Carbohydrate Research, 70 (1979) 313–318

Note

Efficiency of cadmium carbonate as an aryl glycosidation catalyst: effects of lot variations on product compositions*

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(Received May 12th, 1978; accepted for publication, July 2nd, 1978)

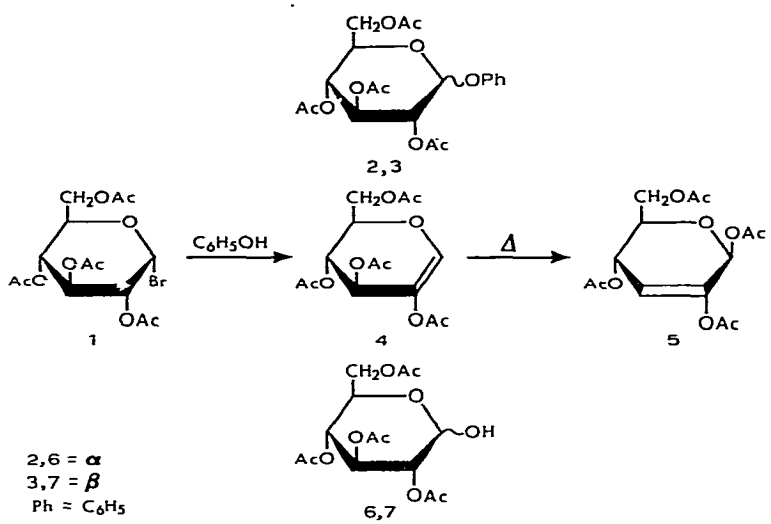
Even though condensations of phenols with carbohydrates are commonplace[1–3], reactions that do not use preformed salts of phenols or acidic catalysts often give indifferent yields of *O*-glycosides. Conrow and Bernstein[4] reported a substantial improvement in yields of aryl steroid *O*-glucosiduronates when cadmium carbonate was substituted for silver carbonate in Koenigs–Knorr condensations. Interestingly, a *C*-glucosiduronate of equilenin was produced in 14% yield together with the expected *O*-analog. Use of cadmium carbonate catalysis was extended to alicyclic sterol glycosidations in a later report[5].

To evaluate cadmium carbonate more fully as an aryl glycosidation catalyst, and to determine whether *C*-glycosides may be expected as commonplace byproducts, eight commercial samples of powdered cadmium carbonate were tried in Koenigs–Knorr condensations of phenol with tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**1**). The stocks, six of recent manufacture and two more than 20 years old, were considered typical of commercial cadmium carbonates. Because particle sizes varied from 10–100+ mesh within a bottle, all samples were sieved without grinding, to obtain fractions that would pass a 100-mesh screen.

Preliminary experiments established that the 1.5-h reaction period used with aryl steroids[4] was too short for most condensations of **1** with phenol. Because neutral, water-free mixtures of **1** and phenol are stable in boiling toluene for at least 24 h, a 24-h reaction period was adopted unless **1** was consumed in less time. The approximate half-life of **1** varied from less than 1 h to more than 24 h, depending on which cadmium carbonate sample was used, with wide variations in the degree to which **1** was consumed by side reactions.

*Dedicated to Professor Roy L. Whistler.

†The mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.



Scheme 1

TABLE I

PRODUCT-MIXTURE COMPOSITIONS[a]

Catalyst[b]	*Sample*	2 + 3	α:β	4 + 5[c]	6 + 7
$CdCO_3$	A	61	1:5	0	36
	B	34	1:3	30	12
	C	21	1:3	27	11
	D	26	1:4	33	9
	E	40	3:7	15	41
	F	23	1:3	41	10
	G	73	1:6	0	24
	H	19	1:3	30	9
Ag_2CO_3		20	1:4	10	62
$BaCO_3$		<1	—	<1	5
$CaCO_3$		<1	—	<1	3
$PbCO_3$		35	1:9	20	36

[a]After 24 h; except A, 2 h; E and G, 3 h; Ag_2CO_3, 1 h. [b]Passed 100-mesh screen. [c]Compound 5 present as 5–8% of total.

