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N-ALKYLATION OF PYRAZOLES WITH MANNICH BASES DERIVED FROM *ortho*-HYDROXYACETOPHENONES*

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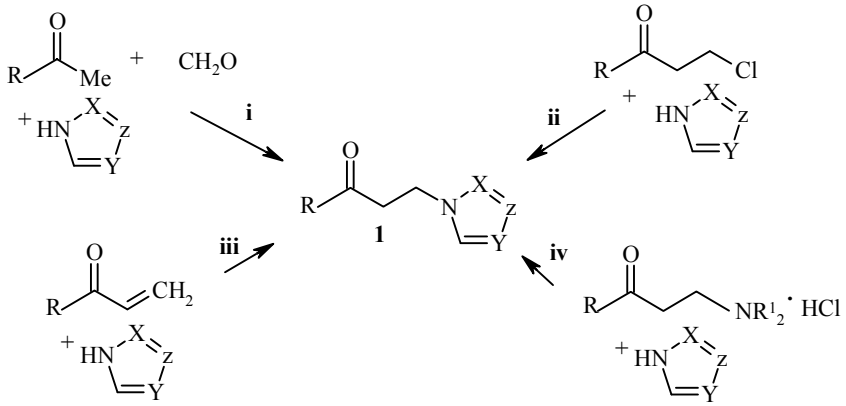
The involvement of Mannich bases derived from ortho-hydroxyacetophenones in amine-exchange reactions with pyrazole and methyl- and/or halogen-substituted pyrazoles was studied. The corresponding β-(pyrazol-1-yl)ethyl ketones resulted in excellent yield and were characterized by elemental analysis, IR, and ^{1}H and ^{13}C NMR spectroscopy.

Keywords: Mannich bases, pyrazole N-alkylation, *ortho*-hydroxyacetophenones.

It is well known that NH-heterocycles act both as substrates and amine components in Mannich reaction [2, 3]. The direct aminomethylation of ketones using formaldehyde and NH-azoles (pathway **i** in Scheme 1) has been reported only scarcely [4, 5]. Other more efficient procedures have been preferred to produce 2-(1-azolyl)ethyl ketones **1,** namely nucleophilic substitution of β-chloro ketones (pathway **ii**) [6, 7], addition to the activated carbon-carbon double bond in α,β-unsaturated ketones (pathway **iii)** [8, 9], and, finally, the amine exchange reaction between a dialkylamine Mannich base and a NH-azole (pathway **iv**) [10].

Scheme 1



* Communication 10 in the series "Synthesis and Reactivity of Mannich Bases"; for communication 9, see [1].

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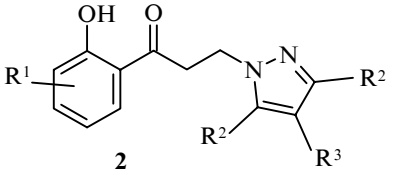
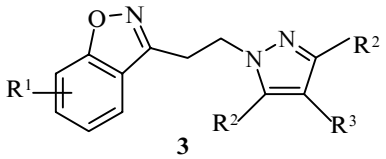
In contrast to imidazole [11, 12] and 1,2,4-triazole [13] derivatives, which are frequently used in the synthesis of antifungal Mannich bases **1a** (X = CH, Z = N, Y = CH) and **1b** (X = CH, Z = N, Y = N) containing an azole as the amine moiety [14], little is known about 2-(l-pyrazolyl)ethyl ketones **1c** (X = N, Z = CH, Y = CH). The present work is devoted to the preparation of some Mannich bases by replacing the easily leaving aliphatic amine residue in β-amino ketones with several N-unsubstituted pyrazoles. The above-mentioned β-amino ketones employed in the N-alkylation of pyrazoles resulted from the direct aminomethylation of *ortho*-hydroxyacetophenones [15, 16]. The resulting pyrazole-containing Mannich bases **2** are valuable intermediates for the synthesis [17] of potentially biologically active 1,2-benzisoxazoles **3**.



