Feature article

Multicomponent Synthesis of Potentially Biologically Active Heterocycles Containing a Phosphonate or a Phosphine Oxide Moiety

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Abstract

Several multicomponent synthetic approaches were elaborated for plenty of novel nitrogen or oxygen heterocycles containing a phosphonate or a phosphine oxide moiety. All multicomponent reactions were optimized through a model reaction in respect of the heating mode, molar ratio of the starting materials, atmosphere, catalyst, temperature, reaction time and solvent applied, and then, the extended preparation of small libraries of structurally-related compounds was performed. Most of the reactions could be considered as "green syntheses", as they were carried out in the absence of any catalyst and/or solvent using microwave (MW) irradiation or even at ambient temperature. The scaling-up of a MW-assisted synthesis was also elaborated in a continuous flow MW system. Altogether more than 150 heterocyclic organophosphorus compounds were synthesized, among them several derivatives showed moderate or promising activity against the HL-60 cell line and *Bacillus subtilis* bacteria.

Keywords: Multicomponent reactions, Heterocycles, Organophosphorus compounds, Microwave chemistry, Biological activity

1. Introduction

In modern synthetic chemistry, the application of efficient and simple reaction routes for the preparation of organic compounds has become more and more important. Therefore, multicomponent reactions (MCRs) attract growing interest. In MCRs, the components react with each other in a "one-pot" manner without isolation of any intermediates, which may save time and energy.[1,2] They can be considered as ideal synthetic methods due to their features, such as the quick and simple procedure, as well as energy saving and high atom efficiency.[3–5] In general, complex structures can be easily formed from inexpensive and simple starting materials by these transformations.[6–9] In addition, these properties make them suitable to create large libraries of structurally-related compounds.[10–12] MCRs especially show their importance in the synthesis of heterocycles.

Heterocycles are present in human and animal organisms, as well as in plants as components of nucleic acids, sugars, enzymes, hormones, vitamins, pigments and hemoglobin.[13–17] In addition, their importance is further enhanced by many synthetic members, such as drugs, pesticides, fine chemicals and cosmetics.[18–22] In the last few decades, the multicomponent synthesis of heterocycles containing phosphonate moieties has become more and more important, due to their promising biological properties.[23,24]

The aim of our research work was to synthesize potentially biologically active nitrogen heterocycles bearing a phosphonate or a phosphine oxide moiety, such as oxoisoindolinyl)phosphonates and -phosphine oxides **1**, (1,2-dihydroisoquinolinyl)phosphonates and -phosphine oxides **2**, (dihydropyrimidinone)phosphonates **3**, (1,2,3-triazol-5-yl)phosphonates 4, as well as ((1,2,3-triazol-4-yl)methyl)phosphinates and -phosphates 5 (Figure 1). In addition, oxygen heterocycles containing a phosphonate or a phosphine oxide moiety, such as (aminochromenyl)phosphonates and -phosphine oxides **6**, as well as 1-alkyl- and 1-alkoxy-1*H*-phoshindole-1-oxides **7** were also aimed to be investigated.

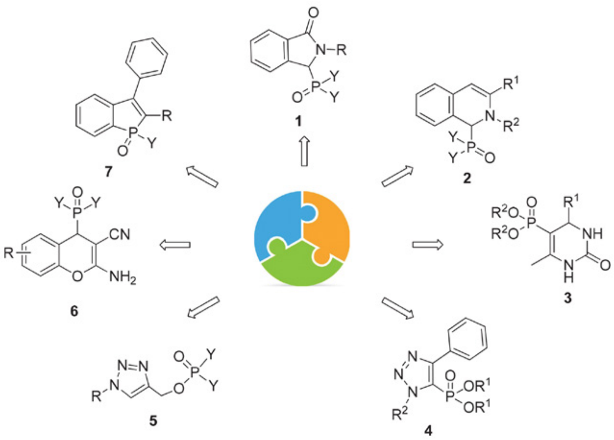


Figure 1. Target molecules

Several derivatives containing the above-mentioned target backbones have biological effects in a wide variety of indications (Figure 2). Some oxoisoindoline carboxylic acid **8** or carboxylic amide derivatives **9** can be found in the literature, which are anticancer or analgesic agents.[25,26] Dihydroisoquinolines are effective in a variety of indications, such as antidepressants, sedatives, antitumor (e.g., Crispine A (**10**)) or as antibacterial drugs.[27–30] Several 3,4-dihydropyrimidin-2(1*H*)-one carboxylates are applied as antitumor (e.g., Monastrol (**11**) or Piperastrol (**12**)), antihypertensive, anti-inflammatory, antibacterial, antiviral or antifungal agents.[31–33] The 1,2,3-triazole derivatives **13** may have antibacterial, antiviral, antifungal, anticancer or anti-inflammatory effect.[34–36] From among *O*-heterocycles, 4*H*-chromenes have various utilizations, especially in pharmaceutical industry, such as the antiallergic and anti-asthmatic sodium chromoglycate (**14**), or in the cosmetic and dye industry, as well as in the agriculture.[37–39]

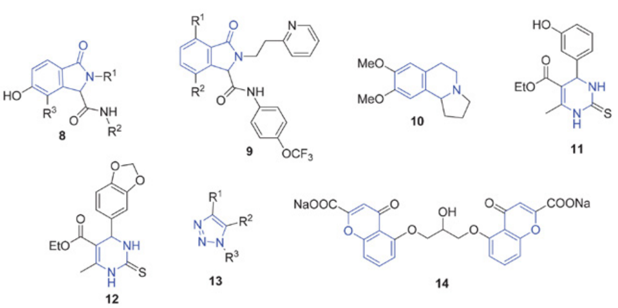


Figure 2. Biologically active *N*- and *O*-heterocyclic derivatives

The biological activity of the phosphorylated heterocyclic compounds is less investigated; however, a few important examples can also be found (Figure 3). For example, 3,4-dihydropyrimidin-2(1*H*)-one phosphonates **15** have anti-inflammatory effect.[40] The 1,2,3-triazolyl phosphonate derivative **16** showed anti-HIV effect.[41] Some 2-amino-4*H*-chromenylphosphonate derivatives **17** have antioxidant and anticancer activity,[42,43] and a few (chromonylaminomethyl)phosphonates **18** also showed antitumor effect.[44] While benzo[*b*]phospholoxide **19** is used in the optoelectronic industry, e.g. in OLEDs.[45]

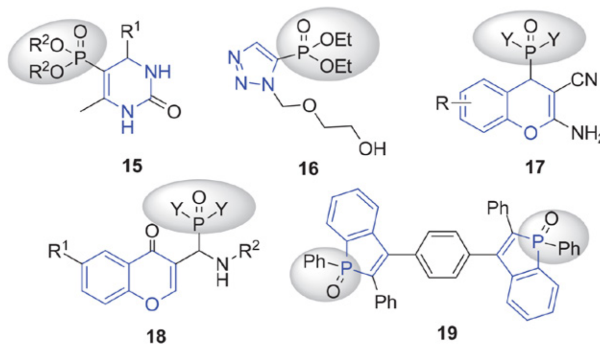


Figure 3. Biologically active phosphorylated heterocyclic compounds

Our main aim was to develop effective and simple methods for the preparation of phosphorylated *N*- and *O*-heterocyclic derivatives *via* multicomponent reactions, as far as possible, in the absence of any solvent and/or catalyst. We aimed at providing comprehensive study on the reactions, and the formation of diverse molecular libraries. We also investigated the *in vitro* cytotoxicity and antibacterial activity of the compounds synthesized. Furthermore, a phosphine oxide derivative was aimed to be utilized as a precursor of a phosphine ligand in the synthesis of a transition metal complex.

2. Multicomponent Synthesis of *N*-Heterocycles

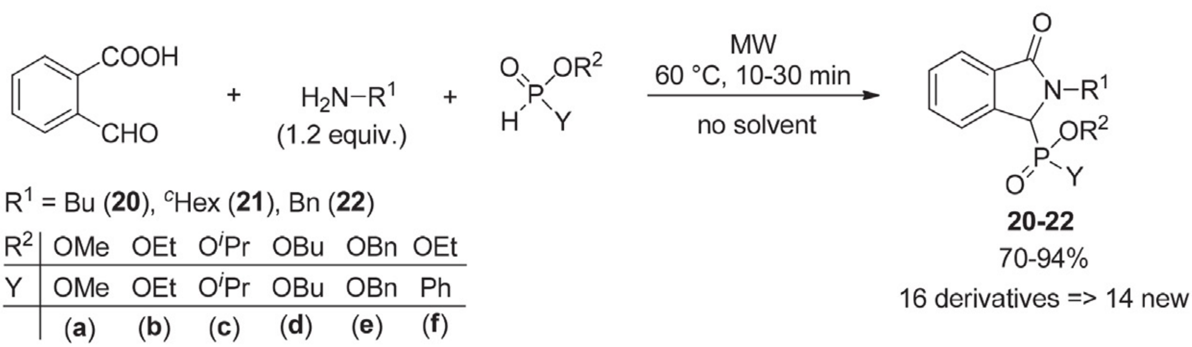
2. 1. Synthesis of (Oxoisoindolin-1-yl) phosphonates

A solvent- and catalyst-free MW-assisted method was developed for the synthesis of (oxoisoindolinyl) phosphonates by the Kabachnik–Fields reaction followed by intramolecular cyclization of 2-formylbenzoic acid, aliphatic primary amines and dialkyl phosphites. In the literature, only a few examples can be found for the condensation of 2-formylbenzoic acid, aromatic amines, amino alcohols or phenylethylamine derivatives and dialkyl phosphites. The reactions were carried out under thermal heating or under MW conditions usually for long reaction times (1–5 h) and in a solvent (methanol, ethyl acetate).[46–49] In a few cases, the transformations were performed in the presence of a catalyst or an additive, such as NaH,[50] $T_3P^{®}$[51] or OSU-6.[52]

In the first step, the reaction of 2-formylbenzoic acid, butyl-, cyclohexyl- or benzylamine and diethyl phosphite was studied and optimized in respect of the heating mode, the molar ratio of starting materials, the temperature and the reaction time.[53] After the optimization, the model reaction was extended for the preparation of further (oxoisoindolinyl)phosphonate derivatives **20**–**22** (Scheme 1). Carrying out the catalyst- and solvent-free MW-assisted condensation of 2-formylbenzoic acid, butylamine and dimethyl-, diethyl-, diisopropyl-, dibutyl- or dibenzyl phosphite at 60 °C for 10 min, the corresponding dialkyl (2-butyl-3-oxo-2,3-dihydro-2*H*-isoindol-1-yl) phosphonates **20a**–**e** were synthesized in high yields (81–94%). Starting from cyclohexylamine and various dialkyl phosphites (dimethyl-, diethyl-, diisopropyl-, dibutyl- or dibenzyl phosphite), under the optimized conditions (60 °C, 30 min) five new (oxoisoindolinyl)phosphonates **21a**–**e** were formed in yields of 70–84%. After that, the reaction was also performed applying benzylamine as the amine component, and five (oxoisoindolin-1-yl)phosphonates **22a**–**e** were synthesized with high yields (80–90%) at 60 °C for 20 min.

Finally, the three-component reaction of 2-formylbenzoic acid, butylamine and ethyl phenyl-*H*-phosphinate as the *P*-reagent was also performed at 60 °C, for 10 min. The desired (oxoisoindolin-1-yl)phosphinate **20f** was obtained in a yield of 78%, as a mixture of diastereomers in a ratio of almost 1:1.

