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Continuous Flow Optimisation of the Pudovik Reaction and Phospha-Brook Rearrangement Using DBN

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Abstract: Flow chemistry has shown significant versatility over the last two decades, offering advantages in efficiency, scalability, and sustainability. In this study, the continuous stirred tank reactor (CSTR) was used to optimise the synthesis of α-hydroxyphosphonates via the Pudovik reaction and their subsequent conversion to phosphates through the phospha-Brook rearrangement. The study highlights that using CSTRs allows for better control over reaction parameters, leading to reduced reaction times and improved yields compared to traditional batch methods. The optimised conditions successfully facilitated a range of organophosphates, including electron-rich and electron-poor derivatives, with high efficiency. Additionally, a one-pot tandem process combining the Pudovik reaction and the phospha-Brook rearrangement was developed, reducing reaction times to two hours while maintaining comparable yields. This work demonstrates the potential of CSTRs in flow chemistry for synthesising complex organophosphorus compounds, achieving higher reaction yields and shorter reaction times, highlighting the effectiveness of continuous flow methodologies.

Keywords: continuous flow; Pudovik reaction; phospha-Brook rearrangement; α-hydroxyphosphonates; phosphates; 1,5-diazabicyclo(4.3.0)non-5-ene

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1. Introduction

Over the last two decades, flow chemistry has proven to be highly versatile, offering significant advantages in terms of efficiency, scalability, and sustainability [1]. In addition, researchers have adopted continuous flow approaches as reaction times are faster, safer, and can facilitate challenging reactions [2]. Different devices and equipment are commercially available to run in continuous transformations (Figure 1), including coil, microchip, and packed-bed reactors; however, additional opportunities are offered by continuous stirred tank reactors (CSTRs) [3]. CSTRs operate continuously with uniform mixing and steady-state conditions, offering effective temperature control, scalability, and flexibility for various reactions. Their design allows for multistep synthesis [3], reducing reaction times, enabling solvent switching, and maintaining product isolation [4]. This flow strategy also provides advantages over multiple coil reactors, ensuring better control of conditions, simpler operation, more efficient heat management, and easier scalability, especially for slow or complex reactions.

Organophosphorus compounds are widely found in nature and have garnered significant attention due to their unique chemical properties and diverse applications across various fields. This class of compound is known for its antiviral, antibacterial, anticancer, and enzyme inhibitory activities, making them valuable in pharmaceuticals, oncology, and chemical pesticides [5–9]. Furthermore, organophosphorus compounds are important in organometallic chemistry and photoelectric materials due to their high chelation affinity and the ease with which they can be modified into functional derivatives [1].

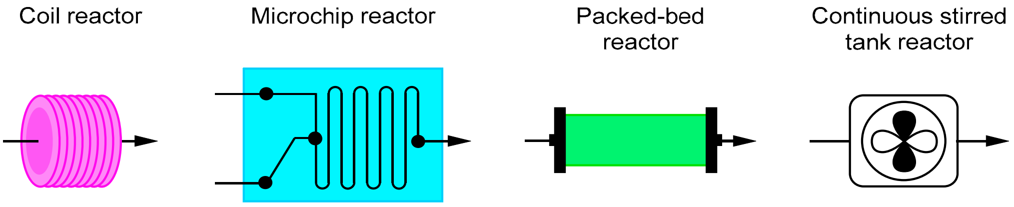
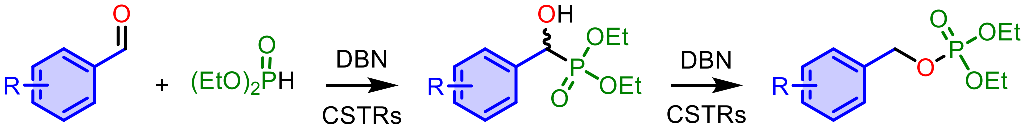


Figure 1. Illustration of coil reactors, microchip reactors, packed-bed reactors, and continuous stirred tank reactors (CSTRs; fReactor) for flow applications.

Organophosphates are a versatile group of compounds with a broad range of applications, particularly in the production of synthetic chemicals for pest control and plastics [10,11]. They play a crucial role in physiological processes, such as linking nucleotides together, stabilising these bonds, and making them resistant to hydrolysis, all while remaining selectively reactive through enzymatic catalysis [12]. In organic synthesis, organophosphates are also used as electrophiles in transition metal-catalysed reactions, including the Kumada reaction, Suzuki reaction, and the phospha-Brook rearrangement [13]. The first phospha-Brook rearrangement, transforming α-hydroxyphosphonates into phosphates, was observed in trichlorfon, an insecticide [14]. This pro-drug converts to 2,2-dichlorovinyl dimethyl phosphate, an acetylcholinesterase inhibitor, through HCl elimination. Strong bases such as sodium ethoxide (NaOEt) [15], sodium hydride (NaH) [16], and potassium *tert*-butoxide (*t*-BuOK) have been reported to facilitate this rearrangement [17]. Chiral homogeneous bases have also been shown to deliver promising yields [18]. Additionally, benzyl phosphates have been synthesised using a one-pot tandem Pudovik reaction followed by the phospha-Brook rearrangement in the presence of butyllithium (BuLi) [19,20]. This process was proposed to take place via formation of an activated lithium diethyl phosphite.

