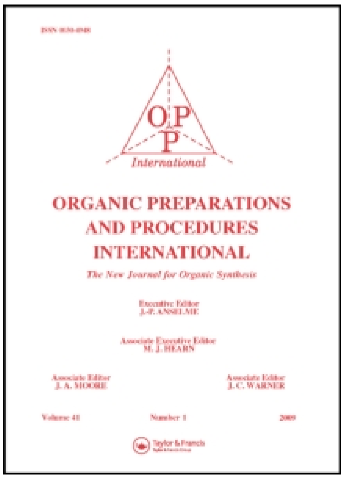

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THE MANNICH REACTION OF DIALKYL KETONES, AROMATIC ALDEHYDES AND AROMATIC AMINES

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

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While the Mannich reaction between ketones, formaldehyde and aliphatic amines (primary or secondary) has been widely described in the literature,[1] the reaction of ketones, aromatic aldehydes and aromatic amines remains practically unexplored.[2] Earlier literature reported that aromatic amines, aromatic aldehydes and ketones could not react directly[3] and thus the corresponding Mannich bases of type **4** could only be obtained indirectly. Snyder *et al.*[4] described the preparation of 5-methyl-1-phenyl-1-phenylamino-3-hexanone, by the addition of 4-methyl-2-pentanone to benzalaniline in the presence of $BF_3{\bullet}Et_2O$. while Archer *et al.*[5] reported that 1-phenyl-1-phenylamino-3-hexanone had been obtained by the addition of aniline to 1-phenyl-1-hexen-3-one. Although these methods can produce Mannich bases, the Schiff bases must be prepared first and the methods are complicated and give low yields (38%).

We now report that Mannich condensation may be carried out smoothly in good to excellent yields (61-90%) between 3-methyl-2-butanone or 2-pentanone, aromatic aldehydes and aromatic amines in the presence of a small amount of conc. hydrochloric acid at 0-20°.

$$\underset{\mathbf{1}}{RCOCH_3} + \underset{\mathbf{2}}{ArCHO} + \underset{\mathbf{3}}{Ar'NH_2} \xrightarrow[\text{2. 10\% NaHCO}_3]{\text{1. conc. HCl, EtOH}} \underset{\mathbf{4}}{RCOCH_2CH(Ar)NHAr'}$$

The amount of hydrochloric acid is critical to the success of the reaction. For one mole aromatic amine, 0.25% mol of conc. hydrochloric acid was sufficient. While the use of lesser amounts of hydrochloric acid depressed the rate of the condensation, the rates of side-reaction were decreased even more. If excess hydrochloric acid was used, no Mannich bases **4** were obtained. The temperature also had a major influence on the reaction. The optimum temperature was 0-20°. Increasing temperatures favor side-reactions and the formation of deeply colored products. Reactions performed at the reflux temperature produced no Mannich bases **4**. Decreasing the temperature decreases the rates of the reaction, but also decreased the rates of side-reactions.

In an earlier report[6] about the orientation of the Mannich reaction of unsymmetrical aliphatic ketones, secondary aliphatic amines and formaldehyde, the condensation occurred mainly at the carbon bearing the least number of H-atoms unless this carbon is severely hindered. However, in our case due to the presence of the ring of the aromatic aldehydes, the reaction occurs at the least substituted carbon.

EXPERIMENTAL SECTION

All mps were determined in an open capillary tube and are uncorrected. The IR spectra were recorded with PK-600FTIR spectrometer. The ^1H NMR spectra were obtained on a Jeol-PMX-60 spectrometer in $CDCl_3$ with TMS as the internal standard. Elementary analyses were Carried out with a Perkin-Elmer 240-CHN elementary analysis instrument. Mass spectra were determined using a Varian MAT112S unit at an ionization potential of 70ev with and a direct inlet system.

Preparation of Mannich Bases. General Procedure.- To a solution of the aromatic amine (5mmol) in EtOH (4-6mL), was added the ketone (5mmol) and the aromatic aldehyde (5mmol). Conc. hydrochloric acid (0.2mL) was added with cooling at 0° in an ice-water bath. The mixture was stirred (**Table 1**) and then left standing overnight at 0°; the mixture was neutralized with 10% sodium bicarbonate until pH 7, and the product were collected and washed with water and 95% ethanol. The pure products were obtained by recrystallization from ethanol. The Mannich bases **4** are thus obtained in 61-90% yields.

