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Abstract: The formation of acid anhydrides from the phosphorous-mediated activation of carboxylic acids was investigated. Under various systems, activation of benzoic acid in the presence of base led to the formation of benzoic anhydride at different rates depending on the reactivity of the reagents. Using the Ph_3P-I_2/Et_3N combination, most aryl acids were converted into the corresponding anhydrides in high yields within 5-10 min. However, for nitro-substituted derivatives, unexpectedly, *N*,*N*-diethylamides were isolated without anhydride formation. These results indicated the pronounced effect of substituents in governing these potential side reactions which can significantly affect the yields of acylation reactions promoted by phosphonium species.

Keywords: substituent effects; triphenylphosphine; iodine; anhydrides; amides

Introduction

Carboxylic acid anhydrides are an important class of reagents and are highly useful as acylating agents as well as key intermediates in organic synthesis.[1] They are usually prepared by the reaction of carboxylate salts with acylating agents such as acid chlorides,[2] coupling of acid chlorides[3] or through a dehydrative coupling reaction of carboxylic acids using reagents such as thionyl chloride,[4] oxalyl chloride,[5] triphosgene,[6] triazine reagents,[7] trichloroisocyanuric acid in combination with triphenylphosphine (Ph_3P),[8] and carbodiimide.[9] While various reagent systems have been developed for the preparation of anhydrides, their formation are often unwanted side reactions which are encountered during the pre-activation of a carboxylic acid for an acyl transfer process.[10]

In the phosphorous-mediated activation of a carboxylic acid, an acyloxyphosphonium salt is commonly proposed as the key intermediate produced upon treatment of a carboxylic acid with an *in-situ* generated phosphonium ions.[10e-g] This highly reactive species could undergo nucleophilic attack with a carboxylate anion to provide the anhydride by-product before reacting with the desired nucleophile. Such side reactions could lead to low yield, long reaction time, harsh reaction conditions or even inexplicable results.

Under the well-known Mitsunobu conditions (Ph_3P/DEAD), it has been suggested that one of the reasons for the lower yields of esters from starting acids with higher pK_a is due to competitive acid anhydride formation *via* acyloxyphosphonium salts.[10d, 11] Indeed, in a study by Jenkins and co-workers,[12] it was found that benzoic acid gave a high yield of the corresponding anhydride, whereas the more acidic 4-nitrobenzoic acid did not lead to any of the anhydride side product.

To explore whether a similar outcome persists with other related phosphine reagent systems and to better explain the outcome of the related acylation reactions, herein, anhydride formation under various phosphorous-mediated carboxylic acid activation conditions was thoroughly investigated using a variety of aromatic acids with a range of pK_a values.

In our initial investigation, benzoic acid was used as a model substrate and various factors affecting anhydride formation including the type of base and halogenated additives were examined. The effect of tertiary amine base was first compared using the combination of Ph_3P-iodine as the acid activation system. As shown in Table 1, benzoic anhydride was quantitatively obtained within *ca.* 5 min using either Et_3N or $^iPr_2NEt$ (entries 1 and 2). Replacing these bases with imidazole gave a lower yield of the corresponding anhydride with a longer reaction time (entry 3).

Various halogenated additives were evaluated in the presence of Et_3N. Under similar conditions, *N*-bromosuccinimide (NBS) gave a lower yield of the anhydride relative to that using I_2 (entry 4 *vs* entry 1). When Ph_3P-*N*-chlorosuccinimide (NCS) or Ph_3P-carbontetrachloride (CCl_4) combinations were used, the reaction was sluggish, requiring longer reaction times or increased temperature (entries 5 and 6). It was noted that using the reported Ph_3P-trichloroacetonitrile (CCl_3CN) system (entry 7),[13] a high yield of benzoic anhydride (92%) was obtained after 1 h at room temperature although, in this case, an acyl chloride was proposed as the key intermediate.

