Tetrahedron Letters No. 24, pp 2141 - 2144, 1974. Pergamon Press. Printed in Great Britain.

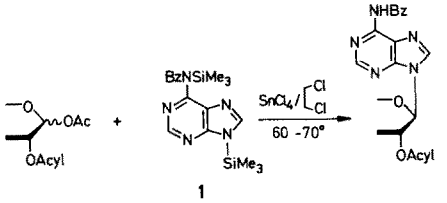
NUCLEOSIDES, XX[1].

STANNIC CHLORIDE CATALYZED GLYCOSIDATIONS OF SILYLATED PURINES WITH FULLY ACYLATED SUGARS

Frieder W. Lichtenthaler, Peter Voss, and Arnold Heerd
Institut für Organische Chemie, Technische Hochschule Darmstadt
61 Darmstadt, Germany

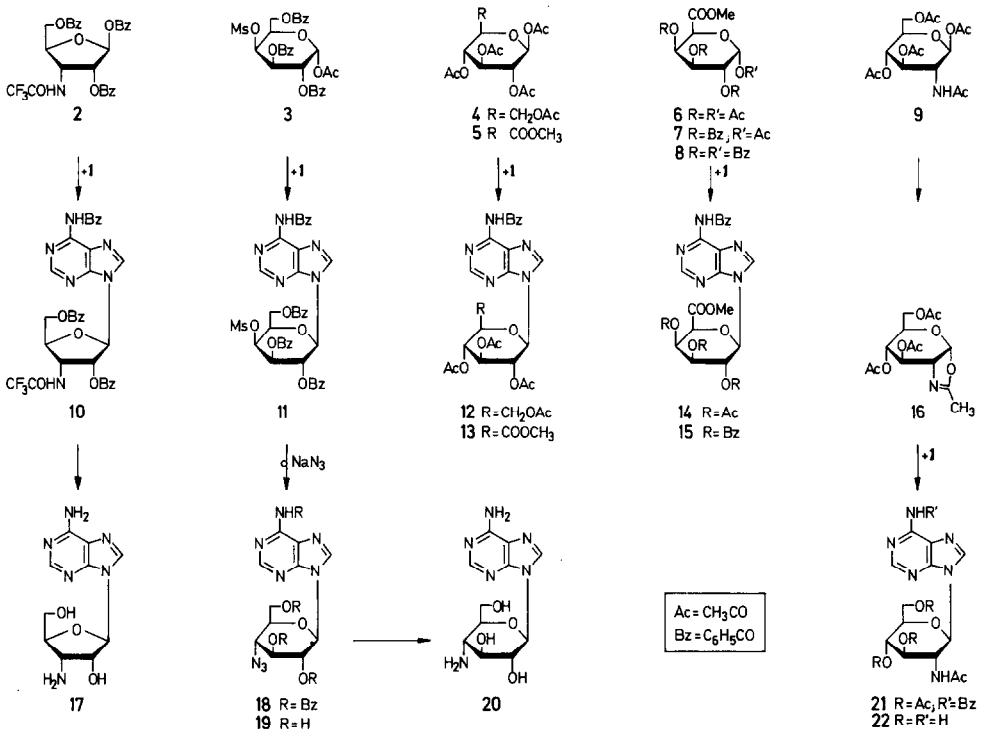
(Received in UK 1 April 1974; accepted for publication 8 May 1974)

For the synthesis of purine nucleosides several procedures have been elaborated that allow 1-O-acyl-glycoses to be utilized rather than the less stable glycosyl halides: (a) the acid-catalyzed or autocatalytic reaction with an unprotected or an N-acylated purine at 130-190° without solvent (fusion method[2]) or in refluxing nitromethane[3], (b) the titanium tetrachloride procedure[4] involving reaction with a 9-chloromercury-purine by $TiCl_4$ in refluxing dichloromethane, and (c) the condensation with N^2- or N^6-alkanoylpurines by Friedel-Crafts catalysts, e.g. aluminium chloride, in refluxing chlorobenzene[5]. Although of considerable preparative utility, these methods have not been entirely satisfactory, (a) giving good results mainly with halo- or N-methyl-purines[2, 3], (b) being limited to the preparation of adenine nucleosides[6] whilst (c)[5] as well as (b)[4b,c,7] are encumbered by the formation of α,ß-anomeric mixtures. An attractive alternative to these procedures appeared to be the utilization of silylated purines[8], e.g. N^6-benzoyl-N^6,9-bis(trimethylsilyl)adenine (1), in Friedel-Crafts catalyzed glycosidations with peracylglycoses, which apparently has not been explored so far. This promoted us to examine wether such a reaction is practicable and of preparative utility.



