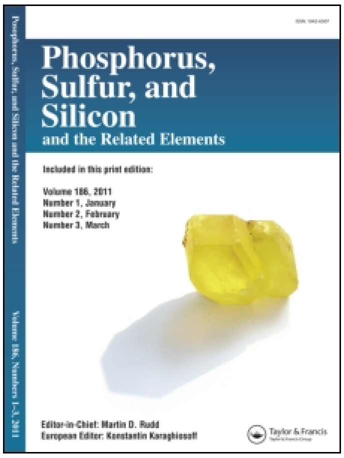

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NUCLEOPHILIC DISPLACEMENT REACTIONS ON PHOSPHORIC ESTERS AND AMIDES BY LITHIUM REAGENTS. A POWERFUL TOOL IN ORGANIC SYNTHESIS.

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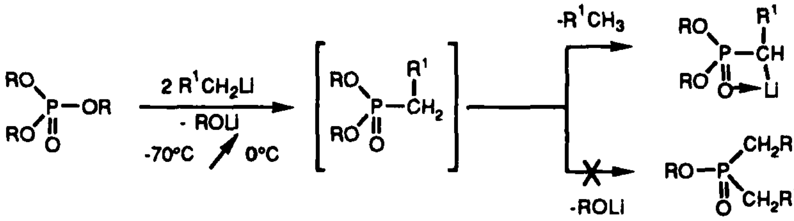
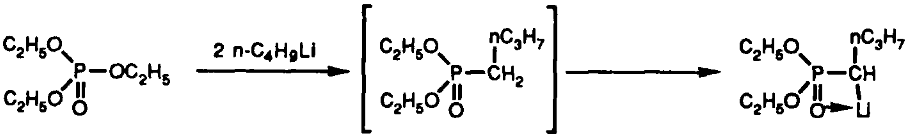
Laboratoire DCPH, Ecole Polytechnique, 91128 Palaiseau cedex, France.

ABSTRACT: Alkylation of phosphoric esters and amides by lithium reagents represents a new route to α-lithioalkylphosphonates conversion of which leads to phosphoryl stabilized anions of synthetic use.

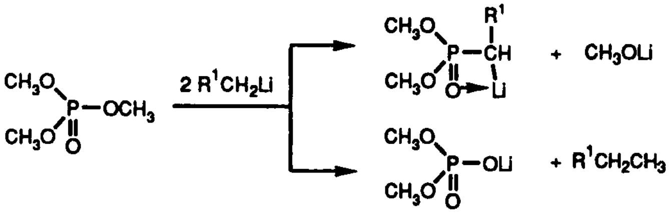
Selective displacement of alcoxy groups at a phosphorus atom by organometallic reagents is a convenient process of synthetic importance for a large variety of compounds. Since lithium reagents are more aggressive carbanionic compounds than corresponding Grignards, we thought that they would react with phosphoric esters to yield phosphonates, which would be then readily trapped by metallation to give α-lithio alkyl-phosphonates.



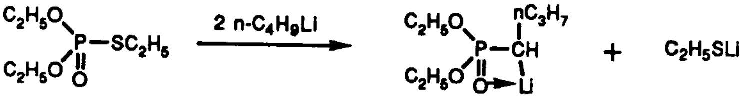
Actually, addition at -70°C of $(C_2H_5O)_3P(O)$ to nC_4H_9Li in two fold excess, followed by warming up to 0°C, quantitatively yields O-O-diethyl α-lithio butylphosphonate. This reaction is very clean because of the facile metallation of the generated alkylphosphonate and stability of the parent carbanion.



