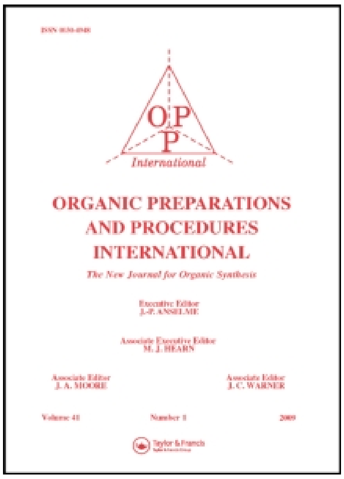

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

THE MANNICH REACTION OF CYCLIC KETONES, AROMATIC ALDEHYDES AND AROMATIC AMINES

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To cite this Article Lin, Yi , Junhua, Zou , Huangshu, Lei , Xiaomei, Lin and Mingxiao, Zhang(1991) 'THE MANNICH REACTION OF CYCLIC KETONES, AROMATIC ALDEHYDES AND AROMATIC AMINES', Organic Preparations and Procedures International, 23: 5, 673 — 676

To link to this Article: DOI: 10.1080/00304949109457926

URL: http://dx.doi.org/10.1080/00304949109457926

THE MANNICH REACTIONOF CYCLIC KETONES, AROMATIC ALDEHYDES AND AROMATIC AMINES

Submitted by
(05/21/91)

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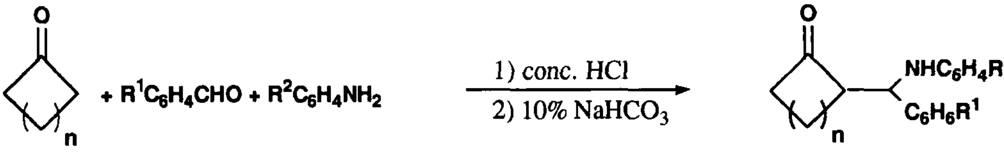
While the Mannich reaction of ketones, formaldehyde and aliphatic amines (primary or secondary) has been widely recorded in the literature,[1] the reaction of ketones, aromatic aldehyde and aromatic amines remains practically unexplored. In earlier reports, the Mannich bases **1** were prepared by the addition of cyclic ketones to Schiff bases in the presence of hydrochloric acid[2,3] or BF_3.[4] Pirrone[5] reported that the Mannich bases **1** ($n = 3$, $R^1 = R^2 = H$) could be obtained directly by reaction of cyclohexanone, benzaldehyde and aniline in ethanol. However, this method requires long reaction time (several days) and is not general in scope. We now report that the Mannich reaction between cyclic ketones, aromatic aldehydes and aromatic amines proceeds smoothly in ethanol containing a small amount of hydrochloric acid at 0-25° for several hours.



1

Thus the Mannich bases **1** were obtained directly in high yields (Table 1). A range of substituted anilines in which R = 4-Me, H, 3-Cl, 4-Cl, 4-Br, 4-I may be used. However, 4-nitroaniline and 3-nitroaniline gave poor results and 2-methylaniline and 2-chloroaniline failed to give **1**. The aromatic aldehyde used included benzaldehyde and 4-methoxybenzaldehyde. When 4-nitrobenzaldehyde was employed as the aromatic aldehyde moiety, no Mannich bases **1** could be isolated.

The amount of hydrochloric acid was critical to the success of the reaction. Use of lesser amounts of hydrochloric acid depressed the rate of the condensation, but decreased the rates of side-reactions even more. Larger amounts of hydrochloric acid increased the extent of side-reactions, thus decreasing the yield of **1**. If excess hydrochloric acid was used, no Mannich base **1** was obtained. For one mole aromatic amine, 0.2 mL of conc. hydrochloric acid was sufficient.The reaction temperature was another important factor. Increasing the temperature favored side-reactions and the formation of deeply colored products. If the reaction was carried out at reflux, no product could be isolated. Decreasing the temperature decreased the rate of the reaction, but also decreased the rates of side-reactions. The best temperature was 0-20°.

TABLE 1. Preparation of Mannich Bases **1**

n	Compd. No.	R¹	R²	Reaction temp. (°C)	Condition time (hrs)	Yield (%)	mp (°C) (lit)
3	**1a**	H	4-Me	10	5	88	116-118 (116-118)[3]
3	**1b**	H	H	0	10	92	138-140 (139-140)[3]
3	**1c**	H	4-Cl	10	5	88	136-138 (137-138)[3]
3	**1d**	H	4-Br	10	5	77	132-133 (131-132)[3]
3	**1e**	H	4-I	0	10	78	134-136 (135-136)[3]
3	**1f**	4-OMe	4-Cl	0	10	81	132-134
3	**1g**	4-OMe	4-Br	0	10	68	144-146
3	**1h**	4-OMe	3-Cl	0	10	89	143-144
2	**1i**	H	4-Me	10	5	81	152-154
2	**1j**	H	H	0	10	78	164-166 (164-165)[2]
2	**1k**	H	4-Cl	10	5	83	144-146
2	**1l**	H	4-Br	0	10	88	158-160
2	**1m**	H	4-I	0	10	79	172-174
2	**1n**	H	3-NO_3	20	10	75	166-168
2	**1o**	4-OMe	4-Br	0	10	72	142-144
2	**1p**	4-OMe	3-Cl	0	10	83	151-153
2	**1q**	4-OMe	4-Cl	0	10	79	127-128

