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A NEW PROTECTING GROUP FOR THE CARBONYL FUNCTION

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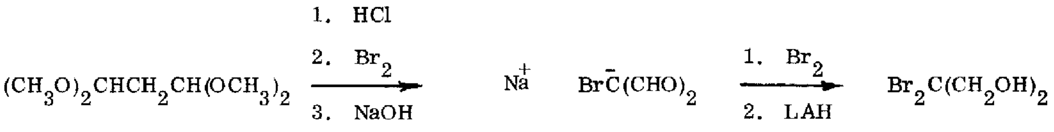
During the course of various synthetic projects under study in these Laboratories we have had occasion to devise and apply a number of new methods for the protection of hydroxyl[1], carbonyl[2] and lactone[3] functions.[4] We now wish to report some recent results on the protection of aldehydes and ketones by conversion to 5,5-dibromo-1,3-dioxane derivatives. This method introduces no new chirality, affords protection of the carbonyl group against many reagents with which it normally reacts (e.g., $NaBH_4$, peracids, diborane), and allows efficient deprotection under neutral conditions by a highly selective reduction.[5] Zinc-silver couple has been found to be an unusually effective reagent for cleavage of the ketal masking group. The diol required for the protection step, 2,2-dibromo-1,3-propanediol (**1**), was previously unknown, but its preparation was accomplished via the known[6] bromomalondialdehyde by the following sequence.



$$(CH_3O)_2CHCH_2CH(OCH_3)_2 \xrightarrow[3.\ NaOH]{1.\ HCl \quad 2.\ Br_2} \overset{+}{Na}\ \ Br\bar{C}(CHO)_2 \xrightarrow[2.\ LAH]{1.\ Br_2} Br_2C(CH_2OH)_2$$

1

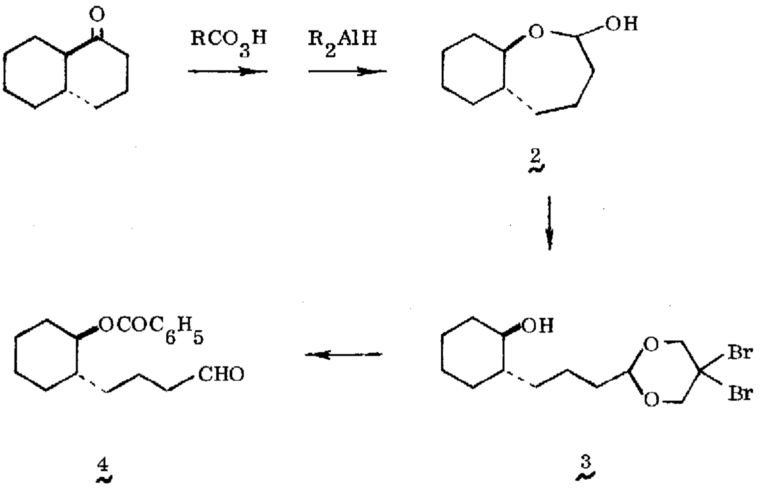
The diol **1** is a colorless, crystalline solid, mp 110-111°, which is readily purified by sublimation. Ketalization reactions were effected in the standard way for 1,2- or 1,3-diols, i.e., heating **1** with the carbonyl compound in benzene containing a catalytic amount of p-toluenesulfonic acid for several hours with azeotropic removal of water.

Regeneration of carbonyl compounds from the 5,5-dibromo-1,3-dioxane derivatives with Zn/Ag couple[7] occurred at 25° in THF containing four equivalents of acetic acid. Zinc-silver couple was more active than activated zinc for reduction of the dibromodioxane. A zinc-silver couple of reproducibly high activity was essential for efficient deprotection. The procedure described below was found to afford satisfactory results.

Yields obtained in the protection (P) and deprotection (D) steps for three test substances were as follows:

4-t-butylcyclohexanone	84% (P), 99% (D)
1-octanal	92% (P), 93% (D)
cyclohexane carboxaldehyde	94% (P), 92% (D)

In a somewhat more complex example the lactol 2 (available from trans-1-decalone) was readily converted to the hydroxy acetal 3 (87% yield), further transformed by benzoylation in the presence of pyridine and deprotection into the benzoyloxy aldehyde 4 (84% yield).



The procedures which follow are illustrative.[8]

2, 2-Dibromo-1, 3-propanediol (1). To a suspension of bromomalonaldehyde sodium salt (5.4 g, 31 mmol) in 250 ml of ether at -30° was added dropwise 1.35 ml of bromine (using a glass syringe with a Teflon needle). With the last drop a yellow color persisted. The solution was further cooled to -78° and 16.5 ml of a 1.1 M ethereal solution of lithium aluminium hydride (72.6 mequiv) was added dropwise. After 1.5 hr the solution was warmed to 0° and poured carefully into 200 ml of cold 10% sulfuric acid. The ether layer was separated and the acid solution washed thrice with 100 ml of ether. The combined ether extracts were washed twice with brine, dried (sodium sulfate) and solvent removed to give an oily, slightly lacrymatory solid. Sublimation at 80° (5 mm) gave 1 as a colorless solid, 2.69 g, (37%); ir ($CHCl_3$) ($Cm.^{-1}$), 3580 (s, OH), 1220 (s, C-O); nmr δ 4.00 (d, 4H, J=7 Hz, CH_2O), 4.90 (t, 2H, J=7 Hz, OH); m/e 234 (P, 2 Br pattern), 234 ($P-H_2O$).

4-*t*-Butylcyclohexanespiro-2'-(5',5'-dibromo-1',3'-dioxane). Diol **1** (0.260 g, 1.11 mmol) and 4-*t*-butylcyclohexanone (0.1515 g, 0.97 mmol) were heated at reflux in benzene containing 5 mg of tosic acid. The flask was topped by a Sohxlet extractor filled with 4Å molecular sieves. After 6 hr the mixture was cooled, washed with $NaHCO_3$, and the benzene layer was dried and concentrated to give a white solid. Passage through silica gel (pentane-ether) gave the ketal as a colorless solid in 84% yield; ir (CCl_4), 1365, 1375 (m, *t*-butyl), 1130 (s, C-O); nmr, 0.85 (s, 9H, *t*-butyl), 1.0-2.3 (m, 9H), 4.32 (m, 4H, OCH_2); *m/e* 370 (P, 2 Br pattern).

General Procedure for Cleavage of 5,5-Dibromo-1,3-dioxanes. Cyclohexanecarboxaldehyde. Zinc-silver couple was prepared by dissolving 0.01 g of silver acetate in 10 ml of acetic acid at 70° under argon, adding zinc dust (0.11 g, 1.7 mmol) and stirring at 70° for 30 sec, then decanting (under argon with a syringe) and washing three times with dry, 25° THF. Then 3 ml of THF was added followed by the 2,2-dibromopropylene acetal of cyclohexanecarboxaldehyde (0.140 g, 0.43 mmol) in 2 ml of THF and acetic acid (0.10 g, 1.7 mmol). After 1 hr at 25° no starting material could be detected by tlc analysis. Analysis by glc (6', 5% OV 17, 80°, *n*-decane internal standard) indicated an 86% yield of cyclohexanecarboxaldehyde. Workup, involving filtration, evaporation of solvent, addition of ether, washing with sat $NaHCO_3$, drying, passage through a pad of silica gel and evaporation of ether gave cyclohexanecarboxaldehyde (spectral properties identical to authentic material) in 74% isolated yield.

References and Notes

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