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Microflow Synthesis of Unsymmetrical *H*-Phosphonates via Sequential and Direct Substitution of Chlorine Atoms in Phosphorus Trichloride with Alkoxy Groups

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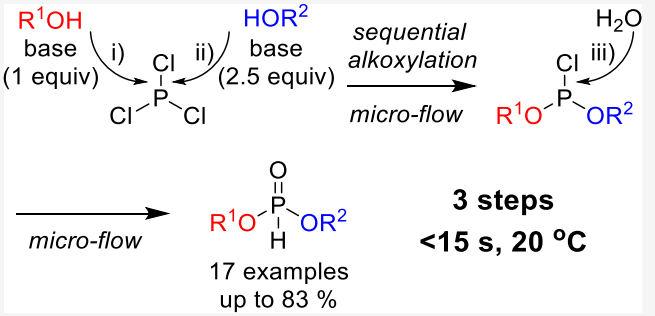
ABSTRACT: Unsymmetrical *H*-phosphonates were synthesized by a rapid (<15 s) and mild (20 °C) process in a microflow reactor as the first example of the sequential direct substitution of the chlorine atoms in PCl_3 with alkoxyl/aryloxy groups using equivalent amounts of PCl_3 and alcohols. The optimal base concentration differed in each step, presumably attributed to differences in the Brønsted basicity of the electrophilic intermediates. Phosphite hydrolysis was observed, and the structure−hydrolysis relationship was quantitatively evaluated.



INTRODUCTION

Organophosphorus compounds are used as pharmaceutical and agricultural chemicals.[1] Recently, oligonucleotide therapeutics[2] and protides,[3] prodrugs of nucleoside phosphates, have garnered much attention. *H*-Phosphonates are used as building blocks in the syntheses of these organophosphorus compounds.[4] Unsymmetrical *H*-phosphonates containing two different alkoxy/aryloxy groups are particularly valuable as such building blocks.

The *H*-phosphonate approach[5] (Scheme 1, a-1) is most frequently used in these syntheses, wherein R^1OH is carefully added to excess phosphorus trichloride (**B**) to give **C**. Hydrolysis of **C** followed by condensation with R^2OH affords the desired unsymmetrical *H*-phosphonates **A**. The phosphoramidite approach,[6] which includes amination of **C**, introduction of R^2OH into **E**, and subsequent hydrolysis, has also been used in synthesizing **A** (a-2). Both approaches require the temporal substitution of chlorine atoms in **C** with OH (a-1) or N*i*-Pr_2 (a-2) to suppress the overreaction, along with purification of the intermediate. This increases the number of synthetic steps and complicates the process. Moreover, approach a-2 requires the use of explosive and toxic tetrazole[7] to activate **E** and **F**. In comparison, approach b is initiated by preparing phosphite **G** by adding excess R^1OH relative to **B**. The subsequent hydrolysis of **G** affords symmetrical *H*-phosphonate **H**. Either transesterification[8] of **H** with R^2OH (b-1) or hydrolysis of **H** and subsequent alkylation[9] of **D** (b-2) affords the desired **A**. Both approaches also require temporal substitution of the chlorine atoms in **B** with an OR^1 group (b-1) or OR^1 and OH groups (b-2) to suppress the overreaction, along with purification of the intermediate. Moreover, as drawbacks, approach b requires harsh conditions due to the mild electrophilicity of **H** and has a limited substrate scope. The ideal synthesis of **A** via the sequential direct substitution of chlorine atoms in **B** with OR^1 and OR^2 groups that does not require excess **B** or alcohols has not been documented.

Our group recently reported the microflow synthesis[10,11] of phosphotriester **J** from **B** via the sequential introduction of R^1OH−R^3OH (Scheme 1c).[12] Although the developed approach did not require intermediate purification steps, the addition of 2 equiv of imidazole to generate **I** was indispensable for suppressing the overreaction during the introduction of R^2OH. Herein, we report the rapid and mild microflow synthesis of unsymmetrical *H*-phosphonates **A** from inexpensive and highly electrophilic **B** via the sequential direct substitution of chlorine atoms in **B** with OR^1 and OR^2 groups (Scheme 1d).

RESULTS AND DISCUSSION

We previously reported that the selective introduction of R^2OH into **C** was more difficult than the introduction of R^1OH into **B** (Scheme 1d).[12] Therefore, the alkoxylation of $EtOPCl_2$ (**1a**) was examined (Table 1). The microflow reactor shown in Table 1 was used for this examination.

