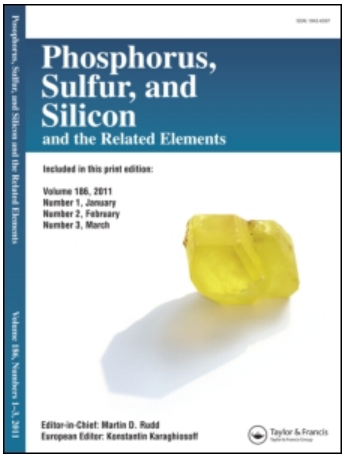

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REDUCTIVE DEHALOGENATION IN THE REACTIONS OF TRIVALENT PHOSPHORUS REAGENTS WITH 2-HALOTHIAZOLES IN PROTIC SOLVENTS. A ROUTE TO 2-UNSUBSTITUTED THIAZOLES, AND AN ALTERNATIVE MEANS OF OXIDATION (AND THIONATION) AT PHOSPHORUS

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REDUCTIVE DEHALOGENATION IN THE REACTIONS OF TRIVALENT PHOSPHORUS REAGENTS WITH 2-HALOTHIAZOLES IN PROTIC SOLVENTS. A ROUTE TO 2-UNSUBSTITUTED THIAZOLES, AND AN ALTERNATIVE MEANS OF OXIDATION (AND THIONATION) AT PHOSPHORUS

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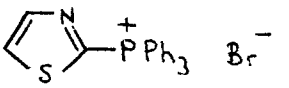
The reaction between 2-bromo- (and 2-iodo-)thiazole with a tertiary phosphine (or phosphorus (III) ester) in alcohol solvents involves nucleophilic attack by phosphorus at halogen, with subsequent formation of thiazole and the phosphine oxide (or phosphorus (V) ester). In the presence of a thiol solvent, the related phosphine sulphide is formed. The latter reaction fails with trialkylphosphites.

Key words: Trivalent phosphorus; positive halogen; carbanion stability; ^{31}P-NMR studies; thiazoles.

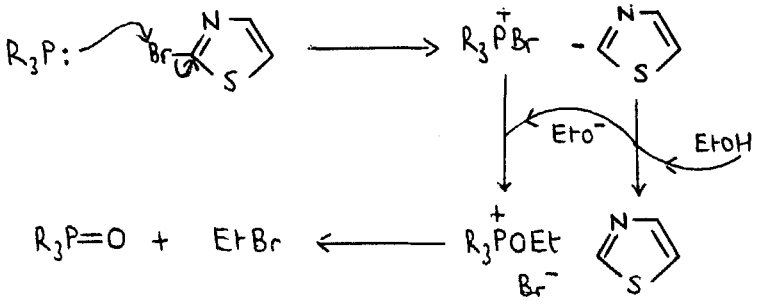
During the course of a study of the reactions of tertiary phosphines with aryl- and heteroaryl-halides, usually promoted by transition metal salts,[1] we investigated the reaction of triphenylphosphine with 2-bromothiazole, with the aim of preparing the heteroarylphosphonium salt (**1**). Unexpectedly, when equimolar amounts of triphenylphosphine and 2-bromothiazole were combined together in dry ethanol, an exothermic reaction occurred with the formation of triphenylphosphine oxide and thiazole. The reaction mixture was also found to contain bromoethane. Similarly, the reaction of tributylphosphine and 2-bromothiazole also resulted in the formation of thiazole and the phosphine oxide. Changing the nature of the halogen present in the 2-halothiazole had a marked influence on the rate of the reaction. While 2-iodothiazole underwent the same vigorous reaction as 2-bromothiazole, no reaction occurred between 2-chlorothiazole and triphenylphosphine *either* in the cold *or* on prolonged heating under reflux in ethanol.

The above reaction between 2-bromothiazole and tertiary phosphines did not occur in aprotic solvents such as acetonitrile or acetone.



(1)

It is likely that these reactions involve initial nucleophilic attack of trivalent phosphorus at halogen with displacement of the relatively stable 2-thiazolyl anion[2] which then suffers protonation by the solvent to form thiazole. The initially-formed bromophosphonium ion is then converted to an alkoxyphosphonium ion which then suffers dealkylation by the halide ion in an Arbuzov manner to form the phosphine oxide. (Scheme).



SCHEME

Nucleophilic attack by trivalent phosphorus at "positive" halogen is well-established in phosphorus chemistry,[3] particularly in situations in which the halogen is bound to carbon bearing electron-withdrawing substituents, e.g. halogens (as in tetrachloromethane),[4] carbonyl,[5–7] or benzenesulphonyl[8,9] groups which are able to stabilise the forming carbanion, but there are few examples of attack at halogen in halo(hetero)arenes. No reaction occurs between triphenylphosphine and *either* 2-bromothiophen *or* 2-bromopyridine under the above conditions.

