Multicomponent reactions: A simple and efficient route to heterocyclic phosphonates

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Abstract
Multicomponent reactions (MCRs) are one of the most important processes for the preparation of highly functionalized organic compounds in modern synthetic chemistry. As shown in this review, they play an important role in organophosphorus chemistry where phosphorus reagents are used as substrates for the synthesis of a wide range of phosphorylated heterocycles. In this article, an overview about multicomponent reactions used for the synthesis of heterocyclic compounds bearing a phosphonate group on the ring is given.

Introduction
Heterocyclic rings are found in many naturally occurring compounds and they compose the core structures of many biologically active scaffolds as well as some industrial compounds [1-3]. On the other hand, phosphonic acid and its related derivatives are considered as potential bioisosters of the corresponding carboxylic acids [4]. Thus, the incorporation of phosphoryl groups into the heterocyclic systems has led to an important class of organophosphorus compounds that has attracted the attention of both industrial and medicinal chemists [5-12]. Many efforts have been made to prepare these bioactive compounds with a variety of publications over the last 60 years [13]. There are two general approaches to the synthesis of heterocyclic phosphonates: (a) the direct electrophilic or nucleophilic phosphorylation of the heterocyclic systems and (b) the ring closure of phosphorylfuntionalized substrates through cyclization or cycloaddition reactions [14-19].

Multicomponent reactions (MCRs) constitute one of the most efficient tools in modern synthetic organic chemistry, since they have all features that contribute to an ideal synthesis: high atom efficiency, quick and simple implementation, time and energy saving, environment-friendly and they offer a target and diversity-oriented synthesis [20]. Therefore, the development of new multicomponent reactions towards biomedical and industrial scaffolds is inevitable at the present time. Furthermore, the combination of established multicomponent reactions with post-reaction transformations opens the way towards a vast number of diverse and complex products. Some of these post-MCR
transformations are: intramolecular cycloaddition reactions, Knoevenagel condensations, metathesis reactions, aza-Wittig reactions, Mitsunobu reactions, etc. [21].

Up to now, two review articles have been reported on azaheterocyclic phosphonates [22,23], but no overview article about the multicomponent synthesis of phosphono-substituted heterocycles has been reported so far. This review focuses on general multicomponent reactions as well as on modified MCR towards heterocyclic phosphonates. It is organized by the reaction types and covers literature published up to September 2015.

Review
1 Biginelli condensation
The classical Biginelli condensation involves the reaction of an aldehyde 1 with urea (2) and a β-ketoester 3 under acidic conditions in refluxing ethanol to yield 3,4-dihydropyrimidin-2-one derivatives 4 (Scheme 1) [24].

![Scheme 1: The Biginelli condensation.](image)

Although, a large number of CH-acidic carbonyl compounds such as β-diketones, β-keto thioesters, acetoacetamides and nitroacetone have been shown to participate in the classical Biginelli reaction [25], β-ketophosphonates 6 were found to be unreactive in similar conditions [26]. However, Yuan et al. developed a modified Biginelli condensation by using ytterbium triflate as a catalyst (Scheme 2) [26] and the 3,4-dihydropyrimidin-2-one derivatives 4 were formed in 15–58% yields depending on the structure of the β-ketophosphonate 6 and aldehyde 5. Based on their investigations, aliphatic aldehydes including propionaldehyde and butyraldehyde were resistant to this reaction.

The trimethylchlorosilane-mediated one-pot reaction of diethyl (3,3,3-trifluoropropyl-2-oxo)phosphonate (8) with aryl aldehydes 9 and urea under Biginelli conditions has been presented by Timoshenko et al. (Scheme 3) [27]. The resulting 4-hydroxytetrahydropyrimidin-2-ones 10 were unstable and underwent dephosphorylation to give dihydropyrimidin-2-ones 11 after one week at room temperature. Also, heating of either the reactants or product 10 in the presence of acetic acid led to the formation of dihydropyrimidin-2-ones 11 (Scheme 3).

However, the authors successfully used trialkyl orthoformates 13 to produce dialkyl (2-oxo-4-(trifluoromethyl)-1,2-dihydropyrimidin-5-yl)phosphonates 14 which were converted to dialkyl (4-alkoxy-2-oxo-4-(trifluoromethyl)-1,2,4-tetrahydropyrimidin-5-yl)phosphonates 15 through the nucleophilic addition of the liberated alcohol to the electrophilic double bond of the CF₃−C=N segment (Scheme 4).

Idris Essid and Soufiane Touil showed that the Biginelli condensation of β-ketophosphonates was highly sensitive to the nature of solvents, acid catalysts and reactants [28]. They found that the use of inorganic acids including HCl and H₂SO₄ or Lewis acids such as SnCl₂, FeCl₃ and VCl₃, as well as heterogeneous catalysts including silica gel supported sulfuric acid and sodium hydrogen sulfate did not affect this reaction. Also, the reaction in the presence of p-toluenesulfonic acid (TsOH), in aprotic solvents proceeded with much better yields than in protic solvents. When diethyl (2-oxopropyl)phosphonate and 4-nitrobenzaldehyde were treated in the presence of 50 mol % TsOH in acetonitrile, 5-phosphonato-3,4-dihydropyrimidin-2-one 18 was obtained in excellent yield (Scheme 5).

![Scheme 2: The Biginelli reaction of β-ketophosphonates catalyzed by ytterbium triflate.](image)
Scheme 3: Trimethylchlorosilane-mediated Biginelli reaction of diethyl (3,3,3-trifluoropropyl-2-oxo)phosphonate.

Scheme 4: Biginelli reaction of dialkyl (3,3,3-trifluoropropyl-2-oxo)phosphonate with trialkyl orthoformates and urea.

Scheme 5: p-Toluenesulfonic acid-promoted Biginelli reaction of β-ketophosphonates, aryl aldehydes and urea.
Kabachnik–Fields reaction and its post-condensation modifications

The one-pot three-component reaction between aldehydes 19 (or ketones), amines 20 and dialkyl phosphonates 21 to afford α-aminophosphonates 22 is traditionally known as the Kabachnik–Fields reaction. This reaction was first reported in 1952 by Kabachnik, Medved and Fields (Scheme 6) [29,30].

Due to their wide range of biological activities, α-aminophosphonates have been extensively investigated and several reviews about their syntheses through the Kabachnik–Fields reaction have been reported [31-33]. However, an important feature of this reaction is that it provides an efficient route to phosphonylated heterocycles. The different applications of the Kabachnik–Fields reaction in the preparation of phosphonylated heterocycles can be classified into two major categories: a) phosphorylation of heterocyclic ketones through a classic Kabachnik–Fields reaction and b) synthesis of heterocyclic phosphonates through modification of the products obtained by the Kabachnik–Fields reaction.

