

Direct Phosphonylation of Aromatic Azaheterocycles

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Contents

1. Introduction	2672
2. Azaheterocyclic Aromatics	2672
2.1. Five-Membered Rings	2673
2.1.1. Pyrroles	2673
2.1.2. Imidazole	2674
2.1.3. Pyrazole	2675
2.1.4. 1,2,4-Triazole	2676
2.2. Six-Membered Rings	2677
2.2.1. Pyridine	2677
2.2.2. Pyrimidine	2685
2.2.3. Triazine	2688
2.3. Annulated Six- and Five-Membered Ring	2690
2.3.1. Indole	2690
2.3.2. Benzimidazole	2690
2.3.3. Purine	2690
2.4. Annulated Six-Membered Rings	2692
2.4.1. Quinoline	2692
2.4.2. Isoquinoline	2695
2.4.3. Quinazoline	2695
2.4.4. Cinnoline	2695
2.4.5. Phthalazine	2695
2.4.6. [1,8]Naphthyridine	2696
2.5. Various Annulated Compounds	2696
2.5.1. Acridine	2696
2.5.2. Phenanthridine	2697
2.5.3. Benzo[<i>f</i>]quinoline	2697
2.5.4. Phenanthroline	2697
2.5.5. Carbazole	2697
2.5.6. β -Carboline	2698
2.5.7. Pyrimido[5,4- <i>b</i>]indoles	2698
2.5.8. Pyrazolopyrimidine	2698
2.5.9. Triazolopyrimidine	2698
3. Aromatic Heterocycles with N and Other Heteroatoms	2699
3.1. Five-Membered Rings	2699
3.1.1. Thiazole	2699
3.1.2. Isothiazole	2699
3.2. Annulated Six- and Five-Membered Rings	2699
3.2.1. Benzothiazole	2699
4. Conclusion	2700
5. Abbreviations	2700
6. Acknowledgments	2700
7. References	2700

1. Introduction

The importance of azaheterocyclic phosphonates in synthetic, agrochemical, and medicinal chemistry has been well-documented throughout the years.¹ Nevertheless, no recent overview has been made on the synthetic methods and applications of aromatic phosphonates. Because of the wide scope of the phosphorylation technology, this review focuses on aromatic azaphosphonates and describes the different synthetic methods for direct phosphorylation of aromatic heterocycles available in scientific and patent literature. When available, the use and biological activity of the compounds is also described.

The review is built up according to the ring size of the azaheterocycles bearing the phosphonate moiety and starts with the smallest rings. The polycyclic derivatives follow the monocyclic ones, and as a last group, a few heterocycles with other heteroatoms apart from nitrogen are discussed. Since several methods are valuable to synthesize phosphonate derivatives of varying ring size, these methods are treated in detail the first time they appear.

The number of synthetic procedures resulting in phosphorus-substituted ring systems has significantly increased during the last few decades. The synthesis and chemistry of phosphorus-bearing aromatic compounds was first reviewed by Freedman² over 50 years ago, and Redmore³ reviewed the heteroaromatic compounds about 15 years later. It was found that the electrophilic potential of the known phosphorylation agents as a rule is not sufficient for electrophilic substitution. Generally known Arbuzov and Michaelis–Becker reactions provide procedures for the formation of carbon–phosphorus bonds⁴ but are not evident for sp^2 hybridized carbon atoms. So most of these reactions are not generally applicable on each heterocyclic compound or require specific activation of the aromatic substrate. A different ring size can also have an influence on the reactivity. An overview is given of the known methods to phosphorylate the carbon atoms of azaheterocyclic aromatic rings (Scheme 1).

2. Azaheterocyclic Aromatics

The number of examples of nitrogen containing heterocyclic systems in which the phosphorus is attached as a ring substituent has grown over the years. Several synthetic methods include the nucleophilic attack of trialkyl phosphites (Arbuzov reaction) or salts of dialkyl phosphonates (Michaelis–Becker reaction) on heterocyclic chlorides or bromides. Some general remarks on these reactions were postulated and are mentioned in advance because they are applicable to many compounds. The displacement reaction likely occurs via addition–elimination and should, therefore, be productive when the electron pair can delocalize toward a heteroatom following the addition step. Conversely,

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displacement processes should be less favored when the incoming lone pair cannot first delocalize toward a heteroatom through direct addition or resonance delocalization. As a result, the juxtaposition of halogen and heterocyclic atoms and the π -electron arrangement are important factors in reactivity and provide an explanation for the failure of this type of reactions for certain compounds. For every type of azaheterocyclic aromatic ring, the possible reaction sequence will be given.

2.1. Five-Membered Rings

2.1.1. Pyrroles

2.1.1.1. Reaction of Metalated Heteroarenes with Phosphorus Halides. In theory, reaction of dialkyl chlorophosphates with 1 equiv of a heterocyclic Grignard or lithium reagent should yield dialkyl phosphonates. In practice, this is not readily accomplished, since the aryl phosphonates compete with the starting halides for reaction with the organometallic reagent, resulting in complex reaction mixtures.

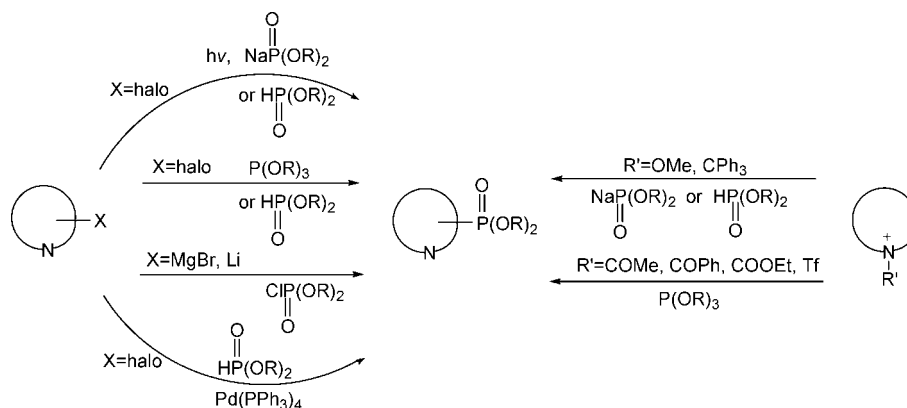
Nevertheless, some early reports have appeared on phosphonylation via reaction of metalated heteroarenes with phosphorus halides.⁵ Diethyl pyrrol-2-ylphosphonate **3** could be successfully prepared⁶ by using the reverse addition technique of Burger and Dawson^{2,5b} with the addition of pyrrolylmagnesium bromide **1** to diethyl chlorophosphate. The 1-methyl analogue **4** was similarly prepared by the addition of 1-methylpyrrolyllithium **2** to diethyl chlorophosphate although with a rather low yield (Scheme 2).

The attempted formation of diethyl 3-(2,5-dimethylpyrrolyl)phosphonate **6** by both direct and reverse addition of 2,5-dimethylpyrrolylmagnesium bromide **5** to diethyl chlorophosphate gave 3-ethyl-2,5-dimethylpyrrole **9** as the sole isolable product.⁶ Phosphonate **6** is postulated as the initial intermediate, forming anion **7**, which undergoes rearrangement to **8** and C–P cleavage to the alkylated product **9** (Scheme 3). Basic hydrolysis (refluxing in 10% aqueous sodium hydroxide) led to quantitative dephosphonylation, indicating the sensitivity of the pyrrole carbon–phosphorus bond to basic media.

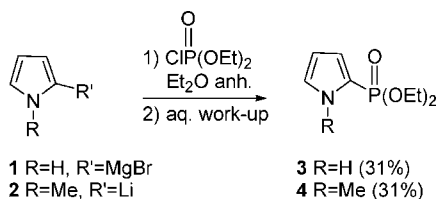
2.1.1.2. Phosphonylation via Radical Intermediates. Several reports are published on the phosphonylation of aromatic compounds via radical intermediates,⁷ e.g., reactions of aryl halides with phosphorus nucleophiles under irradiation.⁸ A new method for direct regioselective phosphonylation of thiazoles, furans, and pyrroles was introduced using dimethyl or diethyl phosphites and $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ as the coupling agent.⁹ The method and the structures of the pyrroles will be discussed in this section; the thiazoles will be reported further in this paper. On the basis of earlier studies, Mn(III)acetate promoted phosphonyl radicals can add to aryl compounds to form phosphonylation products. In the optimized procedure, 2-acetyl-1-methylpyrrole **10** and $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ were added to a solution of dimethyl phosphite in acetic acid and then heated. The 5-phosphonylated product **11** was isolated as the sole product in 91% yield (Scheme 4).

2.1.1.3. Various Syntheses. A valuable property of metaphosphates was encountered, derived from their known ability to perform electrophilic substitutions on aniline derivatives:¹⁰ *N*-substituted pyrroles are highly effective trapping agents for metaphosphates and are phosphonylated specifically at the α -position. This property led to the development of a new method for the synthesis of pyrrolylphosphonates.¹¹ The starting products **12** or a mixture of **13** and **14** are the result of *O*-insertion into phosphinates with peroxy acids. The thermolysis of the cyclic phosphonates was conducted in *N*-methylpyrrole at 110 °C. To establish the identity of the product **16**, it was isolated after esterification with CH_2N_2 and Kugelrohr distillation. The yield of compound **17** was reduced to 23% during the isolation procedure, but this value is not representative for the efficiency of the trapping. No β -substitution products were formed (Scheme 5).

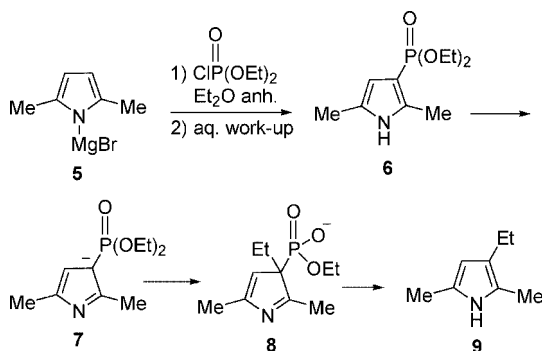
Scheme 1



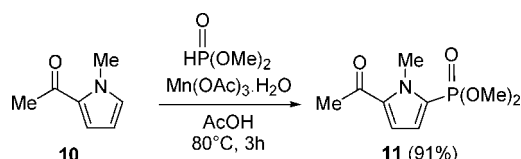
Scheme 2



Scheme 3



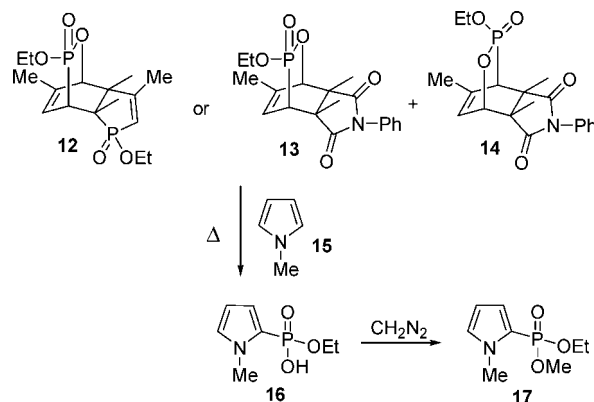
Scheme 4



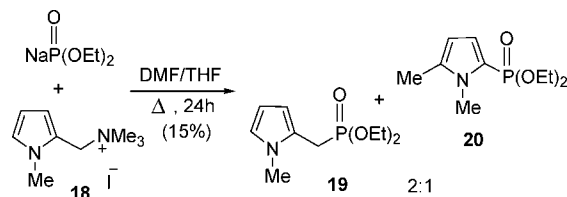
It was found that reaction of 1-methylpyrrol-2-ylmethyltrimethylammonium iodide **18** with sodium diethyl phosphite did not only result in the expected diethyl 1-methylpyrrol-2-ylmethylphosphonate **19**. The isomer, diethyl 1,5-dimethylpyrrol-2-ylphosphonate **20**, was also formed in a 2:1 mixture of compounds **19** and **20**, respectively, which could not be readily separated. The overall yield was only 15% (Scheme 6). This synthesis cannot really be considered as a synthetic method toward these pyrrolylphosphonates but is mentioned for completeness.¹²

Simultaneously with this work,¹² another research group published the preparation of the same compounds through the same reaction. The reaction was performed in both THF and DMF as a solvent, with different outcomes (possibly due to a difference in dielectric constant).¹³ In THF, it resulted in a 44% yield of isomer **19**, with minor impurities (<5%) of compound **20**. In DMF, the resulting oil appeared to be a 3:2 mixture of **19** and **20**. The underlying mechanism is shown in Scheme 7.

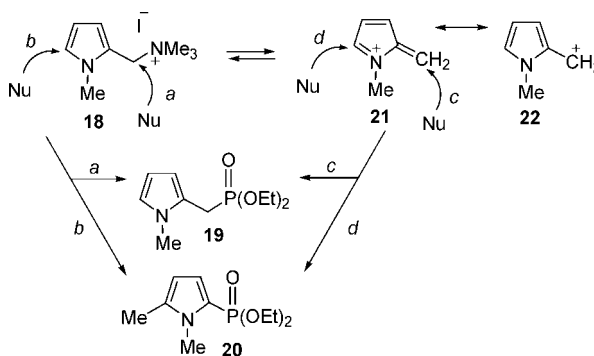
Scheme 5



Scheme 6



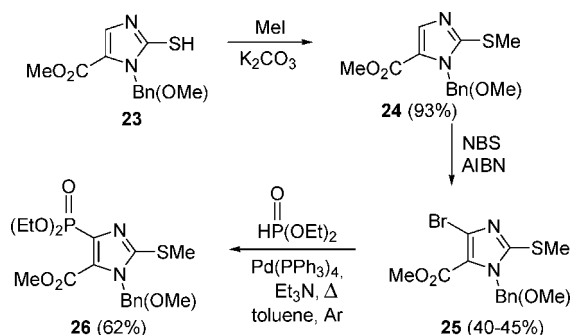
Scheme 7



2.1.2. Imidazole

2.1.2.1. C–P Bond Formation in Cross-Coupling Reactions with Palladium. The formation of a carbon–phosphorus bond can be achieved via a cross-coupling reaction with palladium. The use of palladium as a transition metal catalyst for phosphonylation was first developed by Hirao¹⁴ in 1981 on pyridine substrates. Since this research optimized the conditions and grew to become a general method, the principle and methodology of this type of reaction will be thoroughly discussed in section 2.2.1.4 for pyridine deriva-

Scheme 8

Table 1. Reaction Conditions, Ratios, and Yields for *gluco*-Configuration

entry	R	base ^a	ratio			yield (%)		
			29/28	30/28	31/28	29	30	31
1	Et	Et ₃ N	70:30			62		
2	Et	(<i>i</i> Pr) ₂ EtN	83:17			60		
3	Et	PMP	95:05			71		
4	Me	Et ₃ N		74:26			30	
5	Ph	Et ₃ N			100:0			84
6	Ph	(<i>i</i> Pr) ₂ EtN			100:0			83
7	Ph	PMP			100:0			78

^a PMP: 1,2,2,6,6-pentamethylpiperidine.

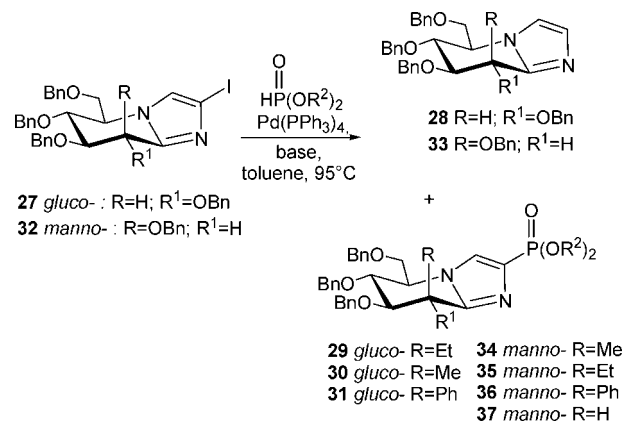
tives. The experimental properties of the applications of palladium cross-coupling on imidazoles will be provided in this section.

Regiochemically defined imidazolylphosphonates could be synthesized from the corresponding 4-bromoimidazoles using this coupling reaction with diethyl phosphite, since the corresponding Michaelis–Arbuzov reaction failed.¹⁵ Methyl 2-mercapto-1-*p*-methoxybenzyl-5-imidazolylcarboxylate **23** was first alkylated at the sulfur atom and brominated at the C-4 position. This precursor **25** was treated with diethyl phosphite, triethylamine, and 20 mol % of tetrakis(triphenylphosphine)palladium(0) under argon and gave 62% of the desired diethyl imidazol-4-ylphosphonate **26**. (Scheme 8) The same reaction with dimethyl phosphite failed. The methoxycarbonyl group could later be converted to an amino group.

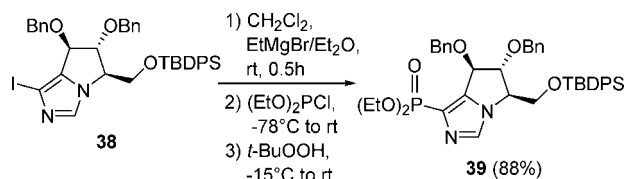
The C-2 position of a *gluco*-configured tetrahydroimidazopyridine¹⁶ could also be phosphorylated through Pd(PPh₃)₄-catalyzed cross-coupling (based on Hirao's procedure¹⁴). Treatment of the monoiodoimidazole **27** with dialkyl or diphenyl phosphites led to mixtures of the phosphonates **28**, **29**, or **30** and the unsubstituted imidazole **31**. The reaction conditions are given in Table 1 and indicate the best results in the case of the diphenyl phosphite (entries 5–7) since only phosphonate **30** is formed. The reaction with dimethyl phosphite is also interesting since it failed with a bromoimidazole,¹⁵ now leading to 30% of phosphonate **29** starting from the iodoimidazole **27** (Scheme 9). The researchers subsequently exchanged the ester groups to prepare *gluco*-phospholipid analogues, which are potential inhibitors of the glucosyl transferase Alg10p.

According to the same methodology, *D*-manno-configured tetrahydroimidazopyridin-2-ylphosphonates **34**–**37** were also synthesized in 24–86% yield.¹⁷ In this case, Et₃N was the only base used. Similarly to the *gluco*-series, phosphorylation with diphenyl phosphite led only to phosphonate **36**, while the other phosphites led to mixtures. However, compound **36** could not be hydrolyzed. Reaction of iodoimidazole with

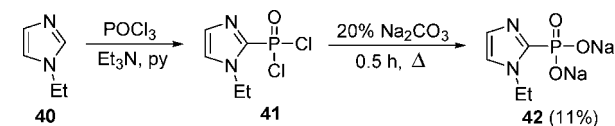
Scheme 9



Scheme 10



Scheme 11



bis(trimethylsilyl) phosphite gave the phosphonic acid **37**. Transesterification of **36** with CsF in boiling EtOH or MeOH gave diethyl and dimethyl phosphonates **34** (84%) and **35** (88%), respectively. Similar results were obtained when CsF was replaced by KF and 18-crown-6 (90% of **34** and 84% of **35**). Phosphonates **34** and **35** could be dealkylated with TMSBr (Scheme 9).¹⁸

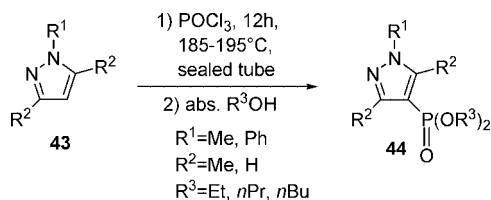
2.1.2.2. C–P Bond Formation via Reaction of Metalated Heterocyclic Arenes with Phosphorus Halides. A *D*-arabino-imidazole derivative **38** could be phosphorylated by conversion of the halogenated compound into a Grignard reagent, followed by reaction with diethyl chlorophosphite at low temperature.¹⁹ This resulted in the diethyl phosphinite that was, without isolation, oxidized with *tert*-butyl hydroperoxide to the corresponding diethyl phosphonate **39** in 88% overall yield. Later on in the reaction sequence, the diethylphosphonate ester moiety could be cleaved quantitatively with TMSBr to the corresponding phosphonic acid (Scheme 10).

2.1.2.3. Various Syntheses. A phosphorylation in two steps could be performed on 1-ethylimidazole **40**.²⁰ The starting compound was first phosphorylated with POCl₃ in the presence of triethylamine and pyridine to give the imidazol-2-ylphosphonic dichloride **41**. This compound was subsequently transformed into the corresponding phosphonic acid sodium salt **42** without isolation. Refluxing for half an hour in 20% Na₂CO₃ resulted in the envisaged compound **42**, in a yield of 11% (Scheme 11).