The mechanism of the condensation was also investigated by *in situ* Fourier transform infrared (FT-IR) spectroscopy by the model reaction of 2-formylbenzoic acid (**FBA**), butylamine (**BA**) and diethyl phosphite (**DEP**) in ethanol. At first, the signal of the solvent (ethanol) was recorded, then the starting materials were added in ten-minute intervals. In the next step, the mixture was heated to 60 °C with an oil bath, and the IR spectrum of the mixture was measured continuously. In the time-dependent IR spectrum, the characteristic absorptions of the reaction components (**FBA**, **DEP**, **BA** and **20b**) can be seen (Figure 4). The lactone form of **FBA** had a strong absorption band at $\nu_{C=O}$ = 1756 cm^{-1}. In the case of **DEP**, signals at 964 cm^{-1} (ν_{P-O-C}) and 1254 cm^{-1} ($\nu_{P=O}$) could be seen. **BA** was identified by the $\delta_{C\text{-}H}$ (1381 cm^{-1}) and $\delta_{N\text{-}H}$ (1605 cm^{-1}) absorptions. Diethyl (2-butyl-3-oxo-2,3-dihydro-2*H*-



Scheme 1. The reaction of 2-formylbenzoic acid, alkyl amines and dialkyl phosphites or ethyl phenyl-*H*-phosphinate

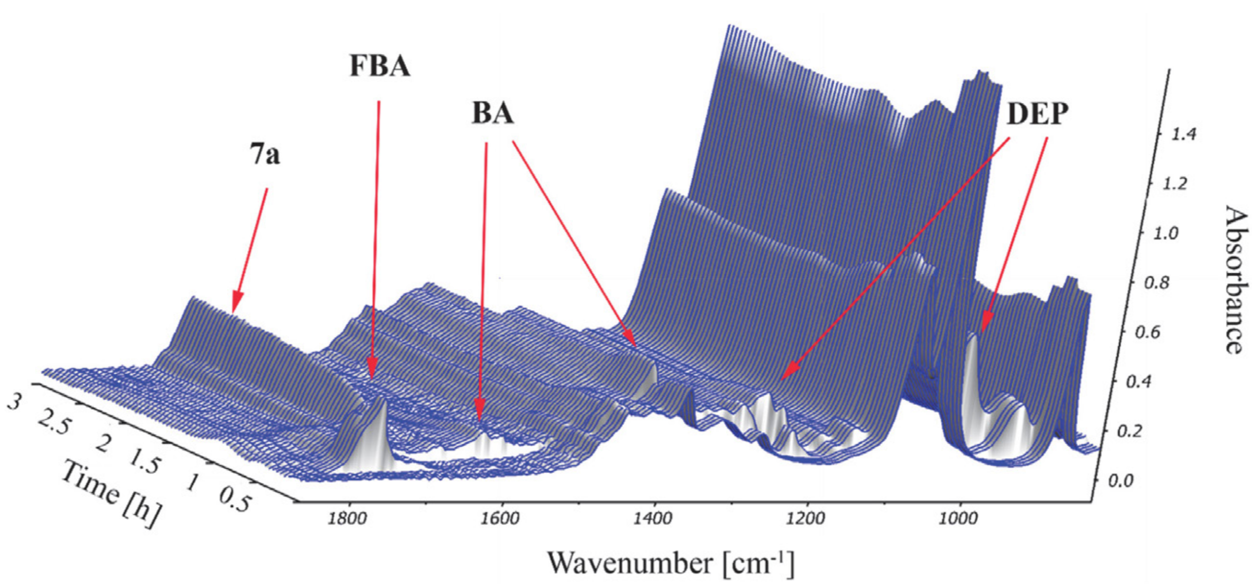


Figure 4. The time-dependent IR spectrum of the reaction of 2-formylbenzoic acid (**FBA**), butylamine (**BA**) and diethyl phosphite (**DEP**) in ethanol

isoindol-1-yl)phosphonate (**20b**) had a $\nu_{C=O}$ characteristic absorption at 1690 cm^{-1}.

During the measurement, the signals of the starting materials decreased, while the signal of product **20b** increased, as it was expected. The signal of **FBA** decreased after the addition of **BA**, however, no signal of an intermediate, for instance an imine, appeared. The reason for the decrease of the signal of **FBA** is the change of IR properties of **FBA** in the reaction mixture.

Furthermore, to increase the productivity, the synthesis of some (oxoisoindolinyl)phosphonates (**20b**, **21b**, **22b**) was elaborated in a continuous flow MW system. The equipment contained a dual HPLC pump and CEM® MW reactor with a commercially available CEM® continuous flow cell. The **FBA** in ethanol (pump A) and the mixture of amines and **DEP** in ethanol (pump B) were fed separately. The temperature was monitored and controlled by the IR sensor of the MW reactor. The leaving mixture was cooled down to 25 °C and was passed through a back-pressure regulator operating at 250 psi (17 bar).

At first, the continuous flow reaction of **FBA**, **BA** and **DEP** was carried out, and it was complete with 1.5 equivalents of both amine and dialkyl phospite, at 60 °C under a residence time of 30 min (at a flow rate of 0.25 mL/min) (Table 1, Entry 1). Starting from cyclohexylamine, a longer residence time of 45 min (at a flow rate of 0.15 mL/min) was needed to obtain a complete conversion (Table 1, Entry 2). While in the case of benzylamine, a residence time of 40 min (a flow rate of 0.18 mL/min) was applied, and the ratio of the (oxoisoindolinyl)phosphonate derivative **22b** was 100% (Table 1, Entry 3).

The productivity of the flow method was 2.3 g/h, 1.4 g/h and 1.8 g/h in the case of compounds **20b**, **21b**, **22b**, which were 1.5–2 times higher as compared to the batch method (1.8 g/h, 0.6 g/h and 1.0 g/h, respectively). The productivity of the batch process was calculated for one h, based on the net reaction time of several consecutive reactions.

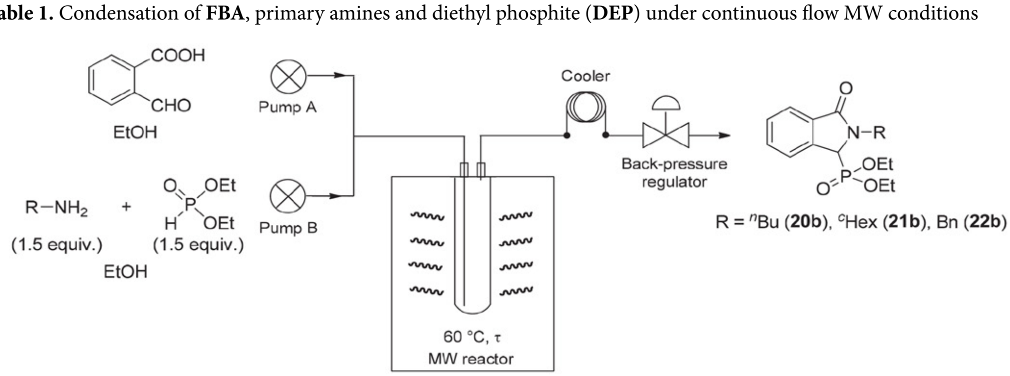
In all, 16 (oxoisoindolin-1-yl)phosphonate derivatives **20**–**22** were synthesized, among them, 14 were new compounds. By the catalyst- and solvent-free MW-assisted method, good results were obtained at a lower temperature for shorter reaction times compared with the literature procedures. The mechanism of the condensation was studied by *in situ* FT-IR spectroscopy, and experiments were successfully performed in a continuous flow MW system to increase the productivity.

2. 2. Synthesis of (Oxoisoindolin-1-yl) phosphine Oxides

Our aim was to carry out the special Kabachnik–Fields reaction of **FBA**, primary amines and secondary phosphine oxides, which is a new method for the synthesis of (oxoisoindolinyl)phosphine oxides. In the literature examples, the desired compounds were formed by multistep reactions, applying special reagents and conditions and in most cases, low yields were obtained.[54–61]

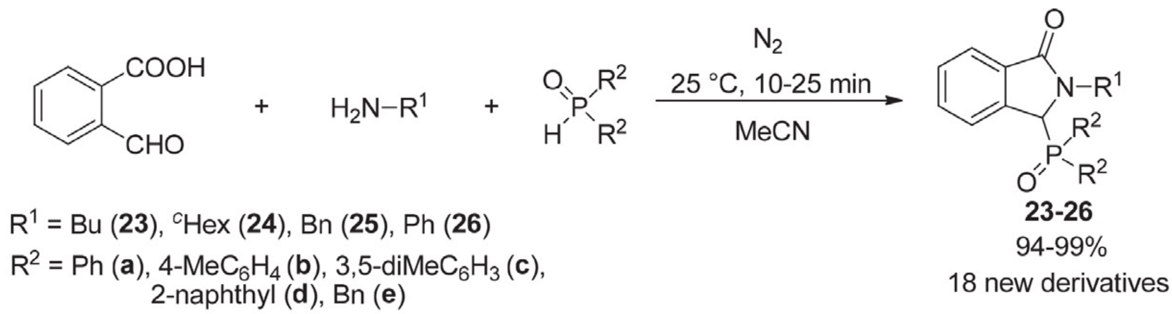
In our research work, the three-component condensation of **FBA**, butyl-, cyclohexyl-, benzylamine or aniline and diphenylphosphine oxide was studied.[62] An efficient method was elaborated by us, where complete conversion was obtained in the absence of any catalyst, at room temperature, after short reaction times (10–20 min) in acetonitrile. The condensation was extended to various secondary phosphine oxides, such as bis(*p*-tolyl)-, bis(3,5-dimethylphenyl)-, bis(2-naphthyl)- or dibenzylphosphine oxides (Scheme 2). In the case of dibenzylphosphine oxide, a longer reaction time of 25 min was necessary to obtain full conversion. Altogether, 18 new (oxoisoindolinyl)

Table 1. Condensation of **FBA**, primary amines and diethyl phosphite (**DEP**) under continuous flow MW conditions



Entry	R	Flow rate [mL/min]	τ [min]	Conversion[a] [%]	Yield[b] [%]	Productivity [g/h] Batch method	Flow method
1	^{n}Bu	0.25	30	100	95 (**20b**)	1.8	2.3
2	^{c}Hex	0.15	45	100	86 (**21b**)	0.6	1.4
3	Bn	0.18	40	100	91 (**22b**)	1.0	1.8

[a]Based on GC. [b]Isolated yield.



Scheme 2. The reaction of **FBA**, primary amines and secondary phosphine oxides

phosphine oxides **23**–**26** were isolated in excellent yields (94–99%).

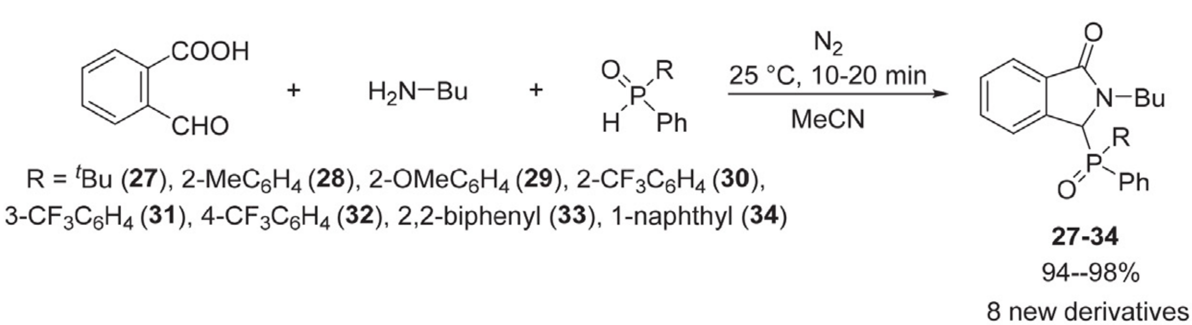
After that, the Kabachnik–Fields reaction of **FBA**, butylamine and various *P*-stereogenic phosphine oxides (*tert*-butyl(phenyl)phosphine oxide, 2-methylphenyl(phenyl)phosphine oxide, 2-methoxyphenyl(phenyl) phosphine oxide, 2-, 3- or 4-trifluoromethylphenyl(phenyl)phosphine oxide, biphenyl(phenyl)phosphine oxide or 1-naphthyl(phenyl)phosphine oxide) was carried out (Scheme 3). Applying the optimized conditions (no catalyst, at 25 °C, for 10–20 min in acetonitrile), eight (3-oxoisoindolin-1-yl)phosphine oxides **27**–**34** were synthesized in high yields (94–98%). Due to the *P*-stereogenic centre on the phosphorus atom, the products **27**–**34** were formed as a mixture of two diastereomers. The diastereomeric ratio (*dr*) was close to 50:50 for most of the compounds **27**–**34** synthesized. 2-Trifluormethylphenyl(phenyl)phosphine oxide as the *P*-reagent was an exception, in that case, the diastereomeric ratio was 35:65. It should be noted that the diastereomers of 1-naphthyl(phenyl) (2-butyl-3-oxo-2,3-dihydro-2*H*-isoindol-1-yl)phosphine oxide (**34**) could be separated by column chromatography because of the bigger difference of the size of the functional groups on the phosphorus atom (phenyl and naphtyl groups).

