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A Facile Synthetic Method for Anhydride from Carboxylic Acid with the Promotion of Triphenylphosphine Oxide and Oxaloyl Chloride

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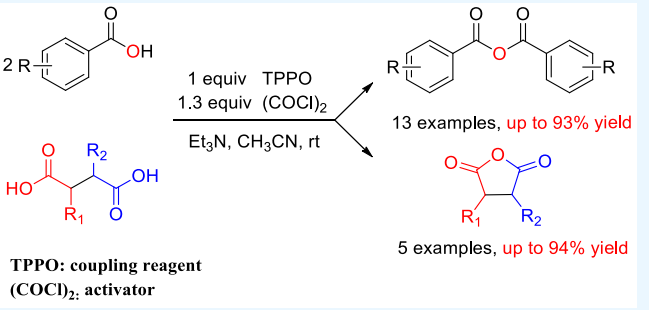
ABSTRACT: A highly efficient synthesis reaction of carboxylic anhydrides catalyzed by triphenylphosphine oxide is described for the quick synthesis of a range of symmetric carboxylic anhydrides and cyclic anhydrides under mild and neutral conditions with a high yield. The system adopts the strong reactive intermediate Ph_3PCl_2 as the catalyst of carboxylic acid salt; driven by catalytic reaction, the synthesis takes a relatively short time to complete.



1. INTRODUCTION

It is well-known that carboxylic anhydrides, one of the most important classes of reagents, are used as acylating agents or intermediates in organic synthesis because of the high electrophilicity of their carbonyl groups and are commonly used in pharmaceuticals, pesticides, resins, power electronics, surfactants, and food processing.[1] Many researchers are interested in developing highly selective and environmentally friendly methods for the synthesis of carboxylic anhydrides because they have a wide range of applications in the preparation of compounds such as amides, esters, and peptides.[2] Anhydrides of aromatic carboxylic acids are usually prepared by rereaction of powerful acylating agents (e.g., acyl chloride) with sodium salts of the same or another carboxylic acid or by treating acyl chloride with pyridine and decomposing the reaction mixture with water.[3] They can also be prepared by a dehydration coupling reaction of carboxylic acid, using reagents (also through dehydrating agents) such as oxalyl chloride,[4,5] thionyl chloride,[6] triphosgene,[7] phosphorus pentoxide,[8] trichloroisocyanuric acid combined with triphenylphosphine,[9] dicyclohexylcarbodiimide,[10,11] or ethoxyacetylene.[12,13] However, when using these reagent systems for the preparation of carboxylic anhydrides, there are certain disadvantages in limiting their application: high costs, low yields, harsh reaction conditions, instability, toxicity, and unwanted side effects during the preactivation of carboxylic acid. The search for a gentle and effective coupling system is therefore particularly important for the further development of synthetic carboxylic anhydrides. Liu[14] et al. developed a one-step synthesis of anhydride from amide by a tandem catalytic mechanism using $Sc(OTf)_3$ catalyst in the presence of water, without the addition of an external nucleophile, in their most recent study on the synthesis of anhydride. It is the first example of the synthesis of an anhydride from amides and opens the door to controlled sequential catalysis by amide N−C bond breaking. However, the method of synthesizing anhydride still has some shortcomings. For example, the method can not produce anhydride directly from carboxylic acid, and the yield of synthesizing anhydride is not high.

Phosphonium salts, hypophosphates, phosphate derivatives, and phosphine oxides have been reported as efficient coupling agents, and in the search for new coupling systems we have found PPh_3 to be a commonly used reagent, frequently applied in a number of well-known reactions such as the Appel reaction,[15,16] the Wittig reaction,[17−21] the Mitsunobu reaction,[22−30] and the Staudinger reaction.[23,31] The Mitsunobu reaction was first reported by Mitsunobu et al. in 1967,[22] and under the well-known Mitsunobu condition (PPh_3/DEAD), it was proposed that one of the reasons for the lower yields of initial acid-forming esters with higher pK_a values was the formation of competitive anhydrides via acylphosphonate salts.[32] A universal combination of PPh_3 and CCl_4 is the initial Appel reagent for batch conversion in the Appel reaction. The stoichiometric intermediate chlorophosphonium salts (Ph_3PCl^+/Cl^-) generated from PPh_3 and CCl_4 can effectively activate carboxylic acids and further react with carboxylates, amines, alcohols, or oximes. CCl_4 is a hepatotoxic substance[33] that contributes to the deterioration of the ozone

