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# SYNTHESIS OF ISOINDOLINONE PHOSPHONATES AND THEIR RELATED DERIVATIVES BY MULTICOMPONENT REACTION

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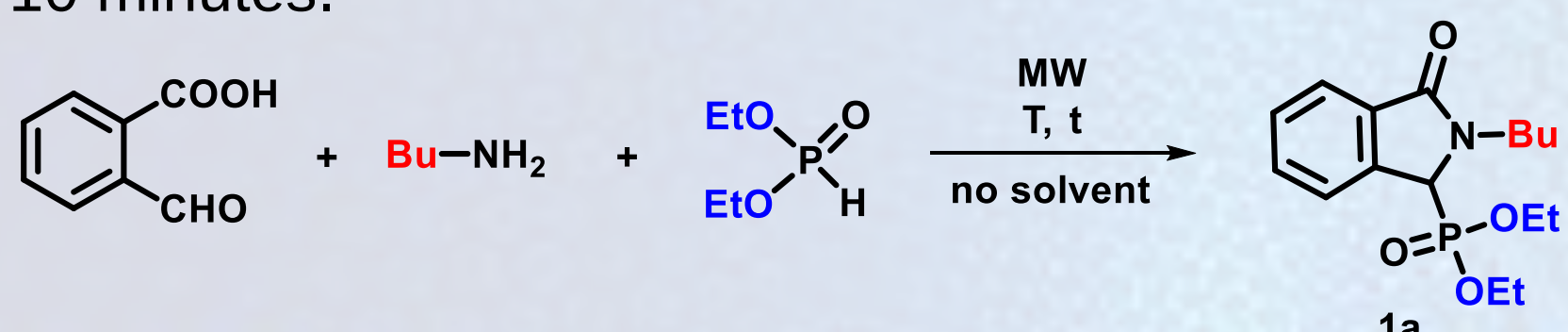
## 1. INTRODUCTION

Isoindolinone derivatives, as an important class of *N*-heterocycles, may show biological activity in several medicinal fields. They proved to be useful as antihypertensives, antibiotics, antiviral- or anticancer agents, and anti-inflammatory- and neuropathic pain drugs, as well [1-4]. Isoindolinone phosphonates may be used as effective plant growth regulators [5], while isoindolinone phosphine oxides are valuable intermediates of cytotoxic compounds [6]. In our research work, our aim was to study the batch and continuous flow preparation of isoindolinone phosphonates by special Kabachnik–Fields reaction starting from 2-formylbenzoic acid, primary amines and various dialkyl phosphites. In order to obtain a “real time” information about the condensation process, a model reaction was followed by *in situ* FT-IR spectroscopy. An optimization for the preparation of an isoindolinone phosphine oxide was also investigated. The condensations were carried out according to the principles of “green chemistry”; in the absence of any catalyst, and - as far as possible - without any solvent.

## 2. PREPARATION OF ISOINDOLINONE PHOSPHONATES AND PHOSPHINATES

### 2.1. OPTIMIZATION OF A MODEL REACTION

At first, the condensation of 2-formylbenzoic acid, butylamine and diethyl phosphite was optimized. The reactions were carried out without any catalyst and solvent. As the conversion was not complete at room temperature, the condensation was investigated further at a higher temperature, under microwave (MW) conditions. At 60 °C, a conversion of 85% was achieved. Increasing the reaction time or the molar ratio of diethyl phosphite, the condensations were not complete. However, changing the molar ratio of butylamine to 1.2 equivalents, a conversion of 100% could be reached at 60 °C after 10 minutes.

