TÜBİTAK

Turkish Journal of Chemistry

http://journals.tubitak.gov.tr/chem/

Review Article

Turk J Chem
(2016) 40: 225 – 247

doi:10.3906/kim-1502-56

Wittig–Horner reagents: powerful tools in the synthesis of 5-and 6-heterocyclic compounds; shedding light on their application in pharmaceutical chemistry

Rizk Elsayed KHIDRE[1,2,*], **Wafaa Mahmoud ABDOU**[1]
[1]Chemical Industries Division, National Research Centre, Dokki, Giza, Egypt
[2]Department of Chemistry, Faculty of Science, Jazan University, Jazan, Saudi Arabia

Received: 09.02.2015 • **Accepted/Published Online:** 22.06.2015 • **Final Version:** 02.03.2016

Abstract: This paper reviews literature over 25 years' activity on phosphoryl carbanion reagents and shows that these compounds are powerful tools in organic chemistry. The main target of this review is to outline some of the reactive peculiarities that make this class of compounds powerful tools in the synthesis of 5- and 6-heterocyclic compounds and/or substituted heterocycle phosphor esters. The importance of these latter compounds in pharmacology is also discussed.

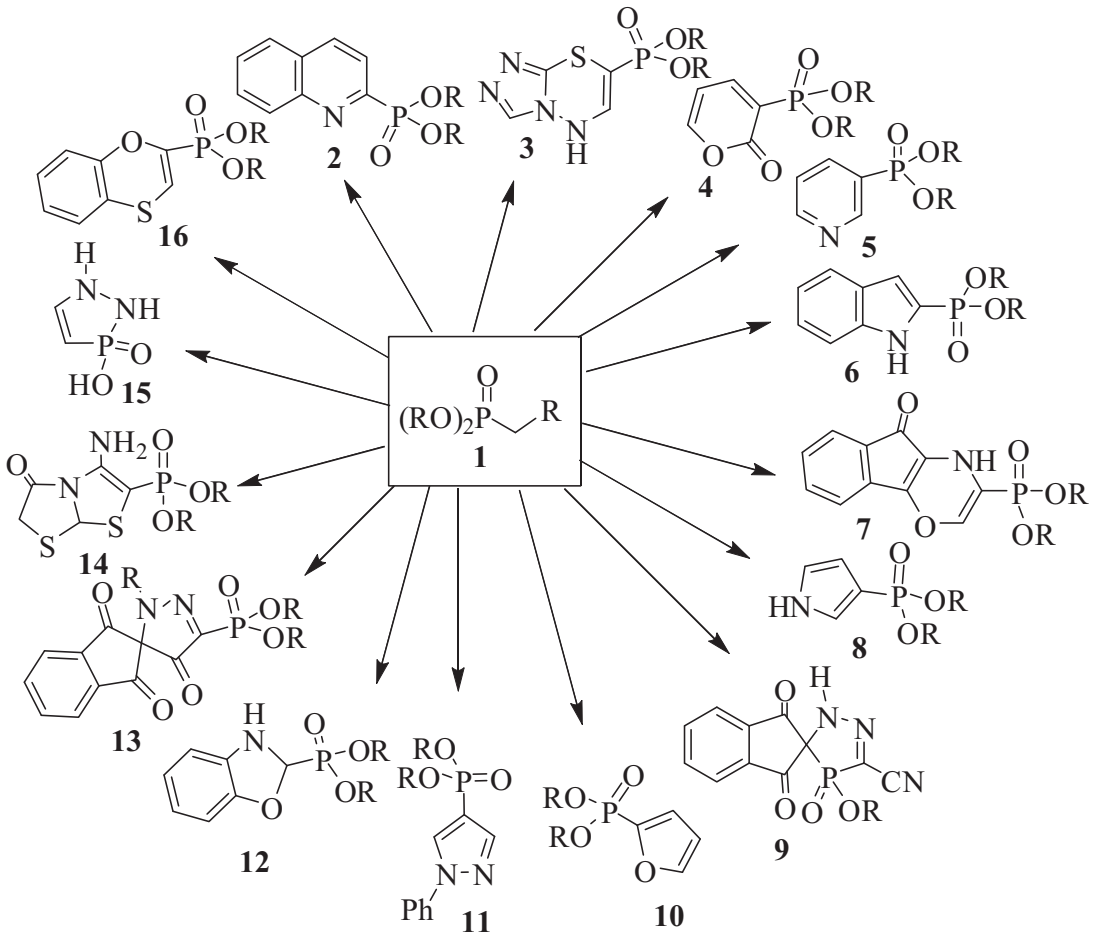
Key words: Phosphonyl carbanions reagents, phospha-Michael (P-Michael) addition, Perkin-type reaction, five-membered heterocycles, six-membered heterocycles, nucleophiles

1. Introduction

Organophosphorus compounds, in parallel, are noteworthy for their biological activity,[1–4] especially when they are associated with various heterocycles.[5] One of the most important of these bioactive heterocycles are the substituted heterocycle phosphor esters and/or heterocycles containing phosphorus groups.[6] In spite of their importance, methods for the direct synthesis of these types of heterocycles are quite limited.[7,8] With this aim, our group and others investigated for over 25 years the usefulness of phosphoryl carbanions (also known as Wittig–Horner (WH) or Wadsworth–Horner–Emmons (WHE) reagents) in the construction of several five- and six-membered heteroring systems. Related substituted heterocycle phosphor esters and/or heterocycles containing phosphorus groups were reported.

This review article describes the progress over last three decades in the chemistry of phosphoryl carbanions, showing their synthetic usefulness as versatile building blocks in the construction of five- or six-membered heterocycles (Scheme 1) and in connection to our previous review articles.[9–14] The classification is based upon the size of the heterocyclic rings (five-membered and six-membered rings) and the number of heteroatoms in the given molecule regardless of the site of attack by the reagent. There are, however, some exceptions to this classification, some of which will emerge in the subsequent discourse. Heterocyclic derivatives, on the other hand, are of great importance in pharmaceutical chemistry. The main purpose of this review is to represent a survey of the utility of phosphonyl carbanions in the synthesis of 5- and 6-heterocyclic compounds and provide useful and up-to-date data for chemists. Furthermore, pharmacological applications of the produced heterocycles are discussed.

*Correspondence: rizkkhidre@yahoo.com



Scheme 1.

2. Synthesis of five-membered heterocycles

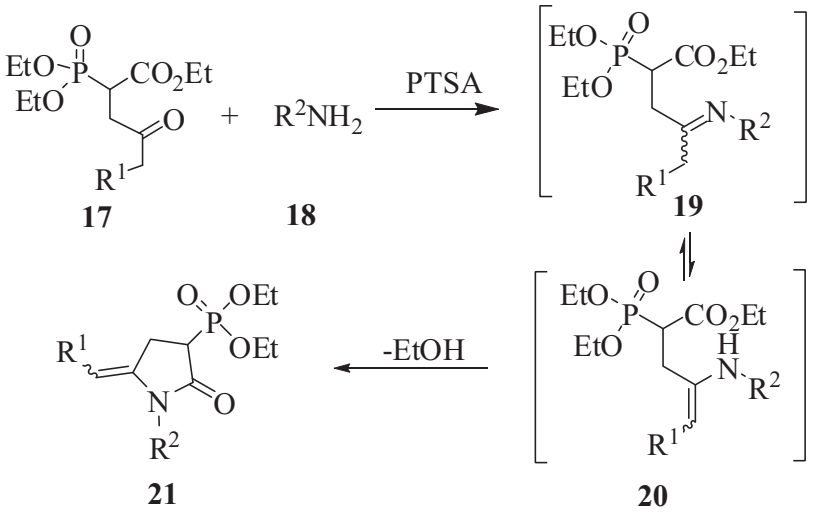
2.1. Five-membered heterocycles with one heteroatom

2.1.1. Pyrroles and their fused systems

Phosphonyl carbanions **17** were reacted with amine **18** in refluxed toluene containing *p*-toluenesulfonic acid (PTSA) to give phosphorylpyrrolidin-2-ones **21** in high yields via formation of intermediates imines **19** and enamines **20** followed by lactamization (Scheme 2).[15]

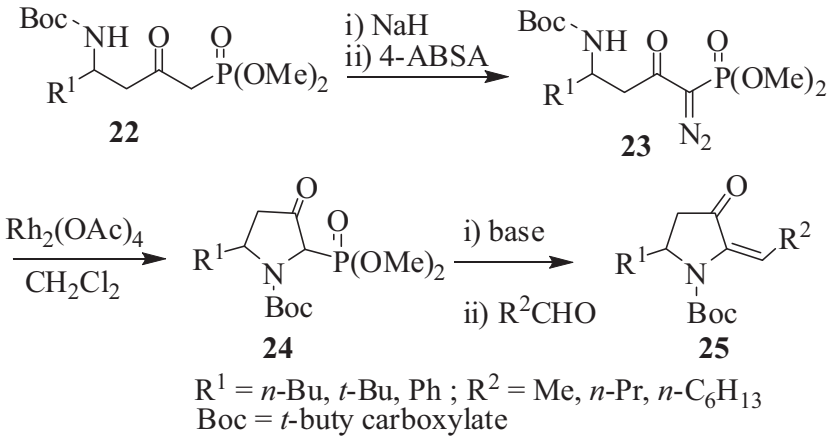
δ-Amino-β-keto-phosphonates **22** were treated with 4-acetamidobenzenesulfonyl azide (4-ABSA) in the presence of NaH to afford δ-amino-α-diazo-β-ketophosphonates **23**. Stereoselective intramolecular cyclization of the latter compounds gives pyrrolidine-2-phosphonates **24**. Olefination reaction of **24** gives 2-ethylidene pyrrolidine **25** in good yields (Scheme 3).[16]

Hydroxypyrroles **29** were obtained, in excellent yields, by reaction of oxime **26a,b** with α-phosphoryl-vinyl-*p*-tolylsulfoxide **27** in DMF containing NaH via intermediates **28** (Scheme 4).[17]



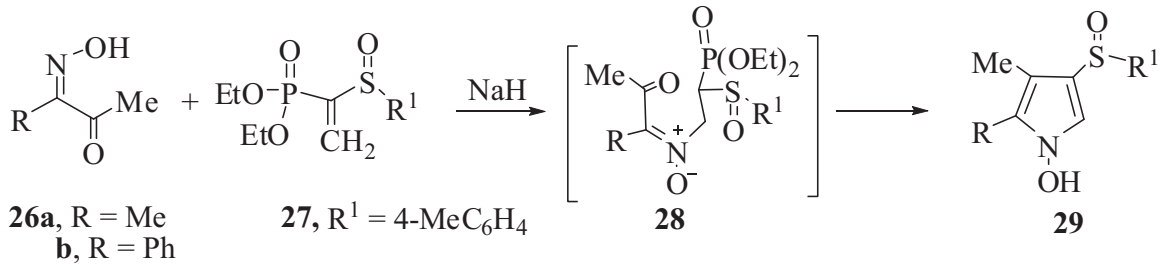
R^1 = Me, n-Bu, Ph, 3,4-$(OMe)_2C_6H_3$
R^2 = *n*-hexyl, benzyl

Scheme 2.



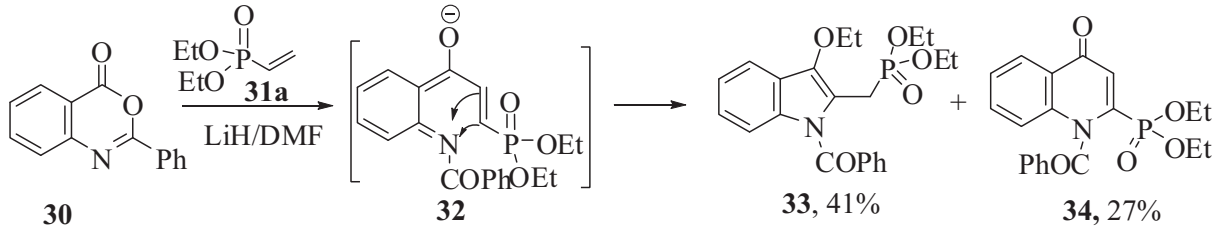
R^1 = *n*-Bu, *t*-Bu, Ph ; R^2 = Me, *n*-Pr, *n*-C_6H_{13}
Boc = *t*-buty carboxylate

Scheme 3.



