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SHORT COMMUNICATION



Synthesis of isoindolinone phosphonates and their related derivatives by multicomponent reaction

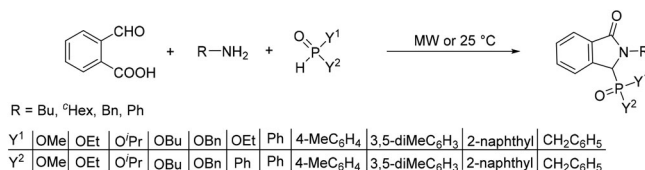
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ABSTRACT

An efficient catalyst-free microwave (MW)-assisted method was elaborated for the batch and continuous flow synthesis of N-alkyl-isoindolinone phosphonates by the three-component reaction of 2-formylbenzoic acid, primary amines and various dialkyl phosphites. The reaction was also extended to various secondary phosphine oxides and primary amines, as well. In order to obtain more information about the condensation, the reaction mechanism was also studied by *in situ* FT-IR spectroscopy.

GRAPHICAL ABSTRACT



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N-heterocycles; isoindolinone phosphonates; isoindolinone phosphine oxides; Kabachnik-Fields reaction; continuous flow reactor; *in situ* FT-IR spectroscopy

Isoindolinone derivatives, as important compounds among nitrogen heterocycles, are proved to be useful in a wide range of applications in the field of medicinal chemistry. They can be used as antibiotics, anticancer, antiarrhythmic and anti-inflammatory drugs.^[1–4]

In this work, at first, a catalyst- and solvent-free MW-assisted method was developed for the synthesis of isoindolinone phosphonates⁵. The Kabachnik-Fields reaction followed by cyclization of 2-formylbenzoic acid, primary amines (butyl-, cyclohexyl- or benzylamine) and dialkyl phosphites (dimethyl-, diethyl-, diisopropyl-, dibutyl- or dibenzyl phosphite) or ethyl phenyl-*H*-phosphinate was studied (Figure 1). After optimization, the isoindolinone phosphonates (1–3) were obtained at low temperature (60 °C) for short reaction times (10–30 min) and isolated in high yields (70–94%). To evaluate the potential of the MW irradiation, the reaction of 2-formylbenzoic acid, primary amines and diethyl phosphite was repeated at the optimized conditions under conventional heating, however, conversions obtained were only 84–90%.

The condensation of 2-formylbenzoic acid, butylamine and diethyl phosphite was also investigated by *in situ* FT-IR spectroscopy.^[5] The reaction mixture was heated to 60 °C in an oil bath and was reacted until completion. In the obtained time-dependent IR spectrum, reaction components can be identified according to their characteristic absorptions (2-formylbenzoic acid: $\nu_{\text{C=O}}$ 1756 cm^{−1}, diethyl phosphite: $\nu_{\text{P–O–C}}$ 964 cm^{−1}, $\nu_{\text{P=O}}$ 1254 cm^{−1}, butylamine: $\delta_{\text{C–H}}$

1381 cm^{−1}, $\delta_{\text{N–H}}$ 1605 cm^{−1}, diethyl (2-butyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)phosphonate $\nu_{\text{C=O}}$ 1690 cm^{−1}). Based on the results, no intermediate indicating the mechanism was detected in the reaction mixture.

The MW-assisted reaction of 2-formylbenzoic acid, primary amines (butyl-, cyclohexyl- or benzylamine) and diethyl phosphite was further investigated in a continuous flow MW system consisting on a CEM Discover MW reactor equipped with a commercially available continuous flow cell (Figure 2).^[5] The condensation in ethanol was complete, applying 1.5 equivalents of amines and diethyl phosphite, using residence times of 30–45 min, depending on the amines. The productivity of the continuous flow method was 1.5 to 2 times higher as compared to the batch method.

Finally, the special Kabachnik-Fields reaction of 2-formylbenzoic acid was also performed with various secondary phosphine oxides (diphenyl-, bis(*p*-tolyl)-, bis(3,5-dimethylphenyl)-, bis(2-naphthyl)- or dibenzylphosphine oxide) and primary amines (butyl-, cyclohexyl-, benzylamine or aniline) (Figure 3).^[6] The reactions were efficiently carried out in the absence of any catalyst, at room temperature for short reaction times (10–25 min), in acetonitrile. Altogether 18 derivatives (4–7) were synthesized in excellent yields (94–99%), and all of them were new compounds.

The biological activity of the isoindolinone phosphine oxides were investigated in *in vitro* cytotoxicity and antibacterial assays. Several 3-oxoisoindolin-1-ylphosphine oxides

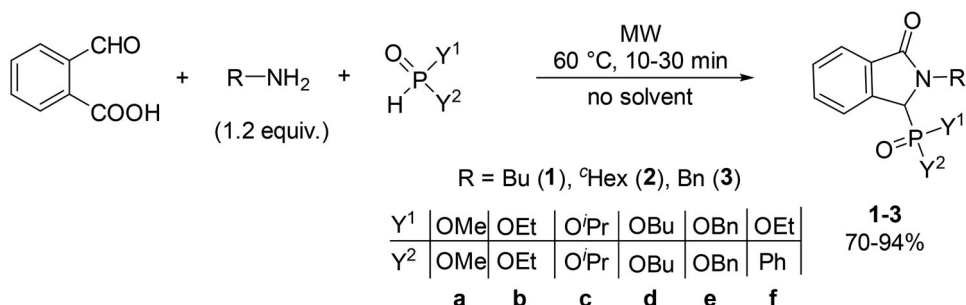


Figure 1. Three-component reaction of 2-formylbenzoic acid, primary amines and dialkyl phosphites.