TABLE 1. The Preparation of Mannich Bases **4**

Cmpd No	R	Ar	Ar'	Reaction temp. (°C)	Conditions Time (hrs)	Yield (%)	mp. (°C)
4a	$(CH_3)_2CH$	C_6H_5	C_6H_5	10	16	85	112-114
4b	$(CH_3)_2CH$	C_6H_5	4-ClC_6H_4	15	16	88	114-116
4c	$(CH_3)_2CH$	C_6H_5	4-BrC_6H_4	10	18	88	119-120
4d	$(CH_3)_2CH$	C_6H_5	4-IC_6H_4	12	20	80	121-122
4e	$(CH_3)_2CH$	C_6H_5	4-$CH_3C_6H_4$	8	15	76	104-105
4f	$(CH_3)_2CH$	C_6H_5	3-$NO_2C_6H_4$	25	26	61	123-124
4g	$(CH_3)_2CH$	C_6H_5	3-ClC_6H_4	15	20	84	122-124
4h	$(CH_3)_2CH$	4-$CH_3OC_6H_4$	C_6H_5	8	20	75	92-94
4i	$(CH_3)_2CH$	4-$CH_3OC_6H_4$	4-ClC_6H_4	8	20	85	95-97
4j	$(CH_3)_2CH$	4-$CH_3OC_6H_4$	4-BrC_6H_4	8	20	82	101-102
4k	$(CH_3)_2CH$	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	8	18	72	91-92
4l	$(CH_3)_2CH$	4-$CH_3OC_6H_4$	3-ClC_6H_4	8	20	78	80-82
4m	$CH_3CH_2CH_2$	C_6H_5	C_6H_5	10	12	75	87-88[a]
4n	$CH_3CH_2CH_2$	C_6H_5	4-$CH_3C_6H_4$	8	12	78	96-98
4o	$CH_3CH_2CH_2$	C_6H_5	4-ClC_6H_4	14	12	90	84-86
4p	$CH_3CH_2CH_2$	C_6H_5	3-ClC_6H_4	20	12	86	94-96
4q	$CH_3CH_2CH_2$	C_6H_5	4-BrC_6H_4	16	16	80	86-88
4r	$CH_3CH_2CH_2$	C_6H_5	4-IC_6H_4	16	16	81	90-92
4s	$CH_3CH_2CH_2$	C_6H_5	4-$NO_2C_6H_4$	30-35	54-70	61	102-104
4t	$CH_3CH_2CH_2$	4-$CH_3OC_6H_4$	C_6H_5	8	12	74	90-92
4u	$CH_3CH_2CH_2$	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	8	12	77	92-94
4v	$CH_3CH_2CH_2$	4-$CH_3OC_6H_4$	4-ClC_6H_4	10	12	82	84-86
4w	$CH_3CH_2CH_2$	4-$CH_3OC_6H_4$	3-ClC_6H_4	10	16	90	78-79
4x	$CH_3CH_2CH_2$	4-$CH_3OC_6H_4$	4-BrC_6H_4	10	12	80	82-84

a) Lit.[5] 87-88°.

TABLE 2. Analytical Data for Mannich Bases (**4a**-**4x**)