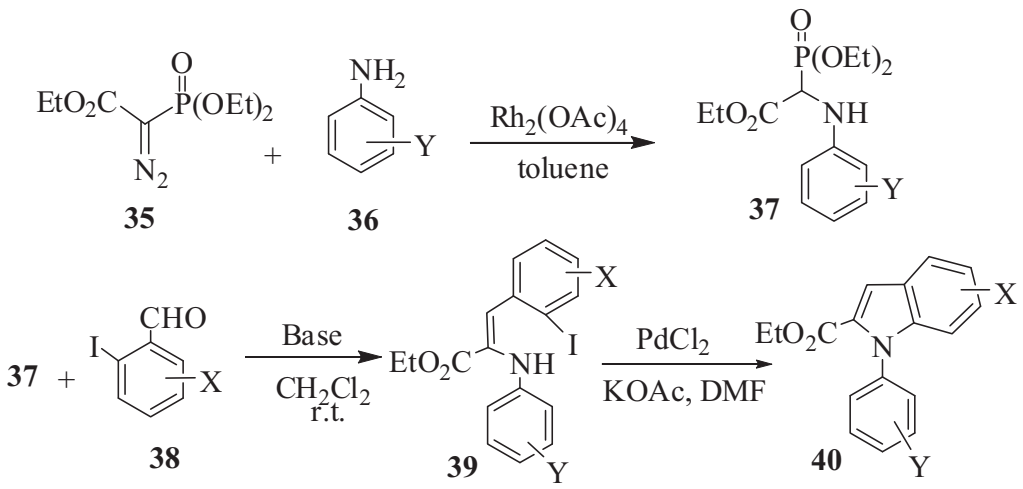
Scheme 4.

Indol-2-yl methylphosphonate **33** and 1,4-dihydroquinolin-2-ylphosphonate **34** were synthesized by reaction of 3-phenyl-[2,4]-benzoxazine-1-one **30** with diethyl vinylphosphonate **31a** (Scheme 5).[18]



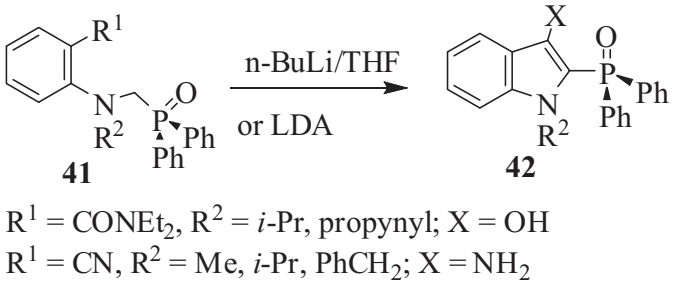
Scheme 5.

N-aryl-α-phosphonylglycine derivatives **37** were formed by reaction of ethyl 2-diazophosphonylacetate **35** and substituted aromatic aniline **36** in toluene in the presence of catalytic $Rh_2(OAc)_4$ at reflux temperature, while the Wittig–Horner reaction of **37** with *o*-iodobenzaldehydes **38** in CH_2Cl_2 gave $Z-$olefinic adducts **39** in high yields. Intramolecular cyclization of **39** in DMF in the presence of $PdCl_2$ and KOAc gave 2-ethyl indole carboxylates **40** in good yields (Scheme 6).[19,20]



Scheme 6.

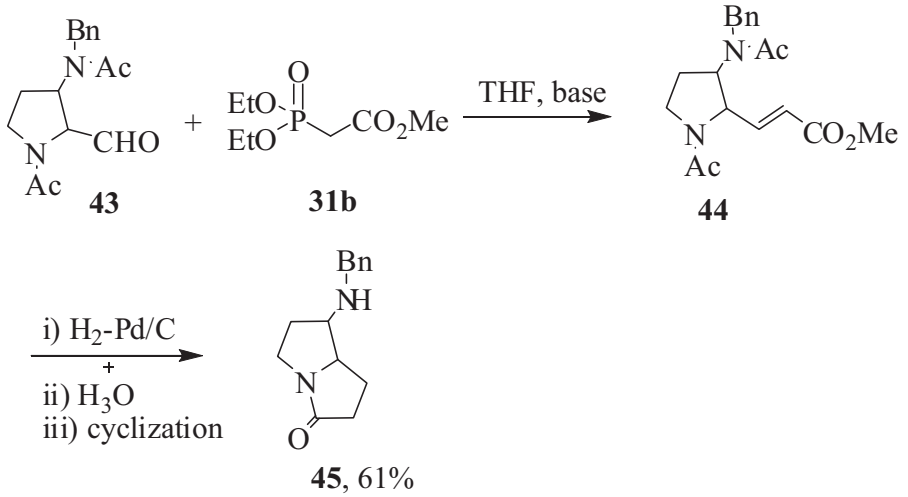
Intramolecular cyclization of *N*-((diphenylphosphoryl)methyl)aniline **41** in THF containing either BuLi at –78 °C [17] or LDA [21] afforded indole-2-diphenylphosphine oxides **42** in high yields (Scheme 7).



Scheme 7.

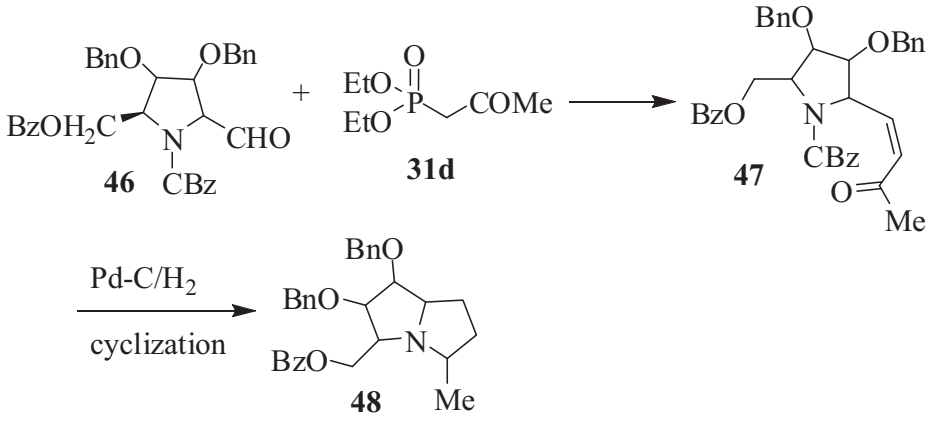
3-Formyl pyrrolidine **43** was treated with triethyl phosphonoacetate **31a** in THF to yield pyrrolidine

acrylate **44**. Hydrogenation, and hydrolysis followed by intramolecular cyclization of **44** gave aminopyrrolizidine **45** (Scheme 8).[22]



Scheme 8.

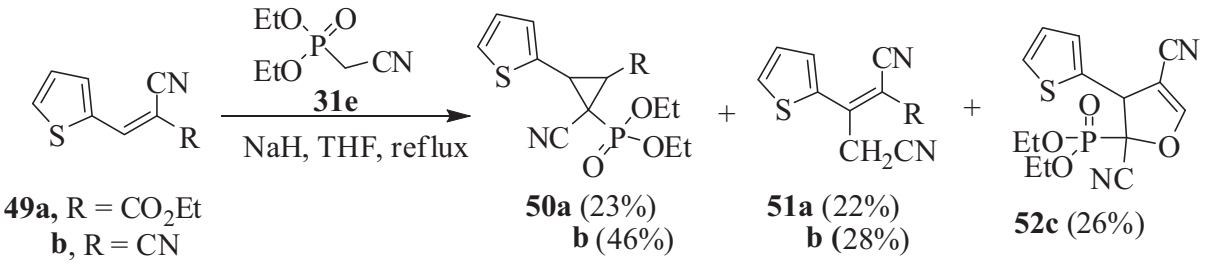
In the same fashion, (1,2-bis(benzyloxy)-5-methylhexahydro-1*H*-pyrrolizin-3-yl)methyl benzoate **48** was synthesized from the reaction of pyrrolidine-2-carbaldehyde **46** with diethyl acetyl methylenephosphonate **31d** to yield adduct **47**, followed by hydrogenation and intramolecular cyclization (Scheme 9).[23–25]



Scheme 9.

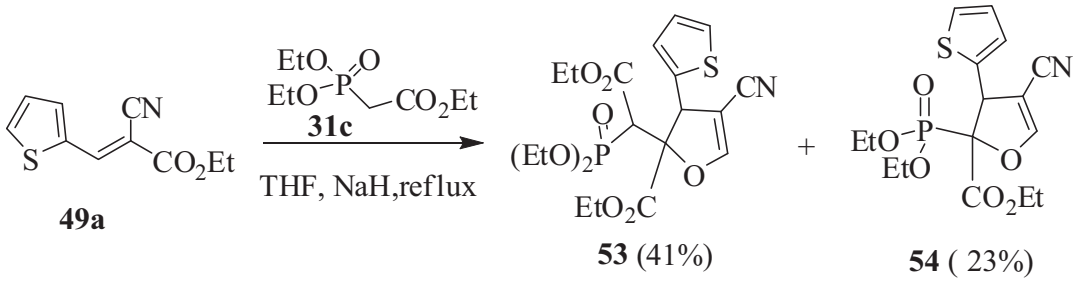
2.1.2. Furans and thiophenes and their fused systems

Cyclopropane phosphonate **50a,b** and 3-(thiophen-2-yl)pent-2-enedinitrile **51a,b** were prepared from the reaction of 3(2-thienyl)acrylonitrile **49a,b** with cyano methylene phosphonate **31e** in THF containing NaH at reflux. In addition, phosphono-substituted furan **52c** was also isolated from **49a** (Scheme 10).[26]



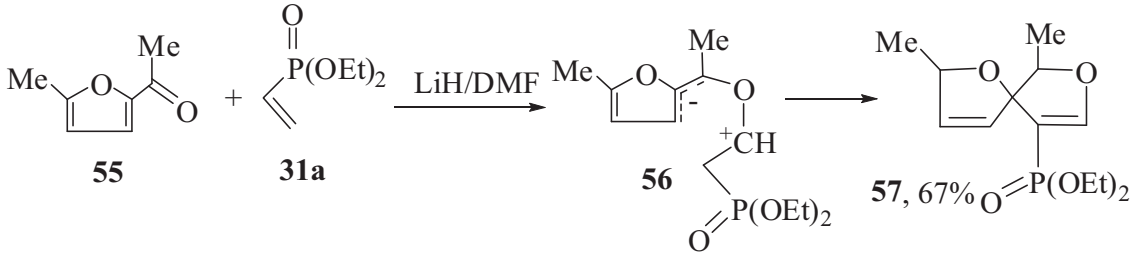
Scheme 10.

Similarly, treatment of **49a** with phosphonoacetate **31c** afforded phosphono-substituted furans **173** and **174** (Scheme 11).[26]



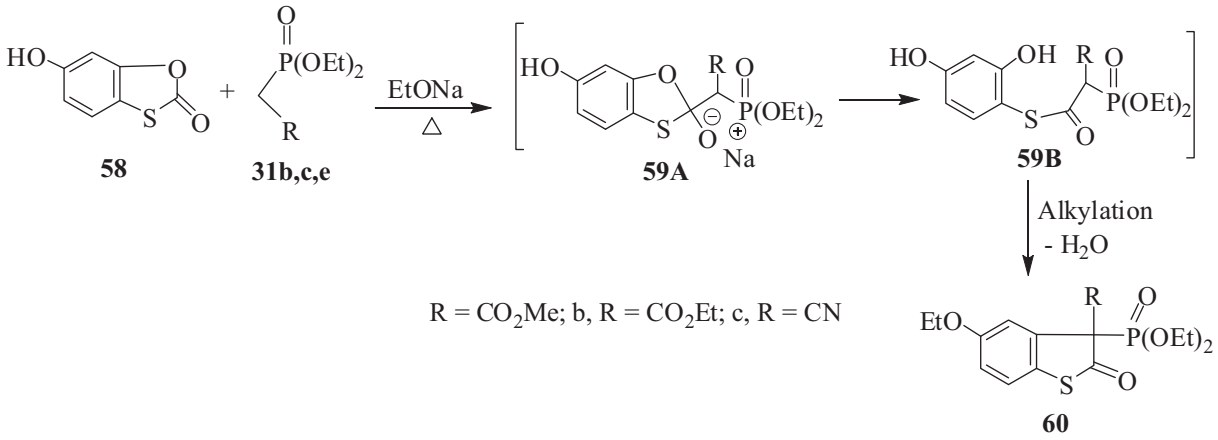
Scheme 11.

