

CHAPTER I

PHOSPHOROUS REAGENTS IN ORGANIC SYSTHESIS

The organic chemistry of phosphorus is based on the existence of numerous stable functional groups that contain the carbon-phosphorus bond or that are organic derivatives of inorganic phosphorus acids. It is a very large and currently highly active field, of interest to academic and industrial chemists alike.

Phosphorous is an extremely versatile element, located below nitrogen in the periodic table in Group V elements and its general application in a diverse range of reactions in organic chemistry are a direct result of its electronic structure $1s^2 2s^2 2p^6 3s^2 3p^3$. Consequently, phosphorous can adopt several stable oxidation states including +3, +5 and +6 whereby the ligands can be both organic and inorganic in nature. The usefulness of phosphorous reagents in organic synthesis stems from the element ability to progress from the lowest to highest coordination number and occasionally in the reverse direction. Key factors of phosphorous include high nucleophilicity of trivalent phosphorous reagents towards electrophiles, strong P=O bonds that are readily formed (also to S, N and the halogens) and the capability of phosphorous to stabilize adjacent anions.

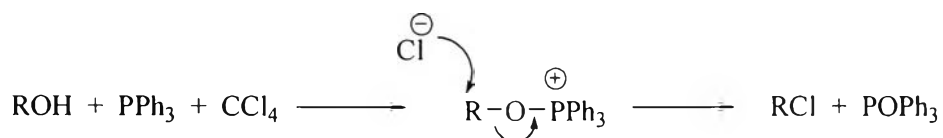
Phosphorous plays an important role in all living things, it provides the stable polymeric backbone for DNA and RNA, as well as interacting almost all biochemical pathways *via* phosphorylation *etc.* However, its use in synthetic chemistry in the last century has revolutionized the number of compounds available to organic chemists. Phosphorous containing polymers also play important roles as fire and smoke retardants in electrical devices.

Phosphorous compounds are frequently employed in combination with polyhalogenoalkanes to generate a wide variety of useful reagents. These two component reagent systems can for example act as dehydrating agents or as mediators in the formation of P-N bonds. Common combinations include tertiary phosphines, *tris*(dimethylamino)phosphine or phosphites in conjunction with halogenated reagents such as CCl_4 or Cl_3CCCl_3 .

1.1 Functional Group Interconversions using Phosphorous Reagents

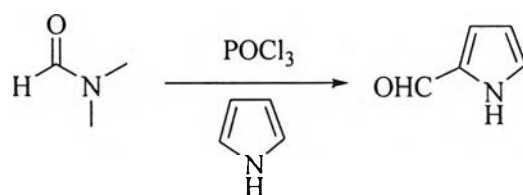
1.1.1 Halogenation of Alcohols Using PPh₃/CCl₄ [1]

A very common reaction is the halogenation of alcohols into the corresponding organohalogen species. Phosphines are used extensively in reactions of this type, where the formation of the strong P-O bond is a key driving force in favor of halogen formation.



1.1.2 Vilsmeier Reaction [1]

Vilsmeier reaction is an extension of the Mannich reaction and involves the conversion of *N,N*-dimethylformamide (DMF) into an iminium intermediate species by treatment with POCl₃. This process is driven by the formation of a strong P-O bond. This reaction is used to generate mono-substituted heteroaromatic systems such as pyrroles (formally introducing a formyl group (CHO)).

