Chinese Chemical Letters Vol. 12, No. 6, pp. 559 – 562, 2001

Preparation of Platinum(II) Complexes with 1-β-*D*-Ribofuranosyl-1,2,4-triazole-3-carboxamide and its Deoxy-analogue

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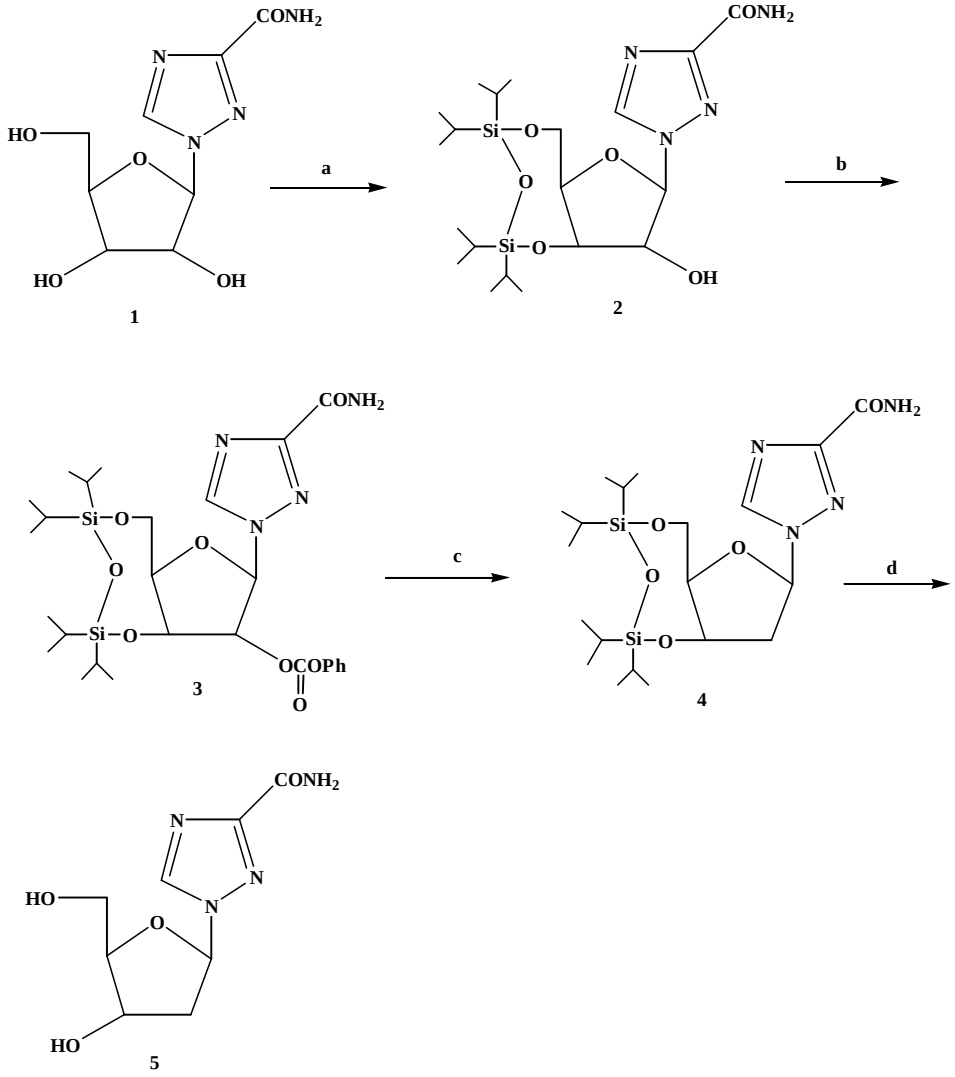
Abstract: The platinum (II) complexes of the [Pt (N^4,N^7-Ribavirin) (DMSO) Cl], [Pt (N^4,N^7-Deoxyribavirin) (DMSO) Cl] were obtained by the reactions of *cis*-[Pt $(DMSO)_2$ Cl_2] and K[Pt (DMSO) Cl_3] with 1-β-*D*-ribofuranosyl-1,2,4-triazole-3-carboxamide (Ribavirin) and its deoxy-analogue (deoxyribavirin). The preparation of 1-(2'-deoxy-β-*D*-ribofuranosyl) -1,2,4-triazole-3-carboxamide was also performed through a four-step procedure, protection of 3', 5'-dihydroxyl group of Ribavirin with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TPDS-Cl), phenoxythiocarbonylation of the 2'-hydroxyl group of 3', 5'-*O*-TPDS-Ribavirin with phenoxythiocarbonyl-chloride (PTC-Cl), reduction of 2′-*O*-phenoxythiocarbonyl ester of 3', 5'-*O*-TPDS-Ribavirin with tri-n-butyltin hydride and AIBN, deprotection of 3', 5'-*O*-TPDS-Ribavirin with tetrabutylammonium fluoride in THF.

