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Three-component synthesis, utilization and biological activity of phosphinoyl-functionalized isoindolinones†

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A new method for the synthesis of 3-oxoisoindolin-1-ylphosphine oxides bearing same or different substituents on the phosphorus atom is described. The one-pot three-component reaction of 2-formylbenzoic acid, primary amines and achiral or P-stereogenic secondary phosphine oxides provided the target compounds under catalyst-free, mild conditions and for short reaction times. The deoxygenation of a 3-oxoisoindolin-1-ylphosphine oxide was also studied, and the phosphine obtained could be converted to a sulphide and to a platinum complex. The crystal structures of a selected phosphine oxide and the corresponding platinum species were investigated by X-ray diffraction analysis. The biological activity, such as *in vitro* cytotoxicity on different cell lines and antibacterial activity of the 3-oxoisoindolin-1-ylphosphine oxides was also investigated. Based on the IC_{50} values obtained, several derivatives showed moderate activity against the HL-60 cell line and two compounds containing 3,5-dimethylphenyl groups on the phosphorus atom showed promising activity against *Bacillus subtilis* bacteria.

Introduction

Nitrogen-heterocycles as one of the major classes of organic compounds play an important role in scientific research. Several papers reported on their synthesis, emphasizing their biological properties as pharmaceuticals or agrochemicals and their utilization as dyes.[1]

Isoindolin-1-ones as naturally occurring and pharmacologically relevant N-heterocycles have attracted considerable attention.[2] They may possess a variety of biological activities, including antiviral,[3] anti-inflammatory and antipsychotic[4] properties. A few derivatives have also been reported to be effective for treating cancer,[5] arrhythmia[6] and diabetes.[7]

Compounds containing both an isoindolinone scaffold and a phosphonate moiety, such as 3-oxoisoindolin-1-ylphosphonates, can act as bioisosteres of natural α-amino acids, and may often show biological effects,[8] such as they may be used as pesticides.[9]

Multicomponent reactions continuously attract great attention as one of the most useful and efficient tools for the synthesis of versatile heterocyclic compounds.[10] The following advantages can be highlighted from the numerous benefits of this synthetic strategy. Products are usually formed in a single step from simple starting materials in high atom efficient reactions. The possibility of applying diverse reagents makes them ideal for creating new molecular libraries. Moreover, in most cases, the principles of green chemistry also prevail to save time and energy.

In recent years, many efforts have been made to synthesize isoindolin-1-ones.[2,11] However, only a few methods have been reported for the preparation of 3-oxoisoindolin-1-ylphosphonates. Ordóñez and his research group described a microwave (MW)-assisted special Kabachnik–Fields reaction of 2-formylbenzoic acid, dimethyl phosphite and as the third component, aromatic amines,[12] aminoacetaldehyde dimethyl acetal[13] or amino alcohols.[14] They also studied the condensation with optically active amines under conventional heating.[15] Others reported syntheses in the presence of a special catalyst or additive, such as NaH,[16] T3P®[17] or OSU-6[18] in MeOH, EtOAc or

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†Electronic supplementary information (ESI) available: Full experimental procedures, characterization data and copies of ^{31}P, ^{1}H and ^{13}C NMR spectra. CCDC 2100126 and 2100127. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ob01610e

EtOH, respectively. In our previous study, we have described an efficient catalyst-free method for the batch and continuous flow synthesis of 3-oxoisoindolin-1-ylphosphonates (**1**) containing alkyl substituents on the nitrogen atom by the three-component reaction of 2-formylbenzoic acid, aliphatic primary amines and dialkyl phosphites or ethyl phenyl-*H*-phosphinate[19] (Scheme 1).

