

INVESTIGATIONS ON MITSUNOBU REACTION OF 5-NORBORNEN-2-OLS

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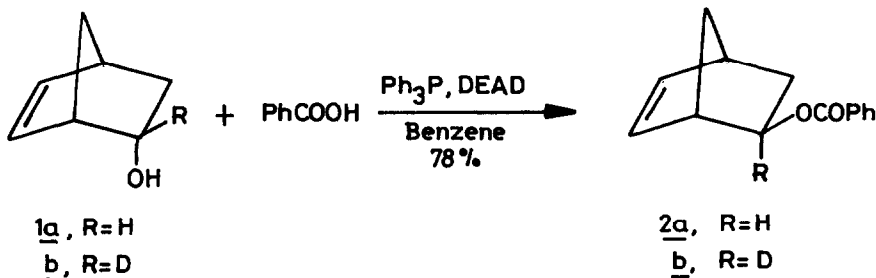
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ABSTRACT : Investigations on the Mitsunobu reaction in exo- and endo- norbornenols were carried out. While the endo alcohol gave the pure exo benzoate and phenyl ether on reaction with benzoic acid and phenol respectively, the exo alcohol furnished only the nortricycyl derivatives.

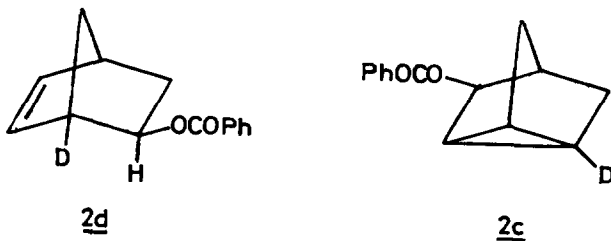
The mechanism of the Mitsunobu reaction¹ has been the subject of several investigations in recent years² on account of its synthetic utility. Hitherto applied mainly in the etherification and esterification of primary and secondary carbinols, we have recently demonstrated its utility for the etherification of secondary and tertiary ethynyl carbinols, free from attendant complications of acetylene-allene rearrangements³. Because of its stereochemical outcome, which is generally a clean inversion, this reaction has been used extensively in inverting the configuration of secondary hydroxy centres^{1,4}. Examples of deviations from clean S_N2 reactions, in terms of allylic shifts in secondary allylic alcohols⁵ and retention of configuration in hindered systems⁶ are known. During the course of our endeavour to apply this strategy for obtaining the potential oxy-Cope substrate, 2-endo-ethynyl-2-exo-norbornenol,⁷ from the easily obtainable 2-exo-ethynyl-2-endo-norbornenol, we became interested in a general study of the behaviour of norbornenol and norbornanol under the Mitsunobu condition. Apart from this consideration we were tempted to take up this study for other reasons as well : non-classical participations are ubiquitous; bimolecular displacement reactions are sparse^{8,9} and these systems are still of theoretical importance¹⁰. Surprisingly, there are very few reports on the use of the triphenylphosphine-diethyl azodicarboxylate mediated reactions in bicyclic and especially the norbornenyl systems. This, as well as the recent findings¹¹ on the Mitsunobu reaction in a related system viz. dicyclopentadienol, prompt us to communicate our findings here.

Endo- norbornenol 1a on reaction with benzoic acid under typical Mitsunobu conditions, in dry benzene, furnished the exo benzoate 2a as a colourless liquid in 78% yield, which was homogenous on TLC, HPLC¹² and NMR. Analysis of the crude product by TLC and ¹H nmr (60 MHz) did not indicate the presence of

any product other than 2a. The spectral data corroborated with that of the authentic sample prepared by the benzylation of pure exo-norbornenol 4¹³. Saponification of 2a afforded the exo alcohol 4. With a view to find out whether part of the benzoate could have arisen from a Wagner-Meerwein shift ($C_6 \rightarrow C_2$ shift) the 2-exo-deutero-2-endo-norbornenol 1b was subjected to an identical coupling reaction with benzoic acid in dry benzene. The product obtained was found to be pure 2-endo-deutero-2-exo-benzoate 2b, as revealed by 60 MHz ¹H-nmr spectrum of the crude as well as purified product.