Ramanjaneyulu et al. have reported the first phospha-Brook reaction performed using flow chemistry [21], utilising a single-step method for the synthesis of α-phosphonyloxy ketones as drug scaffolds. This method uses 1,2-dicarbonyls, which readily combine with trialkyl phosphites and formic acids in a capillary microreactor at room temperature. Although the reaction times in the microreactor were short, the formation of by-products was observed. Recently, it has been shown that 1,5-diazabicyclo(4.3.0)non-5-ene (DBN) can facilitate the phospha-Brook reaction at room temperature under batch conditions, yielding a range of phosphate diesters in excellent yields after 16 h [22]. In this study, the use of CSTRs is explored for the optimisation and synthesis of α-hydroxyphosphonates via the Pudovik reaction and the subsequent formation of phosphates through the phospha-Brook reaction by modifying the amount of DBN used (Scheme 1). Additionally, the study demonstrates that a one-pot tandem Pudovik reaction followed by the phospha-Brook rearrangement can also be achieved, with reaction times significantly reduced compared to batch conditions while maintaining comparable yields.



Scheme 1. Pudovik reaction and phospha-Brook rearrangement.

2. Materials and Methods

2.1. General Experimental

Commercially available analytical grade reagents were purchased from Merck, Gillingham, UK or Thermo Fisher Scientific Inc., UK and used without further purification. Reactions were followed by TLC and compounds were purified by flash column chromatography. The silica gel used was Merck 60 (230–400 mesh). Analytical TLC was carried out on Merck 60 F_{245} aluminium-backed silica gel plates. Short-wave UV (245 nm) was used to visualise components. All experiments were conducted using the Asynt fReactor–classic (Asynt, Cambridgeshire, UK) platform using five modules. The total reactor volume was 8.8 mL, using a PTFE cross-stirrer bar design. A 100 psi back-pressure regulator was used when trying to optimise the reactions. All syringe pumps were AL-1000 Aladdin and were connected to the CSTRs using PTFE tubing (1/8″ O.D.; 1/16″ I.D.) and flangeless male HPLC nuts (1/8″) with flangeless ferrules (1/8″). ^{1}H-NMR, ^{13}C-NMR, and ^{31}P-NMR were recorded on a Bruker AV500 spectrometer operating at 500 MHz for proton, 126 MHz for carbon, and 202 MHz for phosphorus. Spectra were recorded in deuterochloroform and referenced to residual $CHCl_3$ (^{1}H, 7.27 ppm; ^{13}C, 77.0 ppm) and with 85% H_3PO_4 solution as an external standard (^{31}P, 0.0 ppm). Chemical shifts (δ) are reported in ppm and coupling constants (*J*) are reported in Hz. The following abbreviations are used to describe multiplicity: s singlet, d doublet, t triplet, q quartet, and m multiplet. High-resolution mass spectra were recorded on a LTQ Orbitrap XL utilising nanospray ionisation (NSI) with a methanol mobile phase recorded in the positive mode. Low-resolution mass spectra were recorded on an Agilent Micromass Q-TOF premier Tandem Mass Spectrometer from Micromass (Agilent, Santa Clara, CA, USA) utilising electrospray. Melting points were determined using open glass capillaries on a Stuart Scientific SMP3 (Scientific Laboratory Supplies, Nottingham, UK) apparatus and are uncorrected. Infrared spectra were recorded on an Agilent Technologies Cary 630 FT-IR spectrophotometer (Agilent, Santa Clara, CA, USA).

2.2. General Procedure for the Synthesis of α-Hydroxyphosphonates **2**

A solution of DBN (0.19 mmol, 5 mol%) in MeCN (0.038 M) was fluxed at the same flow rate simultaneously with a solution of aromatic aldehyde (3.83 mmol, 1 eq.) and phosphite (3.83 mmol, 1 eq.) in MeCN (0.77 M) at room temperature. The residence time was 120 min. Syringes were placed on syringe pumps, and the five module CSTRs on a stirrer plate, stirring at 500 rpm. The output tube was placed in a beaker containing aqueous dilute HCl (2 M, 10 mL). After this period, the reactor and tubing were thoroughly rinsed with MeCN (20 mL) to recover any residual material. The reaction mixture was extracted with Et_2O (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting mixture was suspended in hexane (20 mL) and filtered under reduced pressure, washing with a 9:1 mixture of hexane:Et_2O (20 mL) to afford the α-hydroxyphosphonate.