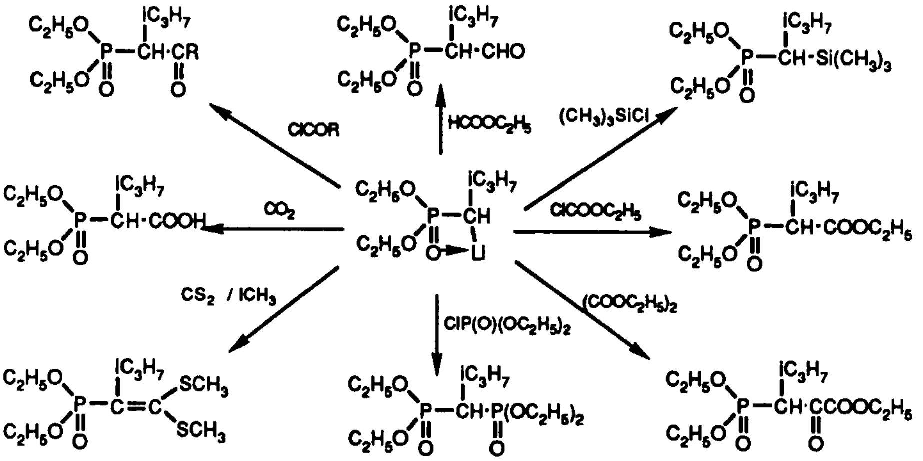
Two solvent systems, THF/ether and THF/hexane, are routinely used. The importance of the presence of lithium salts is noteworthy, because the alkylation step is markedly favoured by the coordination of the phosphoryl group with the Lewis acid. This reaction sequence can be carried out with both linear (R^1=CH_3, C_2H_5, nC_3H_7, ..., $nC_{11}H_{23}$), and ramified alkyllithiums (R^1=iC_3H_7, iC_4H_9). However, the weak nucleophilicity of CH_3Li does not allow the complete displacement of an alcoxy group. This process can be applied to a large variety of symmetrical trialkyl phosphates (R=C_2H_5, nC_3H_7, iC_3H_7, nC_4H_9, iC_4H_9). $(CH_3O)_3P(O)$ is both P- and C-alkylated in a ratio which is lithium salt dependant.



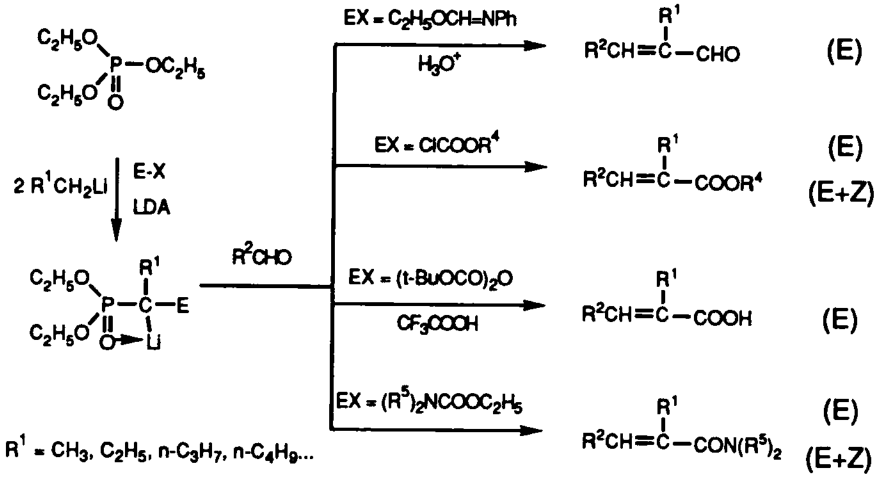
Alkylating umsymmetrical trialkylphosphates or six-membered cyclic phosphates usually affords a mixture of products because the leaving alcoxy group is not univocal. Only O,O-diethyl S-ethyl phosphate gives a single reaction with S-ethyl as the leaving group.



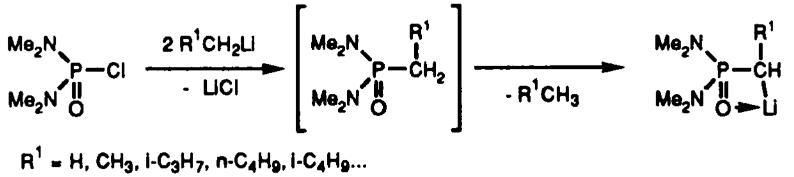
O,O-dialkyl α -lithio alkyl-phosphonate carbanions are stable at 0°C. Hydrolysis gives alkylphosphonates; treatment at low temperature with a functional group precursor (E-X) gives in good yields α-substituted α-functional phosphonates (R^1=iC_3H_7).



