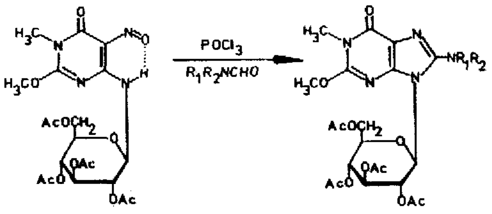
Tetrahedron Letters,Vol.30,No.20,pp 2669-2672,1989
Printed in Great Britain 0040-4039/89 $3.00 + .00
Pergamon Press plc

ON THE REACTION OF 6-GLYCOSYLAMINO-5-NITROSOPYRIMIDINES WITH VILSMEIER-TYPE REAGENTS. SYNTHESIS OF 8-AMINO-9-GLYCOSYLPURINES

M. MELGUIZO, M. NOGUERAS, A. SANCHEZ and Mª L. QUIJANO
Department of Organic Chemistry. University College of Jaén.
University of Granada. 23071-Jaén. Spain

Summary: 8-amino, 8-(N-methyl)amino and 8-(N,N-dimethyl)amino-9-glucopyranosylpurines have been obtained by reaction of the corresponding 6-glycopyranosyl-5-nitrosopyrimidine with Vilsmeier-Type reagents (formamide, substituted formamides and phosphorus oxychloride).

Studies on reactivity and synthetic applications of several 6-glycosylaminopyrimidines have been carried out[1,2,3]. Our interest is focused on the preparation of derivatives with potential biological activity. We report herein the utility of 6-glycosylamino-5-nitrosopyrimidines for the synthesis of 8-amino(N-methylamino and N,N-dimethylamino)purines as shown in the scheme.



1   2, 3, 4, 5

The Vilsmeier-Type reagents (Vilsmeier-Haack or Vilsmeier-Haack-Arnold) provide a very convenient method for the cyclization in the carbocyclic compounds chemistry as well as in the heterocyclic compounds[4]. Furthermore, Vilsmeier reaction exhibits a large dependence on the conditions under which it takes place such as concentration and temperature[5]. We have used this reaction for the formylation of some 6-glycosylaminopyrimidines with excellent yield[6].

K. Senga and coworker have obtained 8-(N-methyl) and 8-(N,N-dimethyl)aminopurines by treatment of 6-amino-5-nitrosopyrimidines with substituted formamides and phosphorus oxychloride in equimolar amounts at high temperature[7]. When the reaction was carried out *with 6-amino-1,3-dimethyl-5-nitroso uracile at room temperature, a dimeric compound was* obtained which converted into the corresponding 8-(N,N-dimethyl)aminopurine by futher heating in the same reagent or by sublimating "in vacuo". Nevertheless, 8-aminopurines were not obtained when the reaction was carried out with formamide; instead, the formation of small amounts of pyrimido[4,5-d]pyrimidines was observed in these cases[8].

In this letter, we present the results of our study on the reactions of 3,4-dihydro-

3-methyl-2-methoxy-4-oxo-6-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamino)pyrimidine (1)[9] with formamide, substituted formamides and phosphorus oxychloride. In Table I and II the results of these reactions are summarized.

TABLE I. Reaction of (1) with DMF/$POCl_3$

(1) Equivalents	$POCl_3$ Equivalents	DMF (ml/mmol)	Temperature	Reaction time	Yield (%) (2)	Yield (%) (3)
1	15	2	Room Temp.	1.5 h	36	43
1	1.1	2	Room Temp.	3.5 h	47	traces

TABLE II. Physical data of 8-aminopurines

Comp.	R_1	R_2	Yield (%)	MP (°C)	MS (M^+)	Formula	Analysis C	Analysis H	Analysis N
(2)	CH_3	CH_3	see table I	125[a)]	553	$C_{23}H_{31}N_5O_{11}$	49.91 (49.62)	5.64 (5.88)	12.65 (12.51)
(3)	H	CH_3	see table I	149[a)]	539	$C_{22}H_{29}N_5O_{11}$	48.98 (49.23)	5.42 (5.51)	12.98 (13.05)
(4)	H	H	78	194(d) (EtOH)	525	$C_{21}H_{27}N_5O_{11}$	48.50 (48.37)	5.18 (6.91)	13.33 (13.60)
(5)	Ac	Ac	69	120[a)]	567[b)]	$C_{25}H_{31}N_5O_{13}$	49.26 (49.20)	5.13 (5.50)	11.49 (11.32)