As shown in Scheme 1 and accompanying Table I, three pairs of major products were formed; the expected phenyl α- and β-glycosides (**2** and **3**), dehydrohalogenation products (**4** and **5**), and hydrolysis products (**6** and **7**). Additionally, five minor products, totaling 2–7% (w/w) of the total product-mixture, were detected by t.l.c. and g.l.c. Use of unsieved catalysts tended to prolong the reaction time, decrease yields of **2** and **3**, and increase production of **4**, causing yield variations of up to one-third of the quantities listed in Table I. Product compositions could be duplicated

only with sieved catalysts, confirming the observation[4] that yields of glycosides are a function of the catalyst's surface area.

Components in the product mixtures were examined by g.l.c.–m.s., and major products were identified by spectral comparisons with authentic samples. Additionally, the major unsaturated derivative, **4**, was isolated crystalline for ^{13}C-n.m.r. analysis.

Absolute structures for the minor products were not determined by isolation and examination of pure components, but preparative t.l.c. afforded fractions rich enough in these compounds for structural assignments by g.l.c.–m.s. analysis. The two most plentiful minor products appear to be anomeric phenyl hexenopyranoside triacetates, which are eluted just before **2** in g.l.c. analyses, and migrate ahead of **2** on t.l.c. plates. The mass spectra of both minor products closely match those obtained for **2** and **3**; they lose phenoxyl groups, to form M — 93 ions (*m/e* 271 for unknowns, *m/e* 331 for **2** and **3**). Furthermore, both of the minor products and the analogous **2** and **3** then eliminate the elements of acetic acid and ketene by major pathways established for acetylated glycopyranosides[6]: *m/e* 271, 229, 169, 109; 271, 211, 169, 127; and 157, 115, and 73. Additionally, the unsaturated glycosides apparently eliminate $C_7H_6O_2$ by a minor cleavage of C-1–C-2 that parallels a retro-Diels–Alder reaction reported[6] for an unsaturated intermediate derived from β-D-glucose pentaacetate, forming the common-ion series *m/e* 242, 200, 140, and 98. The ion series was not seen for **2** and **3**, presumably because elimination of the phenoxyl group occurs more readily than an initial loss of acetic acid followed by C-1–C-2 cleavage. The origin of the unsaturated glycosides is unknown; however, it was determined that they are not formed by the action of cadmium carbonate on mixtures of **4**, **5**, and phenol.

Of greater interest is a trace component (<0.5%) observed in product mixtures after acetylation with pyridine and acetic anhydride; it overlapped the rear edge of **3** on t.l.c. plates and was eluted just after **3** during g.l.c. The mass spectrum was markedly different from that of **2** and **3** in that little phenoxyl elimination to form *m/e* 331 was found, and standard ion-decomposition series of the type *m/e* 331, 271, 229, ... were not seen. Rather, the ion-fragmentations were consistent with a *C*-phenyl D-glucopyranoside pentaacetate structure, even though a molecular ion (*m/e* 466) was not observed in the spectrum. The largest ions found were assigned as M — 42 and M — 120 (*m/e* 424, 346), with further losses of acetic acid and ketene for the proposed series: *m/e* 466, 424, 304, 244, 202; 466, 346, 286, 244; 466, 346, and 304. Cleavage of C-5–C-6 (-73 a.m.u.) suggests *m/e* 346, 273, 231, 189; 304, and 231, and cleavage of C-1–C-2 (-122 a.m.u.) gives the added series *m/e* 424, 259, 139, 97; 259, 217, 97; 217, 157, and 97. All series are consistent with the loss of five acetates from the proposed *C*-phenyl glycoside.

The remaining byproducts could be classified only as apparently unsaturated di- and tri-acetylated hexose derivatives that may be mixtures within each classification. They were not examined further.

Given the extreme differences in glycosidation efficiency seen in Table I, Conrow and Bernstein[4] were fortunate in that both of their cadmium carbonate

samples were highly efficient, even though they differed substantially in glycosidation capability. However, it is clear that, if time permits the testing of several cadmium carbonate samples from various sources, specimens may be found that will efficiently produce **2** and **3**. Fortunately, concurrent dehydrohalogenation to produce **4** is likely to be relatively low for efficient catalysts, because even the highest levels of **4** produced by any of the cadmium carbonate samples were far lower than reported for efficient dehydrogenation agents[7–9].