1

The ready feasibility of Friedel-Crafts-catalyzed reactions between 1 and 1-O-acylglycoses is amply demonstrated by the conversions of peracyl-sugars 2 - 9 into their N^6-benzoyl-adenine nucleosides (10 - 15, 21) by stannic chloride in dichloroethane[9] (conditions, yields and relevant physical data, cf. Table). Except for 14, where difficulties in crystallization afforded only 41 %, the yields obtained for pure 9-ß-nucleosides are in the 60 - 70 % range. Although



the molar ratio-yield profile has has not been investigated in detail, the exact amount of catalyst used appears to be of minor importance being variable between 0.6 - 2.6 molar equivalents (cf. Table), whilst a small excess of $\underline{\underline{1}}$ was found advantageous. With respect to anomeric configuration and site of N-glycosidation in $\underline{\underline{1}}$, the reactions appear to be highly stereoselective, pronouncedly favoring formation of 9-ß-nucleosides. The detection by tlc of slower moving spots in some of the reaction mixtures, however, indicated the presence of isomeric products to the extent of 10 - 15 % (α-anomers or 7-nucleosides), which were readily removed by the usual isolation procedure. Hence, the stereochemistry of this N-glycosidation is controlled by the vicinal 2-acyloxy group via trans-opening of cyclic acyloxonium intermediates. Additional support for this course is adducible from the ready formation of oxazoline $\underline{\underline{16}}$ on treatment of glucosamine pentaacetate $\underline{\underline{9}}$ with stannic chloride or titanium tetrachloride in dichloroethane[1], persuasively suggesting that the conversions $\underline{\underline{9}} \rightarrow \underline{\underline{21}}$ and $\underline{\underline{16}} \rightarrow \underline{\underline{21}}$ proceed via a common intermediate, i.e. an $SnCl_4$-oxazoline complex.

On the basis of these results, the stannic chloride catalyzed glycosidation of $\underline{\underline{1}}$ with peracylsugars appears to be equivalent if not superior with respect to preparative simplicity to other

TABLE. Nucleosides prepared by stannic chloride catalyzed glycosidations of N^6-benzoyl-N^6, 9-bis(trimethylsilyl)adenine (1) with 1-O-acyl-glycoses 2 - 9 (5 h, 60-70° in dichloroethane[a]).

Adenine Nucleoside[b]	Sugar Component[c]	Molar Ratio Sugar : Base : $SnCl_4$	Yield[d] %	mp °C	$[\alpha]_D$ (solvent, °C)
10	2	1 : 1.2 : 1.4	61	157	+ 27 ($CHCl_3$, 20)
11	3	1 : 1.1 : 2.6	59	amorph	- 17 ($CHCl_3$, 20)
12	4	1 : 1.1 : 0.6	68	171-173[f]	+ 7 ($CHCl_3$, 21)
13	5	1 : 1.4 : 2.6	63	128-129	- 52 (CH_3OH, 21)
14	6	1 : 1.4 : 1.3	41	133-135	+ 13 (CH_3OH, 20)
15	7 or 8	1 : 1.4 : 2.6	65	203-205	+ 72 ($CHCl_3$, 20)
22[e]	9 or 16	1 : 1.2 : 2.0	58	236(dec)	- 12 (CH_3OH, 22)

a) Absolutely nonaqueous conditions being imparative the reactions were conducted in the presence of freshly activated molecular sieve — Workup by treatment with cold sodium bicarbonate solution should not exceed 30 min, to avoid de-N-benzoylation to the respective adenine nucleosides that are considerably less amenable to crystallization.

b) All new compounds gave elementary analysis results within 0.3 % of theory, as well as UV (methanol) and NMR data (DMSO-d_6) that were consistent with the structures and anomeric configurations assigned.

c) For preparation of the peracyl-sugars used cf. ref. 1.

d) Yields based on sugar component.

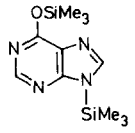
e) Glycosidation followed by deblocking of sirupy 21 with n-butylamine in methanol; data for 22 correlate well with those of M. L. Wolfrom and R. Wurmb, J. Org. Chem., 30, 3059 (1965).

f) N. Yamaoka, K. Aso, and K. Matsuda, J. Org. Chem., 39, 149 (1965), reported mp 171° and $[\alpha]_D^{10}$ + 6° ($CHCl_3$).

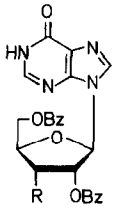
procedures for the synthesis of adenine nucleosides. Thus, its application already rendered possible a facile synthesis of 3'-amino-3'-deoxy-adenosine (17)[10] by deblocking of 10 with n-butylamine in boiling methanol (overall yield from 2: 48 %), as well as a ready access to 4'-amino-4'-deoxy-ß-D-glucopyranosyl-adenine (20), prisms of mp 200° (dec) and $[\alpha]_D^{20}$ + 12° (c 1, water), via displacement of the sulfonyloxy group in 11, de-O-benzoylation (18→19) and hydrogenation (overall yield from 3: 42 %).

