Substituted pyridopyrimidinones: oxidation of 2-hydroxypyrido [1,2-*a*]pyrimidin-4(*H*)-one

Mohamed Abass* and Aisha S. Mayas

Department of Chemistry, Faculty of Education, Ain Shams University, Roxy, Cairo 11757, Egypt

A simple method for the oxidation of 2-hydroxypyrido[1,2-a]pyrimidin-4(*H*)-one is described. Treatment of the title compound with selenium dioxide in dioxane/water, followed by warming leads directly to 1*H*-pyrrolo[2,3-*b*]pyridine-2,3-dione. The method is shown to be effective for preparation of the last compound which is used as a synthon for some antihypertensive agents.

Keywords: pyrido[1,2-*a*]pyrimidine, pyrrolo[2,3-*b*]pyridine, oxidation

Ryono and Lloyd[1] have described a preparation of 1*H*-pyrrolo[2,3-*b*]pyridine-2,3-dione during the preparation of some antihypertensive agents starting from 7-azaindole with overall yield 17%.[2] Parrick *et al.*[3] described a difficult preparation of this compound by reaction of 1*H*-pyrrolo[2,3-*b*]pyridine with *N*-bromosuccinimide in aqueous t-butanol. 2-Hydroxypyrido[1,2-*a*]pyrimidin-4(*H*)-one was prepared for the first time by Tschitschibabin[4] and from then the structure and reactivity of this compound have continued to be studied due to its unusual chemical properties.[5-8] Interestingly our literature survey showed that oxidation of this compound has not been reported up till now, so the oxidation is now described.

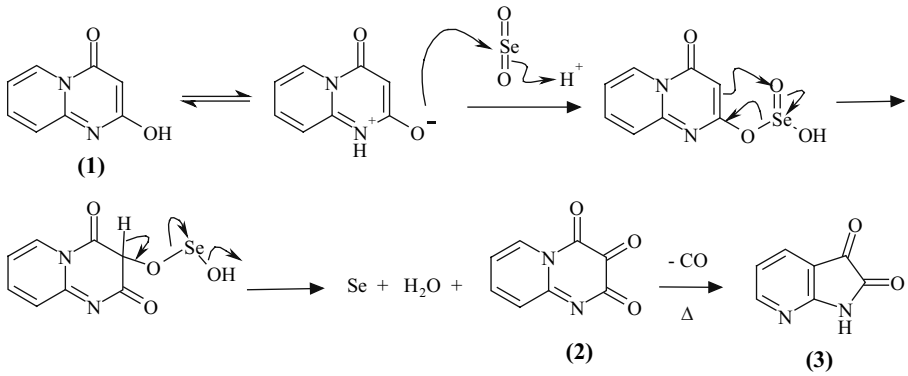
The oxidation reaction of 2-hydroxypyrido[1,2-*a*]pyrimidin-4(*H*)-one (**1**) with selenium dioxide was carried out during our attempt to prepare pyrido[1,2-*a*]pyrimidine-2,3,4-trione (**2**). Elemental microanalyses, mass spectrometry, IR, and ^{1}H NMR spectra of the product of this oxidation reaction surprised us. Hence, elemental analysis indicated a formula with composition $C_7H_6N_2O_3$ (molecular weight 166) whilst mass spectrometry revealed a molecular ion peak at 148 and hence the chemical formula $C_7H_4N_2O_2$ is indicated. This conflict is explained by the presence of a water molecule in the crystallised form, *i.e.* the molecular formula of the proposed structure is the monohydrate of $C_7H_4N_2O_2$. The ^{1}H NMR spectrum exhibited only three different proton signals of the α,β,γ-pyridine system along with the signal of an acidic proton, which appeared at δ = 10.42 which is replaceable with deuterium on addition of D_2O. It is expected that a rearrangement took place resembling that reported for transformation of pyrido[1,2-*a*]pyrimidinones into 1,8-naphthyridinones.[9] This rearrangement is accompanied by carbon monoxide loss and thence the product is identified as 1*H*-pyrrolo[2,3-*b*]pyridine-2,3-dione monohydrate (7-azaisatin) (**3**). In conclusion, the present work describes a new preparation and characterisation for 7-azaisatin, a method which is more convenient and facile than that described by Ryono and Lloyd[1] who did not give any description for the structure (Scheme 1).

