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Synthesis of Phosphonates in a Continuous Flow Manner

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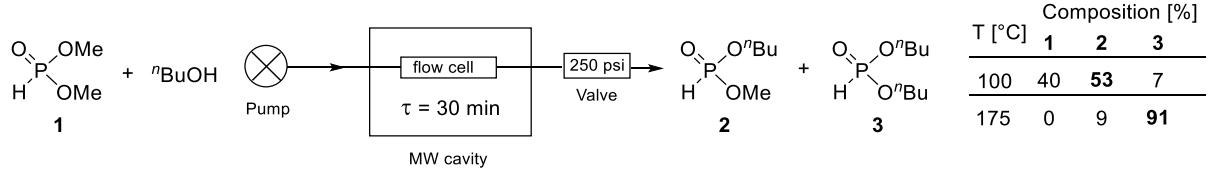
Abstract *The synthesis of dialkyl H-phosphonates and α-aminophosphonates was studied in a continuous flow microwave reactor. Depending on the conditions, the alcoholysis of dialkyl H-phosphonates could be fine-tuned towards the mixed and the fully transesterified products. The continuous flow synthesis of α-aryl-α-aminophosphonates was elaborated utilizing the aza-Pudovik reaction of imines and dialkyl H-phosphonates, as well as the by the Kabachnik-Fields condensation of primary amines, benzaldehyde and >P(O)H reagents.*

Keywords dialkyl *H*-phosphonates; α-aminophosphonates; alcoholysis; Kabachnik-Fields reaction; Pudovik reaction; continuous flow reactor

Microwave (MW)-assistance is a useful technique, however, the size of the reactor is rather limited.[1] MW-assisted reactions on a bigger scale may be carried out in a continuous flow MW equipment.[2] In this work, the synthesis of phosphonates was investigated in a self-developed continuous flow MW system based on a CEM Discover MW reactor equipped with a commercially available CEM continuous flow cell.

The continuous flow alcoholysis of dimethyl *H*-phosphonate (**1**) with *n*-butanol (Scheme 1) was studied in the single pump system based on our experiences in a batch MW reactor.[3] At a residence time of 30 min and 100°C, the *n*-butyl methyl *H*-phosphonate (**2**) was obtained as the main component (53%), while at 175 °C, the di(*n*-butyl) *H*-phosphonate (**3**) predominated (91%). Further increase of the temperature did not change the composition.



T [°C]	Composition [%] 1	2	3
100	40	**53**	7
175	0	9	**91**

Scheme 1 Continuous flow alcoholysis of dimethyl *H*-phosphonate with *n*-butanol.

An efficient method has been developed for the synthesis of α-aryl-α-aminophosphonates (**4**) by the catalyst- and solvent-free MW-assisted aza-Pudovik reaction in a batch MW reactor.[4] To make the procedure flow compatible, a preliminary experiment was carried out for the addition of diethyl phosphite

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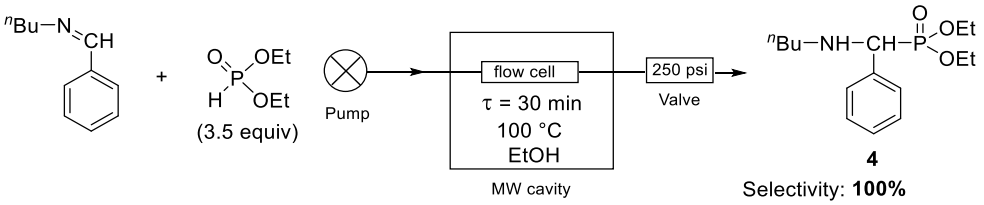
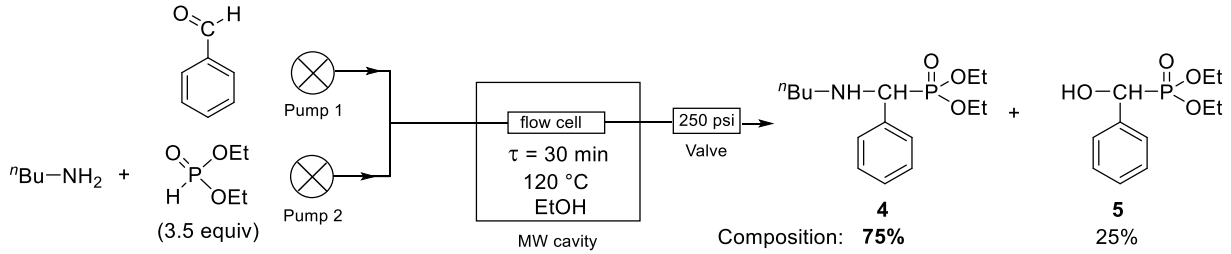
to *N*-benzylidene(*n*-butyl)amine in ethanol as the solvent (Scheme 2). The diethyl ((*n*-butylamino)(phenyl)methyl)phosphonate (**4**) was formed selectively.



Scheme 2 Continuous flow synthesis of diethyl ((*n*-butylamino)(phenyl)methyl)phosphonate by aza-Pudovik reaction.

As an extension, after changing for the dual pump system, the same α-aminophosphonate (**4**) was prepared by the three-component Kabachnik-Fields reaction of *n*-butylamine, diethyl phosphite and benzaldehyde in ethanol without any catalyst (Scheme 3). Although, the aldehyde and the phosphite were pumped form separated vessels, beside the desired product (**4**) (75%), 25% of the α-hydroxyphosphonate (**5**) was also formed.



Scheme 3 Continuous flow reaction of *n*-butylamine, diethyl phosphite and benzaldehyde.

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