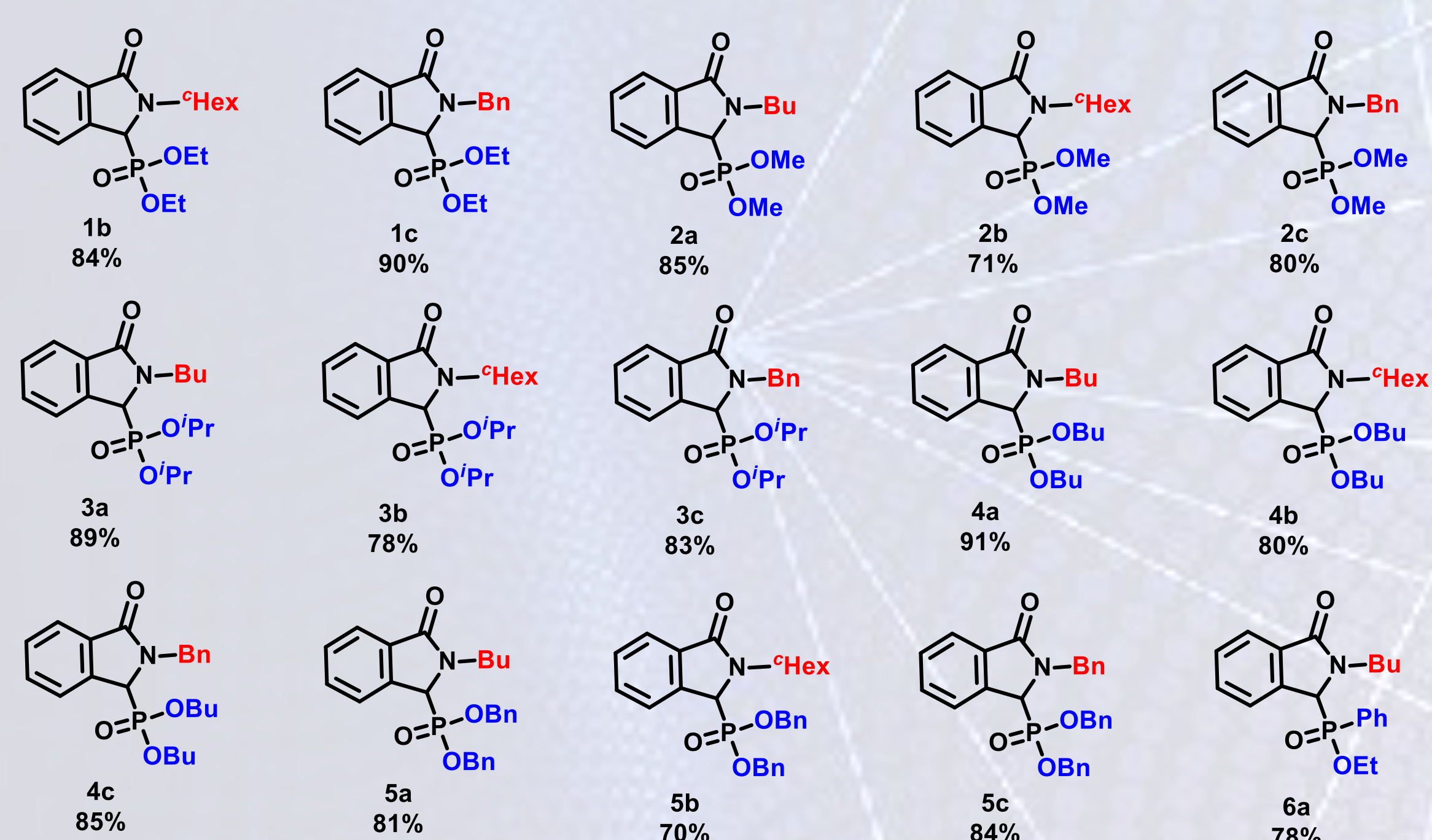
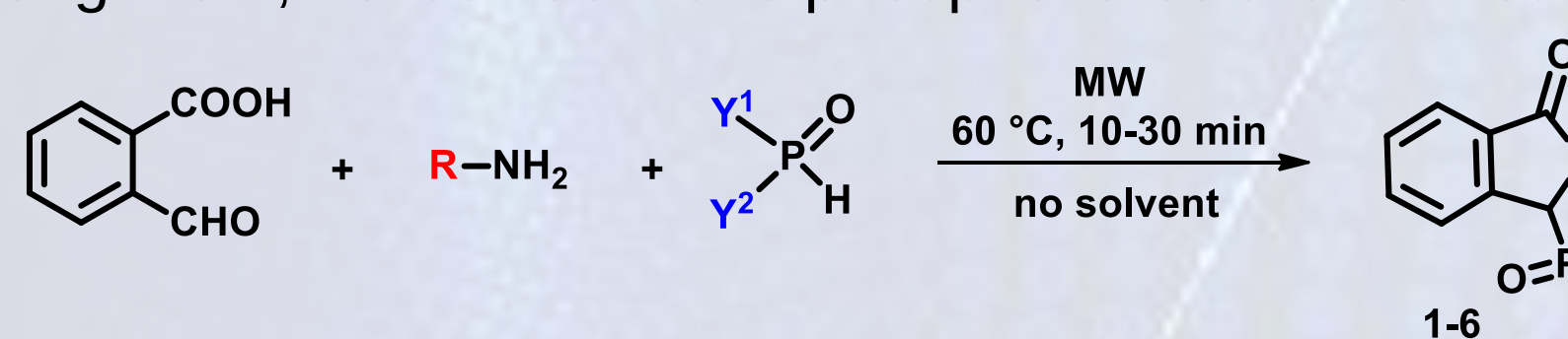