2.3. General Procedure for the Synthesis of Phosphates **3** *from α-Hydroxyphosphonates* **2**

A solution of DBN (3.34 mmol, 1 eq.) in MeCN (0.67 M) was fluxed at the same flow rate simultaneously with a solution of α-hydroxyphosphonate (3.34 mmol, 1 eq.) in MeCN (0.67 M) at room temperature. The residence time was 120 min. Syringes were placed on syringe pumps, and the five module CSTRs on a stirrer plate, stirring at 500 rpm. The output tube was placed in a beaker containing aqueous dilute HCl (2 M, 10 mL). After this period, the reactor and tubing were thoroughly rinsed with MeCN (20 mL) to recover any residual material. The reaction mixture was extracted with Et_2O (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (2:8 hexane:diethyl ether) to afford the phosphate.

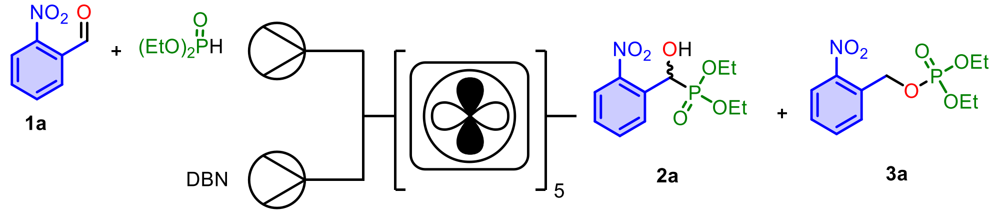
2.4. General Procedure for the Synthesis of Phosphates **3** *from Aromatic Aldehydes and Phosphites*

A solution of DBN (3.83 mmol, 1 eq.) in MeCN (1.5 M) was fluxed at the same flow rate simultaneously with a solution of aromatic aldehyde (3.83 mmol, 1 eq.) and phosphite (3.83 mmol, 1 eq.) in MeCN (1.5 M) at room temperature. The residence time was 120 min. Syringes were placed on syringe pumps, and the five module CSTRs on a stirrer plate, stirring at 500 rpm. The output tube was placed in a beaker containing aqueous dilute HCl (2 M, 10 mL). After this period, the reactor and tubing were thoroughly rinsed with MeCN (20 mL) to recover any residual material. The reaction mixture was extracted with Et_2O (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (2:8 hexane:diethyl ether) to afford the phosphate.

3. Results and Discussion

3.1. Pudovik Reaction

To investigate the phospha-Brook rearrangement, it was first necessary to synthesise α-hydroxyphosphonates. The synthesis of α-hydroxyphosphonates via the Pudovik reaction has been extensively studied [23]. Kabachnik notably reported the successful Pudovik reaction between carbonyl compounds and dialkyl phosphites using 1 mol% DBN with microwave irradiation, achieving high yields and fast reaction times [24]. Building on this study, the Pudovik reaction between 2-nitrobenzaldehyde and diethyl phosphite in the presence of DBN was optimised using the fReactor (Scheme 2). Using a five-module CSTR set-up, a mixture of 2-nitrobenzaldehyde (**1a**) and diethyl phosphite in MeCN and DBN in MeCN were independently fed into the reactor under different reaction conditions (Table 1). 2-Nitrobenzaldehyde was selected as a model substrate due to the electron-withdrawing effect of the nitro group, which enhances the electrophilicity of the carbon atom in the aldehyde.



Scheme 2. Pudovik reaction set-up.

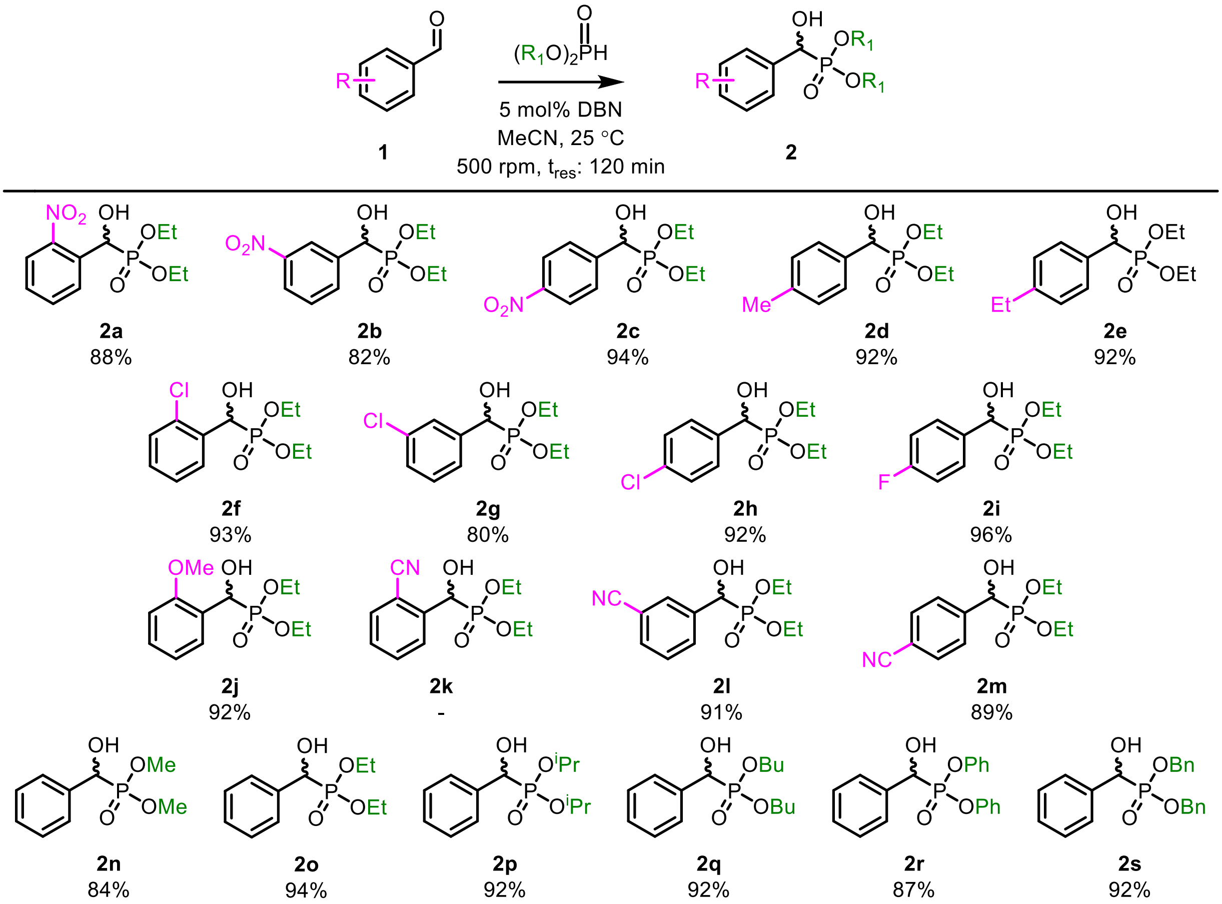
Table 1. Optimisation of the Pudovik reaction using the fReactor.

