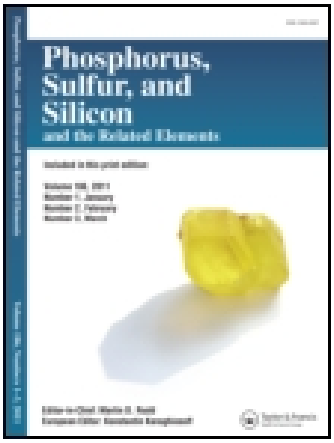

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Bu_4NI-Catalyzed Synthesis of Pyrophosphate Esters from H-Phosphonates

Juan Huang [a] , Wen He [a] & Bin Wang [a]
[a] College of Pharmacy, State Key Laboratory of Medicinal Chemical Biology and Tianjin Key Laboratory of Molecular Drug Research, Nankai University , Tianjin , China
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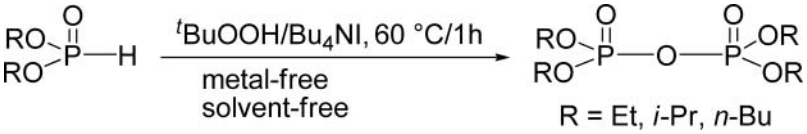
Juan Huang, Wen He, and Bin Wang
College of Pharmacy, State Key Laboratory of Medicinal Chemical Biology and Tianjin Key Laboratory of Molecular Drug Research, Nankai University, Tianjin, China

GRAPHICAL ABSTRACT



Abstract *A n-Bu_4NI/t-BuOOH catalysis system has been developed to promote oxidative dehydrogenative coupling of H-phosphonates to form pyrophosphate tetraesters. This novel iodide (I^-) ion-catalyzed reaction provides easy access to pyrophosphate derivatives in the absence of a metal and solvent.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords Iodide; H-phosphonate; pyrophosphate; tetra-n-butylammonium iodide; *tert*-butyl hydroperoxide

INTRODUCTION

Pyrophosphate linkages are found in many biologically active molecules including adenosine diphosphate (ADP), isopentenyl pyrophosphate (IPP),[1] the substrates and inhibitors of glycosyltransferases,[2,3] as well as food additives, such as sodium pyrophosphate (E450)[4] (Figure 1). The traditional chemical approaches for pyrophosphates synthesis suffer from several problems, such as the need for preactivation of monophosphate partners, low yields, tedious procedures, and incompatibility with some functional groups.[3,5–8]

Recently, Han and coworkers[9] have developed a novel copper-catalyzed preparation of pyrophosphates with H-phosphonates using amine as ligand. From the sustainable chemistry point of view, the metal- and ligand-free process is desirable. The catalytic utilization of hypervalent iodine compounds has received considerable attention due to their

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Address correspondence to Bin Wang, 94 Weijin Road, College of Pharmacy, Nankai University, Tianjin 300071, China. E-mail: wangbin@nankai.edu.cn

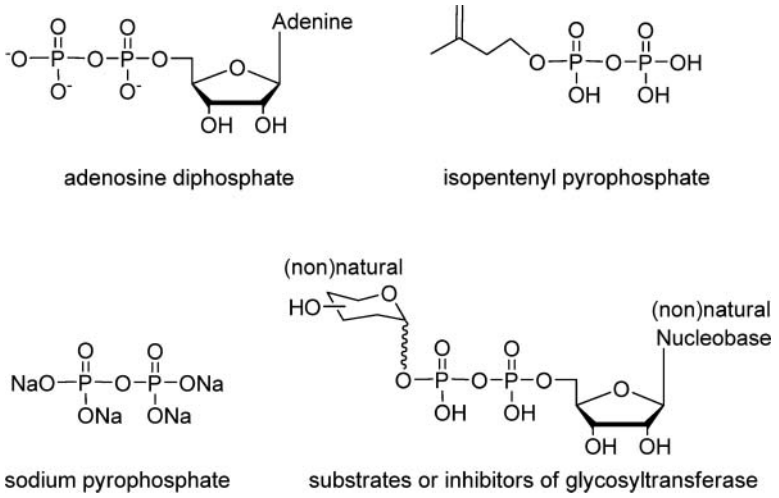


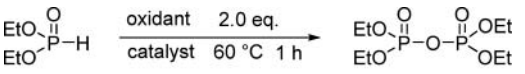
Figure 1 Examples of biologically active molecules that contain pyrophosphate linkage.

mild, safe, and environmentally benign characteristics in organic synthesis.[10–13] They are ideal alternatives to expensive transition metal catalysts and toxic heavy-metal-based oxidants in many organic transformations.[14–20] More recently, a novel tetraalkylammoniumiodide/peroxide oxidants catalysis system has been developed for the C–H functionalization reactions.[21–28] It is proposed that in situ generated hypoiodite ($[IO]^-$) and iodite ($[IO_2]^-$) display higher catalytic activities than the corresponding aryl λ^3-iodanes or λ^5-iodanes and the byproduct iodoarene is completely avoided.[23,25,27] To our knowledge, the iodide (I^-) ion catalyzed P–H bond functionalization reaction is unknown. Herein, we report the first tetra-n-butylammonium iodide (Bu_4NI) catalyzed oxidative dehydrogenative coupling reaction of P–H bonds. This metal-free, solvent-free, and facile process is a useful complementary method for the synthesis of pyrophosphates.

