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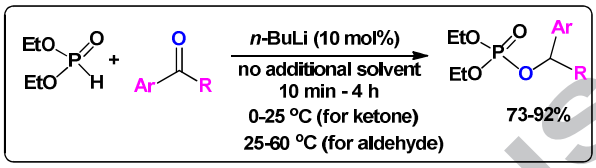

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n-BuLi-Triggered Phospha-Brook Rearrangement: Efficient Synthesis of Organophosphates from Ketones and Aldehydes

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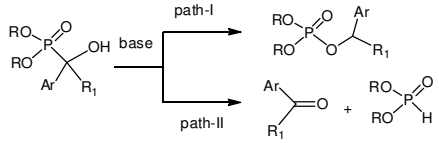
ABSTRACT

A variety of organophosphates are synthesized from *n*-BuLi-triggered, (additional) solvent–free reactions of diethyl phosphite with both activated/unactivated ketones and aldehydes preferably at room temperature *via* phospha-Brook rearrangement. We could successfully synthesize the naphthylic/allylic phosphates using this approach.

The chemistry of organophosphates has been extensively studied because they play significant roles in many major physiological processes such as energy transfer, photosynthesis etc.[1] The phosphates were also successfully used in versatile organic synthesis[2] including Cu/Pd-catalyzed cross-coupling reactions to access di/triarylmethanes.[2b-d] Specifically, the benzylic and allylic phosphates were employed for the conversion of alcohol to azide *via* phosphate activation.[2e] These phosphates were also shown to exhibit the anomalous behaviour to produce allyl or benzyl iodides by the treatment of iodotrimethylsilane.[2f] Therefore, the synthesis of organophosphates has shown a significant topic of interest. The main conventional procedure for the synthesis of phosphates includes the phosphorylation of alcohols with highly air sensitive and hazardous phosphorus halides in the presence of a base.[3] Recently, an efficient synthesis was reported by iodine catalyzed phosphorylation of alcohols in the presence of H_2O_2.[4] The organophosphates were also obtained as a minor/major product from the base mediated synthesis of α-hydroxyphosphonates[5a-b] and α-aminophosphonates[5c-d] starting from aldehydes or few selective ketones *via* phosphorylation rearrangement (phospha-Brook) (path I, Scheme 1). It is also relevant to mention that α-hydroxyphosphonates can also undergo base catalyzed retro-hydrophosphonylation reactions as shown in path-II (Scheme 1).[5] These transformations depend upon the substrates, bases and the reaction conditions employed for a particular reaction.[5-6] This phospha-Brook rearrangement is subjected to vary with the type of aldehydes or ketones and also the bases.[6] The several bases like NEt_3,[5a-b] NaH,[5b] *n*-butylamine,[5c-d] K_2CO_3/KOH (for phosphinate addition to ketones),[5e] cinchona alkaloid/Na_2CO_3 (for asymmetric synthesis of phosphates),[5f] NaOEt[5g] and ^{t}BuOK[5h] were used for phospha-Brook rearrangement reactions to afford organophosphates along with hydroxyphosphonates.



Scheme 1 Transformations of α-hydroxyphosphonates in the presence of base

Most of these routes suffer from several drawbacks like the requirement of stoichiometric amount of bases, higher temperature and the presence of unsafe solvents etc. It has been observed that the aldehydes or ketones only with electron withdrawing substrates prone to undergo this rearrangement.[5,6] The attempt to get phosphates from the reactions of H-phosphonates with acetophenone was not satisfactory as mentioned in most of those reports. Therefore, with our present research on organophosphorus chemistry,[7] we demonstrate here the *n*-BuLi- triggered route for the synthesis of organophosphates from the direct reactions of diethyl phosphite with activated/unactivated ketones or aldehydes preferably at r.t. (25 °C) under additional solvent-free conditions. A related DBU catalytic method is known to afford phosphates only from electron-deficient aldehydes or ketones in the presence of DMF as solvent at elevated temperature (85 °C).[8]