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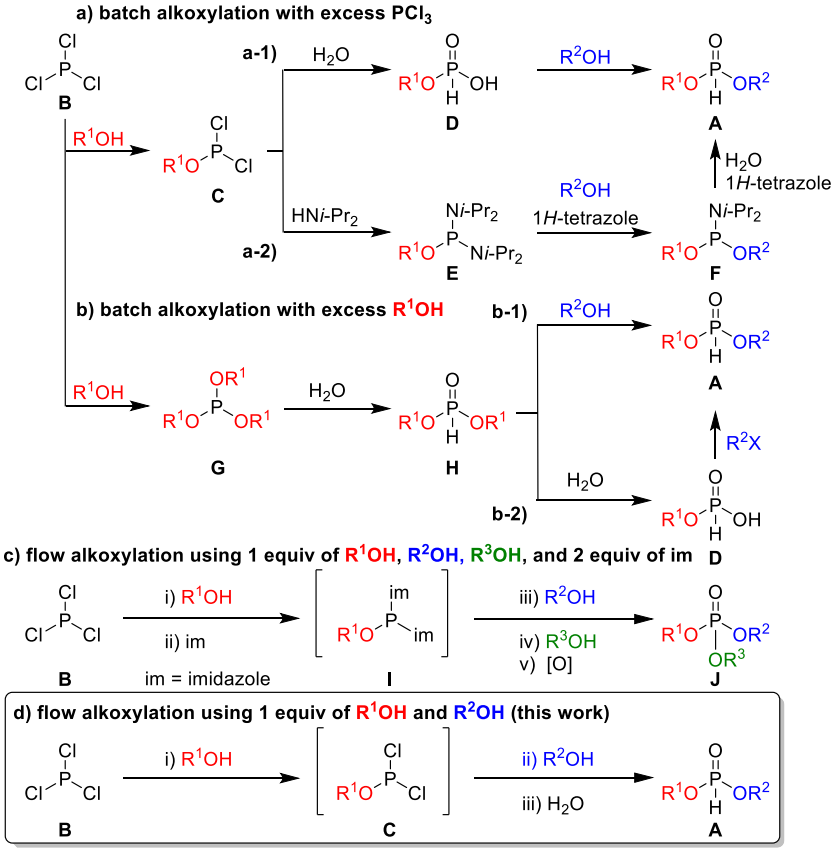
Scheme 1. Previously Reported Approaches and Our Developed Approaches to the Synthesis of Unsymmetrical *H*-Phosphonate



The solvents were then examined (entries 1−8). The flow system was clogged when Et_2O or 2-MeTHF was used (entries 2 and 5) plausibly due to the insufficient solubility of the amine hydrochloride salts in these solvents. Solvents with higher donor numbers[13] afforded higher yields (entries 1, 3, 4, and 6). The highest yield of **4a** was obtained with tetrahydrofuran (THF) (entry 6). The amine type and amount were then examined (entries 9−14). 3 equiv of *n*-Bu_3N afforded the highest yield (entry 14). The reaction time and temperature were optimized (entries 15−19). Shorter reaction time (entry 15) and lower temperature (entry 18) afforded slightly lower yields, presumably due to insufficient progress of the nucleophilic substitution. Longer reaction time (entry 17) and higher temperature (entry 19) also afforded slightly lower yields, presumably due to the decomposition of intermediate **3a**. The optimal conditions (entry 14) were determined for subsequent experiments.

The sequential direct substitution of the chlorine atoms in **5** with two alkoxy groups was also examined (Table 2). The desired intermediate **3b** was hydrolyzed in a flask to give the desired product **4b**. The residence time in reaction tube 1 was examined (entries 1−3); the highest yield was obtained after 5 s of the reaction (entry 2). The amount of *n*-Bu_3N required was then examined (entries 2 and 4−7). Interestingly, 1 and 2.5 equiv of *n*-Bu_3N for the first and second alkoxylations, respectively, afforded the best results (entry 7). The optimal relative amounts of *n*-Bu_3N for trapping the in situ generated HCl seemed to differ for the first and second alkoxylations. However, the observed differences in the yields of the desired product **4b** were somewhat small (≤7%). Therefore, we verified the influence of the amount of *n*-Bu_3N on the overreactions in both alkoxylations, confirming a clear difference between the first and second alkoxylations (for details, see the Supporting Information). An equivalent amount of *n*-Bu_3N (1 equiv) relative to the generated HCl was optimal in the first alkoxylation, whereas excess *n*-Bu_3N (2.5 equiv) was optimal for the second alkoxylation. The yield and reproducibility of the microflow and batch systems were compared (entries 8 and 9). Although similar yields were observed, the space−time yield of flow synthesis (27.7 $g{\cdot}L^{-1}$ min^{-1}) was almost 10 times higher than that of the corresponding batch synthesis (2.8 $g{\cdot}L^{-1}$ min^{-1}). (***Caution:*** *As the reaction is exothermic and is accompanied by the generation of HCl, the batch reaction should be performed with extreme caution. Especially in scale-up synthesis, the use of batch synthesis should be avoided*).

