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Publication details, including instructions for authors and subscription information: <u>http://www.tandfonline.com/loi/gpss20</u>

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To cite this article: A. Mobinikhaledi , N. Foroughifar & M. Fallah (2006) Synthesis of Some N¹-(3-Hydroxy-2-pyridyl)benzamides, Phosphorus, Sulfur, and Silicon and the Related Elements, 181:4, 717-721, DOI: <u>10.1080/10426500500270032</u>

To link to this article: http://dx.doi.org/10.1080/10426500500270032

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Synthesis of Some N¹-(3-Hydroxy-2-pyridyl)benzamides

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Benzoxazoles are of special interest because of having various types of biological properties such as antihistaminic, antihelmintic antifungal and antibacterial activities.^{1–10} Benzamide derivatives, as the possible metabolites of benzoxazoles, show various types of biological activities.^{11,12} Some N-(2-hydroxyphenyl)benzamides, which showed significant activity compared to phenylacetamides and furamides,¹¹ have been synthesized by treating 2-aminophenol with carboxylic acid chlorides under weak basic solution.^{11,12} However, synthesis and especially biological activity of N-(3-hydroxy-2-pyridyl)benzamides were not studied well. Owing to the versatility of benzamides we have extended the reaction of 2-amino-3-pyridinol with different carboxylic acid chlorides in order to preparation of some new benzamide derivatives containing a hydroxypyridyl ring.

Keywords 2-Amino-3-pyridinol; 3-hydroxy-2-pyridyl; benzamide

INTRODUCTION

Benzamide derivatives are of special interest because of biological properties such as antihistaminic, antihelmintic, antifungal, and antibacterial activities.^{1–12} Several article have reported biological activities of some N-(2-hydroxyphenyl) benzamides, phenylacetamides, and furamides. N-(2-hydroxyphenyl)benzamides, which showed significant activity compared to phenylacetamides and a furamides,¹⁰ have been synthesized by treating 2-aminophenol with carboxylic acid chlorides under a weak basic solution. However, the synthesis and especially the biological activity of N-(3-hydroxy-2-pyridyl)benzamides were not studied well. Owing to the versatility of benzamides, we have extended the reaction of 2-amino-3-pyridinol with different carboxylic acid chlorides

Received May 19, 2005; accepted May 24, 2005.

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in order to prepare some new benzamide derivatives containing a hydroxypyridyl ring.

RESULTS AND DISCUSSION

The reaction of carboxylic acids and thionyl chloride in benzene gave the related acid chlorides. A further reaction of the acid chlorides with 2-amino-3-pyridinol afforded N¹-(3-hydroxy-2-pyridyl)benzamides 3(a-i) as shown in Scheme 1.



SCHEME 1

The ¹HNMR spectra of the synthesized compounds are simple and consist of the aromatic protons signals and two OH and NH proton signals. The aromatic protons including pyridine ring protons resonate as a multiple signal at 7.10–8.35 ppm depending on the Ar group. However, the ¹HNMR spectra of **3b**, **3c**, **3d**, and **3f** show a singlet signal in the aliphatic region due to the resonance of the CH₃ or OCH₃ group. On the basis of ¹H NMR spectra, the structures of **3(a-i)** are obtained as a result of the nucleophilic attack on the NH₂ group. In the ¹HNMR spectra of a lower chemical shift as compared to those of the starting material. This is in support of a nucleophilic attack on the NH₂ group.

The IR spectra of 3(a-i) display two absorption bands at 1606–11720 cm⁻¹ and 3200–3502 cm⁻¹, which are assigned to carbonyl and NH groups, respectively, and are in support of the expected reactions.

EXPERIMENTAL

Melting points were determined with an elctrothermal digital melting point apparatus. IR spectra were taken on a Galaxy series FT-IR 5000 spectrophotometer in potassium bromide pellets. ¹H NMR spectra were recorded at 25° C on Bruker 500 MHz spectrometers using Me₄Si (TMS) as an internal standard. Reaction courses and product mixtures were monitored by Thin Layer Chromatography (TLC).

General Procedure for the Synthesis of N¹-(3-Hydroxy-2-pyridyl)benzamides 3(a–i)

Appropriate aromatic carboxylic acid (1 mmol) and thionyl chloride (5 mL) were refluxed for 1–2 h. After the completion of the reaction as monitored by TLC, the reaction mixture was cooled and the excess amount of thionyl chloride evaporated under reduced pressure to give the desired acid chloride. The prepared acid chloride was dissolved in ether (10 mL) and the solution was added dropwise for 1 h to a stirred, ice-cold mixture of 2-amino-3-pyridinol (1 mmol), sodium bicarbonate (1 mmol), diethyl ether (10 mL) and water (10 mL). The mixture was then stirred overnight at r.t. and flittered. The crude product was precipitated out from the filtrate, which recrystallized from a mixture of water and ethanol.

N¹-(3-Hydroxy-2-pyridyl)benzamide (3a)

Yield 40%, m.p. 95–97°C.

IR (KBr): v = 3200, 1630, 1590, 1100 cm⁻¹.

- ¹HNMR (DMSO-d₆): δ = 7.49–7.96 (m, 8H, Ar-H), 11.05 (bs, 1H, OH), 12.95 (bs, 1H, NH).
- Anal. calcd. for $C_{12}H_{10}N_2O_2$: C, 67.2; H, 4.67; N, 13.07%. Found: C, 67.50; H, 4.53; N, 13.01%.