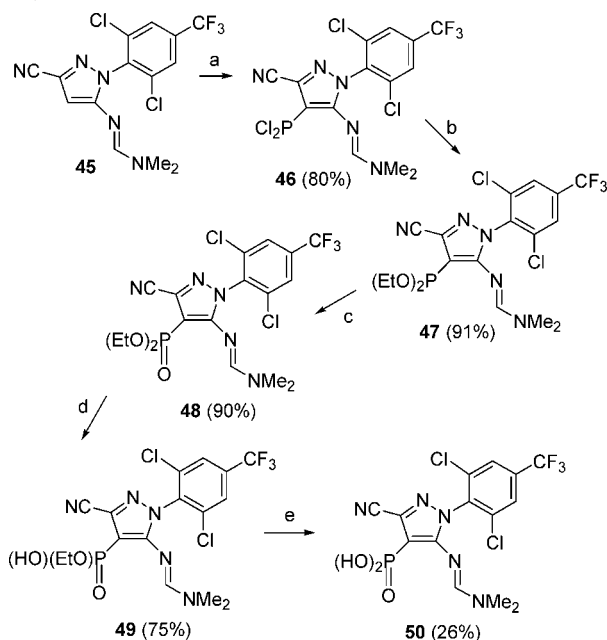
2.1.3. Pyrazole

In 1996, Tolmachev²¹ published a review entitled “C-phosphorylated pyrazoles”. Since this review covers phos-

Scheme 12



Scheme 13. Reactions and conditions: (a) (1) PCl_3 , py, -30°C (15 min); 15°C (2 h); (2) Et_3N , 1 h; (b) Et_3N , EtOH , Et_2O , 0°C (20 min); 20°C (14 h); (c) H_2O_2 in EtOH at -30°C , **47** in EtOH at -50°C (15 min); heating to 20°C and workup; (d) LiN_3 , DMF, 1 h, 95– 100°C ; (e) TMSI, MeCN, 24 h, 20°C

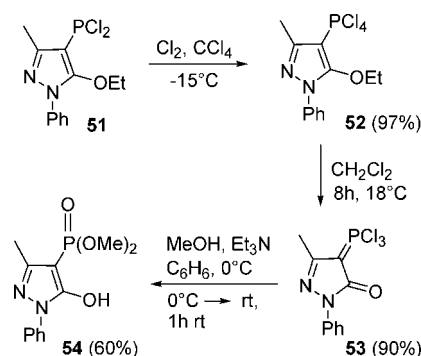


phosphonates and phosphonic acids, only the synthetic methods concerning direct phosphonylation are described in this manuscript.

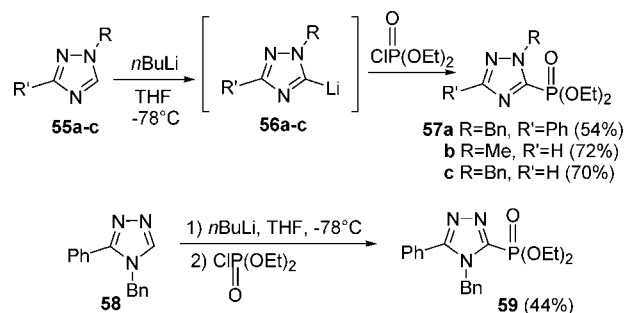
It is known that pyrazoles with unsubstituted 4-positions and lacking electron-acceptor groups in the ring react with POCl_3 to form 4-pyrazolylphosphonyl dichlorides.²² This property was used in the synthesis of a series of phosphonylated pyrazoles.²³ Heating of alkyl substituted pyrazoles **43** and POCl_3 in an ampule for 12 h was followed by treatment with absolute alcohol, concentration and addition of NaOH , and further workup. In this way, three dialkyl 1,3,5-trimethylpyrazol-4-ylphosphonates **44** could be prepared in 31–44% yield (Scheme 12). Also, other substitution patterns were successful with $\text{R}^1 = \text{Ph}$ and $\text{R}^2 = \text{Me}$ or H . The dibutyl 1-phenylpyrazol-4-ylphosphonate could be converted into the monobutyl ester by heating with KOH in propanol, followed by acidification. Hydrolysis of the dialkyl esters with acids gave syrupy phosphonic acids that could not be purified.

The synthesis of diethyl 3-cyanopyrazol-4-ylphosphonate **48** and the corresponding phosphonic acid **50** was patented in 2005.²⁴ The synthetic route is depicted in Scheme 13 and consists of a phosphonylation step, followed by an oxidation to prepare the phosphonate. The dimethyl derivative could also be synthesized according to the same procedure. Conversion to the phosphonic acid **50** occurred in two steps, via the monoalkyl ester. The envisaged end products are used

Scheme 14



Scheme 15



for pest control and preparation of veterinary drugs, since they are useful for the control of arthropods and helminths.

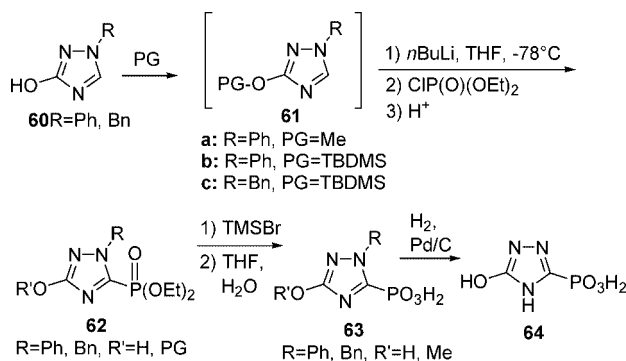
Recently, a new method was developed for the synthesis of dimethyl pyrazol-4-ylphosphonates via a P,P,P -trichloroylide.²⁵ Chlorination of the starting 5-ethoxy-3-methyl-1-phenylpyrazol-4-ylphosphonate **51**, described by the researchers earlier,²⁶ affords phosphorane **52**. This phosphorane undergoes very selective rearrangement into the P -ylide **53** under strictly controlled conditions. This compound reacts with nucleophiles and yields dimethyl pyrazol-4-ylphosphonate **54** upon reaction with methanol (Scheme 14).

2.1.4. 1,2,4-Triazole

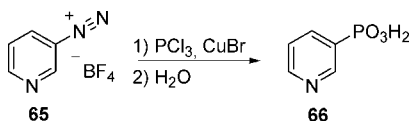
An electrophilic method that utilized a lithiated triazole and a chlorophosphate quench was found to be an attractive approach for the synthesis of triazol-5-ylphosphonates.²⁷ A variety of substituents were introduced at the 1-position to study the effects on the α -lithiation chemistry of 1-substituted-1H-1,2,4-triazoles. The lithiation proceeded exclusively at the C-5 atom. Only the triphenylmethyl group appeared to be too large to allow reaction with the bulky chlorophosphate. The isomeric 3-phenyl-4-benzyl-4H-1,2,4-triazole **58** reacted similarly to give diethyl 3-phenyl-4-benzyl-4H-1,2,4-triazol-5-ylphosphonate **59** (Scheme 15). Treatment of the phosphonates with an excess of TMSBr and subsequent hydrolysis gave the corresponding phosphonic acids.

The same researchers also synthesized 3-hydroxy-1,2,4-triazol-5-ylphosphonic acid **64** via the same lithiation/phosphonylation procedure.²⁸ This compound was prepared as a potential spatial mimic of glyphosate but showed poor activity. Two O -protecting groups (Me , TBDMS) and two N -protecting groups (Ph , Bn) were tested, but only TBDMS combined with Bn gave the envisaged phosphonic acid **64** in good yield (**63** with $\text{R} = \text{Bn}$, $\text{R}' = \text{H}$ in 25% overall yield, **64** in 56% yield) (Scheme 16).

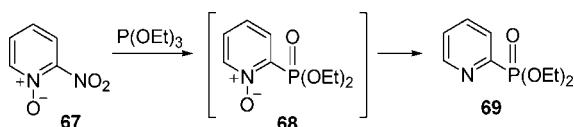
Scheme 16



Scheme 17



Scheme 18



2.2. Six-Membered Rings

2.2.1. Pyridine

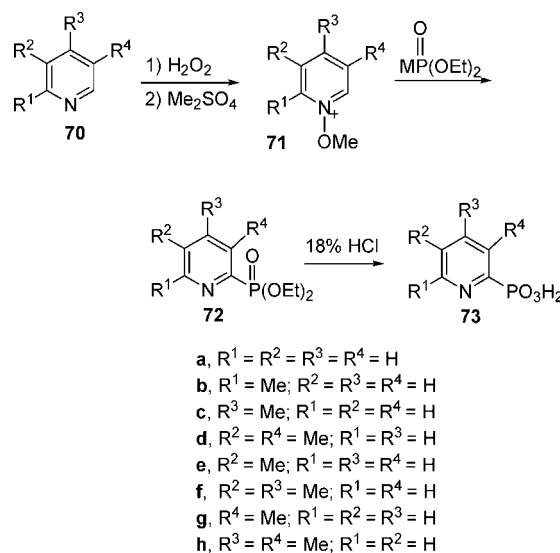
Simple dialkyl phosphonate diesters bearing a 2-pyridyl moiety are widely used as corrosion inhibitors, dispersing and emulsifying agents, antistatics, and lubricant additives in various technological processes.²⁹ Pyridylphosphonates also exhibit a broad spectrum of biological activity, which makes them important constituents of various preparations of pesticides (insecticides, fungicides, herbicides, etc.).³⁰ Among phosphorus-substituted pyridines, 3(5)-phosphonyl derivatives are claimed to be the most difficult to access.³¹

Although no general method for the preparation of pyridine phosphonates has been described, early reports of isolated syntheses can be found. The first synthesis of 3-pyridylphosphonic acid was reported in 1958 by Bennett et al.³² A suspension of the 3-pyridyldiazonium tetrafluoroborate (**65**) in ethyl acetate was cooled to -10°C and treated gradually with phosphorus trichloride and cuprous bromide, followed by workup with water. The applied temperature is lower than described for analogous cases via aryl diazonium salts.³³ The crude pyridin-3-ylphosphonic acid **66** was purified by recrystallization from water and ethanol in 14% yield (Scheme 17).

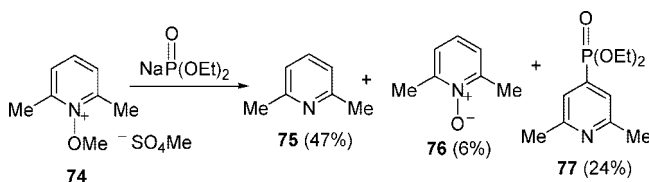
When 2-nitropyridine *N*-oxide **67** is heated with triethyl phosphite, diethyl pyridin-2-ylphosphonate **69** is formed.³⁴ This reaction presumably proceeds via the corresponding *N*-oxide **68** but fails to give the envisaged phosphonate in the case of 4-nitropyridine *N*-oxide (Scheme 18).

2.2.1.1. C–P Bond Formation by Nucleophilic Addition to N-substituted Pyridinium Cations. Many synthetic methods for the preparation of pyridylphosphonates use a nucleophilic attack of a phosphorus nucleophile on an electron-deficient pyridine ring. Most of these follow the same disconnection pattern but differ in the type of phosphorus nucleophile used for the reaction and the mode of activation of the pyridine ring to facilitate attack of the

Scheme 19



Scheme 20



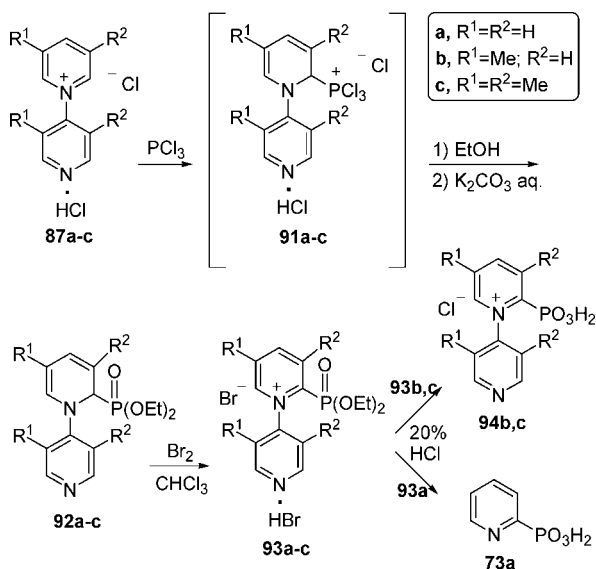
nucleophile. In 1955, both the Arbuzov and the Michaelis–Becker reactions were evaluated with 2-chloro- and 2-bromopyridine by Burger et al.,³⁵ but no conversion seemed to occur. It was anticipated that these unreactive halides could be made more susceptible to displacement by protonation or quaternization. 2-Quinolyl- and 2-lepidylphosphonic acid could be prepared, and their syntheses will be discussed later (section 2.4.1).

Many substituted pyridines can be prepared by the activation of the pyridine ring to nucleophilic attack by conversion into an *N*-alkoxypyridinium salt (via the *N*-oxide).³⁶ Using this methodology, Redmore³⁷ synthesized a series of dialkyl pyridin-2-ylphosphonates **2** in 35–65% yield. The reaction sequence applied to the pyridines **70** is oxidation, *O*-alkylation, and treatment with an alkali metal derivative of diethyl phosphonate. This general synthesis is sometimes also referred to as the Michaelis–Becker–Nylen phosphorylation.³⁸ The esters are readily hydrolyzed (18% HCl) to the corresponding pyridylphosphonic acids **73**. Unsymmetrical 3-methylpyridine **70e** yields a mixture of diethyl 3-methylpyridin-2-ylphosphonate **72g** and the 5-methyl derivative **72h** in a 6:1 ratio, and **70f** yields a mixture of **72h** and **72f** in a ratio of 3:1 (Scheme 19). This reaction is, however, confined to simple dialkyl H-phosphonates.

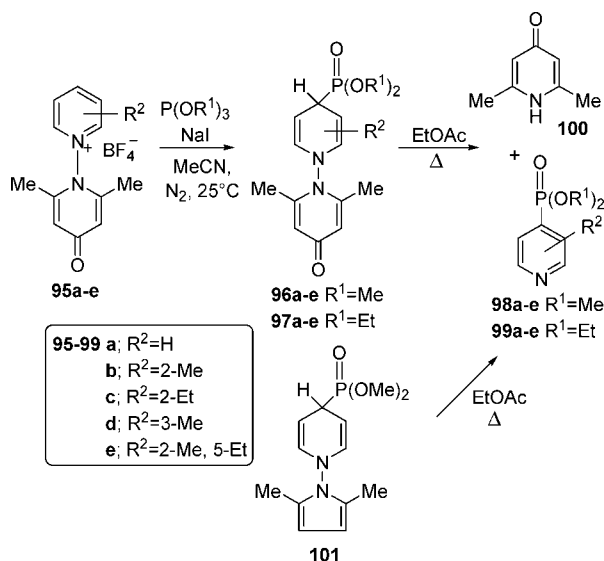
The only example in which 4-substitution had been observed was in the attack of sodium diethyl phosphonate on *N*-methoxy-2,6-dimethylpyridinium methyl sulfate **74** (Scheme 20).

A series of patents was published by Redmore during the following years,^{39,29} in which he extended his methodology to different substituted pyridines and other azaheterocycles. The other heterocycles will be discussed in the following sections, and some of the described pyridine structures are given in Scheme 21.

Scheme 26



Scheme 27

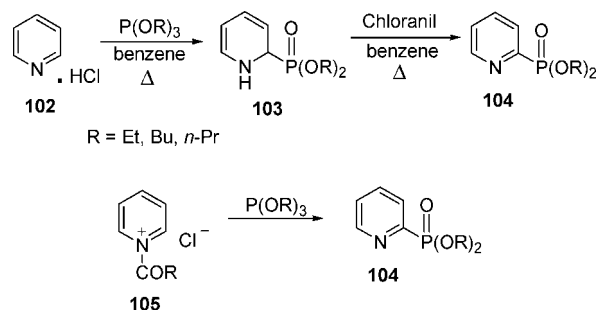


salts **95a–e** in dry MeCN with trialkyl phosphite and sodium iodide gave the dihydro-intermediates **96** or **97**. These compounds were unstable and were converted after isolation into the pyridin-4-ylphosphonates **98** or **99** and the pyridone **100** by heating under reflux in ethyl acetate in high yield (60–96%). The reaction may also be carried out in one step without isolating the dihydro-intermediates (Scheme 27).

In an experiment to evaluate the effectiveness of an alternative *N*-substituent to the pyridone moiety in the salts **95**, *N*-(2,5-dimethylpyrrol-1-yl)pyridinium iodide was converted into intermediate **101** using trimethyl phosphite. The intermediate (formed in 58% yield) was much more stable than **96a–e** and **97a–e** but gave product **98a** in only 47%. However, the disadvantage of this strategy is that the starting pyridinopyridones or alternative compounds need to be especially prepared to perform the phosphonylation.

A series of heterocyclic phosphonates and phosphonic acids could be synthesized according to two different routes, both starting from heteroaromatic cations.⁴⁷ The heterocycles used were pyridine, quinoline, and acridine (the quinoline and acridine derivatives will be discussed in the following

Scheme 28



Scheme 29

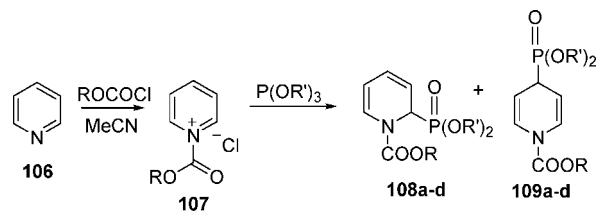


Table 2. Ratios and Yields for Scheme 29

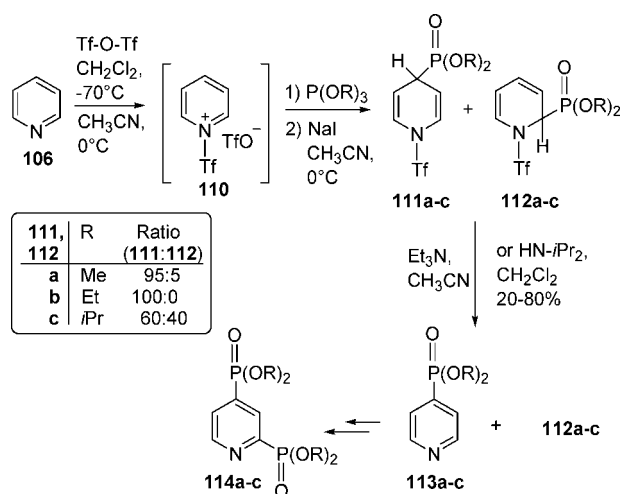
	R	R'	yield (%) 108 + 109	ratio 108/109
a	2,6-di- <i>t</i> Bu-4-Me-C ₆ H ₄	Me	43	49:51
b	Et	Me	55	46:54
c	Et	Et	70	8:92
d	Et	<i>i</i> Pr	73	0:100

sections). The first route is an Arbuzov rearrangement in which the heterocyclic cation **102** was refluxed in benzene together with a trialkyl phosphite, leading to the dihydro-heterocyclic phosphonates **103**. These were oxidized with chloranil to regenerate the aromatic compounds **104**, and heating with HCl resulted in the corresponding phosphonic acids. In the second route, the heterocycle was heated with an acyl chloride and trialkyl phosphite (no details provided). This resulted in dialkyl 2-pyridylphosphonates **104**, and these compounds could subsequently be deprotected to give the corresponding phosphonic acids (Scheme 28).

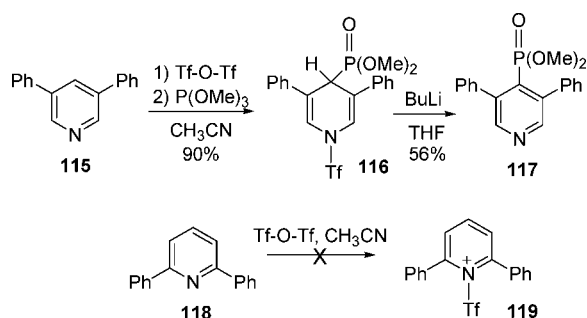
A synthetic route, very similar to the second route described in Scheme 28, concerning acylation followed by phosphonylation, was studied by Akiba et al. The first heteroaromatic cations to be tested were *N*-acylated quinoline and isoquinoline cations (see section 2.4.1 and 2.4.2),⁴⁸ but they also performed the same reactions on pyridine.⁴⁹ They managed to synthesize pure diisopropyl 1-(ethoxycarbonyl)-1,4-dihydropyridin-4-ylphosphonate **109d** starting from the pyridine cation **107**, while in the case of other phosphites, unpredictable molar ratios of isomeric C2/C4 dihydropyridines were observed. The method starts with an acylation reaction to prepare pyridinium cations, followed by phosphonylation (Scheme 29, Table 2). The dihydropyridine compounds **109** were subsequently treated with butyllithium and alkylated. No attempts were made to restore the aromaticity.

A method was described for the regioselective introduction of a PR_3 group into the C4 position of an unsubstituted pyridine ring system.⁵⁰ This method could be extended to phosphites⁵¹ by adjusting a procedure described by Akiba.^{48,49} The procedure starts with the synthesis of cationic *N*-triflylpyridinium triflate **110** for activation toward nucleophilic attack. After reaction of **110** with phosphites, they found that the degree of the regioselective C4 attack depends

Scheme 30



Scheme 31

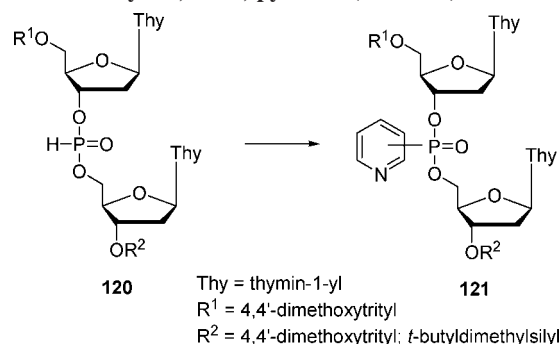


to a significant extent on small changes in the $P(OR)_3$ reactant (Scheme 30). Mixtures of C2- and C4-substituted compounds (**112** and **111**, respectively) were formed in 67–85% overall yield. Separation of the isomers **111** and **112** was not easy, and only the 1,4-dihydro compound **111** could be deprotonated with Et_3N or $HN\text{-}iPr$ to give the aromatic compounds **113** in good yields (54–80%). 1,2-Dihydro compounds **112** remained unchanged. The compounds **112** and **113** could be easily separated by simple extraction. Both monosubstituted **113** and disubstituted (dialkoxy-phosphoryl)pyridines **114** could be prepared according to this procedure, as well as mixed $di(PO(OR)_2/PR_3^+)$ -substituted pyridines (Scheme 30).