The difference in the optimal amount of *n*-Bu_3N in the first and second alkoxylations was tentatively attributed to the difference in the Brønsted basicity of intermediates **C** and **L** (Scheme 2). Intermediate **C** with two chlorine atoms is less basic than intermediate **L** with one chlorine atom, based on the balance between the resonance and inductive effects (Scheme 2a). Therefore, only a small amount of cationic **C-2** was generated, and neutral **C-1** mainly acted as an electrophile during the first alkoxylation. Conceivably, an excess amount (≥2 equiv) of *n*-Bu_3N assisted deprotonation of R^1OH, which accelerated the overreaction to generate **K**, whereas an equivalent amount (1 equiv) of *n*-Bu_3N suppressed the overreaction. In contrast, the more basic intermediate **L** with two oxygen atoms readily trapped protons to generate highly

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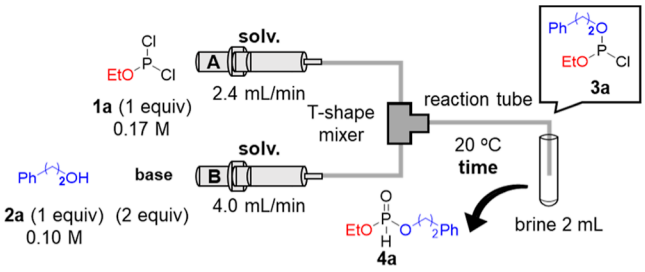
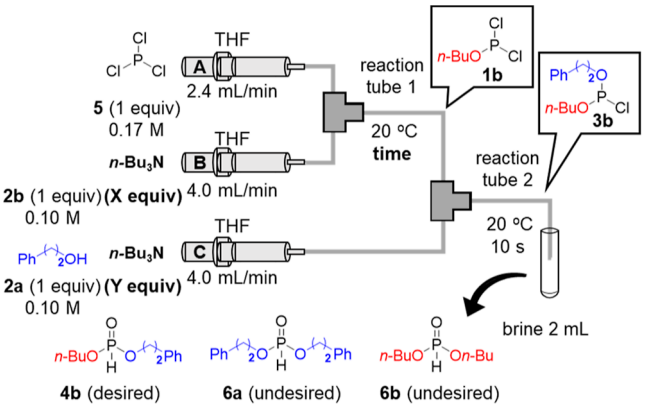
Table 1. Alkoxylation of $EtOPCl_2$



entry	solv. (Gutmann's donor number)[13]	base	time[a] [s]	yield [%][b] 4a
1	CH_2Cl_2 (0)	*i*-Pr_2NEt	10	48
2	2-MeTHF (12.0)	*i*-Pr_2NEt	10	[c]
3	MeCN (14.1)	*i*-Pr_2NEt	10	63
4	1,4-dioxane (14.3)	*i*-Pr_2NEt	10	62
5	Et_2O (19.2)	*i*-Pr_2NEt	10	[c]
6	THF (20.0)	*i*-Pr_2NEt	10	72
7	*t*-BuOMe (−)[d]	*i*-Pr_2NEt	10	62
8	*c*-pentylOMe (−)[d]	*i*-Pr_2NEt	10	56
9	THF	*n*-Bu_3N	10	76
10	THF	NEM	10	71
11	THF	NMM	10	71
12	THF	2,6-lutidine	10	74
13[e]	THF	*n*-Bu_3N	10	62
14[f]	THF	*n*-Bu_3N	10	77 (73)[g]
15	THF	*n*-Bu_3N	1	71
16	THF	*n*-Bu_3N	5	76
17	THF	*n*-Bu_3N	20	68
18[h]	THF	*n*-Bu_3N	10	70
19[i]	THF	*n*-Bu_3N	10	72

