Note

Pyridinium chlorochromate for the oxidation of carbohydrates*

DAVID H. HOLLENBERG[†], ROBERT S. KLEIN[§], AND JACK J. FOX

Laboratory of Organic Chemistry, Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Institute, Sloan-Kettering Division of Graduate School of Medical Sciences. Cornell University, New York, NY 10021 (U. S. A.) (Received November 28th, 1977; accepted for publication, January 27th, 1978)

The synthetic utility of oxo derivatives of monosaccharides as intermediates in the preparation of new sugars has provided an impetus for the investigation of new oxidizing reagents. The oxidative properties of chromium(VI) oxide (chromic anhydride) and its various salts and complexes are well established¹. However, the application of chromium oxide oxidations to carbohydrates has generally been limited to the use of the chromium oxide–pyridine complex, and to chromium oxide in acetic acid². It has been reported that the chromium oxide–pyridine complex is a useful reagent for the oxidation of isolated secondary hydroxyl groups in alditol derivatives³ and in some furanoid and pyranoid systems⁴. This complex has also been shown to oxidize unprotected anomeric hydroxyl groups to yield the corresponding lactones⁵. Oxidation of "isolated endocyclic secondary hydroxyl groups"⁶ in furanoid systems with the chromium trioxide–pyridine complex has been generally unsuccessful^{3,6}.

Recently, Corey and Suggs⁷ demonstrated the general utility of pyridinium chlorochromate, a readily available, stable reagent for the facile oxidation of primary and secondary alcohols to carbonyl compounds. This reagent has been recently applied to the oxidation of a hexopyranoside⁸. We wish to report herein the general application of this reagent to the oxidation of isolated secondary hydroxyl groups in both pyranoid and furanoid systems.

Our interest in this reagent was brought about by our need for large quantities of 1,2-O-isopropylidene- α -D-ribofuranose⁹ (1). This is obtainable by oxidation of 1,2-O-isopropylidene-5-O-methoxycarbonyl- α -D-xylofuranose(2) to the corresponding ketone 4, followed by reduction with sodium borohydride. Although we had previously reported the synthesis of this sugar by use of ruthenium tetraoxide as the oxidant⁹, certain aspects of this reaction were undesirable. Monitoring and main-

^{*}This investigation was supported by funds from the National Cancer Institute, U.S. Public Health Service (Grant No. CA-18601 and CA-08748).

[†]Present address: St. Regis Technical Center, West Nyack, NY 10994, U.S.A.

STo whom all inquiries should be addressed.

taining the pH of the reaction is extremely critical, for if the reaction becomes too basic the 5-O-methoxycarbonyl group can be hydrolyzed whereas too low a pH results in a very slow reaction. In addition the expense of the reagents for a large-scale synthesis can become significant.



Attempts to utilize dimethyl sulfoxide-dicyclohexylcarbodiimide¹⁰, dimethyl sulfoxide-cyanuric chloride¹¹, and other reagents related to dimethyl sulfoxide, which are known to oxidize hydroxyl groups to the corresponding carbonyl group¹⁰, were not successful. Therefore, we chose to investigate pyridinium chlorochromate as an inexpensive, easily-handled alternative reagent that is commercially available.

Following the procedure of Corey and Suggs⁷, dichloromethane was initially employed as the solvent for oxidation. However, it was found that oxidation of secondary hydroxyl groups in sugars was very slow, even in the presence of large excess of oxidant and under reflux conditions. Instead, benzene was found to be a good alternative solvent. Oxidation of sugars 2, 3, 6, 8, and 10 was accomplished readily and in good yield (see Table I), simply by heating under reflux a benzene solution of the sugar in the presence of pyridinium chlorochromate. The products, 4, 5, 7, 9, and 11, respectively, were easily obtained in analytically pure, crystalline form. Pyridinium chlorochromate is also suitable for large scale oxidations. We have successfully oxidized 2 on a molar scale (see Experimental part).

Conditions and properties of compounds obtained	Compounds oxidized				
	2	3	6	8	10
mmol sugar/mmol oxidant	3:5	3:5	3:5	5.2:15	3:5
Reaction time (h)	1.5	1.5	2.5	1.0	3.0
Yield (%)"	73	82	63(85)	84	84(92)
M.p. (°) ^b	81-82.5	96–97 (93–94.5)	106 (111–112)	123–125 (126)	102–103 (102–103)
Anal. ^c C	45.60 (45.46)	61.66 (61.64)	52.36 (52.16)	55.80 (55.78)	55.77 (55.78)
Н	6.25 ^d (6.10)	5.38 (5.52)	7.30 ⁴ (7.29)	6.96 (7.03)	7.10 (7.03)
Reference		12	13	14	15

TABLE I

OXIDATION OF COMPOUNDS 2. 3, 6, 8, AND 10 WITH PYRIDINIUM CHLOROCHROMATE

^aYield of analytically pure material obtained in the first crop. Values in parentheses include material obtained in successive crops. ^bValues in parentheses are the literature melting points from the cited references. ^cValues in parentheses are the calculated analytical values. ^dObtained as the hydrate.

The oxidation of primary hydroxyl groups to the corresponding aldehydes is also readily accomplished with pyridinium chlorochromate under conditions essentially similar to those just described. The oxidation of such groups with chromic anhydride reagents has been reported previously⁶, and the present findings provide a useful modification for the oxidation of primary hydroxyl groups in carbohydrates.

Because of the ease and efficiency with which pyridinium chlorochromate oxidizes primary and secondary hydroxyl groups in both furanoid and pyranoid sugars, this reagent is a valuable addition to the methodology available for the oxidation of carbohydrates.

