Synthesis of novel 1,2,4-oxadiazole heterocyclic compounds containing 2-\(H\) pyranopyridine-2-one moiety and related compounds

N Vasanth Kumar & Uday C Mashelker
Organic Research Laboratory, SS & LS Patkar College, S V Road, Goregaon (West), Mumbai 400 062, India
E-mail: vknalam@yahoo.com

Received 23 January 2006; accepted (revised) 1 September 2006

7-Hydroxy/Amino-5-methyl-6-(5-substituted-[1,2,4]oxadiazol-3-yl)-2-oxo-2\(H\)-pyrano[2,3-b]pyridine-3-carboxylic acid amides 5a-c and 6a-c have been prepared starting from ethyl 2\(H\)-pyrano[2,3-b]pyridine-3-carboxylate 1 and 2, compounds 1 and 2 are treated with aqueous ammonia solution to afford 2\(H\)-pyrano[2,3-b]pyridine-3-carboxamide 3a-b, which are converted to 6-carboxamidoxime 2\(H\)-pyrano[2,3-b]pyridine-3-carboxamide 4a-b by treating with hydroxyl amine in refluxing ethanol. Carboxamidoximes 4a-b are treated with various acid chlorides to obtain 1,2,4-oxadiazole derivatives 5a-c and 6a-c. Carboxamide 3a is reacted with triethyl orthoformate to give 4-amino-5-methyl pyrano[3',2':5,6]pyrido[2,3-b]pyrimidine-7-carboximde 7. Carboxamidoxime 4a is allowed to react with \(N,N\)-dimethyl formamide dimethyl acetal under reflux to obtain N-(6-carbonyl-4-methyl-7-oxo-1,7-dihydropyrano[2,3-b]pyrazolo[4,3-e]pyridine-3-yl)methanamide 8. These compounds are expected to have better hypertensive activity.

Keywords: 1,2,4-oxadiazole, carboxamide, 2\(H\)-pyrano[2,3-b]pyridine-2-one, anti-hypertensive, hydroxyl amine, tyrosine kinase, cyclocondensation, carboxamidoxime.

IPC: Int.Cl. 8 C07D

1,2,4-Oxadiazole rings occur widely in biologically active compounds such as analgesics, anti-inflammatory agents, antimicrobials, antivirals, pesticides and insecticides. Numerous 1,2,4-oxadiazoles have been suggested as potential agonists for cortical muscarinic benzodiazepine and 5-HT\(_{1D}\) (5-hydroxytryptamine) receptors and as antagonists for 5-HT\(_{2}\), or histamine H\(_3\) receptors. They also inhibit the SH2 domain of tyrosine kinase, monoamine oxidase, human nuchetophil elastase, and human DNA topoisomerases. Keeping in mind the biological significance of 1,2,4-oxadiazole derivatives, the synthesis of some new 1,2,4-oxadiazole containing 2\(H\)-pyranopyridine-2-one derivatives are reported.

Results and Discussion

In the present work, 2\(H\)-pyrano[2,3-b]pyridine-3-carboxylates 1 and 2, which were previously prepared, were used as the key intermediate for further synthesis. Thus, when compound 1 and 2 were treated separately with aqueous ammonia 2\(H\)-pyrano[2,3-b]pyridine-3-carboxamides 3a and 3b were obtained. Compounds 3a and 3b were characterized by its IR and \(^1\)H NMR, the IR showed the disappearance of ester absorption at 1750 observed a new absorption at 1704 and 1706 cm\(^{-1}\) correspond to amide, also the \(^1\)H NMR showed the disappearance of ester protons \(\delta\) 1.22-1.29 (t, 3H, -CH\(_2\)-CH\(_3\)) observed new peak at \(\delta\) 10.42 and 10.85 (D\(_2\)O exchangeable) corresponds amide of 3a and 3b respectively.