Entry [a]	DBN (mol%)	Stirring Rate (rpm)	Temperature (°C)	t_{res} (min)		NMR Yield [b] (%)	
					1b	2b	3b
1	5	500	40	20	22	44	34
2	5	500	40	120	4	48	48
3	5	500	60	20	12	51	37
4	5	500	25	20	32	63	5
5	5	500	25	60	29	65	6
6	5	500	25	90	15	78	7
7	5	500	25	120	5	88	7
8	5	500	25	180	10	79	11
9	5	250	25	120	16	75	9
10	5	1000	25	120	13	74	13
11	2.5	500	25	120	34	60	6
12	1	500	25	120	46	52	2

[a] 1 eq. of 2-nitrobenzaldehyde and 1 eq. of diethyl phosphite was prepared in MeCN (0.77 M). DBN was prepared in MeCN (0.038 M). [b] Analyzed by ^{1}H-NMR spectroscopy.

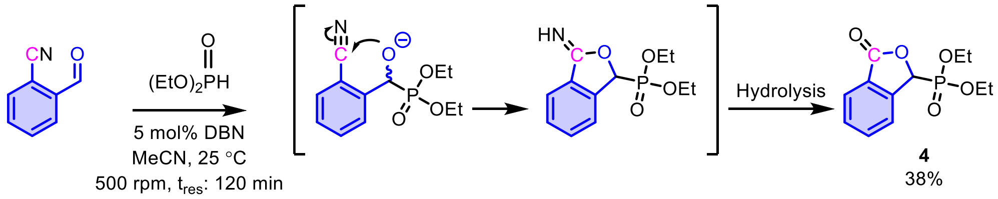
The use of 5 mol% DBN at 40 °C with a 20-min residence time resulted in a 44% conversion to the α-hydroxyphosphonate **2a**, with 22% unreacted starting material and 34% of the mixture having undergone the phospha-Brook rearrangement to the phosphate (Table 1, entry 1). Encouraged by these results, the residence time was increased to 120 min, which led to an approximate 1:1 mixture of the α-hydroxyphosphonate **2a** and rearranged phosphate **3a**, with only a small amount of starting material remaining (entry 2). Although an increased conversion to the α-hydroxyphosphonate was observed at 60 °C with a 20-min residence time, it also resulted in a higher formation of the rearranged phosphate product (entry 3), suggesting that higher temperatures promote the phospha-Brook rearrangement. To mitigate this, the reaction was conducted at room temperature with a 20-min residence time (entry 4). While this resulted in more unreacted starting material, a higher conversion to the α-hydroxyphosphonate was achieved, with the phosphate being a minor component. Varying the residence time between 60 and 180 min further increased the desired α-hydroxyphosphonate (entries 5–8), with a maximum conversion of 88% observed at 120 min (entry 7). However, at 180 min, the conversion to phosphate and the amount of unreacted starting material increased at the expense of the α-hydroxyphosphonate (entry 8), likely due to a retro-Abramov-like reaction [25,26]. Altering the mixing speed from 500 rpm to 250 and 1000 rpm showed that lower speeds led to more unreacted starting material, while higher speeds resulted in more of the rearranged product (entries 9–10). Reducing the catalyst loading also resulted in lower conversions to the α-hydroxyphosphonate with increased unreacted starting material (entries 11–12). In comparison, the reaction attempted under batch conditions with 5 mol% DBN at room temperature for 6 h resulted in only a 23% yield with the major component being unreacted starting material.

