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ARTICLE

Synthesis and Structural Elucidation of 4-Hydroxy-3-methoxy-5-aminomethylbenzaldehydes

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ABSTRACT

Aminoalkylation of vanillin (4-hydroxy-3-methoxybenzaldehyde) was achieved by reactions of vanillin with formaldehyde and suitable amine in acetonitrile. The products aminoalkylated vanillin compounds **1-5** were purified by column and thin layer chromatography and identified by spectroscopic methods *viz.* UV, IR, NMR and mass spectrometry.

KEYWORDS

Vanillin, Aminoalkylation, Formaldehyde, Acetonitrile.

INTRODUCTION

Mannich bases are important synthetic products used in different fields of applied sciences and are known for their biological potential. Mannich bases are used as anticonvulsant [1,2], analgesic [3], cytotoxic [4-7], antimalarial [8], antibacterial [9], antimicrobial [10] and anticancer activities [11,12]. Chalcones exhibit diverse pharmacological activities, including anti-inflammatory [13,14], antimitotic [15], antituberculosis [16], antifungal [17], antimalarial [18,19] properties.

Vanillin exhibits interesting pharmacological activities antifungal and antibacterial activity [20-22], therefore Mannich bases and vanillin in one molecule probably give potential pharmacological activities.

EXPERIMENTAL

The chemicals and reagents *viz.*, formaldehyde solution 37 % (Sigma, USA), morpholine 99 %, piperidine (Sigma-Aldrich, USA), pyrrolone (Fluka, Analytical, Germany), 1-methylpiperazine 99 % (Fluka, Sweden), N-ethylpiperazine 98 %, piperazine 99 %, vanillin 99 % (Aldrich, USA), dimethylamine solution pure 60 % aqueous solution (Kock-Light Laboratories Ltd., England) and acetonitrile (HiPerSolv for HPLC, England) were procured and used as such without further purification.

IR spectroscopy was carried out using Spectrum BX instrument model L1050033, UV/visible spectroscopy was carried out using BECKMAN COULTER instrument model DU 800 Spectrophotometer. NMR spectroscopy was carried out using procker instrument model AVANCE II 600 and using

Asian Journal of Organic & Medicinal Chemistry

Volume: 3

Year: 2018

Issue: 2

Month: April-June

pp: 50-53

DOI: <https://doi.org/10.14233/ajomc.2018.AJOMC-P124>

Received: 18 May 2018

Accepted: 21 June 2018

Published: 27 June 2018

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procker instrumen AVANCE II 300 and MS spectroscopy carried out using MDS SCIEX instrument model API 2000 LC/ MS/ MS System.

Synthesis of 4-hydroxy-3-methoxy-5-pyrrolidinomethylbenzaldehyde (1): Formaldehyde (0.03 mol) was added dropwise to a mixture of vanillin (0.03 mol) and pyrrolidine (0.03 mol) in 20 mL of dioxane. The reaction mixture was stirred at room temperature for 4 h and left overnight. The solvent was removed under vacuum and the product was obtained. Yield: 74 %, m.p. 125-126 °C. The UV spectrum λ_{\max} (ethanol) 262, 308 and 380 nm. IR (ν_{\max} , cm^{-1} , KBr): 869, 1139, 1272, 1438, 1483, 1593, 1652, 2696, 2808 and 2956. $^1\text{H NMR}$ (acetone- d_6): δ 1.90, 1.75, 3.90, 3.95, 7.30, 7.40 and 9.75 ppm. $^{13}\text{C NMR}$ (acetone- d_6): δ 23.5, 53.3, 55.9, 57.9, 109.7, 121.5, 125, 127.7, 148.5, 154.7, 190.8 ppm.

