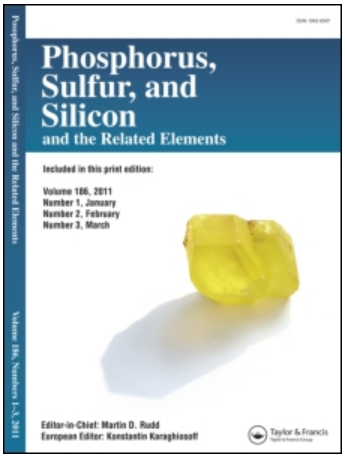

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NEW SYNTHETIC METHODS FOR CARBOCYCLIC AND HETEROCYCLIC COMPOUNDS BEARING PHOSPHONATE MOIETY WITH BIOLOGICAL SIGNIFICANCES

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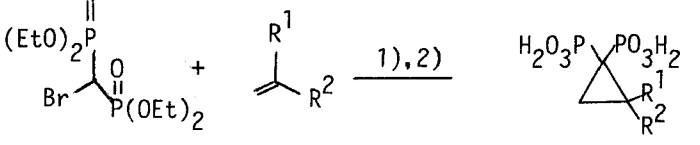
Abstract New synthetic routes leading to various derivatives of cyclopropane, pyrrole, indole and isoxazoline with phosphonate moiety are described.

The successful clinical application of Fosfomycine(**1**) and Cyclophosphonamide(**2**) as wide spectrum antibiotics and anti-cancer drugs respectively, aroused our interests in structure-activity studies of carbocyclic and heterocyclic compounds bearing phosphonate moiety for the evaluation of their biological activities.

Among the carbocyclic compounds, cyclopropylphosphonic acids(**3**) are compounds of particular interest since they can be regarded as the isostere of **1**. A new and facile route to 2-substituted 1,1-cyclopropanediylbis(phosphonic acids) was worked out by us based on the reaction of bromomethylenebisphosphonates with electron-deficient alkenes as Miahael acceptor in the presence of thallium(I) ethoxide followed by subsequent dealkylation with trimethylchlorosilane(TMCS) in the usual manner.[1]



4

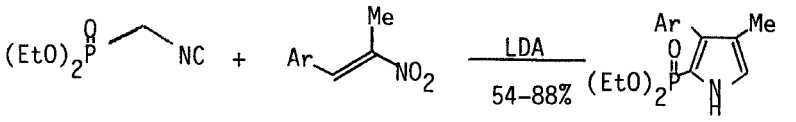
1) EtOTl/THF, reflux, 2-12h, 37-63%.
2) TMCS/KI, MeCN, r.t., 18h. and H_2O, r.t., 24h. 90-95%
R^1= CN, CO_2Et, CO_2Me, H, Me; R^2= H, Me, CN, CHO, C(O)Me

The use of EtOTl is critical in this reaction. As found by us, with EtONa, the reaction products are very complicate with the formation of free radical intermediates as shown by ESR studies. A tentative reaction

mechanism for the formation of cyclopropane ring involving a concerted ionic reaction pathway was postulated. Compound **4** can also be considered as a cyclized methylenebisphosphonate, a skeleton with potential antiviral activity.[2] Besides these, **4** can be used as ligand for cis-platinum complex. In combination with suitable amine, the anti-tumor activity of such complex is expected to be enhanced due to the steric effect and the increase of Pt-O bond energy leading to difficult replacement of nucleophilic group of DNA in a target molecule.[5]

Since heterocyclics comprised as compounds with potential biological activities, herein we wish to report some new synthetic methods for the preparation of derivatives of pyrrole, indole and isoxazoline bearing phosphonate moiety.[3,4]

By the reaction of carbanion derived from dialkoxyphosphorylmethylisonitrile and 1-nitro-2-arylpropene, a series of 4-methyl-3-aryl-2-dialkoxyphosphorylpyrrole(**5**) were synthesized.



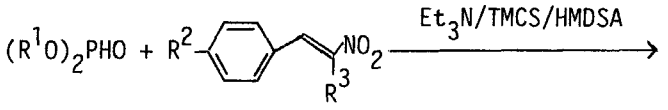
5

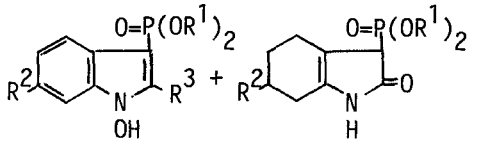
Ar = Ph, p-MePh, p-MeOPh, p-ClPh, o-ClPh, o,pCl_2Ph, p-NO_2Ph, m-NO_2Ph, 2-Furan.

