Tetrahedron Letters,Vol.23,No.9,pp 999-1002,1982 0040-4039/82/090999-04$03.00/0
Printed in Great Britain

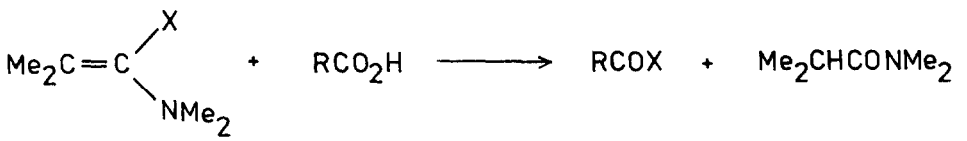
STEREOSPECIFIC HALOGENATION OF ETHYL METHYL PHOSPHOROTHIOIC ACID

C. Richard Hall* and Nancy E. Williams

Chemical Defence Establishment, Porton Down, Salisbury, Wiltshire, SP4 OJQ

Summary Tetramethyl-α-halogenoenamines are useful reagents for the stereospecific conversion of phosphorothioic acids to the corresponding phosphoryl halides.

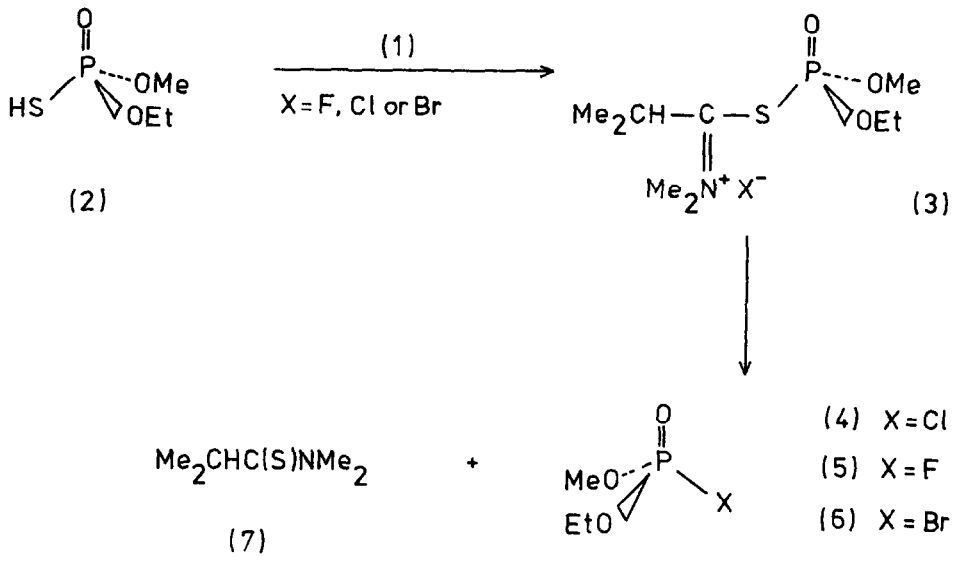
It has recently been shown that tetramethyl-α-halogenoenamines (1) convert carboxylic acids into acyl halides in high yields and under mild conditions (Scheme 1)[1]



(1) X = F, Cl, Br or I Scheme 1

We wish to report that (1, X = F,Cl or Br)[1,2] reacts cleanly and stereospecifically with O-ethyl O-methyl phosphorothioic acid to generate phosphoryl halides Such halides are important both in their own right and because of their ready conversion into a wide range of other organophosphorus compounds[3] Chiral acyclic phosphoryl chlorides have previously been prepared from the now readily accessible chiral thioacids by treatment with phosgene or by reaction of their S-alkyl esters either with a solution of chlorine in carbon tetrachloride or with sulphuryl chloride[3]. The stereochemical course of the ester conversions is however often not predictable[3,4]. The generation of chiral acyclic phosphoryl fluorides (important because of their physiological activity) is limited to the reaction between the corresponding thioacid sodium salts and picryl fluoride[3], a potentially explosive reagent. Chiral acyclic phosphoryl bromides have not been reported.

Treatment of an ice cold anhydrous solution of (+)-(R)-O-ethyl O-methyl phosphorothioic acid (2) in dichloromethane with an equimolar amount of (1) resulted in the rapid formation of a phosphoryl halide (4,5 or 6) and the thioamide (7) (Scheme 2).