| Entry          | T [°C] | t [min] | DEP [equiv.] | BuNH <sub>2</sub> [equiv.] | Conversion [%] <sup>a</sup> | Yield [%] <sup>b</sup> |
|----------------|--------|---------|--------------|----------------------------|-----------------------------|------------------------|
| 1 <sup>c</sup> | 25     | 180     | 1            | 1                          | 77                          | —                      |
| 2              | 40     | 10      | 1            | 1                          | 61                          | —                      |
| 3              | 60     | 10      | 1            | 1                          | 85                          | —                      |
| 4              | 60     | 30      | 1            | 1                          | 91                          | —                      |
| 5              | 60     | 10      | 1.2          | 1                          | 89                          | —                      |
| 6              | 60     | 10      | 1            | 1.1                        | 92                          | —                      |
| 7              | 60     | 10      | 1            | 1.2                        | 100                         | 94                     |

<sup>a</sup>Based on GC; <sup>b</sup>After column chromatography; <sup>c</sup>At room temperature

### 2.2. EXTENSION OF THE MODEL REACTION

After the optimization, the model reaction was extended, and a number of isoindolinone phosphonates (**1-6**) were synthesized using 2-formylbenzoic acid, various primary amines and different dialkyl phosphites. The condensation was also performed starting from ethyl phenyl-*H*-phosphinate. After purification by column chromatography, 15 derivatives were isolated in yields of 70-91%. Among them, 13 isoindolinone phosphonates are new compounds.



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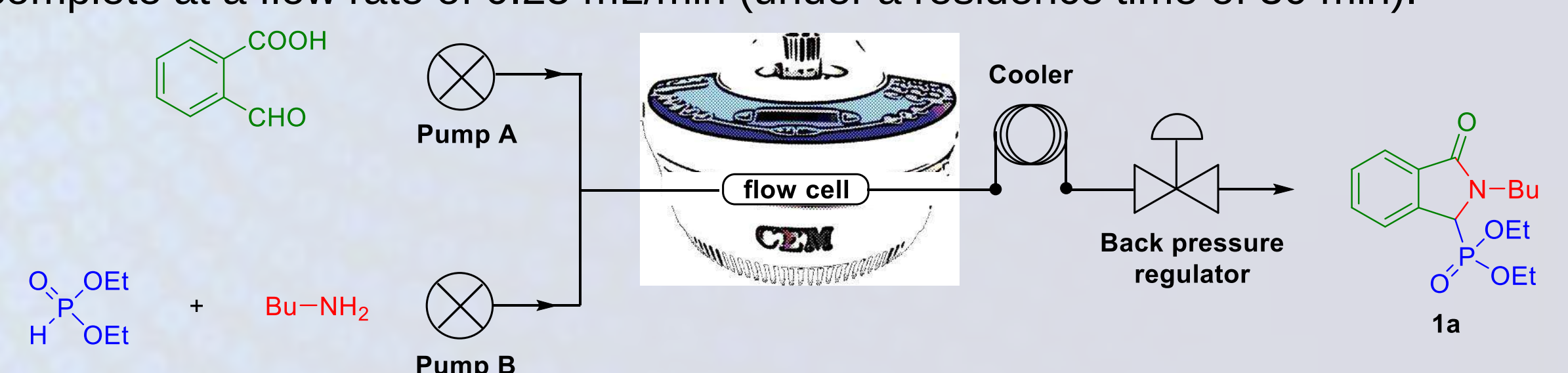
## 8. ACKNOWLEDGMENTS

The project was supported by the Hungarian Research Development and Innovation Office (FK123961), by the National Research, Development and Innovation Fund of Hungary in the frame of the FIEK\_16-1-2016-0007 (Higher Education and Industrial Cooperation Center) project. B.R. was supported by the ÚNKP-20-2-I-BME-255 New National Excellence Program of the Ministry for Innovation and Technology. E.B. was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences.