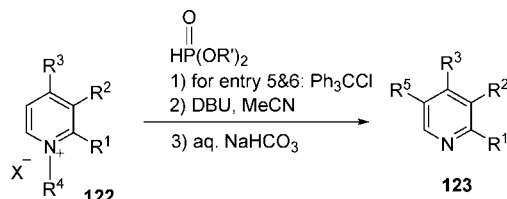
The same research team also investigated the influence of steric hindrance on their method (Scheme 31) and the applicability to quinoline, isoquinoline, and acridine (see further).⁵² These methods resemble the one depicted in Scheme 28,⁴⁷ in which chloride is used as counterion.

Also for the synthesis of nucleotide analogues, the coupling of phosphonate moieties with pyridine was evaluated. Stawinski et al.⁵³ investigated methodologies where the phosphorus–carbon bond would be formed under mild conditions from readily available precursors.^{54,55} Different methods were developed in their laboratories for different substitution positions, and analogues with stereodefined 2-, 3-, and 4-pyridylphosphonate moieties could be synthesized. The reactions they performed to prepare the 2- and 4-pyridylphosphonates were related to the ones Redmore reported.^{37,42} The best results for the synthesis of dinucleoside 3-pyridylphosphonates were achieved using a palladium(0)-catalyzed cross-coupling strategy.^{53c} This strategy could also be performed on the 2- and 4-pyridylphosphonates and led to good results. In Scheme 32, the conditions for the synthesis

Scheme 32. Reagents and conditions for 2-pyridyl derivatives: *N*-methoxypyridinium tosylate, DBU, acetonitrile (80–90%); **for 3-pyridyl derivatives:** $Pd(PPh_3)_4$, Et_3N , 3-bromopyridine, reflux in THF (80–90%); **for 4-pyridyl derivatives:** trityl-Cl, DBU, pyridine (80–90%)



Scheme 33



of different phosphorus derivatives are given. Via the palladium(0) cross-coupling method, bipyridine and terpyridine DNA analogues could also be synthesized.⁵⁶ The cross-coupling strategy will be discussed later in section 2.2.1.4.

Studies were also performed on the synthesis of picolylphosphonate diesters.⁵⁷ A similar strategy as the one described by Redmore⁴² was used to synthesize simple dialkylphosphonates as well as more complex nucleotide analogues (similar to the ones described above in Scheme 32). Starting from methylated pyridinium salts **122**, a series of pyridyl-4-phosphonates and pyridyl-2-phosphonates could be prepared. Only in the case of entry 3, a lack of regioselectivity led to a mixture of 3- and 5-methylpyridin-2-ylphosphonates. The addition of Ph_3CCl to the mixture (entries 5 and 6) directed the reaction to the addition on the 4-position only. The other reactions were also regioselective (Scheme 33, Table 3).

Yang et al.⁵⁸ tried to reproduce the synthesis of diethyl pyridyl-4-phosphonate through a palladium-catalyzed cross-coupling, which had already been reported and is discussed in section 2.2.1.4.^{53c,14} It proved to be very difficult to get reproducible results with this method, and therefore, an alternative synthesis was developed, a modification of the work of Stawinski^{53a} and Redmore.⁴² Pyridine was treated with diethyl phosphite and trityl chloride in the presence of a strong base, DBU, followed by oxidation of the intermediate **124** by iodine to give the phosphonate **86b** (Scheme 34). These phosphonates were incorporated in phthalocyanines as axial ligands, and the complexes are interesting to be used in dye-sensitized solar cells.

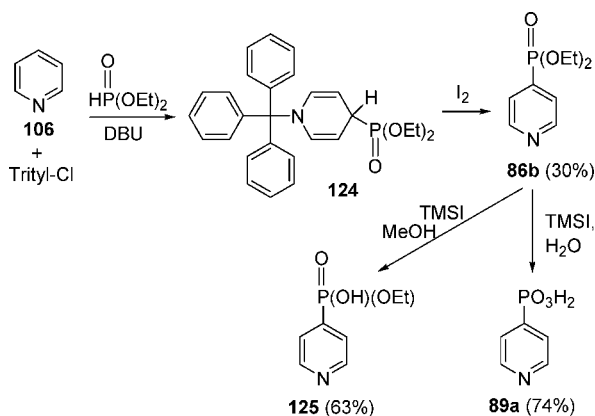
2.2.1.2. Nucleophilic Substitution of Halides in Deactivated Pyridine Rings. Nucleophilic substitution of halides on pyridine rings generally requires harsh reaction conditions, but a few exceptions are known. The synthesis of a series of pyridin-4-ylphosphonates was reported in 1969.⁵⁹ Starting from pentachloropyridine **126**, 4-bromo-2,3,5,6-tetrachloropyridine **127** could be prepared and both of these compounds could be converted into dialkyl pyridin-4-ylphosphonates

Table 3. Ratios and Yields for Scheme 33

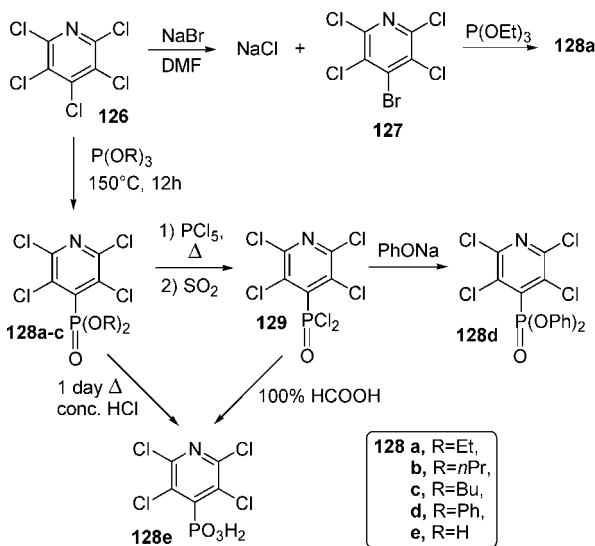
entry	R ¹ (122)	R ² (122)	R ³ (122)	R ⁴ (122)	X ⁻	R'	R ¹ (123)	R ² (123)	R ³ (123)	R ⁵ (123)	yield (%)	ratio
1	Me	H	H	OMe	Sulf ^a	Ph	Phos ^b	H	H	Me	46	
2	Me	H	H	OMe	Sulf ^a	nucleoside	Phos ^b	H	H	Me	40	
3	H	Me	H	OMe	BF ₄ ⁻	Et	Phos ^b	Me	H	H	41	20
							Phos ^b	H	H	Me	41	80
4	H	Me	H	OMe	BF ₄ ⁻	nucleoside	Phos ^b	H	H	Me	56	
5	H	Me	H	OMe	BF ₄ ⁻	Et	H	Me	Phos ^b	H	44	
6	H	Me	H	CPh ₃	Cl ⁻	nucleoside	H	Me	Phos ^b	H	77	
7	H	H	Me	OMe	Sulf ^a	nucleoside	Phos ^b	H	Me	H	40	

^a Sulf = 4-methylbenzenesulfonic acid. ^b Phos = dialkylphosphonate.

Scheme 34



Scheme 35

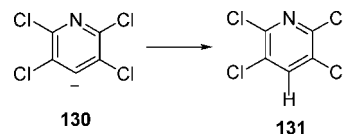


128a–c as the expected products of a Michaelis–Arbuzov reaction by heating with trialkyl phosphites. Treatment of the esters with PCl₅, followed by SO₂, gave 2,3,5,6-tetrachloropyridin-4-ylphosphonic dichloride **129**, which upon treatment with PhONa was converted into the diphenyl phosphonate **128d**. The free phosphonic acid **128e** could be obtained via two ways (Scheme 35).

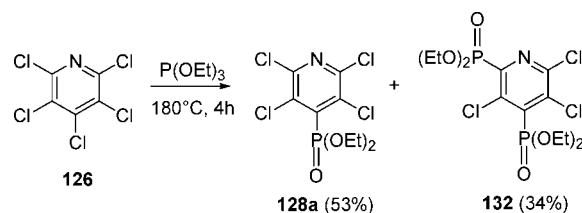
While repeating these reactions, Bratt and Suchitzky found that, during the reaction of **126** with triethyl phosphite, not only was the diethyl phosphonate **128a** formed but also the tetrachloropyridine **131**. The latter results from attack of the phosphite on the 4-chlorine atom with generation of the pyridinide ion **130**, followed by protonation to **131** (Scheme 36).^{59b}

A Russian research group reported in 1977 the conversion of 2,3,4,5,6-pentachloropyridine **126** into a mixture of diethyl

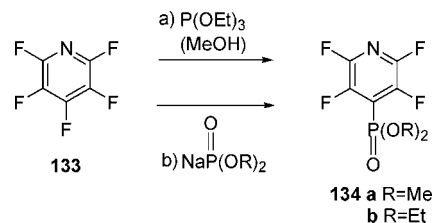
Scheme 36



Scheme 37



Scheme 38



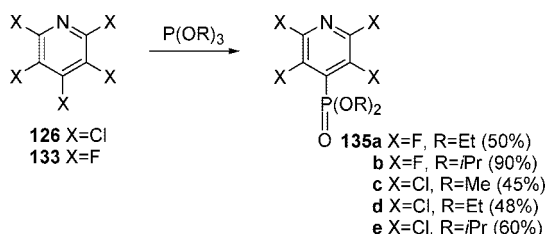
2,3,5,6-tetrachloropyridin-4-ylphosphonate **128a** (53%) and 3,5,6-trichloro-2,4-bis(diethoxyphosphoryl)pyridine **132** (34%) upon treatment with triethyl phosphite at 180 °C for 4 h (Scheme 37).⁶⁰

The preference for 4-substitution by nucleophiles in the polyfluoropyridines is well-documented.⁶¹ The synthesis of dialkyl 2,3,5,6-tetrafluoropyridin-4-ylphosphonates **134a,b** was performed using two different methods, both starting from 2,3,4,5,6-pentafluoropyridine **133**.⁶² The first procedure consisted of a reaction with triethyl phosphite, either without solvent or in methanol. Without any solvent, **134b** was achieved in 27% yield. In the second method, a Michaelis–Becker reaction was executed on **133** with sodium dialkylphosphonate (Me and Et) as the phosphorus species. This reaction yielded **134a** and **134b** in 53% and 50% yield, respectively (Scheme 38).

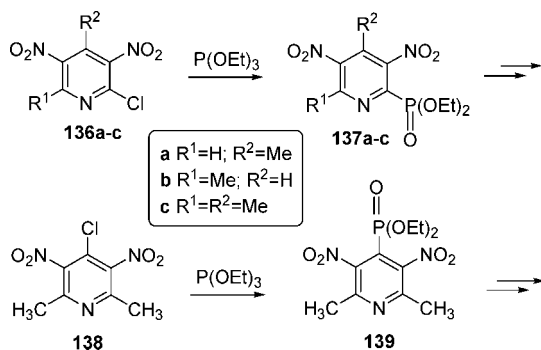
Michaelis–Arbuzov reactions were performed on perhalogenated pyridines for the synthesis of phosphinates⁶³ and phosphonates⁶⁴ of these perhalopyridines. The starting compounds **126** and **133** were heated with the trialkyl phosphites, resulting in the desired dialkyl 2,3,5,6-tetrahalogenpyridin-4-ylphosphonates **135** (Scheme 39). This reaction could be performed with fluoro- and chloro-substituents but failed in the case of trimethyl phosphite with pentafluoropyridine.

Achremowicz⁶⁵ discovered in 1975 that his method for the synthesis of methyl- and dimethyl-3,5-dinitropyridines proceeds through a dephosphonylation step of diethyl py-

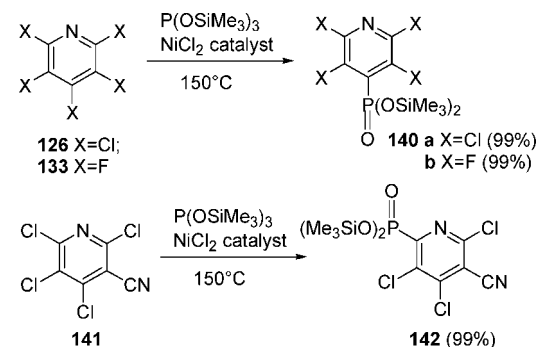
Scheme 39



Scheme 40



Scheme 41

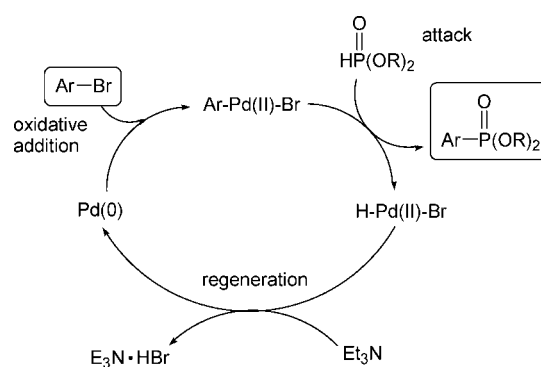


ridylphosphonates. He was able to isolate these pyridylphosphonates in moderate-to-good yields, and it is, therefore, useful to describe this procedure. Chlorodinitromethylpyridines **136** and **138** were heated with triethylphosphite at 120–130 °C for 0.5–3 h. This gave the diethylmethyl- or diethyldimethyl-3,5-dinitropyridinephosphonates **137** and **139** in 39–80% yield (Scheme 40). Dephosphonylation occurred during reflux with 20% hydrochloric acid.

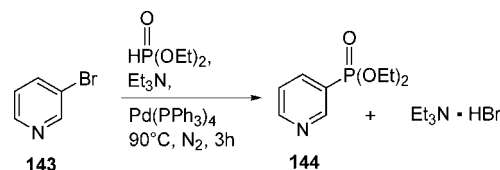
2.2.1.3. Metal Ion Catalysis. The reaction of aryl halides with phosphorus nucleophiles catalyzed by various metal (e.g., Ni, Cu) ions has already been investigated for the phosphorylation of arenes.⁶⁶ Demik et al.⁶⁷ used nickel catalysis to synthesize phosphonylated pyridines. Nickel salts apparently enhance the nucleophilicity of the trialkyl phosphites.^{66a} Bis(trimethylsilyl) 2,3,5,6-tetrahalopyridin-4-ylphosphonates **140a,b** were prepared starting from the 2,3,4,5,6-pentahalopyridines **126** and **133**. When starting from 2,4,5,6-tetrachloro-3-cyanopyridine **141**, bis(trimethylsilyl) 3,4,6-trichloro-5-cyanopyridin-2-ylphosphonate **142** was formed. Heating at 150 °C with a catalytic amount of NiCl₂ led to the envisaged end products in 99% yield. Subsequent treatment of these compounds with MeOH gave the corresponding arylphosphonic acids in quantitative yields (Scheme 41).

2.2.1.4. C–P Bond Formation in Cross-Coupling Reactions with Palladium. A transition metal catalyst for phosphorylation worth being treated in a separate section is

Scheme 42



Scheme 43



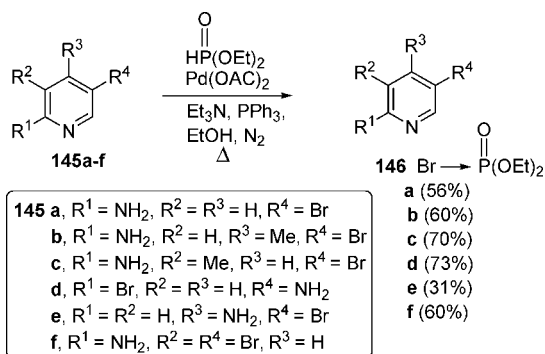
palladium. The formation path of dialkyl arylphosphonates via palladium-catalyzed cross-coupling is outlined in Scheme 42. A palladium(0) species undergoes oxidative addition with an aryl bromide to give the arylpalladium complex, which may be considered to be a key intermediate. The attack of a dialkyl phosphite to the arylpalladium complex leads to a dialkyl arylphosphonate. Triethylamine regenerates the palladium(0) species with the deposition of Et₃N · HBr. The thus-obtained palladium(0) species is then again available for another reaction cycle.

In 1981, Hirao et al.¹⁴ found a new and versatile synthetic route to dialkyl arylphosphonates via cross-coupling using a palladium catalyst and halogenated aryl compounds. Aryl bromides with strongly electron-donating substituents did not undergo the palladium-catalyzed vinylic substitution reaction (which is consistent with the results reported by Heck⁶⁸). The method did seem to work in the case of an azaheterocyclic arene, e.g., 3-bromopyridine **143**. In general, an aryl bromide is added to a stirred mixture of dialkyl phosphite and triethylamine in the presence of a catalytic amount of tetrakis[triphenylphosphine]palladium under a nitrogen atmosphere. The resulting mixture is stirred at 90 °C for 2.5–64 h. When the aryl bromide used is a solid, toluene is added as solvent. In Scheme 43, 3-bromopyridine **143** is used as starting material and yields 77% pyridin-3-ylphosphonate **144**. It was found later that the reaction can also be performed under phase-transfer conditions using potassium carbonate as the base.⁶⁹ Using Hirao's conditions on 2-iodo- and 2-bromopyridines, it appeared that these compounds were less reactive and led to the corresponding derivatives in lower yields.⁷⁰

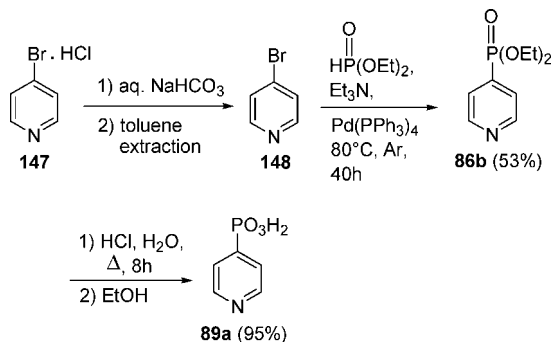
The cross-coupling of dialkyl phosphites with 3-bromopyridine was evaluated with Pd(OAc)₂/PPh₃ as the catalyst, EtOH as the solvent, and a sterically demanding tertiary amine (di(*c*-hex)₂NMe) as the base.⁷¹ No conversion of the starting material was observed although other aryl bromides reacted satisfactorily. The interaction of its donor groups with the palladium, preventing catalytic turnover, was stated as a possible explanation.

It appears that, among the pyridine derivatives, aminopyridines are one of the most difficult coupling partners due to an enhanced palladium complexation by the aminopyridine

Scheme 44



Scheme 45

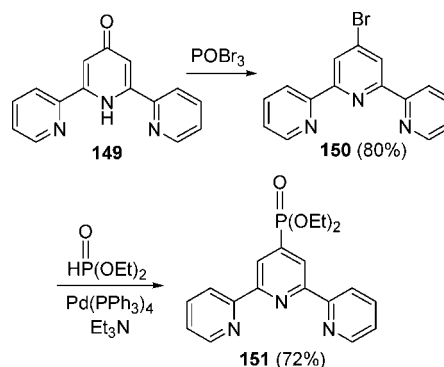


moiety.⁷² In contrast with the findings of Goossen et al. on the failure of the cross-coupling reaction with 3-bromopyridine,⁷¹ aminopyridines could be coupled with this same catalytic system. The optimal reaction conditions for aminopyridine phosphonylation are given in Scheme 44. A series of aminopyridyl phosphonates **146a–f** could be prepared in this way.⁷³ It seems that the reaction depends on the steric bulk of the pyridine bromide. *o*-Bromo or *o*-amino-substituted pyridines were more reactive due to the decrease of the palladium complexation by the pyridine fragment. A diphosphonate **146f** could also be prepared via a one-pot procedure.

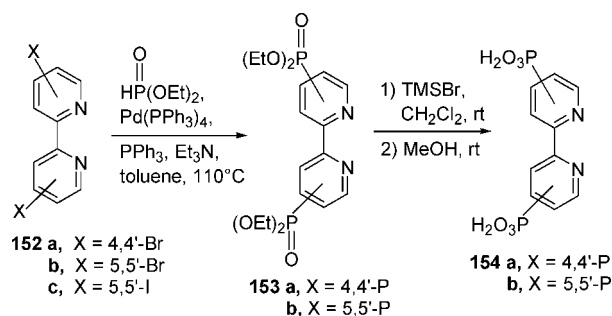
The synthesis of diethyl pyridin-4-ylphosphonate ligands **86b** reported by Konar et al.⁷⁴ took place according to the procedure of Hirao.¹⁴ They started with the neutralization of 4-bromopyridine hydrochloride **147**, resulting in 4-bromopyridine **148**. The coupling was performed under argon for 40 h, and the hydrolysis of the ester to **89b** was performed according to the Redmore procedure⁴² (Scheme 45). This pyridine-4-ylphosphonic acid **89a** was afterward used in reactions with three different divalent metal salts, resulting in the formation of molecular structures of different dimensionality. Another research group⁷⁵ also synthesized diethyl pyridyl-3-phosphonate **144** and diethyl pyridyl-4-phosphonate **86b** and their corresponding acids according to very similar procedures (minor adjustments) and converted these compounds into metal–pyridylphosphonates in 1D, 2D, and 3D coordination networks.

