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A FACILE METHOD FOR MONOACETYLATION OF SYMMETRICAL DIOLS: APPLICATION TO THE TOTAL SYNTHESIS OF Z-8-DODECENYL ACETATE, THE SEX ATTRACTANT OF THE ORIENTAL FRUIT MOTH

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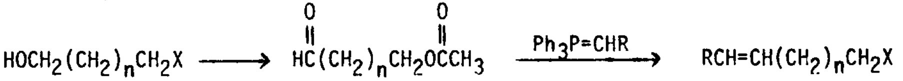
Summary: By the use of continuous extraction of the reaction mixture with a suitable non-polar solvent, several symmetrical 1° and 2° diols were converted in high yield to the corresponding monoacetate derivative in aqueous acetic acid solution.

A recent review[1] mentions that monoprotected derivatives (e.g., 2) of the inexpensive symmetrical diols of general structure 1 are attractive intermediates in synthesizing sex pheromones (e.g., 4) of Lepidoptera.[2] The author also points out that preparing such compounds in solution is complicated by the difficulty in separating the mixtures of diprotected, monoprotected, and unprotected products formed. To solve this problem, C. C. Leznoff and coworkers have developed[1] the use of insoluble polymer supports. In view of the synthetic utility of monoacetates of general structure 2 as precursors of ω-hydroxy aldehydes[3] (for the synthesis of certain insect pheromones) and ω-hydroxy acids[4] (important intermediates in the synthesis of lactones[5]), we wish to report in this communication an economical and efficient method for the monoacetylation of a variety of symmetrical diols in high yield.



$$HOCH_2(CH_2)_nCH_2X \longrightarrow H\overset{O}{\overset{\|}{C}}(CH_2)_nCH_2O\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{Ph_3P=CHR} RCH=CH(CH_2)_nCH_2X$$

1, X=OH 3 4, X=OH, OAc, etc.

2, X=OC(=O)CH_3

A selective esterification was easily accomplished by treatment of diol 1 with a solution[6] of aqueous acetic acid[7] in the presence of a strong acid catalyst at room temperature. As the reaction proceeded, the monoacetate (before it could be converted

TABLE I

Starting Diol[a]	Aqueous Reaction Mixture (ml of H_2O: ml of glacial acetic acid: ml of conc. H_2SO_4)	Time[b]	Solvent Used for Extraction[c]	Product Distribution[d] (%)		
				Diol	Monoacetate[e]	Diacetate
15 mmol of 1,10-decanediol	155:75:0.25	36 hrs	5:1 (v/v) cyclohexane: CCl_4	39[f]	60	1
15 mmol of 1,10-decanediol	120:90:0.25	36 hrs	1:1 (v/v) hexane: cyclohexane	22[f]	75	3
35 mmol of ethylene glycol	160:80:0.50	1 wk	benzene	0	94	6
17 mmol of 1,4-cyclohexanediol[g]	180:45:4.0	4 days	benzene	14[h]	85[i]	1
7 mmol of 1,12-dodecanediol	90:150:0.25	30 hrs	cyclohexane	29[f]	66	5
13.7 mmol of 1,8-octanediol	200:25:4.0	40 hrs	hexane	2	94	4

[a] Available from Aldrich Chemical Co., Milwaukee, Wis., U.S.A. The reaction was initiated by addition of the proper amount of H_2O and H_2SO_4 to a solution of the diol in glacial acetic acid. This mixture was subsequently extracted continuously with the specified nonpolar solvent. [b] The time represents that required for essentially quantitative removal of the starting diol (most of which has been converted to the corresponding monoacetate) from the aqueous reaction mixture using the specific reaction conditions listed in the table. This time should be able to be reduced substantially by increasing the amount of sulfuric acid catalyst, heating the aqueous reaction mixture to a moderate temperature (e.g., 50°C), varying the ratio of water-acetic acid (up to a certain point), and using a more efficient extractor. [c] The solvents utilized in the above reactions do not necessarily represent the optimum one for each particular system. The latter can be ascertained only after extensive development of this process. Suitable nonpolar solvents include alkanes, cycloalkanes, aromatic hydrocarbons, halide derivatives of hydrocarbons, or mixtures thereof. [d] The product mixture was isolated by cooling the solvent used for extraction to room temperature. Any unreacted diol present in the product mixture often precipitated out of the nonpolar solvent at this stage and could be recovered by simple filtration. After drying the filtrate over anhydrous K_2CO_3 and subsequent removal of the extraction solvent under reduced pressure, product ratios were determined by VPC analysis (6'x1/8" SE-30 column). Retention times: diester > monoacetate > diol. [e] The monoacetate derivatives can be purified via chromatography on silica gel (elution with hexane -50% ether). IR and NMR spectra were consistent with the assigned structures [f] A nearly quantitative recovery of unreacted diol can be obtained by filtration of the chilled extracts prior to removal of the solvent. [g] Mixture of *cis*- and *trans*-stereoisomers. [h] Most of this diol can be precipitated out of the benzene layer by the addition of hexane. [i] This monoester has previously been prepared in 60% yield by the partial saponification of the diacetate derivative of 1,4-cyclohexanediol. See J. B. Aldersley, *et al*, *J. Chem. Soc.*, 10 (1940).

to the corresponding diacetate derivative) was removed from the reaction mixture by continuous extraction with a suitable nonpolar solvent in which the starting diol is *virtually insoluble*. The presence of a large amount of water (*always* > 50% on a molar basis) in the aqueous layer permits the extraction of the desired monoester (2) to occur more readily and greatly retards diester formation. As can be seen from the data in Table I, the method was also successful for monoacetylation of a representative symmetrical 2° diol. After further development of this process by changing the reaction conditions as discussed in footnotes b and c in Table I, it should be possible to obtain even higher yields of such monoacetates.