2

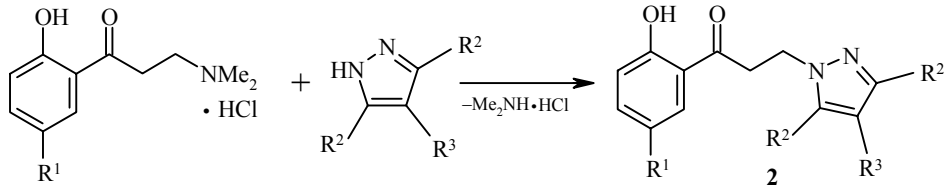


3

A typical amine exchange procedure involves treatment of molar amounts of a Mannich base hydrochloride with an equimolar amount of pyrazole or its C-substituted derivative (ethanol–water 1:1 as the solvent, 1 h) to give the desired products in good to excellent yields. This method, when compared to others, offers the advantage of a simple separation [11] and the use of environmentally friendly solvents [18]. Excess of pyrazole has not been found to significantly improve the yield; on the contrary, in some cases, the separation of the unreacted pyrazole from the reaction mixture together with the target amino ketone **3** hinders the latter's crystallization and renders its purification more difficult. Scheme 2 presents the N-alkylated pyrazoles obtained from Mannich bases of two *ortho*-hydroxyacetophenones. Table 1 summarizes some characteristics for the pyrazole-containing Mannich bases **2a-h**.

From a mechanistic point of view, by using pyrazole as nucleophile, the reaction probably involves elimination of the dialkylamino group followed by a Michael addition or proceeds *via* a nucleophilic substitution pattern.

Scheme 2



2 a–d R^1 = H, **e–h** R^1 = Me; **a, b, e** R^2 = H, **c, d, f–h** R^2 = Me;
a R^3 = H, **b, d, e, g** R^3 = I, **c, f** R^3 = Cl, **h** R^3 = NO_2

The IR spectra of amino ketones **2** exhibit a characteristic sharp absorption band at approximately 1650 cm^{-1} (C=O in aromatic *ortho*-hydroxy aldehydes and ketones) and a wide band at about 3200 cm^{-1} (phenolic hydroxyl).

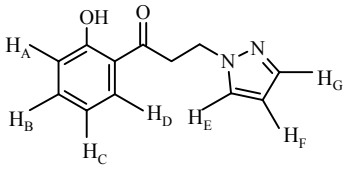
In the ^{1}H NMR spectra (Table 2) the triplets at about 3.6 and 4.4-4.6 ppm have been attributed to methylene protons neighboring the carbonyl group and the pyrazole moiety. The phenolic hydrogen atom gives a broad peak above 12 ppm, showing its involvement in an intramolecular hydrogen bonding. Heterocyclic methyl groups, whenever present, appear as singlets near 2 ppm; note the decrease in the chemical shift for protons in methyl groups attached to the pyrazole ring in compounds **2** compared to those for the corresponding N-unsubstituted 3,5-dimethylpyrazole [19]. The correct assignment for the aromatic protons in most compounds **2** was attempted.

TABLE 1. Characteristics of the Synthesized N-Alkylated Pyrazoles **2**

Compound	Empirical formula	Weight	Found N, % / Calculated N, %	mp, °C	IR, $\nu_{C=O}$, cm^{-1}	Yield, %
2a	$C_{12}H_{12}N_2O_2$	216	13.09 / 12.96	83-84	1655	75
2b	$C_{12}H_{11}IN_2O_2$	342	8.02 / 8.18	105-106	1648	77
2c	$C_{14}H_{15}ClN_2O_2$	278.5	10.19 / 10.05	122-123	1649	86
2d	$C_{14}H_{15}IN_2O_2$	323	8.75 / 8.66	153-154	1640	94
2e	$C_{13}H_{13}IN_2O_2$	356	7.97 / 7.86	124-125	1648	78
2f	$C_{15}H_{17}ClN_2O_2$	292.5	9.75 / 9.57	123-125	1655	96
2g	$C_{15}H_{17}IN_2O_2$	384	7.35 / 7.29	128-129	1650	78
2h	$C_{15}H_{17}N_3O_4$	303	13.98 / 13.86	179-181	1650	41