2.1 Phosphorylation of the parent heterocycles through a traditional Kabachnik–Fields reaction

Heterocycloalkanones may be used as carbonyl components in the Kabachnik–Fields reaction to give cyclic α-aminophosphonates. Unfortunately there are only a few examples of Kabachnik–Fields reactions of heterocycloalkanones in the literature. The tetra(tert-butyl)phthalocyanine–AlCl complex catalyzed three component reaction of N-Boc-piperidin-4-one (23) with (EtO)2P(O)H (24) and benzylamine (25) afforded the cyclic α-aminophosphonate 26 in 99% yield (Scheme 7) [34].

The reaction of isatin (27) with diethyl phosphate and benzylamine under similar conditions gave the corresponding α-aminophosphonate 28 in 90% yield together with small amounts of α-hydroxyphosphonate 29 as a side product (Scheme 8).

The one-pot reaction of substituted isatins 30 with aniline (32) and dimethyl- or diethyl phosphate under solvent-free conditions in the presence of magnetic Fe3O4 nanoparticle-supported
phosphotungstic acid as a recyclable catalyst at 80 °C furnished α-aminophosphonates 33 in yields from 80% to 98% depending on the reaction time and the structure of the dialkyl phosphate and isatin (Scheme 9) [35].

In this way a one-pot three-component reaction between 1-tosylpiperidine-4-one (34), aromatic amines 35 and diethyl phosphonate in the presence of magnesium perchlorate as a catalyst, under neat conditions at 80 °C afforded α-aminophosphonates 36 in good yields (Scheme 10). Some of the resulting α-aminophosphonates showed insecticidal activity against Plutella xylostella [36].

An asymmetric synthesis of heterocyclic α-aminophosphonates has been reported by Fadel et al. [37]. Their studies showed that the three-component reaction of N-Boc-3-piperidinone (37), (S)-configured amines 39 and triethyl phosphite (38), in the presence of 2 equiv of AcOH and 0.8 equiv of MgSO₄ at 50 °C afforded a 60:40 diastereomeric mixture of α-aminophosphonates (R,S)-40 and (S,S)-41 in 75% combined yield. The cleavage of the N-Boc group followed by removal of the benzyl groups and acidic hydrolysis of the resulting (α-amino-3-piperidinyl)phosphonic acids (R)-44 and (S)-45 led to enantiopure α-amino-3-piperidinylphosphonic acids (R)-44 and (S)-45 in good yields (Scheme 11).

2.2 Construction of heterocyclic phosphonates via post-condensation modification of Kabachnik–Fields reaction

2.2.1 2-Pyrrolidinylphosphonate: Post-condensation modifications of Kabachnik–Fields reaction products usually rely on transformations of functional groups present in the formed α-aminophosphonates or by the use of additional reagents. One of the most important sequences for the rapid access of heterocyclic phosphonates is the combination of the Kabachnik–Fields reaction with a subsequent ring closure. Thus, the one-pot reaction of 5-chloro-2-pentanone (46) with ammonia and diethyl phosphonate in ethanol lead to the non-isolable intermediate 47 which was directly converted to diethyl (2-methyl-2-pyrrolidinyl)phosphonate 48 by ring closure through an intramolecular nucleophilic substitution (Scheme 12). Subsequent oxidation of 48 with m-chloroperbenzoic acid afforded the corresponding N-oxide 49 which was used for the in vitro and in vivo spin trapping of hydroxyl and superoxide radicals [38].

2.2.2 2-Phosphono-6-oxazolopiperidines: An asymmetric Kabachnik–Fields reaction between (R)-(−)-phenylglycinol (50), glutaraldehyde (51) and triethyl phosphite has been reported by Royer et al. The reaction furnished a diastereomeric mixture of 2-phosphono-6-oxazolopiperidines 52 with 58%
Scheme 11: An asymmetric version of the Kabachnik–Fields reaction for the synthesis of α-amino-3-piperidinylphosphonic acids.

Scheme 12: A classical Kabachnik–Fields reaction followed by an intramolecular ring-closing reaction for the synthesis of diethyl (2-methyl-2-pyrroldidinyl)phosphonate.

Scheme 13: Synthesis of (S)-piperidin-2-phosphonic acid through an asymmetric Kabachnik–Fields reaction.
Scheme 14: A modified diastereoselective Kabachnik–Fields reaction for the synthesis of isoindolin-1-one-3-phosphonates.

Scheme 15: A microwave-assisted Kabachnik–Fields reaction toward isoindolin-1-ones.

lyst-free conditions at 80 °C afforded (3R,1’S)-isoindolin-1-one-3-phosphonates 57 and (3S,1’S)-isoindolin-1-one-3-phosphonates 58. The best results concerning yield and selectivity were obtained with (S)-methylbenzylamine that furnished isoindolin-1-one-3-phosphonates 57 and 58 in 75% yields and a 95:05 diastereoisomeric ratio.

The same research group found a useful method for the synthesis of isoindolin-1-one-3-phosphonates from aromatic amines [41]. The one-pot reaction of aniline 59 with formylbenzoic acid (55) and dimethyl phosphonate (31) under the above-mentioned conditions at 90 °C afforded the desired isoindolin-1-one-3-phosphonates 60 in only 14% yields after five days. Noteworthy, the treatment of the same reaction mixture under microwave irradiation at 90 °C gave the expected product 60 in 77% yields after several minutes. Subsequently, the isoindolin-1-one-3-phosphonates 60 were dephosphorylated by treatment with lithium aluminum hydride to give isoindolin-1-ones 61 (Scheme 15).

Also the Kabachnik–Fields reaction of formylbenzoic acid (55), dimethyl phosphonate and amines 62 or 66 followed by subsequent Horner–Wadsworth–Emmons reaction of the resulting cycloadducts 63 and 67 with arylaldehydes 64 or 68 afforded the corresponding 3-arylmethylenoiisoindolin-1-ones 65 and 69, respectively (Scheme 16) [42,43].

Recently, an efficient method was developed for the synthesis of ethyl (2-alkyl- and 2-aryl-3-oxoisoiindolin-1-yl)phosphonates 71 from 2-formylbenzoic acid (55), triethyl phosphate and amines 70 using OSU-6, a novel MCM-41-type hexagonal mesoporous silica, as a catalyst (Scheme 17) [44]. The important advantages of this methodology is that the (3-oxoisoiindolin-1-yl)phosphonates 71 are obtained in high yields from benzylic, aliphatic and aromatic amines possessing both, electron-donating and electron-withdrawing groups, in shorter reaction times with minimum purification requirements. Also, the catalyst can be used for up to four reaction cycles without significant loss of activity.