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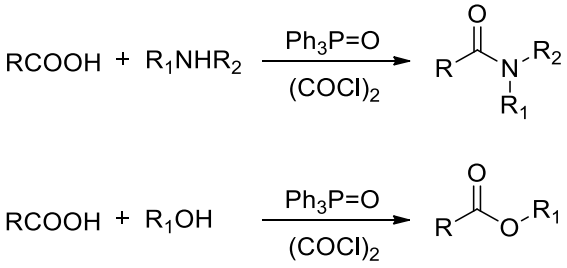
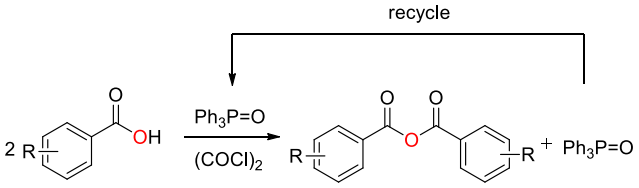
layer. In many applications, scientists stopped using CCl_4 as a solvent for chemical reactions and started to look for alternatives.[34] In the Appel reaction, CBr_4 was used as a substitute for CCl_4, but the cost of the reaction was too high. The replacement of CCl_4 with $BrCCl_3$ has been proposed in some studies in the literature,[33] and $BrCCl_3$ has been found to be superior to CCl_4 because $BrCCl_3$ has less environmental impact and is not classified as an ozone-depleting substance. The application of PPh_3−$BrCCl_3$ in some reactions has been reported, such as amidation reactions,[35] the reaction of aldehydes with dihalogenated vinyl compounds,[36] and the reaction of aldehyde oxime and amide with nitrile;[37] it has also been used in anhydride synthesis reactions.

In reactions catalyzed by Appel-type reagents, the concomitant production of stoichiometric ratios of phosphine oxide byproducts severely affects the atomic efficiency and large-scale applicability of the reaction,[38] and the disposal of phosphine oxide byproducts leads to a waste of resources. In this regard, Appel[39] indicates that it is necessary to consider whether the recovery and reactivation of phosphine oxide are valuable. Furthermore, the purification of the product is not always straightforward. In order to overcome these drawbacks, many studies have favored the reduction of phosphine oxide compounds to phosphine compounds.[40−42] Mecinovic[43] published a reaction for organocatalytic amide synthesis mediated by the PPh_3/CCl_4 system in which TPPO was reduced to PPh_3 in situ. Thanks to O'Brien[19,44,45] and colleagues, who pioneered the catalytic Wittig reaction, this reduction of phosphine oxides has led to breakthroughs in a number of catalytic reactions; examples include the catalytic Appel reaction and Staudinger reaction. The treatment method has achieved a good effect, but we found that the reagents and conditions required for the reduction of TPPO to TPP are relatively harsh, the reaction process is relatively complex, and the operation cost is too high to be suitable for industrial production. This makes the study of the recycling of waste products (TPPO) particularly important and relevant. Cao[46] et al. have successfully developed a new tandem Wittig conjugate reduction reaction in which the in situ generated TPPO is used as a catalyst for the subsequent conjugate reduction step reaction without any treatment and with excellent chemoselectivity and regioselectivity. Denton[38] and colleagues have applied $TPPO/(COCl)_2$ to catalyze the chlorination of alcohols for the first time under Appel conditions and have developed other reactions using this catalytic system. Our review of the literature revealed that the chemical catalysis of $TPPO/(COCl)_2$ combinations was originally proposed by Fukui and Masaki in 1977. Through the application research of these reaction mechanisms, we applied the $TPPO/(COCl)_2$ system to the amidation of carboxylic acids[47] and the esterification of carboxylic acids and alcohols[48] and successfully synthesized the corresponding amides and esters (Scheme 1). Analysis of these reactions revealed that TPPO reacted with $(COCl)_2$ to form an acyl phosphonochloride intermediate, which can promote the activation of carboxylic acids. However, this system has not been studied for the synthesis of acid anhydrides. As a result, we will continue to look into the $TPPO/(COCl)_2$ catalytic system for the catalytic synthesis of symmetrical anhydrides (Scheme 2) and cyclic anhydrides (Scheme 3) from carboxylic acids in this article. Succinic acid is used as the raw material for the synthesis of anhydride. Its important purpose is to prepare five-membered heterocyclic compounds. Succinic acid can be dehydrated by heating or through a dehydrating agent to form a five-membered anhydride, but the required conditions are harsh.