The compounds 3a and 3b were reacted with hydroxylamine in absolute ethanol, which afforded 6-carboxamidoxime 2\(H\)-pyrano[2,3-b]pyridine-3-carboxamides 4a and 4b. These carboxamides 4a and 4b were allowed to react with different acid chlorides namely, acetyl chloride, benzoyl chloride and phenyl acetyl chloride to give compounds 5a-c and 6a-c respectively. On the other hand carboxamide 3a was treated with triethyl orthoformate to give 4-amino-5-methyl Pyrano[3",2":5,6]pyrido[2,3-d]pyrimidine-7-carboximde 7 (Schemes I and II). Also the cyclocondensation of carboxamidoximes \(^{19}\)4a with \(N,N\) dimethyl form amide dimethyl acetal to afforded the \(N\)-(6-carbonyl-4-methyl-7-oxo-1,7-dihydropyrano[2,3-b]pyrazolo[4,3-e]pyridine-3-yl)methanamide 8 (Scheme II).

Experimental Section

Melting points were determined on a Buchi 545 melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 1650 spectrometer, \(^1\)H NMR was recorded in DMSO-\(d_6\), using 200 MHz Bruker spectrometer (chemical shifts in \(\delta\), ppm) with TMS as internal standard and mass spectra on a HP-5989A spectrometer. The Analytical Research Department of Lupin Limited (Lupin Research Park) carried out all analytical work. All the organic extracts were dried over sodium sulfate after work-up.
The dry reactions were carried out under nitrogen with magnetic/mechanical stirring. Unless otherwise mentioned all the solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel plates, which were visualized using UV light.

**General procedure for the preparation of 3a,b.**

To the solution of suitable ethyl pyrano [2,3-b] pyridine-3-carboxylate 1 or 2 (0.01 mole) in ethanol (50 mL) was added aqueous ammonia solution (10 mL). This resulting mixture was stirred at room temperature for 7-12 hr. After completion of the reaction the precipitate was collected by filtration, washed with ethanol, and then dried under reduced pressure. The solid so obtained was recrystallized
from ethanol to give compound 3a or b as a white solid.

7-Amino-6-cyano-5-methyl-2-oxo-2H-pyranopyrido-3-carboxamide 3a. m.p. 326-28°C; yield 95%; IR (KBr, cm⁻¹): 3153.2 (-NH₂), 2215.8 (-CN), 1704 (-C=O, lactone), 1663.1 (-C=O, amide); ¹H NMR (200 MHz, DMSO-d₆): 6 2.30 (s, -CH₃), 8.10 (s, 1H, C₂-H), 10.42 (brs, 1H, -CONH₂, exchangeable). Anal. Found: C, 53.88; H, 2.88; N, 17.14. Calcd for C₁₁H₁₁N₅O₄: C, 51.89; H, 3.39; N, 18.61%.

General procedure for the preparation of 4a-b. A mixture of pyrano [2,3-b] pyridine-3-carboxamide (3a or 3b, 0.01 mole) and ethanolic hydroxylamine (6.62 g in 150 mL ethanol) was heated under reflux for 7 hr. After this period, the reaction mixture was concentrated under reduced pressure. The residue was crystallized from ethanol to give 4a or b.

7-Hydroxy-6-cyano-5-methyl-2-oxo-2H-pyranopyrido-3-carboxamide 3b. m.p. 342-44°C; yield 92%; IR (KBr, cm⁻¹): 3426 (-OH), 2221 (-CN), 1706 (-C=O, lactone), 1655 (-C=O, amide); ¹H NMR (200 MHz, DMSO-d₆): 6 2.37 (s, 3H, -CH₃), 8.30 (s, 1H, C₂-H), 10.42 (brs, 1H, -CONH₂, exchangeable). Anal. Found: C, 51.80; H, 2.91; N, 17.22%.

General procedure for the preparation of 5a-c. A mixture of carboxamidine 4 (0.01 mole) and suitable acid chlorides (10 mL) was refluxed for 10-12 hr. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into crushed ice, stirred the reaction mass for 2 hr and the solid formed was collected by filtration, washed with small amounts of water. The obtained crude solid was crystallized from ethanol.