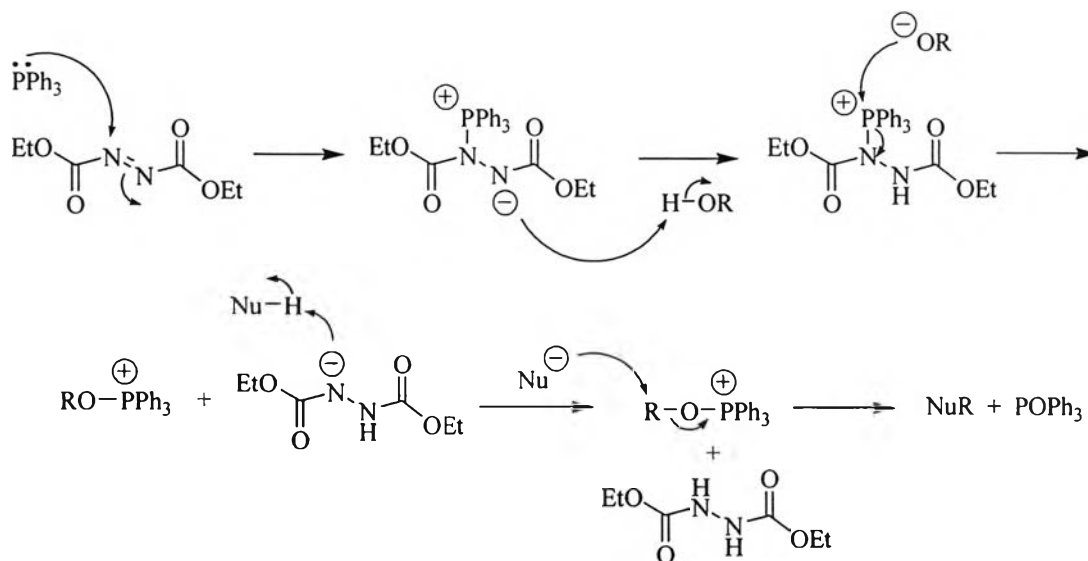


1.1.3 Mitsunobu Reaction [1]

Mitsunobu reaction is a two-step process in which an alcohol is first converted into a better leaving group (such as Cl, Br, I, OTs, OMs) and then reacted with a suitable nucleophilic species. This approach requires two distinct stages. However, a very mild phosphorous mediated reaction “Mitsunobu reaction” enables the direct “one-pot” conversion of an alcohol into the corresponding ether or ester. In this reaction, PPh₃ and diethylazodicarboxylate (DEAD) are combined with the alcohol which serves as the electrophile and to this mixture added the nucleophile.

Mitsunobu reaction is an S_N2 reaction at the phosphorous centre. The stabilized nitrogen anion acts as a base upon the nucleophile, abstracting a proton and therefore activating it for subsequent nucleophilic attack in a substitution reaction at a carbon centre of the alcohol derivatives. Phosphine oxide and the reduced form of DEAD are by-products of this reaction. Overall, the stable C-O bond is broken,

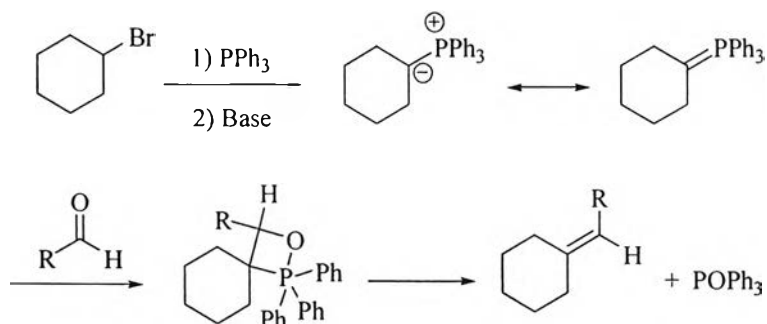
however, this energetically unfavourable process is offset by the formation of very strong P=O and N-H bonds. Since the original C-O bond is broken in Mitsunobu reaction *via* an S_N2 mechanism, inversion of configuration at that carbon centre occurs and indeed, this route has been employed to generate either ethers or esters with inversion of configuration.



1.1.4 Wittig Reaction [1]

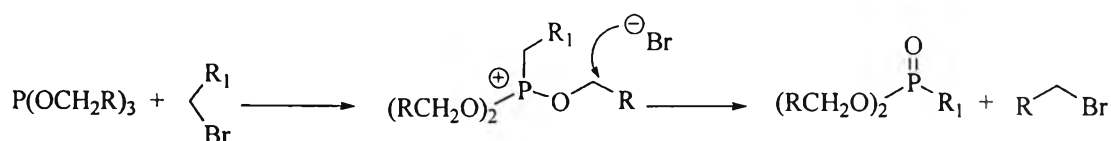
The Wittig reaction is the most common way of constructing alkene moieties in organic compounds *via* a one step process. It is a simple reaction to carry out and requires either the aldehyde or ketone starting material. Phosphorous atoms can serve to increase the acidity of protons adjacent to them on a carbon skeleton. Positively charged phosphorous atoms increase this effect. Phosphonium salts can be made readily by treatment of an alkyl halide with a phosphine (normally triphenylphosphine) and the salts thus formed can be easily deprotonated by moderately strong base (aqueous NaOH) to generate a species called an ylide.