To illustrate the utility of this selective esterification process, 1,8-octanediol monoacetate[8] (2, n=6) was converted in two steps to the sex pheromone of the oriental fruit moth,[9] a pest of peach orchards. Oxidation of the unprotected hydroxyl group using pyridinium chlorochromate[10] afforded the previously reported[11] 8-acetoxyoctanal in 86% yield. Subsequent treatment of the latter aldehyde with the ylid derived from *n*-butyltriphenylphosphonium bromide[12] under "salt-free" conditions[13] gave Z-8-dodecenyl acetate,[14] > 98% pure by VPC analysis,[15] in 45% yield.

We are presently examining the feasibility of an analogous process for converting symmetrical diacids to the corresponding monoesters and are further exploring the utility of these monoesters in organic synthesis.

REFERENCES

1. C. C. Leznoff, *Acc. Chem. Res.*, *11*, 327 (1978).
2. For a survey of recent advances in synthesis of insect pheromones, see C. A. Henrick, *Tetrahedron*, *33*, 1845 (1977) and R. Rossi, *Synthesis*, 817 (1977).
3. For another method recently developed to convert α,ω-diols to ω-hydroxyaldehydes, see G. A. Crosby, *et al*, *J. Am. Chem. Soc.*, *97*, 2232 (1975).
4. To illustrate this, 1,8-octanediol monoacetate was oxidized using the Jones' reagent [See E. R. H. Jones, *et al*, *J. Chem. Soc.*, 39 (1946)], yielding 8-acetoxyoctanoic acid in high yield.
5. For recent reviews, see K. C. Nicolaou, *Tetrahedron*, *33*, 683 (1977) and T. G. Beck *ibid*, 3041.

6. It is not necessary that the diol be totally miscible with the aqueous acetic acid layer. As the reaction proceeds, any residual solid material suspended in the aqueous mixture slowly dissolves.

7. Propionic acid could not be used in this esterification process. Although miscible with water, it is also quite soluble in the nonpolar organic solvent used for extraction and is consequently extracted out of the aqueous mixture. As the flask containing the refluxing nonpolar organic solvent builds up an appreciable concentration of propionic acid, further esterification occurs in this boiling organic solvent mixture, leading to the formation of the undesired diester.

8. ν_{max}(film) 3450(OH), 1750(C=O), 1470, 1435, 1395, 1370, 1245, 1050 cm^{-1}; δ $Me_4Si(CCl_4)$ 4.00 (t, J=6.3 Hz, CH_2OAc), 3.50 (t, J=5.5 Hz, CH_2OH), 1.98 ppm [s, $OC(=O)CH_3$]. Anal. calcd. for $C_{10}H_{20}O_3$: C, 63.76; H, 10.71. Found: C, 64.03; H, 10.69.

9. For previous synthesis of this pheromone, see: (a) W. I. Roelofs, et al, Nature, 224, 723 (1969); (b) G. Holan and D. F. O'Keefe, Tetrahedron Lett., 673 (1973); (c) K. Mori, M. Uchida, and M. Matsui, Tetrahedron, 33, 385 (1977).

10. E. J. Corey and J. W. Suggs, Tetrahedron Lett., 2647 (1975).

11. G. I. Fray, et al, Tetrahedron, 15, 18 (1961).

12. R. Mechoulam and F. Sondheimer, J. Am. Chem. Soc., 80, 4386 (1958).

13. The procedure involved a modification of reaction conditions developed by M. Schlosser and K. F. Christmann, Ann. Chem., 708, 1 (1967). The ylid was formed by addition of the phosphonium salt (23.7 mmol) to a solution of dimsyl sodium (from 21 mmol of NaH) in 20 ml of DMSO. The reaction mixture was diluted with 80 ml of dry benzene prior to the addition of 8-acetoxyoctanal (4.7 mmol). After 2 h at 20°C, the mixture was diluted with 200 ml of H_2O and the product was isolated by extraction with 1:1 ether-hexane. The product was separated from any triphenylphosphine oxide by chromatography on silica gel (elution with hexane-2% ether).

14. The NMR spectrum of the product was identical to that previously reported for this pheromone. See reference 9b.

15. A 6' x 1/8" SE-30 column (oven temp.: 185°C., flow: 15 ml/min, t_R: 9.4 min) was used for this analysis. To further confirm the stereochemical homogeneity of the reaction product, it was treated with 1.4 equiv. of m-chloroperbenzoic acid in anhydrous ether at 20°C for 18 h. The corresponding epoxyacetate was shown to be > 95% pure by VPC analysis using a 6' x 1/8" 2-1/2% Carbowax 20M column (oven temp.: 195°C, flow: 15 ml/min, t_R: 7.8 min). The same method has been used previously for analysis of similar unsaturated acetates. See J. H. Babler and M. J. Martin, J. Org. Chem., 42, 1799 (1977) and references therein.

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