[a]Residence time in the reaction tube. [b]Yields were determined via ^1H NMR analysis using triphenylmethane as an internal standard. [c]The reactor was clogged. [d]Donor number was not reported. [e]1 equiv of *n*-Bu_3N was used. [f]3 equiv of *n*-Bu_3N was used. [g]Isolated yield. [h]Reaction temperature was 0 °C. [i]Reaction temperature was 40 °C. NEM = *N*-ethylmorpholine and NMM = *N*-methylmorpholine.

Table 2. One-Flow Synthesis of Unsymmetrical *H*-Phosphonate from PCl_3



entry	time[a] [s]	*n*-Bu_3N X [equiv]	*n*-Bu_3N Y [equiv]	yield [%][b] 4b	6a	6b
1	1	2	3	66	4	7
2	5	2	3	68	7	6
3	10	2	3	61	6	8
4	5	2	2	68	4	4
5	5	1	3	73	4	3
6	5	1	2	71	3	2
7	5	1	2.5	74	5	1
8[c,d]	5	1	2.5	75 ± 1 (73)[e]	4 ± 1	4 ± 4
9[c,d,f]	5	1	2.5	74 ± 4	7 ± 1	5 ± 3

[a]Residence time in the reaction tube 1 (flow) or reaction time for the introduction of *n*-BuOH into **5** (batch). [b]The yields were determined via ^1H NMR analysis using triphenylmethane as an internal standard. [c]Three independent experiments were carried out. [d]The reaction mixture obtained from the outlet of the flow reactor was poured into 1 M HCl aq. [e]Isolated yield. [f]Mixing was performed using a magnetic stirrer (1000 rpm).

electrophilic cationic **L-2**, which accelerated the overreaction in the second alkoxylation (Scheme 2b). Plausibly, an equivalent amount (1 equiv) of *n*-Bu_3N induced the generation of cationic **L-2**, which accelerated the overreaction to afford **M**, whereas excess (≥2 equiv) *n*-Bu_3N suppressed the generation of **L-2**, decreasing the extent of the overreaction. The results in Table 1 indicate that high-donor-number solvents afforded higher yields during the second alkoxylation step. Plausibly, the coordination of basic solvents to the protons suppressed the generation of **L-2**, although it is undeniable that the difference in the solubility of *n*-Bu_3N·HCl depending on the solvent used also influences the results.

For verification of our hypotheses, the energy differences between the two pairs of intermediates (**C-1** vs **C-2** and **L-1** vs **L-2**) were calculated using density functional theory. First, we verified which atom is likely to be protonated, phosphorus or oxygen in methyl dichlorophosphite (Scheme 3, a-1) and dimethyl chlorophosphite (b-1). It was suggested that the first intermediate preferably undergoes protonation at the phosphorus atom, and the second intermediate preferably undergoes protonation at the oxygen atom (a-1 vs b-1). Then, we calculated the protonation energy of the intermediates (Me_3N·HCl was used as a proton source instead of *n*-Bu_3N·HCl to reduce the calculation cost). The calculation results suggested that the protonation energy of **L-1′** is lower than that of **C-1′** (Scheme 3, a-2 vs b-2), and the second intermediate is more likely to be protonated. These results corroborate our hypothesis (see Scheme 2).

To elucidate the reaction mechanism, possible transesterification of generated *H*-phosphonate was evaluated. Transesterification was not observed under the optimal conditions (for details, see the Supporting Information). Next, hydrolysis of the phosphite (such as **M** in Scheme 2) generated from the overalkoxylation was also evaluated. 3.0 equiv of phenethyl alcohol (**2a**) was reacted with **1a** to generate **7a**. The resultant mixture was collected into a test tube and treated with brine. As a result, the hydrolysis of **7a** was observed. Unsymmetrical and symmetrical *H*-phosphonates **4a** and **6a** were obtained roughly in a 1:2 ratio (Figure 1). This ratio was consistent with the number of substituents in **7a** (one ethoxy group and two phenethyloxy groups); therefore, these alkoxy groups seemed to have similar leaving abilities.