Keywords: Platinum(II) complexes, ribavirin and deoxyribavirin, nucleobase platination, complexation reaction, antitumor agents.

Much attention is currently focused on the design of new generations of platinum anticancer complexes to prevent resistance of cisplatin. We have developed a new platinum-based antitumor agent with broad-spectrum antiviral activity. The *cis*-[$Pt(DMSO)_2Cl_2$] and K[Pt (DMSO) Cl_3] reacted with 1-β-*D*-ribofuranosyl-1,2,4-triazole-3-carboxamide (ribavirin) and its deoxy-analogue (deoxyribavirin) to give the coordinated complexes which exhibited activity against both DNA and RNA viruses[1]. The amino nitrogen and one of the nitrogen of triazole can coordinate with platinum (II) ion to form the platinum (II) complexes of the [Pt (N^4,N^7-ribavirin) (DMSO) Cl], [Pt (N^4,N^7-deoxyribavirin) (DMSO) Cl][2]. The 1-(2'-deoxy-β-*D*-ribofuranosyl)-1,2,4-triazole-3-carboxamide was prepared through a four-step procedure in good yield (**Scheme 1**).

Protection of 3', 5'-dihydroxyl group of ribavirin **1** with 1, 3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TPDS-Cl) in dry pyridine gave the 1-(3', 5'-*O*-TPDS-β-*D*-ribofuranosyl)-1,2,4-triazole-3-carboxamide **2** in 80% yield. Phenoxythiocarbonylation of the 2'-hydroxyl group of compound **2** with phenoxythiocarbonyl chloride (PTC-Cl) and 1-methylimidazole as nucleophilic catalyst to give 1-(3', 5'-*O*-TPDS-2'-*O*-phenoxythiocar-

Scheme 1



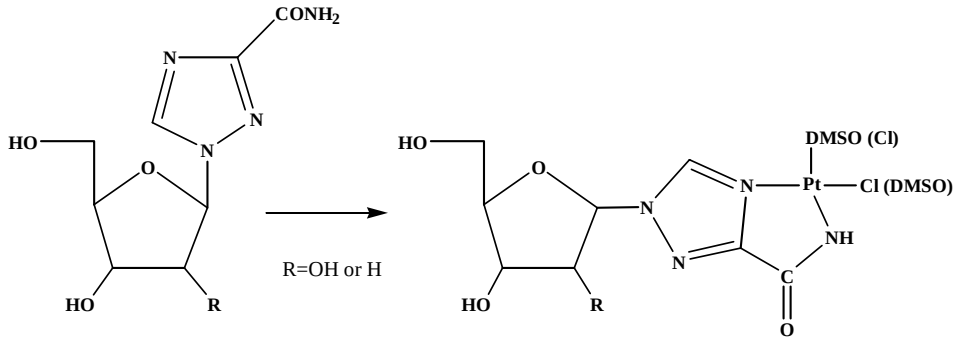
a) 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane, pyridine; b) Phenylchlorothionoformate, dichloromethane, 1-methylimidazole; c) AIBN, Bu_3SnH, toluene; d) Tetrabutylammonium flouride, THF.

bonyl-*β*-*D*-ribofuranosyl)-1,2,4-triazole-3-carboxamide **3** in dry dichloromethane in 83% yield, followed by standard reduction of 2'-*O*-phenoxythiocarbonyl ester of 3', 5'-*O*-TPDS-ribavirin **3** using 2 equiv of tri-*n*-butyltin hydride and 1.5 equiv of AIBN as free radical initiator gave 1-(3', 5'-*O*-TPDS-2'-deoxy-*β*-*D*-ribofuranosyl)-1,2,4-triazole-3-carboxamide **4** in dry toluene in 79% yield. Deprotection of 3', 5'-*O*-TPDS-2'-deoxyribavirin **4** using tetrabutylammonium fluoride (TBAF) in THF gave the corresponding 1-

(2'-deoxy-*β-D*-ribofuranosyl)-1,2,4-triazole-3-carboxamide **5** in 77% yield[3]. Compounds **2**, **3** and **4** are new compounds.

The platinum (II) complexes of [Pt (N^4,N^7-ribavirin) (DMSO) Cl] and [Pt (N^4,N^7-deoxyribavirin) (DMSO) Cl] were formed in almost quantitative yield by the reactions of ribavirin and deoxyribavirin with *cis*-[Pt $(DMSO)_2$ Cl_2] and K[Pt (DMSO) Cl_3] in the solvents of DMF, MeOH, H_2O and buffer solution (triethylammoniumcarbonate in water, PH = 7.4) (**Scheme 2**).