One of the (oxoisoindolinyl)phosphine oxide (**23a**) was reduced to an (oxoisoindolinyl)phosphine **35**, which was utilized as a phosphine ligand in the synthesis of a platinum(II) complex **36** (Scheme 4). In the first step, the deoxygenation of diphenyl (2-butyl-3-oxo-2,3-dihydro-2*H*-isoindol-1-yl)phosphine oxide (**23a**) was performed with phenyl silane ($PhSiH_3$) as the reducing agent. The reaction was carried out under inert atmosphere, applying MW irradiation at 140 °C for 6 h. The phosphine derivative **35** was not isolated, but it was further reacted with 0.5 equiv. of dichlorodibenzonitrile platinum(II) ($Pt(PhCN)_2Cl_2$) precursor at 25 °C in dichloromethane. The monodentate platinum(II) complex **36** was isolated by column chromatography in a yield of 80%.

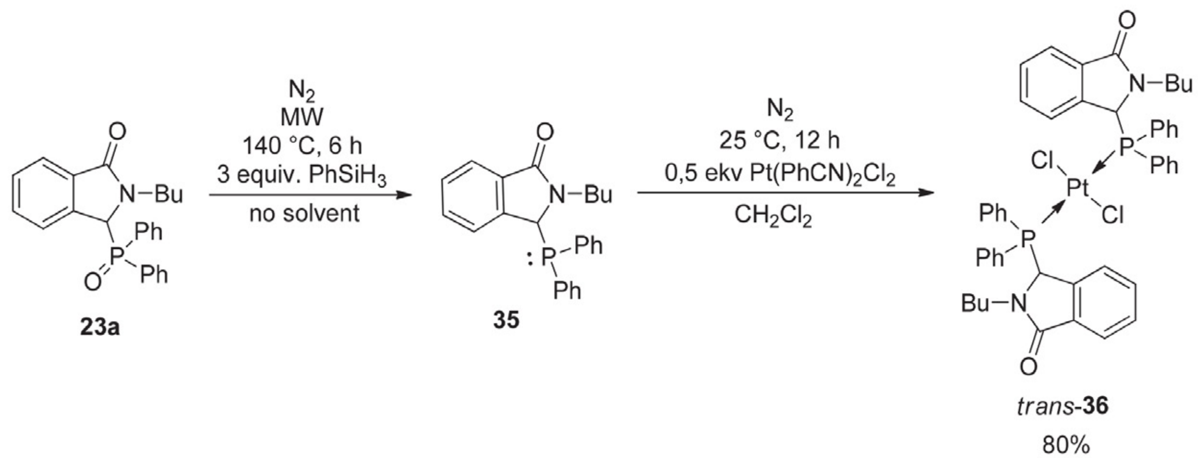
The complex **36** was formed in a relative configuration of *trans*, based on platinum-phosphorus coupling constant ($^1J_{Pt\text{-}P}$) in the ^{31}P NMR spectra. It is known in the literature that the $^1J_{Pt\text{-}P}$ between 3400 to 3600 Hz suggests *cis* complexes, while the $^1J_{Pt\text{-}P}$ coupling constant is 2500–3000 Hz in the case of *trans* arrangements.[63] In our case, the $^1J_{Pt\text{-}P}$ coupling constant was 2519 Hz. The relative orientation of the *trans*-**36** platinum(II) complex was also confirmed by X-ray diffraction measurements.

In addition, it was observed in the ^{31}P NMR spectrum that the central signal consisted of two very close peaks in a ratio of nearly 1:1. This can be explained by the chirality centre on the oxoisoindoline ring, which caused the formation of the complex *trans*-**36** as a mixture of homo- and heterochiral diastereomers.

To conclude, an efficient, simple, one-pot method was developed for the synthesis of (oxoisoindolinyl)phosphine oxides by the Kabachnik–Fields reaction followed



Scheme 3. The reaction of 2-formylbenzoic acid, butylamine and *P*-stereogenic secondary phosphine oxides



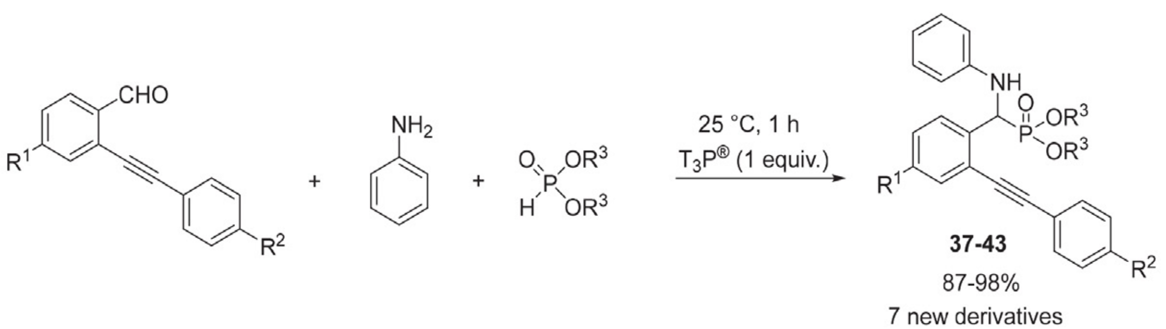
Scheme 4. Deoxygenation of (oxoisoindolinyl)phosphine oxide (**23a**) and formation of platinum(II) complex *trans*-**36**

by intramolecular cyclization of **FBA**, primary amines and secondary phosphine oxides. The condensation was extended to *P*-stereogenic secondary phosphine oxides as well. In all, 26 (3-oxoisoindolin-1-yl)phosphine oxide derivatives **23**–**34** could be synthesized in excellent yields at room temperature after short reaction times (10–60 min). After deoxygenation, diphenyl (2-butyl-3-oxo-2,3-dihydro-2*H*-isoindol-1-yl)phosphine oxide (**23a**) was utilized in the synthesis of a platinum(II) complex *trans*-**36**.

2.3. Synthesis of (Dihydroisoquinolin-1-yl)phosphonates and α-Amino-(2-alkynylphenyl)-methylphosphonates

In the literature, the Kabachnik–Fields reaction of 2-alkynylbenzaldehydes, primary amines and dialkyl phosphites was carried out in the presence of various catalysts. α-Amino-(2-alkynylphenyl)-methylphosphonates were prepared at room temperature or at 60 °C after 4 h in 1,2-dichloroethane, using magnesium perchlorate ($Mg(OCl_4)_2$) or Lewis acids ($FeCl_3$, $In(OTf)_3$, $Bi(OTf)_3$, $Yb(OTf)_3$) as the catalysts.[64,65] However, (1,2-dihydroisoquinolin-1-yl)phosphonates were obtained in the presence of a silver or a copper salt (AgOTf or CuI) in ethanol or in 1,2-dichloroethane at 60 °C for 4–6 h.[64,65] Under ultrasonic conditions, a surfactant-type copper catalyst ($C_{12}H_{25}SO_3Na$ and $CuSO_4$) was used in water.[66] In another example, the condensation was performed applying a chiral spirocyclic phosphonic acid as a chiral additive, and the optically active (dihydroisoquinolinyl)phosphonates were obtained at -10 °C after 3 days.[67] (Dihydroisoquinolinyl)phosphonates were also synthesized by a ring-closure method, starting from α-amino-(2-alkynylphenyl)-methylphosphonates in the presence of silver triflate (AgOTf).[68]

In our research work, the Kabachnik–Fields reaction of 2-alkynylbenzaldehydes, aniline and dialkyl phosphites was studied and optimized in respect of the molar ratio of the starting materials, the temperature, the reaction time, the additive or catalyst and the solvent.[69] Based on our results, depending on the conditions, α-amino-(2-alkynylphenyl)-methylphosphonates **37–43** or (1,2-dihydroisoquinolin-1-yl)phosphonates **44–50** could be syn-



R^1	H	H	F	H	H	H	H
R^2	Me	Me	Me	OMe	Cl	H	H
R^3	Bu	Bn	Bu	Bu	Bu	Bu	Et
	(37)	**(38)**	**(39)**	**(40)**	**(41)**	**(42)**	**(43)**

Scheme 5. $T_3P^{®}$-mediated Kabachnik–Fields reaction of 2-alkynylbenzaldehydes, aniline and dialkyl phosphites

thesized selectively. An efficient procedure was developed for the preparation of α-amino-(2-alkynylphenyl)-methylphosphonates **37–43** at room temperature for 1 h in the presence of $T_3P^®$ (propylphosphonic anhydride) as an additive (Scheme 5). Then, the model reaction was extended to different alkinylbenzaldehydes (2-(phenylethynyl)-, (2-(*p*-tolylethynyl)-, 4-fluoro-2-(*p*-tolylethynyl)-, 2-((4-methoxyphenyl)ethynyl)- and 2-((4-chlorophenyl)ethynyl)-benzaldehyde), as well as dialkyl phosphites (diethyl-, dibutyl- and dibenzyl phosphite), and seven new derivatives **37–43** were prepared in yields of 87–98%.

The condensation may take place through an imine intermediate, which may form by the reaction of 2-alkinylbenzaldehyde and aniline. The role of the $T_3P^®$ is promoting dehydration. After the addition of the phosphorus reagent to the double bond of the intermediate, the α-amino-(2-alkynylphenyl)-methylphosphonates **37–43** are formed.

Performing the three-component reaction at 60 °C for 1 h, in the presence of 5 mol% of copper chloride (CuCl) as the catalyst, and using 2-alkynylbenzaldehyde and aniline in a small excess (1.2 equiv.), (1,2-dihydroisoquinolin-1-yl)phosphonates **44–50** were synthesized selectively (Scheme 6). After the optimization, by changing the 2-alkynylbenzaldehydes and dialkyl phosphites, seven new (dihydroisoquinolin-1-yl)phosphonates **44–50** were prepared in good to high yields (79–86%). In contrast to the literature, in our method, we applied a cheaper catalyst and shorter reaction time.

The first step of the formation of (1,2-dihydroisoquinoline)phosphonates **44–50** is the CuCl-catalyzed Kabachnik–Fields reaction of 2-alkynylbenzaldehydes, aniline and dialkyl phosphites. After that, the catalyst interacts with the triple bond of the α-amino-(2-alkynylphenyl)-methylphosphonates **37–43**, which makes the intramolecular nucleophile attack possible by the amino group, causing the ring closure step.

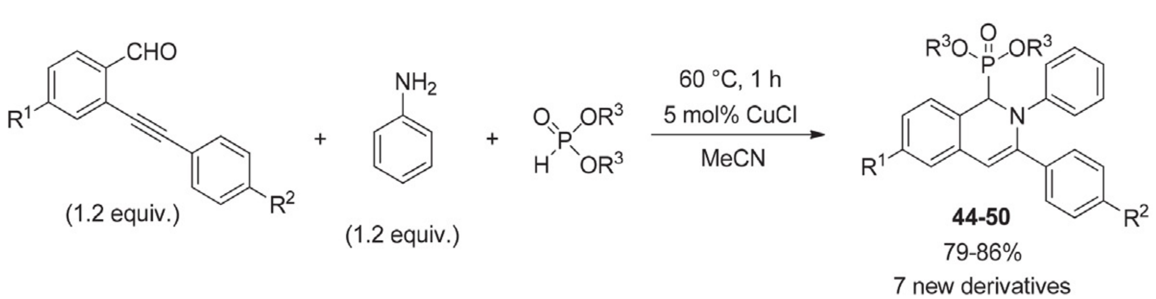
Altogether seven new α-amino-(2-alkynylphenyl)-methylphosphonates **37–43** were prepared in a shorter reaction time (1 h) under milder conditions (25 °C) by the $T_3P^®$-mediated process developed by us as compared to the literature methods, which were carried out in the presence of $Mg(OCl_4)_2$ or Lewis acids for long reaction times. Furthermore, seven new (1,2-dihydroisoquinolin-1-yl)phosphonates **44–50** were also synthesized using a small excess (1.2 equiv.) of alkynylbenzaldehyde and amine, in acetonitrile instead of a halogenated solvent (1,2-dichloroethane) in a shorter reaction time (1 h instead of 4–6 h) using a cheaper catalyst (CuCl), than in the literature.

