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DIFFERENTIATION OF DIOLS; A NEW SYNTHESIS OF BROMOFORMATES AND PROTECTED HYDROXYALDEHYDES

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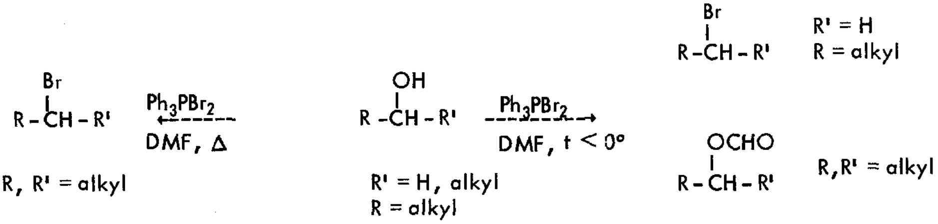
One of the recurring problems in developing practical synthetic routes to complex structures is that of differentiating similar functional groups. In particular, few methods [1,2] are available for the direct preferential oxidation of a primary hydroxyl group in the presence of a secondary alcohol. We describe in this note a simple, one-step transformation which distinguishes these two structural moieties and makes possible a convenient preparation of protected sec-hydroxy aldehydes.

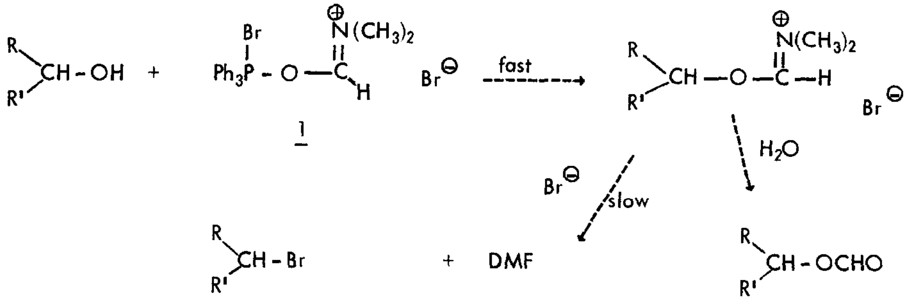
Triphenylphosphine dibromide (Ph_3PBr_2) in dimethylformamide (DMF) has been reported [3] to convert primary and secondary hydroxyl groups to bromides. We have observed that under mild conditions (0° and below) where primary alcohols still afford halides [4], secondary alcohols are converted almost exclusively to the corresponding formate ester (see Scheme I).

SCHEME I



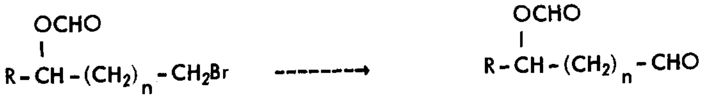
Since complexes such as 1, formed by the reaction of Ph_3PBr_2 and DMF, are well-recognized formylating agents [5], a simple mechanistic rationale may be presented which accounts for our results (Scheme 2) [6]

SCHEME 2



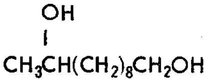
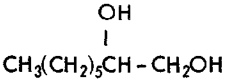
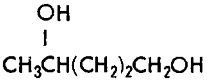
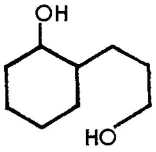
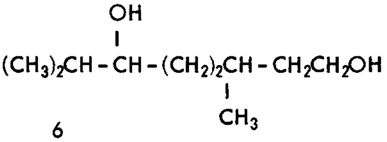
In light of the foregoing analysis, we reasoned that under suitably mild conditions, a primary-secondary diol might be converted specifically to a primary bromo-secondary formate ester. This indeed proved to be the case, and a study of some representative diols is summarized in Table 1. Besides the moderate to excellent yields of desired product, small amounts of dibromide and diformate were formed in each case [7]. The differentiation reaction shows increased selectivity where the polar functions are adjacent [8], although the hydroxyl groups in diol 5 were also very cleanly distinguished, in keeping with the known difficulty of displacement from cyclohexyl systems [9]. Furthermore, the mild conditions of this procedure should be compatible with a variety of functionalities, including double bonds [10].