Ylides formally carry both a positive and negative charge although they can also be represented as neutral double bond phosphorane systems. The highly reactive ylides can then participate in nucleophilic attack at an electrophilic carbonyl centre of either an aldehyde or ketone. This generates a doubly charged species called a betaine; this can cyclize to afford an oxaphosphetane ring. Oxaphosphetanes are very unstable and undergo rapid *syn* elimination to afford the corresponding alkene and phosphine oxide (POPh₃). Although, the oxygen-phosphorous double bond is extremely strong, the formation of this bond drives this reaction forward.

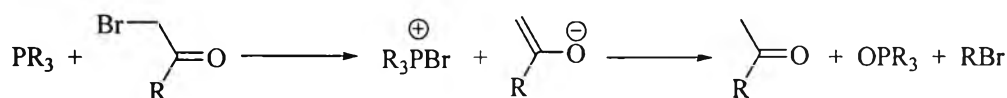


1.1.5 Michaelis-Arbusov Reaction [1-2]

Both neutral and anionic phosphorous compounds are excellent nucleophiles towards electrophiles such as alkyl halides. Reaction of phosphite esters with alkyl halides is referred to as Michaelis-Arbusov reaction. An unstable trialkoxyphosphonium intermediate is produced and subsequently attacked by a halide anion resulting in the formation of a phosphoryl bond.



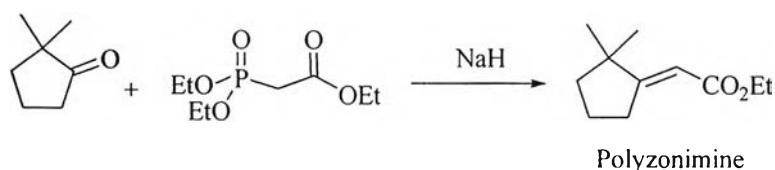
Furthermore, reactions involving α -bromoketones with phosphines and phosphites can proceed *via* an alternative pathway and in protic solvents an enolate intermediate is generated and protonated. Overall, the pathway leads to the dehalogenation of the ketone.



1.1.6 Wadsworth-Horner-Emmons Reaction [1]

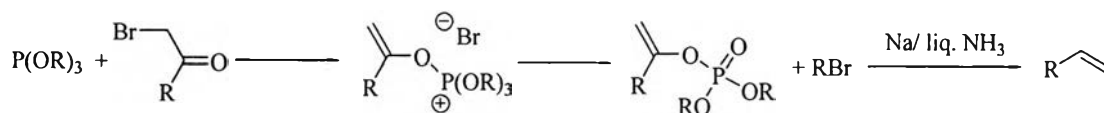
Phosphonate esters can also be deprotonated in a similar fashion with sodium hydride or using alkoxide anions to afford enolate type anions that can react efficiently with aldehydes or ketones to generate *E*-alkenes. Alkene-formation *via* phosphonates is referred to as Wadsworth-Horner-Emmons reaction. The example shown below is the synthesis of polyzonimine that is a natural insect repellent secreted by millipedes. Wadsworth-Horner-Emmons reaction has several practical

advantages over Wittig reaction involving stabilized ylides in that the phosphorous containing by-products are water soluble and easily removed during the work-up.



1.1.7 Perkow Reaction [2]

Perkow reaction of trialkyl phosphites with α -halogeno-ketones affords vinyl phosphates. Nucleophilic attack of the phosphite at the carbonyl carbon affords a zwitterionic intermediate that rearranges to form a cationic species that subsequently dealkylates to afford the corresponding phosphate. This synthetic route has been used to generate a wide range of phosphate derivatives that incorporate natural bases as well as an alternative approach to the synthesis of alkenes.



According to the aforementioned results, a lot of efficient methods for functional group interconversion in organic synthesis have been disclosed by using phosphorus reagents. However, some reactions still remain problems such as side reaction or low yield. The new methodology which could solve those problems is therefore still called for and be a responsible task for organic chemists.

1.2 Goal of Research

The aim of this research is to investigate and to develop the new methodology for carbon-carbon and carbon-heteroatom bond formations by using phosphorus reagent which can be summarized as follows:

1. To study the effect of carbon-sulfur and carbon-carbon bond formations by using a new combination of alkyl diphenylphosphinite, which was derived from the corresponding alcohol and quinone derivatives.
2. To develop a new combination of phosphorus and halogenated reagents and to explore the optimum conditions for the preparation of carbon-halogen bond formation.