TABLE 2. Analytical Data for Mannich Bases 1

No.	Found/Calcd			IR	^{1}H NMR	MS
	C	H	N	(cm^{-1})	(CDCl$_3$, ppm)	m/z(%)
1f	69.86	6.45	4.07	3321	6.31-7.38(m, 8H); 4.62 (d, 1H); 3.61 (s, 3H); 3.08 (s, 1H); 1.14-2.65 (m, 9H)	343(8)
	69.95	6.33	3.92	1702		246(100)
1g	61.86	5.71	3.61	3324	6.32-7.53 (m, 8H); 4.36 (d, 1H); 3.28 (s, 3H); 3.14 (s, 1H); 1.32-2.61 (m, 9H)	387(6)
	61.94	5.54	3.32	1698		290(100)
1h	69.86	6.45	4.07	3390	6.28-7.42 (m, 8H); 4.45 (d, 1H); 3.29 (s, 3H); 3.01 (s, 1H); 1.25-2.46 (m,9H)	343(4)
	69.71	6.29	4.21	1701		246(100)
1i	81.68	7.58	5.01	3382	6.41-7.25 (m, 9H); 4.46 (d, 1H); 3.29 (s, 1H); 2.28 (s, 3H); 1.49-2.56 (m, 7H)	279(6)
	81.92	7.41	4.95	1731		196(100)
1k	72.11	6.05	4.67	3411	6.55-7.17 (m, 9H); 4.31 (d, 1H); 3.66 (s, 1H); 1.63-2.41 (m, 7H)	299(3)
	72.35	5.91	4.42	1728		216(100)
1l	62.80	5.27	4.07	3411	6.61-7.23 (m, 9H); 4.33 (d, 1H); 3.46 (s, 1H); 1.64-2.46 (m, 7H)	343(9)
	62.64	5.01	4.24	1728		260(100)
1m	55.26	4.46	3.58	3378	6.45-7.21 (m, 9H); 4.30 (d, 1H); 3.38 (s, 1H); 1.68-2.52 (m, 7H)	391(9)
	55.41	4.29	3.36	1731		308(100)
1n	69.66	5.85	4.51	3397	6.33-7.18 (m, 9H); 4.30 (d, 1H); 3.49 (s, 1H); 1.43-2.91 (m, 7H)	310(7)
	69.98	5.79	4.34	1736		227(100)
1o	60.97	5.39	3.74	3392	6.21-7.40 (m, 8H); 4.29 (d, 1H); 3.30 (s, 3H); 3.21 (s, 1H); 1.39-2.56 (m, 7H)	373(8)
	61.23	5.25	3.56	1738		290(100)
1p	69.19	6.11	4.25	3410	6.25-7.31 (m, 8H); 4.32 (d, 1H); 3.68 (s, 3H); 3.34 (s, 1H); 1.45-2.61 (m, 7H)	329(5)
	69.32	6.05	4.38	1725		246(100)
1q	69.19	6.11	4.25	3418	6.39-7.41 (m, 8H); 4.45 (d, 1H); 3.60 (s, 3H); 3.31 (s, 1H); 1.46-2.61 (m, 7H)	329(4)
	69.26	6.09	4.28	1726		246(100)

EXPERIMENTAL SECTION

All melting points were determined in open capillary tubes and uncorrected. The IR spectra were recorded with a Hitachi 260-50 spectrometer. The ^{1}H NMR spectra were obtained on a Joel-PMX-60 spectrometer in $CDCl_3$ solution with TMS as the internal standard. Elemental analyses were performed with a Perkin-Elmer 240-C. Mass spectra were obtained from a Varian MAT112S unit using an ionization potential of 70eV and a directed inlet system.

Preparation of Mannich Bases (**1**). General Procedure.- To the aromatic amine (5 mmol) dissolved or suspended in 4-6 mL absolute ethanol, was added with stirring, the cyclic ketone (5 mmol) and the aromatic aldehyde (5 mmol). Conc. hydrochloric acid (0.2 mL) was then added with cooling in an ice-water bath. The mixture was stirred for 5-10 hrs at 0-20° (Table 1) and left standing overnight at 0°. The Mannich base **1** was collected and washed with 95% ethanol and 10% sodium bicarbonate respectively. The pure product was obtained by recrystallization from acetone and 95% ethanol (2:3).

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IMPROVED SYNTHESIS OF A 2-ARYLBENZO[b]FURAN-3-CARBOXYLIC ACID

Submitted by
(06/11/91)

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The stereospecific synthesis of (Z)-marginalin **2** through the pH controlled addition of *p*-hydroxybenzaldehyde to 5-hydroxy-2-coumaranone **1** has been reported.[1] This synthesis allowed the