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Synthetic Methodologies and Biological Importance of Phosphonylpyrazoles

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Abstract: Pyrazole derivatives are an important class of compounds with diverse applications in agrochemicals, coordination chemistry, supramolecular chemistry, and pharmaceuticals. This review focuses on the synthesis and applications of phosphonate-containing pyrazole derivatives. Phosphonates are known to mimic carboxylic acid groups and have been used in drug design to modulate biological activities. The review discusses the nomenclature and types of phosphonylpyrazoles based on the position of the phosphonyl group in the pyrazole ring. Synthetic methods for preparing phosphonylpyrazoles are categorized into three main routes: phosphorylation of the preformed pyrazole ring, ring closure of acyclic phosphorus-containing compounds, and cycloaddition-based strategies. Phosphorylation of the pyrazole ring can be achieved through C-phosphonylation and N-phosphonylation reactions, with palladium-catalyzed cross-coupling reactions being a useful strategy for introducing phosphorus substituents at various positions of the pyrazole ring. Ring closure of acyclic phosphorus-containing compounds can lead to the formation of N-phosphonylpyrazoles and C-phosphonylpyrazoles, with the use of Vilsmeier reagents and cycloaddition-based strategies being prominent approaches. The review also highlights the biological importance of phosphonylpyrazoles, with phosphorus substituents acting as biological activity modulators for antimicrobials and pesticides. The development of new methodologies for synthesizing phosphonylpyrazoles is crucial for both the chemical and pharmaceutical industries, and the review concludes by emphasizing the need for more general and efficient methods

Keywords: *Phosphonylpyrazoles, pyrazole, Bestmann–Ohira Reagent, Phosphonates.*

INTRODUCTION

Recent advances in phosphonylpyrazole chemistry have significantly enhanced the understanding of their synthesis, properties, and applications. Phosphonylpyrazoles are a class of heterocycles that have garnered attention due to their potential biological activities and utility in organic synthesis. The synthesis of these compounds often involves the use of diazo compounds, particularly the Bestmann-Ohira reagent (BOR), which has been pivotal in the development of various synthetic methodologies.

Pyrazoles and their derivatives possess a wide range of biological properties(Zampieri et al., 2008) and important constitutional scaffold of molecules/chemicals having application in pharmaceutical(Khan et al., 2016; Wyatt et al., 2008), agriculture(Giornal et al., 2013; Lamberth, 2007) and as ligands in coordination chemistry(Halcrow, 2009; U. P. Singh et al., 2011; Werner et al., 2018). This has motivated synthetic chemists to develop new synthetic methodologies(R. Singh et al., 2021; Tanwar et al., 2015) and explore the bioactivity of new derivatives(Si et al., 2019). Phosphorous substituents are known to act as biological activity modulators for antimicrobials as well as pesticides.

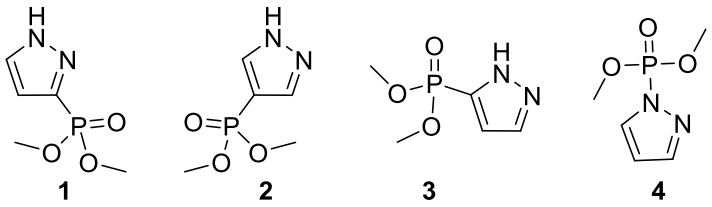

Figure 1: Types of phosphonylpyrazoles based on the position of the phosphonyl group in pyrazole ring

NOMENCLATURE AND TYPES

IUPAC names of phosphonylpyrazoles are generated using the Hantzsch-Widman nomenclature, common names, and the replacement nomenclature.(Favre & Powell, 2013; Leigh, 2011) Based on the position of the phosphonyl group in pyrazole ring, phosphonylpyrazoles could be of four types (**Figure – 1**).