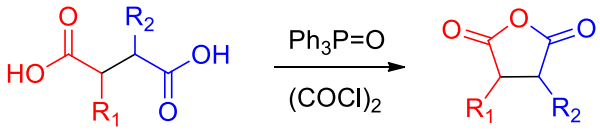
Scheme 1. Synthesis of Amide and Ester by $TPPO/(COCl)_2$ System



Scheme 2. $TPPO/(COCl)_2$ for the Synthesis of Anhydride



Scheme 3. $TPPO/(COCl)_2$ for the Synthesis of Cyclic Anhydride



2. RESULTS AND DISCUSSION

2.1. Optimization of Reaction Conditions. On the basis of the previous research of our group, our research is initiated from screening reaction conditions and the preliminary evaluation of model reactions using 4-methylbenzoic acid as a substrate (Table 1).

We found that carboxylic anhydride could be formed in a high yield (93%) by reacting with 1 equiv of TPPO and 1.3 equiv of $(COCl)_2$ for 1 h (Table 1, entry 1, run 1). Monitoring by thin-layer chromatography analysis showed that the reactants were consumed within 1 h and that extending the reaction time did not improve the reaction yield (Table 1, entries 2 and 3) and that the high temperature may cause some of the resulting carboxylic anhydride to be readily decomposed, affecting the yield of the reaction.

The effect of a range of solvents on the synthesis of the anhydride was assessed, including toluene, methylene chloride, acetonitrile, 1,2-dichloroethane, chloroform, and 1,4-dioxane (Table 1, entries 4−8), all of which were effective for the synthesis of carboxylic anhydride. We found that TPPO was less soluble in PhMe and CH_3CN, and TPPO was able to dissolve rapidly after the addition of oxalyl chloride to CH_3CN. Under the same conditions, higher yields were achieved when CH_3CN was used as a solvent, so CH_3CN was the best solvent; for subsequent investigations, we would choose CH_3CN as our reaction solvent. In this study, the reaction was further optimized by varying the reaction time and the ratio of $TPPO/(COCl)_2$. These results demonstrated that the catalytic amount of TPPO is sufficient to complete the

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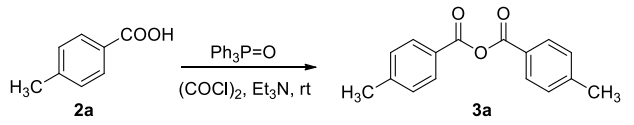
Table 1. Optimization of the Synthesis Reaction of Anhydride by Triphenylphosphine Oxide[a]



2a 3a

entry	solvent (5 mL)	Ph_3PO (equiv)	$(COCl)_2$ (equiv)	time (h)	yield[b] (%)
1	CH_3CN	1	1.3	1	93 run 1
					88 run 2
2	CH_3CN	1	1.3	3	83
3	CH_3CN	1	1.3	5	72
4	CH_2Cl_2	1	1.3	1	89
5	Ph-Me	1	1.3	1	87
6	$C_2H_4Cl_2$	1	1.3	1	69
7	$C_4H_8O_2$	1	1.3	1	68
8	$CHCl_3$	1	1.3	1	90
9	CH_3CN	0.75	1.3	1	72
10	CH_3CN	2	1.3	1	80
11	CH_3CN	1	0.75	1	64
12	CH_3CN	1	1	1	75
13	CH_3CN	1	2	1	85
14	CH_3CN	0	1.3	1	nr[c]
15	CH_3CN	1	0	1	nr[d]

[a]Reaction was carried out with **2a** (5 mmol, 1 equiv) and solvent (5 mL) at room temperature for 1 h. [b]Isolated yield. [c]The reaction was carried out without TPPO. [d]The reaction was carried out without $(COCl)_2$.