## 3. CONTINUOUS FLOW SYNTHESIS

In order to increase the productivity of the MW-assisted synthesis developed, the reaction of 2-formylbenzoic acid, butylamine and diethyl phosphite was further studied using a dual pump continuous flow system containing a CEM® MW reactor equipped with a commercially available CEM® continuous flow cell. The 2-formylbenzoic acid in ethanol, and the mixture of butylamine and diethyl phosphite in ethanol were fed separately into the mixer. During the optimization, the effects of the molar ratio of the starting materials and the residence time were investigated. Applying 1.5 equivalents of butylamine and diethyl phosphite, the reaction was complete at a flow rate of 0.25 mL/min (under a residence time of 30 min).

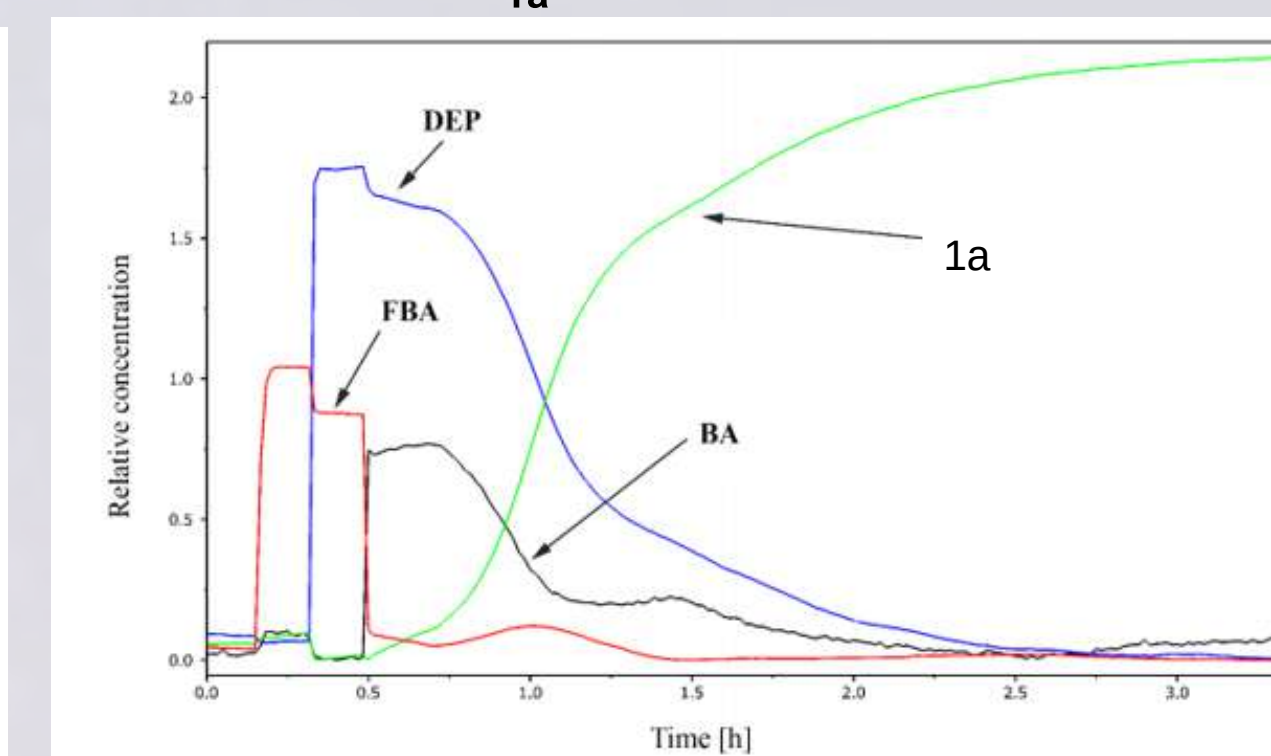
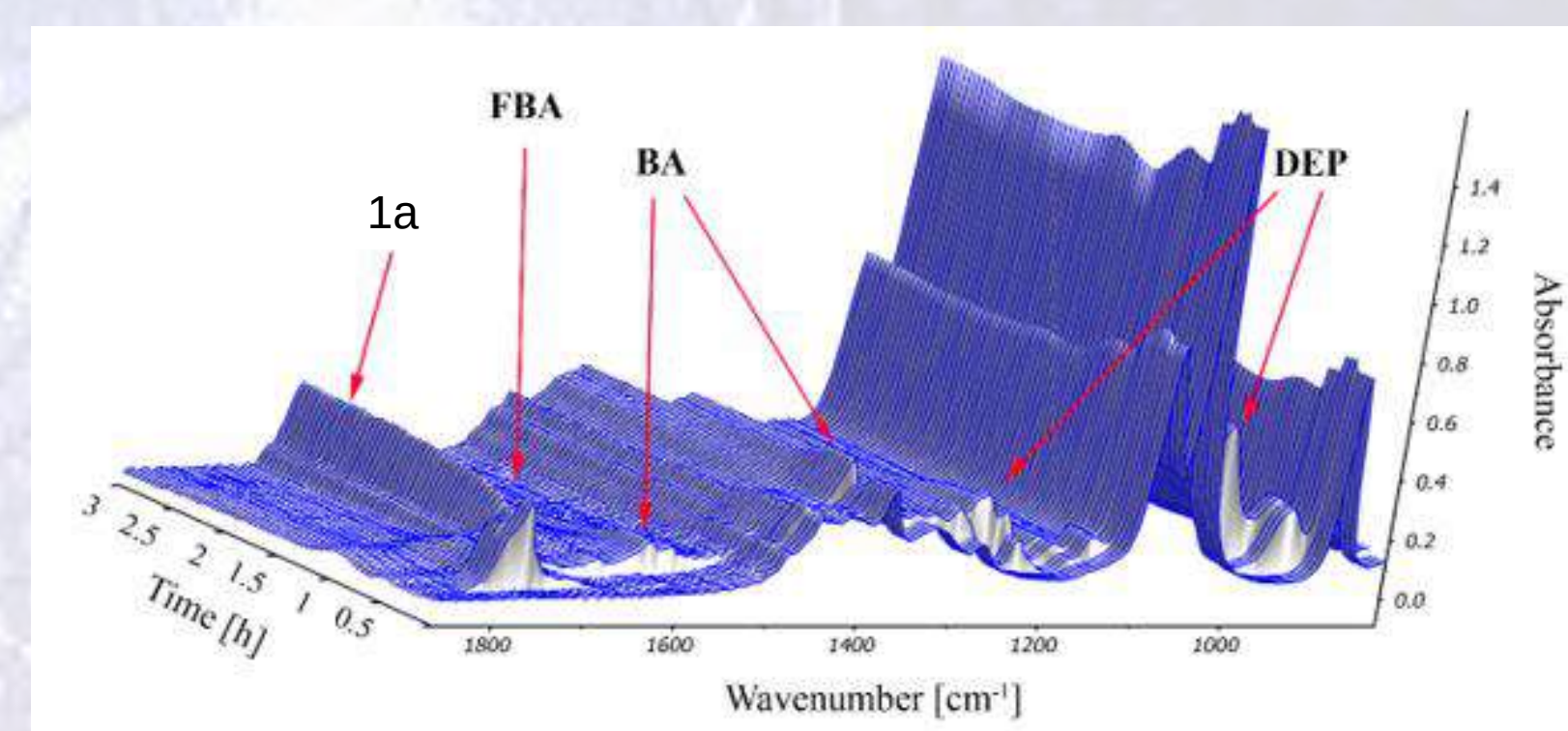
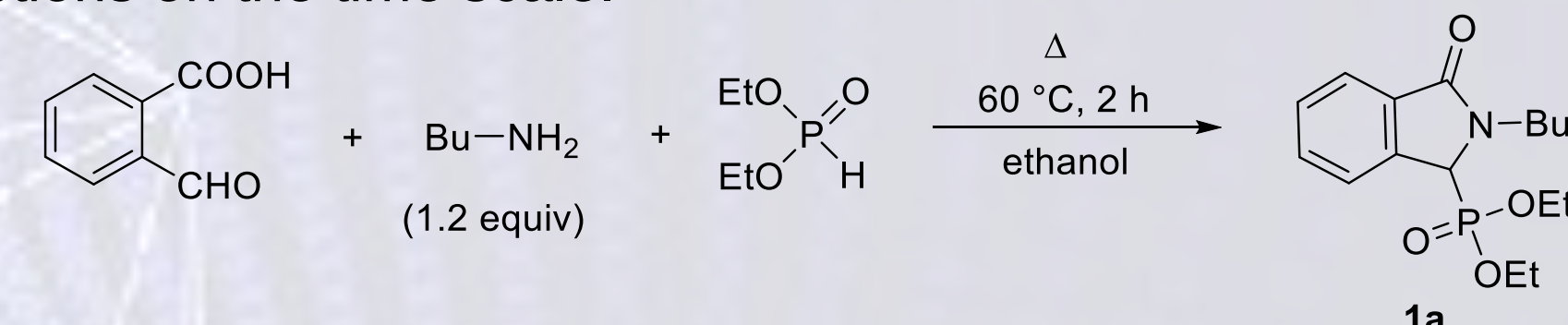