SYNTHETIC METHODS

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Due to the interest in possible and unpredictable changes in various properties of pyrazoles, synthesis of phosphonylpyrazoles appeared as an attractive objective. The reported methods for the synthesis are based on the cyclocondensation of 1,3-difunctional species bearing phosphorus substituent with hydrazine derivatives,(Flores et al., 2005) or 1,3-dipolar cycloaddition of alkenyl or alkynyl phosphonate with diazo compounds.(Molteni, 2007) The synthesis of phosphonylpyrazoles typically employs a one-pot base-mediated regioselective 1,3-dipolar cycloaddition reaction involving diazophosphonates and nitroalkenes. This method has been extensively studied and optimized, leading to the formation of highly functionalized phosphonylpyrazoles with diverse substituents.

Synthetic procedures for the preparation of phosphonylpyrazoles are multistep and complex. The synthesis can be accomplished through three distinct methodologies:

1. Phosphorylation of the preformed pyrazole ring

2. Ring closure of acyclic phosphorus-containing compounds,

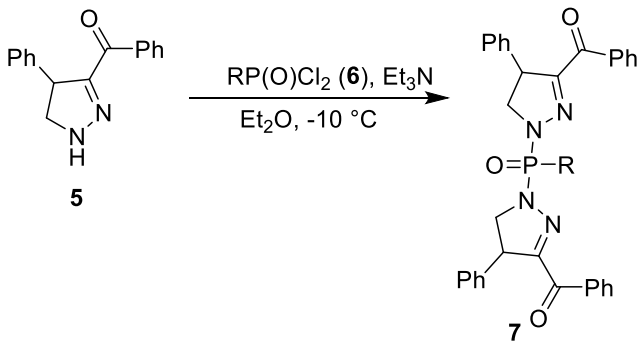
3. Cycloaddition-based strategies

1. Phosphonylation of the Preformed Pyrazole Ring

Phosphonylation of the pyrazole ring takes advantages of availability of differently substituted pyrazoles. In this category, methods could be grouped as C-phosphonylation and N-phoshponylation reactions. However, this methodology is much less documented, and most available methods describes introduction of phosphorus at the C-4 position using environmentally problematic phosphorus−chlorine derivatives such as phosphorous trichloride.(Ali & Abdel-Kariem, 2012) Moreover, it is essential to utilize pyrazoles with an unsubstituted 4-position and devoid of electron-withdrawing groups for successful substitution.

C(sp^2)-P bond formation using palladium-catalyzed cross-coupling reactions is synthetically useful strategy to produce 3-, 4-, and 5-phosphonyl-pyrazoles by palladium catalyzed cross-coupling reaction between H-phosphonates and corresponding halo-pyrazoles. This proved to be a general method allowing the introduction of a great diversity of phosphorus substituents (coupling with H-phosphonates, H-phosphinates, or secondary phosphine oxides) on the different carbons of the pyrazole ring in a one-step process.(Tran et al., 2013) Refluxing of triethyl amine, diethyl phosphorochloridate, and 3,5,5-trimethyl-4,5-dihydro-1*H*-pyrazole in benzene produced diethyl (3,5,5-trimethyl-4,5-dihydro-1*H*-pyrazol-1-yl)phosphonate in 62% yield.(Gryaznov et al., 1996)

3-benzoyl-4-phenyl-2-pyrazoline (condensation product of chalcone and azomethane) reacts with various aryl phosphorodichloridates **6a-e** or trichloromethylphosphonic dichloride **6f** in the presence of a base resulted to produce arylbis (3-benzoyl-4,5-dihydro-4-phenyl-1*H*-pyrazol-1-yl)phosphinates **7a-e** and trichloromethyl-bis (3-benzoyl-4,5-dihydro-4-phenyl-1*H*-pyrazol-1-yl)phosphonate **7f**.(Raghu et al., 1997) These products exhibit moderate antibacterial and antifungal activity (**Scheme-1**).