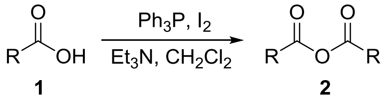
Table 1. Formation of benzoic anhydride using different reagent systems[a]

entry	Reagent	base	time (min)	yield (%)
1	Ph_3P/I_2	Et_3N	5	99
2	Ph_3P/I_2	$^iPr_2NEt$	5	97
3	Ph_3P/I_2	imidazole	30	85
4	Ph_3P/NBS	Et_3N	5	92
5	Ph_3P/NCS	Et_3N	30	88
6	Ph_3P/CCl_4	Et_3N	60	87[b]
7	Ph_3P/CCl_3CN	Et_3N	60	90[13]

[a] Reaction conditions: benzoic acid (0.41 mmol), Ph_3P (0.62 mmol), halogenated reagent (0.62 mmol), base (1.23 mmol), CH_2Cl_2 (2 mL), 25 °C. [b] The reaction was carried out at 60 °C.

To study the substituent effect on this transformation, we systematically investigated anhydride formation using the Ph_3P-I_2/Et_3N conditions using various aromatic acids with a range of pK_a values. According to Table 2, weaker acids (larger pK_a value) such as benzoic acid and those derivatives containing electron-donating substituents (entries 1-8) reacted extremely well to provide the corresponding anhydrides in high yields within 5-10 min. Steric factors had little influence on the reaction and the presence of a substituent at the *ortho* position did not significantly lower the yields (see entries 2, 6). Stronger acids (smaller pK_a value) such as chloro-substituted derivatives (entries 9-11) were also smoothly converted to the corresponding anhydrides. However, using substrates bearing the acetyloxy or hydroxy groups (entries 12-13) led to slightly lower conversion. Apart from benzoic acid derivatives, other aryl acids such as naphthyl derivatives as well as a conjugated system (entries 14-16) also reacted rapidly.

Table 2. Ph_3P-I_2 mediated formation of symmetric anhydrides[a]



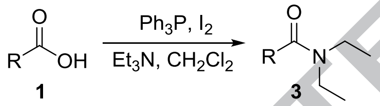
entry	R	pK_a of **1**[14]	yield of **2** (%)
1	C_6H_5	4.19	98
2	2-$CH_3OC_6H_4$	4.09	96
3	4-$CH_3OC_6H_4$	4.47	92
4	3,4-$(CH_3O)_2C_6H_3$	4.36	72
5	3,5-$(CH_3O)_2C_6H_3$	3.97	90
6	2-$CH_3C_6H_4$	3.98	83
7	3-$CH_3C_6H_4$	4.27	89
8	4-$CH_3C_6H_4$	4.37	90
9	2-ClC_6H_4	2.89	90
10	3-ClC_6H_4	2.81	89
11	4-ClC_6H_4	3.98	99
12	2-$AcOC_6H_4$	3.49	72
13	2-HOC_6H_4	2.97	57
14	1-naphthyl	3.69	87
15	2-naphthyl	4.17	89
16	PhCH=CH	4.44	83
17	4-$NO_2C_6H_4$	3.44	0

[a]Reaction conditions: carboxylic acid (0.41 mmol), Ph_3P (0.62 mmol), I_2 (0.62 mmol), Et_3N (1.23 mmol), CH_2Cl_2 (2 mL), 0 °C - RT, 5-10 min.

In contrast to the results obtained with most aryl acids, aromatic acids bearing nitro group(s) were found to behave differently. When 4-nitrobenzoic acid was subjected to the above described conditions (Table 2, entry 17), no trace of the respective anhydride was detected (TLC) which was in accordance with those reported under Mitsunobu conditions.[12] Adjusting the reaction conditions by increasing the amount of the reagents, changing the base or solvents, or increasing the reaction temperature did not lead to any detectable anhydride. We attempted to isolate the product from the reaction of 4-nitrobenzoic acid with polymer-bound Ph_3P-I_2 and Et_3N; however we were also unable to obtain any anhydride product following the work-up procedures described in a reported literature.[15] Thus, it is plausible that the corresponding acyloxyphosphonium salt necessary for anhydride formation was not formed or rapidly decomposed to another less reactive intermediate.