No	Calcd (Found)			IR (cm^{-1})	^{1}H NMR (δ,CDCl$_3$)	MS (m/z, %)
	C	H	N	NH, C=O		
4a	80.85 (80.94)	7.92 (7.84)	5.24 (5.21)	3375 1705	6.30-7.58 (m, 10H), 3.36 (br, 1H), 3.60 (t, 1H), 2.78 (d, 2H), 2.4 (m, 1H), 1.03 (d, 6H)	267 (M+, 16.1) 182 (100)
4b	71.62 (71.79)	6.68 (6.61)	4.64 (4.60)	3377 1702	6.32-7.73 (m, 9H), 3.35 (br, 1H), 3.73 (t, 1H), 2.9 (d, 2H), 2.4 (m, 1H), 1.03 (d, 6H)	301 (M+, 13.3) 216 (100)
4c	62.42 (62.46)	5.82 (5.74)	4.05 (4.01)	3376 1703	6.35-7.75 (m, 9H), 3.43 (br, 1H), 3.65 (t, 1H), 2.82 (d, 2H), 2.4 (m, 1H), 0.98 (d, 6H)	346 (M+, 14.3) 260 (100)
4d	54.95 (54.99)	5.13 (5.15)	3.56 (3.51)	3376 1703	6.35-7.75 (m, 9H), 3.51 (br, 1H), 3.75 (t, 1H), 2.90 (d, 2H), 0.98 (d, 6H), 2.38 (m, 1H)	393 (M+, 10.9) 308 (100)
4e	81.10 (81.19)	8.20 (8.12)	4.98 (5.00)	3375 1695	6.26-7.59 (m, 9H), 3.68 (t, 1H), 3.42 (br, 1H), 2.85 (d, 2H), 2.06 (s, 3H), 0.99 (d, 6H), 2.42 (m, 1H)	281 (M+, 11.7) 196 (100)
4f	69.20 (69.28)	6.46 (6.47)	8.97 (8.94)	3364 1700	6.28-7.68 (m, 9H), 3.68 (t, 1H) 3.43 (br, 1H), 2.9 (d, 2H), 0.98 (d, 6H), 2.41 (m, 1H)	312 (M+, 19.0) 227 (100)
4g	71.62 (71.48)	6.68 (6.62)	4.65 (4.62)	3370 1705	6.12-7.50 (m, 9H), 3.58 (t, 1H), 3.33 (br, 1H), 2.73 (d, 2H), 0.95 (d, 6H), 2.40 (m, 1H)	301 (M+, 13.3) 216 (100)
4h	76.74 (76.80)	7.79 (7.71)	4.71 (4.75)	3370 1705	6.24-7.82 (m, 9H), 4.63 (t, 1H), 3.62 (s, 3H), 4.19 (br, 1H), 2.62 (d, 2H), 2.25 (m, 1H), 0.9 (d, 6H)	297 (M+, 13.6) 71 (100)
4i	68.77 (68.96)	6.68 (6.69)	4.22 (4.18)	3375 1705	6.22-7.80 (m, 8H), 4.57 (t, 1H), 3.62 (s, 3H), 4.3 (br, 1H), 2.78 (d, 2H), 0.91 (d, 6H), 2.27 (m, 1H)	331 (M+, 16.1) 71 (100)
4j	60.65 (60.70)	5.89 (5.91)	3.72 (3.79)	3372 1705	6.19-7.83 (m, 8H), 4.58 (t, 1H), 4.32 (br, 1H), 3.6 (s, 3H), 2.78 (d, 2H), 2.30 (m, 1H), 0.9 (d, 6H)	376 (M+, 9.1) 71 (100)
4k	77.14 (77.22)	8.09 (8.08)	4.50 (4.56)	3368 1705	6.30-7.89 (m, 8H), 4.56 (t, 1H), 4.30 (br, 1H), 3.71 (s, 3H), 2.22 (s, 3H), 2.76 (d, 2H), 2.3 (m, 1H), 0.9 (d, 6H)	311 (M+, 6.8) 71 (100)
4l	68.77 (68.69)	6.68 (6.71)	4.22 (4.27)	3372 1705	6.21-7.88 (m, 8H), 4.62 (t, 1H), 4.31 (br, 1H), 4.66 (s, 3H), 2.78 (d, 2H), 2.38 (m, 1H), 0.9 (d, 6H)	331 (M+, 11.3) 71 (100)
4m	80.85 (80.91)	7.92 (7.86)	5.24 (5.19)	3371 1700	6.40-7.73 (m, 10H), 4.96 (t, 1H), 2.80 (d, 2H), 3.63 (br, 1H), 2.20 (t, 2H), 1.43 (m, 2H), 0.72 (t, 3H)	267 (M+, 6.6) 182 (100)

