-60.1% higher than those of the normal Mannich reactions. In particular rises of yields in entries 8 and 13 were remarkable. Toluperisone (**12c**)[5] and eperisone (**13c**),[6] central muscle relaxants, were also formed in extremely high yields.

Table II. Comparison of the Effect of Acids in Modified Mannich Reactions of **1** and Piperidine Using 1,3-Dioxolane[a]

Entry	HX	HX (eq)[b]	Yield (%)[c]
1	c-HCl	0.00	0.0
2		0.05	98.4
3		0.10	95.5
4		0.20	86.4
5		0.40	79.2
6	$MeSO_3H$	0.00	42.6
7		0.05	96.2
8		0.10	98.1
9	p-TsOH	0.00	81.6
10		0.05	82.3
11		0.10	60.7

a) A mixture of **1** (1.00 g), piperidine•HX (1.2 eq), 1,3-dioxolane (4.0 eq), and HX was heated at 90 ^{o}C (bath temperature) for 8 h. b) Against **1**. c) Maximum yields by HPLC analysis.

Under the conditions of modified Mannich reaction, aminomethylation of aromatics such as antipyrine, N,N-dimethylaniline, indol, and thiophene did not proceed at all. On the other hand, intramolecular aminomethylation, a Pictet-Spengler type reaction, of compounds **19**, **20**, and **23** using 1,3-dioxolane gave compounds **21**,[12] **22** (ticropidine),[13] and **24**[14] in 79.8, 89.0, and 99.8% yields, respectively.

The isolated yields of the hydrochlorides of **10c**, **11a**, **12c**, **13c**, **15b**, and **22** in this modified Mannich reaction[15] were 95, 92, 96, 95, 88, and 85%, respectively.

Table III. Known Normal Mannich Reactions

Entry	Ketone	Product	C-source	Solvent	Yield (%) A[a]	Yield (%) B[b]	Literature
1	**2**	**11a**	$(CH_2O)_n$[c]	EtOH	76.6	68-72	1)
2	**2**	**11b**	$(CH_2O)_n$	EtOH	57.0	45	2)
3	**2**	**11c**	$(CH_2O)_n$	EtOH	75.3	90	3)
4	**2**	**11d**	$(CH_2O)_n$	EtOH	75.6	-[d]	4)
5	**3**	**12c**	$(CH_2O)_n$	AcOEt[e]	90.0	81	5)
6	**4**	**13c**	$(CH_2O)_n$	Pr^iOH	87.1	66	6)
7	**5**	**14c**	$(CH_2O)_n$	EtOH	69.6	-[f]	7)
8	**6**	**15b**	$(CH_2O)_n$	EtOH	42.7	39	2)
9	**6**	**15c**	$(CH_2O)_n$	EtOH	60.9	74	2, 8)
10	**6**	**15d**	$(CH_2O)_n$	EtOH	62.9	46	4)
11	**7**	**16a**	CH_2O	EtOH[g]	52.9	70	9)
12	**7**	**16c**	CH_2O	EtOH[g]	72.1	75	9)
13	**8**	**17a**	$(CH_2O)_3$[h]	EtOH	22.1	39	10)
14	**9**	**18d**	$(CH_2O)_n$	-	60.9	50	11)

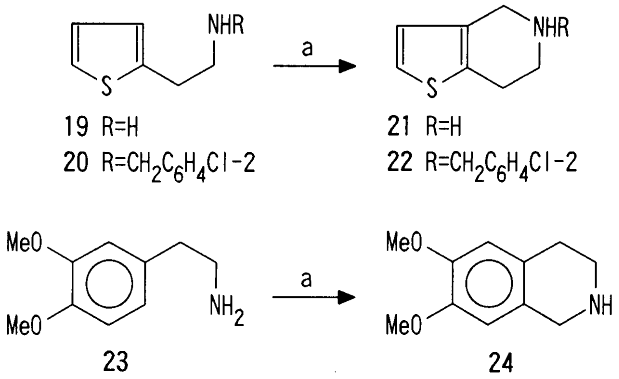
a) Our maximum yields of normal Mannich reactions by HPLC analysis. These reactions were done according to the method described in the literature. b) Isolated yields reported in the literature. c) Paraformaldehyde. d) Excellent yield. e) With removal of water. f) Not noted. g) Not used in the literature. h) 1,3,5-Trioxane.

In conclusion, we found that modified Mannich reaction of ketones using 1,3-dioxolane instead of formaldehyde, paraformaldehyde, or 1,3,5-trioxane afforded the corresponding Mannich bases in high yields. 1,3-Dioxolane also caused Pictet-Spengler type aminomethylation, but did not react with aromatics entirely.

Table IV. Modified Mannich Reactions a)

Entry	Ketone	Product	Yield (%) b)	RT (h) c)
1	**2**	**11a**	96.8	3.5
2	**2**	**11b**	99.3	5.5
3	**2**	**11c**	93.9	7.0
4	**2**	**11d**	91.5	2.0
5	**3**	**12c**	98.9	8.0
6	**4**	**13c**	97.0	6.5
7	**5**	**14c**	99.8	8.0
8	**6**	**15b**	91.4	6.0
9	**6**	**15c**	98.4	8.0
10	**6**	**15d**	89.2	4.0
11	**7**	**16a**	89.9	2.0
12	**7**	**16c**	93.5	5.5
13 d)	**8**	**17a**	82.2	5.0
14 d)	**9**	**18d**	91.5	3.0

a) A mixture of ketone (1.0 eq), amine•HCl (1.2 eq), 1,3-dioxolane (4.0 eq), and c-HCl (0.1 eq) was heated at 90 °C (bath temperature). b) Maximum yields by HPLC analysis. c) Reaction time at which maximum yield was observed. d) Added c-HCl was 0.05 eq.



a) HCl salt, c-HCl, 1,3-dioxolane

Chart 2

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15) Typical examples are as follows.

13c a) A mixture of **4** (10.0 g, 61.6 mmol), 1,3-dioxolane (18.2 g, 246 mmol), piperidine hydrochloride (9.2 g, 75.7 mmol), and c-HCl (0.4 g, 3.8 mmol) was heated at 90 °C (bath temperature) for 8 h. After being cooled the reaction mixture was diluted with water and washed with ethyl acetate. Aqueous layer was made alkaline with sodium hydroxide and extracted with ethyl acetate. Organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo to afford a pale yellow oil, which was converted into the hydrochloride in acetone-ether to give colorless needles (17.3 g, 95%), mp 173-5 °C, (lit.6) 170-2 °C).

b) A mixture of **4** (10.0 g, 61.6 mmol), 1,3-dioxolane (18.2 g, 246 mmol), piperidine methanesulfonate (13.5 g, 74.5 mmol), and methanesulfonic acid (0.3 g, 3.1 mmol) was heated at 90 °C (bath temperature) for 8 h. Further operation as described above gave the hydrochloride (16.8 g, 92%), mp 173-5 °C. Both reactions were completed in 5 h at 110 °C (bath temperature).

(Received February 28, 1994; accepted June 26, 1994)