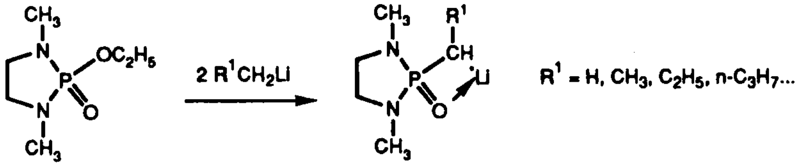
Addition of the precursor (E-X) in the presence of LDA leads to lithiated α-substituted phosphoryl stabilised anions which are of preparative value for the direct synthesis of α-substituted α,β-unsaturated aldehydes, esters, acids, and amides.



Bis(dimethylamino)chlorophosphate fits into this discussion, since chloride ions are readily displaced under the same conditions as alcoxy groups. Thus α -lithio alkyl phosphonamides are prepared in quantitative yields when bis(dimethylamino)chlorophosphate is allowed to react with alkyl-lithiums. All reagents, including methyl-lithium and bulky ones, were shown to attack at the phosphorus. Displacement of chloride ion seems facile and provides stable carbanions.

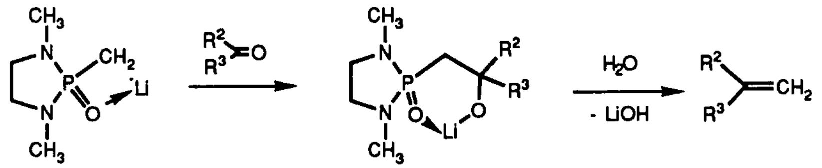


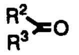
These results prompted us to extend this process to 2-ethoxy 2-oxo 1,3-dimethyl 1,3,2-diazaphospholane. This compound is quantitatively converted by alkyl-lithiums (including CH_3Li), to stable α-lithio alkyl diazaphospholanes. They are better nucleophiles than α-lithio



alkyl phosphonates and able to attack $(C_2H_5O)_3P(O)$ at the phosphorus atom to give quantitatively lithiated alkylidene phosphonate phosphonamides.

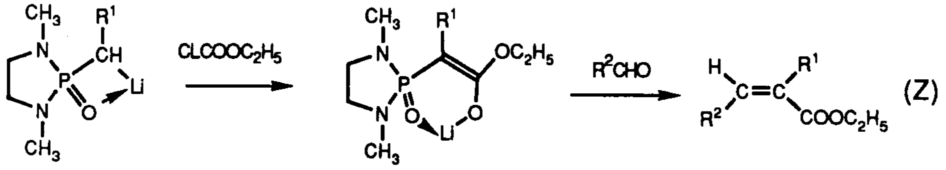
α-Lithio methyl diazaphospholane condenses at low temperature with ketones to give stable tertiary alcohols. Hydrolysis at room temperature eliminates $LiOH,H_2O$ which induces the cleavage of the P-C bond with transfer of the methylene group to the carbonyl compound. This reaction has been applied to a variety of ketones. This diazaphospholane appears as a promising reagent.





$R^2R^3C=O$ = benzophenone, adamantanone, fenchone...

Treatment of α -lithioalkyldiazaphospholane with ethyl chloroformate affords an enolate. This stabilised carbanion is a key intermediate in the synthesis of α-substituted α,β-unsaturated esters of (Z) geometry.



$R^1 = CH_3, C_2H_5, n\text{-}C_3H_7, n\text{-}C_7H_{15}$

$R^2 = CH_3, n\text{-}C_3H_7, i\text{-}C_3H_7, i\text{-}C_4H_9, n\text{-}C_6H_{13}$

Further developments are in progress.

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