N¹-(3-Hydroxy-2-pyridyl)-2-methylbenzamide (3b)

Yield 50%, m.p. 104–106°C. IR (KBr): $v = 3259, 3159, 2659, 1692, 1575, 1067 \text{ cm}^{-1}$. ¹HNMR (DMSO-d₆): $\delta = 2.49$ (s, 3H, CH₃), 7.28–7.82 (m, 7H) 8.10 (bs, 1H, OH), 8.30 (bs, 1H, NH).

Anal. calcd. for $C_{13}H_{12}N_2O_2$: C, 68.35; H, 5.26; N, 12.27%. Found: C, 68.53; H, 5.03; N, 11.95%.

N¹-(3-Hydroxy-2-pyridyl)-3-methylbenzamide (3c)

Yield 55%, m.p. 120–121°C. IR (KBr): $v = 3502, 2970, 1687, 1589, 1215 \text{ cm}^{-1}$.

- ¹HNMR (DMSO-d₆): $\delta = 2.35$ (s, 3H), 7.35–7.76 (m, 7H, Ar-H), 10.20 (bs, 1H, OH), 12.20 (bs, 1H, NH).
- Anal. calcd. for C_{13} $H_{12}N_2O_2$: C, 68.35; H, 5.26; N, 12.27%. Found: C, 68.45; H, 5.14; N, 12.10%.

N¹-(3-Hydroxy-2-pyridyl)-4-methylbenzamide (3d)

Yield 50%, m.p. 122–123°C.

IR (KBr): $v = 3400, 3202, 1606, 1600, 1070 \text{ cm}^{-1}$.

- ¹HNMR (DMSO-d₆): δ = 2.42 (s, 3H), 7.24–7.47 (m, 7H, Ar-H), 9.98 (bs, 1H, OH), 10.65 (bs, 1H, NH).
- Anal. calcd. for $C_{13}H_{12}$ N_2O_2 : C, 68.35; H, 5.26; N, 12.27%. Found: C, 68.10; H, 5.43; N, 12.44.

N¹-(3-Hydroxy-2-pyridyl)-3-nitrobenzamide (3e)

Yield 60%, m.p. 183–184°C.

IR (KBr): $v = 3300, 3100, 1680, 1630, 1010 \text{ cm}^{-1}$.

- ¹HNMR (DMSO-d₆): δ = 7.23–7.34 (m, 4H, Ar-H), 7.95–8.35 (m, 3H, Ar-H), 10.00 (bs, 1H, OH), 10.95 (bs, 1H, NH).
- Anal. calcd. for $C_{12}H_9N_3O_4$: C, 55.56; H, 3.47; N, 16.20%. Found: C, 55.24; H, 3.10; N, 15.93%.

N¹-(3-Hydroxy-2-pyridyl)-4-methoxybenzamide (3f)

Yield 50%, m.p. 123–125°C.

- IR (KBr): v = 3481, 3174, 2947, 1720, 1606, 1078 cm⁻¹.
- ¹HNMR (DMSO-d₆): δ = 3.80 (s, 3H), 7.10–7.12 (m, 7H, Ar-H), 10.00 (bs, 1H, OH), 10.60 (bs, 1H, NH).
- Anal. calcd. for $C_{13}H_{12}N_2O_3$: C, 63.87; H, 4.91; N, 11.46%. Found: C, 64.15; H, 4.71; N, 11.61%.

N¹-(3-Hydroxy-2-pyridyl)-2-chlorobenzamide (3g)

Yield 40%, m.p. 142–144°C.

IR (KBr): v = 3459, 3359, 1667, 1473, 1051 cm⁻¹.

- ¹HNMR (DMSO-d₆): δ = 7.40–7.79 (m, 7H, Ar-H), 11.20 (bs, 1H, OH), 13.30 (bs, 1H, NH).
- Anal. calcd. for $C_{12}H_9ClN_2O_2$: C, 57.90; H, 3.62; N, 11.26%. Found: C, 57.73; H, 3.40; N, 11.53%.

N¹-(3-Hydroxy-2-pyridyl)-4-chlorobenzamide (3h)

Yield 55%, m.p. 119–120°C. IR (KBr): $v = 3440, 3160, 1720, 1620 \text{ cm}^{-1}$.

- ¹HNMR (DMSO-d₆): δ = 7.5–8.20 (m, 7H, Ar-H), 8.90 (bs, 1H, OH), 10.90 (bs, 1H, NH).
- Anal. calcd. for C₁₂H₉ClN₂O₂: C, 57.90; H, 3.62; N, 11.26%. Found: C, 57.98; H, 3.36; N, 11.49%.

N¹-(3-Hydroxy-2-pyridyl)-4-bromobenzamide (3i)

Yield 40%, m.p. 243–245°C.

- IR (KBr): $v = 3270, 2910, 1690, 1587, 1012 \text{ cm}^{-1}$.
- ¹HNMR (DMSO-d₆): $\delta = 7.71-8.35$ (m, 7H, Ar-H) 11.40 (bs, 1H,OH), 13.40 (bs, 1H, NH).
- Anal. calcd. for C₁₂H₉BrN₂O₂: C, 49.13; H, 3.07; N, 9.55%. Found: C, 49.36; H, 3.19; N, 9.77%.

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