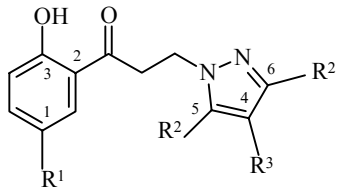
Based on our previous reports on the chemistry of Mannich bases derived from *ortho*-hydroxyacetophenones [15, 16, 20, 21], the assignment of each signal in the ^{13}C NMR spectra (Table 3) of compounds **2** was accurately established. Methylene carbon atoms bridging the two aromatic rings gave signals

TABLE 2. ^1H NMR Spectra of N-Alkylated Pyrazoles **2**



Compound	^1H NMR spectrum, δ, ppm, (*J*, Hz)
2a	3.62 (t, 2H, *J* = 6.8, –COCH–); 4.59 (t, 2H, *J* = 6.6, –CH_2N<); 6.21 (t, 1H, *J* = 2, H_F); 6.85-6.90 (m, 1H, H_A); 6.95-6.99 (m, 1H, H_c); 7.43-7.47 (m, 1H, H_B); 7.49 (d, 1H, *J* = 2, H_E); 7.51 (d, 1H, *J* = 2, H_G); 7.70 (dd, 1H, $J_{1,3}$ = 1.6, $J_{1,2}$ = 8.1, H_D); 12.03 (s, 1H, Ar–OH)
2b	3.56 (t, 2H, *J* = 6.4, –$COCH_2$–); 4.54 (t, 2H, *J* = 6.4, –CH_2N<); 6.82-6.95 (m, 2H); 7.41-7.52 (m, 3H); 7.63–7.65 (m, 1H); 11.93 (s, 1H, ArOH)
2c	2.18 (s, 3H, –CH_3); 2.29 (s, 3H, –CH_3); 3.59 (t, 2H, *J* = 6.6,–$COCH_2$–); 4.37 (t, 2H, *J* = 6.6, –CH_2N<); 6.88–6.91 (m, 1H, H_A); 6.95-6.99 (m, 1H, H_C); 7.44-7.50 (m, 1H, H_B); 7.72 (dd, 1H, $J_{1,3}$ = 1.8, $J_{1,2}$ = 8.1, H_D); 12.01 (s, 1H, Ar–OH)
2d	2.16 (s, 3H, –CH_3); 2.31 (s, 3H, –CH_3); 3.56 (t, 2H, *J* = 6.6, –$COCH_2$–); 4.41 (t, 2H, *J* = 6.6, –CH_2N<); 6.80–6.84 (m, 1H, H_A); 6.88–6.95 (m, 1H, H_C); 7.39-7.47 (m, 1H, H_B); 7.65–7.70 (m, 1H, H_D); 11.97(s, 1H, ArOH)
2e	2.26 (s, 3H, –CH_3); 3.57 (t, 2H, *J* = 6.4, –$COCH_2$–); 4.55 (t, 2H, *J* = 6.4, –CH_2N<); 6.86 (d, 1H, *J* = 8.4, H_A); 7.26 (d, 1H, *J* = 8.4, H_B); 7.43 (s, 1H, H_G); 7.48 (s, 1H, H_E); 7.54 (s, 1H, H_D); 11.80 (s, 1H, Ar–OH)
2f	2.18 (s, 3H, –CH_3); 2.27 (s, 6H, –CH_3); 3.57 (t, 2H, *J* = 6.6, –$COCH_2$–); 4.37 (t, 2H, *J* = 6.6, –CH_2N<); 6.86 (d, 1H, *J* = 8.5, H_A); 7.27 (dd, 1H, $J_{1,3}$ = 2, $J_{1,2}$ = 8.6, H_B); 7.46 (d, 1H, $J_{1,3}$ = 1.7, H_D); 11.84 (s, 1H, Ar–OH)
2g	2.18 (s, 3H, –CH_3); 2.25 (s, 3H, –CH_3); 2.30 (s, 3H, –CH_3); 3.54 (t, 2H, *J* = 6.7, –$COCH_2$–); 4.42 (t, 2H, *J* = 6.6,–CH_2Ar); 6.85 (d, 1H, *J* = 8.6, H_A); 7.24 (s, 1H, H_B); 7.43 (d, 1H, $J_{1,3}$ = 1.5, H_D); 11.80 (s, 1H, Ar–OH)
2h	2.31 (s, 3H, –CH_3); 2.49 (s, 3H, –CH_3); 2.73 (s, 3H, –CH_3); 3.66 (t, 2H, *J* = 6.2, –$COCH_2$–); 4.43 (t, 2H, *J* = 6.2, –CH_2N<); 6.89 (d, 1H, *J* = 8, H_A); 7.31 (d, 1H, $J_{1,2}$ = 8, H_B); 7.49 (s, 1H, H_D); 11.73 (s, 1H, Ar–OH)