In very recent studies, catalytic amount of organolanthanides[9a] and *n*-BuLi[9b] (0.1 mol%) have been used to synthesize α-hydroxyphosphonates from the reactions of unactivated ketones with dialkyl phosphite under mild and solvent-free conditions. By increasing the mol% (5-10) of *n*-BuLi the yield of α-hydroxyphosphonates got reduced due to aforementioned retro-hydrophosphorylation reactions.[9b] The same observation was reported in the presence of hexane, used as additional solvent. Surprisingly, in those reports, the formation of phosphates was not stated under any circumstances. We could isolate phosphates effectively when diethyl phosphite was treated with ketones or aldehydes in the presence of 10 mol% *n*-BuLi (1.6 M in hexane) at r.t. To the best of our knowledge, *n*-BuLi was not explored as a triggering agent to synthesize phosphate before in the literature. It is pertinent to note that the unexpected phosphate formation is one of the major pitfalls for the base catalyzed synthesis of α-hydroxyphosphonates starting from phosphites and ketones/ aldehydes and therefore the Lewis acid catalyzed hydrophosphorylation of ketones is described in the literature.[10]

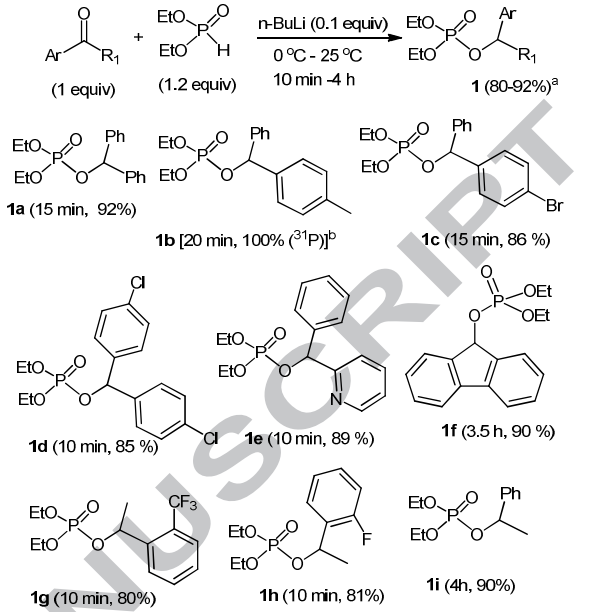
As ketones were proved earlier to be less reactive in phosphate formation,[5c-d,8] we initiated our studies with easily available, cheap benzophenone and diethyl phosphite to optimize the reaction conditions by varying different bases (see Table 1).

Table 1. Screening of reaction conditions to optimize the yield for phosphate **1a**.[a]

Entry	Base (mol %)	Time (h)	Temp (^{o}C)	Yield of **1a**[b]
1	NEt_3 (100)	8 -14	25- 65	n.r[c]
2	DIPEA (100)	8 -14	25-65	n.r
3	K_2CO_3 (100)	14	25	n.r
4	K_2CO_3 (100)	6	65	40
5	^{t}BuOK (100)	8	65	30
6	NaH (100)	12	25	90
7	NaH (10)	8-14	25-65	5
8	Cs_2CO_3 (100)	12	25	92
9	Cs_2CO_3 (10)	14	25	30
10	NMP (100)	8-14	25-60	n.r.
11	piperazine	8-14	25-60	n.r.
12	*n*-BuLi [d](0.1-5)	10	0-25	n.r.
13	*n*-BuLi (10)	0.4	0-25	92