TABLE 2. Continued

No	Calcd (Found)			IR (cm^{-1})	^{1}H NMR (δ,CDCl$_3$)	MS (m/z, %)
	C	H	N	NH, C=O		
4n	81.10 (81.26)	8.24 (8.16)	4.98 (4.84)	3371 1700	6.23-7.83 (m, 9H), 4.7 (t, 1H), 2.8 (d, 2H), 3.7 (br, 1H), 2.1 (s, 3H), 1.1-1.6 (m, 2H), 2.21 (t, 2H), 0.78 (t, 3H)	281 (M+, 4.5) 196 (100)
4o	71.62 (71.78)	6.68 (6.76)	4.64 (4.68)	3385 1700	6.25-7.89 (m, 9H), 4.63 (t, 1H), 2.77 (d, 2H), 3.66 (br, 1H), 2.23 (t, 2H), 1.37 (m, 2H), 0.70 (t, 3H)	301 (M+, 14.0) 216 (100)
4p	71.62 (71.56)	6.68 (6.60)	4.64 (4.52)	3357 1700	6.15-7.78 (m, 9H), 4.6 (t, 1H), 2.8 (d, 2H), 3.65 (br, 1H), 2.23 (t, 2H), 1.38 (m, 2H), 0.77 (t, 3H)	301 (M+, 10.1) 216 (10)
4q	62.42 (62.56)	5.82 (5.91)	4.05 (4.16)	3385 1700	6.03- 7.80 (m, 9H), 4.60 (t, 1H), 2.73 (d, 2H), 3.66 (br, 1H), 2.15 (t, 2H), 1.25 (m, 2H), 0.70 (t, 3H)	346 (M+, 14.6) 260 (100)
4r	54.95 (55.02)	5.13 (5.11)	3.56 (3.51)	3357 1693	6.13-7.80 (m, 9H), 4.63 (t, 1H), 2.79 (d, 2H), 3.61 (br, 1H), 2.22 (t, 2H), 1.39 (m, 2H), 0.8 (t, 3H)	393 (M+, 14.5) 308 (100)
4s	69.20 (69.31)	6.46 (6.40)	8.97 (8.90)	3357 1690	6.29-7.93 (m, 9H), 4.78 (t, 1H), 2.88 (d, 2H), 3.65 (br, 1H), 2.20 (t, 2H), 1.32 (m, 2H), 0.73 (t, 3H)	312 (M+, 9.1) 227 (100)
4t	76.74 (76.84)	7.79 (7.66)	4.71 (4.82)	3362 1693	6.28-7.78 (m, 9H), 4.62 (t, 1H), 3.65 (s, 3H), 2.76 (t, 2H), 3.53 (br, 1H), 2.19 (t, 2H), 1.40 (m, 2H), 0.75 (t, 3H)	297 (M+, 6.8) 171 (100)
4u	77.14 (77.26)	8.09 (8.06)	4.50 (4.48)	3362 1700	6.75-8.26 (m, 8H), 4.62 (t, 1H), 2.76 (t, 2H), 3.65 (s, 3H), 3.53 (br, 1H), 2.19 (t, 2H), 2.10 (s, 3H), 1.4 (m, 2H), 0.75 (t, 3H)	311 (M+, 4.6) 71 (100)
4v	68.77 (68.68)	6.68 (6.66)	4.22 (4.20)	3350 1700	6.20-7.80 (m, 8H), 4.62 (t, 1H) 2.77 (t, 2H), 3.65 (s, 3H), 3.50 (br, 1H), 2.18 (t, 2H), 1.4 (m, 2H), 0.73 (t, 3H)	311 (M+, 6.8) 71 (100)
4w	68.77 (68.91)	6.68 (6.65)	4.22 (4.28)	3328 1682	6.10-7.70 (m, 8H), 4.48 (t, 1H), 2.70 (d, 2H), 3.63 (s, 3H), 2.15 (t, 2H), 3.53 (br, 1H), 1.33 (m, 2H), 0.72 (t, 3H)	331 (M+, 6.8) 71 (100)
4x	60.65 (60.76)	5.89 (5.87)	3.72 (3.70)	3350 1700	6.12-7.76 (m, 8H), 4.59 (t, 1H), 3.59 (s, 3H), 3.54 (br, 1H), 2.67 (t, 2H), 2.13 (t, 2H), 1.39 (t, 2H), 0.74 (t, 3H)	376 (M+, 7.0) 71 (100)

a) Singlet unless otherwise mentioned.

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SYNTHESIS OF *o*-KETOARYL CARBOXYLIC ESTERS USING PHENYLIODOSO DIACETATE

Submitted by (12/11/95)

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o-Hydroxyaryl ketones (**1**) are versatile synthons for heterocyclic synthesis due to the presence of phenolic hydroxy and acyl groups at adjacent positions on the benzene ring.[1] In addition to heterocyclic synthesis, the presence of these functional groups in close proximity can also result in novel rearrangements such as occurs on treatment of the monoacylhydrazones of *o*-hydroxyaryl ketones with lead tetraacetate (LTA) which results in replacement of the phenolic hydroxyl with an acyl group to give 1,2-diacylbenzenes.[2]

As a continuation of our interest in this rearrangement, we examined phenyliodoso diacetate (PID) as an alternative oxidative agent for the synthesis of *o*-ketoaryl esters (**4**,) from ethoxy- and benzyloxycarbonylhydrazones (**3**) of *o*-hydroxyaryl ketones. Since PID has similar reactivity to LTA[4] but is less toxic, its use as an alternative oxidant should be beneficial. Although it is a widely used oxidant in organic synthesis,[5] PID has been rarely used for oxidations of hydrazones in contrast to LTA.[6] Examples include conversion of benzophenone hydrazone to benzhydryl esters on treatment