Synthesis of 4-Hydroxy-3-methoxy-5-piperidinomethylbenzaldehyde (2): Formaldehyde (0.03 mol) was added dropwise to a mixture of vanillin (0.03 mol) and piperidine (0.03 mol) in 20 mL of dioxane. The reaction mixture was stirred at room temperature for 4 h and left overnight. The solvent was removed under vacuum and the product was obtained, recrystallized with *n*-hexane yielded the above mentioned compound as red-brown crystal. Yield: 70 %, m.p. 128-130 °C. The UV spectrum λ_{\max} (ethanol) 254, 316 nm. IR (ν_{\max} , cm^{-1} , KBr): 867, 1143, 1276, 1473, 1519, 1595, 1654, 2694, 2808 and 2943. $^1\text{H NMR}$ (acetone- d_6): δ 1.63, 1.77, 2.93, 3.86, 4.04, 7.30, 7.32, 9.57 ppm. $^{13}\text{C NMR}$ (acetone- d_6): δ 22.3, 24.1, 52.4, 54.4, 59.4, 109.0, 118, 124, 128.4, 150, 161.8, 190.6 ppm.

Synthesis of 4-hydroxy-3-methoxy-5-morpholinomethylbenzaldehyde (3): Formaldehyde (1.6 g, 0.03 mol) was added dropwise to a mixture of vanillin (0.03 mol) and morpholine (0.03 mol) in 20 mL of dioxane. The reaction mixture was stirred at room temperature for 4 h and left overnight. The solvent was removed under vacuum and the obtained product was recrystallized with *n*-hexane, yielded the above mentioned compound as white crystals. Yield: 75 %, m.p. 104-106 °C. The UV spectrum λ_{\max} (ethanol) 262 and 306 nm. IR (ν_{\max} , cm^{-1} , KBr): 869, 1122, 1274, 1471, 1519, 1593, 1649, 2742, 2829, 2864 and 2945. $^1\text{H NMR}$ (acetone- d_6): δ 2.63, 3.77, 3.82, 3.94, 7.18, 7.35, 9.78 ppm. $^{13}\text{C NMR}$ (CDCl_3): δ 52.7, 56.0, 61.0, 66.0, 109.0, 120.3, 125.6, 128.8, 148.6, 153.5 and 190.6 ppm.

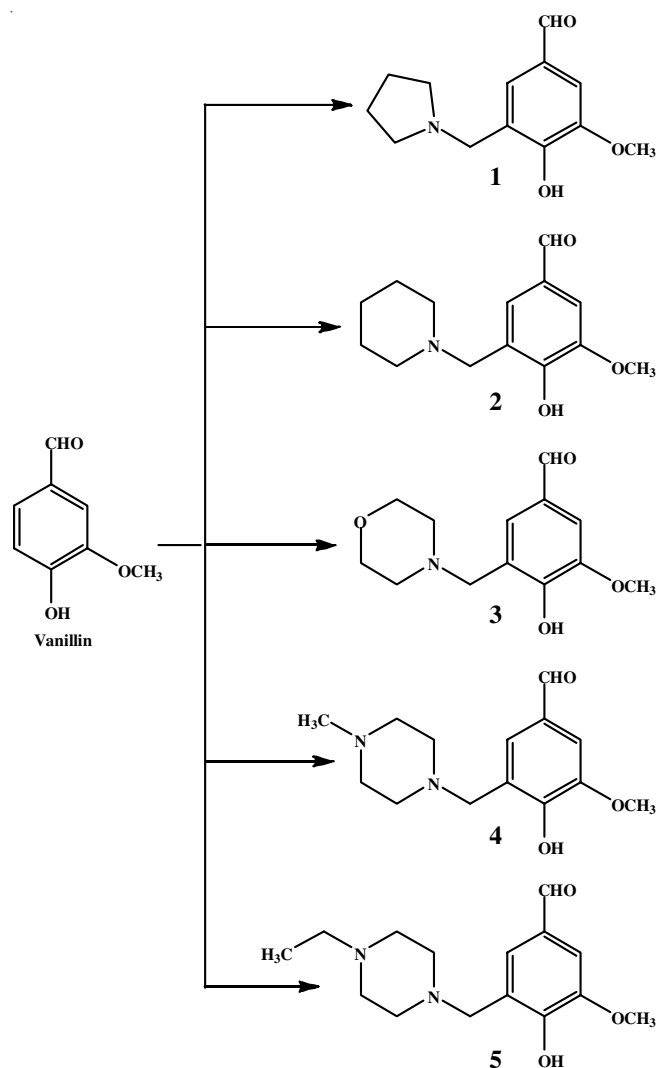
Synthesis of 4-hydroxy-3-methoxy-5-N-methylpiperazinomethylbenzaldehyde (4): Formaldehyde (1.6 g, 0.03 mol) was added dropwise to a mixture of vanillin (0.03 mol) and N-methylpiperazine (0.03 mol) in 20 mL of dioxane. The reaction mixture was stirred at room temperature for 4 hours and left overnight. The solvent was removed under vacuum and the obtained product was recrystallized with *n*-hexane, yielded the above mentioned compound as white crystals. Yield: 55 %, m.p. 119-120 °C. The UV spectrum λ_{\max} (ethanol) 264 and 318 nm. IR (ν_{\max} , cm^{-1} , KBr): 856, 1141, 1280, 1461, 1492, 1587, 1676, 2700, 2740, 2813 and 2941. $^1\text{H NMR}$ (acetone- d_6): δ 2.33, 2.41, 2.63, 3.82, 3.93, 7.16, 7.34, 9.77. $^{13}\text{C NMR}$ (CDCl_3): δ 52.3, 52.4, 55.9, 60.7, 109.6, 120.7, 125.5, 128.2, 148.6, 153.6, 190.6.

