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OXIDATION - REDUCTION ESTERIFICATION BY MEANS OF DIMETHYL MESOXALATE AND TRIPHENYLPHOSPHINE

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The system consisting of trivalent phosphorous compound as oxygen acceptor and some conjugated compound capable of taking up two protons are widely used for inter- and intramolecular dehydrations[1]. These condensations are brought about by active acyl group generated in the oxidation-reduction processes and due to the mild and neutral conditions are utilized for the preparation of acid anhydrides, esters, peptides and nucleotides[1]. Amongst systems employed, the betaine formed from triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) shows exceptional properties as a condensation reagent. In its case the dehydration reaction involves activation of an alcohol and could be viewed as alkylation of an acid by the alkoxyphosphonium salt[2]. The reaction proceeds with inversion of configuration and (with the aid of chiral alcohols) was shown to be highly stereospecific[3].

We have found that dimethyl mesoxalate (DMM) - TPP system can also yield esters in the oxidation-reduction process carried out according to the following procedure.

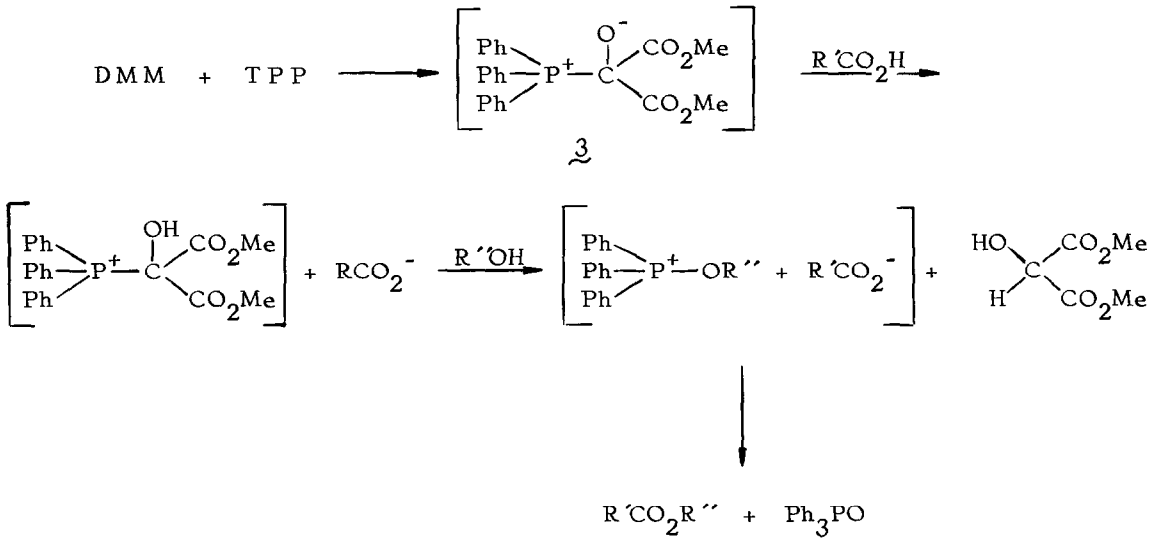
To an alcohol (1 mmol) solution in dry benzene, TPP (2 mmol) and benzoic (1) or p-nitrobenzoic acid (2) (2 mmol) were added, followed by DMM (2 mmol). The reaction mixture was refluxed for 2 hrs, then cooled, washed with sodium bicarbonate solution and the solvent evaporated. The residue was subjected to column chromatography on silica gel. Elution with petroleum ether - ethyl acetate 98:2 to 9:1 mixtures gave benzoate while use of benzene - ethyl acetate 9:1 eluent afforded dimethyl tartronate and triphenylphosphine oxide. Some

unreacted mesoxalate and O-benzoyl dimethyl tartronate were also isolated. All obtained esters had physical properties consistent with literature data[3,4]. The yields and optical rotations for chiral compounds are given below.