An efficient method for the synthetic preparation of diverse (2H-isoindol-1-yl)phosphonates 74 is an FeCl$_3$-catalyzed Kabachnik–Fields reaction of 2-alkynylbenzaldehydes 72, anilines 73, and phosphonates followed by a PdCl$_2$-catalyzed 5-exo-dig cyclization (Scheme 18) [45]. The desired (2H-isoindol-1-yl)phosphonates 74 were obtained under optimized conditions.
Scheme 16: The synthesis of 3-arylmethyleneisoindolin-1-ones through a Horner–Wadsworth–Emmons reaction of Kabachnik–Fields reaction products.

Scheme 17: An efficient one-pot method for the synthesis of ethyl (2-alkyl- and 2-aryl-3-oxoisoindolin-1-yl)phosphonates.

Scheme 18: FeCl₃ and PdCl₂ co-catalyzed three-component reaction of 2-alkynylbenzaldehydes, anilines, and diethyl phosphonate.
conditions (5 mol % of FeCl₃, 5 mol % of PdCl₂, DCE/CH₃CN, 60 °C) in good to excellent yields. One limitation is the use of aromatic aldehydes bearing electron-donating substituents which afforded the desired products in only low yields, because of their reduced electrophilicity. Aliphatic amines were unreactive in this transformation and only arylamines were found to be effective in this reaction. Eventually, the biological evaluation of the (2H-isoiindol-1-yl)phosphonates 74 revealed their potential as HCT-116 inhibitors.

2.2.4 Pyrazolyl- and oxazolylphosphonates: A series of modified Kabachnik–Fields condensations based on the reaction of 6-methyl-3-formylchromone (75) with some 1,2-, 1,3- and 1,4-bi-nucleophiles and diethyl phosphonate under solvent-free conditions have been developed by E. Ali et al. [46]. The resulting α-aminophosphonate intermediates 77 and 80 were non-isolable and interconverted to the corresponding heterocyclic phosphonates via ring opening through an intramolecular nucleophilic attack at the 2-position of the pyrone. Thus, the three-component reaction of 75 with hydrazine derivatives 76 or hydroxylamine 79 in the presence of diethyl phosphonate led to pyrazolylphosphonate 78 and oxazolylphosphonate 81, respectively (Scheme 19).

2.2.5 Pyrimidinylphosphonates: The 1,3-bi-nucleophiles such as thiourea (82), guanidinium carbonate 84 and cyanoguanidine 86, under the above mentioned conditions afforded the pyrimidinylphosphonates 83, 85 and 87, respectively (Scheme 20).

2.2.6 Diazepinyl- and oxazepinylphosphonates: The three-component reaction of 1,4-bi-nucleophiles such as ethanolamine (88), ethylenediamine (89), 2-aminophenol (92) and 1,2-phenylenediamine (93), with 6-methyl-3-formylchromone (75) and diethyl phosphonate afforded the phosphonate derivatives of 1,4-oxazepine 90, 1,4-diazepine 91, 1,5-benzoxazepine 94 and 1,5-benzodiazepine 95, respectively (Scheme 21).

2.2.7 Isoquinolone-1-phosphonates: From Lewis acid catalyzed 6-endo-dig cyclizations of acetylenic Kabachnik–Fields adducts: A modified Kabachnik–Fields reaction for the synthesis of isooquinoline-1-phosphonate derivatives is the three-component reaction of acetylenic aldehydes with various amines and alkyl phosphonate by Lewis acid catalyzed 6-endo-dig cyclizations. Wu et al. reported the one-pot reaction of 2-alkynylbenzaldehydes 96, amines 97, and diethyl phosphonate to afford (2,3-disubstituted-1,2-dihydroisoquinolin-1-yl)phosphonates 98 in the presence of various Lewis acids (Scheme 22) [47,48]. This reaction, under catalyst-free conditions or in the presence of Lewis acids such as FeCl₃, CBr₄, In(OTf)₃, Bi(OTf)₃, and Yb(OTf)₃, exclusively yielded the acyclic α-aminophosphonates 99. However, the reaction in the presence of AgOTf (5 mol %) or Cul (10 mol %) at 60 °C led to isooquinolin-1-ylphosphonates 98 in moderate to high yields.

In addition, this reaction in the presence of palladium catalysts such as Pd(PPh₃)₄Cl₂ and PdCl₂ gave 1,2-dihydroisoquinolin-1-ylphosphonates 98 in 79% and 81% yields, respectively.

Lewis acid–surfactant combined catalysts (LASC) are another catalytic system which has been used for the three-component reaction of 2-alkynylbenzaldehydes, amines, and nucleophiles such as alkynes, nitromethane, or diethyl phosphonate in water under ultrasonic conditions [49]. As depicted in Scheme 23, the reaction of 2-alkynylbenzaldehyde 100, aniline (32) and diethyl
Scheme 20: Three-component reaction of 6-methyl-3-formylchromone (75) with thiourea, guanidinium carbonate or cyanoguanidine in the presence of diethyl phosphonate.

Scheme 21: Three-component reaction of 6-methyl-3-formylchromone (75) with 1,4-bi-nucleophiles in the presence of diethyl phosphonate.

Phosphonate catalyzed by C_{12}H_{25}SO_3Na–CuSO_4 (10 mol %) or Ag(C_{12}H_{25}SO_3) (10 mol %) under ultrasonic conditions in an aqueous medium afforded the desired 1,2-dihydroisoquinolin-1-ylphosphonate 101 in 65% and 79% yields, respectively.