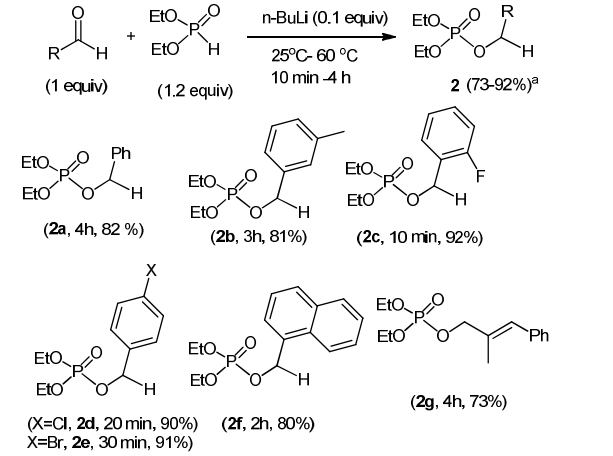
[a]Reaction conditions: benzophenone (1 mmol), diethyl phosphite (1.2 mmol) under additional solvent free conditions (except for entry 4 where THF was used as solvent) in the presence of N_2 balloon. [b]Isolated yield [c]n.r.:No reaction [d]The used *n*-BuLi strength: 1.6M in hexane.

Among different organic and inorganic bases, *n*-BuLi (10 mol%) was much more effective to afford the phosphate **1a.** Surprisingly no reaction could be observed even with 0.1-5 mol% of *n*-BuLi. Although the bases NaH and Cs_2CO_3 were equally effective for this reaction but stoichiometric amount of bases were necessary to access **1a** in higher yield. A range of organophosphates (**1a-i**), synthesized herein, are demonstrated in Scheme 2. To our delight, both benzophenone and acetophenone reacted with diethyl phosphite smoothly to furnish the phosphates **1a** and **1i** respectively in excellent yields under the present conditions whereas the earlier reported attempt to synthesize these phosphates was not satisfactory.[5b-c,8] Unexpectedly, the presence of methyl group(s) in one of the benzene rings for benzophenone also led to the smooth formation of compounds **1b** (100%, verified by $^{31}P/^{1}H$ NMR). Unfortunately **1b** could not be purified using column chromatography (SiO_2) as it got decomposed in the column and afforded the compound phenyl(*p*-tolyl)methanol. Fluorene based phosphate **1f**[5c] was also successfully produced at room temperature in a manner similar to other phosphates. Most of these phosphates were formed within 10-20 min excluding **1f** and **1i** (3-4 h). The presence of electron withdrawing groups in case of **1g-h** (analogues of **1i)** makes the reactions faster as expected. We could not isolate the corresponding α-hydroxyphosphonates under the present reaction conditions in the case of ketones.



Scheme 2. Synthesis of phosphates from the reactions of ketones and diethyl phosphite. [a]yields refer to chromatographically purified products. [b]yield is calculated based on $^{31}P/^{1}H$ NMR of the reaction mixture (see supporting information for details)

Aldehydes also generated the corresponding phosphates **2a-g** (Scheme 3) efficiently as expected. Surprisingly, our attempt to perform these reactions at r.t. was not promising to obtain the phosphates. In the case of compounds 4-chlorobenzaldehyde, 2-fluorobenzaldehyde and 1-naphthaldehyde, the phosphate formation was observed at r.t. only after 8-10 h. The reaction times were reduced by heating the reaction mixture at 60 ^{o}C.



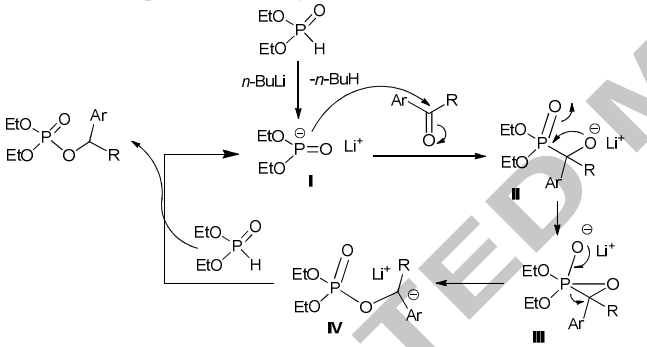
Scheme 3. Synthesis of phosphates from the reactions of aldehydes and diethyl phosphite. [a]yields refer to chromatographically purified products.