2. 4. Synthesis of (Dihydroisoquinolin-1-yl) phosphine Oxides

The Reissert-type reaction of isoquinoline, different acetylenes and secondary phosphine oxides or phosphine sulfides for the synthesis of (1,2-dihydroisoquinolin-1-yl) phosphine oxide derivatives was studied in the literature, however, only in two cases.[70,71] The condensations were performed at high temperature (70–72 °C) for long reaction times (1.5–12 h), applying 1.1–1.5 equiv. excess of isoquinoline and acetylenes. However, starting from acylphenylacetylenes, longer reaction times (45–72 h) were used.[71]

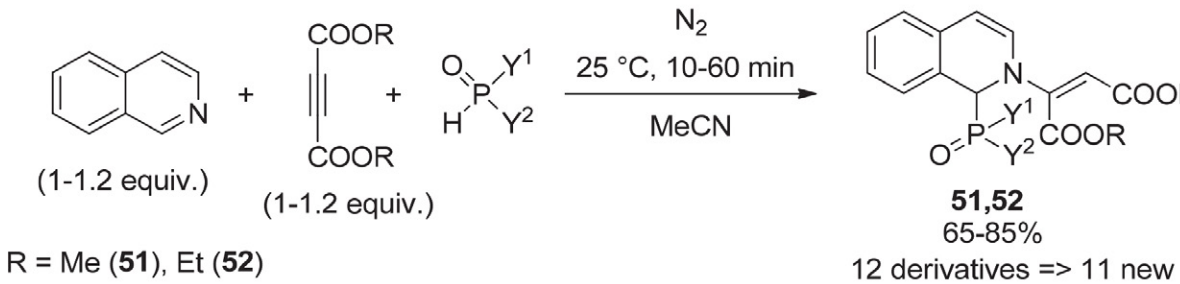
In two other examples, the Reissert-type reaction was performed with dialkyl phosphites in the absence of any catalyst and solvent at room temperature for 2–4 h.[72,73] The (1,2-dihydroisoquinolin-1-yl)phosphonates were obtained in yields of 52–90%.

The Reissert-type reaction of isoquinoline, diethyl acetylenedicarboxylate and diphenylphosphine oxide was investigated, and the effect of the solvent, catalyst, temperature and reaction time was investigated.[74] A complete conversion was obtained using equivalent amount of the starting materials in acetonitrile, at room temperature after 10 min. Under the optimized conditions, the condensation of isoquinoline, dimethyl or diethyl acetylenedicarboxylate and diphenyl-, bis(*p*-tolyl)-, bis(3,5-dimethylphenyl)phosphine oxide or ethyl phenyl-*H*-phosphinate



R^1	H	H	H	F	H	H	H
R^2	Me	Me	Me	Me	OMe	Cl	H
R^3	Bu	Me	Et	Bu	Bu	Bu	Bu
	(**44**)	(**45**)	(**46**)	(**47**)	(**48**)	(**49**)	(**50**)

Scheme 6. CuCl-catalyzed Kabachnik–Fields reaction of 2-alkynylbenzaldehydes, aniline and dialkyl phosphites



Y^1	Ph	4-MeC$_6$H$_4$	3,5-diMeC$_6$H$_3$	Bn	2-naphthyl	Ph
Y^2	Ph	4-MeC$_6$H$_4$	3,5-diMeC$_6$H$_3$	Bn	2-naphthyl	OEt
	(a)	(b)	(c)	(d)	(e)	(f)

Scheme 7. Reissert-type reaction of isoquinoline, diakyl acetylenedicarboxylates, and secondary phosphine oxides or ethyl phenyl-*H*-phosphinate

was performed, and eight (1,2-dihydroisoquinolin-1-yl) phosphine oxide derivatives (**51** and **52**) were formed in yields of 65–85% (Scheme 7). In the case of ethyl phenyl-*H*-phosphinate, the desired dialkyl (*E*)-2-[1-(ethoxy(phenyl)phosphoryl)isoquinolin-2(1*H*)-yl]maleate derivatives (**51f** and **52f**) were obtained as a mixture of diastereomers in a ratio of 60:40.

Starting from dibenzyl-, or di(2-naphthyl)phosphine oxides as the *P*-reagent, a small excess (1.2 equiv.) of isoquinoline and dialkyl acetylenedicarboxylate, as well as somewhat longer reaction time (1 h) were applied to obtain complete conversion. Thus, further four new (1,2-dihydroisoquinolin-1-yl)phosphine oxides (**51d**,**e** and **52d**,**e**) were synthesized in yields of 70–73%.

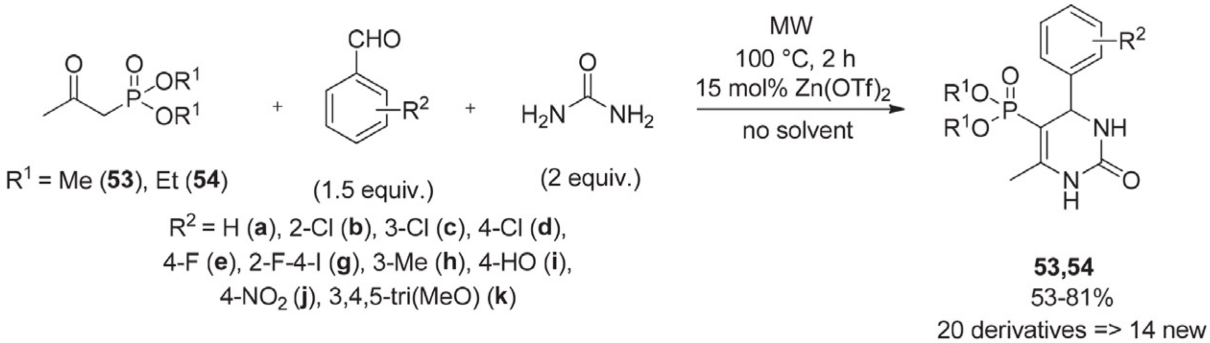
The mechanism of the formation of (1,2-dihydroisoquinolin-1-yl)phosphine oxides **51** and **52** can be explained by the nucleophile addition of isoquinoline to diakyl acetylenedicarboxylates, forming a zwitterion intermediate. Then the products **51** and **52** are formed after the reaction of the intermediate with the *P*-reagent.

In summary, an efficient, rapid process was developed for the synthesis of (dihydroisoquinoline)phosphine oxides **51** and **52** by the Reissert-type reaction of isoquinoline, dialkyl acetylenedicarboxylates and secondary phosphine oxides or ethyl phenyl-*H*-phosphinate. As compared to the literature, a complete conversion was obtained in shorter reaction time (10 min instead of 1.5–72 h) and in most cases, without the excess (1.1–1.5 equivalents) of isoquinoline and acetylene. In all, 12 dialkyl (*E*)-2-[1-(phosphoryl)isoquinolin-2(1*H*)-yl]maleate derivatives **51** and **52** were synthesized, among them 11 compounds were new.

2. 5. Synthesis of (Dihydropyrimidinone) phosphonates

Only a few examples can be found in the literature for the Biginelli reaction of β-ketophosphonates, aldehydes and urea. In one example, the condensation was performed in the presence of 15 mol% of zinc triflate ($Zn(OTf)_2$) in toluene, at high temperature (110 °C) for 3 h.[40] In another case, 50 mol% of *p*-toluenesulfonic acid (PTSA) was used as a catalyst in boiling acetonitrile for longer reaction time (24 h).[75] Finally, the condensation was performed with ytterbium triflate ($Yb(OTf)_3$) in toluene, at reflux temperature for 12 h.[76] In all cases, urea was used in excess. Based on the literature data, the Biginelli reaction of β-ketophosphonates does not take place starting from aliphatic aldehydes.

The Biginelli reaction of diethyl (2-oxopropyl)phosphonate, benzaldehyde and urea was studied by us.[77] The conditions (heating mode, temperature, reaction time, molar ratio of the starting materials, catalyst and solvent) were changed to maximize the conversion. Based on our results, a new solvent-free MW-assisted method was developed for the synthesis of (dihydropyrimidinone) phosphonates **53–57** by the $Zn(OTf)_2$-catalyzed Biginelli reaction. During optimization it was found that besides starting materials and the desired (dihydropyrimidinone) phosphonate **53a**, a by-product containing a styryl group at position six was also in the reaction mixture, which could be formed by the aldol condensation of the product **53a** and benzaldehyde. The optimal parameters for the MW-assisted synthesis of (dihydropyrimidinone)phosphonates were applying 1.5 equiv. of benzaldehyde and 2 equiv. of urea, in the presence of 15 mol% of $Zn(OTf)_2$ at 100 °C for 2 h. After that, the condensation was carried out with different β-ketophosphonates (dimethyl or diethyl (2-oxopropyl)phosphonate), substituted benzaldehydes (benzaldehyde, 2-chlorobenzaldehyde, 3-chlorobenzaldehyde, 4-chlorobenzaldehyde, 4-fluorobenzaldehyde, 2-fluoro-4-iodobenzaldehyde, 3-methylbenzaldehyde, 4-hydroxybenzaldehyde, 4-nitrobenzaldehyde, 3,4,5-trimethoxybenzaldehyde) and urea derivatives (urea or *N*-methylurea) (Scheme 8). In all 20 (dihydropyrimidinone)phosphonates **53** and **54** were obtained in yields of 53–81% after column chromatography, and among them, 14 were new derivatives, not yet described in the literature.



Scheme 8. Biginelli reaction of β-ketophosphonates, substituted benzaldehydes and urea

Starting from *N*-methylurea, dimethyl or diethyl (2-oxopropyl)phosphonate and benzaldehyde, further two new compounds were prepared in slightly lower yields (Scheme 9).

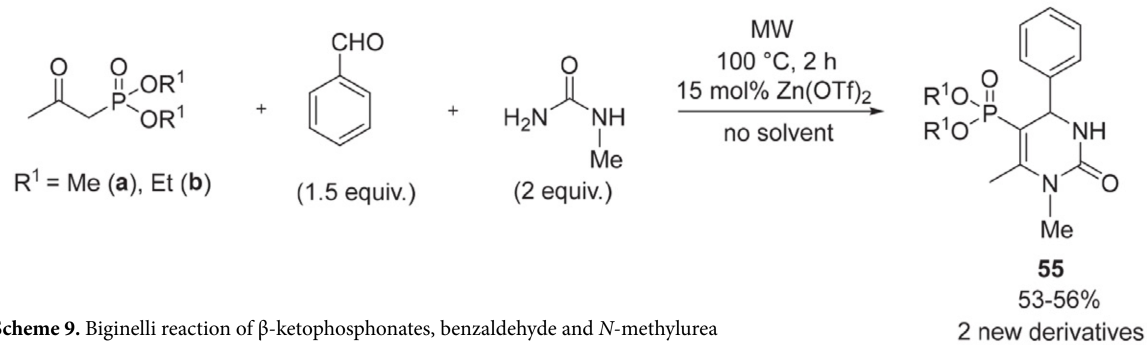
In contrast with the literature procedures, our method was also suitable when using aliphatic aldehydes in the Biginelli reaction of β-ketophosphonates (Scheme 10). The condensation of dimethyl or diethyl (2-oxopropyl) phosphonate, butyraldehyde or isovaleraldehyde and urea was accomplished successfully, and further four new compounds **56** and **57** were isolated in yields of 41–43%.

In counclusion, a new solvent-free MW-assisted process was elaborated for the preparation of (3,4-dihydropyrimidin-2-(1*H*)-one)phosphonates **53**–**57** by the Biginelli reaction of β-ketophosphonates, substituted benzaldehydes and urea derivatives. As compared to the literature examples, the desired compounds **53**–**57** could be obtained in shorter reaction time (2 h instead of 3–24 h) without solvent. The condensation was also successfully performed starting from aliphatic aldehydes. In our research work, a molecular library of 26 (dihydropyrimidinone)phosphonate derivatives **53**–**57** was created, of which 20 compounds were new.

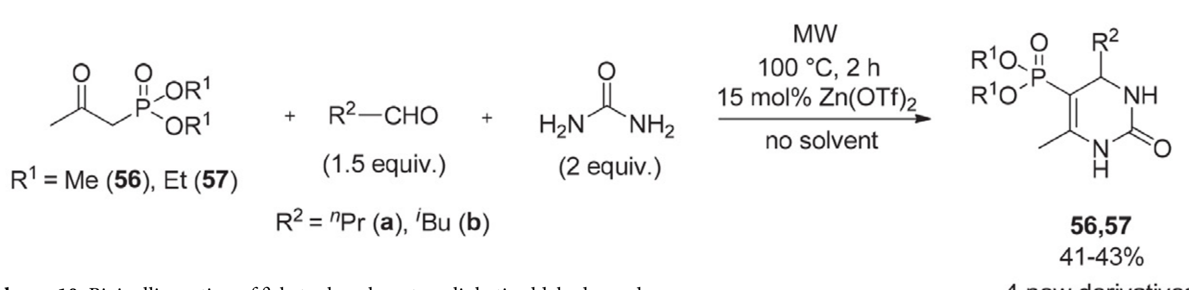
2. 6. Synthesis of (1,2,3-Triazol-5-yl) phosphonates

In the literature, the 1,3-dipolar cycloaddition of azides and alkynyl phosphonates is the most common way for the synthesis of (1,2,3-triazol-5-yl)phosphonates, however, in most cases, the reaction was not selective, since (1,2,3-triazol-4-yl)phosphonates were also obtained besides (1,2,3-triazol-5-yl)phosphonates.