Diethyl (1,7-dioxaspiro-[4.4]nona-3,8-dien-9-yl)phosphonate **57** was recently obtained from reaction of 2-acetylfuran **55** with diethyl vinylphosphonate **31a** in DMF containing lithium hydride (Scheme 12).[27]



Scheme 12.

Knoevenagel condensation reaction of oxathiolone **58** with α-phosphonyl carbanions **31b,c,e** in refluxed ethanol in the presence of EtONa followed by sequential alkylation gave benzothien-3-ylphosphonates **60** in 66% yield (Scheme 13). Benzothienylphosphonate esters **60a**–**c** showed significant antimicrobial activity against a panel of representative gram-positive pathogenic microorganisms, gram-negative microorganisms, and fungi.[28]

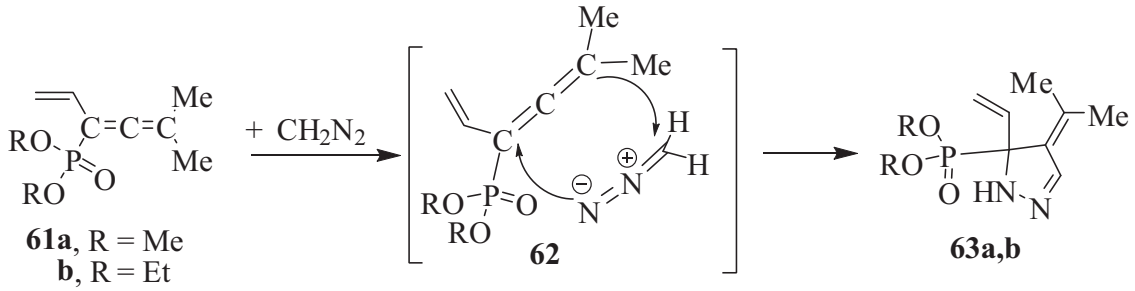


Scheme 13.

2.2. Synthesis of five-membered heterocycles with more than one heteroatom

2.2.1. Pyrazoles and their fused systems

[3+2] Cycloaddition reaction of diazomethane with vinyl-1,2-butadienylphosphonates **61a**,**b** yielded pyrazole-3-phosphonates **63a**,**b** (Scheme 14).[29]

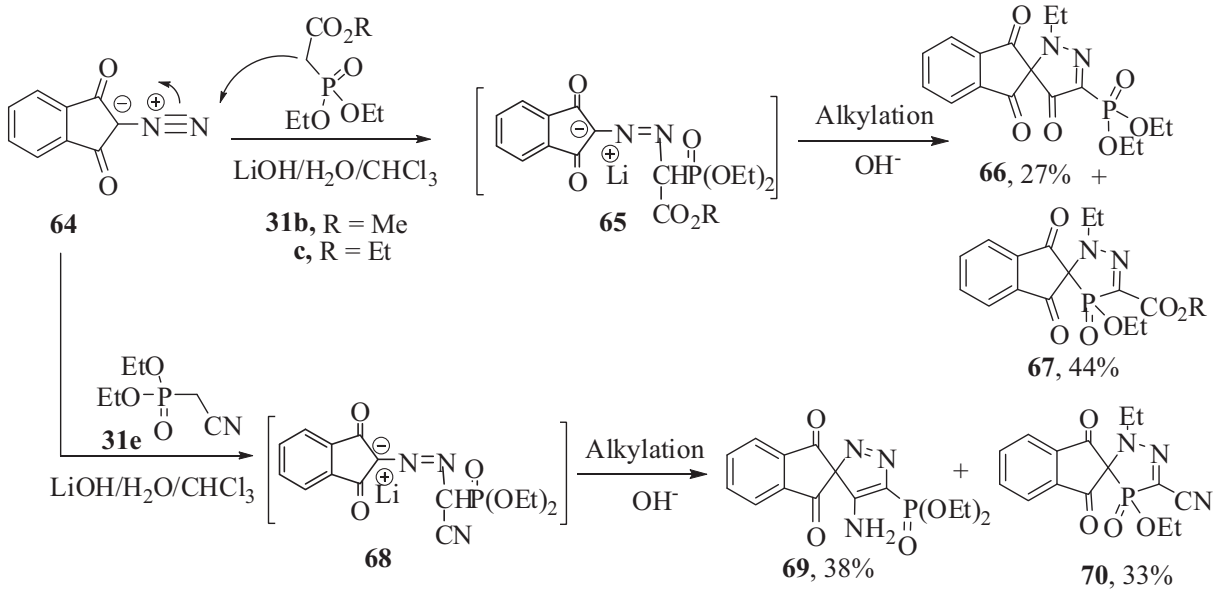


Scheme 14.

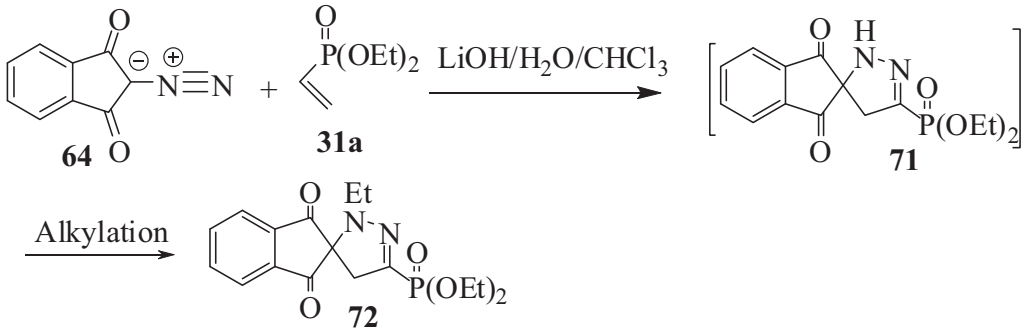
Pyrazolinyl-3-phosphonate **66** and diazaphosphole **67** were prepared in 27% and 44% yields, respectively, from the reaction of 2-diazo-1,3-indandione **64** with phosphonoacetate **31b**,**c** in a mixture of $LiOH/H_2O/CHCl_3$ at reflux. On the other hand, spiroindene-2,3‘-pyrazolyl phosphonate **69** and spiro diazaphosphole **70** were yielded from the reaction of **64** with cyanomethylphosphonate **31e** (Scheme 15).[30]

Similarly, spiro[indene-2,3‘-pyrazol]-5‘-yl)phosphonate **72** was synthesized in 72% yield by treatment of diazoketone **64** with diethyl vinylphosphonate **31a** under phase-transfer catalysis conditions (Scheme 16).[30]

Spiroindene-2,3‘-pyrazolinyl phosphonates (**66**, **69**, and **72**) and spiro diazaphospholes (**67**, **70**) showed more significant antimicrobial activity towards tested organisms (bacteria and fungi). Furthermore, the phosphole derivatives (**67** and **70**) are more active than the phosphonate derivatives (**66**, **69**, and **72**).[30]

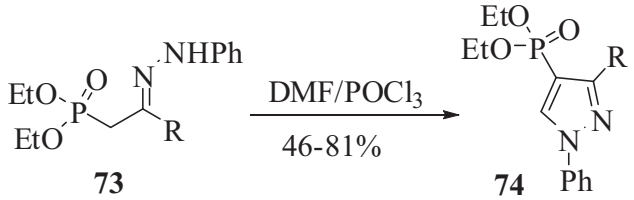


Scheme 15.



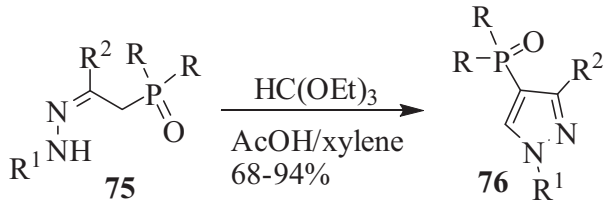
Scheme 16.

Vilsmeier–Haack reaction of phosphonyl ethylene hydrazones **73** gave 1-phenyl-4-diethoxyphosphonylpyrazoles **74** in 46%–81% yields (Scheme 17).[31]



Scheme 17.

Cyclization of β-hydrazonophosphonates **75** into their corresponding 4-phosphonopyrazoles **76** was achieved via their reaction with triethyl orthoformate in xylene containing a few drops of glacial acetic acid (Scheme 18).[32,33]

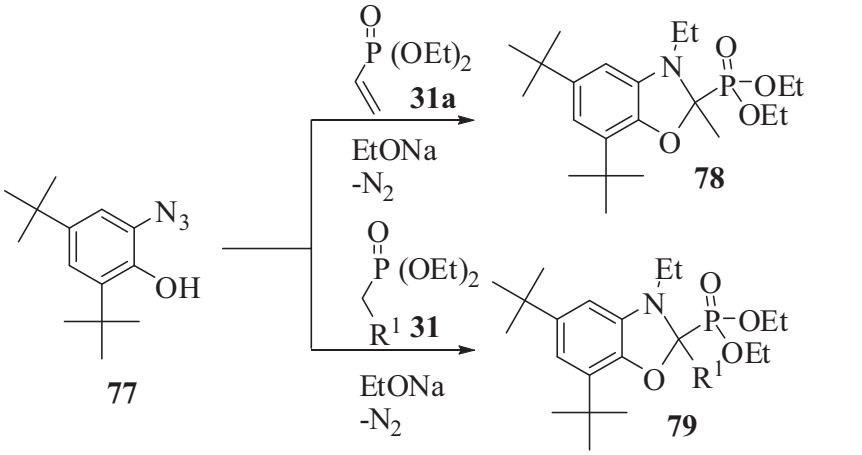


R = Ph, OEt; R^1 = Me, Ph, CH_2CF_3; R^2 = Me, $CH(Me)_2$, Ph

Scheme 18.

2.2.2. Oxazole and its fused systems

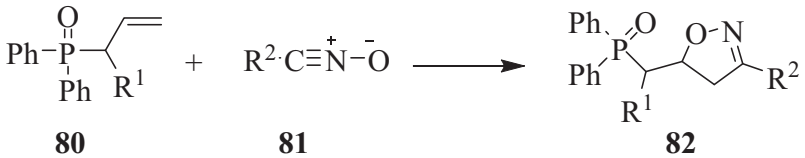
In a recent report, 2-azido-4,6-di-tert-butylphenol **77** was reacted with diethyl vinylphosphonate **31a** in sodium ethanolate solution under reflux to give 2-benzoxazole phosphonate **78** in 74% yield via a coupling cyclization reaction of **77** with **31a** in one step with tandem NH alkylation and extrusion of nitrogen. Similarly, benzoxazole phosphonates **79** (72%) were formed from the reaction of the azide **77** with saturated WHE reagents **31** (Scheme 19).[34]



R^1 = SMe, -C(S)NH_2, C(O)Me, Ph, 4-ClC_6H_4, CN, CO_2Me, CO_2Et

Scheme 19.