Experimental

The melting point was determined in an open capillary tube on a digital Gallen-Kamp MFB-595. IR spectrum was taken on a Perkin-Elmer FT-IR 1650, using sample in KBr disk. ^{1}H NMR spectrum was recorded on Varian Gemini-200 spectrometer (200 MHz) MHz, using DMSO-d_6 as the solvent and TMS as internal reference. Mass spectrum was determined on a HP-MS 5988 mass spectrometer by direct inlet, operating at 70 eV. Elemental microanalysis was performed on a Perkin Elmer CHN-2400 Analyser.

1H-Pyrrolo[2,3-b]pyridine-2,3-dione monohydrate (7-azaisatine monohydrate) (**3**): A warm (60 °C) solution of selenium dioxide (12 mmol) in dioxane (50 mL) and water (5 mL) was added dropwise to a stirred suspension of the compound **1** (10 mmol) in dioxane (25 mL) for 30 min and then heated under reflux for 2 h. The hot reaction mixture was filtered and the filtrate was concentrated to one half of its volume (*ca* 40 mL), then left to stand at room temperature over night. The product was filtered off and crystallised from dioxane/water (50 mL, 9:1) affording reddish-orange crystals. Yield (0.92 g) 55%, m.p. 200–2 °C. IR (ν_{max}, cm^{-1}): 3387, 3267–3106 (H-bonded OH and NH), 1699 (C=O), 1649 (C=O), 1609(C=N), 1528, 1441, 1377, 1299, 1164, 926, 778; ^{1}H NMR (DMSO-d_6), δ: 7.21 (dd, *J, J* = 7.5, 4.9 Hz, 1H, C5-H), 7.87 (dd, *J,J* = 7.4, 1.54 Hz, 1H, C4-H), 8.39 (d, *J* = 4.7 Hz, 1H, C6-H), 10.42 (b, 1H, NH); Mass spectrum *m/z* (*I*%): M$^+$ 148 (100), 149 (7, M + 1), 120 (48, M– CO), 77 (85, pyridine); Anal. Calcd for $C_7H_4N_2O_2.H_2O$: C, 50.61; H, 3.64; N, 16.86. Found: C, 50.55; H, 3.60; N, 16.78%.

Received 16 November 2008; accepted 13 December 2008
Paper 08/0297 doi: 10.3184/030823409X402519
Published online: 24 February 2009



Scheme 1 Oxidation of 2-hydroxypyrido[1,2-*a*]pyrimidin-4(*H*)-one using SeO_2.

* Correspondent. E-mail: m.abass@chemist.com

References

1 D.E. Ryono and J. Lloyd, *Eur. Pat. Appl.*, 1993, EP 0556060A1.
2 J. Lloyd, D.E. Ryono, J.E. Bird, J. Buote, C.L. Delaney, T. Dejneka, K.E.J. Dickinson, S. Moreland, D.E. Normandin, S. Skwish, E.R. Spitzmiller and T.L. Waldron, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 195.
3 J. Parrick, A. Yahya, A.S. Ijaz and J. Yizun, *J. Chem. Soc. Perkin Trans. 1*, 1989, 2009.
4 A.E. Tschitschibabin, *Ber.*, 1924, **57**, 1168.
5 H.R. Snyder and M.M. Robison, *J. Am.Chem. Soc.*, 1952, **74**, 4910.
6 A.R. Katritzky and A.J. Waring, *J. Chem. Soc.*, 1962, 1544.
7 W. Schulte, *Arch. Pharm.*, 1985, **291**, 298.
8 M. Abass and A.S. Mayas, *Heteroatom Chem.*, 2007, **18**, 19.
9 A. Fiksdahl, C. Plug and C. Wentrup, *J. Chem. Soc., Perkin Trans. 2*, 2000, 1841.