| Entry | Flow rate [mL/min] | Amin [equiv.] | DEP [equiv.] | τ [min] | Conversion [%] <sup>a</sup> | Yield [%] <sup>b</sup> |
|-------|--------------------|---------------|--------------|---------|-----------------------------|------------------------|
| 1     | 0.70               | 1.2           | 1            | 10      | 43                          | —                      |
| 2     | 0.35               | 1.2           | 1            | 20      | 52                          | —                      |
| 3     | 0.25               | 1.2           | 1            | 30      | 56                          | —                      |
| 4     | 0.35               | 1.5           | 1            | 20      | 70                          | —                      |
| 5     | 0.35               | 2.0           | 1            | 20      | 73                          | —                      |
| 6     | 0.35               | 1.5           | 1.2          | 20      | 81                          | —                      |
| 7     | 0.35               | 1.5           | 1.5          | 20      | 95                          | —                      |
| 8     | 0.25               | 1.5           | 1.5          | 30      | 100                         | 94                     |

<sup>a</sup>Based on GC; <sup>b</sup>After column chromatography.

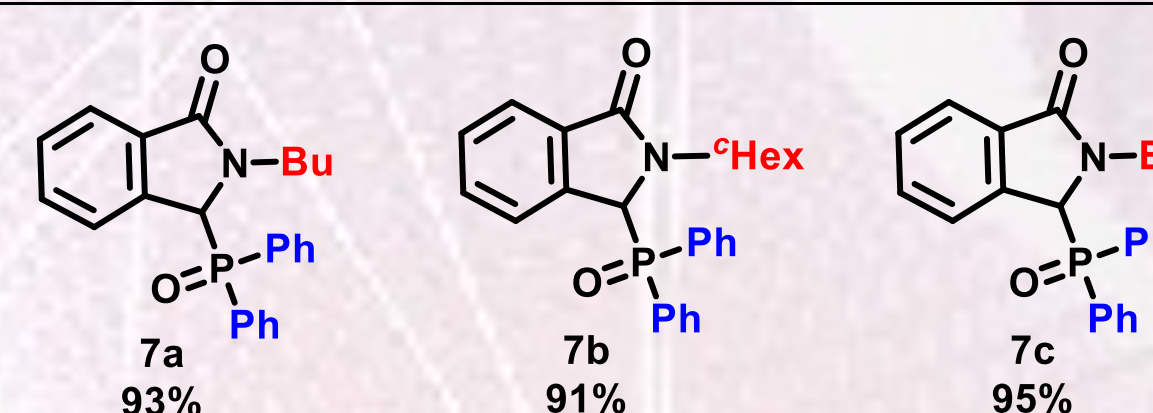
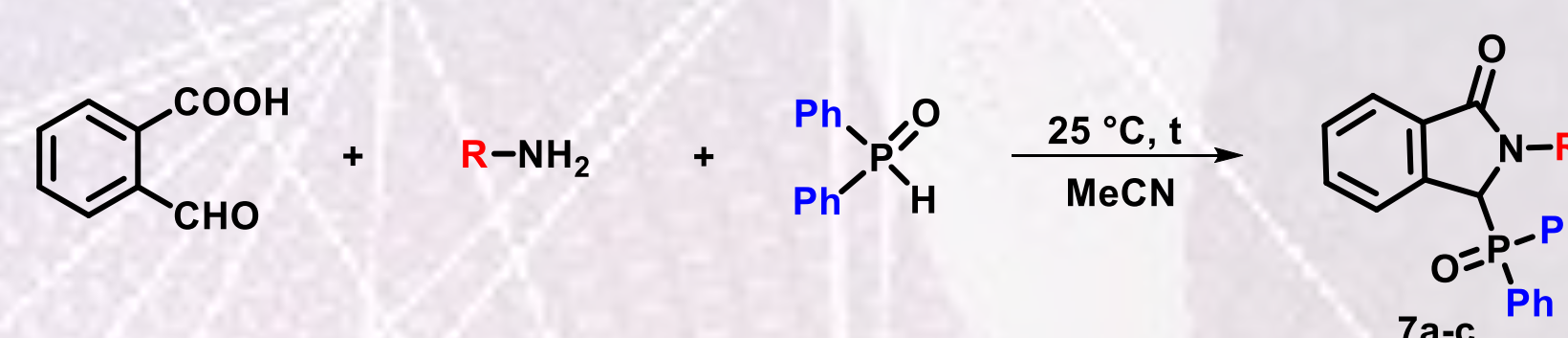
## 4. REACTION MONITORING BY IN SITU FT-IR SPECTROSCOPY