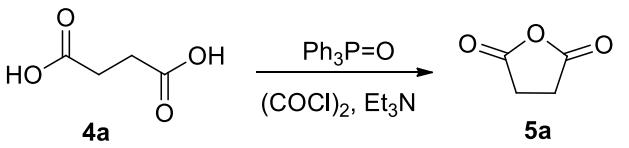
reaction. Reducing the loading of TPPO to 75% resulted in significantly lower yields (Table 1, entry 12). It is known that oxalyl chloride is the chlorinating agent for the in situ generation of acyl chlorides, and in the presence of oxaloyl chloride without the addition of TPPO, we found that no carboxylic anhydride was generated (Table 1, entry 14). At the end of the reaction, TPPO could be recovered, and after the reaction (Table 1, entry 1, run 1) was completed, in addition to TPPO, we again added oxalyl chloride, the reactants, and triethylamine to the reaction vessel; after 1 h of reaction again, the yield of **3a** could reach 88% (Table 1, entry 1, run 2).

On the basis of the above screening, the optimum reaction conditions for the synthesis of anhydride were determined; that is, TPPO (1 equiv) and $(COCl)_2$ (1.3 equiv) were mixed thoroughly in acetonitrile solvent and reacted in a N_2 environment for 10 min, and carboxylic acid (1 equiv) and triethylamine (1 equiv) were added sequentially at room temperature for 1 h.

Next, we investigated whether the TPPO/$(COCl)_2$ reagent system could be used for the synthesis of cyclic anhydride, and we explored the reaction conditions of the model reaction with **4a** (1 equiv) as the substrate using TPPO (1 equiv)/$(COCl)_2$ (1.3 equiv) as the coupling agent. Our preliminary investigations were carried out to optimize the reaction conditions by varying the reaction temperature, reaction time, and different organic solvents, and the best results are summarized in Table 2.

According to the summary in Table 2, it can be found that with CH_3CN as the reaction solvent, a relatively high separation yield of **5a** of 94% could be achieved in 5 h (Table 2, entry 2), and changes in the reaction time affect the yield of the anhydride (Table 2, entries 1 and 3). Changes in temperature also affect the reaction yield, and the yield

Table 2. Effects of Temperature, Time, and Solvent on the Synthesis of Succinic Anhydride[a]



4a 5a

entry	solvent (5 mL)	temp (°C)	time (h)	yield[b] (%)
1	CH_3CN	30	3	71
2	CH_3CN	30	5	94
3	CH_3CN	30	6	81
4	CH_3CN	50	5	80
5	CH_2Cl_2	30	5	84
6	Ph-Me	30	5	36
7	$C_2H_4Cl_2$	30	5	64
8	$C_4H_8O_2$	30	5	74
9	$CHCl_3$	30	5	85

[a]Reaction was carried out with **4a** (5 mmol, 1 equiv), TPPO (5 mmol, 1 equiv), $(COCl)_2$ (6.5 mmol, 1.3 equiv), and Et_3N (5 mmol, 1 equiv). [b]Isolated yield.

decreases as the temperature increases (Table 2, entry 4). The effects of different organic solvents on reaction yields were tested (Ph-Me, CH_2Cl_2, $C_2H_4Cl_2$, $C_4H_8O_2$, $CHCl_3$), and all solvents were effective except toluene (Table 2, entries 5–9), in which there was little difference in the separation yields of **5a**. It follows that CH_3CN is still the best solvent for the reaction in the synthesis of cyclic anhydride from dicarboxylic acids.

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2.2. Preparation of Various Acid Anhydrides. In the context of determining the optimum reaction conditions, we have investigated the extension of the TPPO/$(COCl)_2$ system to the range of suitable substrates for the promotion of anhydride synthesis (testing the generality of the proposed method) and systematically investigated the effect of various substituents as well as different types of dicarboxylic acids on this conversion under the conditions of this system. The results of the study are summarized in Table 3, and most products can achieve moderately high yields. As can be seen from Table 3, benzoic acid and carboxylic acids containing electron-donating substituents, which are weak acids with large pK_a values, have better reactions with shorter reaction times and higher yields of the corresponding anhydrides (Table 3, entries 2–7), while strong acids (with smaller pK_a values) such as chlorinated derivatives and brominated derivatives containing electron-absorbing substituents were also able to synthesize the corresponding anhydrides successfully, but in relatively lower