a) Petroleum ether/ethylic ether/ethanol. b) M^+-CH_2CO

The treatment of (1) with dimethylformamide (DMF) and an excess of $POCl_3$ led, after stirring 1.5 h at room temperature (at this time departure product was not detected in TLC, $CHCl_3$/petroleum ether/EtOH, 8/1/0.5) and fractionation by column chromatography on silica gel ($CHCl_3$/EtOH, growing amounts of EtOH), to a 36% of 8-(N,N-dimethyl)amino-1,6-dihydro-1-methyl-2-methoxy-6-oxo-9-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamino)purine (3) and a 43% of 8-(N-methyl)amino-1,6-dihydro-1-methyl-2-methoxy-6-oxo-9-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamino)purine (4). On the other hand, when (1) was treated with 1.1 equivalents of $POCl_3$ in DMF, 47% of (2) was obtained, whereas only traces of compound (3) were detected (TLC)[10]. When the reaction was performed by adding $POCl_3$ to a (1) DMF solution, after stirring at room temperature, the formation of α-1-chloro-tetra-O-acetyl-glucopyranose was detected.

The compound (3) is also obtained (36%) by treatment of (1) (1 equivalent) with a previosly prepared mixture at 0 °C of N-methylformamide (2 equivalents) and $POCl_3$ (5 equivalents) in CH_2Cl_2 (10 ml/mmol) during 3.5 hours at 40°C . All the compounds have been identified by the usual analytical methods. In the ^1H-NMR spectrum of (3) ($CDCl_3$) the signal assigned to CH_3-N(8) appears at 3.0 ppm as doublet (J=4.6 Hz) due to the coupling of the said group with H-N(8). This signal becames a singlet by adding D_2O. In the ^1H-NMR spectra of all 8-aminopurines derivatives obtained, the signal assigned to one of the acetate groups appears as a singlet shifted about 0.3 ppm to upfield with regard to the signal of the remaining acetates groups, which appears as a singlet at 2 ppm. This fact has been observed in all the acetylated 9-glycosylpurines synthesized by us.

Dimeric-Type compounds were not obtained in these reactions. 8-alkylaminopurines formation can best be explained by assuming an initial electrophilic attack of the Vilsmeier intermediate to the nitrogen atom of the nitroso group, electronic and prototropic rearragement and intramolecular cyclization. (3) can be formed by Cl^- attack to one methyl of the dimethylamino group with CH_3Cl elimination[11] in some of the posible intermediates or in the compounds (2). Compound (3) is only obtained when an excess of $POCl_3$ is used since a high Cl^- concentration is generated in these conditions. Posible nitrone-Type intermediates or final products are reduced "in situ" by the corresponding formamide[12] . α-1-chloro-tetra-O-acetylglucopyranose formations by adding $POCl_3$ to a (1) DMF solution would be due to the breaking of the glycosidic bond favoured by the increasing in temperature through a SN_2 reaction.

Reaction of (1) with a 0 °C previously prepared mixture of formamide/$POCl_3$ led, after stirring 1.75 h (at this time departure product was not detected in TLC, $CHCl_3$/petroleum ether/EtOH 8/1/0.5) and fractionation by colum chromatography on silica gel ($CHCl_3$/petroleum ether/EtOH 8/2/0.2) to a 78% of 8-amino-1,6-dihydro-1-methyl-2-methoxy-6-oxo-9-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamino)purine (4) . The C(8)-NH_2 group has been shown by acetylation with Ac_2O/Py at room temperature during 24 h. After evaporation and purification by column chromatography ($CHCl_3$/petroleum ether/EtOH, 8/2/0.2), 8-(N,N-diacetyl)-1,6-dihydro-1-methyl-2-methoxy-6-oxo-9-*(2,3,4,6-tetra-O-acetyl- β-D-glucopyranosylamino)purine* (5) *was* obtained in 69%. The ^1H-NMR spectrum of (5) ($CDCl_3$) shows two new singlets at 2.2 ppm and 2.5 ppm respectively; in the ^{13}C-NMR spectrum two new quadruplets at 26.26 and 24.88 ppm respectively were observed. Compound (4) was always obtained in good yield although an excess of $POCl_3$ was used.