A more detailed investigation on the catalytic cyclization during Kabachnik–Fields reactions of acetylenic aldehydes with aromatic amines and dialkyl phosphonates has been reported by Čikotienė et al. [50]. They found that the cyclization type...
during these three-component reactions strongly depends on the nature of the acetylenic aldehydes \textsuperscript{102}. The Kabachnik–Fields adducts of various carbocyclic acetylenic aldehydes \textsuperscript{104} and \textsuperscript{105} in the presence of AuBr\textsubscript{3}, PdCl\textsubscript{2}, AgOTf, AgNO\textsubscript{3} or I\textsuperscript{+} underwent a 5-\textit{exo-dig} cyclization to give dialkyl 1\textit{H}-pyrrol-2-ylphosphonates \textsuperscript{106}. However, iodine-mediated cyclizations lead to pyrrol-1-ylphosphonates bearing a carbonyl (\textsuperscript{107}) or 1-idoalkenyl substituent (\textsuperscript{108}) depending on the substituent R. In contrast, electron-deficient heterocycles \textsuperscript{113} and \textsuperscript{114} in the presence of Cul reacted through a tandem imine formation–6-\textit{endo-dig} cyclization to give the corresponding 1,2-dihydropyridin-2-ylphosphonates \textsuperscript{115}. However, electron-rich heterocyclic Kabachnik–Fields adducts were found to be unreactive towards Lewis acid catalyzed cyclization processes. On the other hand, benzene derivatives \textsuperscript{109} can participate in both cyclization modes depending on the catalyst’s nature. They either can cyclize to give the corresponding 1,2-dihydropyridin-2-ylphosphonates \textsuperscript{111} in the presence of CF\textsubscript{3}SO\textsubscript{3}Ag, while in the presence of AuBr\textsubscript{3}, PdCl\textsubscript{2} or I\textsuperscript{+}, they undergo a 5-\textit{exo-dig} cyclization to give dialkyl 1\textit{H}-pyrrol-2-ylphosphonates \textsuperscript{110} or \textsuperscript{112} (Scheme 24).

Other cyclization reactions of Kabachnik–Fields adducts into isoquinolone-1-phosphonates: A one-pot three-component synthesis of \(N\)-arylisoquinolone-1-phosphonates \textsuperscript{119} through the Kabachnik–Fields reaction of ethyl 2-(2-formyl-4,5-dimethoxyphenyl)acetate (\textsuperscript{116}) with anilines \textsuperscript{117} and triethyl phosphite in the presence of trifluoroacetic acid as catalyst has been reported by Borse et al. (Scheme 25) \textsuperscript{[51]}. The desired \(N\)-arylisoquinolone-1-phosphonates \textsuperscript{119} were formed through the intramolecular addition of the amino group to the ester functionality in the Kabachnik–Fields adducts \textsuperscript{118}. The yields ranged between 64% and 74% depending on the nature of the substituent present in the aromatic amines \textsuperscript{117}.

A Cul-catalyzed three-component tandem reaction of 2-(2-formylphenylethanones \textsuperscript{120}, aromatic amines \textsuperscript{121}, and diethyl phosphonate leading to 1,2-dihydroisoquinolin-1-ylphosphon-
nates 123 has been reported by Wu et al. (Scheme 26) [52]. This reaction proceeds via the imine intermediate 122 resulting from the reaction of 2-(2-formylphenyl)ethanones 120 with amines 121. The tandem nucleophilic addition of phosphite to the imine and subsequent condensation of the formed amine with the ketone group leads to 1,2-dihydroisoquinolin-1-ylphosphonates 123. A wide range of substituted aromatic amines and several 2-(2-formylphenyl)ethanones under optimized conditions [CuI (10 mol %), 1,2-dichloroethane, 70 °C] afforded the corresponding 1,2-dihydroisoquinolin-1-ylphosphonates in good to excellent yields.

2.2.8 Benzodiazepinylphosphonates: There are only two publications related to the multicomponent synthesis of benzodiazepinylphosphonates in the literature. Both syntheses are based on o-diaminobenzene as the starting material. In the first method, an YbCl₃-catalyzed three-component reaction between an o-diaminobenzene 124, 2,4-pentanedione (125) and diethyl phosphite under optimized solvent-free conditions (10 mol % of YbCl₃, 22 °C, 1:1:1 molar ratio of starting materials) afforded the undesired diphosphonate 127 in moderate yields (Scheme 27) [53]. The undesired diphosphonate 127 was formed in 1:1:2 or 1:1:4 molar ratio of o-diaminobenzene 124,
Scheme 25: Three-component synthesis of N-arylisoquinolone-1-phosphonates 119.

Scheme 26: CuI-catalyzed three-component tandem reaction of 2-(2-formylphenyl)ethanones with aromatic amines and diethyl phosphonate.

Scheme 27: Synthesis of 1,5-benzodiazepin-2-ylphosphonates via ytterbium chloride-catalyzed three-component reaction.
1,3-butanediones 125 and diethyl phosphite. When butanediones 128 with a larger substituent than Me were used, only monophosphonates 129 were obtained.

The second method comprises a one-pot four-component reaction of diamines 130, ketones 131 and phosphites 132 in the presence of FeCl₃ as a catalyst to give benzodiazepinylphosphonates 133 and 134 and has been reported by Bhattacharya et al. (Scheme 28) [54]. The authors observed that the presence of molecular sieves (4 Å) had a beneficial effect on the yield of the reaction due to trapping of water resulting from the imine formation reaction. The generality of the reaction has been investigated by the use of structurally diverse diamines, ketones and phosphonates. While the reaction proceeded well with different amines and phosphonates, only the use of acetone as the ketone component afforded the corresponding benzodiazepinylphosphonates. With other ketones only ketimine intermediates were obtained which were sterically too crowded for attacking the phosphorus atom of the phosphonates. The use of unsymmetrically substituted diamines led to the corresponding syn-regioisomers as the major product and the anti-regioisomer as the minor product. Some of the synthesized 1,5-benzodiazepin-2-ylphosphonates showed cysteine protease inhibition activities.

2.2.9 Heterocyclic bisphosphonates: A modified Kabachnik–Fields reaction of the substituted amine 135 with triethyl orthoformate followed by reaction with sodium diethylphosphite afforded bisphosphonate intermediate 136 that was converted to the heterocyclic bisphosphonate 137 through an intramolecular cyclization (Scheme 29) [55]. The sequenced reaction of the amine with triethyl orthoformate followed by the addition of sodium diethylphosphite dissolved in toluene considerably increased the yields of bisphosphonates.

In this way, carbamate 138, hexahydrobenzothiophene 140 and benzothiophene 142 were converted to the corresponding bisphosphonates 139, 141 and 143, respectively (Scheme 30). The synthesized heterocyclic bisphosphonates showed anti-inflammatory properties.

3 Knoevenagel-induced domino reactions
An efficient method into phosphorylated heterocycles is the condensation of an activated methylene component with a carbonyl compound followed by subsequent transformations such as intramolecular cyclization, Michael-type addition and hetero-Diels–Alder cycloaddition.