It is likely that nucleophilic attack by phosphorus at halogen is involved in the reactions of triphenylphosphine with 2,4,5-tribromo-[10] and 2,4,5-tri-iodo-imidazole,[11] which provide reagent systems of value for the halogenation of carbohydrates. Nucleophilic attack at bromine has been established in the reaction of triphenylphosphine with 6-bromodihydrodiazepinium salts.[12] Dehalogenation of 8-bromoguanosine by tributylphosphine in a protic solvent has also been reported recently,[13] and so it would seem that the key aspect is the stability of the forming heteroaryl anion in the initial step of the reaction.

The lack of reactivity of 2-chlorothiazole compared with the bromo- and iodo-analogues presumably reflects the relative strengths of the carbon-halogen and phosphorus-halogen bonds being broken and made in the transition state. Similar relative reactivities have been observed for other reactions of this type.[3] However, the cleavage of a given carbon-halogen bond is also influenced by the stability of the forming carbanion. Thus we have also shown that dehalogenation of 2-chloro*benzo*thiazole occurs on heating with triphenylphosphine in ethanol for several hours, the greater stability of the forming 2-benzothiazolyl anion[2] being the crucial factor. A study of the dehalogenation reaction by ^{31}P nmr spectroscopy has lent support to the above mechanistic scheme.

Addition of 2-bromothiazole to a solution of triphenylphosphine in deuteriomethanol resulted in the immediate disappearance of the signal due to triphenylphosphine ($\delta = -7.1$ ppm) and the observation of a signal at $\delta = 31.35$ ppm (due to triphenylphosphine oxide) and a second, less intense, signal at $\delta = 64.1$ ppm. After 10 minutes, the latter had disappeared. It is likely that the latter is due to the intermediate methoxytriphenylphosphonium ion, which suffers dealkylation to form the phosphine oxide. Support for this assignment followed from the observation of a signal at $\delta = 64.1$ ppm on the addition of bromine to a solution of triphenylphosphine in methanol, this signal also disappearing at a similar rate with the appearance of a signal due to triphenylphosphine oxide at $\delta = 33.8$ ppm.

Similarly, the addition of 2-bromothiazole to a solution of triphenylphosphine and neopentyl alcohol in acetonitrile resulted in the formation of a persistent signal at $\delta = 61.3$ ppm, presumably due to the neopentyloxyphosphonium salt, which would be expected to undergo dealkylation by the bromide ion only very slowly.[14] Attempts to trap the forming 2-thiazolyl anion in the presence of reactive carbonyl compounds, e.g. acetone and benzophenone, and also trimethylsilyl chloride, were unsuccessful perhaps indicating that the transition state for the reaction is very reactant-like, and that only in the presence of relatively strong proton donors does the reaction proceed. Nevertheless, a study of the interaction between triphenylphosphine and 2-bromothiazole in acetonitrile using conductivity techniques indicated that the solution had a molar conductivity (1.86×10^{-1} Sm^{-1}) similar to, but slightly lower than those of acetonitrile solutions of tetraphenylphosphonium bromide (4.48×10^{-1} Sm^{-1}) and of the adduct of triphenylphosphine with bromine (2.47×10^{-1} Sm^{-1}), indicating the probability of the formation of quasi-ionic species.

The reaction between tertiary phosphines and 2-bromothioazole offers a means of oxidation of trivalent phosphorus under mild, non-aqueous conditions, which may have some synthetic applications e.g. in the oxidation step of nucleotide synthesis using the phosphotriester approach, in which oxidation under aqueous conditions can have some disadvantages.[15] In order to explore this aspect in principle, we have also studied the reactions of trialkylphosphites, diethyl phenylphosphonite, and ethyl diphenylphosphinite, with 2-bromothiazole, in the appropriate alcohol as solvent. Analysis of the reaction mixture by GC-MS indicated that all of the trivalent phosphorus esters were converted to the corresponding phosphate, phosphonate, and phosphinate esters, respectively, with the concomitant formation of thiazole. The reactions of trialkylphosphites with polyhalogenomethanes have also been used for the synthesis of P(V) esters.[16]