Grätzel et al.⁷⁶ used a modification of Hirao's procedure¹⁴ to synthesize a new phosphonylated terpyridine ligand to be incorporated in Ru(II)-polypyridyl complexes. These complexes appear to be promising candidates as photosensitizers in photoelectrochemical cells. Bromination of 2,6-bis(2'-pyridyl)-4-pyridone **149** using POBr₃ gave 4-bromo-2,2':6,2''-terpyridine **150** in 80% yield. The Br-group was subsequently replaced by a phosphonate group using diethyl phosphite in the presence of tetrakis[triphenylphosphine]-

Scheme 46



Scheme 47



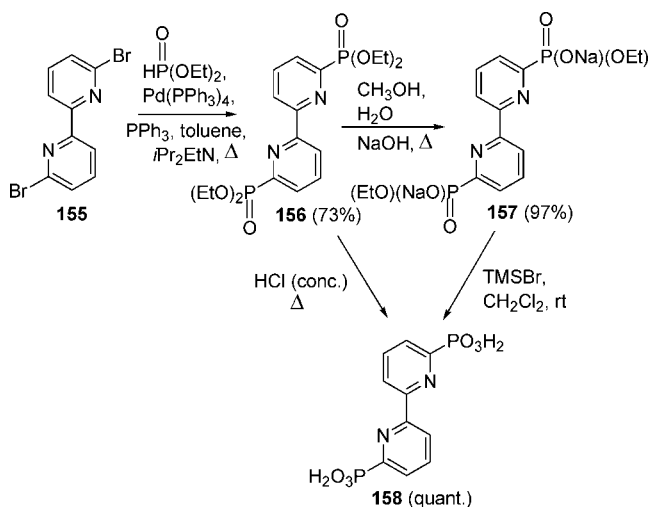
palladium and triethylamine and gave diethyl 2,2':6,2''-terpyridine-4-phosphonate **151** (Scheme 46).

A series of 2,2'-bipyridines bearing two phosphonic acid groups on the (4,4') or (5,5') position could also be prepared.⁷⁷ Hirao's conditions¹⁴ and those modified by Grätzel for the phosphonylation of terpyridine⁷⁶ both failed to provide the desired phosphonates **154a,b**. The strong coordination ability of bipyridine is probably responsible for that failure. Indeed, bipyridine might compete with the triphenylphosphine ligand of the Pd(PPh₃)₄ catalyst, thus leading to its deactivation. In order to prevent this ligand exchange on the palladium center, a large excess of triphenylphosphine (10-fold with respect to bipyridine) was added to the reaction medium. This simple modification resulted in the formation of **153a** and **153b** in 82% and 87% yield, respectively (Scheme 47). Although a large amount of triphenylphosphine is required, the latter is easily separated by chromatography and almost completely recycled. The phosphonate groups were then quantitatively converted into their acidic form under mild conditions using McKenna's method.¹⁸ These reactions were repeated by other research groups, again for the synthesis of photosensitizers in solar cells.⁷⁸

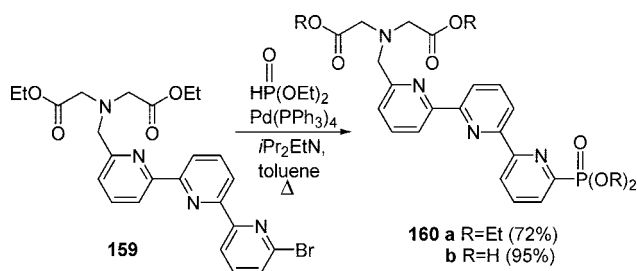
Montalti et al.⁷⁹ used a modification of the procedure described in Scheme 47 to synthesize the diethyl 2,2'-bipyridine-4,4'-diphosphonate **153a** and the phosphonic acid **154a** as ligands in luminescent complexes. Jing et al.⁸⁰ also synthesized **153a** and **154a** according to a slightly modified method.

The preparation of (6'-phosphono-[2,2']bipyridinyl-6-yl)-phosphonic acid **158** was achieved according to a slightly different procedure.⁸¹ The reaction was performed in a Schlenk tube under argon, a catalytic amount of Pd(PPh₃)₄, and only 1 additional equiv of PPh₃ was used. As a base, again diisopropylethylamine was added. Monohydrolysis could be performed when aqueous NaOH (1 equiv), H₂O, and MeOH were used and heated at 80 °C. Conversion to

Scheme 48



Scheme 49



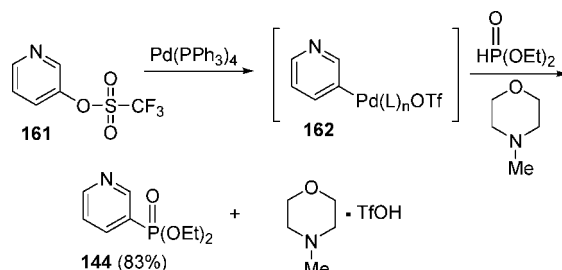
the bisphosphonic acid **158** was achieved with TMSBr .¹⁸ Double hydrolysis of the bisphosphonate **156** was performed with concentrated aqueous HCl (Scheme 48).

Terpyridine ligands could be prepared under the same conditions as described in Schemes 47 and 48 (with use of an excess of PPh_3).⁸² A bromo derivative **159** was converted to the phosphonate **160a** in 72% yield, in the presence of Hünig's base. Both the carboxylic and phosphonic esters were hydrolyzed with concentrated HCl , providing compound **160b** in 95% yield (Scheme 49).

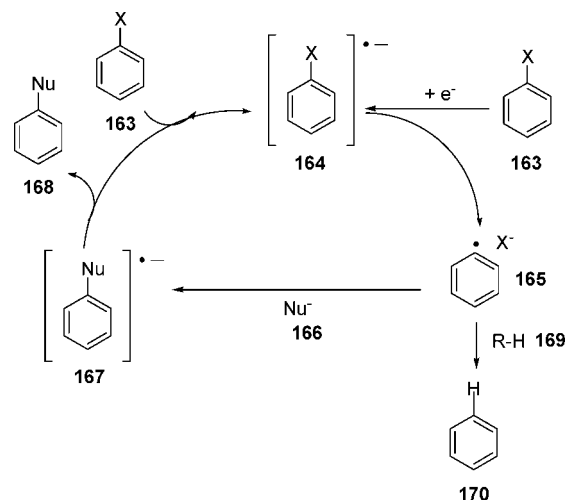
2.2.1.5. Displacement of an Aryl C–O Bond. Besides heterocycles with an aromatic carbon–halogen bond, other functionalities can be considered as precursors for phosphonylation. The direct replacement of an aryl C–O bond by a C–P bond is also reported.⁸³ Trifluoromethanesulfonates (triflates), prepared with *N*-phenyltriflimide, undergo efficient substitution, producing diethyl arylphosphonates. A series of aryl triflates, including also a pyridine compound **161**, could be likewise converted to heteroarylphosphonates. The reaction occurred under nitrogen atmosphere in hot acetonitrile containing diethyl phosphite, *N*-methylmorpholine, and the tetrakis(triphenylphosphine)palladium(0) catalyst, yielding 83% of diethyl 3-pyridylphosphonate **144**. It is postulated that Pd(0) mediates the reaction via the intermediate **162** (Scheme 50).

2.2.1.6. $\text{S}_{\text{RN}}1$. Radical-nucleophilic aromatic substitution or $\text{S}_{\text{RN}}1$ is a type of substitution reaction in which a certain substituent on an aromatic compound is replaced by a nucleophile through a free radical intermediate. The substituent X is a halogen, and in contrast to regular nucleophilic aromatic substitution, deactivating groups on the arene are not required. This reaction type was discovered in 1970 by Bunnett and Kim,⁸⁴ and the abbreviation $\text{S}_{\text{RN}}1$ stands for radical nucleophilic unimolecular substitution as it shares

Scheme 50



Scheme 51



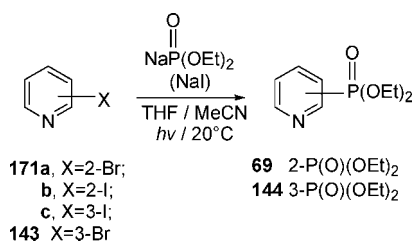
properties with an aliphatic $\text{S}_{\text{N}}1$ reaction. The pathway is given in Scheme 51. In this radical substitution, the aryl halide **163** accepts an electron from a radical initiator, forming a radical anion **164**. This intermediate collapses into an aryl radical **165** and a halide anion. The aryl radical reacts with a nucleophile **166** to a new radical anion **167**, which goes on to form the substituted product by transferring its electron to a new aryl halide in the chain propagation. Alternatively, the aryl radical can abstract any available hydrogen from **169**, forming the arene **170** in a chain-termination reaction.

Phosphonylation at sp^2 -hybridized carbon atoms of aromatic compounds under the photostimulated $\text{S}_{\text{RN}}1$ reaction conditions is now well-established and fully documented.⁸⁵ Sodium or potassium salts of dialkyl phosphites, generated from solutions of alkaline metals in liquid ammonia, proved to be excellent nucleophiles toward variously substituted aryl iodides.^{86,87}

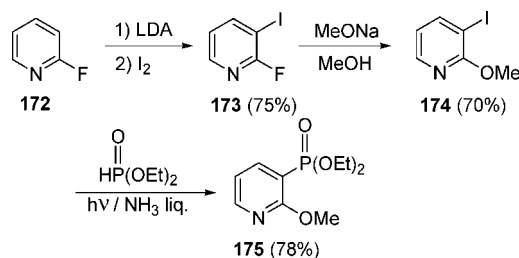
Savignac et al.^{70,88} evaluated two coupling processes for the phosphonylation of 2- and 3-iodo- and bromopyridines. The palladium-catalyzed cross-coupling was discussed in section 2.2.1.4 and gave few positive results. The second method is a photostimulated nucleophilic substitution ($\text{S}_{\text{RN}}1$ reaction) and good results were obtained using this method. Reaction of 2- and 3-iodo- and bromopyridines with sodium dialkylphosphite in an acetonitrile/THF mixture led to the phosphonates in good yields (80%). In the case of 3-bromopyridine, the addition of NaI had a significant accelerating effect on the reaction (Scheme 52).

Increasing the degree of substitution of heterocycles is often difficult with good regio- and chemoselectivity control. A combination of two complementary reactions, such as metalation and $\text{S}_{\text{RN}}1$ substitution, was suggested as an answer to this problem.⁸⁹ This strategy was successful with simple

Scheme 52



Scheme 53



halo- or aminopyridines and with diethyl phosphite as one of the nucleophiles. Selective ortho-lithiation of 2-fluoropyridine **172** by LDA and reaction of the resulting 3-lithio derivative with iodine afforded a high yield of 2-fluoro-3-iodopyridine **173**. The 2-fluorine atom is selectively activated toward nucleophilic substitution under $S_{\text{ArN}}2$ conditions, which allowed a convenient synthesis of 3-iodo-2-methoxy-5-fluoropyridine **174**. This was treated with an excess of diethyl phosphite in anhydrous liquid ammonia, and after 1 h UV illumination, diethyl (2-methoxy-3-pyridinyl)phosphonate **175** was achieved in 78% yield (Scheme 53).

In 1995, Beugelmans and Chbani⁹⁰ reported the polysubstitution of pyridines by sequential photostimulated $S_{\text{RN}}1$ reactions. A few examples of disubstitution on various positions using the $S_{\text{RN}}1$ reaction are known for the pyridine series.⁹¹ The starting product of this new synthetic route is 2-amino-5-bromopyridine **145a**, and under $S_{\text{RN}}1$ conditions, the first nucleophile is attached (Scheme 54). Subsequently, the amino function is substituted by a halogen by dissolving the product in glacial acetic acid, adding a solution of NaNO_2 in sulfuric acid while cooling is continued. This mixture is poured into an aqueous KI solution to obtain iodized products or into HBr to obtain brominated products such as **177**. It is also possible to introduce an extra halogen into compound **176** by dropwise addition of a solution of *N*-bromosuccinimide to **176** in DMF and stirring of the mixture for 3 h. Sequentially performing these different steps eventually leads to di- and trisubstituted pyridines (eg **178** and **181**). The nucleophiles used by Beugelmans were diethyl phosphite, 2-mercaptopyridine, and 2-mercaptopyrimidine.

2.2.1.7. Lithium–Halogen Exchange. Lithium–halogen exchange of 3-bromopyridine **143** with butyllithium was also tested as a synthetic path for the phosphonylation of pyridines. Diethyl 3-pyridylphosphonate **3** was obtained upon preparation of 3-pyridyllithium **182** and rapid reaction with diethyl chlorophosphate with efficient stirring at -80°C under a nitrogen atmosphere.⁹² This resulted in a yield of 36% of diethyl 3-pyridylphosphonate **144**, which could be hydrolyzed to 3-pyridylphosphonic acid **66** (95% yield) with 5N hydrochloric acid (Scheme 55). Other methods were also investigated; however, none of them led to satisfying results.

2.2.1.8. Strong Base-Induced Rearrangement of Aryl (thio)phosphates. The strong base-induced rearrangement

of aryl phosphates to aryl phosphonates had already been investigated in 1981 as a useful method for the directed introduction of a phosphoryl group.⁹³ However, it was not until a decade later that the lithium diisopropylamide (LDA)-induced regioselective [1,3]-*O,C*-rearrangement of 3- and 2-pyridylphosphates into the corresponding 3-hydroxypyridin-4-yl- and 2-hydroxypyridin-3-ylphosphonates was observed and investigated.⁹⁴ On diethyl 3-pyridyl phosphate **184**, readily available from 3-hydroxypyridine **183**, LDA smoothly induces the [1,3]-rearrangement wherein a phosphoryl group migrates predominantly to the C-4 carbon of the heterocycle. This is likely due to the fact that ortho-metalation proceeds predominantly at that position. Acidification of the mixture results in formation of the 3-hydroxypyridin-4-ylphosphonate **187** in 40% yield. It was found that, under similar conditions, a phosphoryl group could also be introduced at a pyridine C-3 carbon and 2-hydroxypyridin-3-ylphosphonate **190** was synthesized in 68% yield (Scheme 56).

Similar to this $\text{O} \rightarrow \text{C}$ migration is the $\text{S} \rightarrow \text{C}$ migration where phosphono-substituted pyridinethione **192b** is prepared from its corresponding thiophosphate **191**.⁹⁵ Phosphorylation of sodium pyridyl-2-thiolate leads easily to *O,O*-diisopropyl *S*-(2-pyridyl)thiophosphate **191**. Reaction of **191** with LDA in THF induces the [1,3]-*S,C*-rearrangement wherein the phosphoryl group migrates to the C-3 carbon, leading to diisopropyl (1,2-dihydro-2-thioxo-3-pyridyl)phosphonate **192b** in 75% yield. As already observed with mercaptopyridines substituted by an electron-withdrawing group,⁹⁶ the researchers observed a quasi-complete displacement of the 2-mercaptopyridine/pyrid-2-thione tautomeric equilibrium toward the thione form **192b** (Scheme 57).

2.2.1.9. Synthesis of Pyridinol Derivatives. Phosphonylated pyridinone derivatives can also be synthesized by treatment of the pyridinone compound **193** and dialkyl chlorophosphate with LDA in THF as solvent.⁹⁷ Reaction details are not provided. This reaction results in phosphonylated compounds **194** or **197** that can be partly deprotected with sodium hydroxide toward compounds **195** and **198** (Scheme 58). Compounds with different substitution patterns could be synthesized. For some of the compounds (**194e** and **197**), the methoxy analogues were also described (**196** and **199**, respectively).

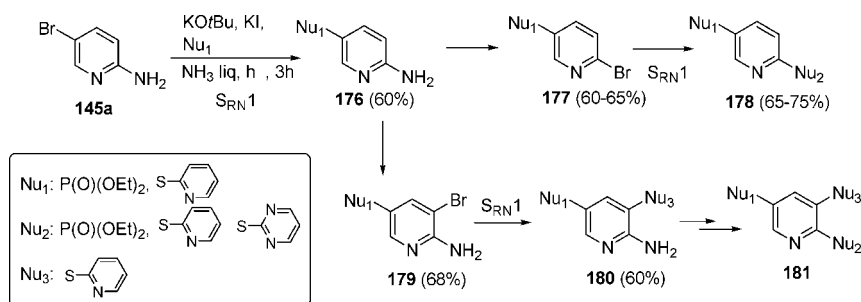
2.2.1.10. Related Nonaromatic Phosphonylation Methods.

An oxidative double phosphonylation of dihydropyridines and pyridinium salts is possible through the use of dialkyl phosphites, DDQ, and triethylamine.⁹⁸ Even though the resulting compounds are no longer aromatic, we believe these reactions should be covered in this overview since they are very strongly related to the subject. The researchers were inspired by the Effenberger oxidative phosphonylation of arenes,⁹⁹ but modification of the method appeared necessary. After optimization, the reaction works well with dihydropyridines **200** and pyridinium salts **201** bearing electron-withdrawing substituents at the β -position. The mechanistic proposal is given in Scheme 59. The yields of the diphosphonates **202** starting from the dihydropyridines **200** are typically 10–20% lower than starting from the pyridinium salts **201**. Isomerization to **203** occurred during stirring in SiO_2 .

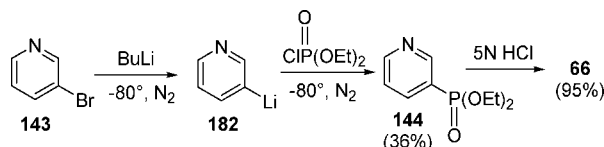
2.2.2. Pyrimidine

Phosphono-substituted pyrimidines in general, and uracils in particular, are of great interest, since numerous uracil

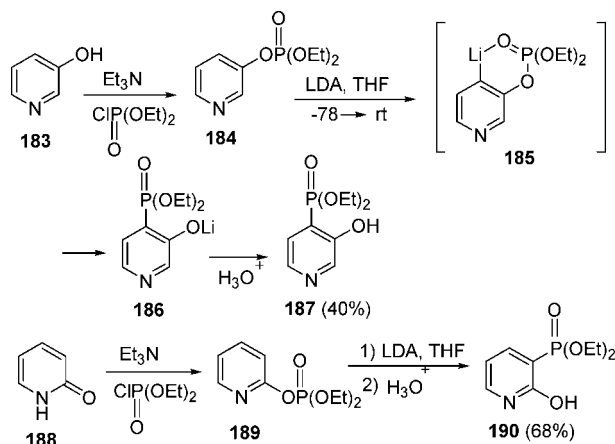
Scheme 54



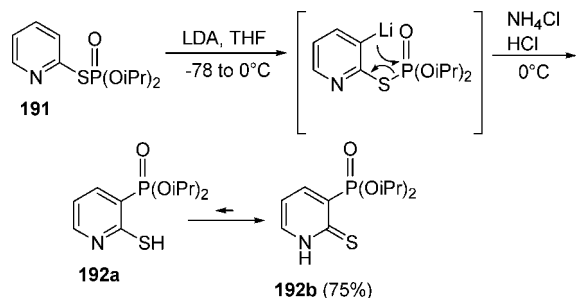
Scheme 55



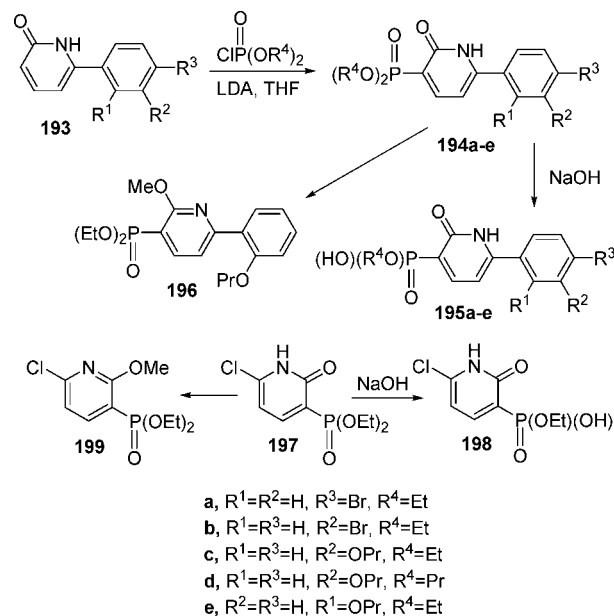
Scheme 56



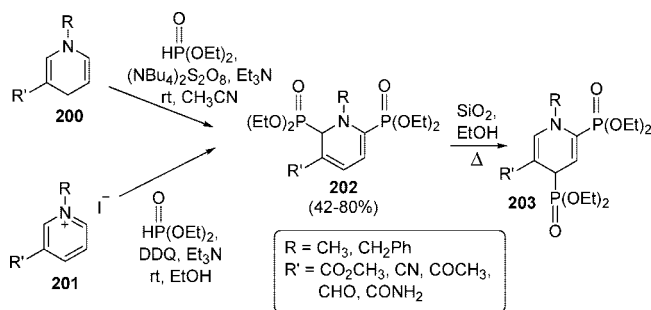
Scheme 57



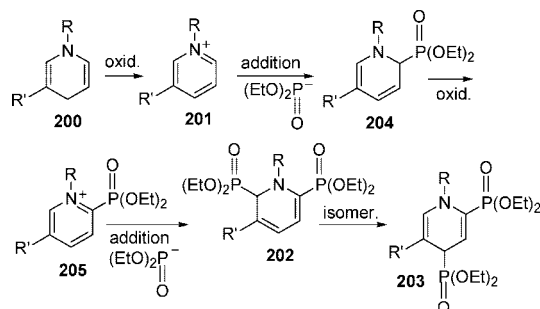
Scheme 58



Scheme 59



Mechanistic proposal

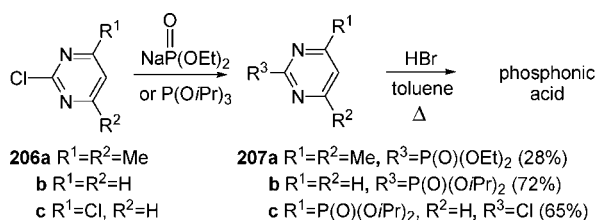


derivatives possess a wide spectrum of biological/pharmacological activities and several derivatives are in clinical use. This led to the investigation of several phosphorylation methods.