3-Oxoisoindolin-1-ylphosphine oxides are much less studied; they have only been mentioned in the literature as intermediates. Couture and co-workers prepared α-amidophosphine oxides **3** by three different methods (method A, B or C), and carried out their ring closure reaction in the presence of potassium bis(trimethylsilyl)amide (KHMDS) and 18-crown-6 (Scheme 2).[20]

Deniau and co-workers developed an asymmetric synthesis of diarylphosphine oxide-substituted isoindolinones bearing an (*S*)-2-alkoxymethyl-pyrrolidin-1-yl type auxiliary (**6**) by a three-step reaction starting from phthalic anhydride and (*S*)-1-amino-2-alkyloxymethylpyrrolidine (**5**) (Scheme 3).[21]

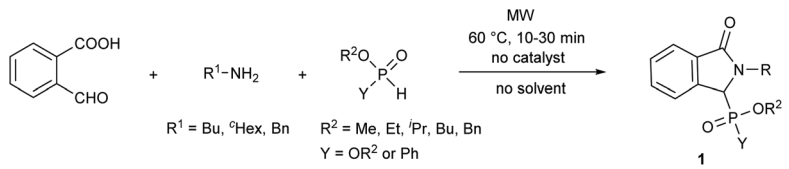
Both approaches applied multistep syntheses using complex and/or expensive reagents and required special treatments.

To the best of our knowledge, there is no example in the literature for the synthesis of 3-oxoisoindolin-1-ylphosphine oxides by a multicomponent reaction, and their utilization has not been investigated yet.

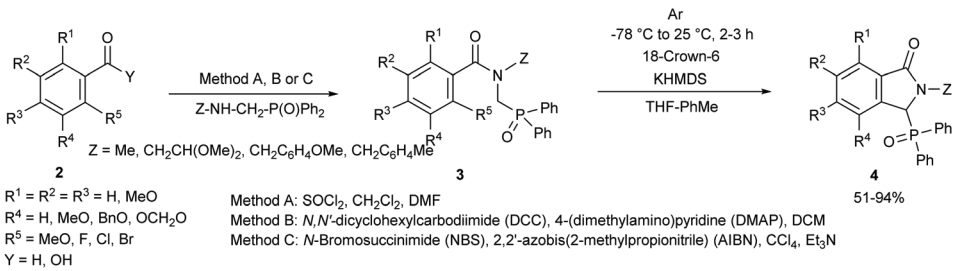
In this paper, we describe the first multicomponent synthetic method for the preparation of 3-oxoisoindolin-1-ylphosphine oxides containing the same or different substituents on the phosphorus atom. Our approach is based on the three-component reaction of 2-formylbenzoic acid, primary amines and achiral or P-chiral secondary phosphine oxides, and this method required neither catalyst/additive nor special conditions. We have also investigated the utilization of a 3-oxoisoindolin-1-ylphosphine oxide as a phosphine ligand precursor. After deoxygenation, the 3-oxoisoindolin-1-ylphosphine obtained was applied as a ligand in the synthesis of a monodentate platinum(II) complex. In addition, the *in vitro* cytotoxicity and antibacterial activity of the title compounds were also studied.

Results and discussion

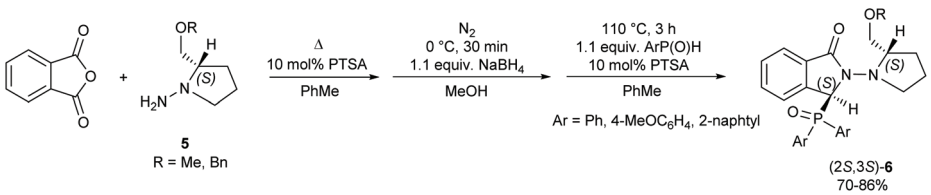
At first, the special Kabachnik–Fields reaction of 2-formylbenzoic acid, primary amines (butyl-, cyclohexyl-, benzylamine or aniline) and diphenylphosphine oxide was investigated without any catalyst (Table 1). Carrying out the condensation



Scheme 1 Synthesis of 3-oxoisoindolin-1-ylphosphonates (**1**) by special Kabachnik–Fields reaction.