From this result, we speculated that under the optimal conditions of Table 1 entry 15, the reaction between **1a** and **2a** afforded the desired **3a** (71%) and overreacted **7a** (9%) (Scheme 4). It is conceivable that ca. two-thirds of **7a** (ca. 6%) was hydrolyzed to afford the desired **4a**, while one-third of **7a** (ca. 3%) was hydrolyzed to afford the undesired symmetrical *H*-phosphonate **6a**.

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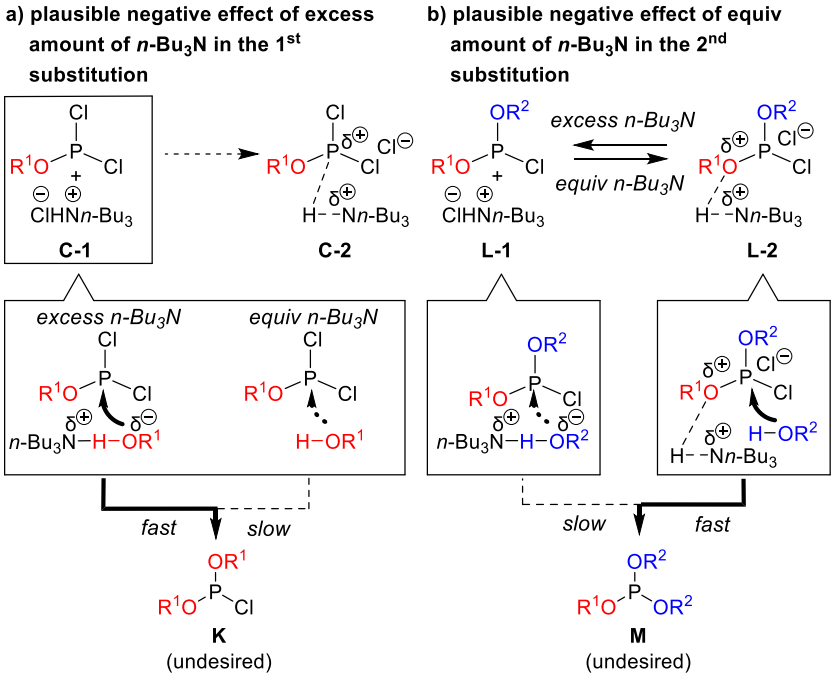
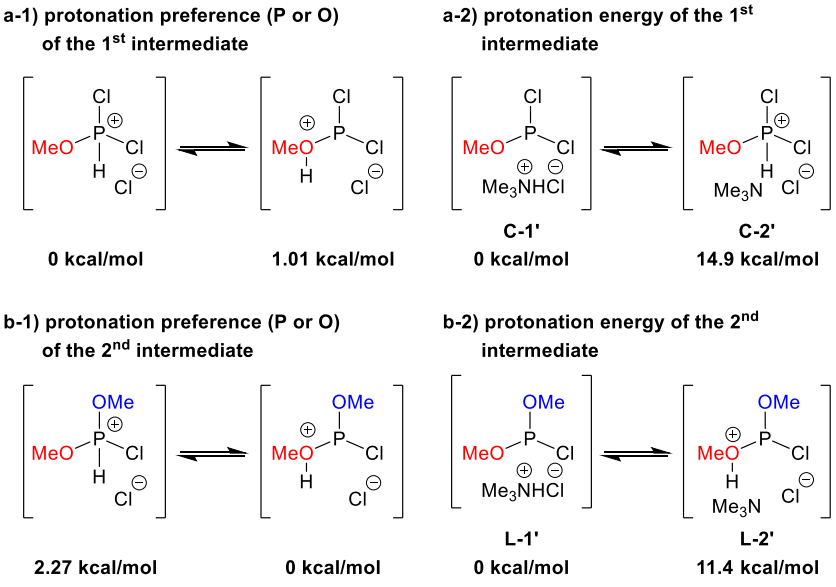
Scheme 2. Plausible Negative Effects of Excess/Equivalent Amounts of *n*-Bu_3N in the 1st/2nd Nucleophilic Substitutions



Scheme 3. Calculation of Protonation Energy of the 1st and 2nd Intermediates



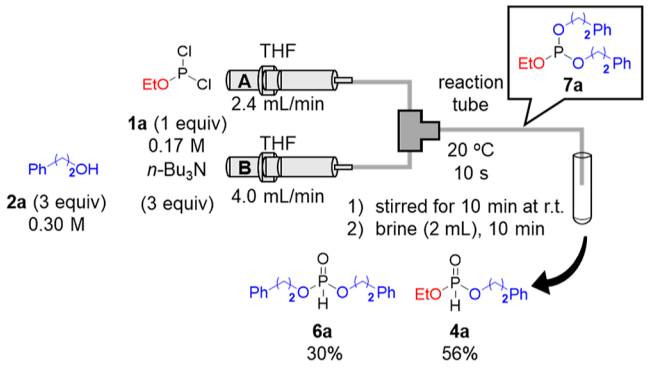


Figure 1. Examination of hydrolysis of trialkyl phosphite 7a.