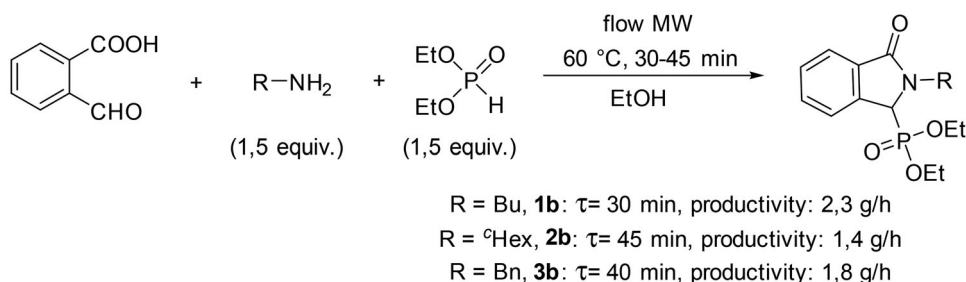


Figure 2. Condensation of 2-formylbenzoic acid, primary amines and diethyl phosphite in a continuous flow MW system.

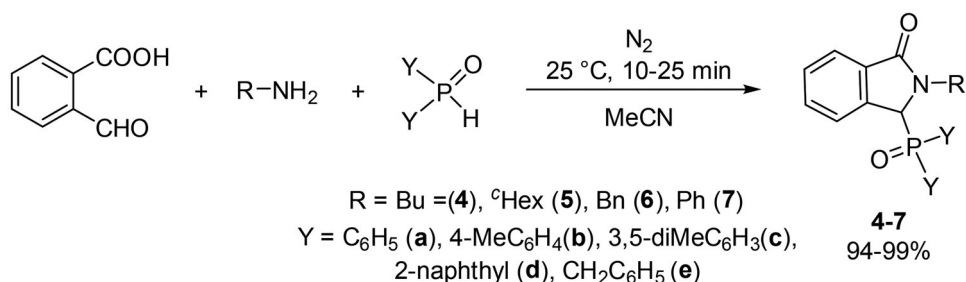


Figure 3. Synthesis of isoindolinone phosphine oxides.

showed modest activity against human promyelocytic leukemia (HL-60) cell line, furthermore, two derivatives incorporating 3,5-dimethylphenyl groups on the phosphorus atom were also active against selected Gram-positive (*Bacillus subtilis*) bacteria.^[6]

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References

- [1] Speck, K.; Magauer, T. The Chemistry of Isoindole Natural Products. *Beilstein J. Org. Chem.* **2013**, *9*, 2048–2078. DOI: [10.3762/bjoc.9.243](https://doi.org/10.3762/bjoc.9.243).
- [2] Adib, M.; Sheikhi, E.; Yazzaf, R.; Bijanzadeh, H. R.; Mirzaei, P. An Efficient, Three-Component Synthesis of Isoindolin-1-One-3-Phosphonates under Mild and Solvent-Free Conditions. *Tetrahedron Lett.* **2016**, *57*, 841–844. DOI: [10.1016/j.tetlet.2015.12.055](https://doi.org/10.1016/j.tetlet.2015.12.055).
- [3] Yao, T.; Larock, R. C. Regio- and Stereoselective Synthesis of Isoindolin-1-Ones via Electrophilic Cyclization. *J. Org. Chem.* **2005**, *70*, 1432–1437. DOI: [10.1021/jo048007c](https://doi.org/10.1021/jo048007c).
- [4] Macsari, I.; Besidski, Y.; Csajnyik, G.; Nilsson, L. I.; Sandberg, L.; Yngve, U.; Ahlin, K.; Bueters, T.; Eriksson, A. B.; Lund, P.-E.; et al. 3-Oxoisoindoline-1-Carboxamides: Potent, State-Dependent Blockers of Voltage-Gated Sodium Channel Na(V)1.7 with Efficacy in Rat Pain Models. *J. Med. Chem.* **2012**, *55*, 6866–6880. DOI: [10.1021/jm300623u](https://doi.org/10.1021/jm300623u).
- [5] Tajti, Á.; Tóth, N.; Rávai, B.; Csontos, I.; Szabó, P. T.; Bálint, E. Study on the Microwave-Assisted Batch and Continuous Flow Synthesis of N-Alkyl-Isoindolin-1-One-3-Phosphonates by a Special Kabachnik–Fields Condensation. *Molecules* **2020**, *25*, 3307. DOI: [10.3390/molecules25143307](https://doi.org/10.3390/molecules25143307).
- [6] Popovics-Tóth, N.; Rávai, B.; Tajti, Á.; Varga, B.; Bagi, P.; Perdih, F.; Szabó, P. T.; Hackler, L.; Puskás, L. G.; Bálint, E. Three-Component Synthesis, Utilization and Biological Activity of Phosphinoyl-Functionalized Isoindolinones. *Org. Biomol. Chem.* **2021**, *19*, 8754–8760. DOI: [10.1039/D1OB01610E](https://doi.org/10.1039/D1OB01610E).