The reaction mechanism consisting Michael addition, intramolecular cyclization and followed by rearrangement was suggested. Analogously, 1,2-diphenylnitroethene, 2-nitro-propene-1 and 1-nitro-hexene-1 provide corresponding phosphoryl pyrrole in different yields.

As shown by us, reaction of dialkylphosphite and 1-substituted nitrostyrene in the presence of triethylamine, TMCS and hexamethyldisilazane(HMDSA) leads to a one-pot procedure for the synthesis of 2-substituted-3-diethoxyphosphoryl-N-hydroxy-indole(**6**) and indole-2-one phosphonate(**7**). Such new indole derivatives are difficult to prepare by conventional methods. The ratios of reactant to silylating agent and base were found to have significant influence on the product composition. Formation of indole derivatives seems to be proceeded via reactive nitronate, resulted from the silylation of the addition product of dialkylphosphite to nitrostyrene. The N-hydroxy-indole derivatives thus

obtained is converted easily to indol-2-one with the aid of silylating agent.



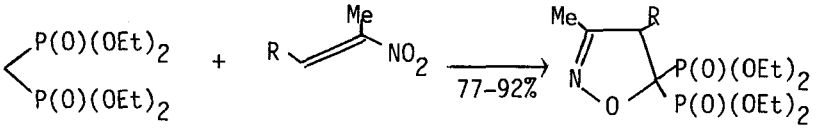


6 **7**

6 R^1= Et, n-Pr, i-Pr, n-Bu; R^2= H, MeO; R^3= H, Me.
7 R^1= Et, i-Pr; R^2= H, Me, MeO.

The structure of the compounds synthesized was elucidated by X-ray crystallogram in addition to IR, NMR, MS and elemental analyses.

Very recently we introduced a novel synthesis of 2-isoxazoline-5,5-diylbisphosphonate(**8**) based on the reaction of methylenebisphosphonate with 1-nitro-alkenes followed by addition of TMCS. This reaction proceeds through the formation of ethylidenebisphosphonates and trimethylsilyl nitronate as 1,3-dipole in almost quantitative yield. These two products, without isolation, upon prolonged reaction at ambient temperature provide **8** via regioselective 1,3-dipolar cycloaddition in high yield.

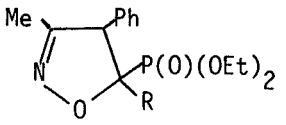


8

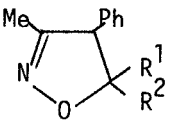
R = Ph, p-ClPh, p-NO_2Ph, o,p-Cl_2Ph, p-MeOPh, p-Me_2NPh; Et, n-Pr.

Instead of nitrostyrene derivatives, 2-nitro-3-alkyl-substituted propene-2 usually gave low yield. R = Et(60%), Pr(65%). 1-Nitrocyclohexene gives corresponding cyclohexoisoxazoline under similar conditions as expected. Variation of the structure of methylenebisphosphonate by substituting one or both phosphoryl groups by other electron-withdrawing groups in this reaction leads to form isoxazoline derivatives **9** or **10**

respectively, via intramolecular 1,3-dipolar cycloaddition.



9



10

9 R = COOMe, CN, SO_2Me

10 R^1= R^2=COOEt(a); R^1= R^2=CN(b); R^1= R^2=COMe(c); R^1= COOEt, R^2= CN(d); R^1= COOEt, R^2= COMe(e); R^1= COOEt, R^2= SO_2Ph(f); R^1= CN, R^2= SO_2Me(g).

The Et_3N or i-$PrNH_2$ used in this reaction has two functions. It serves as the stabilizer of the trimethylsilylnitronate formed and as the initiator of the cycloaddition.The chemical behaviours of 2-isoxazoline derivatives toward acids and bases were examined. Compounds **10**c and **10**e rearranged to corresponding furan derivatives with the aid of a base. This transformation proceeds through deprotonation on position 4 and followed by ring opening and sudsequent elimination of NO^-. The process is proved to be accompanied by ring closure with the formation of corresponding furan derivatives. Compounds **10**b, **10**d and **10**g exist usually in equilibrium with 4-cyano-substituted-2-isoxazolines via elimination and addition of HCN.

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