Using the optimised conditions for the Pudovik reaction—5 mol% DBN, a 120-min residence time, a mixing speed of 500 rpm, and a temperature of 25 °C—a range of substituted α-hydroxyphosphonates **2** were produced in excellent yields (Scheme 3), with the exception of the 2-cyano substitution, **2k**, which has been synthesised previously [22]. All of the synthesised α-hydroxyphosphonates were isolated by concentrating the reaction mixture and suspending the product in hexane, followed by filtration and washing with a small amount of a 9:1 hexane:Et_2O mixture (see Supplementary Materials).



Scheme 3. Isolated yields for the synthesis of α-hydroxyphosphonates **2**.

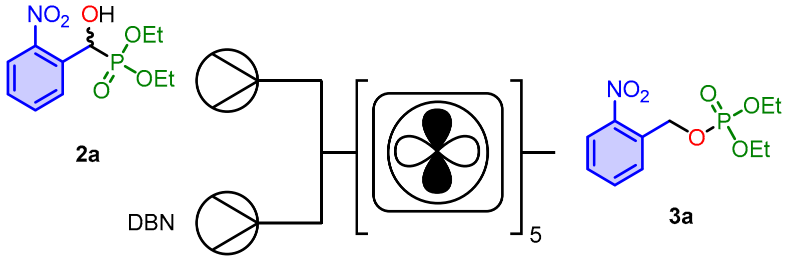
Although TLC analysis of the reaction mixture for the attempted synthesis of **2k** confirmed consumption of the starting materials, spectral data analysis after column chromatography revealed the presence of an ester carbonyl group in the ^{13}C-NMR and IR spectra. Additionally, the ^{31}P-NMR showed a peak at 13.8 ppm, whereas typical α-hydroxyphosphonates exhibit a chemical shift around 20 ppm. Furthermore, the hydroxyl peak was absent in the ^{1}H-NMR spectrum. Based on these findings, combined with 2D NMR analysis, it is proposed that after the Pudovik reaction occurred to form the α-hydroxyphosphonate (see Supplementary Materials), an intramolecular cyclisation takes place between the hydroxyl group and the cyano functionality (Scheme 4). Hydrolysis of the resulting imine results in the formation of a lactone ring, yielding 38% of diethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl) phosphonate **4**. The identity of the product was confirmed as the spectral data for **4** was identical to that reported by Kachkovskyi [27]. The synthesis of **2k** has previously been achieved using dried solvents under an inert atmosphere, conditions that were not employed in this set-up.



Scheme 4. Unexpected lactone formation.

3.2. Phospha-Brook Rearrangement

The phospha-Brook rearrangement was previously optimised by using one equivalent of DBN in MeCN with an α-hydroxyphosphonate at room temperature for 16 h in a batch process [22]. The initial aim was to demonstrate that this rearrangement could be performed using CSTRs, aiming to reduce the reaction time by enhancing the mixing efficiency. The 2-nitro derivative **2a** was used as the model substrate to optimise the conditions for the phospha-Brook rearrangement (Scheme 5 and Table 2).



Scheme 5. Phospha-Brook rearrangement reaction set-up.

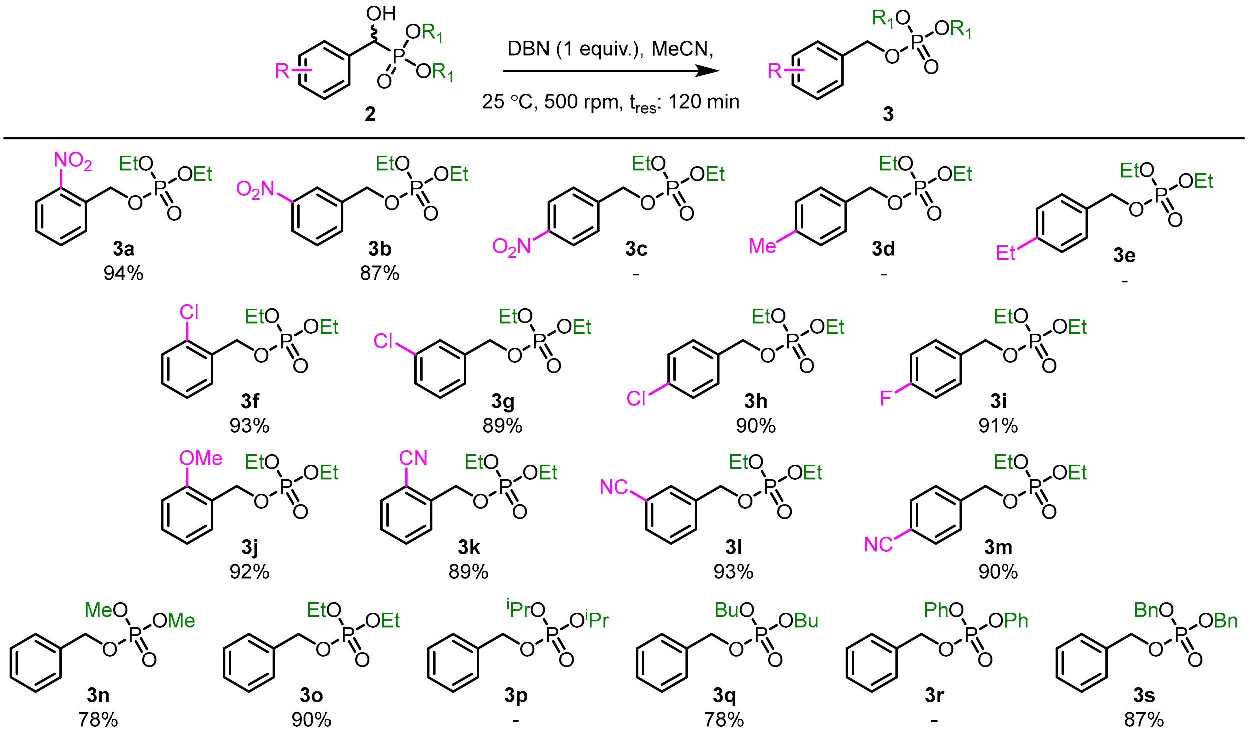
Table 2. Optimisation of the phospha-Brook rearrangement using the fReactor.