RESULTS AND DISCUSSION

Our initial studies focused on the diethyl H-phosphonate **1a** as the substrate for the transformation and various peroxide oxidants were investigated (Table 1, entries 1–5). We were pleased to find that use of 0.2 equiv of Bu_4NI and 2 equiv of *tert*-butyl hydroperoxide (TBHP, 70% aqueous solution) could provide tetraethylpyrophosphate **2a** in 80% yield (Table 1, entry 1). When similar peroxide oxidants were employed instead of TBHP, the reaction took place to afford tetraethylpyrophosphate **2a** in low yields (Table 1, entries 2–4). Only trace product **2a** was obtained by use of H_2O_2 (Table 1, entry 5). Other potential catalysts related to Bu_4NI were also examined (Table 1, entries 6–11). Me_4NI, Bu_4NBr, Bu_4NCl, KI, and I_2 proved ineffective for this reaction (Table 1, entries 6–10). The use of $BnMe_3NI$ instead of Bu_4NI gives the product **2a** in 15% isolated yield under the conditions same as entry 1 (Table 1, entry 11). The reaction of **1a** in the absence of any catalyst did not occur at all (Table 1, entry 12). When the solvent of TBHP was switched from water to decane, the efficiency of the reaction dramatically decreased, affording the product **2a** in only 25% yield (Table 1, entry 13). Reactions conducted at 25 °C or 40 °C gave lower yields than those conducted at 60 °C (Table 1, entry 14, 15). Further optimization revealed

Table 1 Screening of catalyst and peroxide oxidant[a]



1a **2a**

Entry	Catalyst	Oxidant	Yield (%)	Entry	Catalyst	Oxidant	Yield (%)
1	Bu_4NI	TBHP	80	9	KI	TBHP	0
2	Bu_4NI	TBPB	48	10	I_2	TBHP	0
3	Bu_4NI	DTBP	18	11	$BnMe_3NI$	TBHP	15
4	Bu_4NI	CHP	5	12	–	TBHP	0
5	Bu_4NI	H_2O_2	Trace	13[b]	Bu_4NI	TBHP	25
6	Me_4NI	TBHP	0	14[c]	Bu_4NI	TBHP	48
7	Bu_4NBr	TBHP	0	15[d]	Bu_4NI	TBHP	29
8	Bu_4NCl	TBHP	0	16[e]	Bu_4NI	TBHP	80

[a]Unless otherwise noted, the reaction conditions were as follows: **1a** (0.2 mmol, 1 equiv), catalyst (0.04 mmol, 0.2 equiv), oxidant (0.4 mmol, 2 equiv), 60 °C, 1 h, without a solvent. TBHP = *tert*-butyl hydroperoxide (entry 1, 6–12, 14–16, 70% solution in water), H_2O_2 (30% solution in water), TBPB = *tert*-butyl peroxybenzoate, DTBP = di-*tert*-butyl peroxide, CHP = cumyl hydroperoxide; isolated yield.

[b]TBHP (0.5–0.6 M, in decane).

[c]40 °C, 4 h.

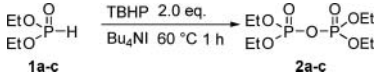
[d]25 °C, 24 h.

[e]Bu_4NI (0.01 mmol, 0.05 equiv).

that 5 mol% of Bu_4NI was required to achieve full conversion of **1a** and the highest yield (80%) is obtained (Table 1, entry 16). Under the optimized conditions described in entry 16 of Table 1, ethyl, isopropyl, and n-butyl H-phosphonates were compatible substrates in this transformation (Table 2, entries 1–3). Moreover, these reactions are facile, good yielding, and easy to work up without requiring chromatography. Although the desired products of other commercially available substrates could be detected by ^{31}P NMR, unfortunately all attempts to separate them from byproducts failed. Silica gel column chromatography and reduced pressure distillation can completely decompose the desired products. It should be noted that no competitive P–P bond coupling reaction such as the formation of hypophosphate was observed in these transformations.

