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Synthesis and Reactivity of Some Mannich Bases. VI. New Arylamine Mannich Bases Derived From 2-Hydroxy-5-Methylacetophenone

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The amine exchange reaction has been applied for obtaining a new series of arylamine Mannich bases from variously substituted aromatic amines and 3-(dimethylamino)-1-(2'-hydroxy-5'-methylphenyl)propan-1-one. The structures of the newly synthesised Mannich bases have been investigated by IR, ^{1}H- and ^{13}C-NMR and shown to be in good agreement with the proposed ones.

Key words: Mannich bases, amine-exchange reaction, arylamines, β-arylaminoketones, *ortho*-hydroxyacetophenones

Introduction

Besides the common alkylamines employed ever since the early work of Carl Mannich, more recent research in the synthesis of Mannich bases has proved that less common alkylamines[1] (mainly used with a view to creating pharmacologically active products), amino acids[2] or phthalimide[3] can be successfully used as amine components in direct aminomethylation reactions. Until the mid-seventies, arylamines were only sporadically presented to react with substrates containing an active hydrogen atom, such as heterocyclic compounds[4,5] or phenols[6]. Lately, Chinese researchers have intensively studied arylaminomethylation of acetophenones[7–9] through their addition to a Schiff base formed *in situ* and produced a large number of arylamine Mannich bases. The amine exchange reaction between an alkylamine Mannich base and arylamines also offers easy access to arylamine Mannich bases in high yield under mild reaction conditions. This method, firstly introduced by Singh[10] and later improved by Cymerman-Craig[11], still is, in spite of recent progress, a valuable preparative way for obtaining arylamine Mannich bases.

The aim of this study was to prepare a series of novel β-arylaminoketones by means of an exchange reaction between an alkyl Mannich base hydrochloride and an arylamine. The present work was undertaken with a view to rounding up the number of this particular sort of Mannich bases obtained from *ortho*-hydroxyacetophenones and to extend the knowledge about this lesser studied type of acetophenones. It should be also noted that arylamine Mannich bases can act as intermediates for obtaining heterocycles such as oxadiazepines[12] or tetrahydropyrimidines[13].

Experimental Part

Melting points were determined on a Boetius melting point microscope and are uncorrected. Microanalysis was performed at the P. Poni Institute for Macromolecular Chemistry. IR spectra were recorded on a SPECORD M 80 spectrometer while ^{1}H-NMR spectra were registered in deuterated chloroform on a VARION INOVA (400 MHz) spectrometer using TMS as internal standard. ^{13}C-NMR spectra were obtained on a VARIAN INOVA (100 MHz) spectrometer. All chemical shifts are reported in ppm downfield from tetramethylsilane.

3-Dimethylamino-1-(2'-hydroxy-5'-methylphenyl)propan-1-one was synthesized according to Comanita et al.[14]. All other reagents were obtained commercially and used without further purification.

General Procedure An amount of 2.435 g (10 mmol) 3-dimethylamino-1-(2'-hydroxy-5'-methylphenyl) propan-1-one was mixed along with 10 mmol of the required arylamine and 12 ml aqueous ethanol (1:1 v/v). The reaction mixture was heated with stirring while a solution formed. In most cases, an emulsion or even a solid separated shortly after refluxing had begun. Heating continued for another hour, when the cooled reaction mixture was filtered and the solid washed with a small volume of cold ethanol. If an oil separated from the cooled reaction mixture, the clear supernatant was removed, the oil was stirred for 5 min with a little ice-cold ethanol, and the solid arylamine Mannich base filtered off. The products were recrystallized from absolute ethanol.

Elemental analysis data as well as the melting points and the yields of the purified arylamine Mannich bases are presented in Table 1.

Table 1. Melting points, yields and microanalysis results for the purified arylamine Mannich bases

Compound	m. p.	Yield	Analyses					
			calculated			found		
	°C	%	%C	%H	%N	%C	%H	%N
2a	110-111	60	57.48	4.79	4.19	57.39	4.86	4.27
2b	106-107	75	71.58	6.66	4.91	71.51	6.73	4.99
2c	116-117	76	72.24	7.02	4.68	72.31	6.94	4.94
2d	147–148	60	72.72	6.40	4.71	72.66	6.49	4.77
2e	96-98	79	71.58	6.66	4.91	71.48	6.61	4.85
2f	92-94	78	72.24	7.02	4.68	72.18	6.91	4.60
2g	93-94	72	66.32	5.52	4.83	66.22	5.43	4.74

3-(2'-Bromophenylamino)-1-(2'-hydroxy-5'-methylphenyl)propan-1-one **2a**
IR (KBr, cm^{-1}): 1649 ($\nu_{C=O}$), 3436 (ν_{NH}).