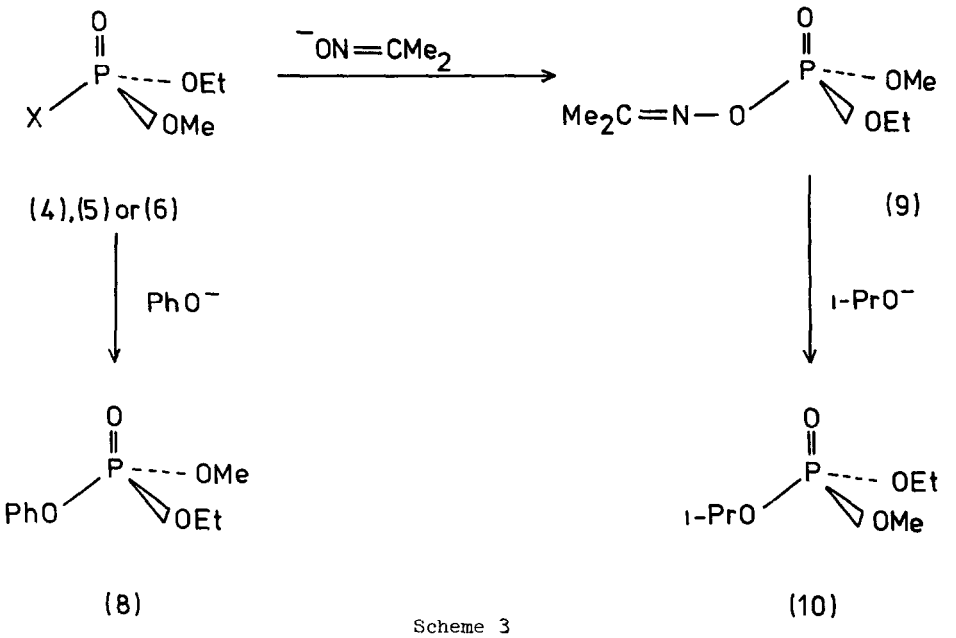


Scheme 2

The reaction presumably occurs by way of an intermediate such as (3), product formation then resulting from the attack of the halide anion at phosphorus. That it is the phosphoryl as opposed to the thiophosphoryl halides that are formed reflects the greater nucleophilicity at carbon of sulphur than of oxygen in the thioacid substrate. Purification of the chloride (4) or fluoride (5) by distillation or rapid chromatography normally resulted in some loss in enantiomeric purity. Typically ^{1}H nmr in the presence of the chiral shift reagent Eu(hfc)$_3$ showed the purified chloride to contain > 95%, and the fluoride > 80% of the major enantiomer. In both cases the P-OMe doublet due to the major enantiomer was at low field relative to that of the minor enantiomer Application of previously described[5,6] empirical rules relating the sense of magnetic non-equivalence induced by Eu(hfc)$_3$ suggests that the products have the (S) configuration and therefore that halogenation occurs with inversion of configuration at phosphorus. This assignment is also supported by previous work[3] The enantiomeric purities, particularly of the fluoride, drop fairly rapidly (days) on storage neat at room temperature. The absolute rotations were too small to be accurately measured The bromide (6) was not isolated but used in situ

That the reported halogenation reactions are stereospecific is apparent since treatment of the crude reaction mixtures with an excess of sodium phenoxide in each case results in enantiomerically pure (+)-(R)-ethyl methyl phenyl phosphate (8)[7], $[\alpha]_D$ + 2 8°C (c 2 3 in $CHCl_3$) (Scheme 3) (Although a specific rotation of between -3 3° and -3 7° has been reported[8] for (-)-(S)-ethyl methyl phenyl phosphate, (8) was essentially a single enantiomer when