To our surprise, it was found that when the standard reaction conditions were applied for a longer period of time, *N*,*N*-diethyl-4-nitrobenzamide was observed after a few hours and significant amounts of the amide could be isolated after 16 h (Table 3, entry 1). Similar results were also obtained when the experiment was repeated with other nitro-substituted aryl acids. As shown in Table 3, all of the test substrates could be converted into the corresponding amide products to different extents at various rates (the yields were un-optimized). Notably, the respective amide from 2-chloro-5-nitrobenzoic acid was produced in high yield within 3 h. Since there was no other source of diethylamine except from triethylamine, it is possible that the *N*,*N*-diethylamides could be derived from amidation of the acids with Et_3N *via* a highly reactive intermediate(s) where both coupling partners are activated toward C-N bond formation.

Table 3. Unexpected formation of *N*,*N*-diethylamides **3** from nitro-substituted aryl acids[a]



entry	R	pK_a of **1**[14]	yield of **3** (%)
1	$4\text{-}NO_2C_6H_4$	3.44	63
2	$3\text{-}NO_2C_6H_4$	3.46	45
3	$3,5\text{-}(NO_2)_2C_6H_3$	2.82	52
4	$2\text{-}NO_2C_6H_4$	2.17	50
5	$2\text{-}Cl\text{-}5\text{-}NO_2C_6H_3$	2.17	75

[a] Reaction conditions: carboxylic acid (0.41 mmol), Ph_3P (0.62 mmol), I_2 (0.62 mmol), Et_3N (1.23 mmol), CH_2Cl_2 (2 mL), 0 °C - RT, 3-16 h.

To determine whether amide formation was correlated to the pK_a of the acids, control experiments were carried out using 3-chlorobenzoic acid and benzoic acid as substrates. It was found that, after 16 h reaction, the reaction of 3-chlorobenzoic acid produced the respective amide in a trace amount, whereas the product from the reaction of benzoic acid was not observed. This data indicated that amide formation is possible when the formed intermediate is sufficiently reactive due to possessing an electron withdrawing group.

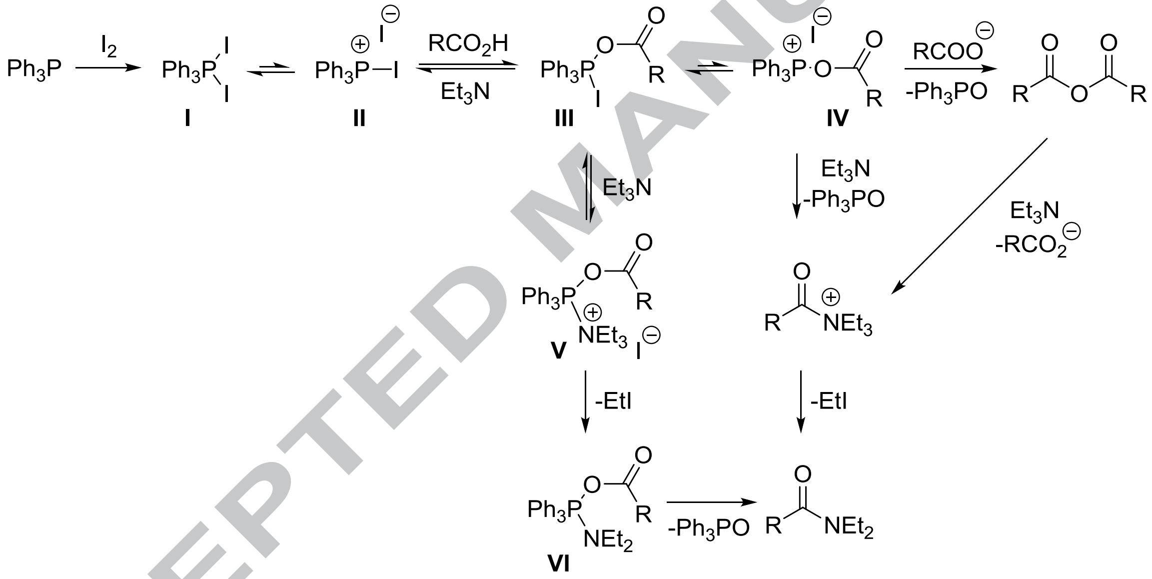
Although the direct amidation of carboxylic acids with tertiary amines has been previously reported, the reaction required metal catalysis and proceeded under more vigorous conditions.[16] Thus, our system is the first reported formation of *N*,*N*-substituted amides from carboxylic acids using tertiary amine nucleophile under metal-free and mild conditions.