^{1}**H-NMR spectrum** (ppm): 2.302 (s, 3H, Ar-CH_3); 3.291 (t, 2H, J=6.4 Hz, -$COCH_2$-); 3.65 (t, 2H, JX = X6 Hz, -C$\underline{H}_2$NHAr); 4.684 (s, 1H, -NHAr); 6.581-7.483 (m, 7H, aromatic protons); 12.075 (s, 1H, Ar-OH).

^{13}**C-NMR spectrum** (ppm): 20.358 (Ar-CH_3); 37.092 and 38.290 (-CO$\underline{C}H_2\underline{C}H_2$NHAr); 110.931, 117.879, 118.099, 128.401, 129.425, 132.459, 137.549 (aromatic CH); 109.922 (-C-Br); 118.797 (-$\underline{C}$-CH_3); 128.006 (-$\underline{C}$-C=O); 144.194 (-$\underline{C}$-$NHCH_2$-); 160.147 (-C-OH); 204.508 (-C=O).

1-(2'-Hydroxy-5'-methylphenyl)-3-(2'-methoxyphenylamino)propan-1-one **2b**

IR (KBr, cm^{-1}): 1648 ($\nu_{C=O}$), 3432 (ν_{NH}).

^{1}**H-NMR spectrum** (ppm): 2.298 (s, 3H, Ar-CH_3); 3.295 (t, 2H, J=6.4 Hz, -$COCH_2$-); 3.634 (t, 2H, J=6.4 Hz, -C$\underline{H}_2$NHAr); 3.832 (s, 3H, -OCH_3); 4.561 (s, 1H, -NHAr); 6.700-7.483 (m, 7H, aromatic protons); 12.410 (s, 1H, Ar-OH).

^{13} **C-NMR spectrum** (ppm): 20.283 (Ar-CH_3); 37.362 and 38.075 (-CO$\underline{C}H_2\underline{C}H_2$NHAr); 55.165 (-$OCH_3$); 109.428, 109.493, 116.585, 117.996, 121.076, 129.488, 137.324 (aromatic CH); 118.876 (-$\underline{C}$-CH_3); 127.857 (-$\underline{C}$-C=O); 137.286 (-C-OCH_3); 146.878 (-$\underline{C}$-$NHCH_2$-); 160.104 (-C-OH); 204.885 (-C=O).

3-(2'-Ethoxyphenylamino)-1-(2'-hydroxy-5'-methylphenyl)propan-1-one **2c**

IR (KBr, cm^{-1}): 1654 ($\nu_{C=O}$), 3442 (ν_{NH}).

^{1} **H-NMR spectrum** (ppm): 1.431 (t, 3H, J=7 Hz, -CH_2C$\underline{H}_3$); 2.291 (s, 3H, Ar-CH_3); 3.299 (t, 2H, J=6.6 Hz, -$COCH_2$-); 3.647 (t, 2H, J=6.6 Hz, -C$\underline{H}_2$NHAr); 4.434 (q, 2H, J=6.8 Hz, -OCH_2-); 4.593 (s, 1H, -NHAr); 6.675-7.483 (m, 7H, aromatic protons);12.147 (s, 1H, Ar-OH).

^{13} **C-NMR spectrum** (ppm): 14.791 (-$CH_2\underline{C}H_3$); 20.317 (Ar-CH_3); 37.346 and 38.245 (-CO$\underline{C}H_2$NHAr); 63.589 (-OCH_2-); 109.633, 110.505, 116.623, 118.023, 120.996, 129.545, 137.355 (aromatic CH); 118.933 (-$\underline{C}$-CH_3); 127.880 (-$\underline{C}$-C=O); 137.217 (-$\underline{C}$-OC_2H_5); 146.230 (-$\underline{C}$-$NHCH_2$-); 160.145 (-C-OH); 205.029 (-C=O).

3-(4'-Acetylphenylamino)-1-(2'-hydroxy-5'-methylphenyl)propan-1-one **2d**

IR (KBr, cm^{-1}): 1651 ($\nu_{C=O}$), 3347 (ν_{NH}).

^{1} **H-NMR spectrum** (ppm): 2.242 (s, 3H, Ar-CH_3); 2.457 (s, 3H, -$COCH_3$); 3.277 (t, 2H, J=6.2 Hz, -$COCH_2$-); 3.638 (t, 2H, J=6.2 Hz, -C$\underline{H}_2$NHAr); 4.748 (s, 1H, -NHAr); 6.572-7.803 (m, 7H, aromatic protons); 11.938 (s, 1H, Ar-OH).

