**Development and Scale-up of the Rapid Synthesis of Triphenyl Phosphites in Continuous Flow**

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**ABSTRACT:** A novel method for the synthesis of triphenyl phosphite and its derivatives has been developed in continuous flow. With a total residence time of 20 s, the target product was prepared in a microreactor, and the reaction time was significantly shortened compared with standard single batch reaction conditions. In addition, the reaction of various substrates gave the corresponding products in good to excellent yields under optimized conditions. The reactants could be employed in a stoichiometric ratio, making the reaction more efficient, economical, and environmentally friendly. In addition, scale-up apparatus was designed and assembled, and the kilogram-scale production (up to 18.4 kg/h) of tris(2,4-di-tert-butylphenyl) phosphite was achieved in 88% yield.

**INTRODUCTION**

Triphenyl phosphites are excellent organic phosphite antioxidants which possess high efficiency, low toxicity, low volatility, and other advantageous characteristics. Generally, triphenyl phosphites are used as stabilizers for polymers, such as polyethylene, polypropylene, polystyrene, polyvinyl chloride, and synthetic rubber. There are a number of available synthetic methods for the preparation of triphenyl phosphites (Table 1). These methods comprised the utilization of various bases to obtain satisfactory yields. In these methods, Na, Et₃N, pyridine amines, and benzothiazole were employed as bases. Excellent yields were given when using pyridine and benzothiazole as bases in the reaction (Table 1, entries 4 and 6). According to the reaction mechanism in Scheme 1, there are three steps to synthesize triphenyl phosphites from phenols and PCl₃. HCl was released in every step. Therefore, using a base as the acid binding agent improved the reaction efficiently. Also, the base were the intermediates of mono-substituted and di-substituted PCl₃ in step 1 and 2, when the base was insufficient to neutralize HCl from the reaction process. Besides, different solvents such as MeOH, tetrahydrofuran (THF), CH₃CN, CH₂Cl₂, xylene, dimethylformamide (DMF), and hexane were utilized in these methods. Mostly, polar aprotic solvents were beneficial for the reaction except for MeOH when using Na as the base (Table 1, entry 1). In addition, only middle yield was given when the reaction was performed under reflux without a base (Table 1, entry 3). Nevertheless, all of these synthetic methodologies are carried out in a batch reactor and require complex operations. Because in batch reaction conditions, PCl₃ was introduced into the reactor by dripping, which cost much time and easily caused uneven distribution of PCl₃ concentration in the reactor.

In recent years, microreactor technology has emerged as an efficient technique because of improved synthetic efficiency and its application to new strategies for various compounds. The most significant advantage behind the utilization of microreactors is that the synthetic approach can enable rapid reaction optimization without compromising safety, which is a result of the large surface-to-volume ratio and the enhanced heat and mass transfer. In addition, microreactor technology can improve the safety of the process, and allows for easy scale-up, in-line workup, and automated operations. Therefore, it is clear that many challenges for traditional methods can be overcome with microreactor technology. Herein, we report a novel procedure for preparing triphenyl phosphites and derivatives under continuous flow conditions.

**RESULTS AND DISCUSSION**

First, the operation conditions were optimized in the batch reactor by exploring the effects of temperature, solvent, and types or amounts of the base. Tris(2,4-di-tert-butylphenyl) phosphite was achieved in 88% yield.
phosphite was chosen as the model product for optimization of the reaction parameters because of its wide use as an antioxidant in polymers. We started our investigation by reacting phosphorus trichloride, $\text{PCl}_3$, with 2,4-di-tert-butylphenol, $\text{I}_a$, in the ratio of 1:1 in a batch reactor. Because the reaction is vigorous when adding phosphorus trichloride to the reaction mixture, the reaction was performed at 40 °C initially to reduce the heat releasing from the reaction mixture. Then, the reaction was performed at a higher temperature to increase the reaction rate for higher yield of the desired product. Different bases such as triethylamine (TEA), pyridine, 4-dimethylaminopyridine (DMAP), $\text{N},\text{N}$-diisopropylethylamine (DIEA), imidazole, and $\text{N}$-methylimidazole were screened under the same conditions (Table 2, entries 1−6). TEA was found to be