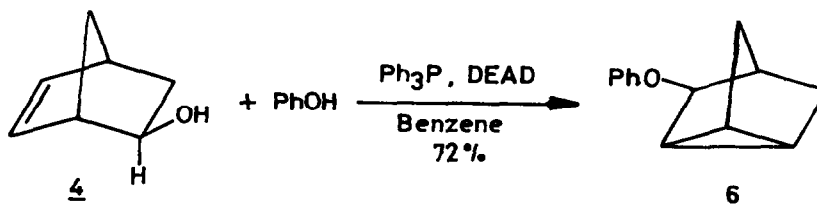
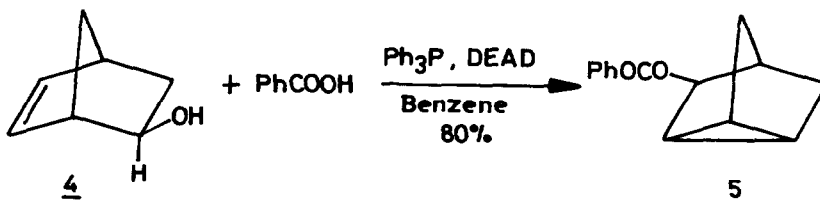
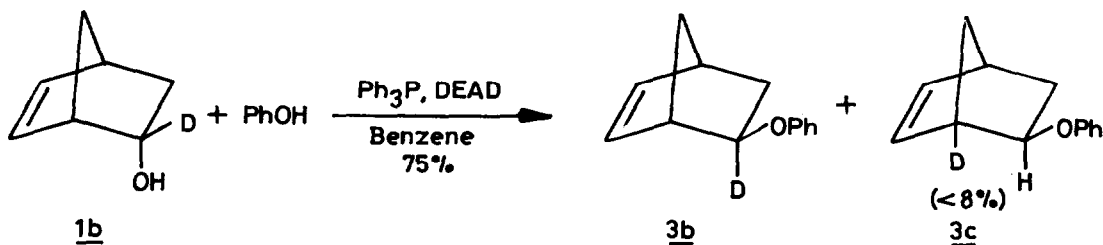
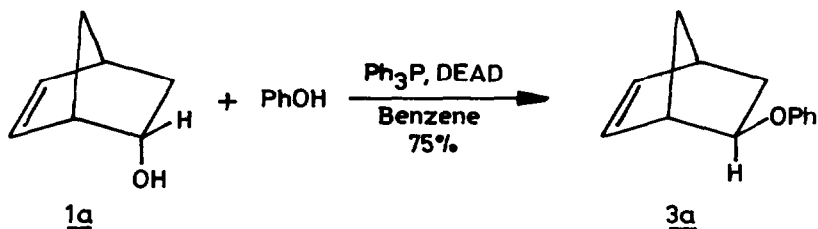
The course of the reaction and the stereochemical outcome were not altered by employing a more polar solvent like THF in the place of benzene. The ¹H and ¹³C nmr data clearly showed the absence of products 2c and 2d which could arise due to π -participation and Wagner-Meerwein shifts respectively¹⁴.



When the alcohol 1a was subjected to Mitsunobu coupling with phenol, a relatively stronger nucleophile compared to benzoic acid, it furnished the exo phenyl ether 3a in 75% yield as a colourless liquid. The product, again, was homogenous on HPLC, TLC and NMR. When this reaction was probed for possible $C_6 \rightarrow C_2$ shifts by employing the alcohol 1b, interestingly the product isolated in 79% yield was a mixture of 3b and 3c, 3c being present to an extent of less than 8%, as indicated by ¹H nmr data¹⁴. Surprisingly, no nortricycyl benzoate or nortricycyl phenyl ether was formed in any of these reactions.

The behaviour of the exo alcohol 4, as anticipated, was in total contrast to that of the endo isomer. When subjected to the Mitsunobu reaction with benzoic acid or phenol under identical conditions, the exo alcohol 4 furnished only the corresponding nortricycyl derivatives 5 and 6 in 80% and

72 % yields respectively and none of the endo or exo norbornenyl benzoate or phenyl ether.



Our studies have shown that both endo- and exo-norbornenols react smoothly under the Mitsunobu reaction conditions. While the endo alcohol affords the exo product, with clean inversion and without any competing π -participation, the exo alcohol in total contrast affords only the nortricyclic derivatives, presumably by π -participation. A competitive Wagner-Meerwein pathway can also contribute in minor amounts to the formation of the exo product, depending on the nature of the substrate employed, as is reflected from the behaviour of benzoic acid and phenol.

To our knowledge there is only one report in literature describing a clean S_N2 reaction in the norbornyl system. Schaefer et al¹⁵ have shown that 2-endo-norbornanol is converted cleanly to 2-exo-bromonorbornane by triphenylphosphine dibromide by an S_N2 process, while the exo alcohol affords a mixture of 12% endo bromide, 79% exo bromide and 9% nortricyclene.

Apart from the mechanistic findings, our observations provide a simple and convenient route for the stereoselective preparation of the exo phenyl ether of norbornenol which is otherwise prepared in poor yield by a Diels-Alder reaction. The phenyl ethers have been reported to be good insecticides, with an activity equalling DDT¹⁶. We are currently investigating the Mitsunobu coupling of norbornanols and 2-ethynyl-2-norbornenols.

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