Some control experiments were carried out to investigate the reaction mechanism. When a radical inhibitor, 2,2,6,6-tetramethylpiperidine-N-oxy l (TEMPO) was used under the optimized conditions, the reaction of **1a** gave pyrophosphate **2a** in 60% yield. This result excluded the possibility of radical process under the present reaction conditions. As shown in Table 1 entry 10 and Table 3 entry 1, neither catalytic amounts nor stoichiometric amounts of the iodine (I_2) can promote this reaction. We also examined polyvalent iodine (I, III, and V) oxidants in this transformation in the absence of a catalyst. As shown in Table 3, the reaction of **1a** offered pyrophosphate **2a** in moderate NMR yields by the use of IOAc, $PhI(OAc)_2$, or IBX as oxidant. We speculate that the in situ generated hypoiodite ($[IO]^-$) and iodite ($[IO_2]^-$) may be the catalytic species in this transformation.[29] To investigate the possible intermediates, the reaction was monitored by ^{31}P NMR spectroscopy. After 15 min, the diethyl phosphate **3** was detected by comparison with the standard sample (^{31}P NMR, δ 0.19). Obviously, the diethyl H-phosphonate was oxidized to diethyl phosphate by TBHP.[30–32] Notably, trace amounts of diethyl phosphoroiodidate **4** were identified

Table 2 Scope of substituted H-phosphonates[a]



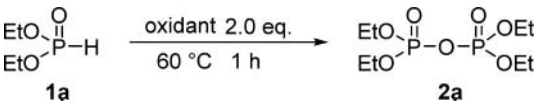
Entry	R (**2**)	Yield (%)	^{31}P NMR (ppm)	^{1}H NMR ($CDCl_3$)[b], δ, J (Hz)	^{1}H NMR ($CDCl_3$)[c], δ, J (Hz)	^{13}C NMR ($CDCl_3$)[b], δ	^{13}C NMR ($CDCl_3$)[c], δ
1	Et (**2a**)	80	−13.1	4.28–4.24 (m, 8H, CH_2) 1.38 (t, 12H, $J = 7.2$, CH_3)	4.25–4.17 (m, 8H, CH_2) 1.34 (t, 12H, $J = 7.0$, CH_3)	65.2, 16.0	65.1, 15.9
2	*i*-Pr (**2b**)	78	−15.2	5.22–4.81 (m, 4H, CH) 1.39 (d, 24H, $J = 6.0$, CH_3)	4.84–4.70 (m, 4H, CH) 1.38 (d, 24H, $J = 6.0$, CH_3)	73.4, 22.7	74.1, 23.5
3	*n*-Bu (**2c**)	84	−12.7	4.21–4.16 (m, 8H, CH_2) 1.72–1.66 (m, 8H, CH_2) 1.45–1.40 (m, 8H, CH_2) 0.94 (t, 12H, $J = 7.6$, CH_3)	4.19–4.15 (m, 8H, CH_2) 1.72–1.66 (m, 8H, CH_2) 1.45–1.38 (m, 8H, CH_2) 0.94 (t, 12H, $J = 7.3$ Hz, CH_3)	68.8, 32.1 18.5, 13.5	Not recorded

[a]The reaction conditions were as follows: **1a–c** (0.2 mmol, 1 equiv), Bu_4NI (0.01 mmol, 0.05 equiv), TBHP (0.4 mmol, 2 equiv, 70% solution in water), 60 °C, 1 h, without a solvent, yield of isolated product.

[b]The data of our experiment.

[c]The data of the Ref. 9.

Table 3 Iodine-mediated reaction of diethyl H-Phosphonate **1a**



1a **2a**

Entry	Oxidant	^{31}P NMR yield (%)
1	I_2	0
2	IOAc	64
3	$PhI(OAc)_2$	65
4	IBX	56

(^{31}P NMR, δ −41.1) (Figure 2). Some phosphorylation processes involving in situ generated iodophosphates have been reported.[33] The iodophophate shows a higher reactivity than that of chloro- and bromophosphate and can be consumed immediately in the presence of nucleophiles.[33–35] Based on these results, a possible mechanism was proposed as shown in Figure 3. The iodide ion (I^-) is oxidized into active hypoiodite ($[IO]^-$) and iodite ($[IO_2]^-$) species by TBHP. The reaction of diethyl H-phosphonate **1a** with the active species offered intermediates diethyl phosphoroiodidate **4** and **5**. A portion of diethyl H-phosphonate