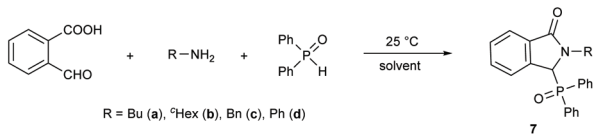


Scheme 2 Preparation of 3-oxoisoindolin-1-ylphosphine oxides (**4**) by ring closure reaction.



Scheme 3 Asymmetric synthesis of diarylphosphine oxide-substituted isoindolinones.

Table 1 Optimization of the three-component reaction of 2-formylbenzoic acid, primary amines and diphenylphosphine oxide[a]

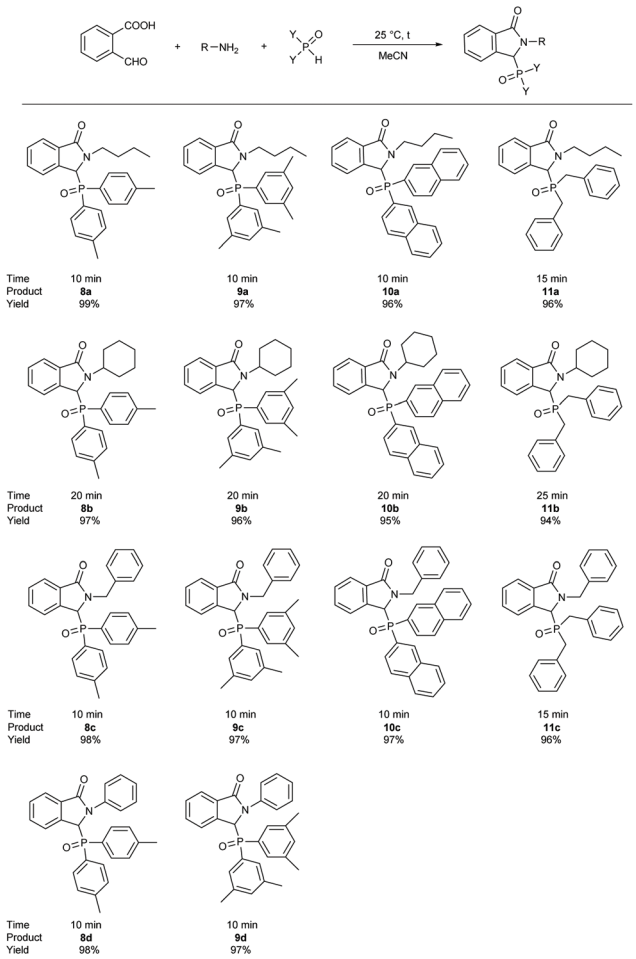


Entry	Solvent	R	t [min]	Conversion[b] [%]	Yield[c] [%]
1	—	Bu	5	58	—
2	EtOH	Bu	5	79	—
3	PhMe	Bu	5	82	—
4	MeCN	Bu	5	88	—
5	MeCN	Bu	10	100	98 (**7a**)
6	MeCN	cHex	10	83	—
7	MeCN	cHex	15	91	—
8	MeCN	cHex	20	100	94 (**7b**)
9	MeCN	Bn	10	100	97 (**7c**)
10	MeCN	Ph	10	100	96 (**7d**)

[a] The reactions were carried out with 1.0 mmol of 2-formylbenzoic acid, 1.0 mmol of primary amine and 1.0 mmol of diphenylphosphine oxide in the absence of any solvent or in 1 mL of solvent. [b] Determined by HPLC (222 nm). [c] Isolated yield.