Investigating mechanism of the reaction, the condensation of 2-formylbenzoic acid, butylamine and diethyl phosphite was followed by *in situ* FT-IR spectroscopy. At first, the starting materials were mixed in ten-minute intervals in the following order: 2-formylbenzoic acid (**FBA**), diethyl phosphite (**DEP**) and butylamine (**BA**). Then, the mixture was heated to 60 °C in an oil bath and was reacted until completion. In the obtained time-dependent IR spectrum (3D diagram), reaction components can be easily identified by their characteristic absorptions. Then, the concentration profile of the starting materials and the product was also prepared by deconvolution, on the basis of the decrease/increase of the different absorptions on the time scale.



## 5. PREPARATION OF ISOINDOLINONE PHOSPHINE OXIDES

The special Kabachnik–Fields reaction was extended to a secondary phosphine oxide - diphenyl phosphine oxide - and various primary amines, as well. The reactions were efficiently carried out at room temperature in short reaction times in the absence of any catalyst in acetonitrile. Altogether 3 new derivatives (**7a-c**) were synthesized in high yields (91-95%).

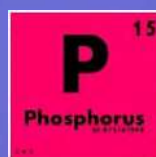


| Entry | R                | t [min] | Conversion [%] <sup>a</sup> | Yield [%] <sup>b</sup> |
|-------|------------------|---------|-----------------------------|------------------------|
| 1     | Bu               | 5       | 88                          | —                      |
| 2     | Bu               | 10      | 98                          | 93 (7a)                |
| 3     | <sup>c</sup> Hex | 10      | 83                          | —                      |
| 4     | <sup>c</sup> Hex | 15      | 91                          | —                      |
| 5     | <sup>c</sup> Hex | 20      | 99                          | 91 (7b)                |
| 6     | Bn               | 10      | 99                          | 95 (7c)                |

<sup>a</sup>Based on HPLC (222 nm); <sup>b</sup>After column chromatography

## 6. CONCLUSION

The special Kabachnik–Fields reaction of 2-formylbenzoic acid, butylamine and diethyl phosphite was optimized in the absence of any solvent and catalyst. Further derivatives were also synthesized starting from different primary amines, and dialkyl phosphites or ethyl phenyl-*H*-phosphinate. Then, the continuous flow synthesis was investigated. The mechanism of the reaction was studied by FT-IR spectroscopy. In a new synthetic route, isoindolinone phosphine oxides were synthesized. Altogether, 19 derivatives were isolated in yields of 70-95%, from which 17 are new compounds.



