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SHORT COMMUNICATION

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Acyloxyphosphonium versus Aminophosphonium Intermediates: Application to the Synthesis of *N*-Acylbenzotriazoles

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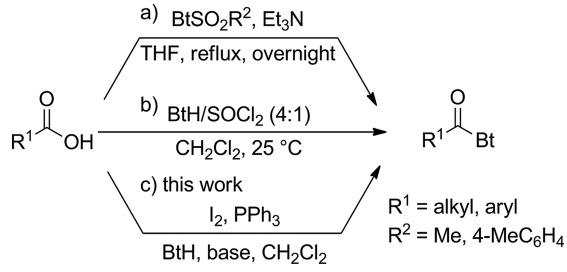
Keywords: Synthetic methods / Carboxylic acids / Triphenylphosphine / Iodine / Reactive intermediates

In attempts to convert carboxylic acids directly into *N*-acylbenzotriazoles by using Ph_3P/I_2 as an acid-activating system, the outcome of the reaction is reversed from no reaction to almost quantitative yield of the expected product simply by switching the order of the addition of the reagents to the presumed acyloxyphosphonium intermediate. If triethylamine was present before treatment with 1*H*-benzotriazole, anhydride was always exclusively generated without a detectable amount of the expected product. However, if the base was applied after the addition of 1*H*-benzotriazole, the reaction proceeded smoothly to afford *N*-acylbenzotriazoles in good to excellent yields within short reaction times. ^{31}P NMR spectroscopy revealed the presence of a benzotriazophosphonium species in preventing the formation of the anhydride by attack of the carboxylate anion at the acyl function of the acyloxyphosphonium salt.

Introduction

N-Acylbenzotriazoles are versatile and efficient neutral acylating agents that have been used as substitutes for the corresponding acid chlorides in *N*-, *C*-, *S*-, and *O*-acylation reactions.[1] The classical method for their preparation involves treating 1*H*-benzotriazole (BtH) with acid chlorides. In this case, the requisite acid chlorides have to be prepared in one step prior to reacting with BtH. Alternatively, *N*-acylbenzotriazoles can be synthesized directly from carboxylic acids by reacting an acid salt with sulfonylbenzotriazole derivatives[2] (Scheme 1, a) or through in situ generation of the acid chloride with thionyl chloride before treatment with an excess amount of BtH (Scheme 1, b).[3] Although the *N*-acylbenzotriazoles are generally obtained in good yields, the reactions still suffer from some limitations, including the use of corrosive or expensive reagents, long reaction times, and the requirement for high temperatures.

Triphenylphosphine (Ph_3P) is a very attractive reagent possessing widespread applications in organic synthesis.[4] Owing to a strong affinity toward oxygen, PPh_3 has been used along with a number of additives such as *N*-bromosuccinimide,[5] hypervalent iodine(III) reagents,[6] $I_2/Zn(OTf)_2$ (Tf = trifluoromethylsulfonyl),[7] and diethyl azodicarboxylate[8] (Mitsunobu reaction) in promoting the direct conversion of carboxylic acids into amides, esters, and thioesters, presumably through formation of highly reactive acylphosphonium intermediates.



Scheme 1. Synthesis of *N*-acyloxybenzotriazoles.

Recently, a combination of Ph_3P and I_2 was introduced as a new acid-activating system in the synthesis of amides and Weinreb amides.[9] The reaction is believed to proceed through an acyloxyphosphonium intermediate that is generated upon mixing a carboxylic acid with Ph_3P and I_2 in the presence of iPr_2NEt. This method is very promising, as the reagents are inexpensive, readily available, and easy to handle. Thus, in searching for an alternative route toward *N*-acylbenzotriazoles, it seems feasible that similar conditions could be adopted to promote the direct conversion of carboxylic acids into their benzotriazole derivatives (Scheme 1, c).

Results and Discussion

The amidation between benzoic acid and BtH mediated by the Ph_3P/I_2 system was investigated under the reported conditions by using Et_3N as the base.[9] Typically, benzoic acid was added to a solution containing a 1:1 molar ratio

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of Ph_3P/I_2 in CH_2Cl_2 at 0 °C. The mixture was allowed to stir for 5 min at the same temperature before the dropwise addition of Et_3N (2 equiv.), which was followed by the addition of BtH (1.1 equiv.). Unfortunately, it was found that within 5 min of stirring at room temperature, benzoic acid was completely consumed and benzoic anhydride was isolated in 98% yield without any detectable amount of the expected *N*-benzoylbenzotriazole product. A similar result was also obtained upon replacing Et_3N with iPr_2NEt. Several attempts to adjust the reaction times before or after adding BtH or changing the molar ratio of Ph_3P/I_2/benzoic acid from 1:1:1 to 2:2:1 also failed to give satisfactory results.