SNo.	R	%Yield
7a	C_6H_5O	46
7b	2-MeC_6H_4O	44
7c	4-MeC_6H_4O	45
7d	2-ClC_6H_4O	43
7e	4-ClC_6H_4O	48
7f	CCl_3	58

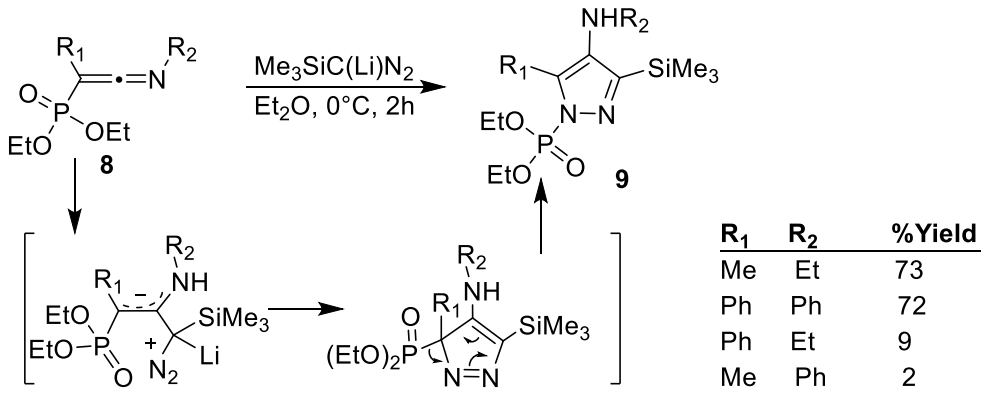
Scheme 1: Phosphonylation of the Preformed Pyrazole Ring of benzoyl-4-phenyl-2-pyrazoline

The cycloaddition of C-substituted N-arylnitrilimines to allenyl phosphonates occurs at the 1,2 double bond of the cumulene, resulting in the formation of a mixture of regioisomeric pyrazoles. The reaction of nitrilimines with propynylphosphonates proceeds regioselectively.