Entry [a]	Stirring Rate (rpm)	Temperature (°C)	t_{res} (min)	NMR Yield [b] (%)
1	500	25	30	20
2	500	25	60	50
3	500	25	120	94
4	500	25	150	92
5	250	25	120	29
6	1000	25	120	63
7	1500	25	120	37
8	500	40	120	90
9	500	50	120	83
10	500	60	120	84
11 [c]	500	25	120	87

[a] 1 eq. of 2-nitrobenzaldehyde and 1 eq. of diethyl phosphite was prepared in MeCN (0.67 M); 1 eq. of DBN was prepared in MeCN (0.67 M). [b] Analyzed by ^{1}H-NMR spectroscopy. [c] Addition of 2 M HCl into the final CSTR.

Using a five-module CSTR set-up, solutions of α-hydroxyphosphonate **2a** in MeCN and DBN in MeCN were independently fed into the reactor at room temperature. The reaction was quenched by directing the outlet flow directly into 2 M HCl. Various residence times were tested (Table 2, entries 1–4), with a 120-min residence time proving to be the most effective, achieving a 94% conversion (entry 3). Subsequently, the stirring rate was investigated by conducting reactions at 250, 500, and 1000 rpm. Inefficient mixing at lower speeds resulted in a low conversion rate of 29% (entry 5), with the starting materials being the major components of the mixture. Although a stirring speed of 1000 rpm showed better conversion than 250 rpm (entry 6), 500 rpm proved to be the most efficient. When the temperature was increased in 10 °C increments (entries 8–10), the conversions were good but lower than those observed at room temperature. Finally, the addition of dilute HCl to the final CSTR module to stop the reaction resulted in a slightly lower conversion of 87%, suggesting that five modules for mixing were required. The optimal conditions for the phospha-Brook rearrangement provided the product in similar conversions to reactions in batch with reactions taking place in 120 min, instead of 16 h, using five CSTRs [22].

With optimised conditions established, a series of organophosphates were synthesised (Scheme 6).



Scheme 6. Isolated yields for the synthesis of substituted aryl phosphates **3**.

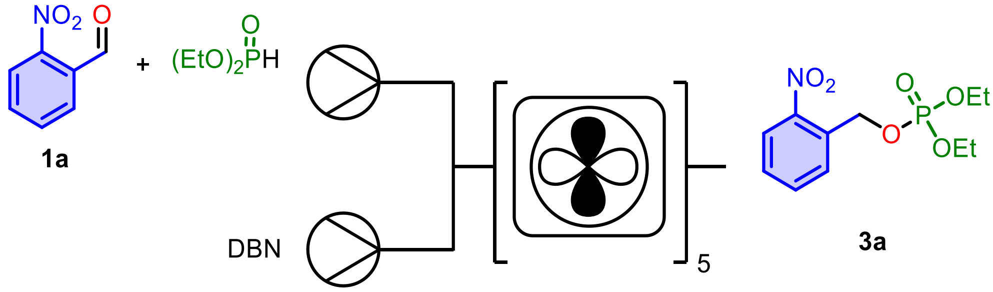
All α-hydroxybenzyl diethyl phosphonates **2**, including the 2-cyano derivative synthesised using a previously reported method [22], rearranged to the corresponding phosphates **3** in excellent yields (see Supplementary Materials), except for the 4-nitro, 4-methyl, and 4-ethyl derivatives (**3c**, **3d**, and **3e**). These derivatives resulted in the recovery of the starting material, even when subjected to higher temperatures and the use of a back-pressure regulator to pressurise the reaction. These findings are consistent with previous results reported involving DBN [22]. The 4-alkyl derivatives have only been obtained at elevated temperatures [19,28], while the 4-nitro derivative **3b** is typically synthesised through a chlorophosphate intermediate not directly via the phospha-Brook rearrangement [29]. When modifying the α-hydroxybenzyl phosphonate diesters, the dimethyl (**3n**), dibutyl (**3q**), and dibenzyl (**3s**) derivatives successfully produced the rearranged phosphate products in very good yields. Unfortunately, the diisopropyl (**3p**) and diphenyl