It should be noted that since pK_a measures equilibrium in aqueous media, it can only be used for a rough estimation regarding the acidity of the carboxylic acids and may not ideally represent their reactivity. Some observed deviation from the trend could result from solvation effects which significantly affects nucleophilicity and the leaving group ability of the formed carboxylate ions. Nevertheless, based on the results observed in Tables 2 and 3, some correlation could be made between the pK_a values of the acids and their ability to form anhydrides or amides. Most of the aryl acids weaker than 4-nitrobenzoic acid generally produce the corresponding anhydrides rapidly, whereas stronger acids could give rise to the *N*,*N*-diethylamides. Both reactions are expected to take place in competition with the acylation reaction involving weak nucleophiles when Et_3N is applied as base. However, competing amidation with the weakly nucleophilic base would be less likely in the presence of other commonly used nucleophiles. Thus, the acylation reaction of acidic substrates is most likely to give significantly improved yields in comparison with those using other less acidic derivatives where the competitive anhydride side reaction would be predominant.

Based on our previous experience and the presented results, a mechanism for the Ph_3P-I_2 mediated reaction toward anhydrides and formation of the unexpected amides was proposed (Scheme 1). Addition of iodine to Ph_3P results in formation of a pentavalent triphenylphosphinediiodide **I** and triphenylphosphonium iodide **II**. Subsequent treatment with the carboxylic acid and Et_3N, produces a pentacoordinate intermediate **III** which is in equilibrium with acyloxyphosphonium **IV**.[17] With weak acid substrates, the formed carboxylate anions are more nucleophilic, and thus could undergo rapid acyl substitution with **IV** to yield the anhydride product. However, with strong aryl acids containing an electron withdrawing group, their corresponding carboxylates are weak nucleophiles. It is highly likely that, once **IV** is produced, the highly electrophilic carbonyl groups of **IV** could undergo nucleophilic substitution with triethylamine with the thermodynamically favourable release of triphenylphosphine oxide leading to the respective amide upon removal of ethyl iodide.

The possibility for acyl substitution of the reactive anhydride with Et_3N could also be envisaged.

It is also possible that **III** could undergo iodide substitution with triethylamine leading to intermediate **V**. Upon de-ethylation, the pentacoordinate phosphorane **VI** is generated. A Berry pseudorotation of the groups around the phosphorus center of **VI** then bring the diethylamino and acyl groups in close proximity.[18] Subsequent intramolecular substitution at the acyl functional group could produce the tertiary amide with the release of triphenylphosphine oxide as a strong driving force. To confirm the proposed mechanism, ^{31}P and ^{13}C NMR studies of the formed intermediates need to be carried out which will be the subject of future work.



Scheme 1. Proposed mechanism for the Ph_3P-I_2 mediated anhydride and amide bond formation.

In summary, we report a systematic study toward anhydride formation using phosphorous-mediated carboxylic acid activation. It was found that the reaction was highly dependent on the electronic nature of the carboxylic acid substrates as reflected by their pK_a values. With the Ph_3P-I_2/Et_3N system, most aromatic acids, except for the more acidic nitro-substituted derivatives, could give rise to anhydrides in high yields within short reaction times, indicating that competitive anhydride formation could be problematic in acylation reactions involving weak nucleophiles. In such cases, anhydride formation could potentially be avoided or minimized if the base is added after introducing the nucleophile.[17a] The unprecedented finding regarding with the unexpected formation of amides may also lead to new interesting organic syntheses using inexpensive, stable, and easy to handle tertiary amines as nucleophiles. Further studies on this amidation reaction are being pursued and will be reported in due course.

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Supplementary Material

General experimental method, spectroscopic data for all the compounds, and ^{1}H and ^{13}C NMR spectra of representative products.

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Graphical Abstract

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