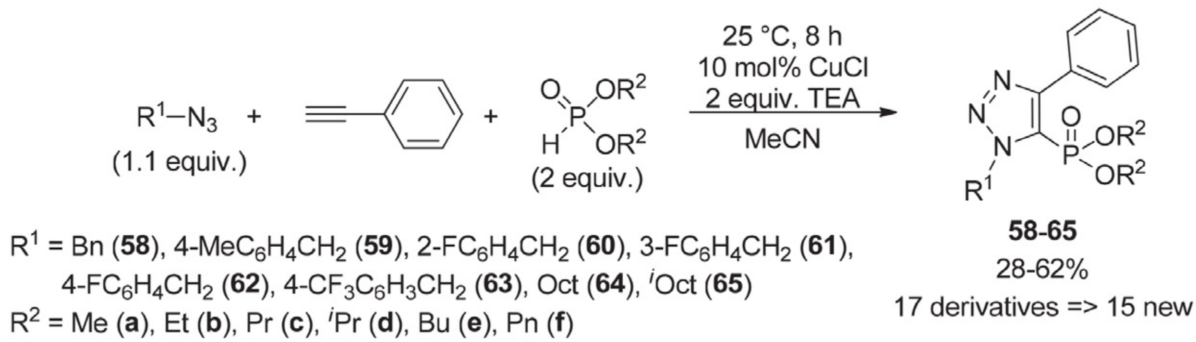
In three cases, the reactions were carried out in the absence of any catalyst, in different solvents, such as toluene,[78] diethyl ether[79] or water.[80] In refluxing toluene, the cy-



Scheme 9. Biginelli reaction of β-ketophosphonates, benzaldehyde and *N*-methylurea



Scheme 10. Biginelli reaction of β-ketophosphonates, aliphatic aldehydes and urea



Scheme 11. Synthesis of (1,2,3-triazolyl)phosphonates **58**–**65** by CuCl-catalyzed domino reaction

cloaddition of ethyl (diethoxyphosphinyl)propynoate and methyl azidoacetate was performed.[78] Trifluoromethylated triazolylphosphonates were synthesized in diethyl ether by the reaction of *tert*-butyl azidoacetate to diisopropyl (3,3,3-trifluoroprop-1-ynyl)phosphonate at room temperature for long reaction time (20 h).[79] When the click reaction of a phosphorylalkyl azide and tetramethoxy acetylenediphosphonate was performed at room temperature for 36 h in water, the desired product was obtained in a high yield.[80] The reaction time could be reduced to 2 h at a higher temperature of 60 °C with the same yield. Next, the cycloaddition of benzyl azide and diethyl ethynylphosphonate derivatives was performed applying copper(II) sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$) and sodium ascorbate as a catalyst in DMF at 170 °C for 12 h.[81] The desired (1,2,3-triazol-5-yl) phosphonates were formed selectively, and were obtained in good to high yields (83–92%). Finally, a MW-assisted solvent- and catalyst-free method was also published, where the ratio of the (1,2,3-triazol-4-yl)phosphonate and the (1,2,3-triazol-5-yl)phosphonate derivative was 34:66.[82]

In the literature, there is only one example regarding the domino synthesis of (1,2,3-triazol-5-yl)phosphonates.[83] The condensation of azides, terminal alkynes, and various dialkyl phosphites was performed using CuCl as a catalyst in acetonitrile at room temperature for 20 h under air atmosphere.

In our work, the synthesis of (1,2,3-triazol-5-yl)phosphonates **58–65** was optimized through the three-component reaction of phenylacetylene, benzyl azide and dibutyl phosphite in respect of the catalyst, base, solvent, molar ratio of the starting materials, atmosphere, temperature, as well as the reaction time.[84] The best result was obtained using 1.1 equiv. of the azide derivative, 2 equiv. of dialkyl phosphite in the presence of 10 mol% of CuCl and 2 equiv. of triethylamine (TEA) in acetonitrile at room temperature after 8 h, using continuous air bubbling. During the optimization, the reaction mixtures contained two triazole derivatives. One of them was the desired (1,2,3-triazol-5-yl) phosphonate and the other compound was the product of the click reaction of phenylacetylene and benzyl azide.

After the optimization, the CuCl-catalyzed domino reaction of phenylacetylene, benzyl azide and dibutyl phosphite was extended to various benzyl azides (benzyl-, 4-methylbenzyl-, 2-fluorobenzyl-, 3-fluorobenzyl-, 4-fluorobenzyl- or 4-(trifluoromethyl)benzyl azide) and dialkyl phosphites (dimethyl-, diethyl-, dipropyl-, diisopropyl-, dibutyl- or dipentyl phosphite) (Scheme 11). After column chromatography, 13 (1,2,3-triazol-5-yl) phosphonate derivatives **58–63** were obtained in yields of 30–62%, of which 11 were new compounds.

Next, the domino reaction was also carried out starting from aliphatic azides (octyl or isooctyl azide), phenylacetylene and different dialkyl phosphites (dimethyl-, diethyl- or dibutyl phosphite) under the optimized conditions (with 10 mol% of CuCl and 2 equiv. of TEA at room temperature for 8 h, in acetonitrile). Further four new (1,2,3-triazol-5-yl)phosphonates **64** and **65** were synthesized in yields of 58% and 28%, respectively.

The synthesis of (1,2,3-triazol-5-yl)phosphonates **58–65** was efficiently performed by the three-component domino reaction of phenylacetylene, various azides and dialkyl phosphites in the presence of CuCl and TEA. In all, 17 (1,2,3-triazol-5-yl)phosphonate **58–65** derivatives were synthesized in good yields, among them 15 were new compounds.

2.7. Synthesis of [(1,2,3-Triazol-4-yl)methyl] phosphinates and [(1,2,3-Triazol-4-yl) methyl]phosphates

The synthesis of (1,2,3-triazol-4-yl)phosphonates can be performed by the Cu(I)-catalyzed 1,3-dipolar (Huisgen) cycloaddition—also known as the click reaction—of azides and phosphorylated alkynes.[85,86]

By the click reaction of benzyl azide and ethyl ethynylphosphonate, 1,2,3-triazolyl-4-phosphonate and 1,2,3-triazolyl-5-phosphonate were synthesized without catalyst in toluene at reflux temperature.[87] In two cases, triazoles containing bisphosphonate unit were obtained by the 1,3-dipolar cycloaddition of organic azides and propargyl-substituted bisphosphonates at room temperature after long reaction times (24–68 h).[88,89] In one case, the reaction was carried out in the presence of copper iodide (CuI) as a catalyst and *N*,*N*-diisopropylethylamine

(DIPEA) as a base, in THF.[88] In another example, $CuSO_4·5 H_2O$ and sodium ascorbate was used as a catalyst, and the solvent was the mixture of *tert*-butyl alcohol and water.[89] The click reaction of azides and ethynyl- or propargyl-substituted phosphonates was carried out with $CuSO_4·5 H_2O$ and sodium ascorbate and α-CF_3-α-aminophosphonates containing triazole unit were formed in yields of 38–92%.[90] A triazole-functionalized phosphate flame-retardant monomer was synthesized by the cycloaddition of 2-azidoethanol and triprop-2-ynyl phosphate at 85 °C for 12 h in toluene.[91]

In our research work, we aimed at the study of the Cu(I)-catalyzed click reaction of propynyl phosphinates, propynyl phosphates—which were prepared by esterification of the corresponding phosphinic acid—and organic azides.[92] At first, the parameters (heating mode, temperature, reaction time and load of the catalyst) of the click reaction of benzyl azide and prop-2-ynyl diphenylphosphinate were investigated in the presence of $CuSO_4·5 H_2O$ and sodium ascorbate in the mixture of *tert*-butyl alcohol and water (4:1). The optimal conditions were 3 mol% of $CuSO_4·5H_2O$, 5 mol% of sodium ascorbate and 60 °C for 10 min. In the next step, the cycloaddition of benzyl-, 4-methylbenzyl-, 2-fluorobenzyl-, 3-fluorobenzyl-, 4-fluorobenzyl- or 4-(trifluoromethyl)benzyl-, octyl-, isooctyl-, cyclohexyl- or phenyl azide and prop-2-ynyl diphenylphosphinate were performed, and 10 new (1,2,3-triazol-4-yl)methyl diphenylphosphinate derivatives **66a**–**j** were isolated in yields of 63–91% (Scheme 12).

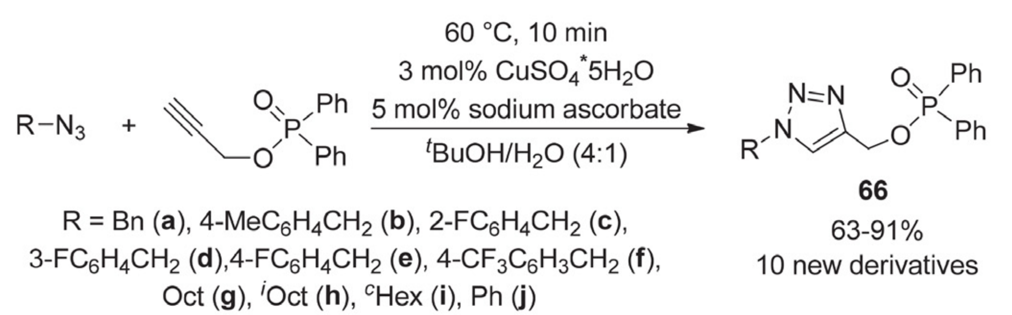
Carrying out the click reaction of azides mentioned above with diethyl prop-2-ynyl phosphate, the conversion was not complete under the optimized conditions found earlier (60 °C, after 10 min) (Scheme 13). In this case, a slightly longer reaction time (30 min) had to be used. In all, 10 new (1*H*-1,2,3-triazol-4-yl)methyl diethyl phosphates **67a**–**j** were synthesized in yields of 51–75%.

To sum up, a simple, fast and efficient method was developed for the synthesis of (1*H*-1,2,3-triazol-4-yl) methyl phosphinates **66a**–**j** and (1*H*-1,2,3-triazol-4-yl) methyl diethyl phosphates **67a**–**j** by the cycloaddition of azides and prop-2-ynyl phosphinate or diethyl prop-2-ynyl phosphate. The target compounds were prepared in the presence of $CuSO_4·5H_2O$ and sodium ascorbate under mild conditions (60 °C) after short reaction times (10–30 min). In all, 20 novel derivatives **66** and **67** were synthesized.