3.1 Domino Knoevenagel/phospha-Michael process
A convenient one-pot ZnO nanorods-catalyzed reaction of isatin derivatives 144 with malononitrile (145) and dialkyl or diphenyl phosphonates 146 has been performed to give 2-oxindolin-3-ylphosphonates 147 (Scheme 31) [56]. The products were ob-
tained in good to excellent yields using 10 mol % of the catalyst under solvent-free conditions at room temperature. However, when using ethyl cyanomalonate instead of malononitrile, the reaction in water led to the corresponding 2-oxoindolin-3-ylphosphonate in good yield. Further, the investigations showed that the recovered ZnO nanorods could be reused up to five times.

Some of the phospha-Michael adducts were converted to new phosphorylated heterocycles through intramolecular cyclization reactions. The phospha-Michael adduct 149 resulting from the three-component reaction of 6-methyl-3-formylchromone with malononitrile 145 or 2-cyanoacetamide 148 and diethyl phosphite is not isolable and spontaneously recyclized to dihydropyridinylphosphonate 150 (Scheme 32) [46].

In this way, the reaction of 6-methyl-3-formylchromone (75) with cyclic 1,3-dicarbonyl compounds such as dimedone (151), 1-phenylpyrazolidine-3,5-dione (153) or barbituric acid (155) afforded the fused phosphonylpyrans 152, 154 and 156, respectively (Scheme 33).

3.2 Three-component synthesis of (2-amino-3-cyano-4H-chromen-4-yl)phosphonates

Because of the widespread biological activities related to 2-amino-4H-chromene derivatives, the synthesis of (2-amino-3-cyano-4H-chromen-4-yl)phosphonates has attracted much attention from organic chemists. The best procedure for the preparation of these compounds involves a one-pot three-component reaction between salicylaldehydes 157, malononitrile (145) and trialkyl phosphite that was first reported by Perumal...
In recent years, several methods using different catalysts have been developed to prepare 2-amino-3-cyano-4H-chromen-4-ylphosphonates. These methods and other aspects of reaction conditions are summarized in Table 1.
Scheme 34: InCl₃-catalyzed three-component synthesis of (2-amino-3-cyano-4H-chromen-4-yl)phosphonates.

Table 1: Different catalytical methods for the synthesis of 2-amino-3-cyano-4H-chromen-4-ylphosphonates.

| Entry | R             | R'          | X        | Catalyst            | T (°C) | Yields (%) | Ref. |
|-------|---------------|-------------|----------|---------------------|--------|------------|------|
| 1     | H, 3,5-di-Cl, 5-Br, 3,5-di-Br, 3,5-di-i, 3-OMe | Et | CN, COOEt | β-CD | 60–70 | 76–88 | [58] |
| 2     | H, 3,5-di-Cl, 5-Br, 3,5-di-Br, 5-Me, 3-OMe, 5-OMe, 5-NO₂, 5,6-(CH=CH)₂ | Et | CN, COOEt | K₃PO₄ | rt | 74–95 | [59] |
| 3     | H, 5-Cl, 3,5-di-Cl, 3,5-di-Br, 5-Me, 3-OMe, 4-Et₂N, 4,5-(CH=CH)₂ | Et, Me | CN, COOEt | PEG-400 | 80 | 81–92 | [60] |
| 4     | H, 5-Cl | Et | CN, COOEt | I₂ | rt | 79–91 | [61] |
| 5     | H, 5-Br, 3,5-di-Br, 3-Me, 5-Me, 4-OMe, 5-OMe, 5-NO₂, 5,6-(CH=CH)₂ | Et | CN, COOEt | EDDA | rt | 40–90 | [62] |
| 6     | H, 5-Cl, 3,5-di-Cl, 5-Br, 3,5-di-Br, 5-Me, 5-OMe, 5-NO₂ | Et | CN | Et₂NH | rt | 90–95 | [63] |
| 7     | H, 5-Cl, 5-Br, 5-Me, 3-OMe, 3-OMe | Et, Me, Bu | CN | electrocatalysis | 20–78 | 88–93 | [64] |
| 8     | H, 5-Cl, 5-Br, 5-Me, 5-OMe, 5-NO₂, 3-f-Bu | Et, Me, Bu, Ph | CN, COOEt | TMG | rt | 65–96 | [65] |
| 9     | H, 5-Cl, 5-Br, 3,5-di-Cl, 3,5-di-Br, 5-Me, 3-OMe, 5-OMe, 5-NO₂ | Et | CN, COOEt | nano-MgO | rt | 68–92 | [66] |
| 10    | H, 5-Br, 3,5-di-Cl, 3,5-di-Br, 3-Me, 5-OMe, 5-f-Bu, 3,5-di-f-Bu, 5,6-(CH=CH)₂ | Et, Me, iPr | CN | catalyst-free | rt | 68–90 | [67] |
| 11    | H, 5-Br, 5-NO₂, 3-f-Bu | Et, Me, Bu, iPr | CN | dibutylamine | rt | 85–96 | [68] |
| 12    | H, 5-Cl, 5-Br, 5-Me, 5-NO₂, 3,5-di-Br, 3-OMe, 3-OEt | Et, Ph | CN | LiOH | rt | 85–97 | [69] |
| 13    | H, 5-Cl, 5-Br, 5-Me, 3-Br, 3-OMe, 3-OEt | Et, Me, iPr | CN, COOEt | silica-bonded 2-HEAA | rt | 71–87 | [70] |
| 14    | H, 5-Br, 5-Cl, 3,5-di-Br, 3,5-di-Cl, 5-Me, 4-OMe, 5-OMe, 5-NO₂ | Et | CN, Fe₃O₄@CS-SO₃H NPs | rt | 88–97 | [71] |

3.2 Domino Knoevenagel/hetero-Diels–Alder process

The one-pot synthesis of dihydropyrans via a three-component reaction between an activated methylene compound, an aldehyde and an electron-rich alkene was firstly reported by Tietze et al. [72]. Collignon et al. applied this protocol for the preparation of phosphonodihydropyrans 163 or 164 starting from phosphonoacetylene 159 or phosphonoacetylene 160, p-nitrobenzaldehyde (161) and ethyl vinyl ether (162) in a reactor equipped with a Dean–Stark separator (Scheme 35) [73]. The yields of the resulting cycloadducts 163 and 164 were 87% and 91%, respectively and were much higher than the overall yields of the
corresponding multi-step reactions. Also, the trans/cis selectivity of phosphonodihydropyrans 163 and 164 was 24:76 and 22:78, respectively.

In this way, Gulea et al. synthesized phosphonodihydrothiopyrans through the one-pot reaction of phosphonodithioacetate, aromatic aldehydes and dienophiles in the presence of piperidine in refluxing toluene (Scheme 36) [74]. The new phosphorylated cycloadducts were isolated in excellent yields and with a trans- or cis-diastereoselectivity.