Table 1. Various Methods for the Preparation of Phosphites in the Traditional Reactor

| entry | author | base | solvent | product | yield (%) | refs |
|-------|--------|------|---------|---------|-----------|------|
| 1     | Seiceira | Na   | MeOH    | triphenyl phosphate | 87 | 2 |
| 2     | Goycoolea | $\text{Et}_3\text{N}$ | THF | triphenyl phosphate | 80 | 3 |
| 3     | Gorniak | CH$_3$CN | tris(4-methylphenyl) phosphate | 58 | 4 |
| 4     | Akbarali | pyridine | CH$_2$Cl$_2$ | tris(2,4-di-tert-butylphenyl) phosphate | 94 | 5 |
| 5     | Herzog | amines | xylene + DMF | tris(2,4-di-tert-butylphenyl) phosphate | 85 | 6 |
| 6     | Hunter | benzothiazole | hexane | tris(2,4-di-tert-butylphenyl) phosphate | 94 | 7 |

Scheme 1. Reaction Mechanism of Synthesis of Triphenyl Phosphites

Table 2. Optimization of Reaction Conditions in Batch Process$^{a}$

| entry | base | equiv$^{b}$ | reaction temp/(°C) | solvent | yield$^{b}$/ (%) |
|-------|------|-----------|--------------------|---------|-----------------|
| 1     | TEA  | 3         | 40 + 50            | toluene | 55              |
| 2     | pyridine | 3         | 40 + 50            | toluene | 52              |
| 3     | DMAP | 3         | 40 + 50            | toluene | 49              |
| 4     | DIEA | 3         | 40 + 50            | toluene | 41              |
| 5     | imidazole | 3         | 40 + 50            | toluene | 33              |
| 6     | $\text{N}$-methylimidazole | 3 | 40 + 50 | toluene | 50 |
| 7     | TEA  | 3.15      | 40 + 50            | toluene | 60              |
| 8     | TEA  | 3.3       | 40 + 50            | toluene | 74              |
| 9     | TEA  | 3.3       | 40 + 50            | CH$_2$Cl$_2$ | 69 |
| 10    | TEA  | 3.3       | 40 + 50            | xylene | 72              |
| 11    | TEA  | 3.3       | 40 + 50            | MeCN    | 70              |
| 12    | TEA  | 3.3       | 40 + 50            | THF     | 63              |
| 13    | TEA  | 3.3       | 40 + 50            | CHCl$_3$ | 72 |
| 14    | TEA  | 3.3       | 40 + 50            | CICH$_2$CH$_2$Cl | 68 |
| 15    | TEA  | 3.3       | 40 + 60            | toluene | 80              |
| 16    | TEA  | 3.3       | 40 + 70            | toluene | 82              |
| 17    | TEA  | 3.3       | 40 + 80            | toluene | 75              |

$^{a}$Reaction conditions: $\text{I}_a$ (0.06 mol), 2 (0.02 mol), 250 mL 3-necked round bottom flask equipped with a stirrer, reflux condenser and dropping funnel, the initial temperature was 40 °C and then reacted at a higher temperature for 3 h. $^{b}$The equivalent of base refers to the molar ratio with phosphorus trichloride. $^{c}$Isolated yield.
the most effective base for the reaction (Table 2, entry 1). Besides, increasing the amount of TEA to 3.3 equiv resulted in a higher yield (Table 2, entries 7 and 8). Then, 3.3 equiv TEA was chosen as the optimal condition in the following studies. In addition, the solvent effect was researched by screening toluene, CH₂Cl₂, xylene, MeCN, THF, CHCl₃, and ClICH₂CH₂Cl (Table 2, entries 8–14). The highest yield was given when using toluene as the solvent (Table 2, entry 8). To the best of our knowledge, high reaction temperature is beneficial for the reaction yield in the preparation of triphenyl phosphites. Therefore, the desired product was produced in 82% yield on increasing the second-stage reaction temperature to 70 °C (Table 2, entry 16). When the reaction was performed at 80 °C, the yield was decreased to 75% because of the volatilization of PCl₃ (Table 2, entry 17).