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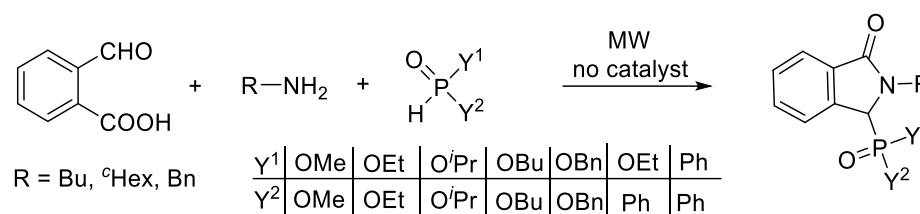
## Synthesis of isoindolinone phosphonates and their related derivatives by multicomponent reaction

Bettina Rávai<sup>1</sup>, Nóra Popovics-Tóth<sup>1</sup>, Ádám Tajti<sup>1</sup>, Erika Bálint<sup>1</sup>

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Isoindolinone derivatives are important compounds among nitrogen heterocycles. They were proved to be useful in a wide range of applications in the field of medicinal chemistry.[1]

During our work, we have elaborated an efficient catalyst-free microwave(MW)-assisted method 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 >P(O)H reagents, such as dialkyl phosphites, ethyl phenyl-*H*-phosphinate or diphenyl phosphine oxide.[2]



Scheme 1. Synthesis of isoindolinone phosphonate derivatives.

The reaction of 2-formylbenzoic acid, butylamine and diethyl phosphite was followed by *in situ* Fourier transform (FT)-IR spectroscopy.

The condensation was also investigated applying different secondary phosphine oxides as the phosphorus component. After deoxygenation of an isoindolinone phosphine oxide, the isoindolinone phosphine obtained was utilized as phosphine ligand in the synthesis of a monodentate platinum complex.

Finally, the cyclization was studied using 8-formyl-1-naphthoic acid instead of 2-formylbenzoic acid to synthesize new polycondensed *N*-heterocycles bearing various phosphorus substituents.

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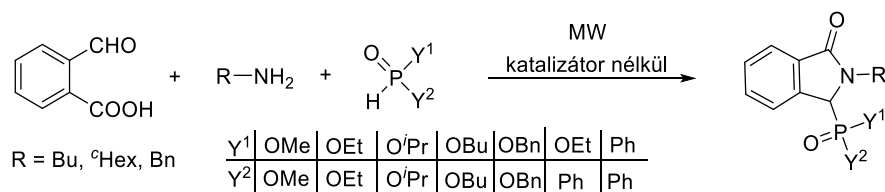
## Multikomponensű reakciók vizsgálata izoindolinon-foszfónátok és származékaik előállítására

Rávai Bettina<sup>1</sup>, Popovics-Tóth Nóra<sup>1</sup>, Tajti Ádám<sup>1</sup>, Bálint Erika<sup>1</sup>

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A nitrogén-heterociklusok fontos képviselői közé tartoznak az izoindolinok, melyek gyógyászati szempontból is több területen bizonyultak hatásosnak.

Kutatómunkánk során egy hatékony, katalizátor nélküli, mikrohullámú körülmények (MW) között megvalósított reakciót dolgoztunk ki *N*-alkil-izoindolinon-foszfónátok szakaszos és folyamatos előállítására a 2-formil-benzoesavból, primer aminokból és különböző >P(O)H reagensből (dialkil-foszfítok, etil-fenil-H-foszfinát és difenil-foszfin-oxid) kiindulva.



1. ábra: Izoindolinon-foszfónátok előállítása

A 2-formil-benzoesav, butilamin és dietil-foszfít reakcióját *in situ* Fourier transzformációs (FT)-IR spektroszkópiával is követtük.

A kondenzációt változatos szekunder foszfin-oxidokra is kiterjesztettük. Majd egy izoindolinon-foszfin-oxid deoxigénezését és a kapott izoindolinon-foszfin foszfin ligandumként történő hasznosítását is megvalósítottuk egy platina komplex szintézisében.

Végül, a gyűrűzárást a 2-formil-benzoesav helyett 8-formil-1-naftalén-karbonsavból kiindulva is vizsgáltuk, további foszfor oldalláncot tartalmazó polikondenzált *N*-heterociklusokat előállítva.

### Köszönetnyilvánítás

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### Irodalom

[1] R. K. Bhatia, *Curr. Top. Med. Chem.*, **2017**, 17, 189-207.

[2] Á. Tajti, N. Popovics-Tóth, B. Rávai, I. Csontos, P. T. Szabó, E. Bálint, *Molecules*, **2020**, 25, 3307.