Although this hydrolysis is known,[14] the structure–hydrolysis susceptibility relationships have not been quantitatively assessed. Therefore, the relative leaving ability (leaving ability score) of the four OR^2 groups was determined in comparison with that of the ethoxy group (Table 3). The leaving ability score was calculated (yield of **4**/yield of **6** × 2) from the yields of products **4** (OR^2 group was substituted) and **6** (OEt group was substituted). The leaving ability of the phenethyloxy group was similar to that of the ethoxy group (entry 1), whereas that of the bulkier 3-pentyl group was lower (entry 2). The benzyloxy group exhibited a slightly higher leaving ability (entry 3). The phenoxy group exhibited a leaving ability much higher than that of the alkoxy group (entry 4). As previously described, the risk of the overreaction was higher in the second introduction of the alkoxy group than

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Scheme 4. Consideration of the Selectivity (4a/6a) in Alkoxylation of Ethyl Dichlorophosphite

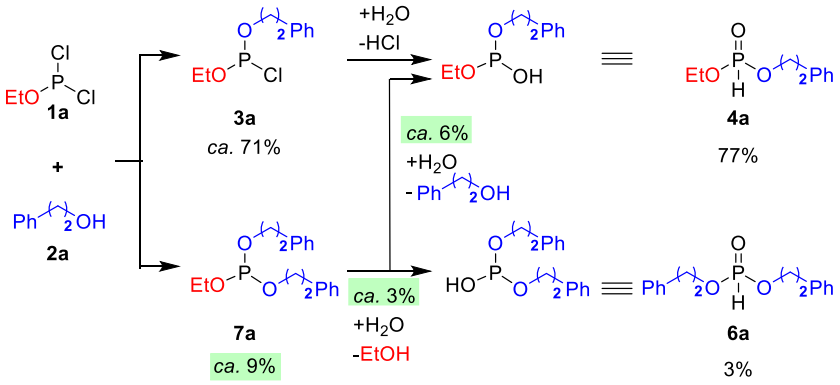
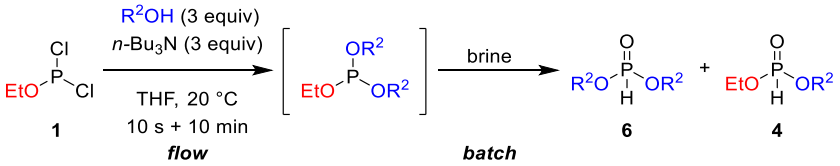


Table 3. Leaving Ability of Alkoxy Groups



		yield [%][a]		leaving ability score[b]
entry	R^2OH	**6**	**4**	**4/6 × 2**
1	PhC_2H_4OH	30	56	0.93
2	3-pentanol	32	25	0.37
3	BnOH	24	56	1.2
4	PhOH	4	63	7.7

[a]Yields were determined via ^1H NMR analysis using triphenylmethane as an internal standard. [b]Leaving ability score = (yield of **4**/yield of **6** × 2).

in the first introduction. These results suggest that alkoxy groups with a higher leaving ability should be introduced in the second introduction because hydrolysis of the overreacted phosphite in the workup process should improve the yields.