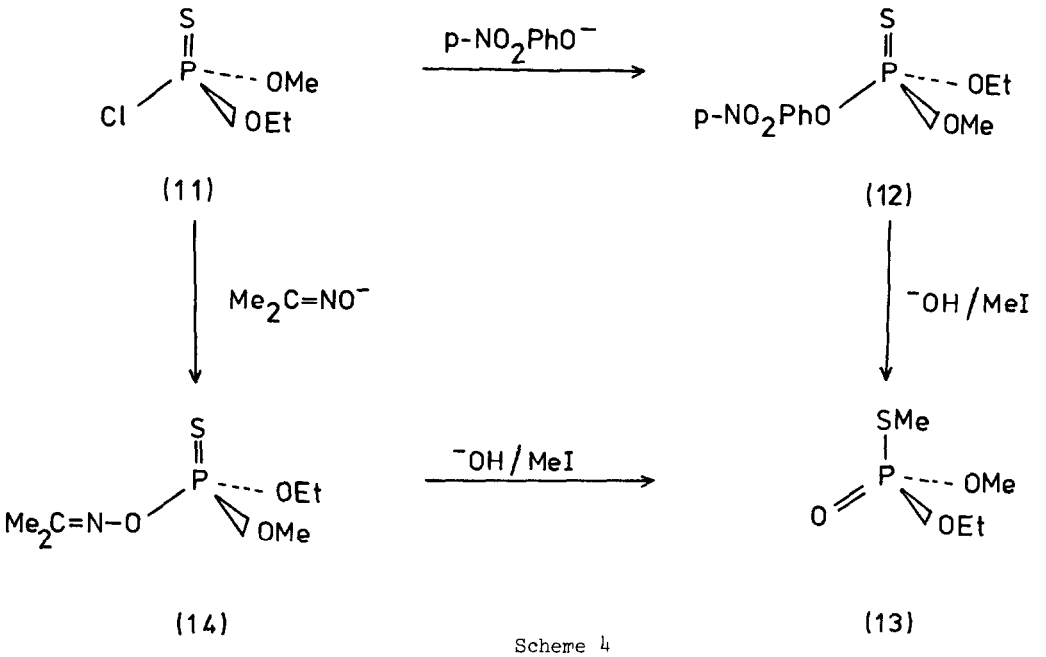
examined by nmr in the presence of $Eu(hfc)_3$) This result corresponds to displacement of chloride and fluoride, and by implication bromide, with inversion of configuration at phosphorus.



Scheme 3

Chloride is also displaced stereospecifically from (4) by treatment with the sodium salt of acetone oxime (Scheme 3). Subsequent reaction of the phosphorylated oxime (9) with sodium isopropoxide yields (+)-(S)-ethyl methyl isopropyl phosphate (10)[5]. Since the conversion of (4) into (10) involves overall retention of configuration, both the generation of (9) and its reaction to give (10) must occur with the same stereochemistry. On the reasonable assumption that this is inversion (9), $[\alpha]_D$ -1 4° (c 5.0 in $CHCl_3$), has the (R) configuration.

A similar reaction sequence, but starting with the thiophosphoryl chloride (11)[3] is outlined in Scheme 4 (-)-(S)-S-Methyl ethyl methyl phosphorothioate (13), generated via the chiral parathion analogue $[\alpha]_D$ -7 8° (c 2 8 in $CHCl_3$) (12), was enantiomerically pure[3,5] but that generated from the phosphorylated oxime (14) contained approximately 30% of the (+)-(R) enantiomer Since P = S containing enantiomers are not resolved in the presence of $Eu(hfc)_3$ it is not apparent which step is non-stereospecific. However because the configurations of (11) and (13) are known[3,5] both halide displacement and subsequent hydrolysis must again occur, at least predominantly, with the same stereochemistry, presumably inversion of configuration.



Scheme 4

REFERENCES

1 A. Devos, J. Remion, A Frisque-Hesbain, A. Colens and L Ghosez, J. Chem. Soc., Chem. Comm., 1979, 1180.

2. A. Colens, M. Demuylder, B. Techy and L. Ghosez, Nouveau J. Chim., 1977, 1, 369.

3. C.R. Hall and T.D. Inch, J. Chem. Soc., Perkin Trans 1, 1979, 1104.

4 B. Krawiecka, J Michalski and E.T. Tadeusiak, J. Am. Chem Soc , 1980, 102, 6582

5. D.B. Cooper, C.R. Hall, J.M. Harrison and T D. Inch, J Chem. Soc., Perkin Trans 1, 1977, 1969.

6. C.R Hall and T.D. Inch, Phosphorus and Sulphur, 1979, 7, 171

7. T Koizumi, Y. Kobayashi, E Yoshii, M. Takamoto, K. Kamiya and H. Asakawa, Tetrahedron Lett., 1980, 3995.

8. Y Kobayashi, T. Koizumi and E. Yoshii, Chem. Pharm. Bull., 1979, 27, 1641

(Received in UK 14 December 1981)