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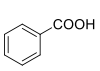
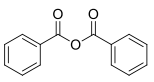
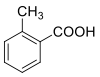
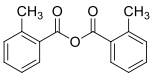
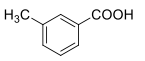
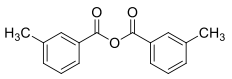
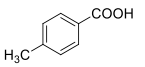
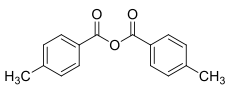
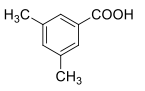
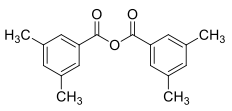
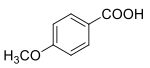
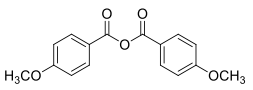
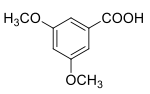
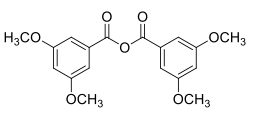
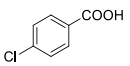
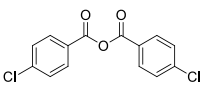
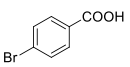
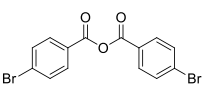
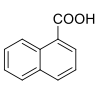
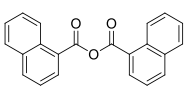
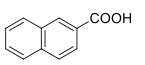
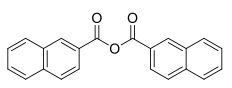
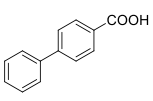
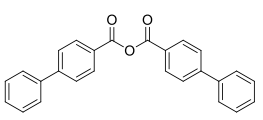
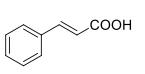
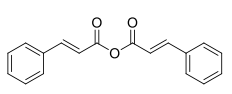
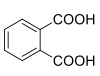
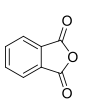
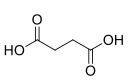
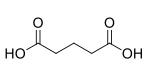
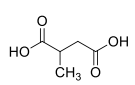
Table 3. Different Anhydrides that Were Synthesized in the TPPO/$(COCl)_2$ System[a]

Entry	Substrate	Product	Yield[b](%)
1			91
2			86
3			89
4			93[c]
5			91
6			91
7			92
8			82
9			80
10			90
11			93
12			90
13			91
14			92
15			94
16			74
17			81
18			84

[a]Addition: To a solution of TPPO (1 equiv) in CH_3CN (5 mL) was added $(COCl)_2$ (1.3 equiv). Acid (1 equiv, 5 mmol) and Et_3N (1 equiv, 5 mmol) were added to the solution after 10 min of reaction and reacted for 1 or 5 h at 30 °C. [b]Isolated yield. [c]Yield was determined by ^1H NMR analysis.

yields (Table 3, entries 8 and 9). From the point of view of the substituents, the effect of the electron-donating and electron-absorbing groups on the yield does vary somewhat, with the yield of *p*-chlorobenzoic anhydride (80%) being slightly lower than that of *p*-methylbenzoic anhydride (93%) because of the poor nucleophilicity of the corresponding carboxylic acid ion. On the basis of previous studies[49] and the results presented in Table 3, the nucleophilic attack of the carboxylate ion on the acylphosphine salt to generate triphenylphosphonate oxide and the corresponding carboxylic anhydride is a decisive step, and as the nucleophilicity of the carboxylic acid increased, the formation of the product would be faster. We found that the spatial factor did not have much effect on the reaction yield, and the presence of neighboring, inter- and para-substituents did not significantly reduce the yield (Table 3, entries 2−5). In addition to benzoic acid and its derivatives, other aromatic acids such as naphthoic acid and acids with conjugated systems also reacted well and rapidly to achieve high yields (Table 3, entries 10, 11, and 13). This indicates that the more nucleophilic aromatic carboxylic acids play a crucial role in the synthesis of anhydrides. We also carried out reactions with *p*-nitrobenzoic acid as well as pyridine-3-carboxylic acid as raw materials but did not obtain the corresponding anhydride. These carboxylic acids have strong electron-absorbing groups, and the corresponding carboxylic acids are more acidic; no products appear in the reaction, probably because the bond-leaving energy of the corresponding acyloxy bond[50] is relatively high. Pyridine carboxylic acids are aromatic heterocyclic compounds that react only under strong reaction conditions, which are demanding. A review of the literature[51] shows that nicotinic anhydride is extremely sensitive to moisture and the reaction must be carried out under strictly anhydrous condition, so we suspect that part of the reason for the lack of formation of nicotinic anhydride may also be due to the decomposition of the nicotinic anhydride formed as a result of moisture generation during the inverse process.