Substrates	Product	Yield (%)	M.p.(b.p.) °C	$[\alpha]_D^{18}$ ($CHCl_3$)
benzyl alcohol, 2	benzyl p-nitrobenzoate	86	86	-
(-)-menthol, 2	(+)-neomenthyl p-nitrobenzoate	60	95	+17.2°
(-)-menthol, 1	(+)-neomenthyl benzoate	49	68-9	+31.5°
(-)-(R)-octanol, 1	(+)-(S)-2-octyl benzoate	72	(95/0.6 torr)	+33.5° *
5, 1	6	77	(120/0.3 torr)	-
5, 4	7	31	120-121	-

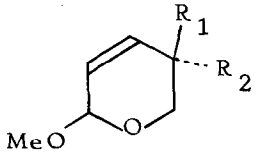
*Sample of the benzoate prepared from (-)-(R)-2-octanol (Fluka AG) by benzoyl chloride - pyridine treatment had $[\alpha]_D$ -34.3° (c 1.5, CH_2Cl_2).

Esterification of (-)-menthol and (-)-(R)-2-octanol resulting in optically pure esters of (+)-neomenthol and (+)-(S)-2-octanol proved that the condensation is stereospecific and proceeds with inversion of configuration at the alcohol carbon atom. This in turn indicates that the mechanism of the TPP - DMM system action is analogous to that of TPP - DEAD betaine and can be formulated as follows:



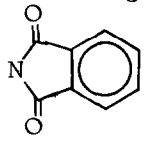
Formation of the betaine 3 as the initial step of the reaction is further supported by the finding that the benzene solution of DMM and TPP prepared without rigorous exclusion of atmospheric moisture and left overnight afforded triphenylphosphine oxide and dimethyl tartronate in good yield, presumedly as the result of hydrolytic cleavage of 3.

Preliminary attempts to alkylate phtalimide (4) in the presence of DMM and TPP were unsuccessful. Only in the case of allylic alcohol: cis-5-hydroxy-2-methoxy-5,6-dihydro-2H-pyran (5) phtalimide derivative 7 (IR: 1700 cm^{-1}; ^1H NMR: δ 7.88-7.66, m, 4H, aromatic; 6.17-5.91, m, 2H, H-3 and H-4; 5.09, bs, 1H, H-2; 4.71, q, 1H, H-5; 4.21, dd, 1H, H-6; 3.91, dd, 1H, H-6'; 3.46, s, 3H, OCH_3; J_{34}=12.0 Hz, J_{45}=4.9 Hz, J_{56}=4.5 Hz, $J_{56'}$=3.2 Hz; Anal.: found C 64.7, H 5.0, N 5.4%; calc. C 64.9, H 5.0, N 5.4%) was obtained. Its trans configuration followed from the coupling constants values[5].



5 R_1 = OH, R_2 = H

6 R_1 = H, R_2 = $OCOC_6H_5$

7 R_1 = H, R_2 = 

Substrates like menthol or 1,2:3,4-di-O-isopropylidene-α-D--galactopyranose (8) failed to react with phtalimide or 4-nitrophtalimide, whereas 8 is known to give 66% of 6-phtalimido derivative when treated with 4 and DEAD - TPP system[6]. The present results indicate lower efficiency of the DMM - TPP dehydrating system as compared with DEAD - TPP, possibly because of competitive esterification of the tartronate ester. However it should be emphasized that DMM is the first proton acceptor shown to carry out esterification through alkoxyphosphonium salt with the stereospecificity observed in reactions proceeding in the presence of azodicarboxylate esters. It is worth noting that ability of phosphine and conjugated proton acceptor to form betaine is not sufficient to bring about esterification. For instance, betaine obtained from TPP and p-benzo-

quinone[7] or TPP and DDQ failed to produce the ester from benzyl alcohol and p-nitrobenzoic acid. Similarly, close structural analogues of DEAD: azodicarboxylate dipiperidide and 4-phenyl-1,2,4-triazolin-3,5-dione react readily with TPP but the resulting betaines are inactive as the esterifying agents.

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