with butylamine in the absence of any solvent at room temperature for 5 min, 58% of diphenyl (2-butyl-3-oxo-2,3-dihydro-2*H*-isoindol-1-yl)phosphine oxide (**7a**) was formed (Table 1, entry 1). To improve the conversion, a small amount of solvent was added to overcome the heterogeneity of the reaction mixture. Among tested solvents (ethanol, toluene and acetonitrile), acetonitrile was the most efficient, since a conversion of 88% was achieved (Table 1, entries 2–4). Increasing the reaction time to 10 min, the reaction was complete (Table 1, entry 5). The acetonitrile and the water formed were eliminated in vacuum, and the crude product was passed through short plug of silica to obtain product **7a** in a yield of 98%. Starting from cyclohexylamine, the condensation was not complete after 10 min, and the conversion was only 83% (Table 1, entry 6). Applying longer reaction time of 15 or 20 min, led to a proportion of 91% and 100% of the desired product (**7b**), respectively (Table 1, entries 7 and 8). The decrease in the reaction rate may be caused by the larger steric hindrance of the cyclohexyl ring. The diphenyl (2-cyclohexyl-3-oxo-2,3-dihydro-2*H*-isoindol-1-yl)phosphine oxide (**7b**) was isolated in a yield of 94%. In case of benzylamine or aniline, a reaction time of 10 min was enough for a complete conversion similarly to the condensation of butylamine (Table 1, entries 5, 9 and 10). The corresponding 3-oxoisoindolin-1-ylphosphine oxides (**7c** and **7d**) were obtained in yields of 97% and 96%, respectively.

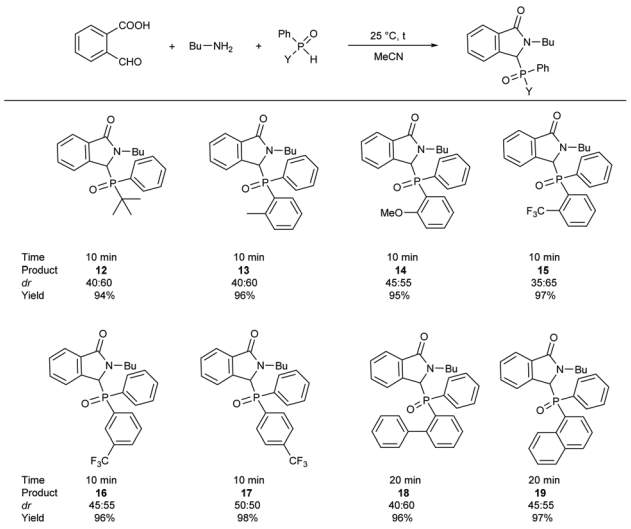
Next, the three-component reaction of 2-formylbenzoic acid with a wide range of primary amines and secondary phosphine oxides was investigated using the optimized conditions (25 °C, 10–20 min) (Scheme 4). Performing the condensation of 2-formylbenzoic acid, butylamine and bis(*p*-tolyl)-, bis(3,5-dimethylphenyl)- or bis(2-naphthyl)phosphine oxide, the corresponding 3-oxoisoindolin-1-ylphosphine oxides (**8a–10a**) were prepared in yields of 96–99%. Dibenzylphosphine oxide was



Scheme 4 Three-component reaction of 2-formylbenzoic acid, primary amines and achiral phosphine oxides. (The reaction was performed with 1.0 mmol of 2-formylbenzoic acid, 1.0 mmol of amine and 1.0 mmol of secondary phosphine oxide in 1 mL of acetonitrile at 25 °C. The listed yield is isolated yield.)

also used as the P-reagent. In this case, a slightly increased reaction time of 15 min was necessary to reach full conversion, and the dibenzyl (2-butyl-3-oxo-2,3-dihydro-2*H*-isoindol-1-yl) phosphine oxide (**11a**) was isolated in a yield of 96%. Carrying out the reaction of 2-formylbenzoic with cyclohexylamine and the secondary phosphine oxides mentioned above, the condensations were slightly slower (20 or 25 min). The desired 3-oxoisoindolin-1-ylphosphine oxides (**8b–11b**) were also obtained in high yields (94–97%). Applying benzylamine or aniline as the amine component, the reactions took place similarly to that with butylamine, and the corresponding products (**8c–11c**, **8d** and **9d**) were synthesized in yields of 96–98%.

