EXTENDED ABSTRACT

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The synthesis of p-esters under continuous flow mw conditions

N. Zs. Kiss

Budapest University of Technology and Economics, Budapest, Hungary

Abstract

Microwave (MW)-assisted organic syntheses has achieved great attention as laboratory-scale chemical equipments have been made commercially available. There have since been many reports employing microwave irradiation in organic syntheses, affording higher yields and purity in shorter reaction time as compared to conventional heating methods. However, such reactions are challenging to scale due to the limited penetration depth of microwaves. To address this issue, the application of continuous flow MW reactors are to be considered if the organic transformation meets the requirements of flow chemistry. Such application may be the synthesis of P-esters, phosphinates or phosphonates under continuous flow MW-assisted conditions.

A novel preparation of phosphinates and phosphonates elaborated by us involves the MW-assisted direct esterification of phosphinic and phosphonic acids with alcohols. However due to the low reactivity, long reaction times are required even under MW assistance. We found that suitable ionic liquids (ILs) applied in a catalytic amount may significantly promote the esterification reactions resulting in shorter reaction times even under milder conditions. The changed reaction parameters made it possible to carry out the direct esterification of P-acids in a continuous flow apparatus. Moreover, transesterification (alcoholysis) of phosphinates and dialkylphosphites was also realized using a MW reactor equipped with a flow cell. Thus, the P-esters became available at a larger scale.

There is a fantastic development has occurred in the spread of microwaveIn synthetic chemistry (MW) equipment. This environmentally friendly methodology, associated often with solventless conditions, has also had a positive impact on organophosphorus chemistry, allowing new reactions to be administered , or increasing the speed , selectivity and yield. In special cases, MW irradiation may replace phase transfer or other forms of catalysts. Reactions, like the the inverse Wittig protocol, derivatization of phosphinic acids, fragmentation-related phosphorylations, phospha-Michael additions, Diels– Alder cycloadditions, the addition of >P(O)H species to carbonyl compounds, Kabachnik–Fields condensations,substitution of alkylation of CH-acidic compounds, α-hydroxyphosphonates, Arbuzov reactions, C–P couplings and transesterifications these all are served as model reactions under MW conditions.

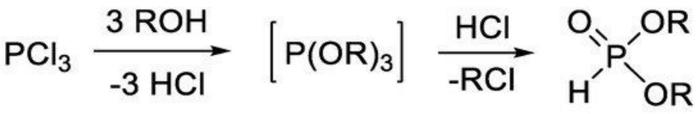
In microwave (MW) chemistry, the continual flow technique represents a special importance. Although applications of the MW technique proved to be useful in many chemical transformations, the scale-up of MW-assisted reactions means a challenge due to the limited geometry of the MW devices [3,4,5,6]. One possibility to solve this problem is the use of continuous flow MW reactors, where the reaction mixture flows through an irradiated flow cell. The MW unit can be of a similar size used in batch mode. During the last decade, the advantages of the applications of continuous flow MW reactors were reported in certain transformations; however, in most cases, the usefulness of the occasional devices may be questionable, as non-professional MW reactors do not allow reproductions, and what is more important, the temperatures were not reported [7,8].

Esters represent a fundamental family among organic compounds. Esters of carboxylic acids may be important intermediates, solvents or products in organic chemistry.

The most common preparations of straightforward carboxylic esters comprise the acid-catalyzed reaction of a acid with alcohol (Fischer esterification) and therefore the reaction of an ester with alcohol (alcoholysis) [10]. Fischer esterifications can be done by continuous flow which can also be administered in systems containing a packed catalyst bed [11,12,13,14,15,16,17,18,19,20] or a heated coil [21,22], also as in microreactors [23]. In a few cases, the esterifications were performed in continuous flow MW systems based on professional MW reactors [24,25,26] or in household MW ovens [27,28]. The continuous flow alcoholysis of carboxylic esters can also be performed in reactors equipped with a heated coil [21,30] or catalyst bed [29]. The alcoholysis is additionally of great importance in biodiesel production, the world of which was recently summarized by Lee and associates [31].

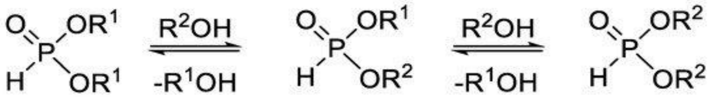
Organophosphorus esters are also of great importance [32]. Dialkyl esters of hypophosphorous acid (dialkyl H-phosphonates) are widely applied building blocks in syntheses [33]. They are important starting materials of the Kabachnik–Fields condensations and therefore the aza-Pudovik reactions [34] , the Pudovik reactions [35] (resulting within the formation of α-hydroxyphosphonates) and further organophosphorus transformations, like the Hirao reaction [36] and therefore the phospha-Michael addition [37]. Dialkyl H-phosphonates bearing different alkoxy groups on the phosphorus atom are valuable intermediates for P-chiral organophosphorus derivatives [38,39].

The industrial synthesis of dialkyl H-phosphonates is comprised of the reaction of phosphorus trichloride with alcohols (Scheme 1) [40,41,42,43,44,45]. Although this transformation is convenient, efficient and may be scaled up, it requires a solvent, and the liberating HCl decreases the atom efficiency. It is also a disadvantage that the synthesis of derivatives with different alkyl groups is not possible.



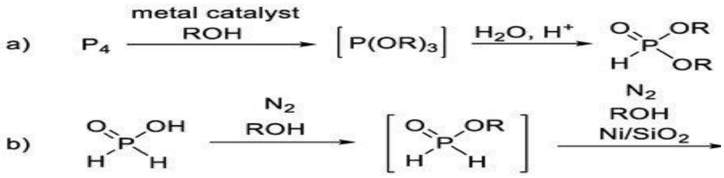
Synthesis of dialkyl *H*-phosphonates from phosphorus trichloride.

Another possibility for the preparation of dialkyl *H*-phosphonates is alcoholysis (Scheme 2), which provides the products in good yields [46,47,48,49,50,51,52,53,54]. The only by-product is the leaving alcohol. The relatively high temperature and the need for the high excess of the alcohol mean disadvantages.



Synthesis of dialkyl *H*-phosphonates by alcoholysis.

Besides the two main routes mentioned above, there are a few less important methods for the synthesis of dialkyl *H*-phosphonates. Such protocols are the oxidative reaction of elemental phosphorus with alcohols (Scheme 3a) [55,56,57,58,59,60] and the Ni-catalyzed oxidation of hypophosphorous esters



Miscellaneous synthesis of dialkyl *H*-phosphonates.

The synthesis of dialkyl-*H*-phosphonates bearing different alkyl groups is not easy and requires special methods (Table 1).

Table 1. Synthetic methods for the preparation of dialkyl *H*-phosphonates bearing two different alkyl groups.

Different alkyl groups of Phosphites may be synthesized by the partial alcoholysis of dialkyl H-phosphonates. The reaction conditions must be controlled strictly to avoid complete transesterification.

Dialkyl H-phosphonates with two different alkyl groups may be obtained by the controlled O–C cleavage of dialkyl H-phosphonates (Table 2, Entries 2 and 3). In the first step of the first method, a phosphite-ammonium salt is prepared, which is then alkylated with alkyl iodides (Table 2, Entry 2), or with alcohols in the presence of pivaloyl chloride and pyridine (Table 2 entry 3) to furnish the target compounds selectively. A serious drawback of these transformations is the low atom efficiency.

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