Notably, the highest yield was obtained when the ratio of the solvent. Encouraged by the positive preliminary results in the batch process, we investigated reaction temperatures of 75 and 80 °C, respectively. In contrast to the previous results, the yields were lower than 91% (Table 3, entries 16 and 17 compared to entry 15). Considering that toluene is the commonly use solvent in the industry, we chose N-methylimidazole as the base to avoid clogging in the microreactor based on the BASF’s method.36,37 Owing to the melting point of the ionic liquid N-methylimidazolium chloride being 75 °C, the reaction was carried out at 80 °C (Table 3, entry 18). However, the microreactor was clogged because the ionic liquid formed during the process was an adhesive colloid at 80 °C. To avoid the microreactor clogging, the reaction temperature was increased to 90 °C. Surprisingly, the reaction proceeded smoothly under this condition in continuous flow. Nevertheless, the corresponding product was obtained in 83% yield (Table 3, entry 19), which is lower than the best results given by using TEA. Because of the excellent solubility of ionic liquids, small amount of the product was lost during the separation of ionic liquid from the reaction mixture. Besides, N-methylimidazole is more expensive and harder to recycle than TEA. Thus, it was decided to use TEA as the base, chloroform as the solvent, and the ratio of 2,4-di-tert-butylphenol 1a, phosphorus trichloride 2, and TEA was 3:1:3.3 as the optimal conditions in further studies.

With the optimized reaction conditions in hand, we probed the applicability of this method with regard to a series of diversely substituted phenols. As shown in Table 4, phenols...
bearing a variety of substituent groups, including electron-donating groups (Me, MeO, t-butyl, t-pentyl) and electron-withdrawing groups (F, Cl, Br, I, Ph), provided the desired triphenyl phosphates in good to excellent yields in continuous flow. Generally, the electron-donating group-substituted phenols (Table 4, 3a, 3c−3j) furnished the corresponding products in higher yields than those electron-withdrawing-substituted phenols (Table 4, 3k−3s, 3w) with the exception of p-methoxyphenol (Table 4, 3t). Moreover, the alkyl-substituted phenols exhibited higher reactivity than those phenols containing halogen substituents with the exception of 2,4-dichlorophenol (Table 4, 3n). In addition, most of the para-substituted phenols gave higher yields of the desired products by comparing with the ortho-substituted phenols (Table 4, compare 3c to 3e, 3g to 3h, 3o to 3p, 3q to 3r). The reason for this phenomenon is probably the steric hindrance of the ortho-substituted groups limiting the nucleophilic ability of the phenolic hydroxyl group. Furthermore, 2-phenylpropan and benzyl-substituted derivatives also produced the corresponding products in satisfactory yields (Table 4, 3x and 3y).

As a further demonstration of the synthetic expediency of this flow method, a pilot-scale equipment was designed and assembled (Figure 1). The preparation of tris(2,4-di-tert-butylphenyl) phosphite was conducted using the optimized reaction conditions. The reactants were conveyed using diaphragm pumps combined with flow meters. BPR (2.0 bar) was used to decrease the pulse of the pump to maintain smooth fluid delivery. The inner diameter of the reaction coil was increased from 0.8 to 4.4 mm. As a result, the reactor volume was increased from 5.0 to 300.0 mL. A cooling coil (ID = 4.4 mm, inner volume 50.0 mL) was attached to the end of the reactor to avoid the gasification of chloroform when the reaction mixture flows out of the system. Additionally, another BPR (6.0 bar) was attached at the end of the flow system to avoid any gasification during the reaction process. Remarkably, the purified tris(2,4-di-tert-butylphenyl) phosphite was obtained in 88% yield in this pilot apparatus with a 20 s residence time. The purified product could be prepared at a rate of up to 18.4 kg/h.