In the next series of experiments, the special Kabachnik–Fields reaction of 2-formylbenzoic acid and butylamine was extended using P-stereogenic phosphine oxides, such as *tert*-butyl(phenyl)phosphine oxide, 2-methylphenyl(phenyl)-phosphine oxide, 2-methoxyphenyl(phenyl)phosphine oxide, 2-, 3- or 4-trifluoromethylphenyl(phenyl)phosphine oxide, as well as biphenyl(phenyl)phosphine oxide or 1-naphthyl(phenyl)phos-



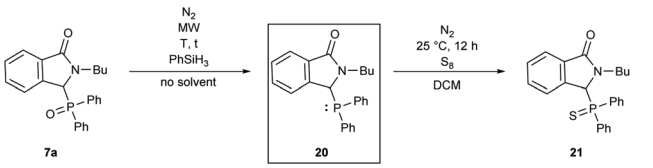
Scheme 5 Three-component reaction of 2-formylbenzoic acid, butylamine and P-chiral phosphine oxides. (The reaction was performed with 1.0 mmol of 2-formylbenzoic acid, 1.0 mmol of butylamine and 1.0 mmol of secondary phosphine oxide in 1 mL of acetonitrile at 25 °C. The listed yield is isolated yield.)

phine oxide (Scheme 5). The condensations were performed at 25 °C, for 10 or 20 min without any catalyst in acetonitrile, according to the method described above. Altogether eight 3-oxoisoindolin-1-ylphosphine oxides (**12–19**) having different substituents on the phosphorus atom were synthesized in excellent yields (94–98%). Due to the P-stereogenic centre in the P-functionality, all products (**12–19**) were formed as a mixture of two diastereomers, and both diastereomers were racemates. Therefore, two signals were observed in the ^{31}P NMR spectra, and two signals were visible in the ^{13}C and ^{1}H NMR spectra. However, the diastereomeric ratio (*dr*) of the compounds synthesized was different. Most of the 3-oxoisoindolin-1-ylphosphine oxides (**12–14**, **16**, **18** and **19**) were obtained as a 40 : 60 or 45 : 55 mixture of the diastereomers based on the ^{31}P NMR spectra. Compound **17** incorporating a 4-trifluormethyl group on the phosphorus atom was formed as an equal (50 : 50) mixture of diastereomers. The condensation was more diastereoselective, when 2-trifluormethylphenyl-(phenyl)phosphine oxide was used as the P-reagent, in this case, the diastereomeric ratio was 35 : 65. Due to the bigger difference of the functional groups on the phosphorus atom of 1-naphthyl(phenyl) (2-butyl-3-oxo-2,3-dihydro-2*H*-isoindol-1-yl) phosphine oxide (**19**), the diastereomers were successfully separated by column chromatography.

Altogether, 26 3-oxoisoindolin-1-ylphosphine oxides (**7–19**) were prepared in high yields at ambient temperature for short reaction times (10–25 min), and fully characterized by ^{31}P, ^{13}C and ^{1}H NMR spectroscopy, as well as by HRMS.

As the next step, the diphenyl (2-butyl-3-oxo-2,3-dihydro-2*H*-isoindol-1-yl)phosphine oxide (**7a**) was utilized as a precursor for a monodentate P-ligand in the synthesis of a platinum complex. First, the deoxygenation of **7a** was studied applying

Table 2 Deoxygenation of diphenyl (2-butyl-3-oxo-2,3-dihydro-2*H*-isoindol-1-yl)-phosphine oxide (**7a**) and formation of sulphide **21**[a]



