Carbohydrate Research, 149 (1986) C1–C4
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Preliminary communication

Nicotinium dichromate: a new cheap reagent for high-yielding large-scale oxidation of carbohydrates*

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(Received January 3rd, 1986; accepted for publication, February 24th, 1986)

The oxidation of alcohols to give ketones is widely used in carbohydrate chemistry[2] as a step in the synthesis of deoxy, amino, and branched-chain sugars. Our study[3] of the addition of carboxylic acid dianions to the carbonyl group in sugars required an efficient large-scale preparation of sugar aldehydes and ketones. Oxidation of hydroxyl groups of carbohydrates by means of chromium trioxide–pyridine, ruthenium tetraoxide, and methyl sulfoxide-based reagents often gives only moderate yields of carbonyl compounds[4]. Pyridinium chlorochromate is a good oxidant for the large-scale preparation of keto sugars[5] and its reactivity is increased when used together with a molecular sieve[6]. However, in our hands, oxidation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose with this reagent gave only 45–50% of the keto sugar (63% reported)[5]. The yield can be increased up to 96% by using pyridinium dichromate–acetic anhydride[7], and more recently the use of a pyridinium dichromate–acetic acid–molecular sieve system has been described[8] for the small-scale oxidation of sugars. In our hands, these methods were not amenable to large-scale reactions.

To our knowledge, no other chromium(VI) reagents have been used for the efficient oxidation of sugars[9]. We have reported[10] on nicotinium dichromate as a new and inexpensive oxidising agent and now report preliminary results on its use for the preparation of some sugar aldehydes and ketones. Oxidation of **3** with nicotinium dichromate to give 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-2,3-hexodiulopyranose **4** was examined under various conditions (Fig. 1). With benzene as solvent, the oxidation was slow, and the rate was only slightly increased by the addition of sodium acetate. In benzene–acetic anhydride, oxidation was retarded and only a low yield of **4** was obtained. However, in benzene, the reagent together with pyridine in the molar ratio 1:2 caused rapid oxidation and gave a high yield of **4**.

Further results using this combination are summarised in Table I; high yields of chromatographically pure products were obtained. Even the unreactive hydroxyl group of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose was oxidised efficiently. Likewise, primary

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*Reagents and Synthetic Methods, Part 56. For Part 55, see ref. 1.

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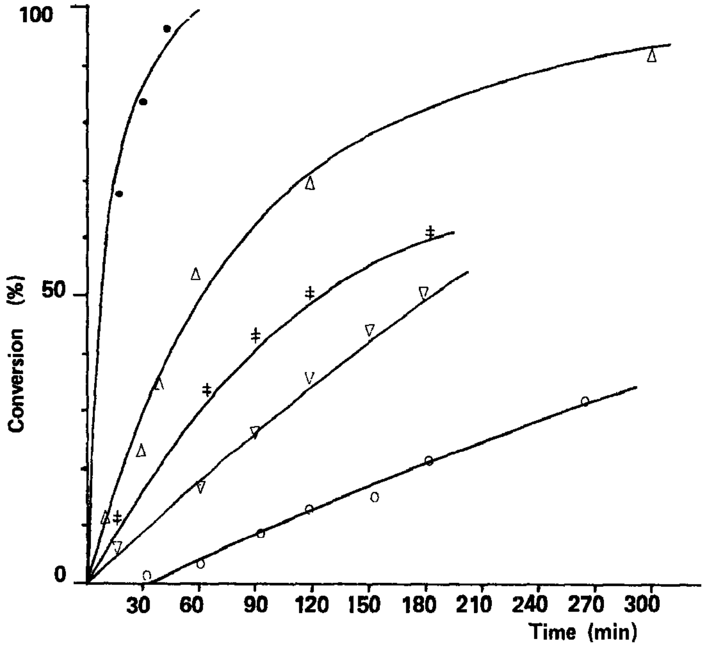


Fig. 1. Oxidation of 3 with nicotinium dichromate in benzene–pyridine (–•–), dichloromethane–pyridine (–△–), benzene–sodium acetate (–‡–), benzene (–▽–), benzene–acetic anhydride (–○–). Conversions were measured by g.l.c. on SE-30 (170°, 20 mL/min, N_2).