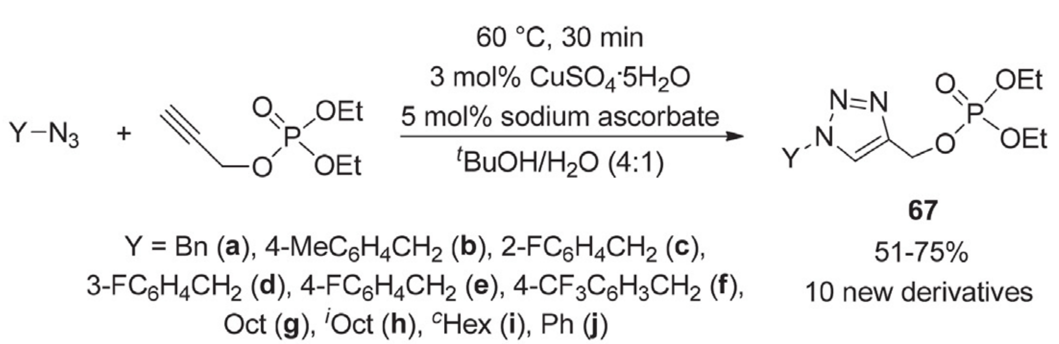
3. Synthesis of *O*-Heterocycles

3. 1. Synthesis of (2-Amino-3-cyano-4*H*-chromen-4-yl)phosphonates and -phosphine Oxides

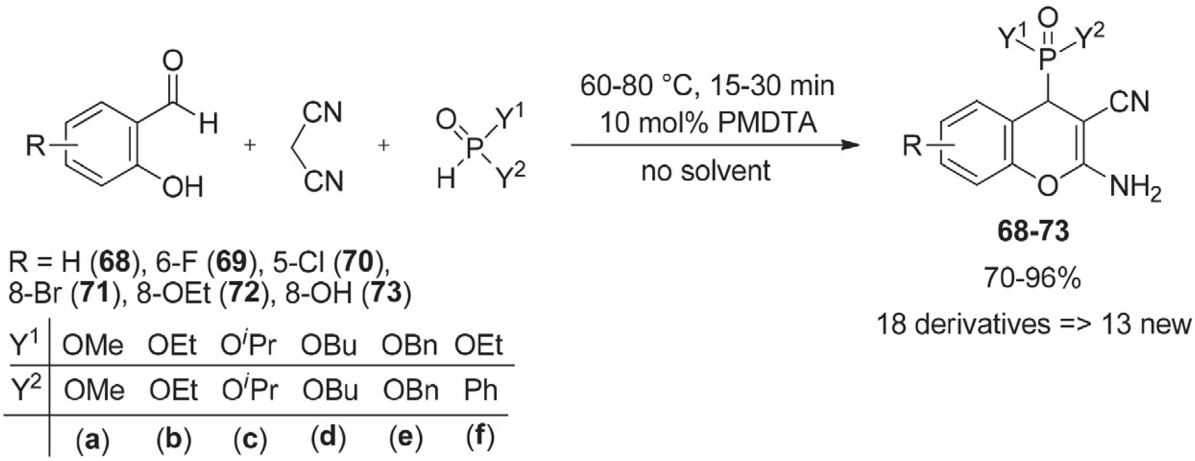
A few publications can be found for the three-component synthesis of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonates starting from salicylaldehydes, malononitrile and dialkyl phosphites or trialkyl phosphites. In most



Scheme 12. Synthesis of (1,2,3-triazol-4-yl)methyl diphenylphosphinates **66a**–**j** by click reaction



Scheme 13. Synthesis of (1,2,3-triazol-4-yl)methyl diethyl phosphates **67a**–**j** by click reaction



Scheme 14. PMDTA-catalyzed reaction of salicylaldehydes, malononitrile and dialkyl phosphites

cases, the reactions were performed in the presence of a basic catalyst and solvent. The condensations were carried out with diethylamine,[93] dibutylamine,[43] triethylamine,[94] dimethylaminopyridine,[95] imidazole,[96] ethylenediamine diacetate,[97] lithium hydroxide,[96] potassium phosphate,[98] magnesium oxide[99] or indium chloride[100] in ethanol, or with iron oxide,[101] iodine[42] or β-cyclodextrin[102] in water. A few examples can be found for the use of special solvents, such as polyethylene glycol,[103] ionic liquids[104] or the mixture of urea and choline chloride.[105] In four cases, the reactions were carried out without solvents, however, special catalysts (silica-bonded 2-HEAA-3 catalyst,[106] ZnO nano-rods,[107] iodine[108]) or a simple catalyst in a large excess (3.5 equiv. of tetramethylguanidine)[109] were needed. In the literature, there is no example for the condensation of salicylaldehydes, malononitrile and secondary phosphine oxides.

The condensation of salicylaldehydes, malononitrile and dialkyl phosphites was studied through a model reaction.[110] The effect of various basic catalysts, solvent, temperature and reaction time was investigated. Based on our results, pentamethyldiethylenetriamine (PMDTA) was the most effective among the bases. A complete conversion was achieved with 10 mol% PMDTA in the absence of any solvent at 60–80 °C after 15–30 min (Scheme 14). A total of 18 (2-amino-3-cyano-4*H*-chromen-4-yl)phosphonate derivatives **68–73** were synthesized in yields of 70–96%, of which 13 were new compounds. The products were isolated from the reaction mixture by a simple filtration. Starting from ethyl phenyl-*H*-phosphinate as the phosphorus

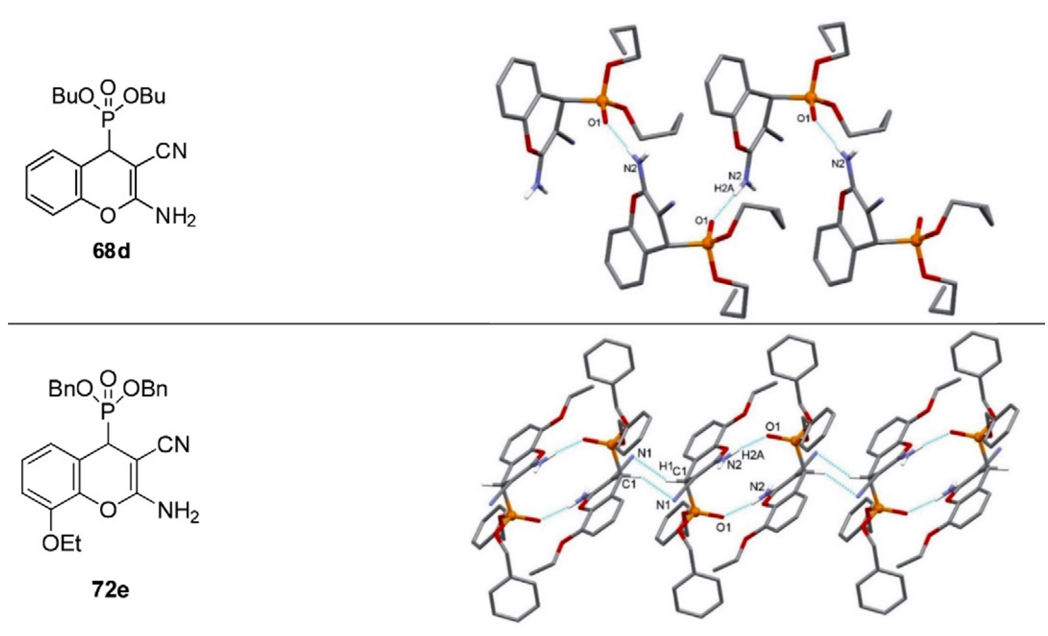
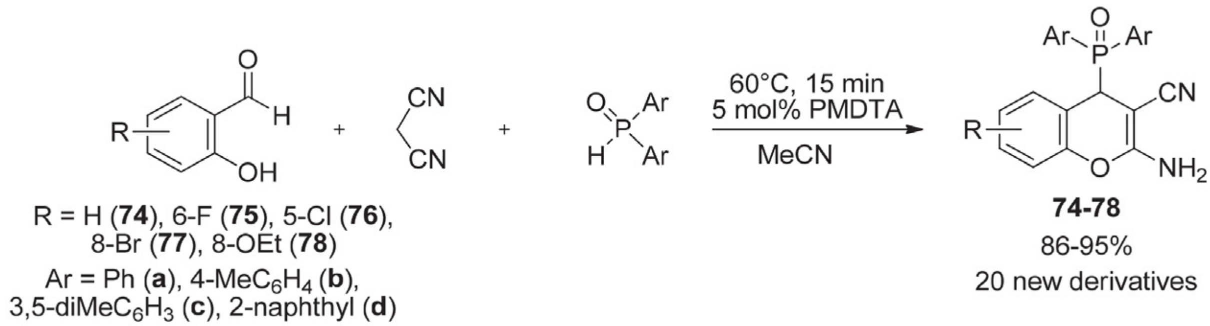


Figure 5. The crystal structure of **68d** and **72e** (2-amino-3-cyano-4*H*-chromen-4-yl)phosphonates



Scheme 15. PMDTA-catalyzed reaction of salicylaldehydes, malononitrile and secondary phosphine oxides

reagent, the desired (aminochromenyl)phosphinate **68f** was obtained in a yield of 86%, as a mixture of diastereomers in a ratio of 1:1.

The crystal structures of dibutyl (2-amino-3-cyano-4*H*-chromen-4-yl)phosphonate (**68d**) and dibenzyl (2-amino-3-cyano-8-ethoxy-4*H*-chromen-4-yl)phosphonate (**72e**) were determined by X-ray diffraction (XRD), as well (Figure 5). In both derivatives (**68d** and **72e**), an intermolecular N–H···O=P hydrogen bonding between the amino group and the phosphonate oxygen atom was

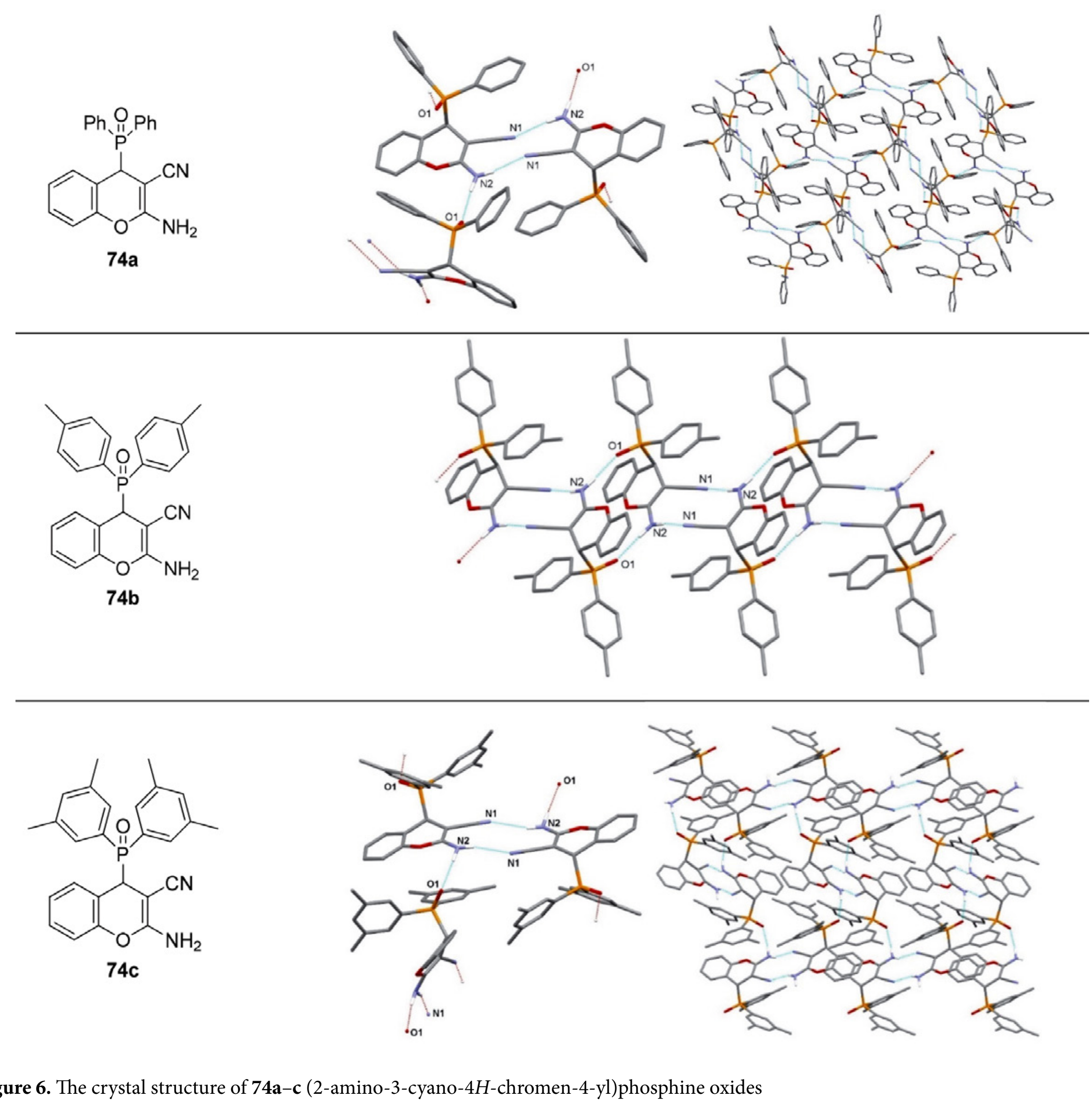


Figure 6. The crystal structure of **74a–c** (2-amino-3-cyano-4*H*-chromen-4-yl)phosphine oxides

found. However, the amino group as a hydrogen bond donor was observed to be involved in the formation of two interactions in the case of the butyl ester (**68d**). The other interaction was a centrosymmetric N–H···N hydrogen bond with the cyano group. Due to these interactions, hydrogen-bonded layers were formed. In the benzyl ester (**72e**), besides the centrosymmetric N–H···O=P interactions, centrosymmetric C–H···N interactions between the chromenyl ring and the cyano group of two adjacent molecules are present, resulting in the hydrogen-bonded chain.