2. Ring Closure of Acyclic Phosphorus-Containing Compounds

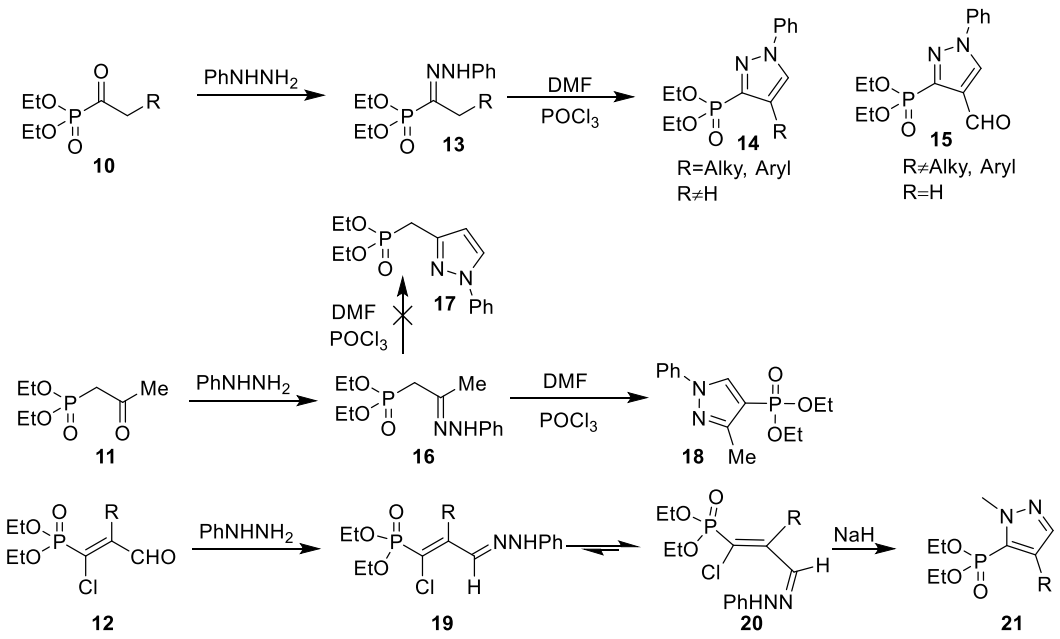
2.1 N-Phosphonylpyrazoles

Phosphoryldiazoalkanes add regiospecifically to methyl propiolate to give the 3H-pyrazoles in which the phosphoryl group undergoes a spontaneous [1,5] shift to give the 1-phosphorylpyrazoles (**Scheme-2**).(Felcht & Regitz, 1976; Hartmann et al., 1974) Similar rearrangement is also reported with 3*H*-pyrazoles prepared by the reaction of ketenimines bearing phosphonyl group at C-2 position with lithium trimethylsilyldiazomethanide via intermediate betains.(Aoyama et al., 1991) The electronegative phosphoryl group at C-2 promotes localization of the anionic center at C-2 instead of N and facilitates the preferential formation of 3*H*-pyrazole via attack of C-2 anion to the diazonium nitrogen. In the absence of an electronegative group at C-2, it gives 1,2,3-triazole via attack of *N*-anion to the diazonium nitrogen.(Shioiri et al., 1989) Migration of phosphoryl group of 3-phosphonyl-3*H*-pyrazole from carbon to nitrogen via [1,5]-shift rearranges N-Phosphonylpyrazoles.(Felcht & Regitz, 1976)



R_1	R_2	%Yield
Me	Et	73
Ph	Ph	72
Ph	Et	9
Me	Ph	2

Scheme 2:



Scheme 3: Reaction of phosphonyl chlorovinylaldehydes with phenylhydrazine

2.2 C-Phosphonylpyrazoles

This synthetic approach is predicated on the cyclocondensation of 1,3-difunctional compounds with hydrazine derivatives, wherein either reactant bears a phosphorus substituent. The formation of regioisomers is feasible when substituted hydrazines are employed..(Dirat et al., 2006)

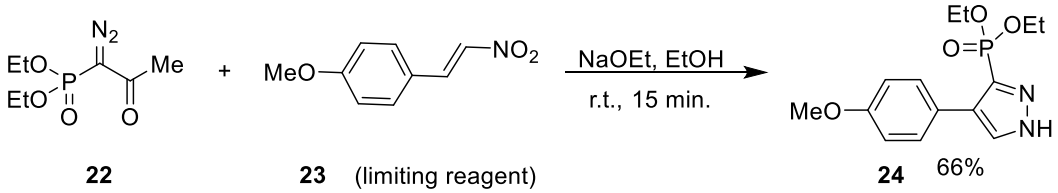
2.2.1 Using Vilsmeier reagent (DMF/POCl3)

Phosphonyl hydrazones react with DMF/$POC1_3$ to afford 3-phosphonyl pyrazoles. Phosphonyl methylene hydrazones react with DMF/$POC1_3$ to provide 4-diethoxyphosphonyl pyrazole instead of 4-diethoxyphosphonyl methyl-ene pyrazole due the effect of the phosphonyl group, the electrophilic substitution of the methylene group by the Vilsmeier reagent took place more readily than that of methyl group. 5-Phosphonyl pyrazoles are obtained from the reaction of phosphonyl chlorovinylaldehydes with phenylhydrazine (**Scheme – 3**).(Chen et al., 1999)

In another approach, 1-*H* or 1-substituted 3-phosphonylpyrazoles has been synthesized by the reaction of readily available 3-ethoxyacryloylphosphonic acid diethyl ester **11** and hydrazines.(Bartnik & Cal, 2010) In a strategy to obtain N-P linked pyrazoles, the Vilsmeier-Haack reaction was used to phosphonic dihydrazones **13** into bis-{4-formyl-3-phenyl-1*H*-pyrazol-1-yl}phosphine oxides.