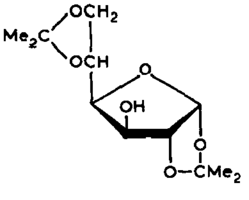
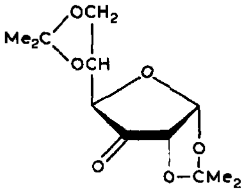
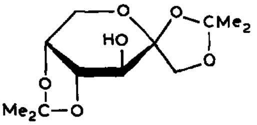
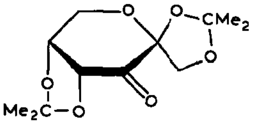
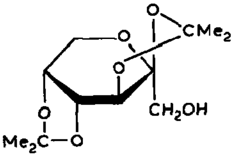
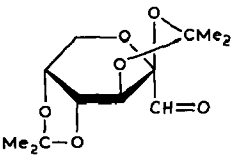
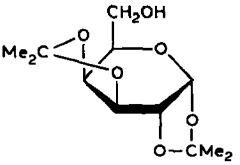
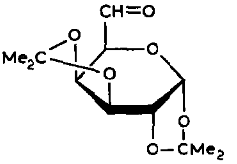
alcohols were rapidly and cleanly converted into the corresponding aldehydes without noticeable over-oxidation. Benzene was the reaction solvent of choice and reactions in dichloromethane were slower. Work-up involved filtration through Celite, concentration, and removal of residual pyridine by azeotropic distillation with toluene. Thus, the yields are high, primary and secondary alcohols are oxidised with equal ease, the reagent is cheap, non-hygroscopic, non-photosensitive, and stable, the work-up is simple, aldehydes are obtained as non-hydrated products, and the method is amenable to the large-scale preparation of sugar aldehydes and ketones.

Nicotinium dichromate was prepared[10] as follows. To a solution of chromium trioxide (48 g, 480 mmol) in water (48 mL) was added nicotinic acid (29.5 g, 240 mmol) at 0–5° (ice–water) with stirring. After 15 min, acetone (100 mL) was added at 0–5° to the red–orange suspension and the mixture was stirred at 0–5° for 15 min. The product was collected, and washed with acetone (4 X 200 mL) and dichloromethane (2 X 200 mL) until the filtrate became colorless, affording nicotinium dichromate (47 g, 85%) as an orange–yellow solid, m.p. 215–217° (dec.).

A general procedure for the oxidation of carbohydrates is as follows. To a stirred mixture of benzene (500 mL) and pyridine (48 mL, 0.6 mol) were added nicotinium dichromate (139.2 g, 0.3 mol) and the substrate (0.1 mol) consecutively at room temperature. The mixture was stirred and boiled under reflux until the oxidation was com-

TABLE I

OXIDATION OF SUGARS WITH NICOTINIUM DICHROMATE[a]

Alcohol	*Product*	*Molar ratio Oxidant/Sugar*	*Time*	*Yield*[b,c]	*Ref.*
 1	 2	3:1	2.5 h	(75) 85	7
 3	 4	3:1	1 h	(85) 94	5
 5	 6	3:1	30 min	(81) 92	4
 7	 8	2:1	20 min	(75) 90	7

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[a] Performed at 80° with 0.1 mol of alcohol and an oxidant/pyridine molar ratio of 1:2. [b] Of isolated pure products (purity, as determined by g.l.c., was >98%). The numbers in parentheses indicate yields after distillation or crystallisation. [c] N.m.r. and i.r. data accorded with those in the literature.

plete (assessed by g.l.c., see Table I), then cooled to room temperature, and filtered through Celite. The dark precipitate was washed with benzene (2 X 200 mL), the combined filtrate and washings were concentrated to dryness, and a solution of the residue in toluene (50 mL) was concentrated to dryness. This operation was repeated twice in order to remove the residual pyridine. The crude product was then dissolved in benzene, the residual nicotinic acid was removed, and the filtrate was concentrated to give the chromatographically pure aldehyde or ketone in high yield.

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