According to the proposed mechanism of the formation of (2-amino-3-cyano-4*H*-chromen-4-yl)phosphonates **68**–**73**, at first, the Knoevenagel condensation of the salicylaldehyde and malononitrile takes place. Next, iminocoumarine is formed by the intramolecular Pinner-like reaction from the 2-(2-hydroxybenzylidene)malononitrile intermediate. Finally, the phospha-Michael addition of dialkyl phosphites leads to (2-amino-3-cyano-4*H*-chromen-4-yl)phosphonates **68**–**73**.

The PMDTA-catalyzed condensation of salicylaldehydes (salicylaldehyde or 5-fluoro-, 2-chloro-, 3-bromo-, or 3-ethoxysalicylaldehyde), malononitrile and *P*-reagents was extended to secondary phosphine oxides (such as diphenyl-, bis(*p*-tolyl)-, bis(3,5-dimethylphenyl)- or bis(2-naphthyl)phosphine oxides), as well. A new family of compounds, (2-amino-3-cyano-4*H*-chromen-4-yl)phosphine oxides **74**–**78** were formed with 5 mol% PMDTA at 60 °C after 15 min, in acetonitrile (Scheme 15). In our work, 20 new (aminochromenyl)phosphine oxides **74**–**78** were synthesized in excellent (86–95%) yields.

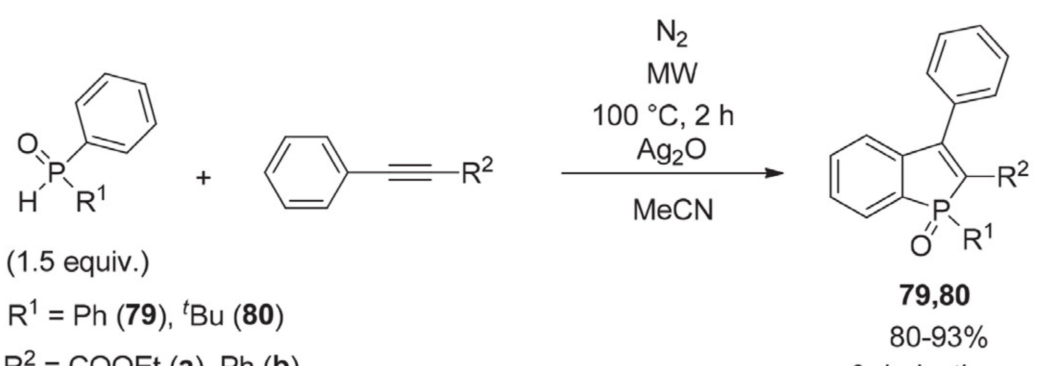
Single crystals were also grown from three derivatives **74a**–**c** in acetonitrile and their structures were investigated by XRD (Figure 6). Based on our results, an intermolecular N–H···O=P hydrogen bond is formed between the amino group and the phosphine oxide side chain. Furthermore, the amino group is involved in a centrosymmetric N–H···N interaction with the cyano group of the adjacent molecule. In the case of (diphenyl)(2-amino-3-cyano-4*H*-chromen-4-yl)phosphine oxide (**74a**) and [bis(3,5-dimethylphenyl)](2-amino-3-cyano-4*H*-chromen-4-yl)phosphine oxide (**74c**), N–H···O=P interactions lead to the formation of layers. A difference can be observed in the crystal structure of [bis(*p*-tolyl)](2-amino-3-cyano-4H-chromen-4-yl)phosphine oxide (**74b**), where a centrosymmetric N–H···N interactions (between the amino and the cyano groups) and centrosymmetric N–H···O=P hydrogen bonds led to the formation of hydrogen-bonded chains.

Summarizing our results, the model reaction of salicylaldehyde, malononitrile and dialkyl phosphites was studied and optimized. By our solvent-free PMDTA-catalyzed method, 18 (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonate derivatives **68**–**73** were prepared in good to high yields (70–96%). Our method was also suitable for the domino Knoevenagel-phospha-Michael reaction of secondary phosphine oxides, and 20 new (2-amino-3-cyano-4*H*-chromen-4-yl)phosphine oxides **74**–**78** were synthesized, which are members of a new family of compounds in the literature.

4. Synthesis of *P*-Heterocycles

4. 1. Synthesis of 1-Alkyl-1*H*-phoshindole-1-oxides and 1-Alkoxy-1*H*-phoshindole-1-oxides

In the literature, phoshindole-1-oxide derivatives were prepared by the intermolecular radical cycloaddition of secondary phosphine oxides or phosphinates and internal alkynes.[111] In the examples, several oxidizing agents were used, and in general, a long reaction time (8–24 h) was applied to obtain complete conversion, for example: Ag_2O (8–10 h),[112,113] AgOAc (4–18 h),[114–116] $Mn(OAc)_2/MnO_2$ (4 h),[117] $K_2S_2O_8$ (24 h)[118] or *N*-etoxy-2-methylpyridinium tetrafluoroborate (48 h).[119] In one case, a shorter reaction time of 30 min was enough, however, beside the oxidant (*tert*-butyl hydroperoxide), a catalyst ($CuSO_4$) and a base (NH_3) were necessary.[120] Our aim was to find a fast and simple method for the synthesis of phoshindole-1-oxides.



Scheme 16. Cycloaddition of secondary phosphine oxides and ethyl phenylpropiolate or diphenylacetylene

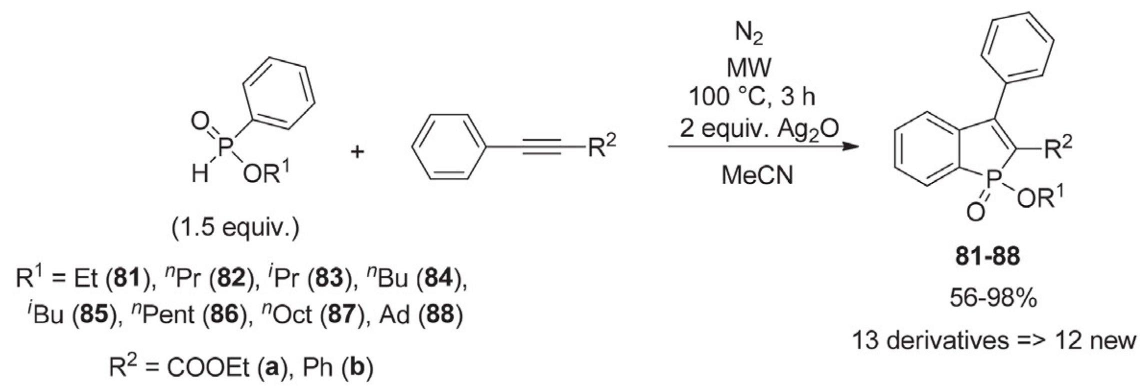
The first step of our work was the study and optimization of the MW-assisted cycloaddition of diphenylphosphine oxide and ethyl phenylpropiolate in respect of the oxidant, temperature and reaction time in acetonitrile as the solvent.[121] It was found that complete conversion could be obtained under MW conditions, applying 1.5 equivalents of diphenylphosphine oxide, 2 equivalents of Ag_2O as the oxidizing agent, at 100 °C for 2 h in acetonitrile (Scheme 16). Using the optimal conditions, the reaction of diphenyl acetylene and diphenylphosphine oxide or *tert*-butyl(phenyl)phosphine oxide was performed. The three benzophosphole oxide derivatives **79a**, **79b** and **80b** were obtained after column chromatography, in yields of 80–93%.

In the next series of experiments, the cycloaddition was extended to alkyl phenyl-*H*-phosphinates and different acetylenes in the presence of Ag_2O (Scheme 17). The MW-assisted reaction of ethyl phenyl-*H*-phosphinate and ethyl phenylpropiolate was optimized in respect of temperature and reaction time. Based on our results, the reaction was complete after a slightly longer (3 h) reaction time as compared to the reactions carried out with secondary phosphine oxides. Then, the cycloaddition was performed starting from further alkyl phenyl-*H*-phosphinates (*n*-propyl-, isopropyl-, *n*-butyl-, isobutyl-, *n*-pentyl-, *n*-octyl- and adamantyl phenyl-*H*-phosphinate) and ethyl phenylpropiolate or diphenyl acetylene. In all, 13 1-alkoxy-1*H*-phoshindole-1-oxides were synthesized in yields of 56–98%. Slightly lower yields (56–68%) were obtained starting from *n*-pentyl-, *n*-octyl- and adamantyl phenyl-*H*-phosphinate, due to the steric hindrance.

A single crystal was grown of 1-isopropoxy-2,3-diphenylphosphindole 1-oxide (**83b**) and the structure was analyzed by XRD (Figure 8). The analysis showed the formation of hydrogen-bonded wavy layer through two intermolecular C–H···O=P hydrogen bonds between two phenyl rings and the O=P group. The layers formed a 3D network *via* C–H···π interactions between the phenyl groups of adjacent molecules.

In order to investigate the efficiency of our MW-assisted method, two scaled-up reactions were also performed at a "gram-scale". The condensation of diphenylphosphine oxide or ethyl phenyl-*H*-phosphinate and diphenyl acetylene was carried out on a 25-times-bigger scale. The desired 1,2,3-triphenylphosphindole 1-oxide (**79b**) and 1-ethoxy-2,3-diphenylphosphindole 1-oxide (**81b**) were obtained in yields of 94% and 70%.

To sum up, a MW-assisted, fast (2–3 h instead of 8–24 h) and efficient approach for the synthesis of benzo[*b*]phosphole oxides **79–88** by the oxidative cycloaddition of secondary phosphine oxides or alkyl phenyl-*H*-phosphinates with acetylenes (diphenylacetylene or ethyl phenylpropiolate) was developed. Altogether 16 derivatives **79–88** were prepared, among them 12 were new.



Scheme 17. Condensation of alkyl phenyl-*H*-phosphinate and ethyl phenylpropiolate or diphenylacetylene

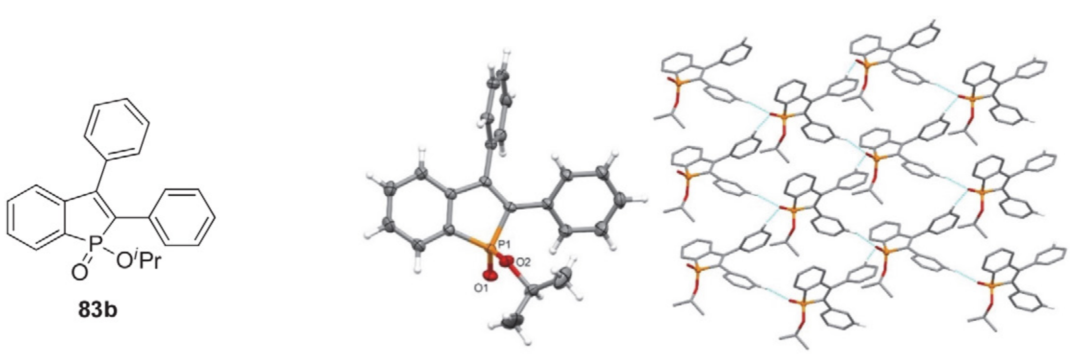


Figure 8. The crystal structure of 1-isopropoxy-2,3-diphenylphosphindole 1-oxide (**83b**)

5. Biological Activity Investigations

The *in vitro* cytotoxicity and antibacterial activity of all compounds synthesized was also investigated. In Table 2 only the most active derivatives are shown.

The cytotoxicity evaluations were performed on three different cell lines, such as human lung adenocarcinoma (A549), mouse fibroblast (NIH/3T3) as healthy cell line and human promyelocytic leukemia (HL-60) using the fluorescent Resazurin assay as described previously.[122] Positive controls were doxorubicin for A549 and NIH/3T3 (IC_{50} = 0.31 ± 0.24 μM and 5.65 ± 0.81 μM, respectively) and bortezomib for HL60 (IC_{50} = 7.42 ± 2.60 nM). The antibacterial activity of the compounds was tested on green fluorescent protein (GFP) producing *Bacillus subtilis* (Gram-ositive) and *Escherichia coli* (Gram-negative) bacterial cells. The GFP producing bacteria are effective tools for screening for the antibacterial activity, since the GFP signal measured by fluorimetry is proportional to the number of the bacterial cells. Active compounds kill bacterial cells, which results in the decrease in the GFP fluorescence signal, therefore it is suitable for evaluating the antimicrobial effect of different agents. Positive controls were doxycycline and gentamicin for *Bacillus subtilis* (IC_{50} = 0.04 ± 0.01 μM and 0.49 ± 0.14 μM) and for *Escherichia coli* (IC_{50} = 0.10 ± 0.02 μM and 4.23 ± 0.99 μM) bacterial cells. The IC_{50} values (50% inhibiting concentration) determined are shown in Table 2.