The β-configuration of the sugar moieties in all compounds obtained has been confirmed by the values of the coupling constants $J_{1',2'}$ and by the chemical shifts of the anomeric proton and carbon.

ACKNOWLEDGEMENTS

The authors thank the "Consejeria de Educacion y Ciencia, Junta de Andalucia" for the award of a fellowship of the "Plan de Formación del Pesornal Investigador" to two of them (M. Melguizo and Mª L. Quijano).

REFERENCES AND NOTES

1 J. Baddiley, B. Lythgoe and A. R. Todd, J.Chem. Soc, **1943**, 551.

2 W. Pfleiderer and E. Bühler, Chem. Ber, **99**, 3022 (1966).

3 R.Asenjo, M. Melgarejo, M. Nogueras, M. Rodriguez, C. Rodriguez and A.Sánchez, Nucleosides and Nucleotides, **3(2)**, 207 (1984); A. Sánchez, C. Rodriguez, M. Rodriguez, M. Nogueras, M. Melgarejo and R. Asenjo, Heterocycles, **22**, 1555 (1984); R. Asenjo, M. Melgarejo, C. Rodriguez, M. Nogueras and A. Sánchez, An. Quím, **79C**, 417 (1983); M. Nogueras, A. Sánchez, R. Asenjo, M. Melgarejo, M. Rodriguez and C. Rodriguez, An. Quím, **80C**, 234 (1984); M. Nogueras, Mª.L. Quijano, M. Melgarejo and A. Sánchez, Nucleosides and Nucleotides, **5(3)**,301 (1986); M. Melgarejo, C. Rodriguez, M. Melgarejo, R. Asenjo, M. Nogueras and A. Sánchez, Nucleosides and Nucleotides, **6(5)**, 887 (1987).

4 O. Meth-Cohn, B. Tarnowiki, Advances in Heterocyclic Chemistry, vol. 31 (A. R. Katritzky, ed). Academic Press, 1982, 207-236.

5 J. A. Montgomery, H. Hewson, J. Org. Chem, **30**, 1528 (1965).

6 J. Negrillo, M. Nogueras, A. Sánchez and M. Melgarejo, Chem. Pharm. Bull, **36(1)**, 386 (1988).

7 F. Yoneda, M. Higuchi, T. Matsumura and K. Senga, Chem. Phar. Bull, **46**, 1836 (1973); F. Yoneda, T. Matsumura and K. Senga, Chem. Commun, **1972**, 606.

8 H. Bredereck, F. Ettenberger and R. Sauter, Chem. Ber, **95**, 2049 (1962).

9 M. Nogueras, R. López, A. Sánchez and Mª. D. Gutierrez, J. Thermal Analysis, **34**, 1335 (1988).

10 The reaction was carried out by adding (1) to a 0 C previously prepared mixture of the corresponding formamide and $POCl_3$. The mixture was stirred at room temperature during the necessary time until no departure product is detected in TLC and next the reaction was diluted with $CHCl_3$ and neutralized with a saturated $NaHCO_3$ aqueous solution. The organic layer was washed with water, dried over anhydrous Na_2SO_4, concentrated in vacuo and applied on a chromatographic column of silica gel eluting with the solvent indicate in each case.

11 H. J. Robins, B. Vznanski, Can. J. Chem,**59**, 2601 (1981); H. Gershon, A. Greit, J. Heterocyclic Chem, **21**, 1161 (1984)

12 E. C. Taylor, E. E. Garcia, J. Am. Chem. Soc, **86**, 4721 (1964); K. Hirota, T. Sugiyama, Y. Kitade and S. Senga, Synthesis, **1982**, 1097; K. Hirota, T. Sugiyama, Y. Kitade, S. Senga and Y. Maki, J. Chem. Soc. Perkin I, **1984**, 583.

(Received in UK 10 April 1989)