EXPERIMENTAL

General method of oxidation. — A solution of the sugar (see Table I) in benzene (100 ml) was stirred vigorously with a mechanical stirrer and heated to reflux. Pyridinium chlorochromate (3.3 g., 15 mmol) was added and the stirring continued. Upon completion of the reaction, as determined by t.l.c. (see Table I for approximate reaction times), the hot reaction mixture was filtered through Celite. The dark gummy precipitate was triturated with hot benzene and filtered through Celite, the combined benzene solutions were evaporated to dryness, and the residue was heated on a steam bath with heptane. Filtration removed residual insoluble chromium compounds. Upon cooling, the products crystallized from heptane in analytically pure form (See Table I for yields). In general, additional amounts of material could be obtained from the mother liquors.

Large-scale preparation of 1,2-O-isopropylidene-x-D-ribofuranose (1). — A vigorously stirred suspension of pyridinium chlorochromate (520 g, 2.4 mol) in

benzene (7.6 L) was brought to reflux and 1,2-O-isopropylidene-5-O-methoxycarbonyl- α -D-xylofuranose (2) (240 g, 0.97 mol) was added*. After 2.5 h, the reaction mixture was filtered through Celite, and the reaction vessel and Celite were washed with benzene (3 × 400 ml). The filtrate was concentrated in vacuo to ~800 ml and then passed through a pad of Silica 60 (300-400 g). The silica was washed with ethyl acetate and the combined filtrates evaporated to provide the crude ketose 4. This material was then reduced directly to 1,2-O-isopropylidene- α -D-ribofuranose (1). Crude 4 was dissolved in a mixture of ethanol (1 liter) and water (150 ml), and cooled in an ice bath while a solution of sodium borohydride (32 g) in water (100 ml) was slowly added with stirring. The reaction mixture was allowed to come to room temperature and stirring was continued overnight. The inorganic solids were collected and washed with ethanol, and the combined filtrates were treated with Bio-Rad AG-50 (H^+) and then with Amberlite IR-45 (OH⁻) ion-exchange resins. The solution was evaporated and the residue crystallized from benzene-ethyl ether. Filtration provided 1 (98.5 g); concentration of the mother liquor yielded additional 1 (4.8 g, 56% overall yield).

REFERENCES

- 1 For a discussion of chromic anhydride reagents, see L. F. FIESER AND M. FIESER, *Reagents for Organic Synthesis*, Vol. I, Wiley, New York, 1967, p. 144 and following volumes.
- 2 For a review of oxidations in the field of carbohydrates, see R. F. BUTTERWORTH AND S. HANESSIAN, Synthesis, (1971) 70-88.
- 3 G. Y. WU AND M. SUGIHARA, Carbohydr. Res., 13 (1970) 89-95.
- 4 A. S. JONES, A. R. WILLIAMSON, AND M. WINKLEY, Carbohydr. Res., 1 (1965) 187–195; E. WALTON,
 J. E. RODIN, C. H. STAMMER, F. W. HOLLY, AND K. FOLKERS, J. Am. Chem. Soc., 80 (1958) 5168–5173; M. L. WOLFROM AND S. HANESSIAN, J. Org. Chem., 27 (1962) 2107–2109.
- 5 S. HANESSIAN AND T. H. HASKELL, J. Heterocycl. Chem., 1 (1964) 55-56.
- 6 R. E. ARRICK, D. C. BAKER, AND D. HORTON, Carbohydr. Res., 26 (1973) 441-447.
- 7 E. J. COREY AND J. SUGGS, Tetrahedron Lett., (1975) 2647-2650.
- 8 D. R. HICKS AND B. FRASER-REID. J. Chem. Soc., Chem. Commun., (1976) 869-870.
- 9 G. R. RITZMANN, R. S. KLEIN, D. H. HOLLENBERG, AND J. J. FOX, Carbohydr. Res., 39 (1975) 227-236.
- 10 K. E. PFITZNER AND J. G. MOFFATT, J. Am. Chem. Soc., 85 (1963) 3027-3028; 87 (1965) 5661-5670; 87 (1965) 5670-5678.
- 11 J. D. Albright, J. Org. Chem., 39 (1974) 1977-1979.
- K. OKA AND H. WADA, J. Pharm. Soc. Jpn., 83 (1963) 890-891; Chem. Abstr., 60 (1964) 1825:d;
 R. F. NUTT, M. J. DICKINSON, F. W. HOLLY, AND E. WALTON, J. Org. Chem., 33 (1968) 1789; H. YANAGISAWA, M. KINOSHITA, S. NAKADA, AND S. UMEZAWA, Bull. Chem. Soc. Jpn., 43 (1970) 246-252.
- 13 D. C. BAKER, D. HORTON, AND C. G. TINDALL, JR,. Carbohydr. Res., 24 (1972) 192-197.
- 14 D. HORTON AND J. S. JEWELL, Carbohyar. Res., 2 (1966) 251-260.
- 15 R. S. TIPSON, R. F. BRADY, JR., AND B. F. WEST, Carbohydr. Res., 16 (1971) 383-393.

^{*}In order to avoid unmanageably large volumes of solvent in scaling up these preparations, concentrated solutions of reagents were employed. Under these conditions, the partially insoluble pyridinium chlorochromate had a tendency to cake and settle rapidly when added to solutions of the sugar. It was found more efficient, in such cases, to add the sugar to the hot and well-stirred suspension of the oxidizing agent.