Tetrahedron Letters No. 23, pp 1977 - 1980, 1977. Pergamon Press. Printed in Great Britain.

DIPHENYLPHOSPHORYL AZIDE
A NOVEL REAGENT FOR THE STEREOSPECIFIC SYNTHESIS OF AZIDES FROM ALCOHOLS[1†]

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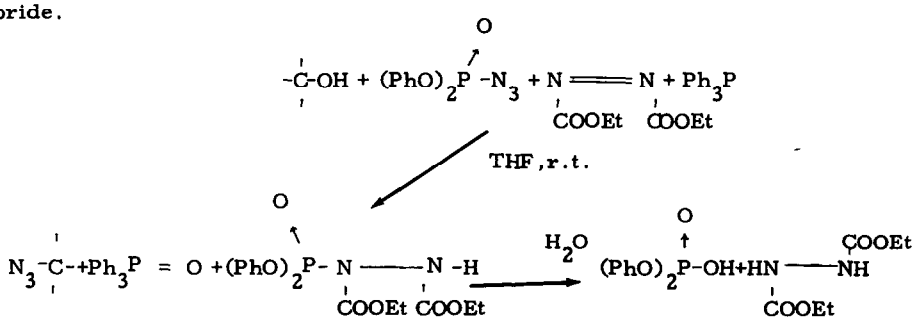
(Received in USA 3 January 1977; received in UK for publication 29 April 1977)

Recently[2] the synthesis of a new reagent, diphenylphosphoryl azide (1), which is a stable, distillable azide was described. It was reported that I is useful for peptide bond formation (see eq. 1). This reagent was also shown to be very convenient for carrying out the Curtius reaction[2] (see eq. 2).

$$RCO_2H + \underset{(I)}{(PhO)_2P(O)N_3} \xrightarrow[Et_3N]{R'NH_2} RCONHR' \qquad \text{Equation 1}$$

$$RCO_2H + (PhO)_2P(O)N_3 \xrightarrow[Et_3N,]{R''OH} RNHCO_2R'' \qquad \text{Equation 2}$$

In continuation of our studies[1,3,4] on the stereospecific conversion of sterols to esters, ethers, halides, etc., we have observed a novel reaction of diphenylphosphoryl azide. When an appropriate alcohol is allowed to react with I, triphenylphosphine and diethyl azodicarboxylate (II), an azide is formed in 60-90% yield (see Table 1). Thus, decyl alcohol gave decyl azide (60%) which can be reduced and characterized as the N-acetyl derivative of decylamine. Cyclohexanol gave cyclohexyl azide (60%) which was reduced and isolated as cyclohexylamine hydrochloride.



† This communication is dedicated to Professor R.B. Woodward on the happy occasion of his sixtieth birthday.

The sterospecific nature of the reaction was revealed when sterols were used as the alcohol component; 3β-cholestanol led exclusively to 3α-cholestanyl azide[6] in 75% yield and cholesterol gave 3α-azido-5-cholestene[7] (85%) exclusively. It is well known[8] that in most replacement reactions Δ^5-sterols give a mixture of products because of the participation of an i-steroid intermediate. The reaction of sodium azide with the tosylate of a Δ^5-3β-sterol produces a mixture of 3α-,3β-,6α-, and 6β-azido steroids[7]. Even the reaction of an acid with cholesterol in presence of triphenylphosphine and diethyl azodicarboxylate leads to a mixture of esters[9]. The reagent (I), therefore, is particularly convenient for reaction with Δ^5-sterols for preparing azides of known stereochemistry. This synthesis of azide is more convenient than the traditional route (alcohol→tosylate→azide) which is longer and also prone to alkene formation.

The presence of a keto group in the molecule does not interfere with azide formation. Thus, 3α-azido-5αandrostan-17-one[10] was obtained in 75% yield from 5α-androstan-3β-ol-17-one when an extra mole of triphenylphosphine was used to co-ordinate with the keto group during the reaction.

In conformity with other reactions of alcohols mediated by triphenylphosphine and diethyl azodicarboxylate[11] studied in our laboratory[3,4], the azide formation reaction too was found to be sensitive to steric hindrance. Neither a 17β-hydroxy-nor a 3α-hydroxy-5α-steroid underwent azide formation under the standard conditions.

Various applications of the convenient method described here for azide formation from an alcohol with inversion of stereochemistry will be reported elsewhere. A typical experimental procedure for converting an alcohol to an azide by this method is described below.

Cholestanyl-3α-azide- To a magnetically stirred solution of dihydrocholesterol (3.88 g: 0.01 mole), triphenylphosphine (2.62 g; 0.01 mole) and diethylazodicarboxylate (1.74 g; 0.01 mole) in dry tetrahydrofuran, a solution of diphenylphosphoryl azide (2.75 g; 0.01 mole) was added over a period of 15 minutes and stirring was continued for about 24 hours. When the solvent was removed from the reaction mixture on a rotary evaporator under reduced pressure, a thick, oily liquid was obtained which solidified on standing. This material was chromatographed over a Florisil column using benzene-hexane (50: 50) as eluant. The first few fractions (50 cc) contained most of the title compound, m.p.[6],52-54°. Recrystalization from an ethyl acetate-ethanol-water mixture gave the pure azide as colorless needles, m.p. 62.5-63°; IR (Nujol) 2085 cm^{-1} ($-N_3$). The axial conformation of the azido group was indicated by a one proton broad singlet (width at ½ height, 9 Hz) at δ3.9 in the ^1H NMR spectrum.

Table 1

Conversion of alcohols to azides:

Alcohol	Azide	Yield %	Reference
3β-Cholestanol	3α-azido cholestane	78	6
Cholesterol	3α-azido-5-cholestene	80-85	7
5α-Androstan-3β-ol 17- one	3α-azido-5α-androstan-17-one	75	10
5-Androstene-3β-ol-17 - one	3α-azido-5-androstene-17-one*	68	
3α-cholestanol	No reaction		
5α-Androstan-17β-ol-3-one	No reaction		
Cyclohexanol	Cyclohexyl azide*	60	
Decyl alcohol	Decyl azide*	68	
ℓ-menthol	(+) menthyl azide •	90	6

* These compounds were converted to amino derivatives and found identical in all respects with the known ones.

Acknowledgement. We wish to thank Stevens Institute of Technology for financial assistance to one of us (B.N.P.) and support for this research.

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