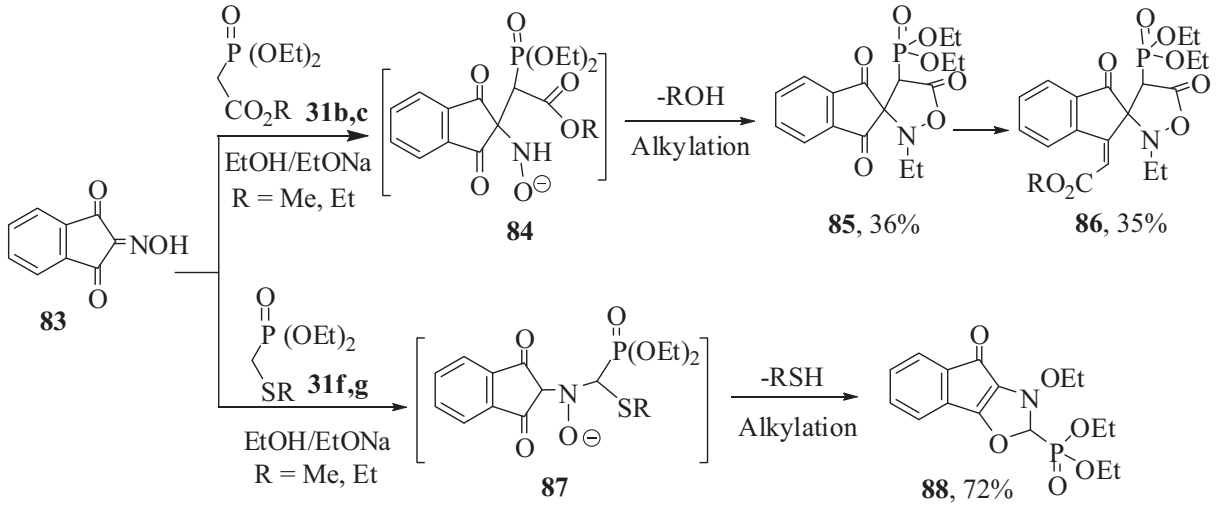
Stereoselective 1,3-dipolar cycloaddition of allyldiphenylphosphine oxides **80** with nitrile oxides **81** afforded Δ^2-isoxazolines **82** (Scheme 20).[35,36]



R^1 = H, Me, Et, n-Pr, *i*-Pr
R^2 = Me, Et, n-Pr, hexyl, Ph, CO_2Et, $(CH_2)_nCO_2$Me (n = 2,3)

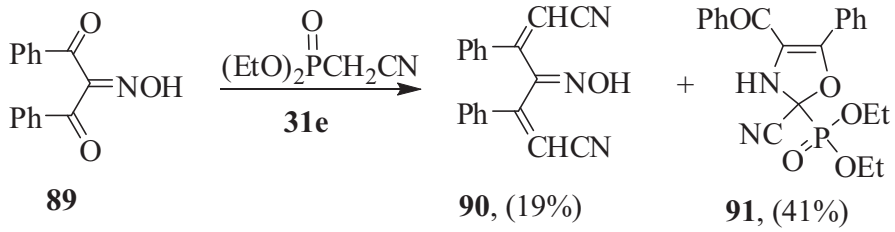
Scheme 20.

Treatment of diethyl phosphonoacetates **31b**,**c** with triketoindane-2-oxime **83** in EtOH/EtONa at reflux temperature yielded spiroindene-2,3'-isoxazolidinylphosphonate **85** and adduct **86**. Compound **83** was treated with (methylthio)methylphosphonate **31f**,**g** in EtOH/EtONa at reflux to give diethyl(3-ethoxy 4-oxo-4-hydroindeno[2,1-*d*][1,3]oxazol-2yl)phosphonate **88** (Scheme 21). Compounds **85**, **86**, and **88** were screened against some gram-positive bacteria, gram-negative bacteria, and fungi. Compound **85** showed feeble activity against gram-positive bacteria. Compounds **86** and **88** displayed no activity against the tested bacteria. Compound **86** is moderately active against *D. specifera* at 780 μg/cm^3 while compounds **85** and **88** are more active against *D. specifera* at 780 μg/cm^3. Compounds **85** and **88** registered 100% spore germination inhibition of *F. oxysporum* at 320 μg/cm^3.[37]



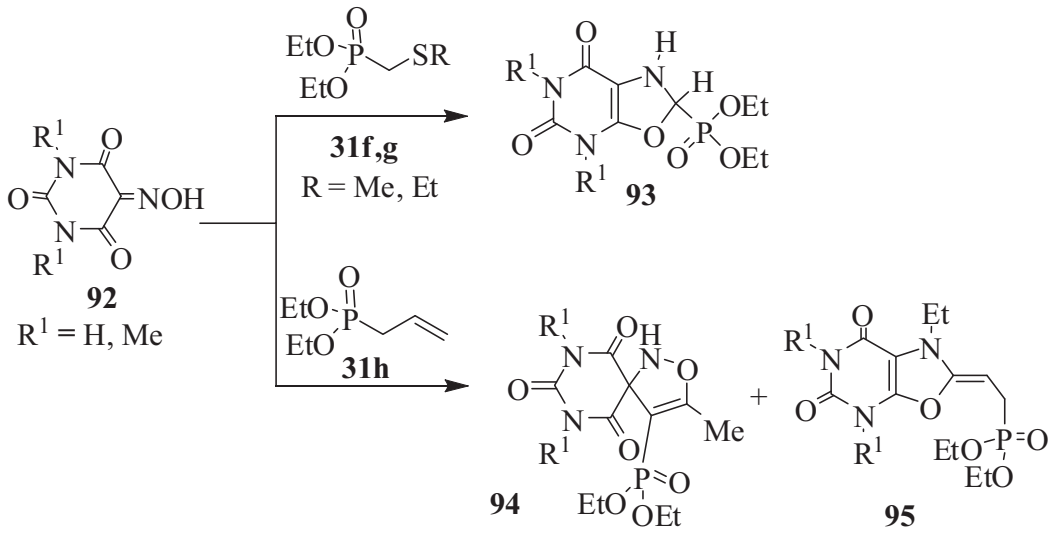
Scheme 21.

Oxazolophosphonate **91** and the diolefin **90** were obtained from the reaction of 2-(hydroxyimino)-1,3-diphenylpropane-1,3-dione **89** with phosphoacetonitrile **31c** (Scheme 22).[38]



Scheme 22.

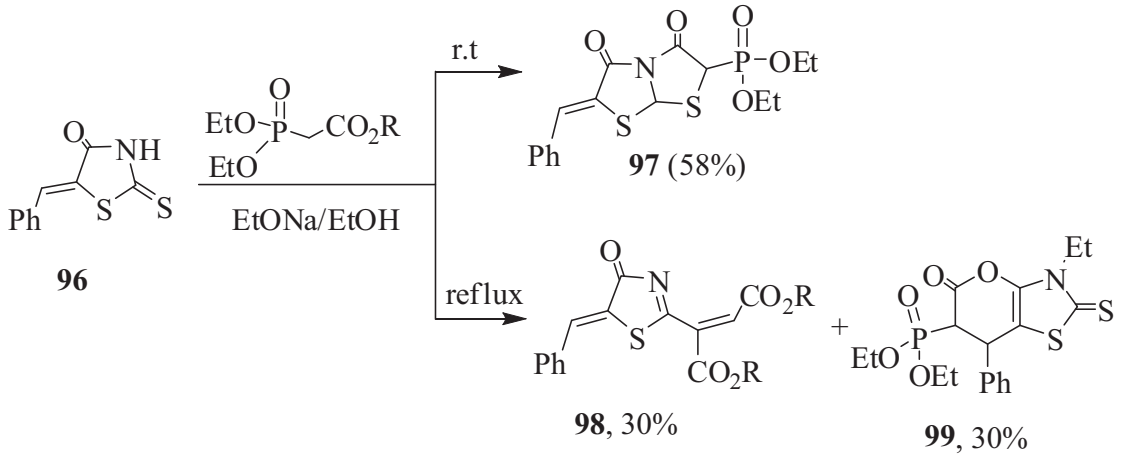
The reaction between alloxan-5-oxime derivatives **92** with thiomethylphosphonates **44f,g** to give the corresponding fused substituted [1,3]oxazolo[4,5-*d*]2-pyrimidinylphosphonate **93** was reported. Triazaspiro[4,5]dec-3-en-4-ylphosphonate **94** and [1,3]oxazolo[4,5-*d*]pyrimdin-2-ylidene ethylphosphonate **95** were obtained from the reaction of **92** with allyl phosphonates **31h** (Scheme 23).[39]



Scheme 23.

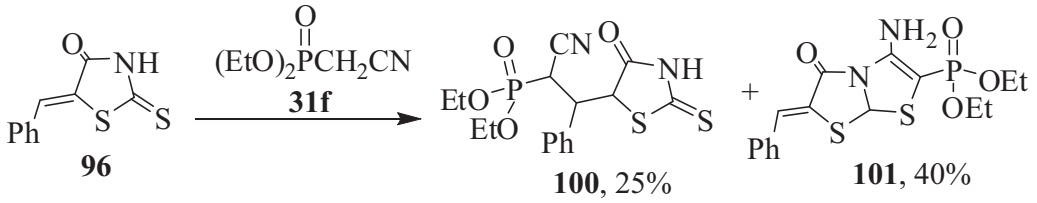
2.2.3. Thiazole and oxaphosphole and their fused systems

5-Benzylidene-4-thiazolidines **96** was reacted with phosphonoacetates **31b**,**c** in EtOH/EtONa at room temperature to yield diethyl 6-benzylidene-3,5-dioxotetrahydro-2*H*-thiazolo[2,3-*b*]thiazol-2-ylphosphonate **97**. Fused phosphonopyranones **99** together with olefins **98** were regioselectivity synthesized when the above reaction occurred at reflux temperature (Scheme 24).[40]



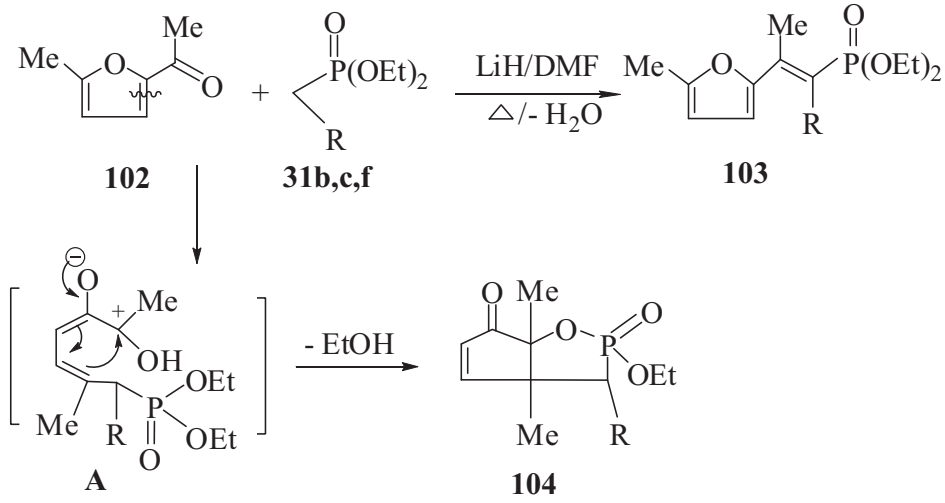
Scheme 24.

On the other hand, compound **96** was reacted with phosphonoacetonitrile **31f** in DMF containing LiH at reflux temperature to afford Michael addition product **100** along with thiazolo[2,3-*b*]thiazolo-phosphonate **101** (Scheme 25).[40]



Scheme 25.

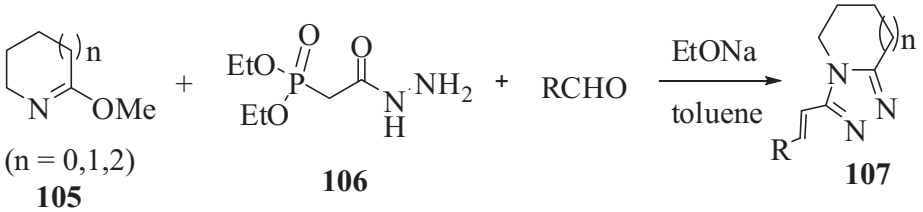
Treatment of phosphonyl carbanions **31b,c,f** with 1-(5-methylfuran-2-yl)ethanone **102**, in DMF containing LiH under reflux, afforded oxaphospholes **104** (55%–48.2% yield) along with phosphonate **103** (17%–22.6% yield) (Scheme 26).[28]



Scheme 26.

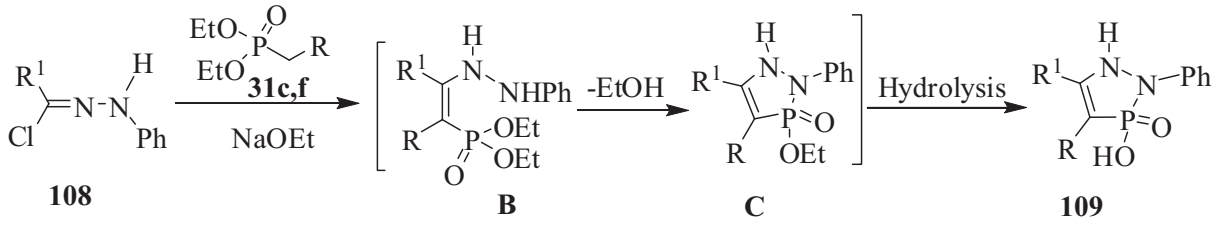
2.2.4. Triazoles and diazaphosphole and their fused systems

One pot reaction of methoxyimine **105**, phosphonyl acetohydrazide **106**, and aromatic or/and heterocycles aldehyde gave 1,2,4-triazoles **107** in moderate to excellent yields (Scheme 27).[41]



Scheme 27.