Scheme 2



Firstly, based on literature method[4], to the solution of *cis*-[Pt $(DMSO)_2$ Cl_2] in DMF added one equivalent of $AgNO_3$ in the same solvent, the platinum (II) complexes were obtained with 1:1 ratio of *cis* and *trans* isomers. When the reactions were also proceeded in the solvents of DMF, MeOH, H_2O and buffer solution of triethylammoniumcarbonate in water (PH = 7.4) the same results were obtainen even without $AgNO_3$. When K[Pt(DMSO)Cl_3] reacted with ribavirin and deoxyribavirin, the platinum (II) complexes were almost only in *cis* form (> 98%). The structures of these platinum (II) complexes were confirmed by NMR (^1H, ^{13}C and ^{195}Pt), IR, MS and elemental analysis[5]. The machanism of formation of the complexes and their biological properties will be examined later.

References and notes

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2. T. Komorita, A. Fuyuhiro, K. Tanimoto, K. Yamauchi, K. Fujita, *Bull. Chem. Soc. Jpn*., **1995**, *68*, 1593.
3. Deprotection of Compound **4** was effected by addition of 1.2 molar equiv of 1 mol/L TBAF/THF directly to the reaction mixture. After stirring for 10 minutes at room temperature volatile materials were evaporated and the residue was purified on a column of silica gel (MeOH-CH_2Cl_2, v/v = 1/3) to give product 1.5 g (77%). The product was recrystallized from MeOH/CH_2Cl_2/H_2O. mp: 112-113 °C is consistent with literature[1].
4. L. S. Hollis, A. R. Amundsen, W. Stern, *J. Med. Chem*., **1989**, *32*, 128.
5. Compound **1:** mp: > 190°C (dec.), IR (KBr) 3323, 2923, 2853, 1638, 1384, 1130, 1026, 353, 339, 319 cm^{-1}; ^1H-NMR (DMF-d_7, δ ppm): 9.51 (s, 1H, H-5), 6.47 (s, 1H, N-H), 6.15 (d, 1H, *J* = 3.4 H_Z, H-1', 5.86 (d, 1H, J = 5.4 Hz, OH-2´), 5.31 (d, 1H, J = 5.6 Hz, OH-3'), 5.10 (t, 1H, J = 5.4Hz, OH-5', 4.58 (dd, 1H, J = 4.9, 8.3 Hz, H-2', 4.36 (dd, 1H, J = 5.4, 10.5 Hz, H-3', 4.13

(m, 1H, H-4'), 3.64 - 3.83 (m, 1H, H-5', H-5'); ^{13}C-NMR (DMF-d_7, δ ppm): 143.1 (C=O), 94.8 (C-3), 87.2 (C-5), 76.0 (C-1'), 71.0 (C-2'), 62.1 (C-3'), 44.0 (C-4'), 43.9 (C-5'); ^{195}Pt-NMR (DMF-d_7, δ ppm): –3109; MS (FAB, %): *m/z* 553 $(M+H)^+$, 421 (55), 460 (35), 482 (26); Anal. Calcd for $C_{10}H_{17}N_4O_6SClPt$: C 21.76, H 3.10, N 10.15. Found: C 21.81, H 3.20, N 10.11 (%). Compound **2:** mp: > 170°C (dec.); IR (KBr): 3356, 3012, 2918, 2361, 2342, 1641, 1558, 1490, 1484, 1436, 1384, 1317, 1296, 1113, 1052, 950, 701, 668, 540, 433 cm^{-1}; ^{1}HNMR (DMF-d_7, δ ppm): 9.39 (s, 1H, H-5), 6.55 (dd, 1H, *J* = 4.9, 6.6 Hz, H-1', 6.45 (s, 1H, N-H), 5.51 (d,1H, *J* = 4.4 Hz, OH-3', 4.99 (t,1H, *J* = 5.4 Hz, OH-5'), 4.57 (m, 1H, H-3'), 4.03 (m, 1H, H-4'); ^{13}C-NMR (DMF-d_7, δ ppm): 142.8 (C = O), 90.8 (C-3), 90.0 (C-5), 71.2 (C-1'), 62.6 (C-3'), 44.0 (C-4'), 43.9 (C-5'), 40.5 (C-2'); ^{195}Pt-NMR (DMF-d_7, δ ppm): -3110 (To high field of Na_2PtCl_6 in D_2O); MS (FAB,%): *m/z* 537 $(M+H)^+$, 421 (72), 154 (base peak), 136 (80); Anal. Calcd for $C_{10}H_{17}N_4O_5SClPt$: C 22.41, H 3.20, N 10.46. Found: C 22.38, H 3.16, N 10.40 %.

Received 26 May, 2000
Revised 27 March, 2001