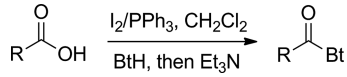
Given that benzoic anhydride was always exclusively obtained following the above-described procedure, we turned our attention to examine the effect of the addition sequence of the reagents on the reaction outcome. To our delight, it was found that if BtH was added 10 min before treatment with Et_3N, the expected *N*-benzoylbenzotriazole product was afforded in 81% yield after 30 min without the formation of benzoic anhydride. The best result (95% yield) was achieved with a prolonged acid-activation step for 30 min prior to adding BtH.

To demonstrate the efficiency and versatility of the revised protocol, a series of *N*-acylbenzotriazoles were synthesized from aromatic and aliphatic carboxylic acids. According to Table 1, the reactions with aromatic acids, especially those containing electron-donating groups (Table 1, entries 2–7) generally proceeded smoothly to give the expected *N*-acylbenzotriazoles in good to excellent yields. Only in the case of 2-methoxybenzoic acid (Table 1, entry 5) was a slightly lower yield of the corresponding product observed, probably as a result of steric hindrance from the OMe group. Whereas halogen substituents (Cl) on the aromatic ring of benzoic acid had little effect on the yield of the reaction (Table 1, entries 8–10), a strong electron-withdrawing substituent (NO_2), however, significantly decreased the product yield even with extended reaction times (Table 1, entries 11 and 12). The reaction with relatively steric 2-naphthoic acid (Table 1, entry 13) also gave the desired product in moderate yield.

Aliphatic acids were found to be less effective than aromatic acids. Under the standard reaction conditions, the yields of the benzotriazole derivatives of 5-phenylvaleric acid and hexanoic acid were only 37 and 51%, respectively (Table 1, entries 14 and 16). With prolonged reaction times, 5-phenylvaleric acid, hexanoic acid, and octanoic acid (Table 1, entries 15, 17, and 18) gave the corresponding *N*-acylbenzotriazoles in high yields. On the basis of these results, it is possible that π–π stacking interactions between the benzene ring of the aromatic acids and those of the phosphine intermediate may be responsible for the rate enhancement observed with the aromatic carboxylic acids.

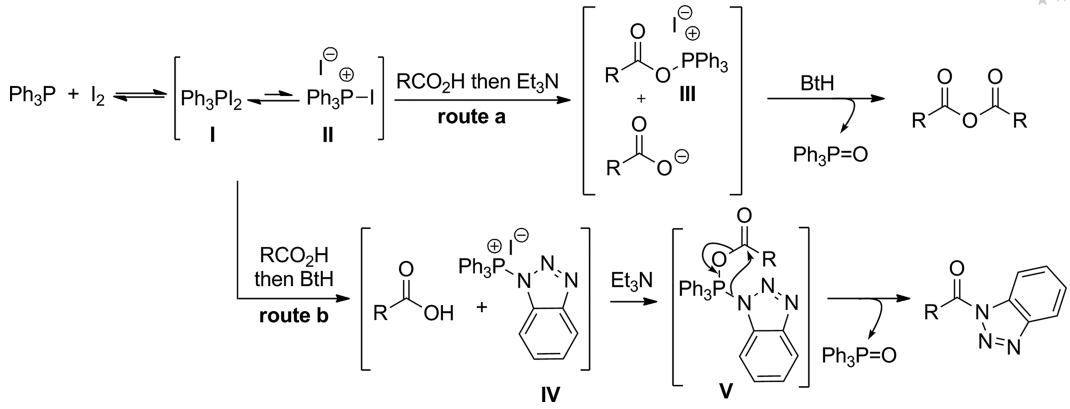
To gain mechanistic insight into the reaction, a $^{31}P\{H\}$ NMR spectroscopy experiment was performed to monitor the phosphorus-containing intermediates in the ongoing reaction between benzoic acid and BtH. Upon adding I_2 to a solution of Ph_3P in $CDCl_3$, the color of the solution turned light yellow and then changed to brown after a few seconds. According to the $^{31}P\{H\}$ NMR spectra (Figure 1, a, b), upon the addition of I_2, a slight shift in the free phosphine signal from δ = –5.31 ppm to –5.83 ppm was observed with the appearance of two new resonances. The upfield shift of the signal to δ = –17.07 ppm suggested the formation of a pentacoordinate phosphorus species between Ph_3P and I_2,[9,15] whereas the downfield shift to δ = 45.98 ppm was indicative of the presence of triphenylphosphonium iodide.[16,17] Subsequent addition of benzoic acid to the Ph_3P/I_2 mixture resulted in slight shifts of all signals, which could be accounted for by certain interactions between the acid and the phosphorus species (Figure 1, c). After the addition of BtH, the color of the reaction mixture changed from dark brown to light yellow, and a yellowish precipitate formed. The $^{31}P\{H\}$ NMR spectrum of the solution (Figure 1, d) showed a downfield shift of the signal at δ = –17.64 ppm to –14.64 ppm with the appearance of a new signal at δ = 36.13 ppm, which is characteristic of compounds with a P–N bond.[17–19] This result strongly indicated that the equilibrium was shifted toward the formation of a benzotriazophosphonium species. The reaction mixture turned to a clear colorless solution immediately after the addition of Et_3N. The $^{31}P\{H\}$ NMR spectrum of the mixture after about 20 min in the presence of base (Figure 1, e) showed the appearance of an exclusive signal at δ = 29.28 ppm, which was attributed to the release of the $Ph_3P{=}O$[17] byproduct upon complete conversion of benzoic acid into *N*-benzoylbenzotriazole.