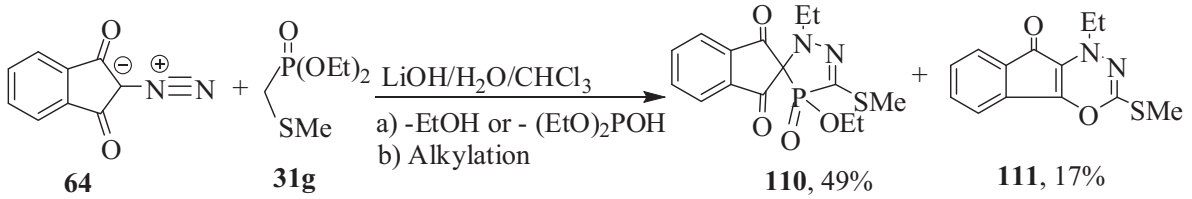
Hydrazonyl halides **108** were reacted with WH reagents **31c,f** in NaOEt at room temperature to yield diazaphospholes **109** via cyclization followed by hydrolysis of intermediates **B** and **C**, respectively (Scheme 28).[42]



R^1 = CO_2Et, Ph, COPh; R = CO_2Et, CN

Scheme 28.

Diazoketone **64** was reacted with diethyl (methylthio)methylphosphonate **31g** to yield spiro[1,2,4-diazaphosphole-3,2'-indene]-1',3'-dione-4-oxide **110** along with indeno-[2,1-*e*][4,1,2]oxadiazin-9(1*H*)-one **111** (Scheme 29).[30] Compound **110** showed more significant antimicrobial activity than the unphosphorylated oxadiazine **111**.



Scheme 29.

Nucleophilic addition of HWE reagents **31b,c,f** to 1,2,4-triazole-3-thiol-4-aminoarylidenes **112** in DMF containing LiH yielded β-amino-phosphonates **113** ($\approx$55% yield) and thiadiazoles **114**. On the other hand, thiadiazoles **114** were, however, exclusively obtained in 75%–80% yield when the reaction (**112** and the same WHE reagents) proceeded in MeOH/MeONa containing a catalytic amount of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (Scheme 30).[43]

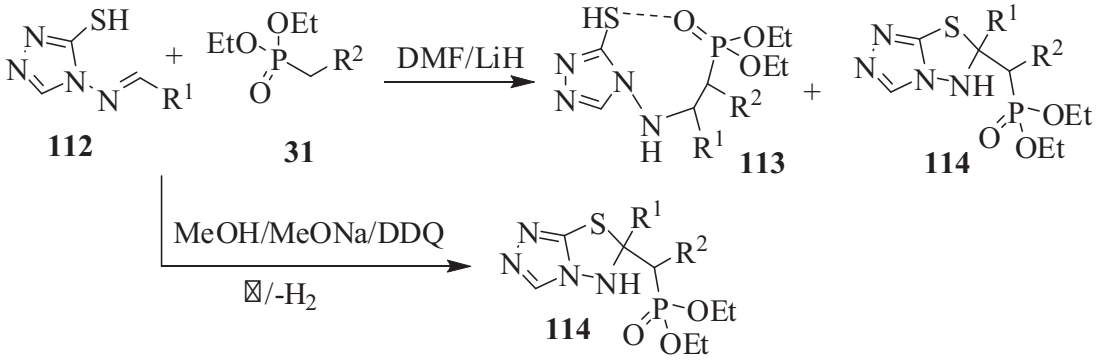
Compounds **114** showed more significant antimicrobial activity, with minimal inhibitory concentration (MIC) of 54–140 and 22–143 mmol L^{-1} and minimal bactericidal concentration (MBC) values of 70–439 and 44–268 mmol L^{-1} compared with MIC/MBC for ciprofloxacin of 48–386 (MIC, mmol L^{-1}) and 55–396 for (MBC mmol L^{-1}) and MIC/MBC for chloramphenicol of 70–439 (MIC, mmol L^{-1}) and 65–619 (MBC mmol L^{-1}) against a panel of gram-positive and gram-negative bacterial pathogens: *Klebsiella pneumoniae* 2011E, *Pseudomonas aeruginosa* 6065 Y, *Escherichia coli* BW54, *Escherichia coli* BW55, *Acinetobacter haemolyticus* BW62, *Stenotrophomonas maltophilia* D457R, *Staphylococcus epidermis* 887E, *Bacillus cereus* ATCC 11778, *Staphylococcus aureus* ATCC 29213, and *Sarcina lutea*.[43]

3. Synthesis of six-membered heterocycles

3.1. Synthesis of six-membered heterocycles with one heteroatom

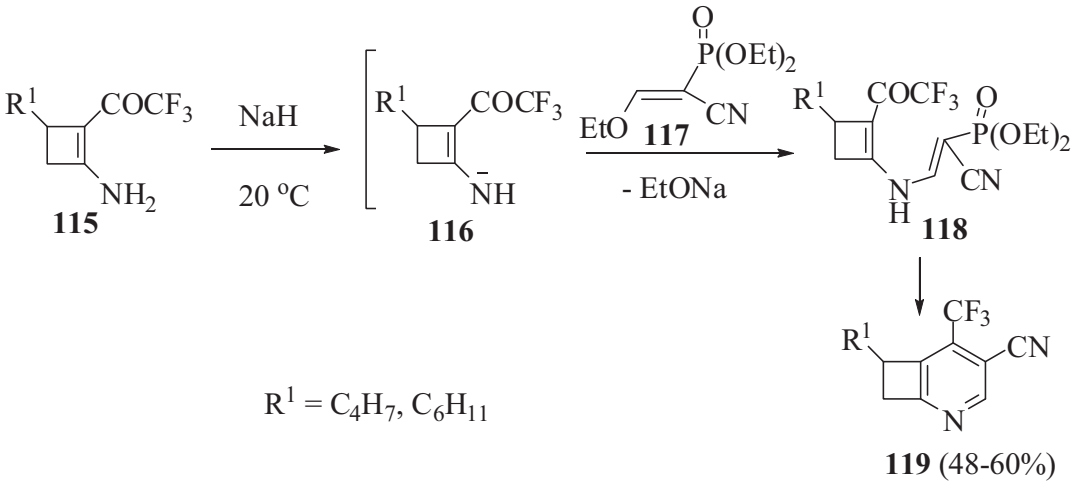
3.1.1. Pyridines and pyrans and their fused systems

Diethyl 1-cyano-2-ethoxyvinylphosphonate **117** was reacted with cyclobutenyl amine **115** in a mixture of DMF and THF (1:1) containing sodium hydride to afford pyridine-3-carbonitriles **119** (Scheme 31).[44]



R^1= 4-$Me_2NC_6H_4$, 4-ClC_6H_4; R^2 = CO_2Me, CO_2Et, CN

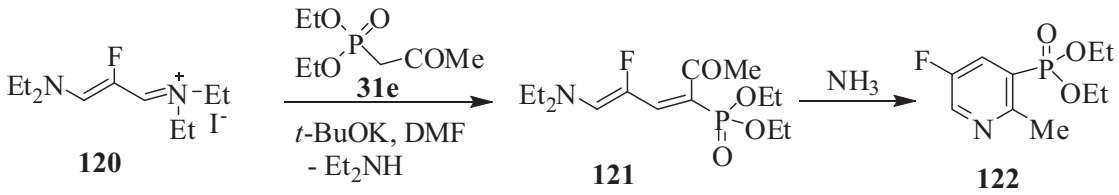
Scheme 30.



R^1 = C_4H_7, C_6H_{11}

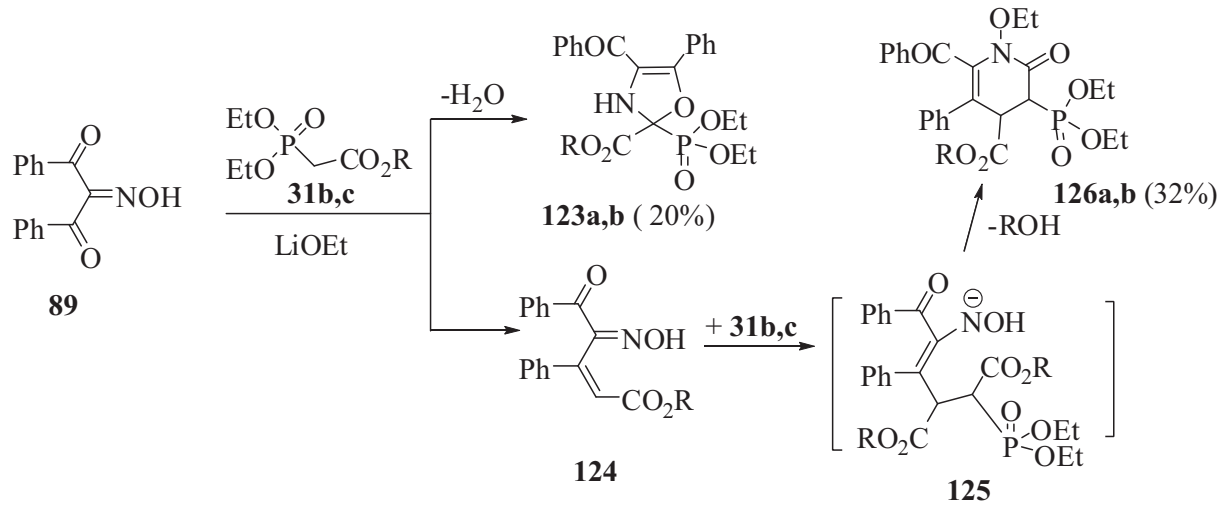
Scheme 31.

Reaction of β-fluoroamidinium salt **120** with acetyl methylene phosphonate **31e** in DMF containing t-BuOK gave the 1,3-butadienylphosphonates **121** in good yields. The latter compound was treated with ammonia to afford pyridin-3-ylphosphonate **122** in 60% yield (Scheme 32).[45]



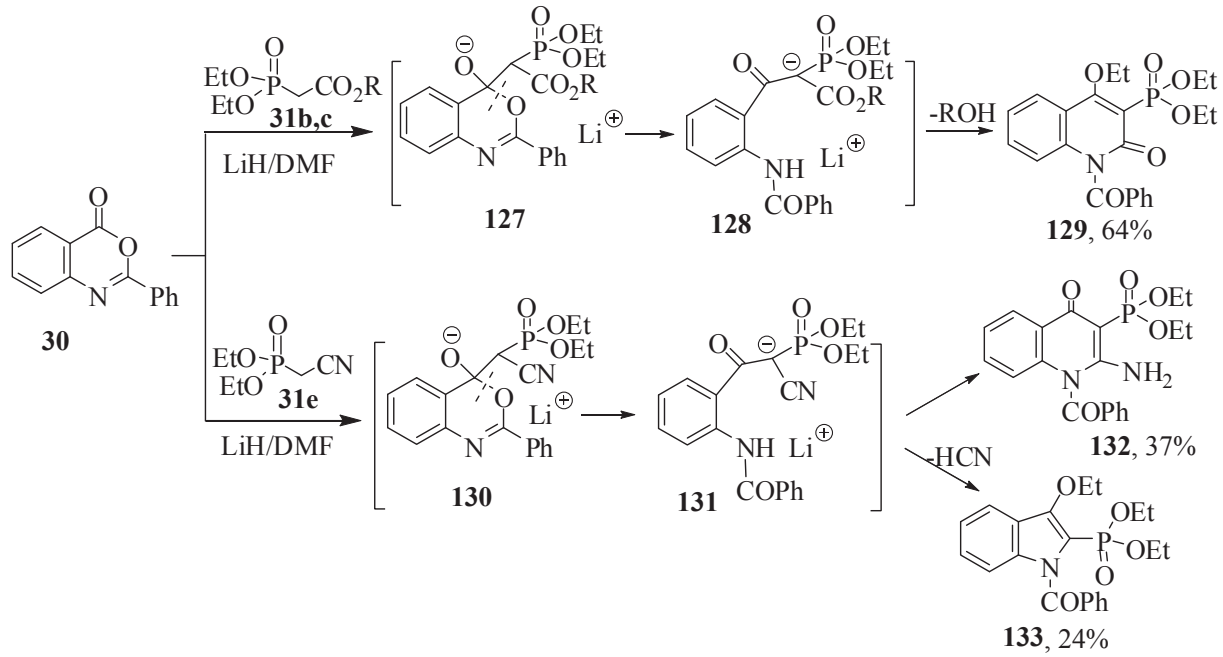
Scheme 32.