The substrate scope was examined (Figure 2). Introducing two different primary alcohols into **5** afforded the desired products **4b**−**4f** in moderate to good yields (52−79% in 3 steps). Expectedly, introducing secondary alcohols with lower leaving abilities, followed by the introduction of primary alcohols with higher leaving abilities, afforded the desired products **4g**−**4l** in good to high yields (69−83%). In fact, the yield was decreased (*ca.* 10%) when the introduction order of alcohols was switched in the synthesis of **4h**. The synthesis of **4h** was successfully scaled-up (6 mmol scale) without a significant decrease in the yield (79%, productivity: 37.9 mmol·h^{-1}). The reaction was significantly slowed when two secondary alcohols were introduced during the synthesis of **4m**. An excess amount (5 equiv) of 2-indanol improved the yield (74%). Products **4n** and **4o**, which contain the base-labile Fmoc carbamate moiety and acid-labile acetonide, respectively, were obtained in good yields (60−67%). Product **4p**, which contains both bulky steroid and deoxynucleoside moieties, was obtained in a good yield (62%), whereas product **4q**, which contains a phenoxy group, was obtained in a moderate yield (54%). Unsurprisingly, the developed procedure was applicable to the synthesis of symmetrical *H*-phosphonate (the first alkoxylation: 1 equiv of PhC_2H_4OH and 1 equiv of *n*-Bu_3N; the second alkoxylation: 1 equiv of PhC_2H_4OH and 2.5 equiv *n*-Bu_3N). The desired product **4r** was obtained in a high yield (84%). We also confirmed that a similar yield (84%) was observed when 2 equiv. PhC_2H_4OH and 3.5 equiv *n*-Bu_3N were reacted with PCl_3 (for details, see the Supporting Information). The conventional approach[16] to symmetrical *H*-phosphonates requires acidic conditions. In contrast, the present approach can be used to synthesize *H*-phosphonates containing an acid-labile functional group and, thus, can complement conventional approaches.

CONCLUSIONS

In conclusion, we successfully demonstrated the rapid and mild microflow synthesis of unsymmetrical and symmetrical *H*-phosphonates from the inexpensive and highly electrophilic PCl_3. To the best of our knowledge, this is the first report demonstrating the sequential direct substitution of chlorine atoms in PCl_3 with two different alkoxy/aryloxy groups without the use of excess PCl_3 and alcohols. Interestingly, the optimal amounts of the base differed in the first and second alkoxylations, presumably due to differences in the Brønsted basicity of the intermediates in each step. We also found that the primary alcohol should be introduced in the second substitution because the hydrolysis of a small amount of undesired phosphite generated from the overreaction in the workup process improved the yield of the desired products. The structure−hydrolysis susceptibility relationship was quantitatively assessed for the first time. This study is expected to accelerate the development of organophosphorus-based pharmaceutical and agricultural chemicals.

EXPERIMENTAL SECTION

General Information. NMR spectra were recorded on a JEOL-ECS400 (400 MHz for ^1H, 100 MHz for $^{13}C\{^1H\}$, and 162 MHz for $^{31}P\{^1H\}$) or JEOL-ECZ400 (400 MHz for ^1H, 100 MHz for $^{13}C\{^1H\}$,

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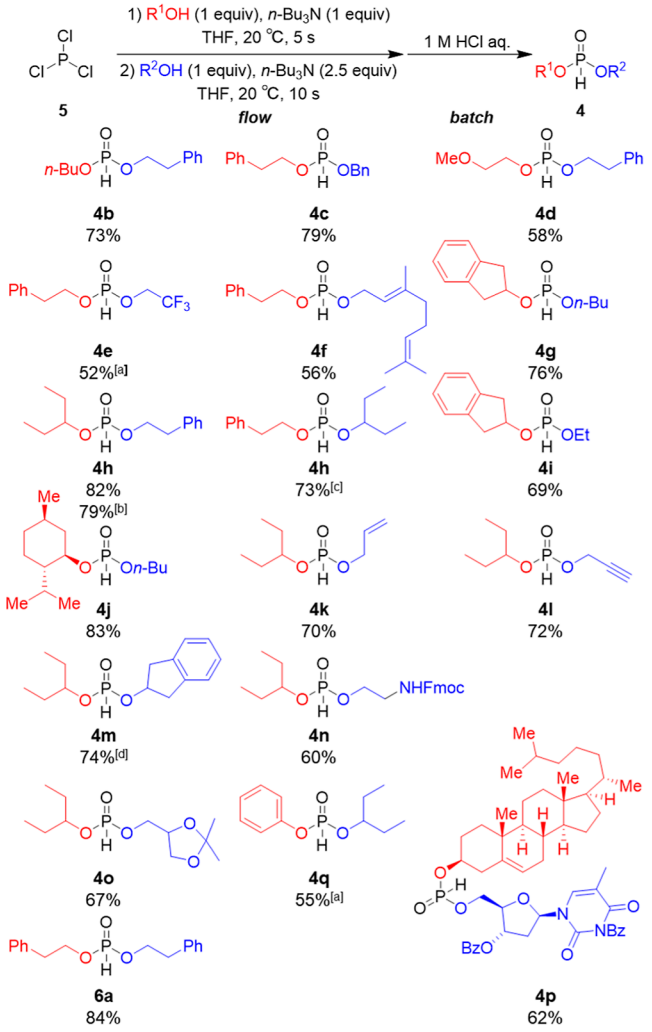