7-Amino-5-methyl-6-(5-methyl-1,2,4-oxadiazolyl-3-yl)-2-oxo-2H-pyranopyrido-3-carboxamide 5a. m.p. 305-07°C; yield 68%; IR (KBr, cm⁻¹): 3488.9 (-NH₂), 1702 (-C=O, lactone), 1641.7 (-C=O, amide); ¹H NMR (200 MHz, DMSO-d₆): 6 1.9 (s, 3H, -CH₃), 2.35 (s, 3H, -CH₃), 8.16 (s, 1H, C₄-H), 11.3 (s, -CONH₂, exchangeable). Anal. Found: C, 51.83; H, 3.68; N, 23.25. Calcd for C₁₅H₁₁N₅O₄: C, 51.89; H, 3.72; N, 23.20%.

7-Amino-5-methyl-6-(5-benzyl-1,2,4-oxadiazolyl-3-yl)-2-oxo-2H-pyranopyrido-3-carboxamide 5b. m.p. 292-94°C; yield 69%; IR (KBr, cm⁻¹): 3452.3 (-NH₂), 1706 (-C=O, lactone), 1682 (-C=O, amide); ¹H NMR (200 MHz, DMSO-d₆): 6 2.39 (s, 3H, -CH₃), 7.45 (m, 3H, Ar), 8.06 (s, 1H, C₄-H), 8.21 (d, 2H, Ar), 10.3 (s, -CONH₂, exchangeable). Anal. Found: C, 59.50; H, 3.61; N, 19.28. Calcd for C₁₅H₁₁N₅O₄: C, 59.61; H, 3.69; N, 19.32%.

7-Amino-5-methyl-6-(5-benzyl-1,2,4-oxadiazolyl-3-yl)-2-oxo-2H-pyranopyrido-3-carboxamide 5c. m.p. 292-94°C; yield 70%; IR (KBr, cm⁻¹): 3326 (-OH), 1700 (-C=O, lactone), 1623 (-C=O, amide); ¹H NMR (200 MHz, DMSO-d₆): 6 2.39 (s, 3H, -CH₃), 8.06 (s, 1H, C₄-H), 10.30 (s, -CONH₂, exchangeable). Anal. Found: C, 51.61; H, 3.69; N, 18.56. Calcd for C₁₅H₁₁N₅O₄: C, 51.69; H, 3.39; N, 18.61%.

7-Hydroxy-5-methyl-6-(5-benzyl-1,2,4-oxadiazolyl-3-yl)-2-oxo-2H-pyranopyrido-3-carboxamide 6a. m.p. 285-87°C; yield 70%; IR (KBr, cm⁻¹): 3415 (-OH), 1708 (-C=O, lactone), 1644 (-C=O, amide); ¹H NMR (200 MHz, DMSO-d₆): 6 2.39 (s, 3H, -CH₃), 2.60 (s, 3H, -CH₃), 8.06 (s, 1H, C₄-H), 10.30 (s, -CONH₂, exchangeable). Anal. Found: C, 51.66; H, 3.33; N, 18.54. Calcd for C₁₅H₁₅N₅O₄: C, 51.69; H, 3.39; N, 18.61%.

General procedure for the preparation of 7a-c. A mixture of carboxamidine 4 (0.01 mole) and suitable acid chlorides (10 mL) was refluxed for 10-12 hr. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into crushed ice, stirred the reaction mass for 2 hr and the solid formed was collected by filtration, washed with small amounts of water. The obtained crude solid was crystallized from ethanol.

7-Amino-5-methyl-6-(5-benzyl-1,2,4-oxadiazolyl-3-yl)-2-oxo-2H-pyranopyrido-3-carboxamide 6b. m.p. 292-94°C; yield 72%; IR (KBr, cm⁻¹): 3432 (-OH), 1710 (-C=O, lactone), 1620 (-C=O, amide); ¹H NMR (200 MHz, DMSO-d₆): 6 2.39 (s, 3H, -CH₃), 7.45 (m, 3H, Ar), 8.06 (s, 1H, C₄-H), 8.21 (d, 2H, Ar), 10.3 (s, -CONH₂, exchangeable). Anal. Found: C, 59.34; H, 3.32; N, 15.38. Calcd for C₁₅H₁₅N₅O₄: C, 59.41; H, 3.38; N, 15.42%.