Synthesis of 5-N-ethylpiperazinomethyl-4-hydroxy-3-methoxybenzaldehyde (5): Formaldehyde (0.03 mol) was added dropwise to a mixture of vanillin (0.03 mol) and N-ethylpiperazine (0.03 mol) in 20 mL of dioxane. The reaction

mixture was stirred at room temperature for 4 h and left overnight. The solvent was removed under vacuum and the obtained product was recrystallized with *n*-hexane, yielded the above mentioned compound as white crystals. Yield: 50 %, m.p. 122-123 °C. The UV spectrum λ_{\max} (ethanol) 260, 315, 365 and 375 nm. IR (ν_{\max} , cm^{-1} , KBr): 862, 1143, 1272, 1442, 1490, 1595, 1664, 2700, 2745, 2840 and 2960 cm^{-1} . $^1\text{H NMR}$ (acetone- d_6): δ 1.07, 2.42, 2.60, 2.64, 3.81, 3.93, 7.16, 7.33, 9.76. $^{13}\text{C NMR}$ (CDCl_3): δ 52.3, 52.4, 55.9, 60.7, 109.6, 120.7, 125.5, 128.2, 148.6, 154.0, 190.6.







RESULTS AND DISCUSSION




Five new compounds of vanillin with Mannich side chains were synthesized and illustrated in **Scheme-I**.




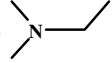
Scheme-I: Mannich bases and final products of 4-hydroxy-3-methoxybenzaldehyde






Compound **1-5** showed UV spectrum at λ_{\max} (ethanol) ranged between 264-254 and 318-306, which is consistent with absorption pattern of enolic chromophore (210 and 270 nm). The extension to 300-318 nm may be due to the presence of an auxochrome (OH) and electron releasing alkyl groups. The IR spectrum of compounds **1-5** showed the peaks at 1143-1122 $\nu(\text{CN})$, 1280-1272 $\nu(\text{C-O})$ and 2700-1649 $\nu(\text{C=O})$.

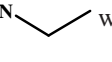
The ^1H NMR spectrum showed signals at δ 1.90 (s, 4H) assigned for the methylene groups of , while the signals at δ 2.60 (s, 4H) characteristic for the methylene group of N. The methoxyl protons resonate at δ 3.90 (s, 3H). The peak at δ 3.95 (s, 2H), was assigned for . The signals at δ 7.30 (d, H, $J_{2,6} = 6\text{Hz}$) and 7.40 (d, H, $J_{2,6} = 6\text{Hz}$) are the characteristic of meta coupled aromatic protons at C-2 and C-6. The aldehydic proton resonate at δ 9.75 (s, 1H). The ^{13}C NMR spectrum of compound **2** showed a pattern characteristic of a C_{13} system. The ^1H NMR spectrum showed a signal at δ 1.62 (2H) characteristic of $-\text{CH}_2-$ of piperidine moiety, the signal centered at δ 1.78 (4H) was assigned for the  protons, while the resonance at δ 2.95 (4H) was assigned for N of piperidine ring. The methoxyl protons resonate at δ 3.8 (s, 3H). The signal at δ 4.04 (s, 2H), is a characteristic of . The signal δ 7.32 (2H, $J_{2,6} = 6\text{Hz}$) is characteristic of the meta coupled aromatic protons at C₂ and C₆. The aldehydic proton gave a singlet at δ 9.75 (s, 1H), this proton resonance at low field due to the electron-withdrawal effect of C=O function and the anisotropic effect of π -electrons of C=O group. ^1H - ^1H cosy NMR demonstrated a diagonal relationship between all proton of piperidine ring. The ^{13}C NMR spectrum of compound **2** showed a pattern characteristic of a C_{14} system. The apt experiment showed 8 carbons in positive (four $-\text{CH}_2-$, four quaternary carbons) and 4 carbons in negative mode ($-\text{CH}_3$, $-\text{CHO}$, $=\text{CH}-$).