2-(hydroxyimino)-1,3-Diphenylpropane-1,3-dione **89** was reacted with diethyl phosphonoacetates **31b,c** to yield oxazolophosphonate **123a,b** (20%) and phosphono-1-ethoxypyridinone **126a,b** (32%) (Scheme 33).[38]



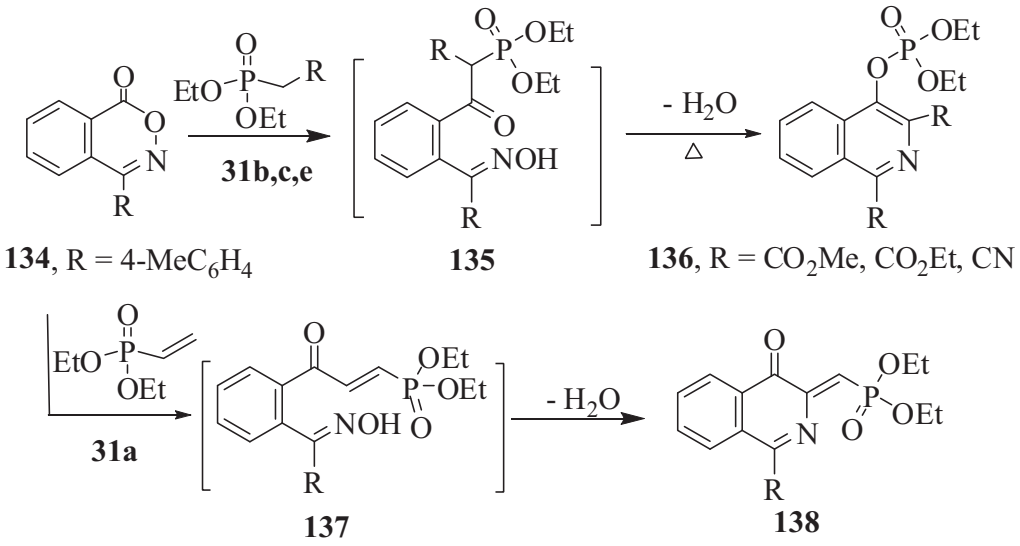
Scheme 33.

Quinolinyl phosphonate **129** and 2-aminoquinolin-3-ylphosphonate **132** along with 1 *H* -indol-2-ylphosphonate **133** were synthesized from the reaction of 3-phenyl-2,4-benzoxazine-1-one **30** with phosphonoacetate **31b,c** and phosphonoacetonitrile **31e**, respectively (Scheme 34).[18]



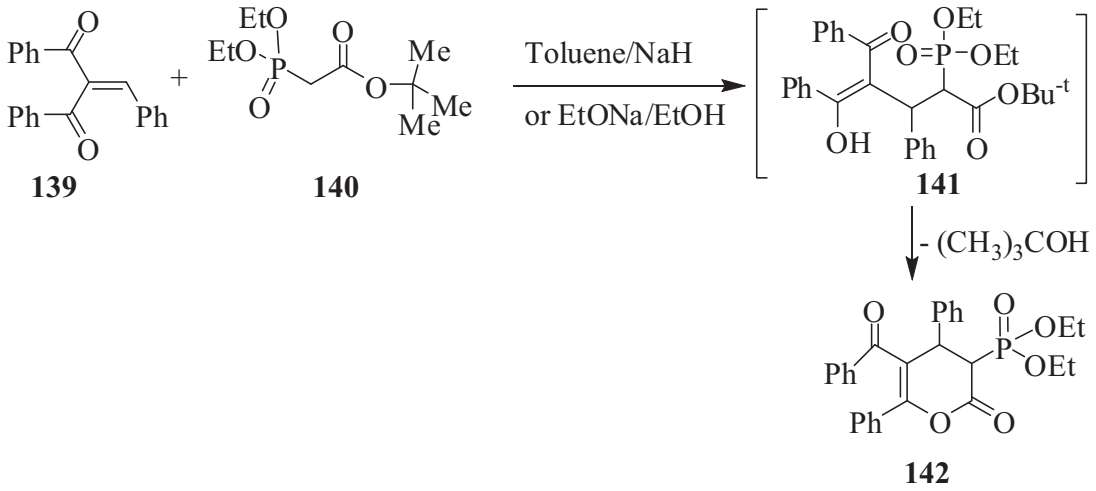
Scheme 34.

4-(*p*-tolyl)-2,3-Benzoxazine-1-one **134** was treated with phosphonyl carbanion **31a**–**c,e** to give the substituted isoquinoline derivative **136** and **138**, via intermediates **135** and **138**, respectively (Scheme 35).[18]



Scheme 35.

2-(phenylmethylene)-1,3-Diphenylpropanedione **139** was reacted with phosphonyl carbanion **140** in the presence of NaH and/or NaOEt to afford substituted pyran-3-ylphosphonate **142** via intermolecular 1:4 addition followed by intramolecular cyclization **141** (Scheme 36).[46]

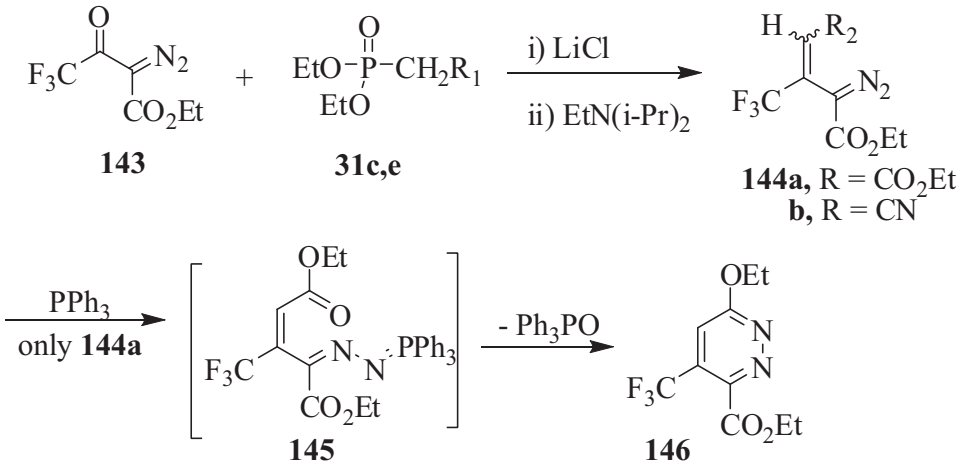


Scheme 36.

3.2. Synthesis of six-membered heterocycles with more than one heteroatom

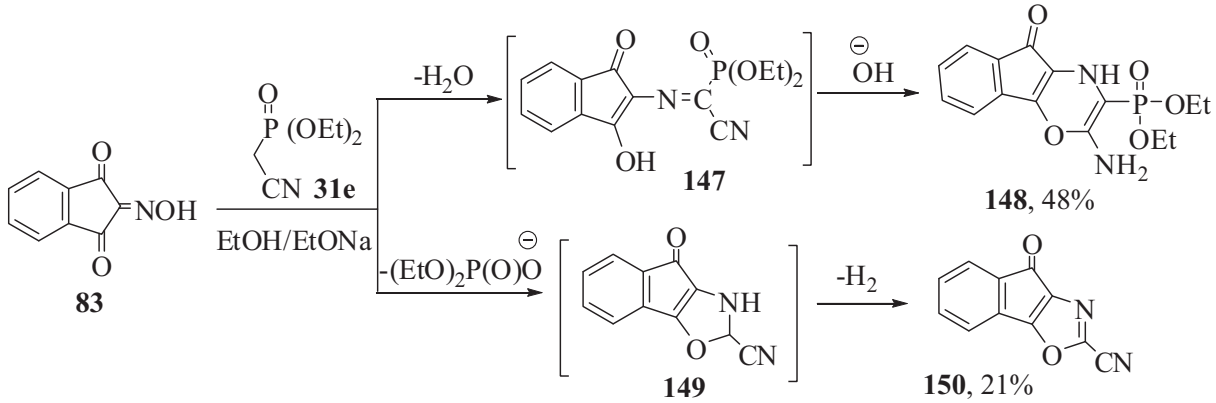
3.2.1. Pyridazines, oxazines, and oxathiines and their fused systems

2-Diazotrifluoroacetoacetate **143** was allowed to react with phosphonyl carbanion reagents **31c,e** in acetonitrile to give olefinic adduct **144a,b**. Reductive cyclization of **144a** using triphenylphosphine yielded pyridazines **146** (Scheme 37).[47]



Scheme 37.

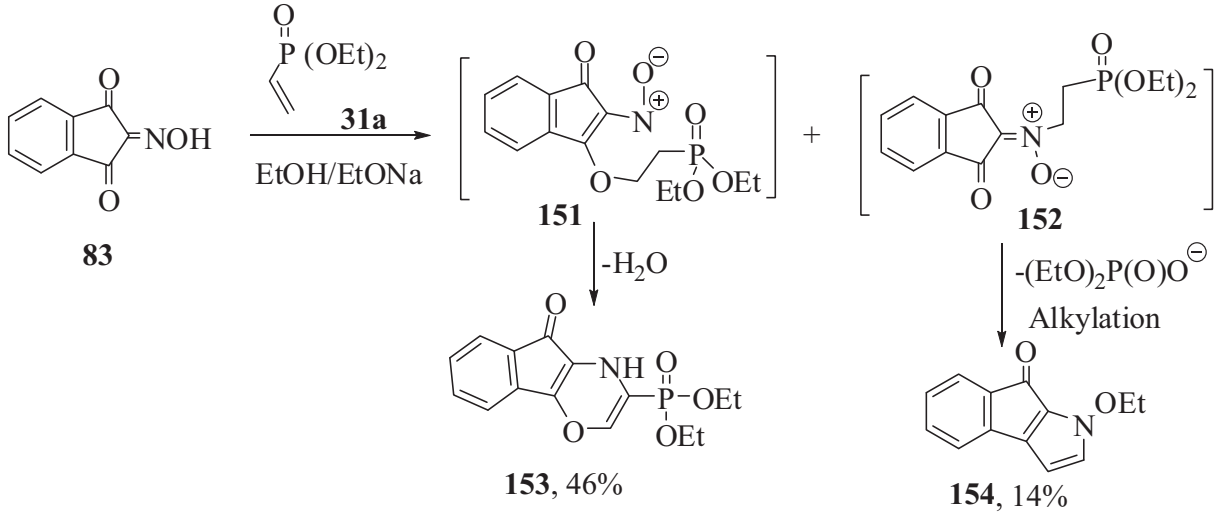
When compound **83** was reacted with diethyl cyanomethylphosphonate **31e**, indeno-[1,2-*b*][1,4]oxazin-3yl)phosphonate **148** together with indeno[2,1-*d*][1,3]-oxazole-2-carbonitrile **150** was obtained (Scheme 38). Compound **148** showed more significant antifungal activity against *D. specifera* and *F. oxysporum*.[37]