4 Metal-catalyzed multicomponent reactions

Transition metals, especially Pd and Cu, are well-known catalysts for multicomponent reactions. Carbopalladation reactions of allenes, alkynes and carbon monoxide are very important processes in multicomponent syntheses. Additionally, copper-catalyzed multicomponent reactions such as azide–alkyne cycloadditions and various A3-coupling reactions are useful procedures in heterocyclic chemistry. However, several methods based on these protocols have also been developed for the synthesis of heterocyclic phosphonates.

The 1,2-dihydroisoquinolin-1-ylphosphonates were formed through a one-pot reaction of 2-bromobenzaldehydes, alkynes, amines, and diethyl phosphonate under multicomponent conditions including palladium and copper salts (Scheme 37) [75]. This process presumably involves a sequential Sonogashira coupling/cyclization-nucleophilic addition reaction, which is catalyzed by PdCl2(PPh3)2 and Cul whereas Cu(OTf)2 acts as a Lewis acid. The desired 1,2-dihydroiso-
quinolin-1-ylphosphonates 169 were isolated under optimized conditions [PdCl2(PPh3)2 (2 mol %), CuI (1 mol %), Cu(OTf)2 (10 mol %), Et3N, 4 Å molecular sieves, THF, 50–60 °C] in 40–70% yields.

A CuI-catalyzed four-component reaction through a methyleneaziridine ring-opening process has been developed for the synthesis of α-aminophosphonates [76]. Thus, the one-pot reaction between methyleneaziridines 173, Grignard reagents 174, alkyl halides 175 and dialkyl phosphonates in the presence of CuI afforded acyclic α-aminophosphonates 176. However, using difunctionalized electrophiles such as 1,3-diiodopropane 178 resulted in piperidinylphosphonates 179 with moderate yields (Scheme 38). This one-pot transformation involves an aziridine ring opening, C-alkylation, and hydrophosphorylation of the formed imine to create three intermolecular bonds.

A ruthenium–porphyrin complex-catalyzed three-component reaction of α-diazophosphonates 180, nitrosoarenes 181, and alkynes 182 to give multifunctionalized aziridinylphosphonates 183 has been reported by Reddy et al. (Scheme 39) [77]. The desired aziridinylphosphonates 183 were isolated in 45–98% yields and 90:10 to >99:1 diastereoisomeric ratio depending on the structure of substituents present on nitrosoarenes 181 and alkynes 182. The use of internal alkynes gave only poor yields of the corresponding aziridinylphosphonates due to their low reactivity. This process involves the 1,3-dipolar cycloaddition of alkynes 182 with in situ generated nitrone 185 to afford isoxazolines 186 which rapidly rearrange to aziridinylphosphonates 183.

An efficient method for the synthesis of 1,2,3-triazoles is the copper(I)-catalyzed Husigen cycloaddition of azides with alkynes. Based on this method, Li et al. have developed a copper(I)-catalyzed three-component reaction between alkynes 187, azides 188 and dialkyl phosphonates 189 to give 1,2,3-triazolyl-5-phosphonates 190 (Scheme 40) [78]. The desired products were obtained in 62–88% yield under optimized conditions [CuCl (0.015 mmol), TEA (0.3 mmol), MeCN, rt, 20 h].
5 Isocyanide-based multicomponent reactions

Although isocyanide-based multicomponent reactions (IMCRs) are one of the most important routes into heterocyclic compounds, there are only a few publications related to the isocyanide-based multicomponent synthesis of heterocyclic phosphonates in the literature. However, three different isocyanide-based multicomponent reactions for the synthesis of heterocyclic phosphonates are described here.

A one-pot three-component reaction between the acylphosphonates 192 formed by treatment of triethyl phosphate and acyl chlorides 191, isocyanides 193 and dialkyl acetylenedicarboxylates 194 to afford 2-phosphonofuran derivatives 196 has been reported by our group (Scheme 41) [79]. The desired furanyl phosphonates were isolated in 52–67% yield at rt in CH₂Cl₂. In this transformation the zwitterionic intermediate 195, resulting from reaction of isocyanide with dialkyl acetylenedicarboxylate, added to the carbonyl group of the acylphosphonate followed by an intramolecular cyclization.

A palladium-catalyzed isocyanide-based three-component pathway into phosphorylated quinazolines has been described by Wu et al. [80]. The one-pot reaction of carbodiimide 197, isocyanide 199 and dialkyl phosphonates 198 under optimized conditions affords the phosphorylated quinazolines 196.

![Scheme 40: Copper(I)-catalyzed three-component reaction towards 1,2,3-triazolyl-5-phosphonates.](image)

![Scheme 41: Three-component reaction of acylphosphonates, isocyanides and dialkyl acetylenedicarboxylate to afford 2-phosphonofuran derivatives.](image)
conditions (10 mol % of Pd(OAc)$_2$, 10 mol % of FeCl$_3$, 10 mol % of DPPF, 3.0 equiv of Cs$_2$CO$_3$, toluene, reflux) led to (4-imino-3,4-dihydroquinazolin-2-yl)phosphonates 203 in 37–78% yields (Scheme 42). This process involves an initial nucleophilic addition of phosphite to carbodiimide 197 affording intermediate 200 which undergoes an oxidative addition of Pd(0) to give Pd(II) species 201. Subsequently, the insertion of isocyanide 199 to species 201 affords intermediate 202, which finally generates phosphorylated quinazoline 203 through reductive elimination.

A silver-catalyzed three-component reaction of α-isocyanophosphonates 206, ketones 205 and amines 204 under microwave irradiation to afford (2-imidazolin-4-yl)phosphonates 210 has recently been reported (Scheme 43) [81]. The yields of the products under optimized conditions were 53–89%. This process involved a Mannich-type addition of a silver-activated α-isocyanophosphonate anion 208 to an iminium salt 207, resulting from reaction of amine 204 and ketone 205, to give intermediate 209 which cyclizes to afford (2-imidazolin-4-yl)phosphonates 210.
6 1,3-Dipolar cycloaddition-based multicomponent reactions

1,3-Dipolar cycloaddition-based multicomponent reactions usually involve the cycloaddition of in situ generated 1,3-dipoles and dipolarophiles to give five-membered heterocycles. In recent years, many heterocyclic phosphonates have been prepared via this efficient method.