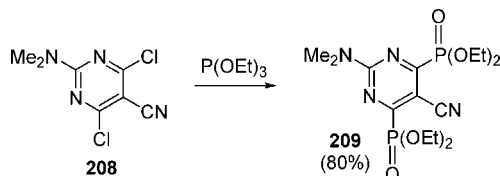
2.2.2.1. Phosphonylation via Arbuzov or Michaelis–Becker Reaction. In 1947, Kosolapoff already showed that the conventional Arbuzov and Michaelis reactions may be applicable for the synthesis of phosphonates from an azaheterocycle bearing a halogen atom¹⁰⁰ (see section 2.5.1). This specific approach was also used for the synthesis of various pyrimidines.¹⁰¹ The very low reactivity of 5-halopyrimidine prevented the synthesis of 5-pyrimidylphosphonate, but the analogous 2- and 4-isomers were prepared successfully from the chloro-derivatives after treatment with triisopropyl phosphite or sodium diethyl phosphite (Scheme 60). The remaining halogen in **207c** can be further converted into

other functionalities, but displacement in an Arbuzov reaction with the same phosphite to give the diphosphonate was not successful.

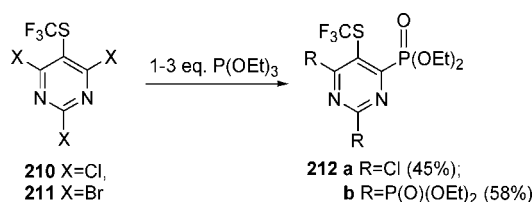
Scheme 60



Scheme 61



Scheme 62



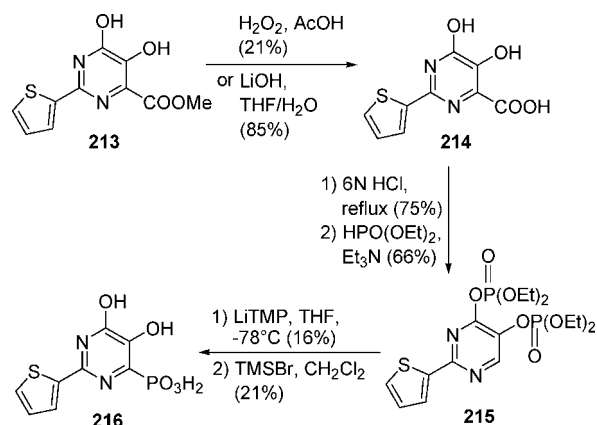
It was found that the addition of triethyl phosphite to a solution of 4,6-dichloro-2-(dimethylamino)-5-pyrimidinecarbonitrile **208** resulted in the synthesis of 80% of the envisaged dimethyl 5-cyano-6-(diethoxyphosphoryl)-2-(dimethylamino)pyrimidin-4-ylphosphonate **209** (Scheme 61).¹⁰²

An Arbuzov type reaction on compounds **210** and **211** was reported to result in the formation of phosphonylated compounds like **212a** or **b**, depending on the number of equivalents of triethyl phosphite added.¹⁰³ The starting products were dissolved in hexane and were treated with triethyl phosphite. After 5 h of reflux, the end products could be isolated in 45–58% after distillation (Scheme 62).

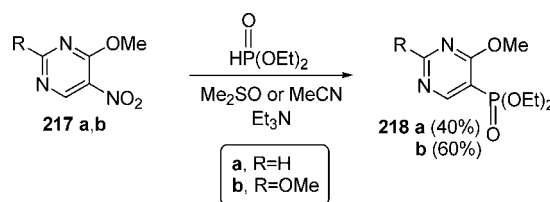
2.2.2.2. Strong Base-Induced Rearrangement of Arylphosphates. A synthesis of the C4 phosphonic acid derivative of pyrimidine **216** was reported,¹⁰⁴ starting from 2-aryl-5,6-dihydropyrimidine-4-carboxylic acid **213** (prepared according to a literature procedure¹⁰⁵). The target compound could be accessed using a phosphate–phosphonate rearrangement strategy. The 2-thienyl pyrimidine **214** was obtained from **213** by treatment with LiOH and decarboxylation, followed by conversion of the resulting diol to the bis-diethylphosphate derivative **215**. LiTMP-mediated rearrangement proceeded with loss of the C6 phosphate group and the resulting C4 phosphonate ester, isolated after RP-HPLC purification, was deprotected using TMSBr by the McKenna method¹⁸ (Scheme 63).

2.2.2.3. Various Syntheses of Pyrimidinylphosphonates. Synthesis of phosphonylated pyrimidines could also be achieved through a nucleophilic substitution of the nitro group in methoxynitropyrimidines by dialkyl phosphites.¹⁰⁶ This reaction was applied to 4-methoxy-5-nitropyrimidine **217a** and 2,4-dimethoxy-5-nitropyrimidine **217b** in Me₂SO or MeCN with diethyl phosphite in the presence of Et₃N. The envisaged pyrimidin-5-ylphosphonates **218a** and **218b** could be prepared in reasonable yields (40–60%) (Scheme 64).

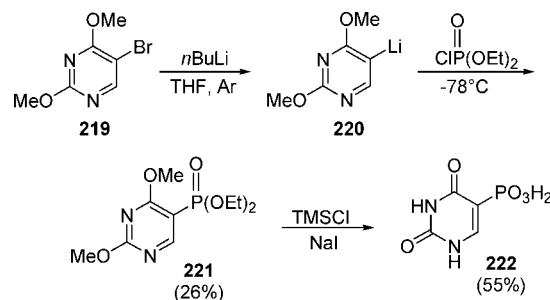
Scheme 63



Scheme 64



Scheme 65



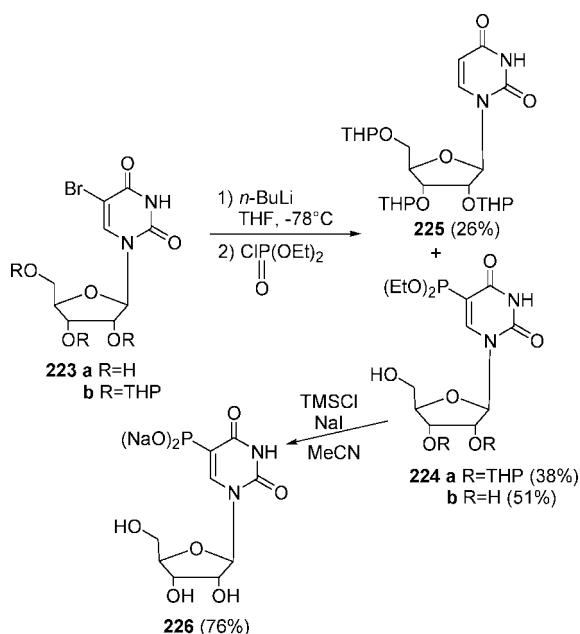
2.2.2.4. Uracil. Uracil can be seen as a special, naturally occurring type of pyrimidine. Maruyama et al.¹⁰⁷ reported the synthesis of some phosphono derivatives of pyrimidine bases based upon a lithium–halogen exchange reaction of bromopyrimidine followed by phosphonylation. Conversion into the corresponding phosphonic acid was obtained after reaction with iodotrimethylsilane (Scheme 65).

This type of reaction could also be performed on uracil derivatives bearing a saccharide moiety.¹⁰⁸ 5-Bromouridine **223a** was first protected with dihydropyran in DMF in the presence of *p*-toluenesulfonic acid to give **223b**. Successive treatment of **223b** with *n*-butyllithium and diethyl chlorophosphate provided **224a** and **225**. Deprotection of **224a** with pyridinium *p*-toluenesulfonate (PPTS) resulted in diethyl uridine-5-ylphosphonate **224b**. Hydrolysis of this ester gave 5-phosphonuridine **226** (Scheme 66).

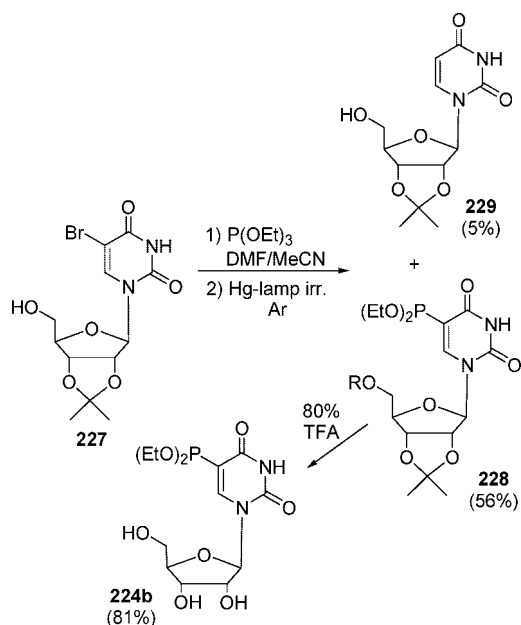
The same compound could also be synthesized through a photochemical synthesis by an attack of nucleoside radicals on trialkyl phosphites.¹⁰⁹ Addition of triethyl phosphite to a solution of **227**, followed by irradiation with a mercury lamp under argon gas, afforded diethyl 2',3'-*O*-isopropylideneuridine-5-phosphonate **228** and 2',3'-*O*-isopropylideneuridine **229** in 56% and 5% yield, respectively. Deacetonation of **228** provided diethyl uridine-5-phosphonate **224b** (Scheme 67).

The same researchers also explored other reactions. The protection of 2',3'-*O*-isopropylideneuridine **229** with 2,3-

Scheme 66



Scheme 67

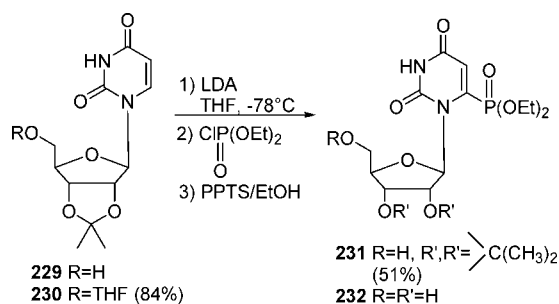


dihydrofuran provided the 5'-*O*-(tetrahydro-2-furanyl) derivative **230**. Treatment of **230** with lithium diisopropylamide (LDA) and with diethyl chlorophosphate, followed by removal of the THF group with PPTS, afforded the diethyl phosphonate derivative **231**. The isopropylidene group could be removed with trifluoroacetic acid, and hydrolysis of the ester **232**, again with TMSCl and NaI in the presence of pyridine, yielded 51% of sodium 6-phosphonoridine (Scheme 68).¹⁰⁸

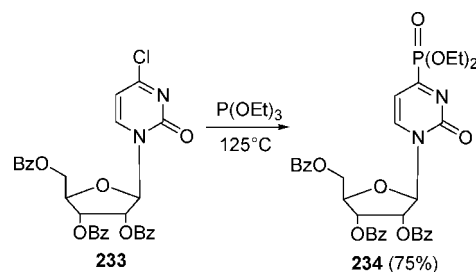
An Arbuzov reaction could be performed on halogenated pyrimidinones. Compound **233** was treated with triethyl phosphite at 125°C , resulting in the 4-diethyl phosphonate derivative **234** (Scheme 69).¹⁰⁸

2-Thiouracil **235** and 5-nitrothiouracil **240** also react with trialkyl phosphites and dialkyl phosphites.¹¹⁰ In the case of reaction of 2-thiouracil **235** with trialkyl phosphites, a mixture of four main compounds was formed, which could

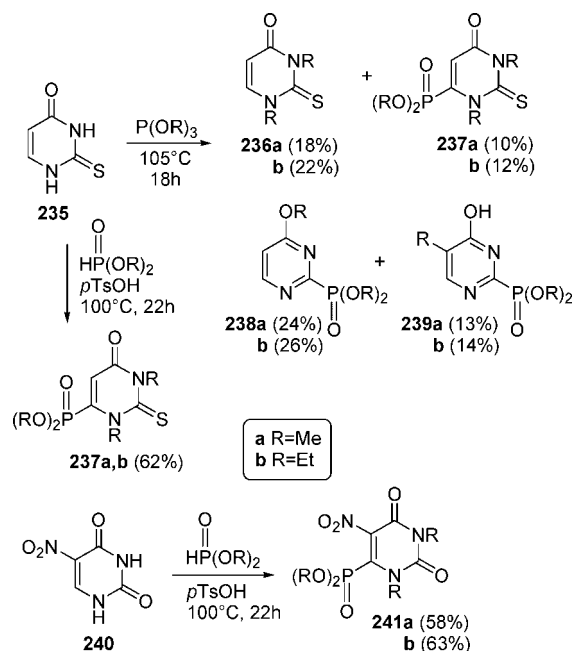
Scheme 68



Scheme 69



Scheme 70



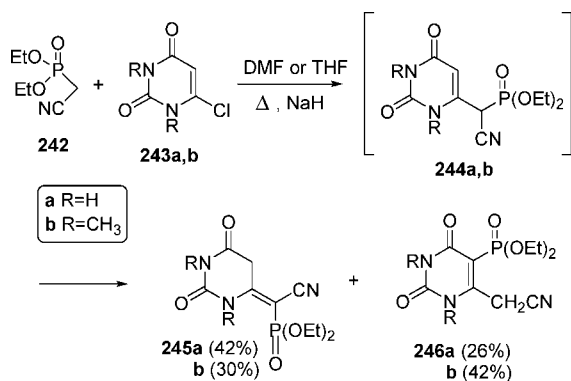
be separated by chromatography. The different potential mechanisms leading to phosphonylation on different positions or *N*-alkylation are suggested in the publication. The reaction products are depicted in Scheme 70.

The reaction of diethyl cyanomethylphosphonate **242** with 6-chlorouracil **243** in a solvent containing NaH was found to result in vinylphosphonates **245** and phosphono-substituted uracils **246** by the same researchers.¹¹¹ The formation of **246** was the result of a thermal rearrangement, and compounds **245** and **246** could be separated by chromatography (Scheme 71).

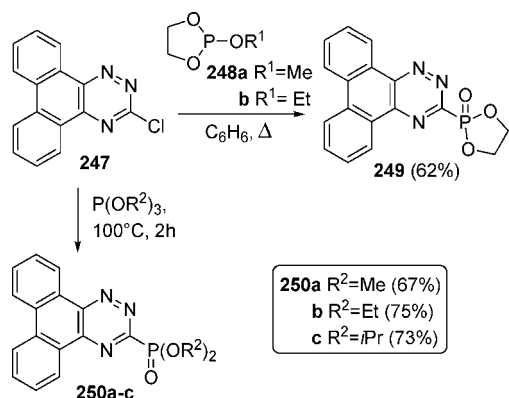
2.2.3. Triazine

2.2.3.1. 1,2,4-Triazine. Reaction of 3-chlorotriazine derivative **247** with cyclic phosphites **248a,b** and acyclic trialkyl phosphites according to the Michaelis–Arbuzov

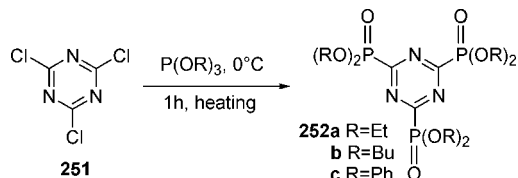
Scheme 71



Scheme 72



Scheme 73



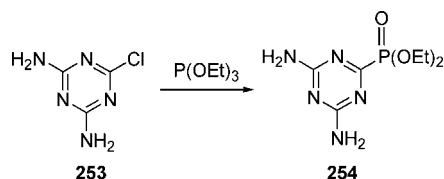
mechanism allowed the preparation of regioselectively phosphorylated products at C-3.¹¹² With 2-methoxy-1,3,2-dioxo-phospholane **248a** and the ethoxy derivative **248b**, a cyclic phosphonate **249** was formed in good yield after reflux in benzene. Reaction with the acyclic phosphites in the absence of solvent and with an excess of phosphites led to the phosphonates **250a–c** in about 70% yield (Scheme 72).

2.2.3.2. 1,3,5-Triazine. For these azaheterocycles, the only known phosphorylation procedures are Arbuzov or Michaelis–Becker reactions. These reactions can be performed without any need of activation of the halogenated triazines, demonstrating their high susceptibility to the displacement of halides.

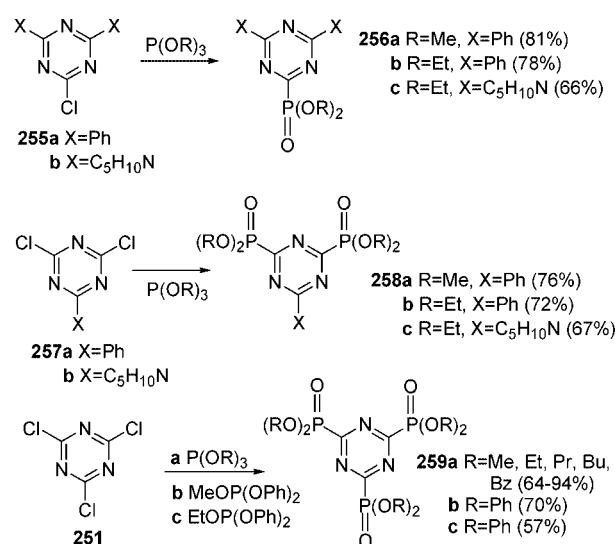
In 1954, a patent¹¹³ by Coover described the synthesis of phosphorylated 1,3,5-triazines via an Arbuzov reaction. Cyanuric chloride **251** was treated with trialkyl or triaryl phosphite, and the vigorous reaction was controlled at 0 °C, followed by heating, and yielded after workup the tris(di-alkylphosphoro)triazine **252a,b** or tris(diphenylphosphoro)triazine **252c** (yield not provided). The products are useful as plasticizers, solvents, insecticides, and intermediates (Scheme 73).

Morrison¹¹⁴ also performed similar reactions two years later, synthesizing the methyl, ethyl (**252b**), and β -chloroethyl esters in 89%, 99%, and 76% yield, respectively. The experimental conditions were slightly different, as the

Scheme 74



Scheme 75



preparation could also be done using benzene as solvent for the phosphites, and also the reaction times differed (15 min, 30–60 °C; followed by 15 min, 100 °C, and 1 h, room temperature). The corresponding phosphonic acids could not be obtained in pure form.

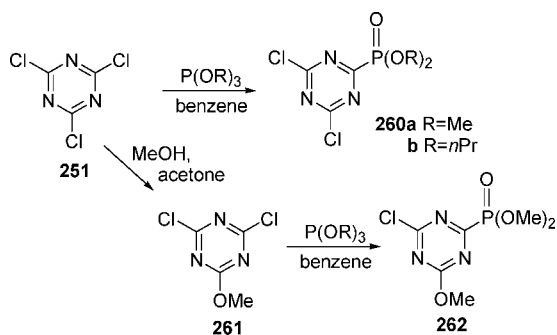
Starting from the chloro-derivative **253**, diethyl 4,6-diamino-1,3,5-triazin-2-ylphosphonate **254** could be synthesized.¹¹⁵ An excess of triethyl phosphite was refluxed with **253** for 8 h and gave the desired phosphorylated compound **254**, again according to the Arbuzov mechanism (Scheme 74).

It was already demonstrated that Arbuzov reactions of chloro-1,3,5-triazines with phosphorus(III) alkyl esters gave 1,3,5-triazinylphosphonates. A series of compounds could be prepared in this way (Scheme 75).¹¹⁶ The relatively easy replacement of chlorine in 4,6-disubstituted 2-chloro-1,3,5-triazines is discussed in terms of the electron-withdrawing effect of the 4,6-substituents and of groups X in the esters X₂POR. Another interesting observation is that, when cyanuric chloride **251** is allowed to react with 2 equiv of trimethyl phosphite, only trisubstituted triazine **259a** and unreacted chloride **251** are isolated. This suggests that the phosphonate group may in fact enhance the reactivity of the remaining chlorine to nucleophilic displacement. The reaction of an excess of cyanuric chloride with triethyl phosphite, however, did result in a monosubstituted product.