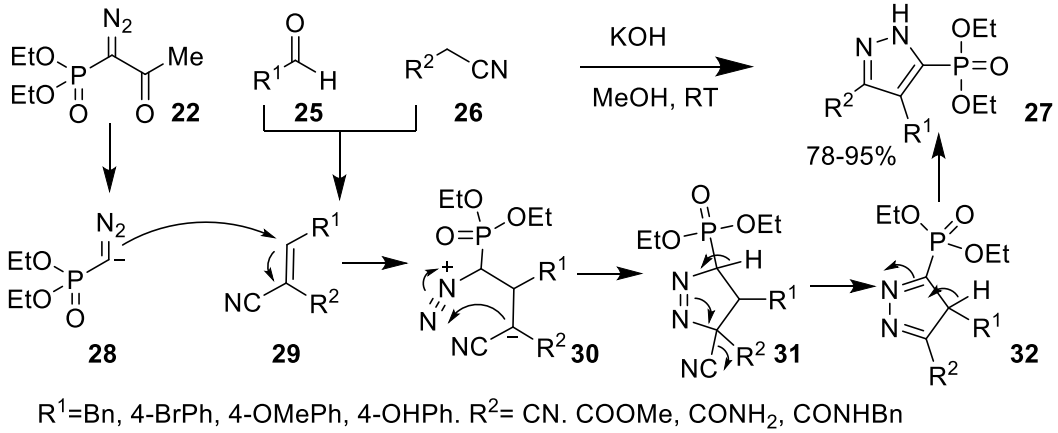
2.2.2. Cycloaddition Addition based Strategies

A number of nitroalkenes (nitrostyrenes) **23** bearing a range of electron-donating and electron-withdrawing groups were converted into phosphonylpyrazoles through 1,3-dipolar cycloaddition reactions with diethyl 1-diazo-2-oxopropylphosphonat **22** (Bestmann-Ohira Reagent). Dynamic NMR studies unraveled the existence of two tautomers in solution with a small energy difference but considerable barrier to interconversion (Scheme-4).(Muruganantham et al., 2007; Muruganantham & Namboothiri, 2010)



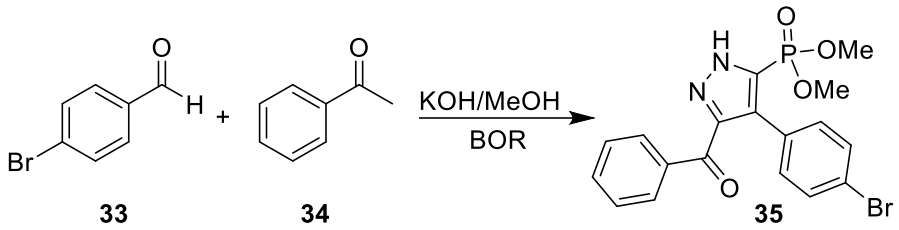
Scheme 4: Conversion of nitrostyrenes into phosphonylpyrazoles through 1,3-dipolar cycloaddition reactions

Synthesis of substituted phosphonyl pyrazoles using a multicomponent one-pot procedure was reported by Mohanan and co-workers using an aldehyde, a cyanoacid derivative, and the Bestmann–Ohira reagent (BOR). The methodology takes advantage of faster Knoevenagel condensation of malononitrile with an aldehyde than the homologation reaction (Scheme-5).(Mohanan et al., 2010)



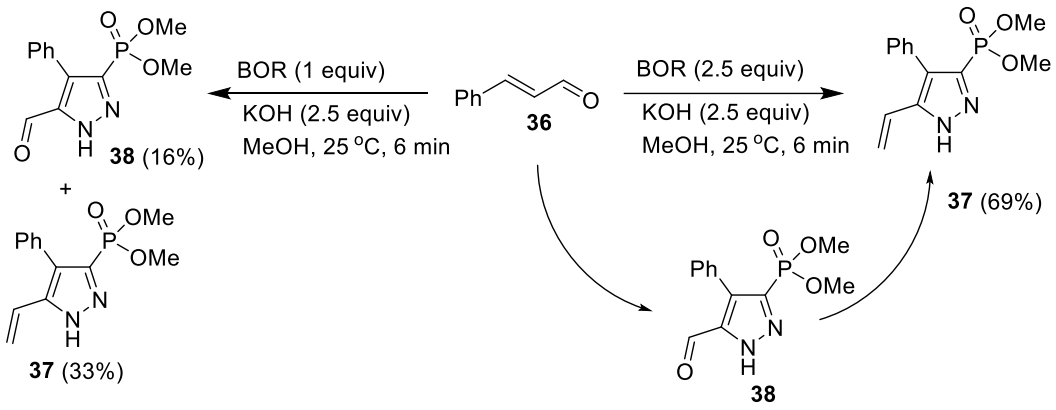
Scheme 5: Synthesis of substituted phosphonyl pyrazoles using a multicomponent one-pot procedure