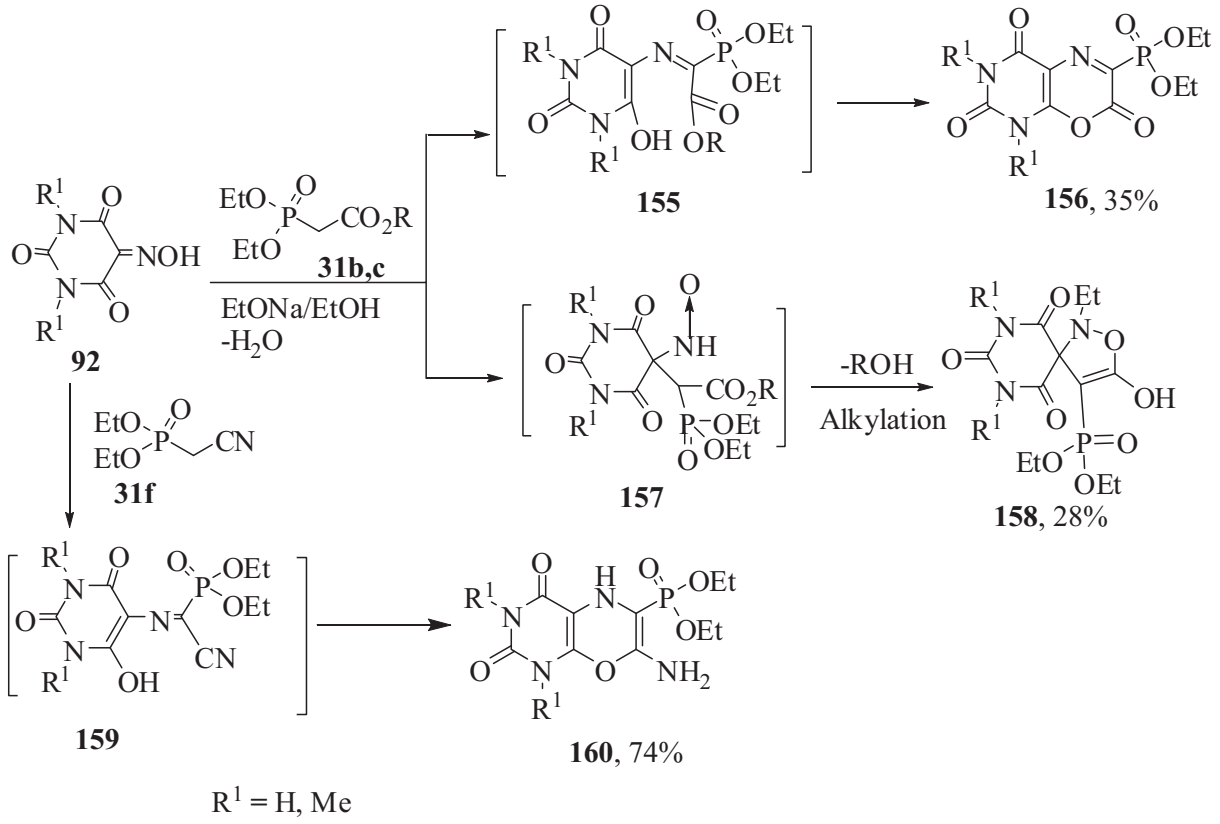
Scheme 38.

In a systematic study, the behavior of indandione oxime **83** towards diethyl vinylphosphonate **31a** was reported and indeno[1,2-*b*][1,4]oxazin-3-yl)phosphonate **153** along with indeno[*a*]pyrrole **150** was obtained (Scheme 39).[37]

Barbituric acid-5-oximes **92** were reacted with phosphonyl carbanion reagents **31b,c** to afford the pyrimidino[4,5-*b*][1,4]oxazin-3yl)phosphonate **156** and spiro[pyrimidine[5,3‘][1,2]oxazole]-4‘yl)phosphonate **158** via intermediates **155** and **157**, respectively. Moreover, [1,4]oxazino[3,2-*d*]pyrimidin-2,4-dione phosphonates **160** were obtained via Perkin-type condensation of **92** with phosphonoacetonitrile **31f** (Scheme 40).[39]

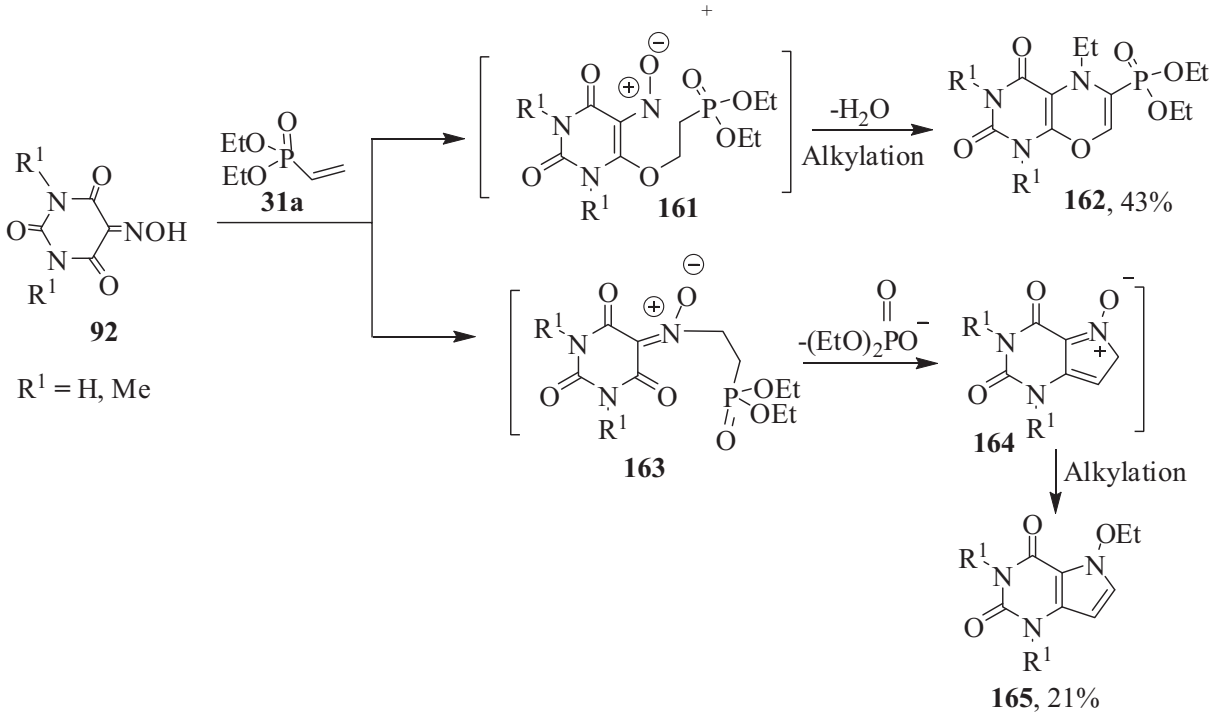


Scheme 39.



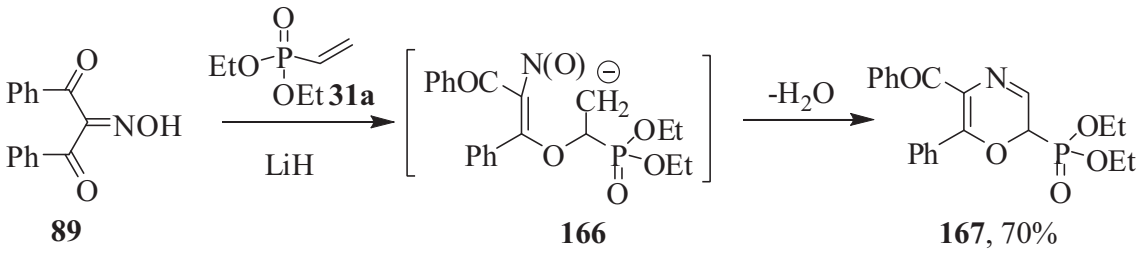
Scheme 40.

Similarly, pyrimido[4,5-*b*][1,4]oxazin-6-ylphosphonate **162** via intermediate **161**, and pyrrolo-[3,2-*d*]pyrimidine-2,4-dione **165** were obtained from the reaction between compound **92** and vinylphosphonate **31a** (Scheme 41).[39]



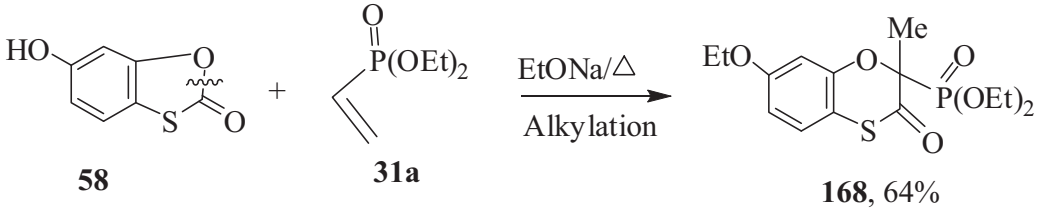
Scheme 41.

Diethyl vinylphosphonate **31a** was reacted with oxime **89** to give [1,4]oxazinephosphonate **167** via intermediate **166** (Scheme 42).[38]



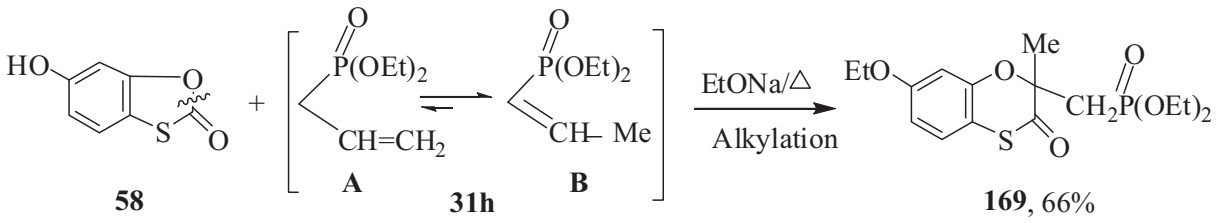
Scheme 42.

6-Hydroxybenzo[*d*][1,3]oxathiol-2-one **58** was reacted with diethyl vinylphosphonate **31a** in EtONa solution to furnish 1,4-benzoxathiin-2-ylphosphonate **168** in 64% yield via a cycloaddition reaction and tandem OH-alkylation as displayed in Scheme 43.[28]



Scheme 43.

In the same fashion, 1,4-benzoxathiin-2yl-methylphosphonate **169** was obtained from the reaction between **58** and allylphosphonate **31h** (Scheme 44).[28]

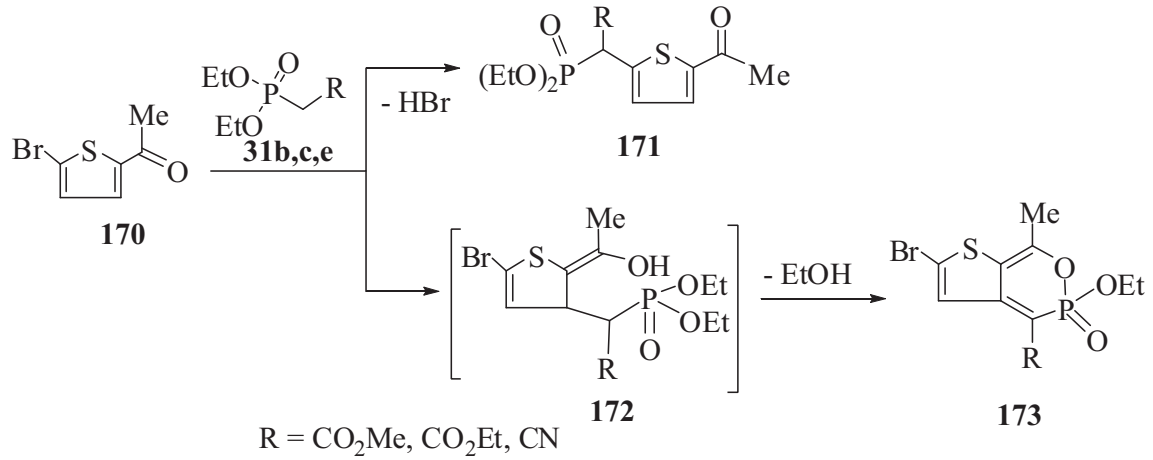


Scheme 44.