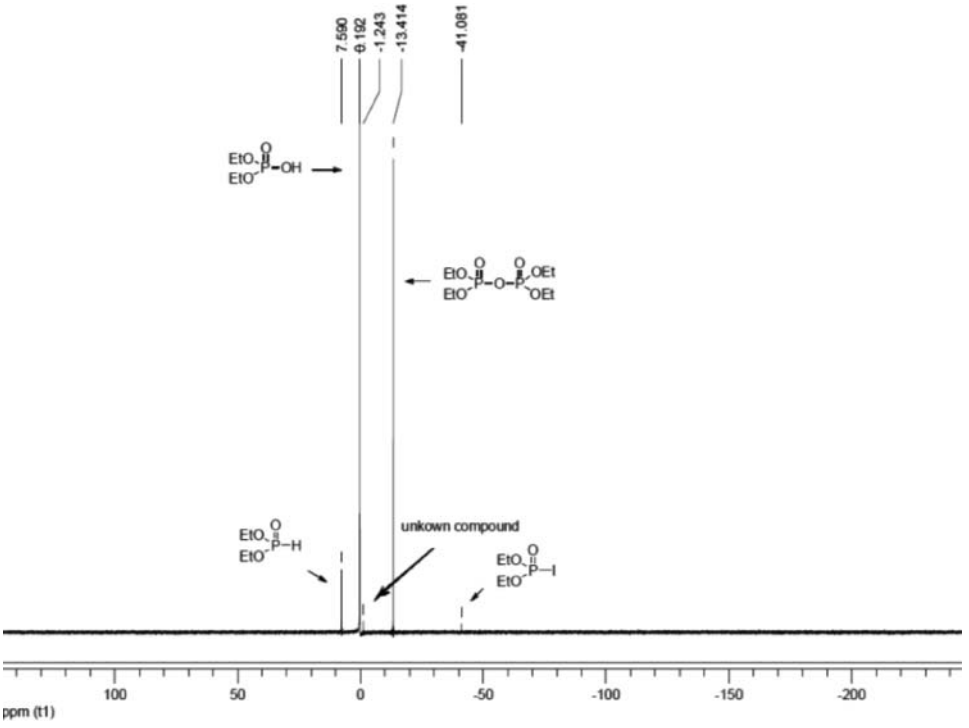


Figure 2 ^{31}P NMR spectra of reaction mixture after 15 min.

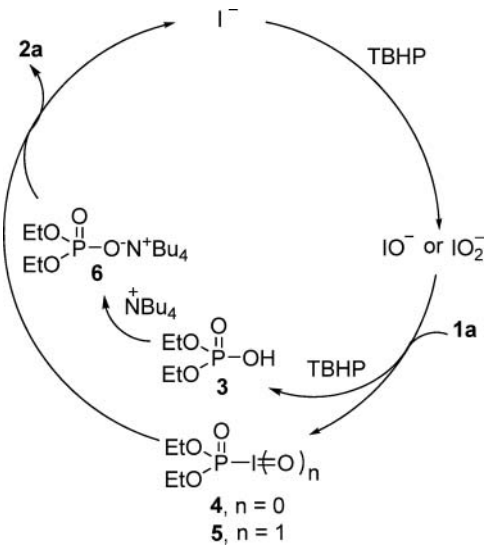


Figure 3 A possible pathway for the synthesis of pyrophosphate **2a**.

1a was oxidized to diethyl phosphate **3** by TBHP and further transformed into ammonium **6**. The final pyrophosphate product **2a** was obtained through a nucleophilic attack of ammonium **6** to diethyl phosphoroiodidate **4** or **5**.

CONCLUSIONS

In summary, we have developed a mild reaction for construction of pyrophosphate esters based on the Bu_4NI/TBHP catalyzed dehydrogenative coupling of H-phosphonates. This metal- and solvent-free reaction constitutes a simple and economical protocol for the synthesis of pyrophosphate esters. Further studies of the detailed mechanism of this process are currently underway.

EXPERIMENTAL

^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded on a Bruker AV 400 spectrometer (400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR, and 162 MHz for ^{31}P NMR spectroscopy). $CDCl_3$ was used as the solvent and 85% H_3PO_4 was used as an external standard for ^{31}P NMR measurement. Chemical shifts were reported in parts per million downfield from tetramethylsilane (TMS) as the internal standard and coupling constants in hertz (Hz). Data were reported as follows: chemical shift, multiplicity (d = doublet, t = triplet, m = multiplet, q = quartet), coupling constant, and integration.

A General Procedure for Synthesis of Pyrophosphate Esters 2a–c

To 20 mL tube were added Bu_4NI (0.1 mmol, 36.9 mg), H-phosphonates (2 mmol), and TBHP (4 mmol, 500 μL) under air, and then the tube was sealed. The reaction mixture was stirred at 60 °C for 1 h. The resulting mixture was extracted with $CHCl_3$ (8 mL), dried

over $MgSO_4$, and filtered. The organic phase was concentrated under vacuum to give NMR spectroscopically pure products.[9]

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