Martin and co-workers reported a regioselective preparation of 3-carbo-5-phosphonyl pyrazoles using Claisen–Schmidt/1,3-dipolar cycloaddition/oxidation sequence for an aldehyde, methyl ketone and the BOR in one-pot reaction (**Scheme-6**).(Martin et al., 2011)



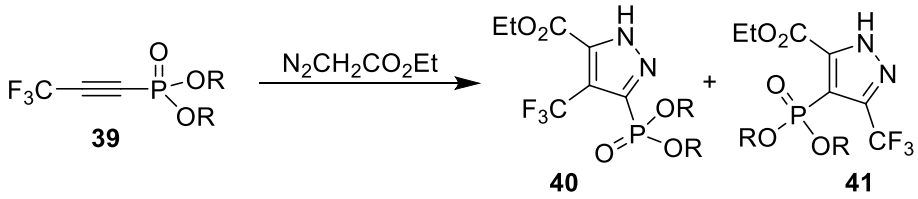
Scheme 6: Regioselective preparation of 3-carbo-5-phosphonyl pyrazoles

Efficient synthesis of vinyl pyrazole derivatives was developed as a domino process involving the reaction of α,β-unsaturated aldehyde with excess BOR in moderate to excellent yields under mild conditions, and completes in very short time(six minutes).(Ahamad et al., 2015) The reaction course is independent of the substituent pattern on the aldehyde moiety. The reaction tolerates electron-donating and electron-withdrawing substituents on the aromatic ring. β-heteroaryl substituted enals, aliphatic enal and enal with extended conjugation underwent smooth annulation reactions to yield vinylpyrazoles in moderate to good yields. The reaction uses two molecules of BOR, the first is used to converts enal to pyrazoline carboxaldehyde, and second molecule converts the later into vinyl pyrazole derivatives. A control reaction using one equivalent of BOR produces pyrazoline carboxaldehyde (16%) and vinyl pyrazole (33%). The control reaction establishes the fact that the reaction is proceeding through pyrazoline carboxaldehyde (**Scheme-7**).



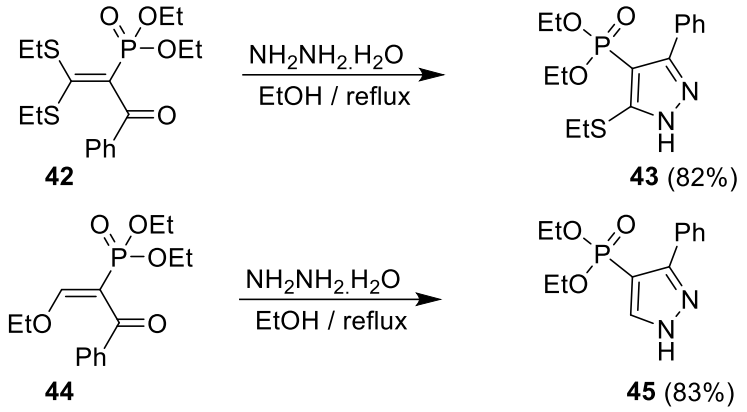
Scheme 7: Preparation vinyl pyrazole derivatives

Perfluoroalkylated heterocyclic phosphonates have been conveniently synthesized by 1,3-dipolar cyclo-addition of aromatic nitrile oxides (or ethyl diazoacetate or tert-butyl azidoacetate) and perfluoroalkylated alkynylphosphonates in good to excellent yields with high regioselectivity (**Scheme-8**).(Shen et al., 1995)



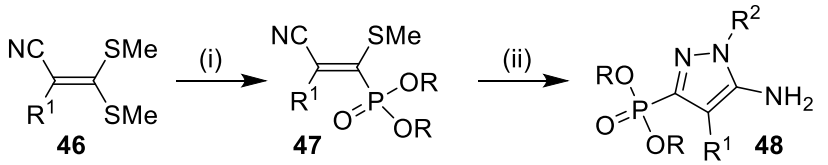
Scheme 8: Synthesis of Perfluoroalkylated heterocyclic phosphonates