In contrast, aliphatic dicarboxylic acids take a long time to react to form the corresponding anhydrides (Table 3, entries 15−18) and are somewhat less reactive than aromatic carboxylic acids, which react more easily than aliphatic carboxylic acids. Phthalic acid, an aromatic dibasic acid, can also be converted to phthalic anhydride with a high yield (Table 3, entry 14).

2.3. Possible Mechanism of Acid Anhydride Synthesis. According to previous reports,[42,52,54−56] the intermediate for the reaction of TPPO and $(COCl)_2$ was identified as triphenylchlorophosphonium salt[53] (Scheme 4, intermediate A), which can also be produced from the reaction of PPh_3 with CCl_4. We successfully prepared anhydride by applying the TPPO and $(COCl)_2$ system. To illustrate the effect of the intermediate formed by TPPO and $(COCl)_2$ in the synthesis of the anhydride reaction, we used a ^{31}P NMR spectrum to detect and follow the course of the reaction (Figure 1) and deduce a plausible mechanism for the reaction (Scheme 4).

First, TPPO was detected by ^{31}P NMR in acetonitrile solution as exhibiting a singlet at 29.28 ppm (Figure 1, I), and then oxalyl chloride was added and the TPPO solid and immediately reacted and dissolved, which was different from

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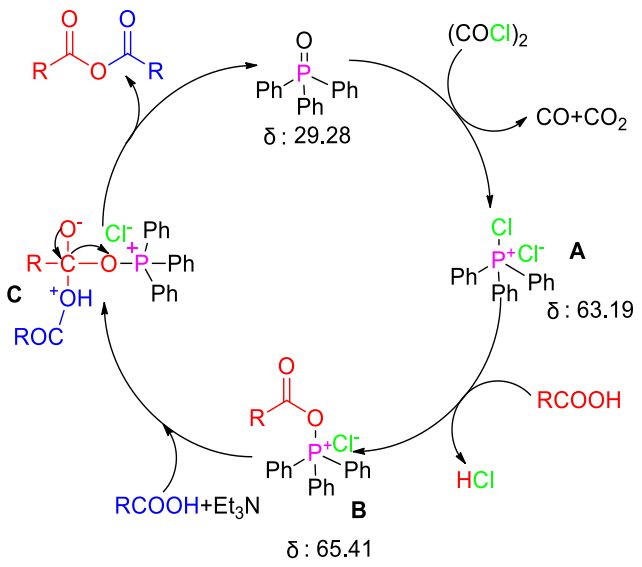
Scheme 4. Mechanism of TPPO/$(COCl)_2$ Mediated Anhydride Synthesis



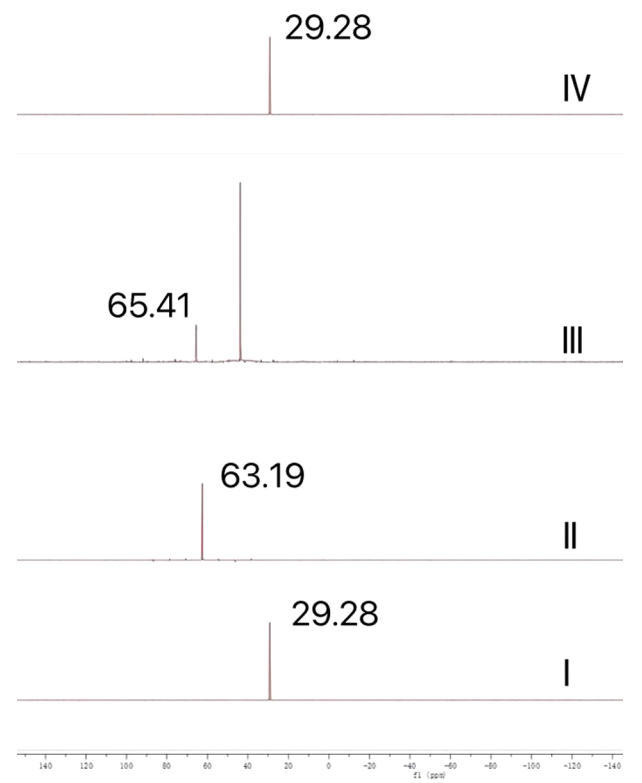


Figure 1. ^{31}P NMR spectrum of the formation of **3a** from **2a**. I: TPPO (1 equiv), CH_3CN (5 mL). II: Addition of $(COCl)_2$ (1.3 equiv) to I. III: Addition of **2a** (1 equiv) to II. IV: reaction solution after reaction for 1 h.