**CONCLUSIONS**

In summary, we have developed an efficient method for the preparation of triphenyl phosphate and its derivatives in continuous flow. Because of the enhanced mass and heat transfer in the microreactor, this method provides many advantages such as simplified operation, the use of a theoretical dosage of PCl₃, and short reaction time. A wide range of products were obtained in good to excellent yields by employing reactants in a stoichiometric ratio, using TEA as the base and by conducting the reaction in chloroform at 70 °C over 20 s. This method allows for the preparation of triphenyl phosphate with a lower operating cost and enhances process safety for easy scale-up in the industry.

**EXPERIMENTAL SECTION**

All reagents and solvents were commercially available and used without any further purification. Unless otherwise noted, all reactions were run under air and the indicated reaction temperature was that of the water or oil bath. Purification of reaction products was carried out by recrystallization with isopropanol alcohol or flash chromatography using 100−200 mesh silica gel. ¹H and ¹³C NMR spectra were recorded on a
Optimization Studies for Tris(2,4-di-tert-butylphenyl) Phosphite in the Batch Process. To a 250 mL 3-necked flask equipped with a condenser and a magnetic stir bar, 2,4-di-tert-butylphenol (0.06 mol, 3 equiv), the base, and the solvent (100.0 mL) were sequentially added. Phosphorus trichloride (0.02 mol, 1 equiv) and the solvent (5.0 mL) were charged in the dropping funnel. The 3-necked flask was submerged into a water bath at 25 °C. The mixture in a dropping funnel was added to the 3-necked flask dropwise over 40 min, and then maintained at a temperature of 40 °C for 1 h. Next, the reaction mixture was cooled down to room temperature after the reaction was complete. The reaction mixture was sequentially washed with water (10.0 mL) and 1 mol/L NaOH aq. (10.0 mL) twice, and the solvent was removed by distillation. When the desired product was solid, the crude product was recrystallized with isopropyl alcohol to obtain the purified product. When the desired product was liquid, purification of reaction products was carried out by column chromatography using 100–200 mesh silica gel. The purities of the obtained products were higher than 98.5% according to the analysis of the HPLC results.

General Procedure for the Synthesis of Triphenyl Phosphites in Continuous Flow. The reactants were introduced into a PTFE tube (ID = 4.4 mm) with an inner volume of 300.0 mL via diaphragm pumps. 2,4-Di-tert-butylphenol (3.6 mol, 3.0 equiv) and Et₃N (3.96 mol, 3.3 equiv) were combined, then they were dissolved in chloroform and diluted to 3000 mL. Then, the solution was loaded in one tank. Phosphorus trichloride (1.2 mol, 1.0 equiv) was dissolved in chloroform and diluted to 3000 mL. The solution was loaded in another tank. The two fluids were mixed in a PTFE T-mixer (ID = 4.4 mm) before entering into the flow tube reactor. The flow tube reactor was cooled and put into a water bath at 70 °C, and another PTFE tube (ID = 4.4 mm, 50 mL inner volume) was cooled and put into a water bath at 25 °C to cool the reaction mixture. The flow rate of each pump was 450 mL/min; hence, the flow rate in the microreactor was 900 mL/min. BPR (2.0 bar) after the pump was used to decrease the pulse of the pump to maintain smooth fluid delivery. Another BPR (6.0 bar) was attached at the end of the flow system to avoid any gasification during the reaction process. The reaction mixture (5000 mL) was collected in a round bottom flask. The reaction mixture was sequentially washed with water (600 mL) and 1 mol/L NaOH aq. (600 mL) twice, and the solvent was removed by distillation. The crude product was recrystallized with isopropyl alcohol to obtain the purified product in 88% yield. The melting point of the product was 183.2–184.5 °C.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c00716.

**1H and 13C NMR spectra for the products (PDF)**

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Notes
The authors declare no competing financial interest.

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