The tertiary phosphine-2-bromothiazole system also provides an alternative route to phosphine sulphides. Addition of triphenylphosphine to a solution of 2-bromothiazole in ethanethiol (or an ethanethiol-acetonitrile mixed solvent system) resulted in the rapid formation of triphenylphosphine sulphide. Unfortunately, triethylphosphite was largely unchanged after 24 hours in the presence of 2-bromothiazole and ethanethiol, thus blocking a potentially facile route to thio-phosphate esters. In this connection, it is noteworthy that the reaction of trialkylphosphites with bromotrichloromethane in the presence of thiols results in the formation of dialkyl-O,O-phosphoro-monoalkyl-thiolate esters *via* various mechanistic routes, depending on the nature of the solvent.[17,18] The reaction of triphenylphosphine with tetrachloromethane in the presence of alkanethiols has been shown to result in the conversion of the thiol into the related chloroalkane, presumably with the concomitant formation of triphenylphosphine sulphide, although this aspect was not dealt with in the publication.[19]

The reaction between 2-bromothiazole and trivalent phosphorus reagents may also have some application in the synthesis of thiazoles free of substituents in the 2-position. Most syntheses of the thiazole ring system result in the presence of a 2-substituent which, subsequently, may have to be removed. Various methods have been published for this step, including the reduction of diazonium salts derived from 2-aminothiazoles,[20] and the dehalogenation of 2-halothiazoles using *either*

zinc-acetic acid[21] *or* electrochemical reduction.[22] The present reaction of 2-bromothiazole with trivalent phosphorus reagents would seem to have considerable advantages in terms of the mild conditions and rapidity, and assuming the use of a deuteriated solvent, e.g. CH_3OD, should also provide access to thiazoles labelled specifically at position-2. (In this connection it should be noted that base-promoted deuterium exchange of thiazoles in which positions 2 and 5 are unsubstituted results in deuteriation at both positions to approximately equal extents.[2])

These reactions seem limited to trivalent phosphorus nucleophiles. No reaction was observed between triphenylarsine or triphenylstibine and 2-bromothiazole on heating together in ethanol. Examples of the nucleophilic attack at halogen by trivalent arsenic and antimony reagents are much less common.[3] It is of interest that oxygen and sulphur nucleophiles behave quite differently to phosphorus nucleophiles, the reactions of both alkoxide and benzenethiolate anions with 2-halothiazoles proceeding *via* an S_NAr2 addition-elimination pathway, with the formation of the related 2-alkoxy- or 2-arylthio-thiazoles.[23–25]

EXPERIMENTAL

^{31}P n.m.r. spectra were recorded on a Bruker WPSY 80 MHz spectrometer operating at 32.4 MHz. Chemical shifts were recorded with respect to 85% orthophosphoric acid as external standard ($\delta = 0$ ppm). Shifts to high field are negative in sign. GC-MS analyses were carried out using a Hewlett-Packard 5890 Gas Chromatograph linked to a VG TRIO-1 Mass Spectrometer in Electron-Impact mode, using the VG Lab-Base data system. Conductivity studies were made using a Wayne-Kerr bridge. 2-Chloro[20]- and 2-Iodothiazoles[26] were prepared as previously described. All other compounds were obtained from commercial sources.

Reaction of triphenylphosphine with 2-Halothiazoles in EtOH. Triphenylphospine (10^{-3} mol) was added to a solution of 2-bromothiazole or 2-iodothiazole (10^{-3} mol) in ethanol (3 cm^3). The phosphine dissolved, and the solution became warm. The reaction was completed by heating under reflux for 1–2 hr. On cooling, the solution was analysed by GC-MS, which confirmed the presence of thiazole. Subsequent GC analysis at lower temperature confirmed the presence of bromoethane in the reaction mixture. The solution was then poured into dilute aqueous hydrochloric acid to give a solid, identical with triphenylphosphine oxide.

In a similar manner, the reaction of tributylphosphine gave thiazole and the phosphine oxide, identical with authentic material. The related reaction of triphenylphosphine with 2-chlorobenzothiazole was also carried out as described above. The formation of benzothiazole was confirmed by GC-MS, and triphenylphosphine oxide was isolated from the reaction mixture.

The reactions of trialkylphosphite and related P(III) esters with 2-bromothiazole. The phosphorus (III) ester (10^{-3} mol) and 2-bromothiazole (10^{-3} mol) were heated together under reflux in the appropriate alcohol (3–5 cm^3) for 1–2 hr. On cooling, the solution was then analysed by GC-MS, using the authentic P(V) oxidation products of the esters for comparison. The presence of thiazole was confirmed in all of the reaction mixtures.

The reaction of triphenylphosphine with 2-bromothiazole in ethanethiol. The reaction was conducted in the cold as in (a) above, using ethanethiol as the solvent in place of ethanol. GC-MS analysis indicated the formation of thiazole. Evaporation of the solvent followed by trituration with ether gave triphenylphosphine sulphide, identical with the authentic material.

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