A mild method for the hydrolysis of acetal groups attached to sugars and nucleosides

Acetal groups are among the most useful protecting groups in sugar and nucleoside chemistry. Their removal, usually by aqueous acid, is, however, often difficult and is sometimes incompatible with other groups present. For removing these groups, we now report a new technique that is unusually mild, very rapid, and compatible with most of the common functional groups that are used in carbohydrate chemistry.

As part of an unambiguous synthesis of 1,6-dichloro-1,6-dideoxygalactitol[1], it was necessary to remove the acetal groups from 1,6-dichloro-1,6-dideoxy-2,4:3,5-di-*O*-isopropylidenegalactitol[2]. Aqueous acetic acid was ineffective, and use of a strongly acidic, ion-exchange resin in aqueous ethanol resulted in incomplete removal of the acetal groups, accompanied by solvolysis of the primary halide groups. When the protected sugar was dissolved in 90% (v/v) aqueous trifluoroacetic acid at room temperature, a high yield of deacetalated material of analytical purity was obtained within 10 min. The method has been extended to a variety of sugars, and the results are presented in Table I. It is clear from this summary that the method is applicable to benzylidene, as well as isopropylidene, acetals, and that the reagent does not noticeably affect halogen, benzoyl, sulfonyl, amino, or azido groups. We have noted no cleavage of the glycosyl–base linkage in the deacetalation of the one purine nucleoside derivative thus far studied. The applicability to a hexos-3-ulose derivative is also noteworthy. The trifluoroacetic acid reagent has excellent solvent properties and high volatility, thus simplifying processing procedures.

In a typical procedure, the protected compound (1 g) was dissolved in 10 ml of 9:1 (v/v) trifluoroacetic acid–water. After the compound had dissolved, the mixture was kept for 5–10 min at room temperature; the solvent was then evaporated off *in vacuo* (bath temperature <50°). Ordinarily, trituration of the residue with ether left a crystalline solid that was either analytically pure or could be recrystallized readily. For ether-soluble compounds, trituration of the residue with hot hexane usually removed traces of trifluoroacetic acid and, for example, benzaldehyde. In a number of cases, the product crystallized from the trifluoroacetic acid solution.

Further extension of the method to nucleoside chemistry is in progress, as is a study of the conditions necessary for hydrolysis of methylene acetals. Extension of the method to the hydrolysis of trityl ethers is also under investigation.

ACKNOWLEDGMENT

This work was conducted under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. PH-43-64-500. The opinions expressed are those

TABLE I[a]

HYDROLYSES WITH AQUEOUS TRIFLUOROACETIC ACID

Starting material	*Product*	*Yield (%)*[b]	$[\alpha]_D$, *degrees*[c]	m.p., *degrees*[d]
1,6-Dichloro-1,6-dideoxy-2,4:3,5-di-*O*-isopropylidene-galactitol[2]	1,6-Dichloro-1,6-dideoxy-galactitol[1]	83–96		181–182
2,4:3,5-Di-*O*-isopropylidene-1,6-di-*O*-(methylsulfonyl)-galactitol[3]	1,6-Di-*O*-(methylsulfonyl)-galactitol[4]	83–84		140–141
2,4:2,5-Di-*O*-isopropylidene-1,6-di-*O*-*p*-tolylsulfonyl-galactitol[5]	1,6-Di-*O*-*p*-tolylsulfonyl-galactitol	76		127–129
1,6-Di-*O*-benzoyl-2,4:3,5-di-*O*-isopropylidene-galactitol[1]	1,6-Di-*O*-benzoyl-galactitol[1]	90		210–215
1,2:5,6-Di-*O*-isopropylidene-D-glucofuranose	D-Glucose	64	+52.3	144–147.5
1,2:5,6-Di-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-D-allofuranose[6]	3-*O*-*p*-Tolylsulfonyl-D-allose	82–84	+ 3.5	140–143[e]
6-Azido-6-deoxy-1,2-*O*-isopropylidene-D-glucofuranose[7]	6-Azido-6-deoxy-D-glucose	68	+58.2	133.5–138
1,2:5,6-Di-*O*-isopropylidene-D-*ribo*-hexos-3-ulose[8]	D-*ribo*-Hexos-3-ulose[9]		+55.6[f]	119–125
3,5-*O*-Benzylidene-1,2-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-D-glucofuranose[10]	6-*O*-*p*-Tolylsulfonyl-D-glucose[11]	44	+37.6	109–112[g]
Methyl 4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside[12]	Methyl 2-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside[13]	60	+87.5 ($CHCl_3$)	137–138
Methyl 4,6-*O*-benzylidene-3-*O*-*p*-nitrobenzoyl-2-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside	Methyl 3-*O*-(*p*-nitrobenzoyl)-2-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside	65		180–182
5′-*O*-Acetyl-8-bromo-2′,3′-*O*-isopropylideneadenosine[14]	5′-*O*-Acetyl-8-bromoadenosine trifluoroacetate	51		145–149