R-Acylated vinylphosphonates **42** and **44** were transformed into phosphono-containing pyrazoles **43** and **45** in 82% and 83% yields, respectively, by refluxing with hydrazine monohydrate in EtOH (**Scheme-9**).(Kouno et al., 1998)



Scheme 9: Preparation phosphono-containing pyrazoles **43** and **45**

Conjugate addition of the phosphite to the ketene dithioaeetal **46** occurs to afford the corresponding phosphonyl/S-methyl α-cyano (or ethoxycarbonyl) ketene acetals **47**. The later cyclizes with hydrazine hydrate or phenyl hydrazine to give 5- amino-4-cyano(ethoxy-carbonyl)-3-phosphonyl pyrazole **48** at -5 to 0 °C(**Scheme-10**).(Lu & Yang, 1997) Previous attempts to cyclize at reflux resulted in polymerization.(Lu & Yang, 1997)



R	R^1	R^2	%Yield of A	%Yield of B
Et	CN	H	99	95.8
Et	CO_2Et	H	94.5	94.5
Pr-i	CN	H	91.3	90.2
Et	CN	Ph	99	94.2
Et	CO_2Et	Ph	94.5	92.5
Pr-i	CN	Ph	91.3	88.8

Scheme 10: Reagents and conditions: (i) 3equiv. $HOP(OR)_2$, 2 equiv. NaH, THF; (ii) R^2NHNH_2, EtOH

BIOLOGICAL IMPORTANCE

Phosphorus substituents can modulate the biological activities of pesticides, antiviral and antimicrobial compounds. Phosphorous substituents are known to act as biological activity modulators for antimicrobials and pesticides.

The properties of phosphonylpyrazoles are closely tied to their structural characteristics, which can be finely tuned through synthetic modifications. The presence of the phosphonyl group significantly influences the electronic properties of the pyrazole ring, potentially enhancing its reactivity and biological activity. Research has indicated that pyrazolines with incorporated phosphonates exhibit promising bioactivities due to their ability to interact with various biological targets (Chandrasekharan et al., 2022; Zheng et al., 2019). The structural diversity achieved through different synthetic routes allows for exploring a wide range of biological activities, making phosphonylpyrazoles attractive candidates for further investigation in drug discovery.

Regarding applications, phosphonylpyrazoles have been recognized for their potential in developing novel pharmaceuticals. Their structural similarity to known bioactive compounds positions them as promising candidates for further exploration in medicinal chemistry. Incorporating phosphonyl groups into pyrazole derivatives has been linked to enhanced pharmacological profiles, including anti-inflammatory, antimicrobial, and anticancer activities(Mayorquín-Torres et al., 2024). The ongoing research into the biological activities of these compounds is expected to yield new insights into their mechanisms of action and therapeutic potential.

Furthermore, the application of phosphonylpyrazoles extends beyond pharmaceuticals into agrochemicals, where they can serve as effective pest control and crop protection agents. The unique properties of these compounds, combined with their synthetic versatility, make them suitable for developing new agrochemical formulations that can address the challenges of modern agriculture(Chandrasekharan et al., 2022; Kommera et al., 2020). Exploring their efficacy in agricultural applications is an exciting area of research that could lead to developing environmentally friendly and sustainable pest management solutions.

CONCLUSION

Phosphonate-containing pyrazole derivatives represent a versatile and significant class of compounds with wide-ranging applications in various fields, including pharmaceuticals and agrochemicals. The phosphoryl or substituted phosphoryl group has played a key role in modifying the properties of pyrazole derivatives. Therefore, the development of new methodologies will be useful in the chemical as well as the pharmaceutical industries. Although Pd-catalyzed and cycloaddition approaches have provided access to differently substituted phosphonylpyrazoles, there is a need to develop more general and efficient methods.

FUTURE SCOPE

Future research should focus on developing more efficient and general synthetic methodologies for phosphonylpyrazoles to enhance their utility in the chemical and pharmaceutical industries.

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