Ismail similarly prepared 2-phosphorylated 4,6-disubstituted 1,3,5-triazines in good yields (88–93%) with OAr groups as substituents (Ar = C₆Cl₅, 2,3,4,6-tetrachlorophenyl, 2,4,5-trichlorophenyl, 2,4,6-tribromophenyl). Trialkyl phosphites $\text{P}(\text{OR})_3$ with R = Et, CH₂CH₂Cl were used as nucleophiles.¹¹⁷

The tautomerization of phosphorylated 1,3,5-triazines was discussed in 1986 together with a brief description of the synthesis of the investigated compounds.¹¹⁸ The starting product here was also cyanuric chloride **251**, converted

Scheme 76



Scheme 77

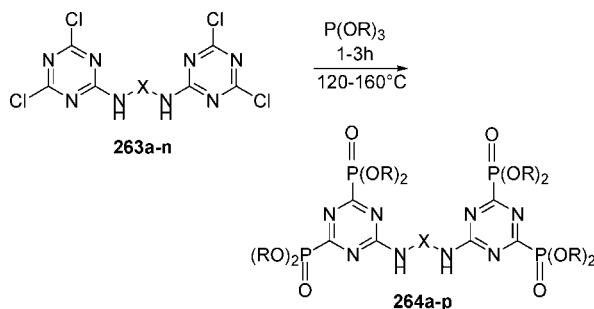


Table 4. Details and Yields for Scheme 77

263	264	–X–	R	yield (%)
a	a	1,3-phenylene	Me	51
a	b	1,3-phenylene	Et	72
a	c	1,3-phenylene	<i>i</i> Pr	84
b	d	1,4-phenylene	Et	45
c	e	1,2-phenylene	Et	47
d	f	2-methyl-1,3-phenylene	Et	33
e	g	2,4,6-trimethyl-1,3-phenylene	Et	39
f	h	1,3-xylylene	Et	42
g	i	diphenylmethane-4,4'-diyl	Et	70
h	j	1,2-ethylene	Et	53
i	k	1,3-propylene	Et	42
j	l	2,2-dimethyl-1,3-propylene	Me	44
k	m	1,6-hexylene	Et	30
l	n	1,12-dodecylene	<i>i</i> Pr	63
m	o	1,8-(3,6-dioxaoctylene)	Et	91
n	p	pyrid-2,6-diyl	Et	53

directly into the phosphonate **260a,b** with trialkyl phosphite or first to the methoxy derivative **261** (Scheme 76). The synthesis of tris(dialkylphosphoro)triazines **259a–c** according to Coover¹¹³ was also mentioned, but no experimental details were provided.

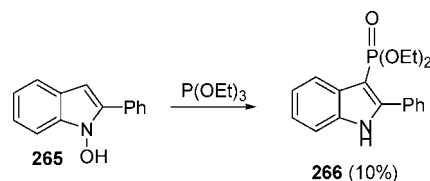
The phosphorylation of triazine-related heterocyclic ring-systems **263a–n** (bis(4,6-dichloro-1,3,5-triazin-2-yl)diamines) was also achieved via an Arbuzov reaction.¹¹⁹ The procedure was analogous to the ones previously described,^{113–118} using trialkyl phosphites and heating, but the substrates differed (Scheme 77 and Table 4).

2.3. Annulated Six- and Five-Membered Ring

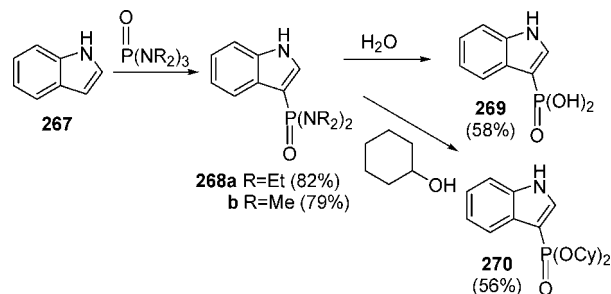
2.3.1. Indole

Diethyl 2-phenylindolyl-3-phosphonate **266** can be synthesized by deoxygenation of 1-hydroxy-2-phenylindole **265** with triethyl phosphite (Scheme 78). This formation is postulated to proceed via radical intermediates.¹²⁰ The generation of aryl radicals by photolysis of aryl iodides in the presence of trimethyl or triethyl phosphites is found to give good yields of aryl phosphonates.^{8f}

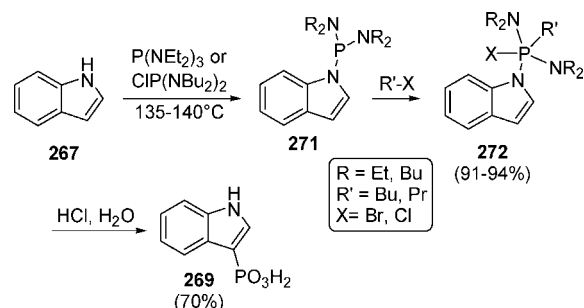
Scheme 78



Scheme 79



Scheme 80



C-phosphonylation of indoles could also be achieved by reaction of the indole **267** with hexaethylphosphoric triamide or the hexamethyl derivative.¹²¹ This results in the phosphonic diamides **268a** and **268b** in good yields, which in turn can be converted into the indol-3-ylphosphonic acid **269** or the dicyclohexyl phosphonate **270** (Scheme 79).

The same Russian researchers also developed another route toward these compounds.¹²² This pathway starts with the synthesis of *N*-phosphorylated derivatives (*N,N,N',N'*-tetraethyl-*P*-(1-indolyl)phosphonous diamide **271**) as a result of heating indole with phosphorus triamides (for 1.5–2 h). After reaction with butylchloride or -bromide, a diaminophosphonium salt **272** was formed. Isomerization of these *N*-phosphorylated derivatives to the 3-phosphonylated derivative occurred during treatment with H_2O , resulting in indol-3-ylphosphonic acid **269** (Scheme 80).

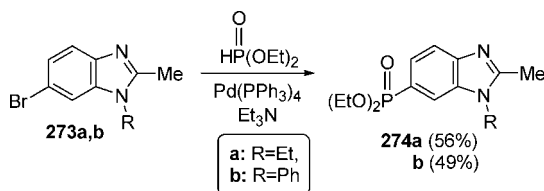
2.3.2. Benzimidazole

Russian researchers described the phosphorylation of benzimidazole derivatives¹²³ using a palladium-catalyzed coupling reaction similar to the one presented by Hirao.¹⁴ Triethylamine was added as a base, and the desired diethyl (1-ethyl-2-methyl-6-benzimidazolyl)phosphonate **274a** and diethyl (1-phenyl-2-methyl-6-benzimidazolyl)phosphonate **274b** were synthesized in good-to-moderate yields (Scheme 81).

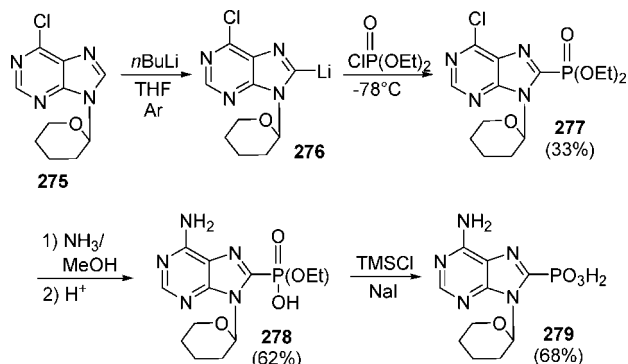
2.3.3. Purine

A purine derivative **275** could be phosphorylated in a similar way as previously described for uracil (see section 2.2.2.4).¹⁰⁷ A lithium–halogen exchange reaction was fol-

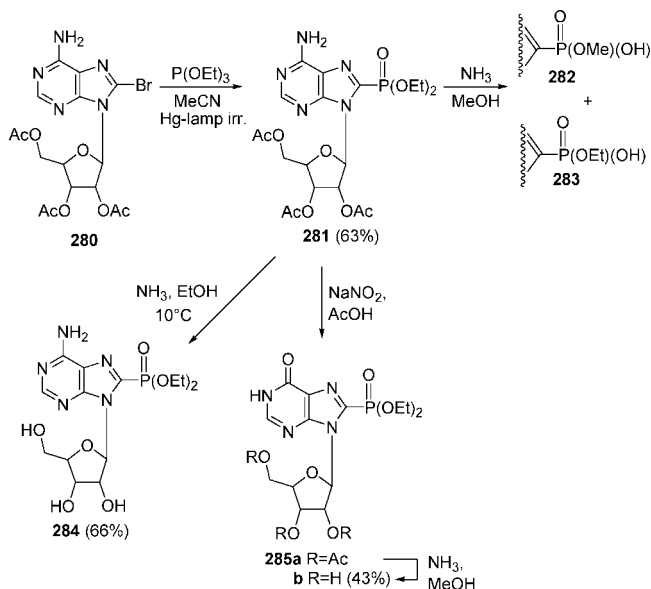
Scheme 81



Scheme 82



Scheme 83

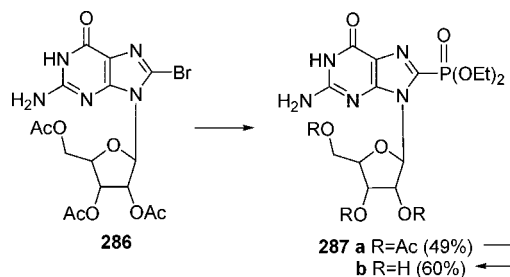


lowed by phosphonylation with diethyl chlorophosphate and treatment with methanolic ammonia and trifluoroacetic acid to give monoethyl 8-adenylphosphonate **278**. The corresponding phosphonic acid **279** was formed after treatment with iodotrimethylsilane (Scheme 82).

The phosphonylation of an adenine compound **280** could be performed through a photochemical reaction with triethyl phosphite.^{109,124} The procedure is similar to the pyrimidine-based ones described earlier (see section 2.2.2.4). An inosine analogue could also be prepared by conversion of phosphonate **281**, resulting in **285a** that could be deprotected to form **285b** in the presence of methanolic ammonia (Scheme 83). The difference in the behavior of **281** and **285a** toward methanolic ammonia could be explained by dissociation of the N¹ proton in **285a** followed by delocalization of the N¹ negative charge and unfavorable nucleophilic attack of the reagent on the phosphorus atom.

A similar photochemical reaction was applied on a guanosine compound **286**, resulting in phosphonate **285a**.

Scheme 84



After deprotection, diethyl guanosine-8-phosphonate was formed in 60% yield (Scheme 84).¹⁰⁹

The same researchers also performed a reaction on a similar compound **289** in which the phosphorus substitution led to an intramolecular cyclization.¹²⁴ The substitution reaction here was again accomplished under photoirradiation and resulted in two diastereomers, the ethyl hydrogen *P*,5'-anhydro-2',3'-*O*-isopropylideneadenosine-8-phosphonate structures **290a** and **290b**. The reaction mechanism was described in a subsequent publication.¹²⁵ Deacetonation of **290a** or **290b** with 80% trifluoroacetic acid afforded trifluoroacetic salts **291a** or **292b**. Treatment of either **291a** or **291b** with ammonium hydroxide afforded *P*,5'-anhydroadenosine-8-phosphonic acid **292** (Scheme 85).

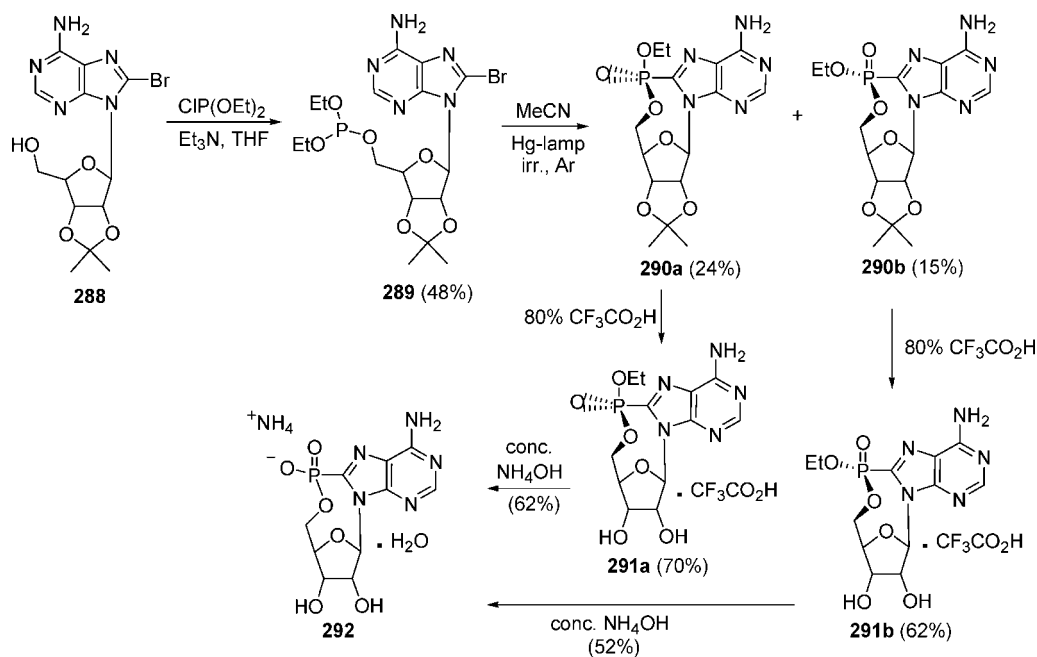
A phosphonylation reaction through lithiation, already described for pyrimidine derivatives (see section 2.2.2.4), was also performed on a purine compound **293a**.¹⁰⁸ The reaction sequence is almost the same as previously described, with some minor adjustments. If **294b** is treated with DMF saturated with ammonia, compound **295a** is formed. In case this treatment is followed by reaction with iodotrimethylsilane in acetonitrile containing a small amount of pyridine, 8-phosphoadenosine **295b** is formed (Scheme 86).

An alternative method for the synthesis of these ribonucleosides by a photoinduced coupling reaction was developed.¹⁰⁹ The reaction conditions have already been described in section 2.2.2.4 and are also applicable to purine derivatives.

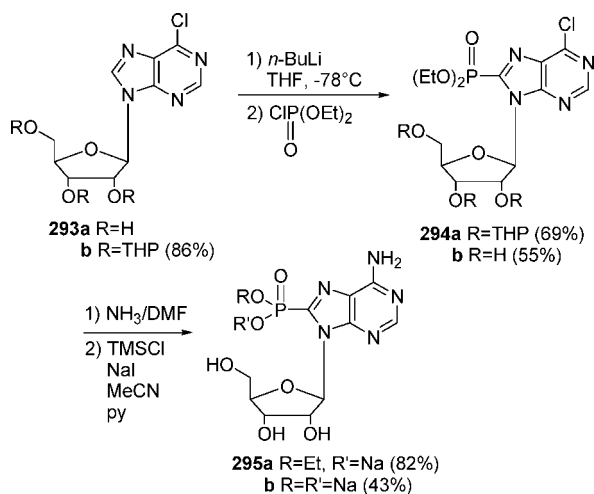
In the next synthesis, the phosphonylated purine compound **298** is not the target compound of the reaction but a byproduct. Since the conditions can be modified so that the yield of that byproduct is higher than 25%, it seemed interesting to mention this method.¹²⁶ Starting from the bromohydrin **296**, the reaction with triethyl phosphite was performed at 100 °C (procedure a) resulting in 85% of the target compound **297**. The temperature must be this low to avoid the displacement of the 6-chlorine atom of the purine by triethylphosphite (S_NAr reaction) that would lead to compound **298**. Above 120 °C, the byproduct **298** was formed in 25% yield (procedure b) (Scheme 87).

A procedure based upon a microwave-assisted S_NAr-Arbusov reaction was applied to the synthesis of novel C6-phosphonylated purine nucleosides **300** (including a series of nonsugar carbon nucleosides).¹²⁷ Since reaction of 6-chloropurine gave rise to a complex mixture, it was postulated that the unprotected N-H at N9 position prevented the usual reaction. To avoid this side reaction, only N9-substituted purine compounds **299** were used as substrates (Scheme 88). The kind of substituents at N9 had little impact on the yields of the products, but the replacement of the chloride at C2 by H or NH₂ led to lower yields, indicating that the electron-donating effects on C2 could lead to decrease of the yields. The use of microwave irradiation to generate phosphonated

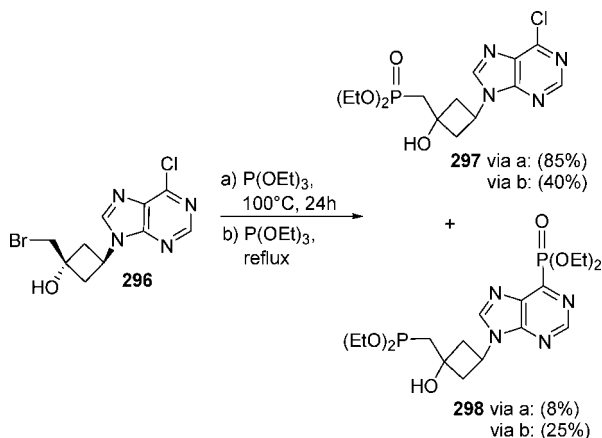
Scheme 85



Scheme 86

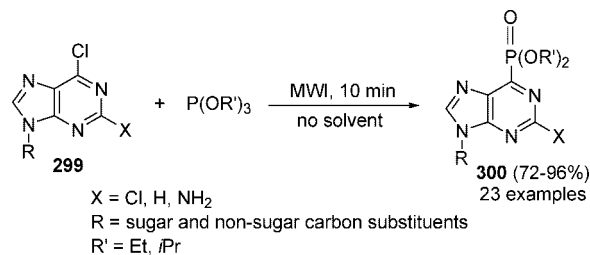


Scheme 87

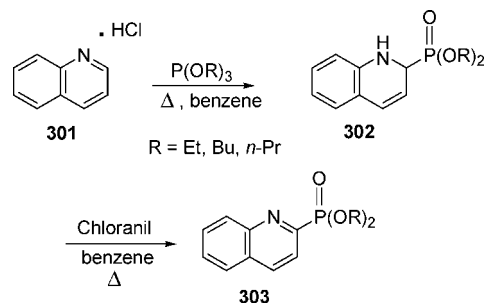


compounds was also tested on other heterocyclic scaffolds, for example on 4-chloropyrazolopyrimidine (see section 2.5.8).

Scheme 88



Scheme 89



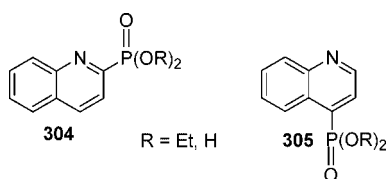
2.4. Annulated Six-Membered Rings

2.4.1. Quinoline

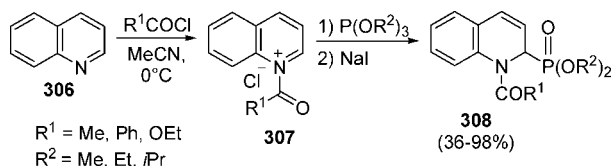
2.4.1.1. C–P Bond Formation by Nucleophilic Attack on N-substituted Quinolinium Cations. In 1970, the preparation of a series of heterocyclic phosphonates including quinolinylphosphonates was reported.⁴⁷ The method starts from the heteroaromatic cations and has already been described in this review under section 2.2.1. The researchers were able to synthesize three dialkyl quinolin-2-ylphosphonates **303** and the quinolyl-2-phosphonic acid. (Scheme 89)

A series of patents were published by Redmore^{29,39} about the phosphorylation of full aromatic nitrogen heterocycles. In these patents, the method developed in 1970³⁷ was applied to all kinds of azaheterocycles, including quinolines. The methodology was explained in section 2.2.1.1 and proceeds via a nucleophilic attack on the *N*-alkoxyquinolinium salt

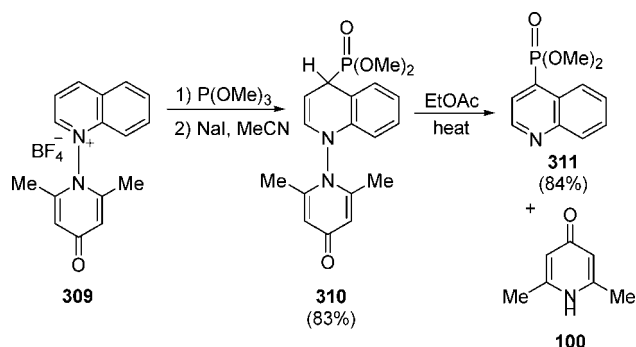
Scheme 90



Scheme 91



Scheme 92



(via the *N*-oxide). The structures of the synthesized quinolines are given in Scheme 90.

It is known that Reissert-type reactions can be applied to heterocyclic compounds.¹²⁸ The first nitrogen-containing derivatives to be tested were quinoline and isoquinoline.^{48,129} In section 2.2.1.1, the reactions on pyridine are already described,⁴⁹ but the experimental conditions were provided in more detail in the case of quinoline. In contrast with the pyridine derivatives, only 1,2-adducts of quinolines **308** (and isoquinolines) were formed in good yields (36–98%) (Scheme 91).

Katritzky et al.⁴⁶ also applied his procedure, described in section 2.2.1.1, to quinoline. Starting from *N*-(2,6-dimethyl-4-oxopyridin-1-yl)quinolinium salt **309**, the reaction led to intermediate **310** and dimethyl quinolin-4-ylphosphonate **311** in good yields (Scheme 92).

The method of Haase,^{51,52} already described for pyridines, can also be applied to quinolines. The procedure was described in section 2.2.1, and the reaction sequence for quinoline, is given here (Scheme 93). In contrast to the related dihydropyridines, it is more convenient to separate the dihydroquinolines **313** and **314** by simple column chromatography. Both dihydro isomers could be successfully deprotonated with Et₃N either in the crude reaction mixture or after column chromatography to obtain **311** and **315**. This behavior contrasts with that of related pyridine systems,⁵¹ in which only the 1,4-dihydro compounds could be deprotonated. The researchers tried to obtain disubstituted compounds by repeating their procedure using compound **311** as the starting material (as well as compounds with PPh₃-substitution on the 4-position). Unfortunately, the yields were very low.