the position of the single peak of TPPO (29.28 ppm). At this time, a new singlet appeared at 63.19 ppm (Figure 1, II), which was roughly the same as the peak position of the phosphine chloride intermediate recorded in the literature[42] and indicated the formation of triphenylchlorophosphine **A**. After 10 min of reaction, the carboxylic acid and triethylamine were added; after the disappearance of the solids, the ^{31}P NMR spectra the reaction were measured, and a new resonance was generated at 43.62 ppm (Figure 1, III), indicating the formation of acylphosphonate **B**.[46] Finally, due to the action of catalyst Ph_3PO, the reaction recovered to a singlet at 29.28 ppm after a period of time (Figure 1, IV). The singlet of about 29.28 ppm is likely to be mistaken for intermediate **C**. In fact, **C** is a transient intermediate, which cannot exist continuously under the action of carboxylic acid and the organic base, and the reaction will continue.

3. CONCLUSIONS

In summary, we have successfully exploited a novel route for the efficient and rapid synthesis of anhydrides using the TPPO/$(COCl)_2$ system. The reaction method is simple to operate and can be used in industrial production. Compared with other methods of synthesizing anhydrides, this process system has many advantages: (1) The acid can be directly converted to anhydride in a relatively short time at room temperature. (2) The process is safe, simple, and easy to operate; the cost is low, and the reaction raw materials are cheap and easy to obtain. (3) The TPPO produced can be recycled, and the only byproducts of the reaction are CO, CO_2, and HCl, which have a high atomic utilization rate. (4) The postreaction treatment is relatively simple, the reaction solution can be purified by column chromatography directly, and the product purity is high. We detected the reaction process by ^{31}P NMR spectroscopy and speculated on the possible mechanism of the reaction. As a waste product of industrial production, TPPO can have many applications, and its application can be further explored.

4. EXPERIMENTAL SECTION

4.1. Materials. The information about the materials is found in the Supporting Information.

4.2. General Procedure for the Synthesis of Anhydrides. To a three-neck flask containing acetonitrile (5 mL), 1.4 g of triphenylphosphine oxide was added (1 equiv, 5 mmol), and 0.55 mL of oxalyl chloride (1.3 equiv, 6.5 mmol) was slowly added dropwise under magnetic stirring; the violent reaction (the solid disappears immediately) releases a large amount of gas. After reacting for 10 min, the resulting solution is a uniform and transparent solution. At this time, the raw material carboxylic acid (1 equiv, 5 mmol) and a certain amount of triethylamine (0.69 mL, 5 mmol) are added, and the reaction continued for 1 h under the protection of N_2 (30 °C). The reaction process is followed by thin-layer chromatography (TLC). After the reaction is completed, the triphenylphosphine oxide is removed by filtration, the filtrate is washed with a 10% sodium bicarbonate aqueous solution, the extracted organic phase is dried with anhydrous sodium sulfate, and the solvent is evaporated in a vacuum. Finally, the column chromatography is performed with the eluent of PE:EA = 40:1. Purification by column chromatography is used to determine yield.

4.3. Procedure for Recycling TPPO. The procedure for entry 1, run 2, of Table 1 is as follows: TPPO (1.4 g, 1 equiv, 5 mmol), CH_3CN (5 mL), $(COCl)_2$ (0.55 mL, 1.3 equiv, 6.5 mmol), 4-methylbenzoic acid (0.68 g, 1 equiv, 5 mmol), and triethylamine (0.69 mL, 5 mmol) were added to the reaction vessel according to the previously described steps. After reacting at room temperature for 1 h, $(COCl)_2$ (0.55 mL, 1.3 equiv, 6.5 mmol), 4-methylbenzoic acid (0.68 g, 1 equiv, 5 mmol), and triethylamine (0.69 mL, 5 mmol) were added

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again. The final yield is 88% after 1 h of reaction under the same conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c03991.

Selection of various variable factors, characterization of the catalysts, detailed experimental procedures, and characterization data, such as ^{1}H NMR and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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