In addition, the N-glycosidation technique described is not limited to the preparation of adenine nucleosides. It may be applied to O, 9-bis(trimethylsilyl)-hypoxanthine (23) as evidenced by the ready conversions of 2 and of 1-O-acetyl-2, 3, 5-tri-O-benzoyl-ß-D-ribofuranose into 24 [mp 165-167°, $[\alpha]_D^{20}$+48°(c1, CH_3OH)] and the known[11] tribenzoylinosine 25, in yields of 67 and 71%, respectively. A less uniform course is expectedly[12] observed for the corresponding ribosidation of bis(trimethylsilyl)-allopurinol (26)[13], which afforded the major product, N-1-nucleoside 27 [mp 229-231°, $[\alpha]_D^{20}$-44° (c 0.5, acetone)], in 39% yield after separation (PLC)

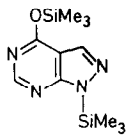
from minor components, presumably N-2 and/or α-isomers. On de-O-benzoylation with methanolic ammonia, 27 was readily converted into 1-(ß-D-ribofuranosyl)allopurinol 28[14].



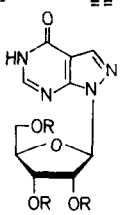
23



24 R = $NHCOCF_3$
25 R = OBz



26



27 R = Bz
28 R = H

This N-glycosidation technique may also be employed for the preparation of guanine nucleosides as indicated by reactions of bis(trimethylsilyl)-N-acetylguanine with 2 and 4, in which, however, the amount of stannic chloride appears to be of importance. The optimal ratio of sugar, base and catalyst is presently being elaborated.

References

(1) Part XIX: F. W. Lichtenthaler, A. Heerd, and K. Strobel, Chemistry Lett., 1974, in press.

(2) T. Sato, T. Shimadate, and Y. Ishido, Nippon Kagaku Zasshi, 81, 1440, 1442 (1961); W. W. Zorbach, Synthesis, 333 (1970).

(3) Y. Ishido, H. Tanaka, T. Yoshino, M. Sekiya, K. Iwabuchi, and T. Sato, Tetrahedron Lett., 6245 (1967).

(4) (a) B. R. Baker, R. E. Schaub, J. P. Joseph, and J. H. Williams, J. Amer. Chem. Soc., 77, 12 (1955); (b) B. R. Baker, R. E. Schaub, and H. M. Kissman, ibid., 77, 5911 (1965); (c) L. Goodman, J. W. Marsico, and R. B. Angier, ibid., 78, 4173 (1956).

(5) Y. Furukawa and M. Honjo, Chem. Pharm. Bull. (Tokyo), 16, 1076 (1968); W. W. Lee, A. P. Martinez, and L. Goodman, J. Org. Chem., 36, 842 (1971).

(6) The chloromercury derivative of 2-acetamido-6-chloropurine gave unsatisfactory results, cf. G. L. Tong, W. W. Lee, and L. Goodman, J. Org. Chem., 32, 1984 (1967).

(7) D. H. Murray and J. Prokop, J. Pharm. Sci., 56, 865 (1967); D. Horton and C. G. Tindall, Jr., Carbohyd. Res., 17, 240 (1971); L. M. Lerner, ibid., 19, 255 (1971).

(8) Trimethylsilyl-purines have only been used in glycosidations with acylglycosyl halides (fusion at 150-160°), giving α, ß-anomeric mixtures that require column chromatography for separations; cf. T. Nishimura, et al., Agric Biol. Chem. Jap., 28, 224 (1964); Chem. Pharm. Bull. (Tokyo), 12, 1471 (1964); Synth. Proc. Nucleic Acid Chem., 1, 135 (1968).

(9) These are standard conditions for N-glycosidations of silylated pyrimidines with 1-O-acylglycoses; cf. U. Niedballa and H. Vorbrüggen, Angew. Chem., 82, 449 (1970), ref. 1 and other literature cited there.

(10) Physical data agree well with those reported previously[4b].

(11) J. J. Fox, I. Wempen, A. Hampton, and I. L. Doerr, J. Amer. Chem. Soc., 80, 1669 (1958).

(12) cf. J. A. Montgomery, S. J. Clayton, and W. E. Fitzgibbon, J. Heterocycl. Chem., 1, 215 (1964).

(13) Obtained in nearly quantitative yield as stout crystals of mp 86° and λ_{max} 250 nm (dioxan) by refluxing pyrazolo[3, 4-d]pyrimidin-4-one (allopurinol) in hexamethyldisilanzane.

(14) Physical data correlated well with those of T. A. Krenitsky et. al., J. Biol. Chem., 2[illegible] 2675 (1967).