2.4.1.2. C–P Bond Formation in Cross-Coupling Reactions with Palladium. Tolmachev et al.¹²³ synthesized diethyl 2-methyl- and diethyl 4-methylquinolin-6-phospho-

nates **319a** and **319b** through a cross-coupling reaction catalyzed by palladium. The reaction conditions for lepidine, the trivial name of 4-methylquinoline, have already been explained in section 2.2.1.4. The palladium species used was tetrakis[triphenylphosphine] palladium, and triethylamine was added as the base. The phosphonylated quinolines were obtained in reasonably good yields (Scheme 94).

Cordi et al.¹³⁰ patented their synthesis of novel 2-(1*H*)-quinolinone-3-phosphonate derivatives as excitatory amino acid neurotransmitter antagonists. These compounds are useful in the treatment of cerebral vascular accidents, cerebral or spinal trauma, epilepsy, and neurodegenerative diseases. The compounds were prepared in 5 steps, as depicted in Scheme 95 for 5,7-dichloro-2(1*H*)-quinolinone-3-carboxylic acid **320a**. Bromination in pyridine gave the 3-bromo lactam derivative **321a**, which was treated with phosphoric trichloride to give 3-bromo-2,5,7-trichloroquinoline **322a**. The next step was methoxylation of the 2-position, followed by phosphonylation toward **324a**. A palladium-catalyzed cross-coupling reaction was used to introduce the phosphonate, with diethyl phosphite and triethylamine in THF. The final step was the deprotection of compound **324a** to give the lactam functionality in **325a**. Compound **325b** was synthesized similarly. A series of analogues **326** was prepared, and their structures are also given in Scheme 95.

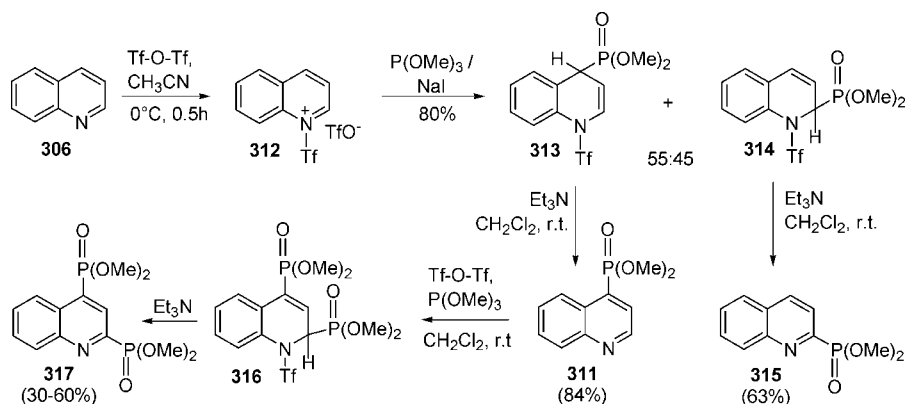
2.4.1.3. S_{RN}1. The radical-nucleophilic aromatic substitution, or S_{RN}1, has already been described in the section of the pyridines (section 2.2.1.6). This method can also be applied to quinolines, as reported by Beugelmans and Bois-Choussy.¹³¹ The photostimulated reaction of the anion of diethyl phosphite with 5-chloro-7-iodo-8-isopropoxy-quinoline **327** led predominantly to monosubstitution on the 7-position and gave compound **328** in 70% yield (shows no amebicide activity). Traces of the product with a reduced 7-position **329** were also found in the mixture. This compound **329** was also the result of the reaction when it is performed in the dark, preventing the S_{RN}1 reaction (Scheme 96).

2.4.1.4. C–P Bond Formation by Nucleophilic Attack of Metal Dialkyl Phosphite on Halogenoquinoline (Micaelis–Becker Reaction). In 1955, Burger et al.³⁵ reported the synthesis of 2-quinolylphosphonic acid **332a** from a reactive halogenoquinoline **330a** and sodium dibutyl phosphite in dry xylene. Dibutyl lepidin-2-ylphosphonate **331b** and lepidin-2-ylphosphonic acid **332b** could also be synthesized according to this same procedure (Scheme 97).

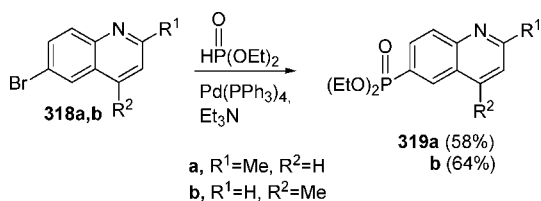
During the investigation of the reaction of methylquinoline derivatives with phosphorus pentachloride in phosphoryl chloride, and the reaction of the chlorinated product (trichloromethylquinoline) with trimethyl phosphite, phosphonylated products could be identified. While most of the substrates underwent C-alkylation during reaction with trimethyl phosphite, Kato et al.¹³² noticed the presence of dimethyl quinoline-4-phosphonates in the reaction mixtures of two compounds. When 4-chloro-2-dichloromethyl-3-nitroquinoline **333** and 4-chloro-3-nitro-2-trichloromethylquinoline **336** were treated with trimethyl phosphite under heating, either complete (**334**) or partial (**338**) phosphonylation of the 4-position occurred. (Scheme 98) These observations should not be considered as a new phosphonylation method, since the compounds were unwanted side products, but it nevertheless led to the phosphonylated heterocycles.

A new reaction of bicyclic nitroarenes with dimethyl phosphite was reported, resulting in α-amino phosphonates

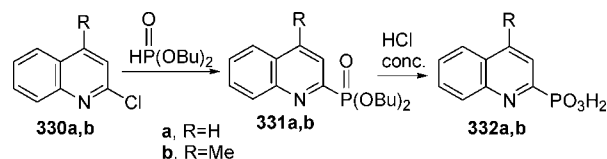
Scheme 93



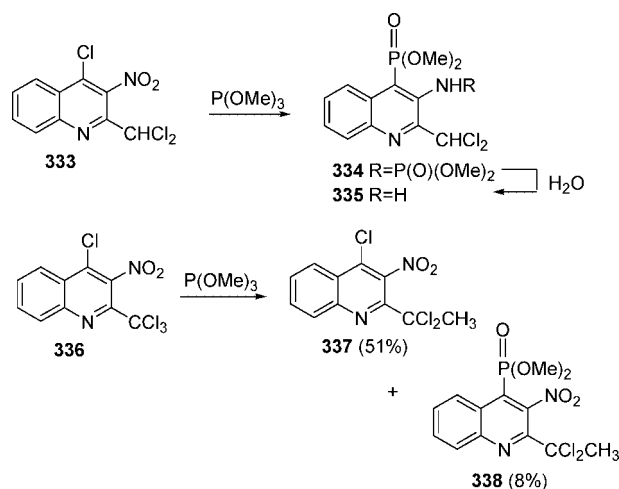
Scheme 94



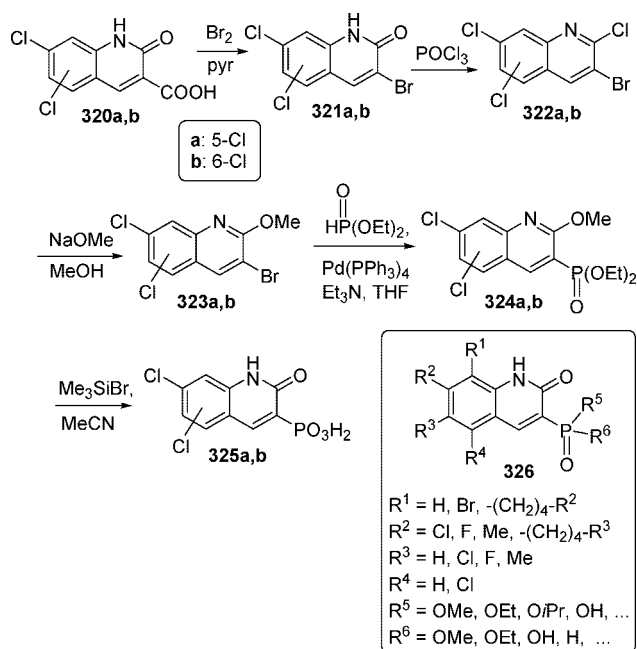
Scheme 97



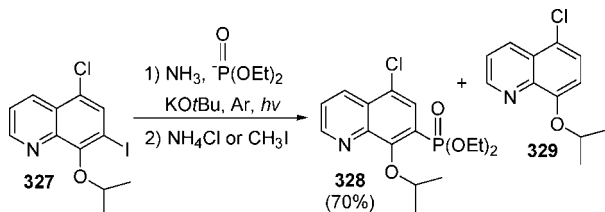
Scheme 98



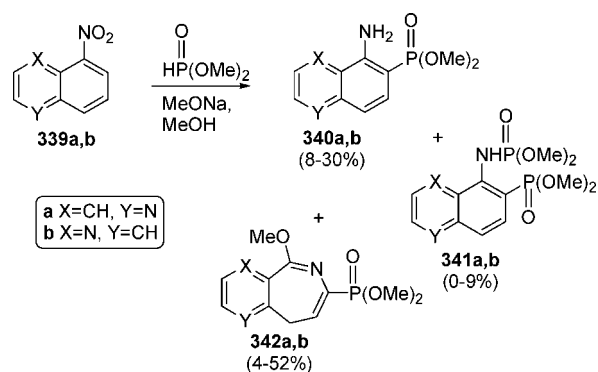
Scheme 95



Scheme 96



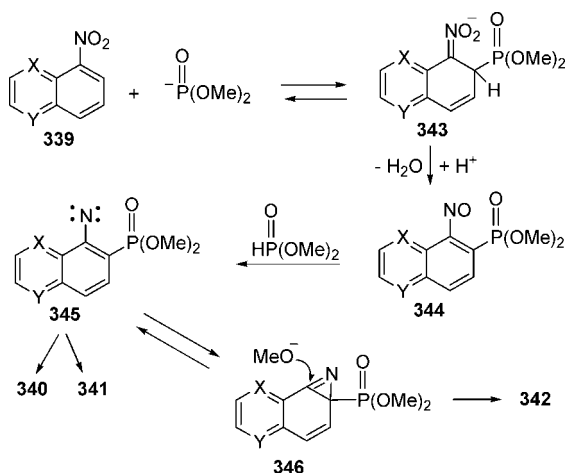
Scheme 99



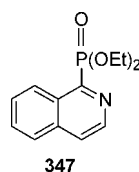
(Scheme 99).¹³³ In a strongly basic medium, the reactions proceed via addition of the phosphite anion to the nitroarenes and further transformations of the σ -complexes, also involving a nitrene intermediate. These transformations are depicted in Scheme 100.

Two different methods were evaluated. In method A, the heterocycle and dimethyl phosphite in MeOH were added dropwise to MeONa in MeOH at 5 °C and the mixture was stirred for 15–60 min followed by workup and separation. In method B, the methanolic solution of MeONa was added dropwise to the heterocycle and dimethyl phosphite in MeOH at 40 °C. After 10 min of reflux, the workup was the same as for method A. Procedure B gave mainly mixtures of **340**

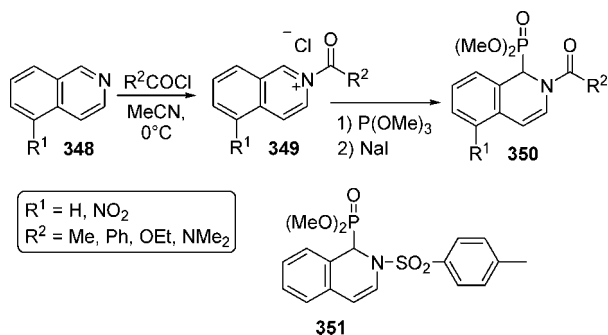
Scheme 100



Scheme 101



Scheme 102



and **341**. The latter were readily hydrolyzed to give **340**, so it can be considered as a route to aminoaryl phosphonates.

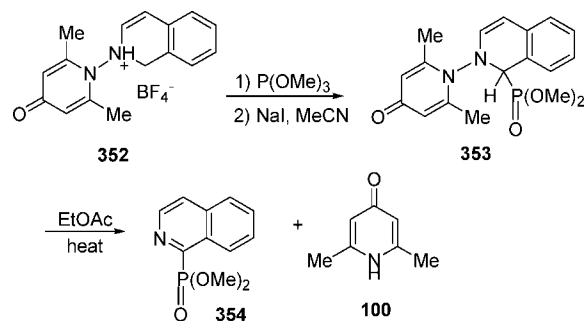
2.4.2. Isoquinoline

The method Redmore developed for the synthesis of pyridine-2-ylphosphonates³⁷ (section 2.2.1.1) and phosphonylated quinolines (section 2.4.1) has also been used to prepare diethyl isoquinolin-1-ylphosphonate **347** (depicted in Scheme 101) and was described in a series of patents.^{29,39}

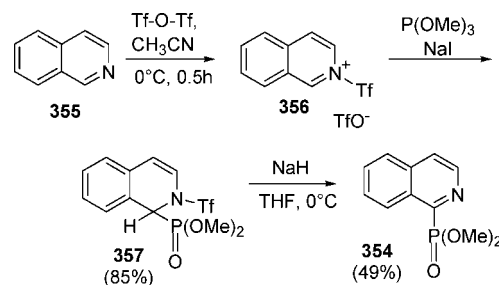
Reissert-type reactions were already discussed for pyridines and quinolines and were also performed on isoquinolines by Akiba et al.^{48,49} and other research groups.¹²⁸ Only 1,2-adducts were formed here, and the method is also applicable to the synthesis of *N*-sulfonyl derivatives, such as **351**. The derivatives were synthesized in good yields (22–94%) and are depicted in Scheme 102.

Katritzky et al.⁴⁶ used the method of a heterocyclic cation as an activation step for the aromatic compound, already described in section 2.2.1.1, also on *N*-(2,6-dimethyl-4-oxopyridin-1-yl)isoquinolinium salts. This method leads to intermediates **352** and **353**. The latter was, due to instability, isolated in admixture with the final product **354**. Heating in ethyl acetate resulted in 53% overall yield of **354** (Scheme 103).

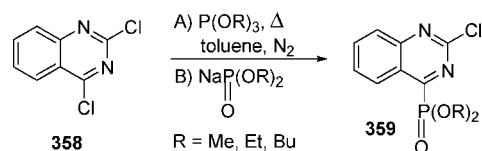
Scheme 103



Scheme 104



Scheme 105



The 1,2-dihydroisoquinoline **354** can be obtained by methods earlier described for pyridine and quinoline (sections 2.2.1.1 and 2.4.1, respectively).^{51,52} In the case of isoquinoline, however, it is necessary to use a stronger base than Et₃N for the deprotonation step, namely, NaH at −20 °C. Subsequent quenching of the reaction mixture and aqueous workup yielded compound **354** in 49% (Scheme 104).

2.4.3. Quinazoline

Michaelis–Arbuzov reaction of 2,4-dichloro-quinazoline **358** with trialkyl phosphites or Michaelis–Becker reaction with sodium dialkyl phosphite salts gave the 4-substituted derivatives **359** (R = Me, Et, or *n*Bu) in moderate-to-good yields (37–78%). No substitution of the 2-position was observed according to Issleib et al. (Scheme 105).¹³⁴

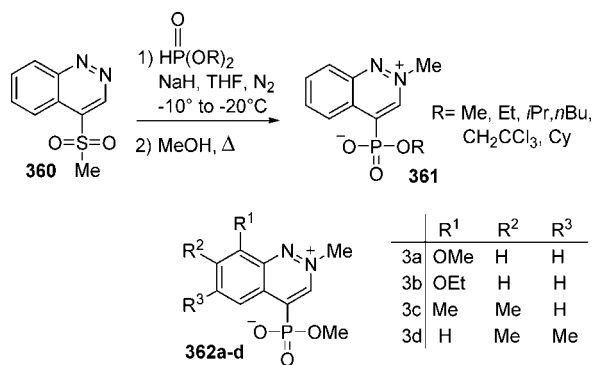
2.4.4. Cinnoline

A patent appeared¹³⁵ on the synthesis of herbicidal 2-methyl-4-phosphonocinnolinium hydroxide inner salts. A THF solution of 4-(methylsulfonyl)cinnoline **360** was treated with a THF solution containing dialkyl phosphite and NaH under a nitrogen atmosphere. A series of analogues was synthesized with various ester groups (**361**) and different substituents (**362a–d**) (Scheme 106).

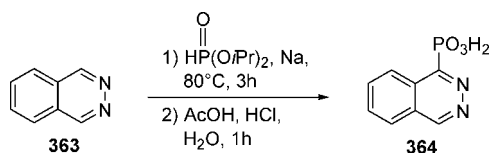
2.4.5. Phthalazine

Diisopropyl phosphite and sodium cause an unexpected nucleophilic substitution in *o*-phthalazine.¹³⁶ When an excess of diisopropyl phosphite is used, followed by hydrolysis of the mixture with acetic acid and concentrated hydrochloric

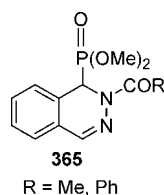
Scheme 106



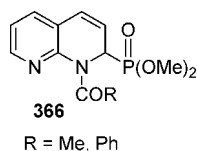
Scheme 107



Scheme 108



Scheme 109



acid, the reaction results in the formation of 1-phthalazine-phosphonic acid **364** in 24% yield (Scheme 107).

The Reissert reaction has been described in various previous sections^{48,49} and could also be applied to phthalazine.¹²⁸ Acylation and the corresponding cations with various acyl chlorides (RCOCl ; $\text{R} = \text{Me, Ph}$) and subsequent treatment with trimethyl phosphite in the presence of sodium iodide gave dimethyl phosphonates **365** (Scheme 108).

2.4.6. [1,8]Naphthyridine

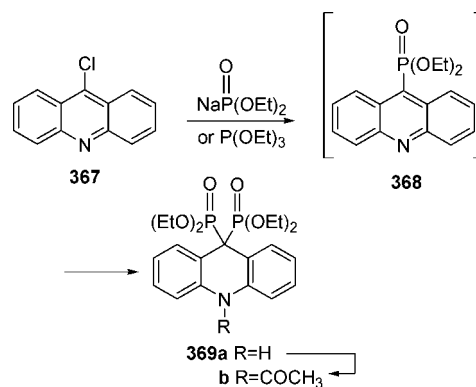
On [1,8]naphthyridine too, the Reissert reaction was applied.¹²⁸ This resulted in the synthesis of 1,2-adducts only. Dimethyl phosphonates **366** could be prepared by using this method (Scheme 109).

2.5. Various Annulated Compounds

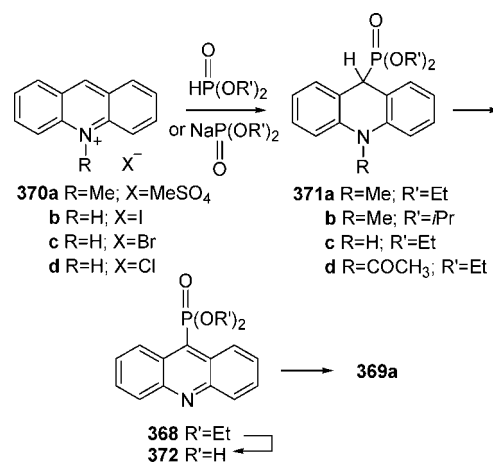
2.5.1. Acridine

In 1947, Kosolapoff described a Michaelis–Arbuzov reaction on 9-chloroacridine **367** with triethyl phosphite, yielding diethyl acridyl-9-phosphonate **368**.¹⁰⁰ Redmore repeated this reaction, but only the diphosphonate **369a** could be isolated in 34% yield.¹³⁷ No product corresponding to that described by Kosolapoff was formed. Redmore found that this diphosphonate is the product of the reaction of **368** with diethyl sodium phosphonate, suggesting that diethyl acridyl-

Scheme 110



Scheme 111

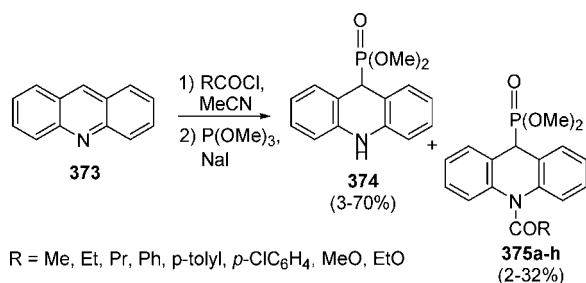


9-phosphonate **368** is the initial product of Arbuzov and Michaelis–Becker reactions of 9-chloroacridine, but undergoes facile nucleophilic addition reactions. The diphosphonate **369a** is readily acetylated to produce the acetate **369b**¹³⁷ (Scheme 110).

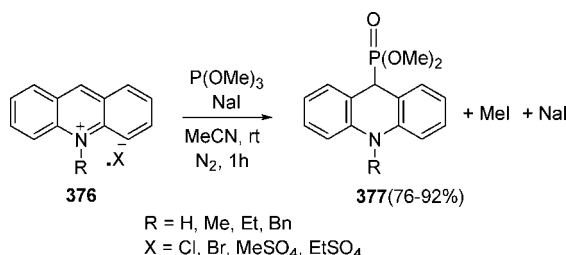
Acridine undergoes 1,4-addition of phosphorus nucleophiles; thus, dihydroacridylphosphonate **371c** is formed in quantitative yield by the addition of diethyl phosphonate to acridine in the presence of catalytic amounts of base. This same phosphonate **371c** and the homologues **371a** and **371b** are also the products (in 40–68% yield) of the addition of dialkyl sodium phosphonate to the salts **370a–c**.^{137,39a} Dehydrogenation of the diethyl phosphonate **371c** was achieved upon heating in benzene with chloranil to yield 66% of **368**, which itself will add diethyl phosphonate to yield the diphosphonate **369a**, as described earlier. Hydrolysis of **368** gave acridyl-9-phosphonic acid **372** (Scheme 111).