^{13} **C-NMR spectrum** (ppm): 20.396 (Ar-CH_3); 25.911 (-CO$\underline{C}H_3$); 37.047 and 37.684 (-CO$\underline{C}H_2\underline{C}H_2$NHAr); 111.336, 118.239, 129.312, 129.409, 130.778, 137.429, 137.757 (aromatic CH); 118.808 (-$\underline{C}$-CH_3); 126.750 (-$\underline{C}$-$COCH_3$); 128.172 (-$\underline{C}$-$COCH_2$-); 151.468 (-$\underline{C}$-$NHCH_2$-); 160.210 (-C-OH); 196.222 (-$\underline{C}OCH_3$); 204.476 (-$\underline{C}OCH_2$-).

1-(2'-Hydroxy-5'-methylphenyl)-3-(3'-methoxyphenylamino)propan-1-one **2e**

IR (KBr, cm^{-1}): 1653 ($\nu_{C=O}$), 3417 (ν_{NH}).

^{1} **H-NMR spectrum** (ppm): 2.267 (s, 3H Ar-CH_3); 3.262 (t, 2H, J=6.2 Hz, -$COCH_2$-); 3.584 (t, 2H, J=6.2 Hz, -C$\underline{H}_2$NHAr); 3.759 (s, 3H, -OCH_3); 6.182-7.460 (m, 7H, aromatic protons); 12.033 (s, 1H, Ar-OH).

^{13} **C-NMR spectrum** (ppm): 20.415 (Ar-CH_3); 37.240 and 38.465 (-CO$\underline{C}H_2$-$\underline{C}H_2$NHAr); 55.025 (-OCH_3); 98.911, 102.639, 106.034, 118.201, 129.583, 130.065, 137.590 (aromatic CH); 118.960 (-$\underline{C}$-CH_3); 128.066 (-$\underline{C}$-CO-); 148.816 (-$\underline{C}$-$NHCH_2$-); 160.240 (-C-OH); 160.859 (-$\underline{C}$-OCH_3); 205.094 (-C=O).

3-(4'-Ethoxyphenylamino)-1-(2'-hydroxy-5'-methylphenyl))propan-1-one **2f**

IR (KBr, cm^{-1}): 1652 ($\nu_{C=O}$), 3397 (ν_{NH}).

^{1} **H-NMR spectrum** (ppm): 1.359 (t, 3H, J=7 Hz, -CH_2C$\underline{H}_3$); 2.264 (s, 3H, Ar-CH_3); 3.243 (t, 2H, J=6.2 Hz, -$COCH_2$); 3.537 (t, 2H, J=6.2 Hz, -C$\underline{H}_2$NHAr); 3.941 (q, 2H, J=7 Hz, -OC$\underline{H}_2$$CH_3$); 6.584-7.457 (m, 7H, aromatic protons); 12.049 (s, 1H, Ar-OH).

^{13} **C-NMR spectrum** (ppm): 14.806 (-$CH_2\underline{C}H_3$); 20.298 (Ar-CH_3); 37.195 and 39.542 (-CO$\underline{C}H_2$-

$\underline{C}H_2NHAr$); 63.858 (-O$\underline{C}H_2CH_3$); 114.325, 114.469, 115.630, 115.792, 118.068, 129.443, 137.427 (aromatic CH); 118.831 (-$\underline{C}$-CH_3); 127.895 (-$\underline{C}$-CO-); 151.452 (-$\underline{C}$-$NHCH_2$-); 160.123 (-C-OH); 205.132 (-C=O).

3-(3'-Chlorophenylamino)-1-(2'-hydroxy-5'-methylphenyl)propan-1-one **2g**

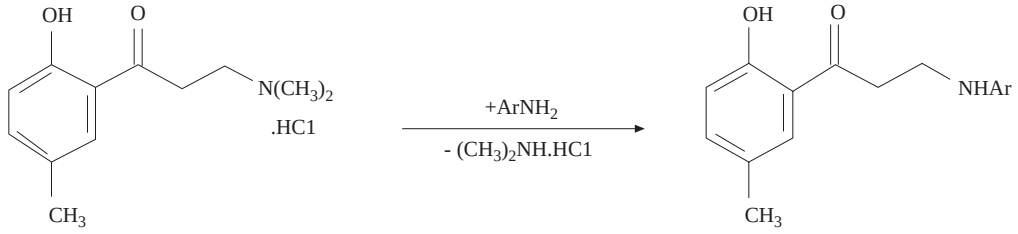
IR (KBr, cm^{-1}): 1648 ($\nu_{C=O}$), 3396 (ν_{NH}).

