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Note

Ready preparation of sugar acetals under ultrasonic irradiation*

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Syntheses starting from naturally occurring sugars[2] frequently involve as a first step the protection of hydroxyl groups, especially by acetalation[3]. When this reaction occurs under heterogeneous conditions (processes under homogeneous conditions are also available), yields are often low. Because of the efficiency of ultrasonic waves in the promotion of solid–liquid reactions as demonstrated in our group[1,4] and other laboratories[5], we investigated the possibility of improving acetalation of sugars by these physical procedures. Some years ago, an increase of the rate of formation of 1,2:5,6-di-*O*-isopropylidene α-D-glucofuranose by ultrasonic waves was reported[6], but that work seemed to be essentially a phenomenological study. To the best of our knowledge, no synthetic application of these results has been disclosed in the literature. Some examples, and scaling-up to a preparative level, are reported here.

For the sake of convenience, experiments were tested on the 0.5–1-g scale. When submitted to sonication, the mixture of the sugar and acetone reacts in the presence of a sulfuric or perchloric acid. The reaction times, when compared to those of standard literature procedures, are substantially decreased. Interestingly, in the preparation of cyclohexylidene acetals, the presence of an inert cosolvent such as ethyl acetate or acetonitrile permits the use of cyclohexanone in limited amounts (4 molar equivalents per mol of carbohydrate) without increasing the reaction time. Neutralization of the acid may also be effected under sonication by addition of pulverized sodium or potassium carbonate. In this way, the sometimes lengthy neutralization process may be effected readily (~30 min). In each instance, the final mixture consists (t.l.c.) of the expected acetal, contaminated only by small amounts of unreacted starting-material. A simple recrystallization, when possible, provides the desired product in high yield and purity. No reaction occurs in the absence of acid, as shown by comparative experiments.

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*Part 8 of the series: Ultrasound in Organic Synthesis. For part 7, see ref. 1.

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TABLE I

SONOCHEMICAL PREPARATION OF SUGAR ACETALS

Starting material	*Ketone*	*Reaction time (min)*	*Product (yield, %)*[a]	*M.p. (degrees)*	$[\alpha]_D$ *(degrees)*	*Literature data*				
						Reaction time (h)	*Yield, %*	*M.p. (degrees)*	$[\alpha]_D$ *(degrees)*	*Ref.*
D-Glucose	Acetone	50–60	1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (62)	105–106°	−18.7 (acetone)	5	42	105–109°	−19 (acetone)	3b
	Cyclohexanone	45	1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose (75)	131–132°	+1.6 ($CHCl_3$)	12	43[b]	131–132°	+1.6 ($CHCl_3$)	8
D-Galactose	Acetone	75	1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (72)	$E_{0.06}$ 92°	−53 ($CHCl_3$)	24	76–92[b]	$E_{0.1}$ 110–120°	−52.6 ($CHCl_3$)	7
D-Mannose	Acetone	15	2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (86)	124–125°	+16 (ethanol)	3–4	92[b]	122–123°	+16 (ethanol)	3b
	Cyclohexanone	60	2,3:5,6-di-*O*-cyclohexylidene-α-D-mannofuranose (43)	122–123°	+13.2 ($CHCl_3$)	16	66	120–121°	+13.4 ($CHCl_3$)	9

[a] Isolated yield of recrystallized compounds. [b] "Crude" yields given in the literature.

In larger-scale preparations, no major problems are encountered when starting from 10 g of sugar. For instance, D-glucose and D-mannose reacted with acetone to give 68 and 84% isolated yields of purified material, respectively. No increase in the sonication time was required in comparison to small-scale runs. Starting from 50 g of D-glucose required the reaction time to be slightly increased (80 instead of 60 min) and a less-pure product was obtained. This effect may be attribued to the limited energy of the sonicator used in our experiments. The nominal energy emitted by this 50-KHz generator is 240 W, but the actual energy transmitted to the reaction medium depends strongly on the geometry of the reaction vessel and the temperature. (Sedimentation of the solid occurs during sonication of 50 g of starting material, whereas complete dispersion is observed for a smaller-scale preparation). In the same way, neutralization by the solid alkaline carbonate becomes sluggish, and has to be accomplished by bubbling gaseous ammonia (without sonication) into the solution, in accordance with the procedure of Ballou and Fischer[7].

Thus far, acetalation of a *trans*-glycol (*trans*-1,2-cyclohexanediol) remains unsuccessful. Extension of our method to D-ribose seems to offer no improvement with respect to known procedures. In parallel to other efficient and well known methods, the use of ultrasonic conditions for the preparation of carbohydrate acetals should find useful applications, despite some present limitations.

EXPERIMENTAL

Sonications. — Reactions were performed in a SHE 2500 Sonoclean® ultrasonic bath, equipped with a stainless-steel coil. Running tap-water in the coil ensured an almost constant temperature in the bath (~15–18°). Commercial reagents and solvents (reagent grade) were used without purification. Compounds were identified by comparison with literature data, and by spectroscopy and polarimetry.

Standard procedure. — (*a*) A suspension of 1 g of sugar in 30 mL of acetone is sonicated in the presence of 0.8 mL of 98% sulfuric acid or 0.15 mL of 70% perchloric acid. The solid dissolves progressively. At completion, the pale-yellow solution is treated with ~1 g K_2CO_3 or Na_2CO_3 under sonication for 30 min. After filtration of the slurry, the filtrate was evaporated and the residue crystallized (from heptane or cyclohexane) or distilled (for the D-galactose derivative).

(*b*) A suspension of 1 g of sugar, 2.2 g of cyclohexanone and 30 mL of ethyl acetate (or acetonitrile) is sonicated and processed as already indicated to give the di-*O*-cyclohexylidene derivatives.

Larger-scale preparations: typical procedure. — A flat-bottomed flask (which ensures efficient energy transmission; round-bottomed vessels disperse the ultrasonic energy, possibly by reflection) containing 36 g (0.2 mol) of dry D-glucose and 700 mL of acetone was placed in the ultrasonic bath and 96% sulfuric acid (29 mL) was added dropwise over a 5-min period under sonication. After 50 min, a small amount of unreacted D-glucose remained in the slightly turbid pale-yellow mixture. The flask was cooled (ice bath) and ammonia was bubbled in until the pH reached 7–8. Usually, the solution became colorless when made neutral. The precipitated ammonium sulfate was filtered off and acetone was evaporated off at 20–25°. The solid residue was dissolved in 300 mL of ethyl acetate, ammonia was bubbled in to ensure an alkaline pH (~8), and the organic phase was washed twice with 30 mL of saturated ammonium chloride. After drying and evaporation, 52 g of a solid residue (quantitative yield) was collected and recrystallized from cyclohexane to give 32 g (62%) of pure 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, m.p. 104°.

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