Among (3-oxo-2,3-dihydro-2*H*-isoindol-1-yl)phosphine oxides **23**–**34**, derivatives containing 3,5-dimethylphenyl- or naphthyl groups on the phosphorus atom showed activity.[62] The *N*-butyl and *N*-benzyl bis(3,5-dimethylphenyl) (3-oxo-2,3-dihydro-2*H*-isoindol-1-yl) phosphine oxides **23c** and **25c** were slightly active in HL-60 cell line. However, against Grampositive bacteria (*B. subtilis*), the same derivatives (**23c** and **25c**) showed promising activity, as their IC_{50} values (4.60 ± 1.13 μM and 3.61 ± 1.25 μM) were close to the reference value. In the case of bis(2-naphthyl) (2-butyl-3-oxo-2,3-dihydro-2*H*-isoindol-1-yl)-phosphine oxide (**23d**), no antibacterial activity was shown, but against all the three investigated cell lines (A549, NIH/3T3 and HL-60) modest cytotoxicity was observed. The IC_{50} value was the smallest against HL-60 cells (12.26 ± 1.02 μM).

The biological activity of the α-amino-(2-alkynylphenyl)methylphosphonates **37**–**43** was investigated, as well. According to our results, some butyl esters showed modest activity against HL-60 cells. The IC_{50} value of the chloro (**41**) or the unsubstituted derivatives (**42**) were in the range of 13–15 μM.

The results of the bioactivity tests of the (1,2-dihydroisoquinoline)phosphonates **44–50** also showed that the butyl esters were more active as compared to the other derivatives. Compounds containing methyl (**47**), methoxy (**48**), or chloro group (**49**) on the *para* position of the phenyl group, showed *in vitro* cytotoxicity. The (1,2-dihydroisoquinoline)phosphonate **47** was effective in A549, NIH/3T3 and HL-60 cell lines. In addition, the IC_{50} value was close to the reference against human promyelocytic leukemia cells (4.36 ± 1.31 μM).

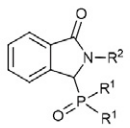
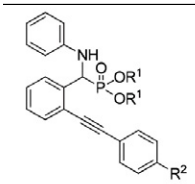
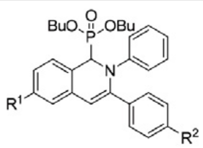
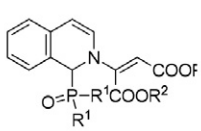
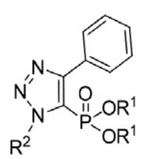
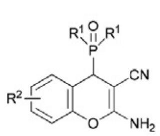
The (1,2-dihydroisoquinoline)phosphine oxides containing 3,5-dimethylphenyl (**51c** and **52c**) or naphthyl groups (**51e**) on the phosphorus atom showed *in vitro* cytotoxicity and antibacterial activity.[74] Dimethyl and diethyl (*E*)-2-{1-[bis(3,5-dimethylphenyl)phosphoryl]isoquinolin-2(1*H*)-yl}maleates (**51c** and **52c**) were slightly active in HL-60 cell line, however the IC_{50} value was closer to the reference in the case of the methyl ester **51c** (IC_{50} = 4.58 ± 1.08 μM *vs.* 12.59 ± 1.18 μM). Compound **52c** also showed modest activity against *B. subtilis* (IC_{50} = 9.06 ± 1.01 μM). Among the (1,2-dihydroisoquinoline)phosphine oxides, dimethyl (*E*)-2-{1-[di(naphthalen-2-yl)phosphoryl]isoquinolin-2(1*H*)-yl}maleate (**51e**) had the most significant *in vitro* cytotoxicity against HL-60 cells (IC_{50} = 3.58 ± 1.16 mM).

Based on the IC_{50} values of (1,2,3-triazolyl)phosphonates, some derivatives were active against HL-60 cells.[84] The dimethyl [1-(4-methylbenzyl)-4-phenyl-1,2,3-triazol-5-yl]phosphonate (**59a**), dipropyl (1-benzyl-4-phenyl-1,2,3-triazol-5-yl)phosphonate (**58c**), dibutyl [1-(2-fluorobenzyl)-4-phenyl-1,2,3-triazol-5-yl]phosphonate (**60e**) and dibutyl [1-(4-trifluoromethyl)-4-phenyl-1,2,3-triazol-5-yl]phosphonate (**62e**) showed activity in the range of 9–13 μM.

Among chromenylphosphonates, the dibenzyl (2-amino-3-cyano-4*H*-chromen-4-yl)phosphonates **68e**, **69e**, **70e**, **71e** and **72e** were the best candidates.[110] The anti-cancer activity in NIH/3T3 cell line was close to the reference in the case of the unsubstituted (**68e**) or the 8-bromo derivatives (**71e**) (IC_{50} = 8.73 ± 1.17 μM or 9.33 ± 1.18 μM, respectively). In addition, all benzyl esters synthesized (**68e**, **69e**, **70e**, **71e** and **72e**) showed good or moderate activities against HL-60 cells. The IC_{50} value obtained was the smallest in the case of the 6-fluoro (**69e**) or 8-bromo (**71e**) substituted (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonates (IC_{50} = 3.62 ± 1.38 μM or 4.79 ± 1.08 μM, respectively).

The biological activity investigations showed that the [bis(3,5-dimethylphenyl)](2-amino-3-cyano-4*H*-chromen-4-yl)phosphine oxides were effective against human promyelocytic leukemia cells and Gram-positive bacteria.[110] The IC_{50} values of the 6-fluoro (**69e**) and 8-bromo derivatives (**71e**) were in the rage of 10 μM in HL-60 cell line. The growth of *B. subtilis* was reduced the most by the unsubstituted, 6-fluoro and 5-chloro [bis(3,5-dimethylphenyl)](2-amino-3-cyano-4*H*-chromen-4-yl)phosphine oxides (**74c**, **75c** and **76c**) (IC_{50} = 8.92 ± 1.21 μM, 5.03 ± 1.28 μM and 5.29 ± 1.38 μM, respectively).

Table 2. *In vitro* cytotoxicity and antibacterial activity of the compounds synthesized.[a]

Compound	R¹	R²	*In vitro* Cytotoxicity] [IC$_{50}$, µM			Antibacterial Activity IC$_{50}$, µM]	
			A549	NIH/3T3	HL-60	*B. subtilis*	*E. coli*
	3,5-diMeC$_6$H$_3$	^{n}Bu (**23c**)	>30	>30	17.55±1.70	**4.60±1.13**	>10
	3,5-diMeC$_6$H$_3$	Bn (**25c**)	>30	>30	18.31±1.33	**3.61±1.25**	>10
	2-naphthyl	^{n}Bu (**23d**)	28.2±1.05	25.94±1.06	12.26±1.02	>10	>10
	Bu	Cl (**41**)	>30	>30	13.66±1.08	>10	>10
	Bu	H (**42**)	>30	>30	15.09±1.17	>10	>10
	F	Me (**47**)	11.64±1.11	14.17±1.38	**4.36±1.31**	>10	>10
	H	OMe (**48**)	>30	>30	13.16±1.22	>10	>10
	H	Cl (**49**)	>30	13.58±1.09	13.33±1.14	>10	>10
	3,5-diMeC$_6$H$_3$	Me (**51c**)	>30	>30	**4.58±1.08**	>10	>10
	3,5-diMeC$_6$H$_3$	Et (**52c**)	>30	>30	12.59±1.18	**9.06±1.01**	>10
	2-naphthyl	Me (**51e**)	>30	>30	**3.58±1.16**	>10	>10
	Me	4-MeC$_6$H$_4$CH$_2$ (**59a**)	>30	19.8±1.2	11.0±1.2	>10	>10
	^{n}Pr	Bn (**58c**)	>30	>30	12.6±1.7	>10	>10
	^{n}Bu	2-FC$_6$H$_4$CH$_2$ (**60e**)	>30	27.5±1.1	11.7±1.2	>10	>10
	^{n}Bu	4-CF$_3$C$_6$H$_4$CH$_2$ (**62e**)	>30	23.1±1.2	**9.7±1.1**	>10	>10
	OBn	H (**68e**)	26.46±1.02	**8.73±1.17**	**6.25±1.06**	>10	>10
	OBn	6-F (**69e**)	>30	21.2±1.71	**3.62±1.38**	>10	>10
	OBn	5-Cl (**70e**)	>30	23.49±1.09	**7.51±1.02**	>10	>10
	OBn	8-Br (**71e**)	28.65±1.22	**9.33±1.18**	**4.79±1.08**	>10	>10
	OBn	8-OEt (**72e**)	>30	27.99±1.06	14.37±1.24	>10	>10
	3,5-diMeC$_6$H$_3$	H (**74c**)	>30	>30	>30	**8.92±1.21**	>10
	3,5-diMeC$_6$H$_3$	6-F (**75c**)	>30	>30	**10.06±1.25**	**5.03±1.28**	>10
	3,5-diMeC$_6$H$_3$	5-Cl (**76c**)	>30	>30	>30	**5.29±1.38**	>10
	3,5-diMeC$_6$H$_3$	8-Br (**77c**)	>30	>30	**9.80±1.33**	>10	>10
	Doxorubicin		0.31±0.24	5.65±0.81	–	–	–
	Bortezomib		–	–	$7.42\times10^{-3}\pm 2.60\times10^{-3}$	–	–
	Doxycycline		–	–	–	0.126±0.029	0.10±0.02
	Gentamicin		–	–	–	0.115±0.001	4.23±0.99

[a] Data were expressed as mean ± standard deviation.

Summarizing the results of the biological activity investigations, heterocyclic phosphonates (butyl, benzyl) or phosphine oxides (3,5-dimethylphenyl, naphthyl) containing larger groups on the phosphorus atom showed promising activity against human promyelocytic leukemia (HL-60) cells and *B. subtilis* Gram-positive bacteria.

6. Conclusions

In conclusion, the multicomponent synthesis of the target *N*- and *O*-heterocycles containing a phosphonate or a phosphine oxide moiety and the synthesis of *P*-heterocyclic derivatives was elaborated successfully. The procedures developed are more effective and acceptable according to the principles of "green chemistry" as compared to the literature data. Altogether more than 150 derivatives were synthesized and fully characterized, and most of them were new compounds. According to the biological activity investigations, it was found that in the case of phosphonates butyl- and benzyl esters of α-amino-(2-alkynylphenyl)-methylphosphonates, (1,2-dihydroisoquinolinyl)phosphonates, (1,2,3-triazol-5-yl)phosphonates and (aminochromenyl)phosphonates were effective, however, from among phosphine oxides, those derivatives showed promising antibacterial and/or anticancer effects, which contained large groups (3,5-dimethylphenyl or 2-naphtyl) on the phosphorus atom, especially (oxoisoindolyl)phosphine oxides, (1,2-dihydroisoquinolinyl)phosphine oxides, and (aminochromenyl) phosphine oxides.

The development of highly convergent syntheses is an ongoing evergreen of heterocyclic chemistry. Multicomponent reactions are significant for this diversity-oriented chemistry, they are an excellent tool for exploring the chemical molecular space. Multicomponent chemistry is now more active than ever, and new approaches are being developed every day to address the challenges of contemporary organic chemistry.

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7. References

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Povzetek

Razvili smo več multikomponentnih sinteznih pristopov do množice novih dušikovih in kisikovih heterociklov, ki vsebujejo fosfonatne ali fosfin oksidne skupine. Za vse multikomponentne reakcije smo na primerih modelnih reakcij optimizirali reakcijske parametre: način segrevanja, množinsko razmerje izhodnih spojin, atmosfero, katalizatorje, temperature, reakcijske čase in topila. Na tak način dobljeni reakcijski parametri so bili uporabljeni za priprave majhnih knjižnic strukturno sorodnih spojin. Večino reakcij lahko smatramo kot skladnih s principi »zelene kemije«, saj so potekale brez prisotnosti katalizatorjev in/ali topil ter pod pogoji obsevanja z mikrovalovi (MW) ali celo že pri sobni temperaturi. S pomočjo pretočnega MW sistema smo nekatere mikrovalovne sinteze izvedli tudi na večji skali. Skupno smo pripravili več kot 150 heterocikličnih organofosforjevih spojin; nekateri izmed pripravljenih derivatov so izkazali zmerne do obetavne aktivnosti na HL-60 celično linijo ter na bakterije *Bacillus subtilis*.