^{1} **H-NMR spectrum** (ppm): 2.276 (s, 3H, Ar-CH_3); 3.244 (t, 2H, J=6.2 Hz, -$COCH_2$-); 3.554 (t, 2H, J=6 Hz, -$C\underline{H}_2NHAr$); 4.173 (s, 1H, -NHAr), 6.462-7.450 (m, 7H, aromatic protons), 11.998 (s, 1H, Ar-OH).

^{13} **C-NMR spectrum** (ppm): 20.408 (Ar-CH_3); 37.013 and 38.211 (-CO$\underline{C}H_2$-$\underline{C}H_2NHAr$); 111.253, 112.258, 117.306, 118.205, 129.485, 130.236, 137.685 (aromatic CH); 118.850 (-$\underline{C}$-CH_3); 128.131 (-$\underline{C}$-CO-); 135.011 (-C-Cl); 148.600 (-$\underline{C}$-$NHCH_2$-); 160.206 (-C-OH); 204.787 (-C=O).

Results and Discussion

The replacement of the dimethylamine moiety in the hydrochloride of the Mannich bases derived from 2-hydroxy-5-methylacetophenone by arylamines is illustrated in Figure 1.



1 **2**

2a : Ar=2-bromophenyl

2b : Ar=2-methoxyphenyl

2c : Ar=2-ethoxyphenyl

2d : Ar=4-acetylphenyl

2e : Ar=3-methoxyphenyl

2f : Ar=4-ethoxyphenyl

2g : Ar=3-chlorophenyl

The reaction was conducted in an ethanol-water mixture under reflux. Besides favouring the elimination of the easily leaving dimethylamino group, the mixture assures the complete dissolution of both reactants and the comfortable separation of the resulting arylamine Mannich bases, which are insoluble or soluble to a small extent in such a mixture. Refluxing for an hour provided good yields of the desired products, although a shorter reaction time (30 min) was found to give satisfactory results in the case of **2d**. The same product required a larger volume of the solvents' mixture to prevent bumping due to the massive separation that occurred just after refluxing had begun.

The amine exchange products separate from the reaction mixture either as an emulsion or as a solid product. It was noticed that product separation often takes place before refluxing begins or soon after, but heating was prolonged to allow the reaction to finish. The yields of the raw products were always higher than 90%, but considerable loss was incurred in recrystallization, as can be seen from the yields reported in Table 1. In spite of this minor inconvenience, the method still offers satisfactory results. The pure arylamine Mannich bases are yellowish substances that are soluble in acetone, chloroform, diethyl ether or dimethylsulfoxide, slightly soluble in alkali and cold ethanol and insoluble in water. All the reported compounds gave correct elemental analysis results. Products **2a, 2b** and **2c** arising from *ortho*-substituted arylamines tend to form

well-defined crystals. Old samples exhibit lower melting points than those determined soon after purification, and their NMR spectra also show that some decomposition occurred with time.

In the products' IR spectra, the carbonyl group in the arylamine Mannich bases gave an intense sharp absorption band at about 1650 cm^{-1}, the formation of a hydrogen bonding between this group and the adjacent phenolic one being responsible for the low absorption frequency. A single medium to intense sharp absorption band, attributed to N-H bond vibration, was identified in the 3350-3450 cm^{-1} region. The phenolic group produced a broad absorption band at values higher than 3500 cm^{-1}.

The common structural features of the substituted propiophenone moiety introduced in the newly synthesised arylamine Mannich bases by the initial dimethylamine Mannich base contributed to the facile and sure assignment of some signals in the NMR spectra of the former substances. The protons from the methyl group grafted to the aromatic ring provides an intense peak at δ 2.25-2.3 ppm whereas the protons of the two methylenic groups neighbouring the carbonyl and the secondary amino group give two distinct triplets, at δ 3.25-3.3 ppm and 3.55-3.65 ppm respectively. The signal at about 12 ppm was attributed to the phenolic proton, thus confirming its involvement in a hydrogen bond with the carbonyl group. The signals in the aromatic region of the spectra, difficult to ascribe to a particular proton because of their mingling, are presented as a multiplet; however, their number always agreed with the compound's structure.

^{13}C-NMR spectra were also registered and a precise assignment was intended for each signal. Again, the resemblance between the compounds' structure was exploited to assure an accurate designation for the signals provided by the carbon atoms from the substituted propiophenone remainder.

The investigated amine exchange reaction furnished the desired products, and no anomalies (such as arylamine C-alkylation) were noticed. The reaction's smoothness as well as the lack of by-products recommends this type of reaction for synthesising secondary arylamine Mannich bases.

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