An accompanying paper [11] outlines a general method for the oxidation of primary bromides to aldehydes. This technique ($AgBF_4$, DMSO, Et_3N, room temperature) afforded the desired protected hydroxyaldehydes in good yields (Table 1).



$$R-\overset{\displaystyle OCHO}{\overset{|}{CH}}-(CH_2)_n-CH_2Br \dashrightarrow R-\overset{\displaystyle OCHO}{\overset{|}{CH}}-(CH_2)_n-CHO$$

TABLE I

Substrate	Time (hrs) (Temp)	1° - halo - 2° - formate [a,b]	(δ) n.m.r.	2° - formate - aldehyde [a,b]
 $CH_3\overset{OH}{\overset{\mid}{C}}H(CH_2)_8CH_2OH$ 2	120 (-20°)	64%	7.87 (s, 1H) 4.91(sextet, 1H, J=6) 3.30 (t, 2H, J=6)	60%
 $CH_3(CH_2)_5\overset{OH}{\overset{\mid}{C}}H - CH_2OH$ 3	24 (-5°)	90%	8.00 (s, 1H) 5.05 (quintet, 1H, J=6) 3.40 (d, 2H, J=5)	---[c]
 $CH_3\overset{OH}{\overset{\mid}{C}}H(CH_2)_2CH_2OH$ 4	36 (-5°)	50%	7.97 (s, 1H) 5.02 (sextet, 1H, J=6) 3.36 (t, 2H, J=6)	50-55%[d]
 [e] 5	96 (-5°)	78%[e]	7.93 (s, 1H) 5.07, 4.53 (m, 1H) 3.30 (t, 2H, J=6)	70%
 $(CH_3)_2CH - \overset{OH}{\overset{\mid}{C}}H - (CH_2)_2\underset{CH_3}{\underset{\mid}{C}}H - CH_2CH_2OH$ 6	36 (-5°)	66%	8.00 (s, 1H) 4.80 (quartet, 1H, J=6) 3.50 (t, 2H, J=6)	63%

(a) Yields reported are isolated amounts of distilled or chromatographed material.

(b) All substances also had satisfactory ir and mass spectral data.

(c) Starting formate was recovered at room temperature; at 100° cleavage of the formate occurred.

(d) The product is water soluble; continuous extraction with ether is required.

(e) This compound is a mixture of *cis*-*trans* isomers.

The following is a typical experimental procedure: a solution of Ph_3P (4 equiv) in dry DMF (10 ml/g) at 0° under nitrogen was treated with bromine (4 equiv) dropwise. To the resulting light yellow-orange solution was added the diol (1 equiv) in a small amount of DMF. The mixture was stored in the cold until analysis of an aliquot (tlc or vpc) showed product formation had reached a maximum. The reaction was then poured into saturated brine, the products isolated by ether extraction and purified by distillation or chromatography (SiO_2).

We anticipate that this method will prove useful for selective halogenation [12] as well as for the selective oxidation of primary hydroxyl functions -- transformations which are often required in complex synthetic schemes.

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2. R.P.A. Sneeden, R.B. Turner, J. Amer. Chem. Soc., 77, 190 (1955)
3. (a) L. Horner, H. Oediger, H. Hoffmann, Ann., 126 26 (1959); (b) G.A. Wiley, R.L. Hershkowitz, B.M. Rein, B.C. Chong, J. Amer. Chem. Soc., 86, 964 (1964) (c) G.A. Wiley, B.M. Rein, R.L. Hershkowitz, Tetrahedron Lett., 2509 (1964)
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5. (a) H.J. Bestmann, J. Lienert, L. Mott, Ann., 718, 24 (1968); (b) T. Dahl, R. Stevenson, J. Org. Chem., 36, 3243 (1971)
6. The product formate is stable to the reaction conditions (no halide formation).
7. Spectral data (nmr and ir) support these assignments. If the reactions are conducted above 0°, a considerable amount of dibromide is formed.
8. The reactions of diols 2, 4, and 6 produced small amounts (10 - 20%) of the isomeric 2°bromo - 1° - formates. The structures of these byproducts were established by their oxidation ($AgBF_4$/DMSO) to the corresponding ketoformates which showed characteristic nmr absorptions for methyl or isopropyl ketones.
9. J. March, Advanced Organic Chemistry, McGraw-Hill, N.Y. 1968, p. 286
10 Little or no HBr addition to olefins occurs under these conditions, e.g. $(CH_3)_2C=CH-(CH_2)_3-CH(OH)-CH_3 \longrightarrow (CH_3)_2C=CH-(CH_2)_3-CH(OCHO)-CH_3$
11. B. Ganem, R.K. Boeckman Jr., Tetrahedron Lett., 0000 (1974)
12. For other methods see (a) R.F. Dods, J.S. Roth, J. Org. Chem.,34, 1627 (1969); (b) K. Kikugawa, M. Ichino, Tetrahedron Lett., 87 (1971); (c) J.P.H. Verheyden, J.G. Moffatt, J. Org. Chem., 35, 2319 (1970), 37, 2289 (1972); (d) M.M. Ponpipom, S. Hanessian, Carb. Res., 18, 342 (1971); S. Hanessian, M.M. Ponpipom, P. Lavallee, Carb. Res., 24, 45 (1972)