Benzoxathiinphosphonates **168** and **169** showed more significant antimicrobial activity than some known drugs ciprofloxacin and ketoconazole (standards) against a panel of representative gram-positive pathogenic microorganisms, gram-negative microorganisms, and fungi.[28]

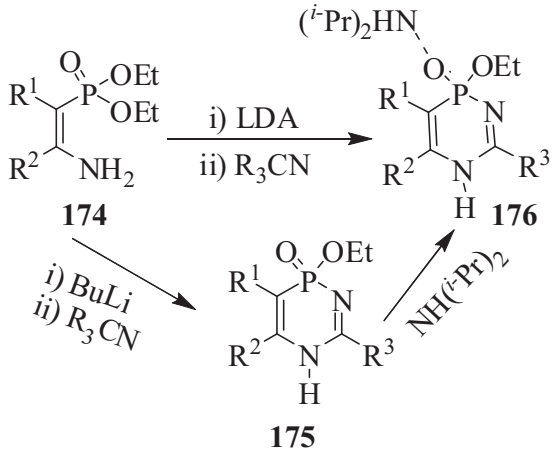
3.2.2. Oxaphosphinine, diazaphosphinine, and thiadiazine and their fused systems

Phosphonates **171** and oxaphosphinine oxides **173** were synthesized, in almost equal yields, by reaction of 5-bromo-2-acetylthiophene **170** with phosphonyl carbanion **31b,c,e** in dry DMF containing LiH under reflux temperature (Scheme 45).[27] The antiinflammatory activity in vivo of compound **173** was examined at 50 mg/kg body weight and displayed inhibitory activities, which were equivalent to that of the standard indomethacin at 100 mg/kg.[27]



Scheme 45.

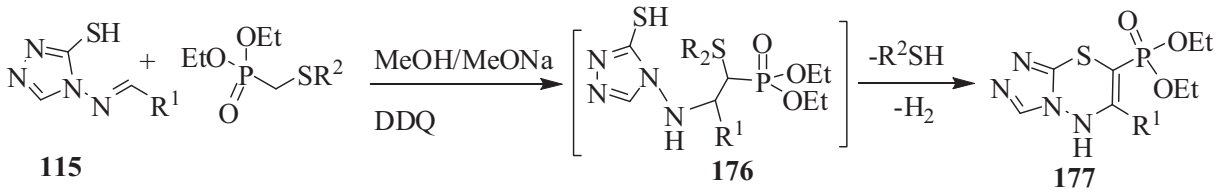
Enamine phosphonates **174** was reacted with nitriles to afford 1,5,2-diazaphosphine-2-oxides **175**. While highly stable hydrogen-bonded amine-dihydrodiazaphosphinine adducts **176** were synthesized either by addition of diisopropyl amine to diazaphosphine oxide **175** or by the reaction of phosphonate **174** with nitriles in the presence of lithium diisopropylamine (LDA) (Scheme 46).[48]



R^1 = H, Me, Ph
R^2 = C_2F_5, CF_3, Ph, 2-furyl, 2-pyridyl
R^3 = CF_3, C_2F_5, C_7H_5, 2-furyl, 2-pyridyl

Scheme 46.

Reactions between 1,2,4-triazole-3-thiol-4-aminoarylidenes **115** and diethyl [methyl(thioalkyl)]phosphonates methanolic sodium methoxide in the presence catalytic amount of DDQ yielded thiadiazine-2-phosphonates **177** (≈72% yield). As displayed in Scheme 47, compounds **177** were formed via elimination of the alkylthiol motif from intermediate **176**, followed by intramolecular cyclization (Scheme 47).[43]



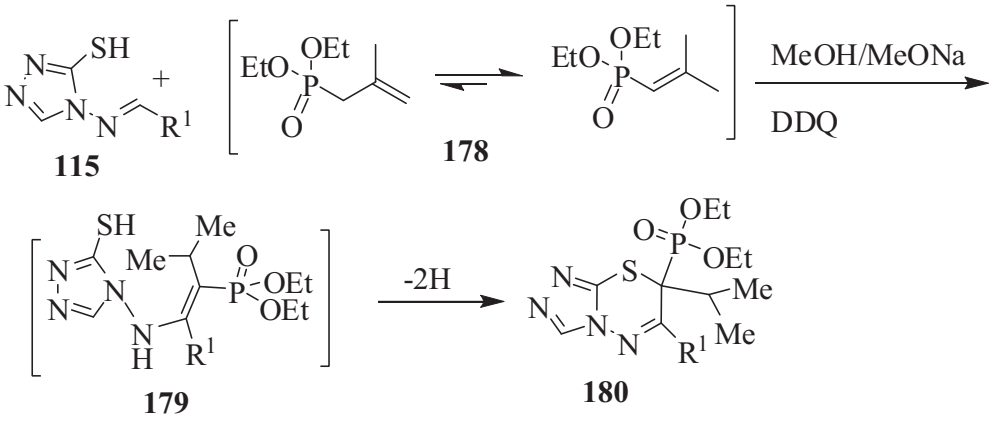
R^1 = 4-$Me_2NC_6H_4$, 4-ClC_6H_4; R^2 = Me, Et

Scheme 47.

1,2,4-Triazole-3-thiol-4-aminoarylidenes **115** were reacted with diethyl(2-methylallyl)phosphonate **178** in MeOH/MeONa/DDQ solution to give the fused thiadiazine-5-methylphosphonates **180a,b** in ≈75% yield. According to the mechanism outlined in Scheme 48, Michael addition by imine **115** onto the isomerized ylide form of the phosphonate reagent resulted in the formation of final products **180** via tandem loss of the H_2 molecule from the initially formed intermediate **179**.[43]

4. Conclusion

Phosphoryl carbanions (WHE) are versatile and convenient intermediates for construction of many types of five- and six-membered heterocycles. This survey attempted to summarize the synthetic potential of phosphoryl carbanions, as starting precursors, in the synthesis of 5- and 6-membered heterocycles since 1985.



Scheme 48.

References

1. Wardle, N. J.; Bligh, S. W. A.; Hudson, H. R. *Curr. Org. Chem.* **2005**, *9*, 1803-1828.
2. Manier, M. L.; Hachey, D. L.; Bachmann, B. O. *Org. Lett.* **2005**, *7*, 2763-2765.
3. Seto, H.; Kuzuyama, T. *Nat. Prod. Rep.* **1999**, *16*, 589-596.
4. Fields, S. C. *Tetrahedron* **1999**, *55*, 12237-12273.
5. Franco, S.; Melendez, E.; Merchan, F. L. *J. Heterocycl. Chem.* **1995**, *32*, 1181-1183.
6. Muruganantham, R.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett.* **2007**, *9*, 1125-1128.
7. Konovets, A. I.; Kostyuk, A. N.; Pinchuk, A. M.; Tolmachev, A. A.; Fischer, A.; Jones, P. G.; Schmutzler, R. *Heteroat. Chem.* **2003**, *14*, 452-458.
8. Tolmachev, A. A.; Sviridon, A. I.; Kostyuk, A. N.; Pinchuk, A. M. *Heteroat. Chem.* **1995**, *6*, 449-459.
9. Abdel-Wahab, B. F.; Khidre, R. E. *Turk. J. Chem.* **2014**, *38*, 1-27.
10. Khidre, R. E.; Abdel-Wahab, Bakr F. *Turk. J. Chem.* **2013**, *37*, 1-27.
11. Abdou, W. M.; Khidre R. E. *Curr. Org. Chem.* **2012**, *16*, 913-930.
12. Abdel-Wahab, B. F.; El-Mansy, Khidre, R. E. *J. Iran. Chem. Soc.* **2013**, *10*, 1085-1102.
13. Abdou, W. M.; Barghash, R. F.; Khidre, R. E. *Monatsh. Chem.* **2013**, *144*, 1233-1242
14. Abdel-Wahab, B. F.; Khidre, R. E. *J. Chem.* **2013**, Article ID 851297.
15. Albrecht, A.; Kedzia, J.; Koszuk, J. F.; Warzycha, E.; Janecki, T. *Tetrahedron Lett.* **2006**, *47*, 2353-2355.
16. Davis, F.A.; Wu, Y.; Xu, H.; Zhang, J. *Org. Lett.* **2006**, *8*, 2273-2276.
17. Mikolajczyk, M.; Krysiak, J. A.; Midura, W. H.; Wieczorek, M. W.; Rozycka-Sokolowska, E. *J. Org. Chem.* **2006**, *71*, 8818-8823.
18. Kamel, A. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2007**, *182*, 765-777.
19. Ferris, L.; Haigh, D. Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2885-2888.
20. Brown, J. A. *Tetrahedron Lett.* **2000**, *41*, 1623-1626.
21. Broekhof, N. L. J. M.; van Elburg, P.; Hoff, D. J.; van der Gen, A. Recueil des Travaux Chimiques des Pays-Bas 1984, 103, 317-321.
22. Langlois, N.; Radom, M. O. *Tetrahedron Lett.* **1998**, *39*, 857-860.
23. Izquierdo, I.; Plaza, M. T.; Tamayo, J. A.; Rodriguez, M.; Martos, A. *Tetrahedron* **2006**, *62*, 6006-6011.

24. Izquierdo, I.; Plaza, M. T.; Franco, F. *Tetrahedron: Asymmetry* **2004**, *15*, 1465-1469.
25. Robins, D. J. *Nat. Prod. Rep.* **1995**, *12*, 413-418.
26. Abdou, W. M.; Salem, M. A. I.; Barghash, R. F. *Synth. Commun.* **2003**, *33*, 1341-1357.
27. Abdou, W. M.; Kamel, A. A.; Shaddy, A. A. *Eur. J. Med. Chem.* **2010**, *45*, 5217-5224.
28. Abdou, W. M.; Khidre, M.D. Kamel, A. A.; Awad, G. E. A. *Monatsh. Chem.* **2014**, *145*, 675-682.
29. Khusainova, N. G.; Irtuganova, E. A.; Pudovik A. N. *Russ. J. Gen. Chem.* **2001**, *71*, 337-338.
30. Abdou, W. M.; Khidre, M. D.; Khidre, R. E. *Eur. J. Med. Chem.* **2009**, *44*, 526-532.
31. Chen, H.; Qian, D.; Xu, G.; Liu, Y.; Chen, X.; Shi, X.; Cao, R.; Liu, L. *Synth. Commun.* **1999**, *29*, 4025-4033.
32. Akacha, A. B.; Ayed, N.; Baccar, B.; Charrier, C. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1988**, *40*, 63-68.
33. Hassen, Z.; Akacha, A. B.; Hajjem, B. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2003**, *178*, 2349-2356.
34. Barghash, R. F.; Ganoub, N. A.; Abdou, W. M. *Monatsh. Chem.* **2014**, *145*, 1621-1630.
35. Armstrong, S. K.; Warren, S.; Collington, E. W.; Nayler, A. *Tetrahedron Lett.* **1991**, *32*, 4171-4174.
36. Armstrong, S. K.; Collington, E. W.; Knight, J. G.; Naylorb, A.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, *13*, 1433-1447.
37. Abdou, W. M.; Sediek, A. A.; Khidre, M. D. *Monatsh. Chem.* **2008**, *139*, 617-623.
38. Abdou, W. M.; Salem, M. A. I.; El-Khoshnieh, Y. O.; Barghash, R. F. *Synlett.* **2002**, *9*, 1417-1422.
39. Abdou, W. M.; Salem, M. A. I.; Barghash, R. F. *Arkivoc* **2007**, *xv*, 45-60.
40. Abdou, W. M.; Khidre, M. D. *Phosphorus, Sulfur and Silicon* **2004**, *179*, 1307-1322.
41. Liu, F.; Palmer, D. C.; Sorgi, K. L. *Tetrahedron Lett.* **2004**, *45*, 1877-1880.
42. Mohamed, N. R.; El-Saidi, M. M. T.; Hassaneen, H. M.; Erian, A. W. *Phosphorus, Sulfur Silicon Relat. Elem.* **2004**, *179*, 521-528.
43. Abdou, W. M.; Ganoub, N. A.; Sabry, E. *Acta Pharm.* **2014**, *64*, 267-284.
44. Koldobskii, A. B.; Solodova, E. V.; Godovikov, I. A.; Verteletskii, P. V.; Kalinin, V. N. *J. Fluorine Chem.* **2010**, *131*, 873-878.
45. Arimitsu, S.; Konno, T.; Gupton, J. T.; Ishihara, T.; Yamanaka, H. *J. Fluorine Chem.* **2006**, *127*, 1235-1241.
46. Arsanious, M. N.; Maigali, S. S.; Boulos, L. S. *Int. J. Chem. Tech. Res.* **2013**, *5*, 2003-2010.
47. Guillaume, M.; Janousek, Z.; Viehe, H. G. *Synthesis* **1995**, *8*, 920-922.
48. Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; López de Munain, R.; Oyarzabal, J.; Ezpeleta, J. M. *Tetrahedron* **2005**, *61*, 1087-1094.