Table 1. Synthesis of *N*-acylbenzotriazole promoted by Ph_3P/I_2.[a]



Entry	R	Time [h][b]	Yield [%]
1	C_6H_5	0.5	95[2a]
2	2-$CH_3C_6H_4$	0.5	92[10]
3	3-$CH_3C_6H_4$	0.5	97[1f]
4	4-$CH_3C_6H_4$	0.5	85[2a]
5	2-$CH_3OC_6H_4$	0.5	77[2b]
6	4-$CH_3OC_6H_4$	0.5	93[11]
7	3,4-$(CH_3O)_2C_6H_3$	0.5	99[12]
8	2-ClC_6H_4	0.5	86[1g]
9	3-ClC_6H_4	0.5	91[2b]
10	4-ClC_6H_4	0.5	84[2b]
11	3-$O_2NC_6H_4$	1	70[1n]
12	4-$O_2NC_6H_4$	1	36[2b]
13	2-naphthyl	0.5	77[1o]
14	5-phenylvaleryl	0.5	37
15	5-phenylvaleryl	1	86
16	hexanoyl	0.5	51
17	hexanoyl	1	97[13]
18	octanoyl	1	99[14]

[a] Unless otherwise specified, the reactions were performed by adding the carboxylic acid (0.41 mmol) to a mixture containing I_2 (0.45 mmol) and Ph_3P (0.45 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min before adding BtH (0.45 mmol), and the mixture was stirred for another 10 min. After adding Et_3N (0.82 mmol), the mixture was stirred at room temperature for the specified time. [b] Time after the addition of Et_3N.



Scheme 2. Proposed mechanism for the reaction mediated by the Ph_3P/I_2 system if Et_3N is added before (route a) or after the addition of BtH (route b).

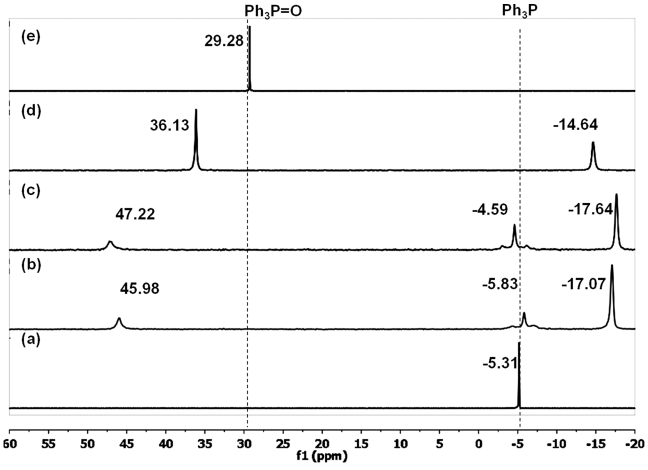


Figure 1. $^{31}P\{H\}$ NMR monitoring of the progress of the reaction between benzoic acid and BtH in $CDCl_3$: (a) Ph_3P, (b) the solution after the addition of I_2, (c) the reaction after the addition of benzoic acid, (d) the reaction after 10 min past the addition of BtH, and (e) the reaction after the addition of Et_3N.