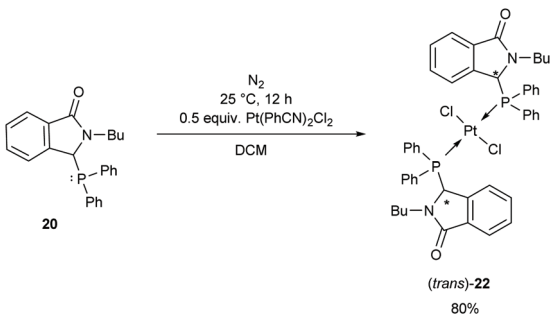
Entry	T [°C]	t [h]	Conversion[b] [%]	Yield[c] [%]
1	100	2	17	—
2	140	4	60	—
3	140	6	100	81 (**21**)

[a] First step of the reaction was performed with 1.0 mmol of **7a** and 3.0 mmol of phenylsilane without any solvent under N_2 atmosphere in a microwave reactor. In the second step, 1.2 mmol of sulphur in 10 mL of degassed DCM was added to **20**. [b] Determined by ^{31}P NMR. [c] After column chromatography.

phenylsilane as a reducing agent under microwave (MW) irradiation in the absence of any catalyst and solvent (Table 2). The phosphine (**20**) obtained was immediately converted to a sulphide (**21**), and the mixture was analyzed by HPLC-MS and ^{31}P NMR. Performing the reaction at 100 °C for 2 h, the reduction was not complete (Table 2, entry 1). Applying a higher temperature of 140 °C for 4 h, the conversion significantly increased to 60% (Table 2, entry 2). After an irradiation of 6 h, the reduction was complete, and the sulphide (**21**) was isolated in a yield of 81% after column chromatography (Table 2, entry 3).

Finally, the diphenyl (2-butyl-3-oxo-2,3-dihydro-2*H*-isoindol-1-yl)phosphine (**20**) obtained after deoxygenation was converted to a monodentate platinum(II) complex (**22**) by the reaction with 0.5 equiv. of dichlorodibenzonitrile platinum at 25 °C in dichloromethane (Scheme 6). The platinum(II) complex (**22**) could be isolated in a yield of 80% by column chromatography, and it was characterized by ^{31}P, ^{13}C, ^{1}H NMR and HRMS, as well as by single crystal X-ray diffraction analysis.

The relative spatial orientation (*cis* or *trans*) of platinum-phosphine coordination compounds can be inferred from the

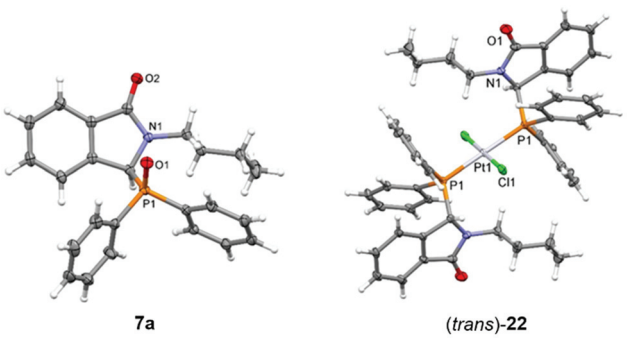


Scheme 6 Synthesis of the platinum(II) complex of diphenyl (2-butyl-3-oxo-2,3-dihydro-2*H*-isoindol-1-yl)phosphine. (The reaction was carried out with 1.0 mmol of **20** and 0.5 mmol of bis(benzonitrile)dichloroplatinum in 10 mL of degassed dichloromethane.)

magnitude of the stereospecific platinum-phosphorus coupling constant ($^1J_{Pt-P}$) in the ^{31}P NMR spectrum. It is known from the literature that the $^1J_{Pt-P}$ coupling constant is between 3400 to 3600 Hz for *cis* arrangements, while *trans* complexes display typical $^1J_{Pt-P}$ coupling constants of 2500–3000 Hz.[22]

The $^1J_{Pt-P}$ coupling constant was 2519 Hz, which means that the *trans* platinum complex ((*trans*)-**22**) was formed. Moreover, in the ^{31}P NMR spectrum of the platinum(II) complex ((*trans*)-**22**), two very close peaks in a ratio of *ca.* 1 : 1 and their satellites could be observed. As the isoindolinone ring contains a stereogenic centre, the platinum complex ((*trans*)-**22**) was obtained as a mixture of a homochiral and heterochiral diastereomer.