One of the best strategies is based on the use of Bestmann–Ohira reagent (BOR) as the 1,3-dipole precursor. Smietana et al. accomplished a related three-component reaction with different aldehydes 211, nitrile derivatives 212 and dimethyl diazomethylphosphonate 213 to prepare phosphonopyrazoles 217 in the presence of KOH in MeOH in 73–95% yields (Scheme 44) [82]. Based on their explanation, the treatment of dimethyl diazomethylphosphonate 213 with a nucleophilic base generates diazo compound 215. The subsequent [3 + 2] cycloaddition reaction of 215 with Knoevenagel adduct 214, resulting from condensation of aldehydes 211 and nitrile derivatives 212, lead to cycloadduct intermediates 216 which cyclize to phosphorylated pyrazoles 217.

In this way, a one-pot three-component reaction of aldehydes 218, methyl ketones 219 and the Bestmann–Ohira reagent has been developed for the preparation of different 3-carbo-5-phosphonylpyrazoles 223 (Scheme 45) [83]. The corresponding phosphonylpyrazoles 223 were formed via a Claisen–Schmidt/1,3-dipolar cycloaddition/oxidation process under basic conditions in MeOH in 30–91% yields.

The dual reactivity of diethyl (1-diazo-2-oxopropyl)phosphonate (225) in a one-pot, two-step three-component method for the synthesis of phosphonopyrazoles has been presented by Kumar et al. The phosphonate 225 acted both as a 1,3-dipole precursor and as a Horner–Wadsworth–Emmons (HWE) reagent. Therefore, the reaction of phosphonate 225 with aldehydes 224 generated terminal acetylenes 226 which cyclized with the second molecule of phosphonate 225 in the presence of Cu(I) to afford (5-methyl-1H-pyrazol-3-yl)phosphonates 230 in 46–81% yields (Scheme 46) [84].

Also, a domino reaction based on the dual reactivity of BOR as a homologation reagent as well as cycloaddition reactant for the

![Scheme 44: Three-component synthesis of phosphonopyrazoles.](image-url)
Scheme 45: One-pot three-component synthesis of 3-carbo-5-phosphonylpyrazoles.

Scheme 46: A one-pot two-step method for the synthesis of phosphonylpyrazoles.

The desired vinylpyrazoles were obtained in 46–95% yields under optimized conditions (2.5 equiv BOR, 2.5 equiv KOH, 25 °C, 6 min, MeOH). In this reaction, the generated diazomethyl anion underwent a 1,3-dipolar cycloaddition with α,β-unsaturated aldehydes to give pyrazolinecarboxaldehyde. The subsequent reaction of aldehyde with...
Scheme 47: A one-pot method for the synthesis of (5-vinylpyrazolyl)phosphonates.

Another molecule of BOR afforded pyrazoline alkyne intermediate 233 which, after a 1,3-hydrogen shift, aromatized to vinylpyrazoles 234.

Recently, the [3 + 2] cycloaddition of phosphonate azomethine ylides 235 with ynones 236 to give substituted 1H-pyrrol-2-ylphosphonates 237 has been described by Yu et al. (Scheme 48) [86].

The desired 1H-pyrrol-2-ylphosphonate 241 could also be obtained through the three-component reaction of 4-chlorobenzaldehyde (238), aminomethylphosphonate 239 and ynones 240 in 57% yield (Scheme 49).

7 Reissert-type multicomponent reactions
The traditional Reissert reaction is a one-pot treatment of quinoline (242) with acid chlorides 243 and KCN to afford Reissert

Scheme 48: Synthesis of 1H-pyrrol-2-ylphosphonates via the [3 + 2] cycloaddition of phosphonate azomethine ylides with ynones.

Scheme 49: Three-component synthesis of 1H-pyrrol-2-ylphosphonates.
compound 244 which can be hydrolyzed to give quinoline-2-carboxylic acid (245) (Scheme 50) [87].

This reaction can also be applied to isoquinolines and some pyridines. Additionally, a wide range of activating groups such as chloroformates, acetylenic esters, R₃SiOTf, Tf₂O and various nucleophiles can be utilized in this reaction. For example, the one-pot reaction of isoquinoline (246) with KCN and chlorophosphates or chlorothiophosphates 247 has been described by Spatz and Popp. The corresponding N-phosphorylated isoquinolines 248 were obtained in 21–85% yields in CH₂Cl₂ at room temperature (Scheme 51) [88].

Further, 1-acyl-1,2-dihydroquinoline-2-phosphonates 251 and 2-acyl-1,2-dihydroisoquinoline-1-phosphonates 252 have been prepared via the one-pot reaction of quinoline (242) or isoquinolines 249 with acyl chlorides 250 and trimethyl phosphate in the presence of NaI in 22–94% yields depending on the nature of the acyl chlorides and substituents X (Scheme 52) [89,90]. The three-component reaction of dimethyl phosphate, acetyl chloride and isoquinoline under refluxing in CH₂Cl₂ in the presence or absence of triethylamine led to the desired 1,2-dihydroisoquinoline-1-phosphonates in 66% and 45% yields, respectively. However, the reaction of trimethyl phosphate, acetyl chloride and isoquinoline in MeCN at 0 °C followed by heating at 50 °C gave the corresponding 1,2-dihydroisoquinoline-1-phosphonate in 85% yield.

Albouy et al. discovered an unexpected route towards 1,2-dihydropyridinylphosphonates during their studies of the base-cata-

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**Scheme 50:** The classical Reissert reaction.

**Scheme 51:** One-pot three-component synthesis of N-phosphorylated isoquinolines.

**Scheme 52:** One-pot three-component synthesis of 1-acyl-1,2-dihydroquinoline-2-phosphonates and 2-acyl-1,2-dihydroisoquinoline-1-phosphonates.
lyzed Pudovik reaction [91]. Unlike most other bases, the pyridine-mediated reaction of ethyl propiolate (253) and dialkyl phosphonates 254 led to 1,2-dihydropyridinylphosphonates 256. Thus, the 1,2-dihydropyridinylphosphonates 256 were synthesized via a one-pot three-component reaction of pyridine 255, ethyl propiolate (253) and dialkyl phosphonates 254 in moderate to good yields at 20 °C (Scheme 53). Under similar conditions, no reaction occurred with 2,6-lutidine (257) whereas 4-dimethylaminopyridine (258, DMAP) was efficiently converted to dialkylated 1,2-dihydropyridine-3-phosphonate 259.

Yavari et al. have described the phosphorylation of benzothiazole (263) and isoquinoline (246) through a one-pot three-component reaction with activated acetylenes 260 and diphenyl phosphonate (261) under solvent-free conditions at room temperature (Scheme 54) [92]. Moderate to good yields (60–90%) of the desired heterocyclic phosphonates 262 and 264 were obtained.