(**3r**) derivatives did not yield any of the corresponding phosphates. This result is ascribed to steric hindrance caused by the interaction between the bulkier DBN base and the larger ester groups. This observation is consistent with the findings of Khan et al., who reported the absence of phosphate products when α-hydroxybenzyl phosphonates were treated with potassium *t*-butoxide [30]. Results indicate that both electron-rich and electron-poor α-hydroxyphosphonates were quite well tolerated, showing similar reactivity to produce the corresponding phosphates in very good yields, unlike what has been observed in previous studies [31–33]. To evaluate the effectiveness of the CSTRs, the reaction was scaled up to gram-scale quantities using optimised continuous flow conditions, resulting in a 93% yield.

3.3. One-Pot Pudovik–Phospha-Brook Rearrangement

After demonstrating that the reaction time for the phospha-Brook rearrangement of an α-hydroxyphosphonate to a phosphate ester could be reduced to 120 min using CSTRs, the focus was to explore the feasibility of combining the Pudovik reaction and phospha-Brook rearrangement into a one-step process using DBN in continuous flow. This reaction has previously been reported to occur catalytically in the presence of strong bases such as BuLi [19,20], 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) [32], the proton sponge diazatetracyclo[4.4.0.13,10.15,8]dodecane (DTD) [34], and more recently using Cu(OTf)$_2$ as a Lewis acid catalyst [35].

The reaction was optimised using 2-nitrobenzaldehyde **1a** and diethyl phosphite by varying the amount of DBN, stirring rate, temperature, and residence time in the reactor (Scheme 7 and Table 3).



Scheme 7. One-pot Pudovik–phospha-Brook rearrangement reaction set-up.

Table 3. Optimisation of the one-pot Pudovik–phospha-Brook rearrangement using the fReactor.

Entry [a]	DBN (equiv)	Stirring Rate (rpm)	Temperature (°C)	t_{res} (min)	NMR Yield [b] (%)
1	0.1	500	40	120	47
2	0.1	500	40	180	79
3	0.2	500	40	180	80
4	0.5	500	40	180	82
5	1	500	40	180	85
6	1	500	40	120	90
7	1	500	25	120	90
8	1	500	25	60	71
9	1	1000	25	120	88
10	1	250	25	120	83

[a] 1 eq. of 2-nitrobenzaldehyde and 1 eq. of diethyl phosphite was prepared in MeCN (1.5 M); 1 eq. of DBN was prepared in MeCN (1.5 M). [b] Analyzed by ^{1}H-NMR spectroscopy.

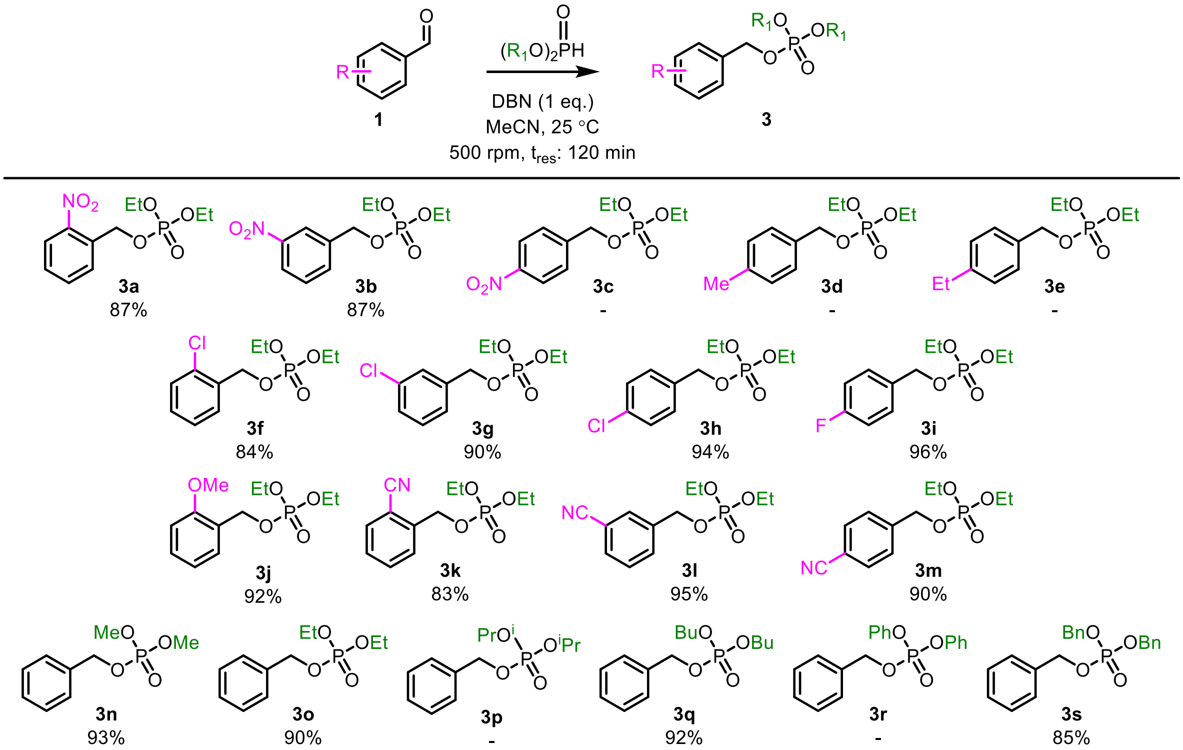
Based on previous studies that employed catalytic conditions for the one-pot reaction [19,20,32,34,35], an initial experiment was conducted using 10 mol% DBN at 40 °C with a residence time of 120 min, resulting in a 47% conversion to the phosphate **3a** (Table 1, entry 1). Extending the residence time to 180 min nearly doubled the conversion (entry 2).