Individual samples of barium, calcium, silver, and lead carbonate, sieved to pass a 100-mesh screen, were also tested as aryl glycosidation catalysts. Variations in catalytic efficiency among different lots were not tested. Silver carbonate, the standard by which other Koenigs–Knorr catalysts are judged, formed **2** and **3** as efficiently as three of the cadmium carbonate samples, whereas lead carbonate equaled or surpassed all but three of the eight cadmium carbonate samples tested. Barium and calcium carbonates were ineffective, leaving approximately 95% of **1** unchanged after 24 h. For barium carbonate, extending the reaction period to 72 h afforded modest yields of glycosides (**2** and **3**, 14%), unsaturated compounds (**4** + **5**, 30%), and hydrolysis products (**5** + **6**, 10%).

EXPERIMENTAL

General. — Proton-n.m.r. spectra were recorded at 100 MHz with a Varian HA-100 spectrometer, and ^{13}C-n.m.r. spectra were measured with a Bruker WH-90 instrument with tetramethylsilane ($\delta = 0.0$) as the internal standard. Solute concentrations were approximately 20% (w/v). Chemical shifts were measured directly. An F & M Model 810 chromatograph, fitted with a 2-mm i.d. × 1.22-m length of glass tubing packed with 3% of DEXSIL 300 GC on 100–120 mesh Supelcoport, was used for g.l.c. A DuPont 21-491 mass spectrometer, operated at 70 eV and coupled to a Bendix 2600 gas chromatograph, was used for g.l.c.–m.s. analyses. The column for the g.l.c.–m.s. analyses was a 2-mm i.d. × 1.22-m length of glass tubing packed with 3% of OV-1 on 80–100 Gas Chrom Q. G.l.c. columns were programmed from 150–250° at 4 d.p.m. with helium as the carrier gas. Precoated, activated plates of Silica Gel F-254 (E. Merck, Darmstadt, Germany) were used for t.l.c. Layer thicknesses were 0.25 and 2.0 mm for analytical and preparative separations, respectively. All chromatographic solvents were proportioned on a v/v basis. Toluene was dried over calcium hydride.

Materials and methods. — Samples of **1**, **3**, **4**, **5**, and **7** were prepared by standard methods[1,9–11]. Calcium carbonate was purchased from J. T. Baker Chemical Co.; barium, silver, and lead carbonates from Fisher Scientific Co. The cadmium carbonate samples were: Matheson, Coleman and Bell CX-28(A) and CX-30(B); Ventron Alfa Products, No. 87360 (two lots, C and D) and No. 20131 (ultrapure), E; Fisher Scientific Co., F; Merck and Co., G; Mallinckrodt (AR), H. All but G and H were of recent manufacture. Particle sizes for each sample varied from 10–100+ mesh, the bulk falling within 40–100 mesh except for A (90% passed a 100-mesh screen).

All samples were sieved without grinding to obtain samples that passed a 100-mesh screen.

Condensations were performed in a two-necked, 500-mL round-bottom flask fitted with a Soxhlet extractor that contained Davison 4Å molecular sieve (50 g, 14–30 mesh) in a 33 × 94 mm thimble and was protected from moisture. A slurry of metal carbonate (10 mmol), phenol (1.1 g, 11.7 mmol), and toluene (175 mL) was stirred magnetically and boiled under reflux for 15–20 min before adding a solution of **1** in toluene (2.1 g, 5.1 mmol; 25 mL). Stirring and refluxing were continued for 24 h, unless **1** was consumed before then. Samples (1 mL) were withdrawn periodically for g.l.c. and t.l.c. analyses. Corrections were applied for non-equivalent detector responses of the individual compounds. Despite on-column injection, 25% of the residual **1** was pyrolyzed in the 300° injection port to form **4** and **5**. After 24 h, the mixture was filtered and a 100-mL portion was stirred with silver acetate (1.5 g) for 18 h at 25°. The solution was then treated with pyridine and acetic anhydride (2:1, 6 mL) for 48 h at 25° and washed with dilute, aqueous cupric sulfate to remove pyridine. Product-mixture compositions before and after acetylation were calculated from g.l.c. analyses, and corrected for a 10–12% conversion of residual **1** and phenol into **3** during the treatment with silver acetate.