The same group has also reported another Reissert-type reaction for the synthesis of 1,2-dihydroisoquinolin-1-ylphospho-
nates via activation of isoquinoline with isocyanate or isothiocyanate. In this case, the one-pot three-component reaction of isoquinoline and diphenyl phosphite with isocyanates 265 or isothiocyanates 266 furnished (dihydroisoquinolin-1-yl)phosphonates 267 or 268 in 96–99% yields under solvent-free conditions at room temperature (Scheme 55) [93].

A solvent-free stereoselective synthesis of 1,2-dihydroquinolin-2-ylphosphonates 271 and 1,2-dihydroisoquinolin-1-ylphosphonates 272 via the three-component reactions of quinoline or isoquinoline, dialkyl acetylenedicarboxylates 269, and dialkyl phosphonates 270 has been described by Shaabani et al. (Scheme 56) [94]. The corresponding products 271 and 272 were isolated in 52–61% yields and their nOe analysis revealed the geometry of the alkene bonds to be E.

A tandem 1,4–1,2 addition of dimethyl trimethylsilyl phosphate (DMPTMS, 273) to diazaheterocyclic compounds under microwave irradiation in acidic medium led to diphosphorylated products [95]. The 1,5-naphthyridine 274 and phenanthrolines 276, 278 and 280 in the presence of more than 2 equiv of DMPTMS were converted to the corresponding diphosphorylated products 275, 277, 279 and 281 with a high diastereoisomeric ratio (Scheme 57). In this reaction, the 1,4-addition of DMPTMS as a nucleophilic reagent on the N-protonated heterocycle followed by a 1,2-addition of DMPTMS on the N-silylated species lead to the diphosphorylated heterocycles after aqueous work-up.

8 Miscellaneous multicomponent reactions

The reaction of pentanedial (284) with acetamide (283) and acetyl chloride (282) in the presence of PCl₃ and acetic acid gives a 1:1 mixture of piperidinylidiphosphonic acid 285 and acyclic (diaminoalkyl)diphosphonic acid 286. However, butanedial (287) under similar conditions affords exclusively pyrrolidinyldiphosphonic acid 288 in 39% yield (Scheme 58) [96].

An oxidative domino three-component reaction of α-ketophosphonates 290, ammonium acetate and various 1,3-dicarbonyl compounds 289 to give pyridinylphosphonates 291 has been described. This method allowed the synthesis of highly functionalized pyridinylphosphonates 291 in 63–80% yields in refluxing AcOH/toluene 4:1 in the presence of 4 Å molecular sieves (Scheme 59) [97].
Scheme 57: Diphosphorylation of diazaheterocyclic compounds via a tandem 1,4–1,2 addition of dimethyl trimethylsilyl phosphite.

Scheme 58: Multicomponent reaction of alkanedials, acetamide and acetyl chloride in the presence of PCl₃ and acetic acid.

A sequential three-component enamine–azoene annulation reaction of primary aliphatic amines 292, activated methylene compounds 293, and 1,2-diaza-1,3-dienes (DDs, 294) has been reported to give polysubstituted pyroles 295 (Scheme 60) [98]. The desired phosphono-substituted pyroles were isolated in 41–87% yield under solvent and catalyst-free conditions. Kaboudin et al. described a three-component, catalyst-free decarboxylative coupling of proline (296) with aldehydes 297 and dialkyl phosphonates to afford pyrrolidinylphosphonates 300. The corresponding pyrrolidinylphosphonates 300 were isolated in 43–86% yields under refluxing in toluene (Scheme 61) [99]. The reaction was proposed to proceed through the conden-
Scheme 59: An oxidative domino three-component synthesis of polyfunctionalized pyridines.

Scheme 60: A sequential one-pot three-component synthesis of polysubstituted pyrroles.

Scheme 61: Three-component decarboxylative coupling of proline with aldehydes and dialkyl phosphites for the synthesis of pyrrolidinylphosphonates.

An efficient protocol comprising a domino aza-Wittig/phosphamannich sequence for the phosphorylation of isatin derivatives has been reported by Kumar et al. According to this method, the one-pot reaction of isatin derivatives 301, iminophosphorane 302, and diphenyl phosphonate in the presence of Cinchona-
derived thiourea as the catalyst afforded α-aminophosphonates 303 in 70–81% yields and with 70–84% ee (Scheme 62) [100].

The trans-1,5-benzodiazepines 307 bearing both, perfluoroalkyl and phosphate groups, were stereoselectively synthesized through a one-pot three-component condensation of o-phenylenediamines 304, fluorinated alkynylphosphonates 305 and aldehydes 306 (Scheme 63) [101]. The corresponding 1,5-benzodiazepines 307 were isolated in 56–89% yields under optimized conditions. In this reaction aromatic aldehydes afforded slightly higher yields than aliphatic aldehydes. Also, the yields of aromatic aldehydes bearing electron-donating substituents were higher than those bearing electron-withdrawing substituents.

Yavari et al. described the synthesis of phosphorylated 2,6-dioxohexahydropyrimidines 311 via a three-component reaction [102]. This method involved the one-pot reaction of N,N'-dimethyleneurea (310) and dialkyl acetylenedicarboxylates 309 in the presence of trialkyl phosphites 308 at room temperature (Scheme 64). The desired products were obtained in high yields between 84 and 94%.

Scheme 62: Three-component domino aza-Wittig/phospha-Mannich sequence for the phosphorylation of isatin derivatives.

Scheme 63: Stereoselective synthesis of phosphorylated trans-1,5-benzodiazepines via a one-pot three-component reaction.

Scheme 64: One-pot three-component synthesis of phosphorylated 2,6-dioxohexahydropyrimidines.
Conclusion

In this article the use of different multicomponent reactions (MCRs) for the synthesis of heterocyclic phosphonates has been reviewed. This review demonstrates the synthetic potential of multicomponent reactions for the construction of phosphon-substituted heterocyclic rings. The Kabachnik–Fields reaction can be considered the starting point of multicomponent synthesis of this class of compounds. However, the major advancements in this interesting field have been achieved in recent years. More than 75% of the cited literature in this review has been published within the last six years, of which more than three quarters dealt with the synthesis of new heterocyclic phosphonates from non-heterocyclic phosphorus reagents. The remaining works reported the phosphorylation of parent hetero-phonates from non-heterocyclic phosphorus reagents. The three quarters dealt with the synthesis of new heterocyclic phosphonates. U.S. Patent 4,606,757, Aug 19, 1986.

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