The reactions of aldehydes with diethyl phosphite generated corresponding *α*-hydroxyphosphonates initially at r.t. and subsequently formed phosphates upon heating. In comparison to the earlier report on DBU-catalayzed phosphate synthesis,[8] important phosphates **2d** and **2f** were synthesized here in excellent yields using *n*-BuLi as a triggering agent. Replacement of *n*-BuLi with NaH failed to afford the product **1i** as reported earlier.[5b]

Furthermore, we could generate very useful allylic phosphate **2g** successfully from the reaction of (*E*)-*α*-

methylcinnamaldehyde with diethyl phosphite in the absence of any additional solvent. The room temperature reaction produced compound **2g** along with the corresponding α-hydroxyphosphonate as a mixture (1:1), from which compound **2g** was isolated in moderate yield (40%). The yield of **2g** was improved to 73% when the reaction was performed at 60 °C. Notably this compound **2g** has been used in asymmetric allylic silylation[11a] and formation of enantioselective intermediates that have applications to natural product synthesis.[11b] It is interesting to note that the alkyl lithium mediated reverse phosphate- α-hydroxyphosphonate rearrangement is reported in the literature[12], however, we could not observe such a fact from our studies.

Based on the earlier reports[5,6] and our experimental observations, the mechanistic scheme for synthesis of phosphates is presented in Scheme 4. In case of aldehydes, the intermediate **II** was isolated and the corresponding product α-hydroxyphosphonates were obtained upon work-up whereas the intermediate **II** could not be isolated for ketones as mentioned earlier. To understand this difference in reactivity, density functional theory (DFT) studies were performed and that revealed the carbanion **IV** is formed *via* three-membered transition state **III**. It was found that the activation energy to form **III** is much higher (~10 Kcal/mol, see SI for details) in case of benzaldehyde compared to benzophenone. Therefore, the transformation from **II** to **IV** is much slower for benzaldehyde. Presumably, for that reason, we could isolate the corresponding *α*-hydroxyphosphonates for aldehydes but not for ketones at r. t. Thus, we can also explain the favourable phosphate formation for ketones in comparison to aldehydes.



Scheme 4. Plausible Mechanistic pathway for the formation of phosphates

From this scheme 4, it is clear that *n*-BuLi triggers the reaction. This could explain the fact that the transformation does not work at lower loadings of this reagent because the concentration of the carbanion would be too low to maintain a workable concentration of the phosphite anion, and the catalytic cycle would fade out. The stability of the intermediate **IV** in the presence of electron donating substituent(s) could be explained by the fact of tight ion-pair formation (not much polar bond) with smaller alkali metal Li. The extra stability of this intermediate could also arise due to the coordination of Li ion with the phosphoryl (P=O) oxygen and that led to the formation of stable five membered chelate ring.[13]

In conclusion, both ketones and aldehydes are conveniently used to generate phosphates from the *n*-BuLi-triggered reactions with diethyl phosphites under solvent-free and mild conditions. In this approach, the ketones with electron donating substituents can also be applied successfully. The synthetically useful allylphosphate also could be synthesized using this protocol. Mechanistic studies on this rearrangement for other substrates and applications of these phosphates towards organic synthesis are currently ongoing in our laboratory.

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General Procedure: *n*-BuLi (0.17 mL of a 1.6 M solution in hexanes, 0.274 mmol, 0.1 equiv) was added drop wise to diethyl phosphite (0.45 mL, 3.29 mmol) at room temperature (rt) under N_2 balloon at 0 °C. The resulting solution was stirred at rt for 2 min. Then, benzophenone (500 mg, 2.74 mmol) was added and the resulting solution was stirred at rt for 15 min. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated NH_4Cl solution. The aqueous layer was extracted with ethyl acetate (3 x 25 ml). After filtration and removal of solvent in vacuum, the crude product was purified by column chromatography using ethylacetate/ pet ether (20/80) as the eluent to afford **1a**. Unless otherwise stated, all the other compounds **1b-i** were prepared analogously using similar molar quantities of carbonyl compounds, diethyl phosphite and *n*-BuLi. In case of aldehydes, reactions were performed in a manner similar to the phosphates **1a-i** at 60 °C. All the spectroscopic data is included in the supporting information.

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