Another route toward acridylphosphonates, already described for pyridine and quinoline, was reported without experimental details.⁴⁷ A Reissert-type reaction with dihydroacridine **371d**, a trialkyl phosphite, and acetyl chloride resulted in acridyl-9-phosphonic acid **372** (Scheme 111). Attempts to repeat this reaction failed however, suggesting that the reaction has not taken place as claimed.¹³⁸ This was confirmed by a report on the reaction of *N*-acylacridinium salts with trimethyl phosphite. The researchers determined that this reaction results in mixtures of dimethyl *N*-acylacridin-9-ylphosphonates **375a–h** and the *N*-unsubstituted acridin-9-ylphosphonate **374** in different ratios (Scheme 112).^{139,140} The Reissert-type reaction was already discussed in previous sections for various heterocycles.^{48,128}

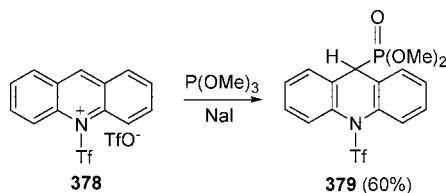
Scheme 112



Scheme 113



Scheme 114

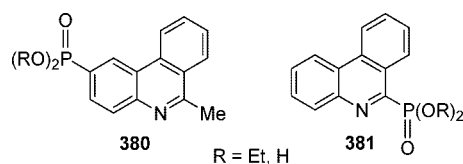


A different route is based on an Arbuzov rearrangement.⁴⁷ Dialkyl 9-acridinylphosphonates such as **368** ($\text{R}' = \text{Et, Bu, } n\text{Pr}$) were prepared by reaction of acridinium chloride **370d** with trialkyl phosphite to give dihydroacridines such as **371a–d** (with $\text{R}' = \text{Et, Bu, or } n\text{Pr}$ and $\text{R} = \text{H}$), followed by aromatization with chloranil in benzene (Scheme 111). Deprotection to the corresponding phosphonic acid **372** was also reported. While investigating the chemoluminescence in autoxidation of phosphonate carbanions, Motoyoshiya et al.¹⁴¹ prepared weakly fluorescent 9-phosphonoacridines such as **368** in good yields (41–70%). The synthesis is very similar to the one just described,⁴⁷ except for the use of the hydrobromide salt as starting material and different trialkyl phosphites (P(OMe)_3 , P(OEt)_3 , P(OEt)(OiPr)_2 , and P(OEt)(OPh)_2).

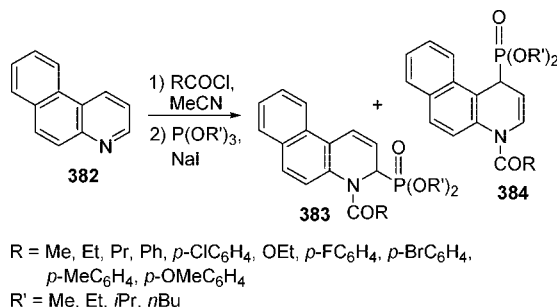
Akiba et al.¹⁴² treated acridinium cations **376** with trimethyl phosphite in the presence of sodium iodide in acetonitrile. This Michaelis–Arbuzov reaction took place at room temperature and gave the corresponding phosphonates **377** in high yields (76–92%). The results are given in Scheme 113. Varveri et al.¹⁴³ also synthesized phosphonate **377** ($\text{R} = \text{Me}$, $\text{X} = \text{MeSO}_4$; **376** (53%); **377** (83%)) in order to perform Horner–Wittig reactions on these derivatives. In this case, dimethyl phosphite was used instead of trimethyl phosphite as the phosphorus species.

Haase et al. tried to synthesize dimethyl 9-acridinylphosphonate according to the same procedures as for pyridine, quinoline, and isoquinoline.⁵² It was impossible to isolate the dihydro species **379**, since all attempts to purify resulted in decomposition. The researchers verified the presence of compound **379** by ^1H NMR and MS but made no attempts to deprotonate it (Scheme 114).

Scheme 115



Scheme 116



2.5.2. Phenanthridine

The procedure Redmore developed³⁷ for phosphonylated pyridines was already described a couple of times for other heterocycles (sections 2.2.1.1, 2.4.1.1, 2.4.2,...) and could also be applied to *N*-alkoxyphenanthridinium cations to synthesize diethyl 6-methylphenanthridin-2-ylphosphonate **380** and diethyl phenanthridin-6-ylphosphonate **381** and their corresponding phosphonic acids (Scheme 115).^{39b}

The Reissert reaction, as earlier described,⁴⁸ was performed on phenanthridine by Suezawa et al.¹²⁸ Phenanthridine was acylated with different acyl chlorides (RCOCl , $\text{R} = \text{Me, Et, Ph}$) to give the corresponding cations and was subsequently phosphonylated with trimethyl phosphite. These reactions resulted in 1,2-addition of the phosphite.

2.5.3. Benzo[*f*]quinoline

The reaction of benzo[*f*]quinoline **382** with acyl chloride and trialkyl phosphite has already been described for various other azaheterocycles.^{48,49,128,142} When benzo[*f*]quinoline **382** was used as a substrate, the corresponding 1,2-adducts **383** (α -phosphonates) and 1,4-adducts **384** (γ -phosphonates) were formed.¹⁴⁴ The ratio of **383/384** decreased as the bulkiness of R' increased (Scheme 116).

2.5.4. Phenanthroline

The same Reissert-type reaction as described in previous sections was also performed on *N*-phenanthroline salts.^{128,139} In the case of 1,7-phenanthroline **385**, a mixture of 1,2-adducts **387** and 1,4-adducts **386** was formed. For 4,7-phenanthroline **388**, the reactions resulted in a mixture of regio- and stereoisomeric diphosphonates **389** and **390** (Scheme 117, Table 5). The isomeric adducts were separated by column chromatography. Other research groups reported different ratios.¹²⁸

Similarly, the treatment of 4,7-phenanthroline with 4-substituted benzoyl chlorides and trimethyl phosphite in the presence of NaI gave phosphonates *cis*- and *trans*-**391**, *cis*- and *trans*-**392**, **393**, and **394** (Scheme 118).¹⁴⁵

2.5.5. Carbazole

Free phosphonyl radicals, generated from diethyl phosphite and *t*-butyl peroxide, react with carbazole **395** to give

Scheme 117

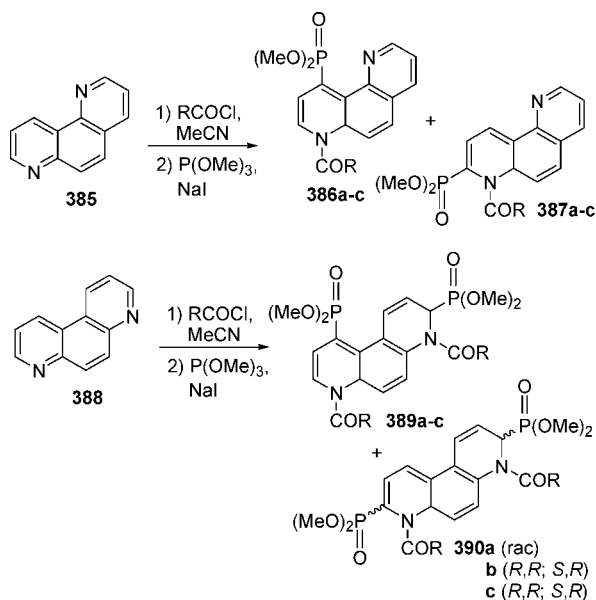
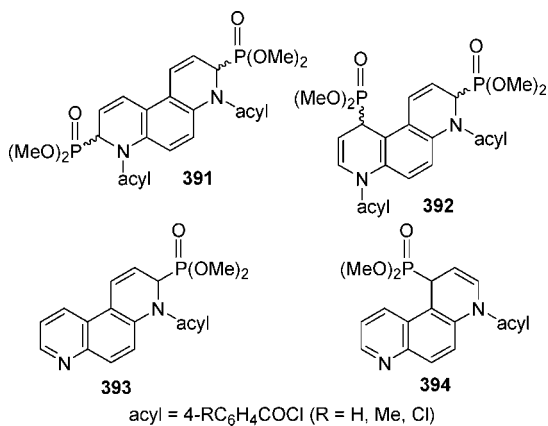


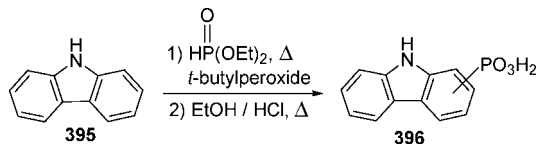
Table 5. Details, Ratios, and Yields for Scheme 117

substrate	products	R	overall yield (%)	ratio 386/387
1	386a , 387a	Me	44	52:48
1	386b , 387b	Ph	52	50:50
1	386c , 387c	EtO	90	36:64
2	389a , 390a	Me	8	
2	389b , <i>R,R</i> - 390b , <i>S,R</i> - 390b	Ph	37	
2	389c , <i>R,R</i> - 390c , <i>S,R</i> - 390c	EtO	79	

Scheme 118



Scheme 119

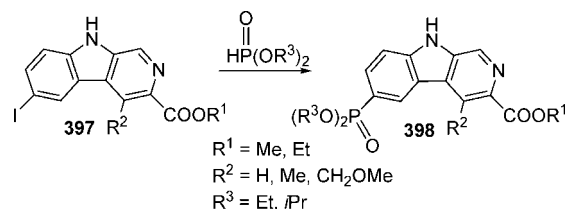


phosphonic acid derivatives.^{7b} Subsequent hydrolysis resulted in the deprotection of the phosphonate into the corresponding phosphonic acid **396**. The wide melting point range of the product indicated that it consisted a mixture of isomeric phosphonic acids **396** (Scheme 119).

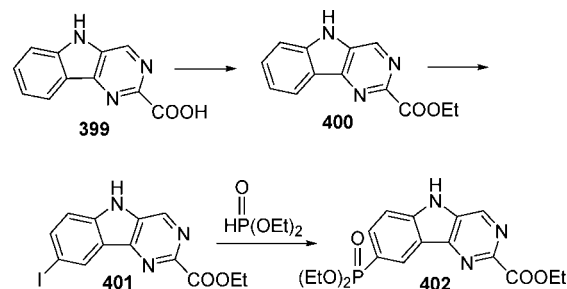
2.5.6. β -Carboline

The synthesis of dialkyl β -carbolin-6-ylphosphonates **398** and one dialkyl β -carbolin-5-ylphosphonate was reported in

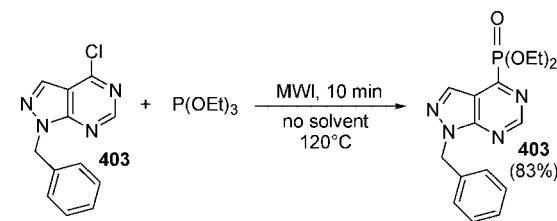
Scheme 120



Scheme 121



Scheme 122



a patent.¹⁴⁶ Treatment of the halogenated compounds **397** with dialkyl phosphites resulted in the phosphonates **398**; no experimental details were provided (Scheme 120). It appeared that 3-substituted β -carbolines were useful as tranquilizers, anticonvulsants, antiaggressives, and anxiolytics. Another patent also reported the synthesis of unsubstituted dialkyl β -carbolin-3-ylphosphonates.¹⁴⁷

2.5.7. Pyrimido[5,4-*b*]indoles

The next synthesis deals with 5*H*-pyrimido[5,4-*b*]indoles and the substitution of such compounds. The starting carboxylic acids **399** are esterified to form **400** are then halogenated and subsequently phosphonylated by reaction with diethyl phosphite. This yielded the envisaged end product **402**, but no reaction details were provided (Scheme 121).¹⁴⁸

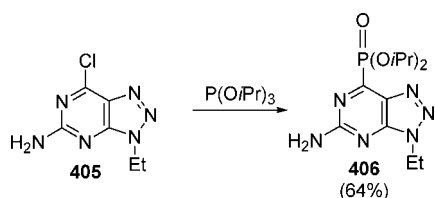
2.5.8. Pyrazolopyrimidine

The microwave-assisted $\text{S}_{\text{N}}\text{Ar}$ -Arbuzov reaction can be used to generate 4-phosphonylated pyrazolopyrimidine **404** from the corresponding 4-chloropyrazolopyrimidine **403**.¹²⁷ The conditions are similar to the ones already described in section 2.3.3, and this further demonstrates the generality of the reaction to generate phosphonylated heterocyclic scaffolds (Scheme 122).

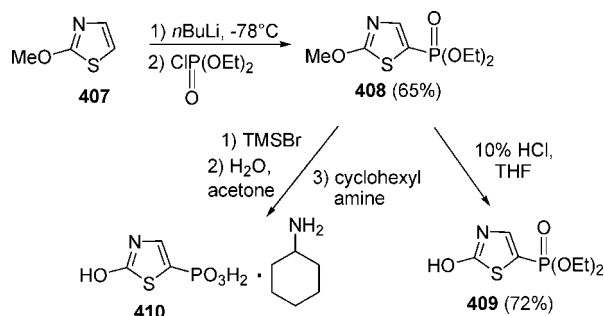
2.5.9. Triazolopyrimidine

An Arbuzov reaction with triisopropyl phosphite on the halogenated compound **405** yields the triazolopyrimidylphosphonate **406** in 64% yield (Scheme 123).¹⁴⁹

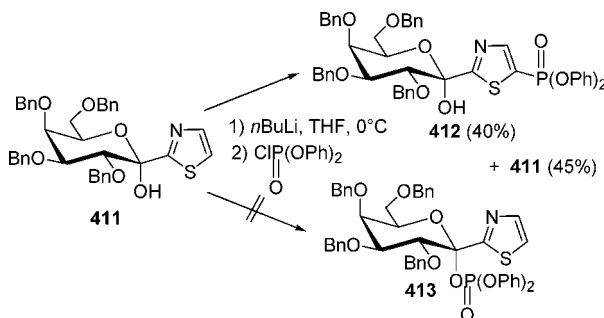
Scheme 123



Scheme 124



Scheme 125



3. Aromatic Heterocycles with N and Other Heteroatoms

The most common heterocycles with other heteroatoms apart from nitrogen are discussed in this section; very rare compounds are not included.

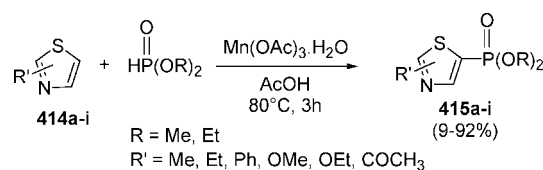
3.1. Five-Membered Rings

3.1.1. Thiazole

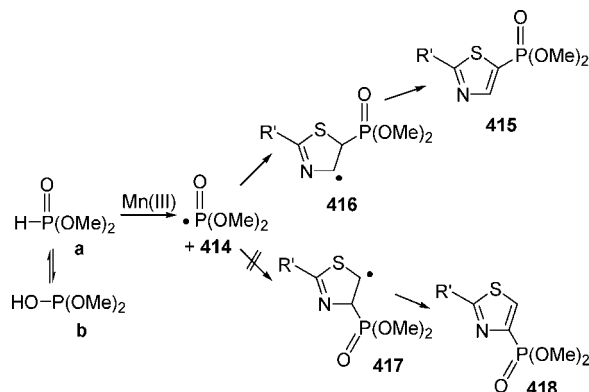
The same procedure as previously described for 1,2,4-triazol-5-ylphosphonates (section 2.1.4) could also be applied to synthesize 2-hydroxythiazol-5-ylphosphonic acid **410**, starting from 2-methoxythiazole **407** (prepared from 2-bromothiazole).²⁸ The low-temperature metalation of **407** can be achieved selectively at the 5-position with *n*-BuLi, and subsequent electrophilic trapping with diethyl chlorophosphate produces diethyl 2-methoxythiazol-5-ylphosphonate **408**. Removal of the methyl protecting group is accomplished with HCl; conversion to the corresponding phosphonic acid **410** as its cyclohexylammonium salt results from treatment with TMSBr (Scheme 124).

During the synthesis of oligosaccharides by iterative glycosidation of ketoses, a thiazolyl phosphonate **412** was isolated as the unexpected end product together with unreacted thiazolylketose **411**.¹⁵⁰ Treatment of **411** with butyllithium and diphenyl chlorophosphate did not result in the expected *O*-phosphate derivative **413** but gave a mixture of 40% thiazolyl phosphonate **412** and 45% **411** (Scheme 125).

Scheme 126



Scheme 127



The radical phosphonylation method using dimethyl or diethyl phosphites and $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ as the coupling agents was already described for pyrroles in section 2.1.1.2.⁹ The procedure applied to the thiazoles is the same as for pyrroles, and several thiazoles were tested to investigate the phosphonylation regioselectivity (Scheme 126). Reaction on the unsubstituted thiazole indicates that the 2-position of thiazole is most reactive for phosphonylation, followed by the 5-position. The 4-position is the least reactive site. No double or triple phosphonylation products were detected from the reaction of unsubstituted thiazoles.

A mechanism for the regioselective phosphonylation is proposed in Scheme 127. Reaction of $\text{Mn}(\text{OAc})_3$ with tautomer **a** gives the phosphonyl radical. This radical could attack the thiazole ring at the 4- or 5-position. In compound **416**, the radical next to an imine function is more stable than the radical in compound **417**, which is adjacent to a sulfur atom. Formation of **416** is more favorable and leads to 5-phosphonylated thiazole **415** via air or Mn(III) oxidation to regain the aromaticity of the thiazole ring.

3.1.2. Isothiazole

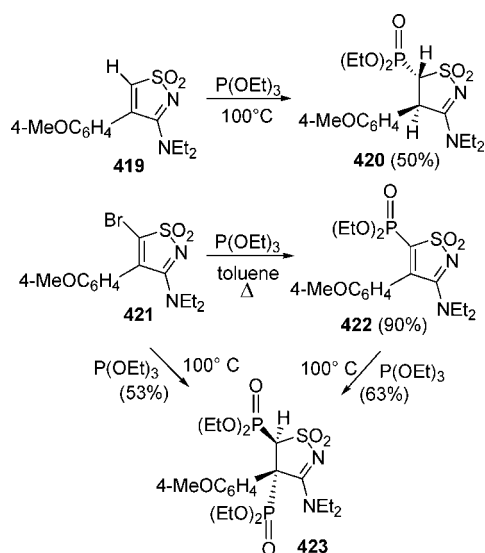
Isothiazolylphosphonates could be synthesized by treatment of isothiazoles with triethyl phosphite.¹⁵¹ Reaction of **419** with triethyl phosphite as the solvent gave compound **420** as the sole reaction product. When the reaction was performed on **421** in toluene and with an equimolecular amount of triethyl phosphite, compound **422** was obtained through an addition–elimination process. The latter was transformed into **423** via reaction with triethyl phosphite as the solvent at 110 °C. The same product **423** could be obtained directly by heating **421** in triethyl phosphite as the solvent (Scheme 128).

3.2. Annulated Six- and Five-Membered Rings

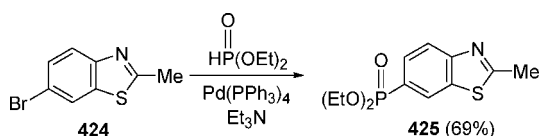
3.2.1. Benzothiazole

Tolmachev et al. prepared a phosphonylated benzothiazole **425** according to the same procedure they used for benzimidazoles¹²³ (see section 2.3.2). They used a palladium-catalyzed coupling reaction similar to the one presented by

Scheme 128



Scheme 129



Hirao.¹⁴ Triethylamine was added as a base, and the desired diethyl 2-methyl-1,3-benzothiazol-6-ylphosphonate **425** was synthesized in good yield (Scheme 129).

4. Conclusion

Aminophosphonates and aminophosphonic acids have already proven to be of great interest in different fields such as agrochemical and medicinal chemistry and also for metal complexation. Because of these interesting properties, the purpose to develop many of the described syntheses of aromatic azaheterocyclic phosphorus compounds was to determine their physiological activity. A few positive results have already been reported; however, this continuing research will certainly result in the revelation of more interesting properties by testing the boundaries of the synthetic possibilities.

5. Acknowledgments

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6. Abbreviations

Ac	acetyl
Ar	aryl
AIBN	azoisobutyronitrile
Bn	benzyl
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	dimethylformamide
LDA	lithium diisopropylamide
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
MWI	microwave irradiation
PG	protecting group
Ph	phenyl

PMP	1,2,2,6,6-pentamethylpiperidine
PPTS	pyridinium <i>p</i> -toluenesulfonate
Py	pyridine
TBDMS	<i>tert</i> -butyldimethylsilyl
Tf	triflyl
THF	tetrahydrofuran
THP	tetrahydropyran
Thy	thymine
TMSBr	trimethylsilyl bromide
TMSCl	trimethylsilyl chloride
TMSI	trimethylsilyl iodide

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