On the basis of these results, mechanistic details for the reactions following the different addition sequence of the reagents were proposed (Scheme 2). Upon mixing Ph_3P with I_2, pentacoordinate phosphorus species **I** is predominantly formed, and a small amount of phosphonium iodide **II** is generated. Treatment with a carboxylic acid leads to slow formation of acyloxyphosphonium salt **III**. However, in the presence of Et_3N (Scheme 2, route a), the equilibrium is rapidly shifted toward intermediate **III**, which undergoes rapid nucleophilic displacement with the carboxylate anion to give the anhydride side product. As a result, upon addition of BtH, no further reaction proceeds because of the insufficient reactivity of the anhydride under the applied conditions.

Upon treating the reaction mixture with BtH in the absence of base (Scheme 2, route b), tetracoordinate benzotriazophosphonium species **IV** is predominantly formed, because BtH is a stronger nucleophile than carboxylic acid. Upon the addition of the amine base, the carboxylic acid is rapidly deprotonated and undergoes condensation with **IV** presumably through attack of the carboxylate ion at the phosphorus center of **IV** to form pentacoordinate species **V**.[20] Intramolecular acyl substitution then gives the *N*-acylbenzotriazole with concomitant loss of $Ph_3P=O$.

It is important to note that anhydride formation has already been encountered in several reactions involving the acyloxyphosphonium salt owing to competitive acyl substitution with a highly nucleophilic carboxylate anion.[8,9,15] Nevertheless, its formation was somehow under-emphasized and no further attempts were made to circumvent this undesired side reaction. By using our developed protocol, the formation of anhydride is avoided, and aminophosphonium species **IV** is highly reactive and acts as a dual activating agent for the nucleophilic acyl substitution of carboxylic acids to provide the *N*-acylbenzotriazoles in high yields.

Conclusions

In summary, the significance of the addition sequence of the reagents in the reaction involving an acyloxyphosphonium intermediate was demonstrated. By simple alteration of the addition order of the amine base and BtH, carboxylic acids can be readily converted into *N*-acylbenzotriazoles in high yields in short reaction times without the formation of the anhydride by product. In the absence of base, the presence of benzotriazophosphonium salt **IV** clearly indicates that nucleophilic attack by nitrogen at the phosphorus center of the phosphonium salts was more favorable, which allows for more controlled activation of the acid through the pentacoordinate species **V**. This strategy could be potentially useful in enhancing the outcomes of various reactions involving carboxylic acids and related functionalities. Studies toward this direction are in progress and will be reported in due course.

Supporting Information (see footnote on the first page of this article): Experimental details, including complete experimental procedures and copies of the ^1H NMR and ^{13}C NMR spectra of all described compounds.

Acknowledgments

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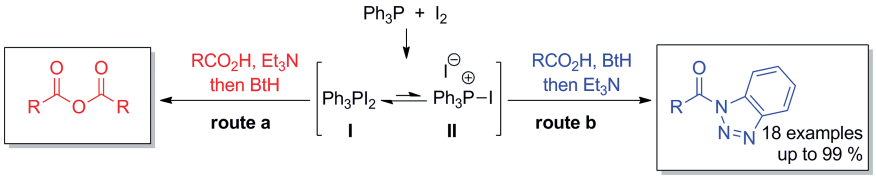
Carboxylic Acid Conversion



In synthesizing *N*-acylbenzotriazoles by using Ph_3P/I_2 as an acid activator, anhydride is exclusively generated upon adding Et_3N to the presumed acyloxyphosphonium intermediate before treatment with 1*H*-benzotriazole (BtH). In the absence of base, benzotriazophosphonium iodide is predominantly formed, which rapidly reacts with carboxylate ions to afford *N*-acylbenzotriazoles in good to excellent yields.

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Acyloxyphosphonium versus Aminophosphonium Intermediates: Application to the Synthesis of *N*-Acylbenzotriazoles

Keywords: Synthetic methods / Carboxylic acids / Triphenylphosphine / Iodine / Reactive intermediates