TABLE 3. ^{13}C NMR Spectra of Pyrazole-containing Mannich Bases **2**



Compound	Ar–CH_3	–CO$\underline{C}H_2\underline{C}H_2N$<	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C=O	Heterocycl. CH_3	Other aromatic carbon atoms
2a	—	38.42; 45.19	129.80	118.54	162.36	105.40	130.07	139.75	203.24	— —	119.13; 136.74
2b	—	38.54; 46.92	130.11	119.01	162.76	56.30	135.01	145.13	203.12	— —	119.45; 119.60; 137.27
2c	—	37.93; 43.54	129.89	118.55	162.36	107.48	135.77	144.89	203.24	9.36; 11.34	119.13; 136.76
2d	—	38.01; 43.83	129.79	118.44	162.23	62.53	140.80	149.64	203.11	11.93; 13.98	119.03; 136.66
2e	20.46	38.10; 46.54	128.28	118.62	160.20	55.85	134.55	144.63	202.52	— —	118.26; 129.34; 137.89
2f	20.45	37.97; 43.69	128.27	118.82	160.27	107.48	135.82	144.85	203.16	9.34; 11.34	118.23; 129.60; 137.83
2g	20.39	38.06; 43.98	128.15	118.69	160.13	62.50	140.82	149.62	203.03	11.90; 13.99	118.12; 129.49; 137.73
2h	20.46	37.08; 43.27	128.38	118.52	160.26	124.77	140.88	146.48	202.26	11.54; 14.20	118.33; 129.34; 138.06

at about 37-38 and 44-47 ppm. Aromatic carbon atoms linked to hydroxyl and carbonyl groups presented peaks at about 160 and above 200 ppm, respectively. In the series of Mannich bases **2f-h** derived from 2-hydroxy-5-methylacetophenone and variously 4-substituted 3,5-dimethylpyrazoles we note the modification of the δ value for the C-4 atom in the pyrazole ring with the substituent.

EXPERIMENTAL

The melting points were taken on a Büchi 540 B apparatus and are uncorrected, IR spectra were determined on a Specord M80 (Carl Zeiss, Jena) spectrophotometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian INOVA 300 instrument. All chemical shifts are reported in ppm downfield from tetramethylsilane.

4-Chloro-3,5-dimethylpyrazole [22], 4-iodo-3,5-dimethylpyrazole [23], and 3,5-dimethyl-4-nitropyrazole [23] were prepared by literature methods. The required Mannich bases were obtained as described [15, 16].

1-(2-Hydroxyphenyl)-3-(pyrazol-1-yl)propan-1-one (2a). 3-Dimethylamino-1-(2-hydroxyphenyl)propan-1-one hydrochloride [16] (2.295 g, 10 mmol) and pyrazole (0.68 g, 10 mmol) were refluxed in 12 ml 1:1 (v/v) ethanol–water mixture for 1 h. The oily reaction product crystallized on cooling. The solid was filtered off, washed with water, and recrystallized from ethanol. All other N-alkylated pyrazoles **2** were prepared in a similar manner.

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