Isolation of **4**. — A slurry of **1** (2 g) and cadmium carbonate sample "F" (3.4 g) in toluene (200 ml) was stirred and boiled under reflux as before for 48 h, and then filtered and stirred with silver carbonate (2 g) for 24 h at 25°. The mixture was filtered and the filtrate evaporated, and the syrupy residue was then streaked on four preparative t.l.c. plates. Two solvent ascents (4:1 hexane–acetone), followed by extraction of the major band of highest R_F value, gave a crude syrup (0.8 g) that was distilled (200°/1 torr) and examined by ^{1}H-n.m.r. and mass spectroscopy. All spectral data matched closely those reported[12–14] for **4**. Crystallization from ethanol gave **4**; m.p. 60–62° (lit.[8] 61–62°); ^{13}C-n.m.r. ($CDCl_3$): δ 170.4 (s, CO), 170.1 (s, CO), 169.4 (s, CO), 139.3 (d, C-1), 127.6 (s, C-2), 74.2 (d), 67.7 (d), 66.5 (d), 61.0 (t, C-6), 20.7 (q, CH_3), and 20.4 (q, CH_3).

Mass-spectral comparisons. — The three unknowns incorporating phenol were identical in glycosidations catalyzed by barium carbonate or any cadmium carbonate sample, as judged by g.l.c.–m.s. Fractions enriched in the unknowns were obtained by preparative t.l.c. as described for **4**, and checked by g.l.c. For comparison, principal ions and relative intensities are listed for **3**, the presumed anomeric phenyl hexenopyranoside triacetates, and the probable *C*-phenyl D-glucopyranoside pentaacetate.

Mass spectrum of **3**. — (*m/e*, %) 331 (M − 93, 19), 271 (2.4), 229 (1.7), 211 (2.1), 169 (89.3), 157 (1.0), 139 (6.3), 127 (15.5), 115 (6.9), 109 (100), 97 (8.0), 94 (14), 73 (1.3), and 43 (90.7).

Byproduct glycosides. — *m/e* 271 (M − 93, 9.7), 242 (0.2), 229 (0.4), 211 (1.3), 200 (0.1), 169 (43.0), 157 (1.3), 140 (0.8), 139 (5.1), 127 (10.0), 115 (2.3), 109 (53.1), 98 (8.3), 97 (11.8), 94 (14.5), 73 (1.0), and 43 (100).

Byproduct C-glycosyl compounds — *m/e* 424 (M − 42, 0.8), 346 (M − 120, 0.8), 331 (M − 93, 0.9), 304 (1.5), 286 (6.7), 273 (6.8), 259 (1.9), 244 (4.8), 231 (10.4), 217

(0.8), 202 (11.0), 189 (5.0), 157 (2.5), 139 (6.5), 123 (3.6), 115 (3.6), 97 (5.8), 94 (1.7), 91 (8.0), and 43 (100).

REFERENCES

1 T. D. AUDICHYA, T. R. INGLE, AND J. L. BOSE, *Indian J. Chem.*, 9 (1971) 315–317.
2 J. CONCHIE AND G. A. LEVVY, *Methods Carbohydr. Chem.*, 2 (1963) 335–336, 345–346.
3 J. CONCHIE, G. A. LEVVY, AND C. A. MARSH, *Adv. Carbohydr. Chem.*, 12 (1957) 157–178.
4 R. CONROW AND S. BERNSTEIN, *J. Org. Chem.*, 36 (1971) 863–870.
5 J. P. JOSEPH, J. P. DUSZA, AND S. BERNSTEIN, *Biochemistry*, 10 (1971) 2941–2947.
6 H. BUDZIKIEWICZ, C. DJERASSI, AND D. H. WILLIAMS, *St:ucture Elucidation of Natural Products by Mass Spectroscopy*, Vol. II, Holden–Day, San Francisco, 1964, pp. 203–240.
7 D. R. RAO AND L. M. LERNER, *Carbohydr. Res.*, 22 (1972) 345–350.
8 H. PAULSEN AND J. THIEM, *Chem. Ber.*, 106 (1973) 115–131.
9 R. J. FERRIER, *Methods Carbohydr. Chem.*, 6 (1972) 307–311.
10 F. J. BATES AND ASSOCIATES, *Polarimetry, Saccharimetry and the Sugars, Natl. Bur. Stand.*, Circ. C440, 1942, p. 500.
11 C. M. MCCLOSKEY AND G. H. COLEMAN, *Org. Syn. Coll. Vol.*, 3 (1955) 434.
12 R. U. LEMIEUX AND D. R. LINEBACK, *Can. J. Chem.*, 43 (1965) 94–105.
13 M. RICO AND J. SANTORO, *Org. Magn. Reson.*, 8 (1976) 49–55.
14 A. ROSENTHAL, *Carbohydr. Res.*, 8 (1968) 61–71.