Single-crystal XRD analysis was used to reveal the molecular structures of **7a** and **22** (Fig. 1). In the crystal lattice, **7a**, molecules are connected into a hydrogen-bonded chain through C–H···O=P interactions along the *c*-axis, and these chains are further connected into 3D network *via* C–H···O2 interactions with the isoindolin-1-one oxygen atom as well as C–H···π interactions (Fig. S1 and Table S2†). The XRD analysis also confirmed the *trans* geometry in platinum complex **22**. A hydrogen-bound layer is formed through the C–H···O1 interactions, and a 3D network is achieved *via* C–H···π interactions (Fig. S2 and Table S2†).



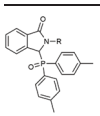
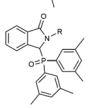
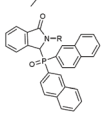
7a (*trans*)-**22**

Fig. 1 Molecular structures of compounds **7a** and (*trans*)-**22**.

The biological activity, such as *in vitro* cytotoxicity and antibacterial activity of 3-oxoisoindolin-1-ylphosphine oxides bearing the same substituents on the phosphorus atom (**7–11**) were also studied. Cytotoxicity assays used the human lung adenocarcinoma A549 cell line, the mouse fibroblast NIH/3T3 as a healthy cell line and the human promyelocytic leukemia HL-60 cell line. During the measurements, the fluorescent Resazurin assay as described previously was applied.[23] For the A549 and NIH/3T3 cell lines, doxorubicin was the positive control (IC_{50} = 0.31 ± 0.24 μM and 5.65 ± 0.81 μM, respectively), while for HL60, it was bortezomib (IC_{50} = 7.42 ± 2.60 nM). The antibacterial activity of the compounds was investigated on green fluorescent protein (GFP) producing *Bacillus subtilis* (Gram–positive) and *Escherichia coli* (Gram–negative) bacterial cells. The GFP producing bacteria are efficient tools for screening 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 decreases the GFP fluorescence signal, therefore it is convenient for evaluating the antimicrobial effect of different agents. Positive controls were doxycycline and gentamicin for *Bacillus subtilis* (IC_{50} = 0.126 ± 0.029 μM and 0.115 ± 0.001 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) obtained are shown in Table 3.

According to the results, those (3-oxo-2,3-dihydro-2*H*-isoindol-1-yl)phosphine oxides (**8–10**) showed activity to some extent, which contain substituted phenyl groups (*p*-tolyl or 3,5-dimethylphenyl) or naphthyl rings on the phosphorus atom. Among the bis(*p*-tolyl) (3-oxo-2,3-dihydro-2*H*-isoindol-1-yl) phosphine oxides, only the *N*-butyl substituted derivative (**8a**)

Table 3 *In vitro* cytotoxicity and antibacterial activity of (3-oxo-2,3-dihydro-2*H*-isoindol-1-yl)phosphine oxides[a]

Compound	R	*In vitro* cytotoxicity [IC_{50}, μM]			Antibacterial activity [IC_{50}, μM]	
		A549	NIH/3T3	HL-60	*B. subtilis*	*E. coli*
	Bu (**8a**)	>30	>30	25.03 ± 2.07	>10	>10
	^{c}Hex (**8b**)	>30	>30	>30	>10	>10
	Bn (**8c**)	>30	>30	>30	>10	>10
	Bu (**9a**)	>30	>30	17.55 ± 1.70	**4.60 ± 1.13**	>10
	^{c}Hex (**9b**)	>30	>30	>30	>10	>10
	Bn (**9c**)	>30	>30	18.31 ± 1.33	**3.61 ± 1.25**	>10
	Bu (**10a**)	28.2 ± 1.05	25.94 ± 1.06	**12.26 ± 1.02**	>10	>10
	^{c}Hex (**10b**)	>30	>30	28.81 ± 1.17	>10	>10
	Bn (**10c**)	>30	>30	25.61 ± 1.12	>10	>10
Doxorubicin		0.31 ± 0.24	5.65 ± 0.81	—	—	—
Bortezomib		—	—	$7.42 \times 10^{-3} \pm 2.60 \times 10^{-3}$	—	—
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.