Encouraged by this result, while aiming to minimise reaction time, 20 mol% DBN was tested; however, this led to only a slight increase in the conversion (entry 3). Increasing the DBN concentration to 50 mol% afforded a marginal improvement in the conversion; however, the reaction proved not to be efficient under catalytic conditions (entry 4).

Given the observations in Tables 1 and 2 and previous batch reactions involving DBN, it was decided to use 1 equivalent of the base. This resulted in an 85% conversion to the phosphate with a 180-min residence time at 40 °C (entry 5). However, the presence of multiple peaks in the ^{1}H-NMR suggested product decomposition. To address this, the residence time was reduced to 120 min, which increased the conversion to 90%, though some decomposition was still observed (entry 6). Decreasing the temperature to 25 °C achieved the same conversion (entry 7), but the α-hydroxyphosphonate **2a** was detected as the main by-product, indicating that temperature played a critical role in preventing product decomposition under basic conditions.

When the residence time was further reduced to 60 min, conversion decreased to 71%, with a greater amount of α-hydroxyphosphonate observed as a by-product (entry 8). Altering the stirring rate, either increasing or decreasing it, led to a lower conversion to the phosphate (entries 9 and 10). The optimal conditions for the one-pot Pudovik reaction–phospha-Brook rearrangement were determined to be 1 equivalent of DBN at room temperature, with a stirring rate of 500 rpm and a residence time of 120 min. Under batch conditions for 24 h, these parameters resulted in only a 34% conversion to the phosphate **3a** and 45% conversion to the α-hydroxyphosphonate **2a**. Although this approach uses stoichiometric amounts of base, it eliminates the need for strong bases or inert conditions while offering shorter or comparable reaction times and conversion rates relative to previous studies [19,20,32,34].

With optimised conditions determined, a range of phosphates were synthesised using the one-pot Pudovik–phospha-Brook rearrangement using continuous flow (Scheme 8).



Scheme 8. Isolated yields for the synthesis of substituted aryl phosphates.

The one-pot conversion of aldehydes **1** to phosphates **3** using 1 equivalent of DBN at room temperature produced yields similar to those of the phospha-Brook rearrangement from α-hydroxybenzyl phosphonates, including **3k** which had previously undergone cyclisation to lactone **4** when starting the reaction from a phosphite and aldehyde. Compared to the earlier report on DBU-catalysed phosphate synthesis, the 4-chloro derivative was formed in excellent yield [32]. However, the 4-nitro, 4-methyl, and 4-ethyl aromatic substituted derivatives (**3c**, **3d**, and **3e**), as well as the diisopropyl (**3p**) and diphenyl (**3r**) phosphate ester derivatives, did not yield the rearranged product; however, the α-hydroxybenzyl phosphonates were formed in excellent yields (see Supplementary Materials).

4. Conclusions

In conclusion, a time-efficient and tunable method has been developed for synthesising both α-hydroxyphosphonates via the Pudovik reaction and phosphates via the phospha-Brook rearrangement, all at room temperature under continuous flow conditions, depending on the amount of DBN utilised. Reaction times have been significantly reduced to 2 h compared to traditional batch processes. This methodology was successfully applied to a wide range of substrates, yielding α-hydroxyphosphonates and phosphate diesters in excellent yields, demonstrating its broad applicability. While the phospha-Brook rearrangement was unsuccessful in forming compounds **3c–e**, **3p**, and **3r**, this may be attributed to steric hindrance or the need for higher temperatures [19]. Additionally, lactone **4** was formed from the 2-cyano derivative due to an intramolecular cyclisation of α-hydroxyphosphonate **2k**. Further studies are currently underway to explore the scope of the reaction and to develop a telescoped synthesis process for active pharmaceutical ingredients.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/reactions5040042/s1, File S1: physical and NMR data of all products [22,27,36].

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