7-Hydroxy-5-methyl-6-(5-benzyl-1,2,4-oxadiazolyl-3-yl)-2-oxo-2H-pyranopyrido-3-carboxamidine 6c. m.p. 285-87°C; yield 70%; IR (KBr, cm⁻¹): 3415 (-OH), 1708 (-C=O, lactone), 1644 (-C=O, amide); ¹H NMR (200 MHz, DMSO-d₆): 6 2.39 (s, 3H, -CH₃), 8.06 (s, 1H, C₄-H), 10.30 (s, -CONH₂, exchangeable). Anal. Found: C, 51.66; H, 3.33; N, 18.54. Calcd for C₁₅H₁₅N₅O₄: C, 51.69; H, 3.39; N, 18.61%.
Preparation of 8-oxo-8H-pyrido[3",2":5,6]pyrido[2,3-d]pyrimidine-7-carboximide 7. A mixture of 7-Amino-6-cyano-5-methyl-2-oxo-2H-pyran [2,3-b] pyridine-3-carboxamide 3a, (10.0 g, 0.04 mole) and triethyl orthoformate (100 mL) was refluxed for 8-10 hr. After completion of the reaction, the reaction mixture was cooled and excess reagent was removed under reduced pressure. The residue was dissolved in chloroform, treated with reagent was removed under reduced pressure. The reaction mixture was heated under reflux for 4-5 hr. The mixture was heated under reflux for 4-5 hr. The resulted mixture was then allowed to cool to room temperature and the solvent was concentrated under reduced pressure. Purification of the residue by crystallization from ethanol to get 8, m.p. 364-366°C; yield 52%; IR (KBr, cm^{-1}): 3147 (-NH_2), 1701 (-C=O, amide); 1H NMR (200 MHz, DMSO-d_6): δ 2.27 (s, 3H, -CH_3), 7.80 (s, 1H), 8.66 (s, 1H, -NH), 10.0 (s, -CONH_2, exchangeable). Anal. Found: C, 53.14; H, 3.34; N, 25.90.

Preparation of N-(6-carboxyl-methyl-7-oxo-1,7-dihydropyra[2,3-b]pyrazolo[4,3-e]pyridine-3-y1) methanamide 8. To a stirred solution of 7-aminoo-6-carboxamidoxime-5-methyl-2-oxo-2H-pyrano [2,3-b] pyridine-3-carboxamide 4a, (1.0 g, 0.0028 mole) in toluene (15 mL) was added N, N-dimethylformamide dimethyl acetal (0.47 g, 0.004 mole) and the reaction mixture was heated under reflux for 4-5 hr. The resulting solution was then allowed to cool to room temperature and the solvent was concentrated under reduced pressure. Purification of the residue by crystallization from ethanol to get 8, m.p. 364-366°C; yield 58%; IR (KBr, cm^{-1}): 3435.1(-NH_2), 1689 (-C=O, lactone), 1638.1 (-C=O, amide); 1H NMR (200 MHz, DMSO-d_6): δ 2.17 (s, 3H, -CH_3), 7.90 (s, 1H), 8.4 (s, 1H, -CHO), 10.30 (s, -CONH_2, exchangeable). Anal. Found: C, 50.18; H, 3.16; N, 24.38. Caled for C_{12}H_{12}N_{7}O_{4}; C, 50.23; H, 3.19; N, 24.43%.

Acknowledgement
The authors are thankful to Lupin Limited (Lupin Research Park) for supporting this work. Co-operation extended by all the colleagues of the analytical R & D division is gratefully acknowledged.

References


20 Hydroxylamine was prepared from 6.62 g of hydroxylamine hydrochloride and an ethanolic solution of sodium ethoxide 13.2 g stirred for 15 min and filtered the NaCl, the ethanolic solution of hydroxylamine used as such.