showed modest activity against HL-60 cell line (IC_{50} = 25.03 ± 2.07 μM). In case of bis(3,5-dimethylphenyl) (3-oxo-2,3-dihydro-2*H*-isoindol-1-yl)phosphine oxides, compounds containing butyl (**9a**) or benzyl (**9c**) group on the nitrogen atom were slightly effective against HL-60 cells. Furthermore, these 3-oxoisoindolin-1-ylphosphine oxides (**9a** and **9c**) also showed promising antibacterial activity, since the growth of *Bacillus subtilis* bacteria was reduced by them, and the IC_{50} values obtained (4.60 ± 1.13 μM and 3.61 ± 1.25 μM) were slightly close to the value of doxycycline and gentamicin, respectively. Among the derivatives containing 2-naphthyl groups on the phosphorus atom, compounds **10b** and **10c** were rather active against HL-60 cells. In contrast, the bis(2-naphthyl) (2-butyl-3-oxo-2,3-dihydro-2*H*-isoindol-1-yl)-phosphine oxide (**10a**) showed cytotoxicity against all the three cell lines, and the best activity was showed against HL-60 cells (12.26 ± 1.02).

The most active compounds were the bis(3,5-dimethylphenyl) (2-butyl-3-oxo-2,3-dihydro-2*H*-isoindol-1-yl)phosphine oxide (**9a**) and the bis(3,5-dimethylphenyl) (2-benzyl-3-oxo-2,3-dihydro-2*H*-isoindol-1-yl)phosphine oxide (**9c**), since they showed activity in the 3–4 μM range against Gram positive bacteria.

Conclusions

In conclusion, we have developed a new and practical catalyst-free method to novel phosphinoyl-functionalized isoindolin-1-ones (**7–19**) by the special Kabachnik–Fields reaction of 2-formylbenzoic acid, primary amines and achiral or P-chiral secondary phosphine oxides at ambient temperature for short reaction times (10–25 min). This procedure means a promising approach to attain these new heterocycles, since it applies mild and easily operational conditions (no special reagents, catalysts or additives, no heating). Altogether 26 new 3-oxoisoindolin-1-ylphosphine oxides (**7–19**) were synthesized in high to excellent yields and these derivatives were fully characterized. One of the 3-oxoisoindolin-1-ylphosphine oxides (**7a**) has been utilized as P-ligand for the synthesis of a monodentate platinum complex (*trans*-**22**). The crystal structure of compound **7a** and platinum(II) complex **22** was studied by single-crystal XRD analysis. The biological activity of the (3-oxo-2,3-dihydro-2*H*-isoindol-1-yl)phosphine oxides (**7–11**) was also tested in *in vitro* cytotoxicity and antibacterial assays. Several 3-oxoisoindolin-1-ylphosphine oxides showed modest activity against HL-60 cell line, furthermore, two derivatives **9a** and **9c** incorporating 3,5-dimethylphenyl groups on the phosphorus atom were also active against selected Gram-positive bacteria.

Author contributions

E. B. and N. P.-T. planned the experiments, N. P.-T. and B. R. carried out the experiments, B. V. and P. B. synthesized the P-stereogenic secondary phosphine oxides, F. P. performed the crystal structure analysis, P. T. Sz. carried out the high-resolution mass spectrometric measurements, L. H. performed the biological evaluation (screening), E. B. and L. G. P. contributed reagents/materials/analysis tools, E. B., B. R. and N. P.-T. wrote the paper. Á. T., B. V., P. B., L. H. and L. G. P. reviewed the paper. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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