[a] Correct elemental analyses were obtained for all new compounds, and their n.m.r. and i.r. spectra were consistent with the structures assigned. All other compounds had been reported in the literature, and their physical constants compared well with the literature values, except where otherwise noted. [b] Yield of analytical material. [c] End values in water (*c*, 1.0) unless otherwise noted. [d] Uncorrected. [e] Prior to recrystallization from ethanol, the product had m.p. 123.5–125°. [f] Reported[9] as the hydrate isolated from hydrolysis of "3-ketosucrose" The reported $[\alpha]_D^{26}$ value of +14.8° may indicate incomplete anomeric equilibration. [g] The lit.[11] values are $[\alpha]_D^{26}$ +39° and m.p. 132–133°. We attribute the difference in m.p. to anomeric differences, as the elemental analysis was correct.

of the authors, and not necessarily those of the Cancer Chemotherapy National Service Center.

Life Sciences Research,
Stanford Research Institute,
Menlo Park, California 94025 (U. S. A.)

JAMES E. CHRISTENSEN
LEON GOODMAN

REFERENCES

1 K. Butler and W.A.W. Cummings, *J. Chem. Soc.*, (1956) 636.
2 T.P. Bird, W.A.P. Black, E.T. Dewar and J.B. Hare, *Chem. Ind.* (London), (1961) 1077.
3 S.S. Brown and G.M. Timmis, *J. Chem. Soc.*, (1961) 3656.
4 L. Vargha, J. Kuszmann and B. Dumbovich, Austrian Patent 214,417; *Chem. Abstr.*, 55 (1961) 15365.
5 R.M. Hann, W.D. Maclay and C.S. Hudson, *J. Amer. Chem. Soc.*, 61 (1939) 2432.
6 D.T. Williams and J.K.N. Jones, *Can. J. Chem.*, 45 (1967) 7.
7 F. Cramer, H. Otterbach, and H. Springmann, *Ber.*, 92 (1959) 384.
8 O. Theander, *Acta Chem. Scand.*, 18 (1964) 2209.
9 S. Fukui and R.M. Hochster, *J. Amer. Chem. Soc.*, 85 (1963) 1697.
10 A.S. Meyer and T. Reichstein, *Helv. Chim. Acta*, 29 (1946) 139.
11 J. Compton, *J. Amer. Chem. Soc.*, 60 (1938) 395.
12 R.W. Jeanloz and D.A. Jeanloz, *J. Amer. Chem. Soc.*, 79 (1957) 2579.
13 H.B. Wood, Jr., R. Allerton, H.W. Diehl, and H.G. Fletcher, Jr., *J. Org. Chem.*, 20 (1955) 875.
14 M. Ikehara and H. Tada, *Chem. Pharm. Bull.*, (Tokyo), 15 (1967) 94.

(Received May 31st, 1968)

Carbohyd. Res., 7 (1968) 510–512