The ^1H NMR spectrum showed a peak at δ 1.78 (4H) assigned for the protons N of morpholine, while the other methylene protons of morpholine O resonate at δ 3.77 (4H). The methoxyl protons resonate at δ 3.94 (s, 3H), while the resonance at δ 3.82 (s, 2H) was assigned for . The signals at δ 7.18 (d, H, $J_{2,6} = 6\text{Hz}$) and 7.35 (d, H, $J_{2,6} = 6\text{Hz}$) are characteristic of meta coupled aromatic protons at C₂-H and C₆-H aldehydic proton gave a low field signal at δ 9.78 (s, 1H) due to the electron-withdrawal effect of C=O function and anisotropic effect of π -electrons of the C=O group. ^1H - ^1H cosy NMR showed off a diagonal peak indicating coupling between The ^{13}C NMR spectrum of compound **3** showed a pattern characteristic of C_{13} system.

The ^1H NMR spectrum showed singlet at δ 2.33 (3H) assigned for methyl group due to the electron-withdrawal effect of nitrogen. The signal centered at δ 2.41 was assigned for 8 protons of N-methylpiperazine ring. The signal at δ 3.93 (s, 2H), is characteristic of . The methoxyl protons resonate at δ 3.8 (s, 3H). The double doublet centered at δ 7.16 (H, $J_{2,6} = 6\text{Hz}$) and 7.34 (H, $J_{2,6} = 6\text{Hz}$) is characteristic of meta coupled aromatic protons at C₂-H and C₆-H. The formyl group gave a singlet at δ 9.77 (s, 1H). The ^{13}C NMR spectrum of compound **4** showed a pattern characteristic of C_{14} system.

The apt experiment showed seventh carbons in positive mode (three $-\text{CH}_2-$, four quaternary carbons) and four carbons in negative mode ($-\text{CH}_3$, $-\text{CHO}$, $=\text{CH}-$). ^1H - ^{13}C -HMBC of compound **4** demonstrated long range coupling between protons of methylene group  and C₁, C₅ and C₆ of aromatic system and this furnish evidence for Mannich side chain.

The ^1H NMR spectrum of compound **5** showed triplet at δ 1.07 (t, 3H, $J = 7.4$ Hz) assigned for methyl group of N, while the quartet at δ 2.42 (t, 2H, $J = 7.4$ Hz) is characteristic of methylene of  moiety. The signal at δ 2.60 (m, 4H) was assigned for N-Et while the signal at δ 2.64 (m, 4H) was assigned for N of N-ethylpiperazine moiety. The singlet peak at δ 3.81 (s, 2H), is characteristic of . The methoxyl protons resonate at δ 3.93 (s, 3H). The signals at δ 7.16 (d, H, $J_{2,6} = 6\text{Hz}$) and 7.33 (d, H, $J_{2,6} = 6\text{Hz}$) is characteristic of meta coupled aromatic protons at C₂ and C₆. The aldehyde group gave a singlet at δ 9.76 (s, 1H). The ^{13}C NMR spectrum of compound **5** showed a pattern characteristic of C_{15} system.

The apt experiment of compound **5** showed 7 carbons in positive (four $-\text{CH}_2-$, three quaternary carbons) and 5 carbons in negative mode (two $-\text{CH}_3$, one $-\text{CHO}$, two $=\text{CH}-$). The HMBC of compound **5** demonstrated coupling between protons of methylene group  with carbon 1, 2 and 4 of benzene ring.

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