Figure 2. Substrate scope of the developed continuous-flow synthesis of *H*-phosphonates. [a]Brine was used instead of 1 M HCl aq.[15] [b]Six mmol scale. [c]The yield was determined via ^{1}H NMR analysis using triphenylmethane as an internal standard. [d]5 equiv of R^{2}OH was used.

and 162 MHz for $^{31}P\{^1H\}$) instrument in the indicated solvent. Chemical shifts were reported in units of parts per million (ppm) relative to tetramethylsilane (0.00 ppm) for ^{1}H NMR, $CDCl_3$ (77.16 ppm) for $^{13}C\{^1H\}$ NMR, and phosphoric acid (0.00 ppm) for $^{31}P\{^1H\}$ NMR. Multiplicities were reported by using the following abbreviations: s; singlet, d; doublet, t; triplet, q; quartet, m; multiplet, br; broad, td; triplet of doublets, qd; quartet of doublets, *J*; coupling constants in Hertz (Hz). IR spectra were recorded on a JASCO Corporation FT/IR-4100 FT-IR spectrometer. Only the strongest and/or structurally important peaks were reported as the IR data given in cm^{-1}. High-resolution mass spectra (HRMS) were obtained on a Bruker Daltonics Compact instrument by the electrospray ionization (ESI) method. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) with UV light, visualized by 10% ethanolic phosphomolybdic acid and/or ethanolic *p*-anisaldehyde containing acetic acid and H_2SO_4. Flash column chromatography was performed on Silica Gel PSQ 60B purchased from Fuji Silysia Chemical Ltd. Gel permeation chromatography (GPC) for purification was performed on Japan Analytical Industry model LC-5060 (recycling preparative HPLC) on a Japan Analytical Industry Model UV-600 NEXT ultraviolet detector with a polystyrene gel column (JAIGEL-1H, 20 mm × 600 mm), using chloroform as a mobile phase (10 mL/min). EtOH, dimethoxyethane, methoxyethanol, and trifluoroethanol were dried by flame-dried molecular sieves 3 Å. 2-MeTHF, *t*-BuOMe, and *c*-pentylOMe were dried by flame-dried molecular sieves 4 Å. CH_2Cl_2, 1,4-dioxane, Et_2O, and THF were dried by a Nikko Hansen Glass Contour MINI.

General Procedure for the Examination of the Substrate Scope of Unsymmetrical *H*-Phosphonate 4. A solution of alcohol **2** (0.10 M, 1.0 equiv) and *n*-Bu_3N (0.10 M, 1.0 equiv) in THF (flow rate: 4.0 mL/min) and a solution of PCl_3 (**5**) (0.17 M, 1.0 equiv) in THF (flow rate: 2.4 mL/min) were introduced to the first T-shape mixer at 20 °C with syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.80 mm, length: 1061 mm, volume: 534 μL, reaction time: 5 s) at the same temperature. A solution of alcohol **2** (0.1 M, 1.0 equiv) and *n*-Bu_3N (0.25 M, 2.5 equiv) in THF (flow rate: 4.0 mL/min) and the resultant mixture from reaction tube 1 were introduced to the second T-shape mixer at the same temperature with the syringe pumps, and the mixture was passed through reaction tube 2 (inner diameter: 0.800 mm, length: 3450 mm, volume: 1734 μL, residence time: 10 s). After being eluted for *ca.* 40 s to reach a steady state, the resultant mixture was poured into 1 M HCl (2.0 mL) for 30 s at the same temperature in the air. After Et_2O (10 mL) was added to the reaction mixture, it was stirred for 1 min at the same temperature in air. The resultant mixture was washed with 1 M HCl twice and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography or GPC.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c02467.

A description of the general experimental techniques, detailed procedure for microflow and batch syntheses, computational details, and spectral data for all new compounds (PDF)

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Author Contributions

The manuscript was written with contributions from all authors. All the authors approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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