Tetrahedron Letters No. 35, pp 3263 - 3264.
©Pergamon Press Ltd. 1979. Printed in Great Britain.

0040-4039/79/0822-3263$02.00/0

IODOMETHYLETHERS FROM 1,3-DIOXOLANE AND 1,3-OXATHIOLANE: PREPARATION OF ACYCLIC NUCLEOSIDE ANALOGS

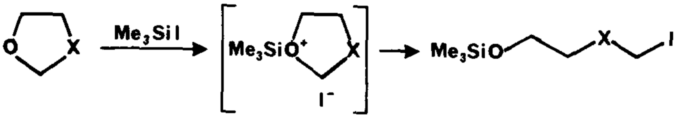
Gene E. Keyser, Jerry D. Bryant, Jorge R. Barrio*

School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

Abstract - Purine and pyrimidine anions were alkylated using the iodomethyl ether and thioether generated *in situ* by the reaction of 1,3-dioxolane and 1,3-oxathiolane with trimethylsilyl iodide.

1,3-Dioxolane and 1,3-oxathiolane react rapidly and smoothly with trimethylsilyl iodide[1] at temperatures ranging from -78° C to 0° C to afford iodomethyl trimethylsilyloxyethyl ether (**1a**) or thioether (**1b**), respectively. Compounds **1a** and **1b** are efficient alkylating agents and react with a variety of purine and pyrimidine anions at -63° C to provide nucleoside analogs **2** and **3** (70 - 80% yields) with an acyclic side chain identical to that of 9-(2-hydroxyethoxymethyl)guanine, a compound reported to possess potent antiviral activity (ED_{50}: 0.1 μM) against *Herpes simplex* virus type I.[2]

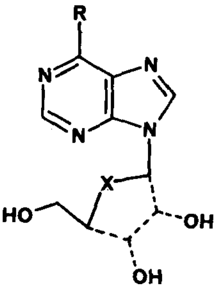
The following procedure is representative. To a stirred mixture of 1,3-dioxolane (81 mg, 1.1 mmol) in cyclohexene (0.25 mL) at -78° C under N_2 was added trimethylsilyl iodide (0.14 mL, 1.0 mmol). Conversion to **1a** was essentially complete in less than 10 min: NMR ($CDCl_3$) δ 0.2 (s, 9, $Si(CH_3)_3$), 3.67 (m, 4, CH_2CH_2), 5.87 (s, 2, ICH_2O).



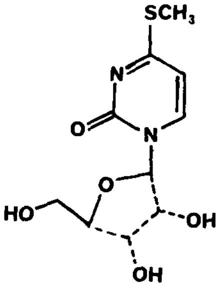
1a X = O
1b X = S

In the reaction of trimethylsilyl iodide with 1,3-oxathiolane,[3] preferential formation of the oxonium ion is expected because of the weak character of the Si-S bond.[1b] For the synthesis of the thioether **1b**, the most favorable reaction conditions included stirring for 16 h at 0° C under N_2: NMR ($CDCl_3$) δ 0.2 (s, 9, $Si(CH_3)_3$), 2.77 (t, 2, CH_2S, *J* = 6 Hz), 3.83 (t, 2, CH_2O, *J* = 6 Hz), 4.45 (s, 2, ICH_2S).

In a typical alkylation procedure, the sodium salt of 6-chloropurine (generated with NaH)[4] in dry DMF was treated with the alkylating agent (*vide supra*) (10% excess) at -63° C. The mixture was warmed to 25° C over 2 h and after adding aqueous 10% KF and 10% $KHCO_3$ the solvent was evaporated and the residue extracted (EtOAc). Concentration of the organic layer followed by



2a R = Cl; X = O
2b R = Cl; X = S
2c R = SCH_3; X = O



3

neutral alumina chromatography afforded analytically pure 2a (72% yield) mp 149-150° C; MS m/e 228 (M^+); 198 (M^+-HCHO); 183 (M^+-C_2H_5O); 168 (M^+-$C_2H_4O_2$); 167 (M^+-$C_2H_5O_2$); 155 (M^+-$C_3H_5O_2$); 154 (M^+-$C_3H_6O_2$); B = 45. 6-Chloro-9-(2-hydroxyethylthiomethyl)purine (2b), mp 98-99° C, 9-(2-hydroxyethoxymethyl)-6-methylthiopurine (2c), mp 137-138° C and 1-(2-hydroxyethoxymethyl)-4-methylthio-2-pyrimidinone (3), mp 73-74° C were obtained similarly from the corresponding starting materials.

This methodology can be used to synthesize a variety of potential antibiotic, antitumor and antiviral agents.

The authors express their appreciation for the encouragement Professor N. J. Leonard and the financial support provided by research grant GM 05829 from the National Institutes of Health, U.S. Public Service.

References and Notes

1) For reaction of trimethylsilyl iodide with acetals, ketals and cyclic ethers, see: a) M. E. Jung, M. A. Mazurek and R. M. Lim, Synthesis 588 (1978); b) M. E. Jung, W. A. Andrus and P. L. Ornstein, Tetrahedron Lett. 4175 (1977), and references therein; c) M. G. Voronkov, V. E. Puzanova, S. F. Pavlov and É. I. Dubinskaya, Izv. Akad. Nauk. SSSR, Ser. Khim. 448 (1975); d) M. G. Voronkov, É. I. Dubinskaya, V. G. Komarov and S. F. Pavlov, Zh. Obshch. Khim. 46, 1908 (1976).
2) G. B. Elion, P. A. Furman, J. A. Fyfe, P. de Miranda, L. Beauchamp and H. J. Schaeffer, Proc. Nat. Acad. Sci. USA 74, 5716 (1977).
3) 1,3-Oxathiolane was prepared from the sodium salt of β-mercaptoethanol and chloromethylmethyl ether followed by distillation in the presence of small amounts of anhydrous methanolic HCl (yield 65%), bp_{760} 132-136° C. Previously reported methods produced very poor yields of 1,3-oxathiolane. See, for example: a) F. Kipnis and J. Ornfelt, J. Amer. Chem. Soc. 71, 3555 (1949); b) K. Schank, R. Wilmes and G. Ferdinand, Int. J. Sulfur Chem. 8, 397 (1973).
4) When anhydrous K_2CO_3 in DMF was used for alkylation, a small amount (<5%) of the N-7 isomer, in addition to the N-9 product (2), was obtained.

(Received in USA 24 April 1979)