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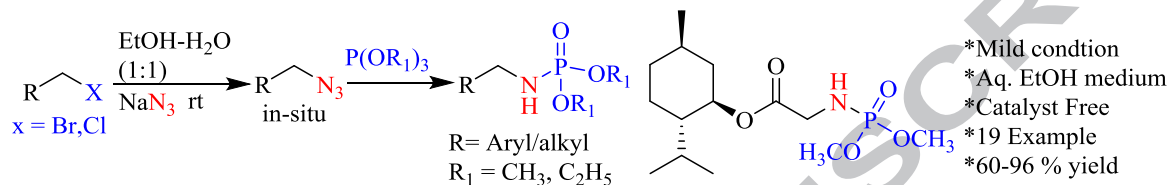
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An efficient synthesis of phosphoramidates from halides in aqueous ethanol

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ABSTRACT

An environment friendly and efficient synthesis of primary phosphoramidates has been developed from benzyl/allyl/alkyl/propargyl halides in aqueous ethanol as a green reaction medium via *in-situ* formation of azide. The method is simple, metal free and high yielding at room temperature with wide substrate scope and functional group compatibility. The optimized protocol can be used for synthesis of phosphoramidate intermediates used as prodrug moieties to improve therapeutic potential of the parent drug.

Keywords:

Phosphoramidates

Menthol

Aqueous ethanol

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1. Introduction

Phosphoramidates have gained considerable interest from last few decades as they have various applications in different area of medicinal chemistry. They have been used in enantioselective Lewis base activated catalytic conversion such as Aldol and allylation reactions.¹ In addition to catalytic applications, N-arylphosphoramidates have been used as precursors for the synthesis of various heterocycles such as azetidines, aziridines, quinazolinones and imines.^{2,3} Besides this, they are also used to synthesize phosphate esters in nucleotides chemistry.⁴ In analytical chemistry, phosphoramidates improve ionization efficiency and suppress matrix related ion effects in MALDI-TOF mass spectrometry.⁵ McGuigan et al. (1992) reported that phosphoramidates can be used as prodrug moieties to improve therapeutic potential of the parent drug.⁶ Phosphoramidates serve as surrogates for amide bond in the synthesis of peptide based protease inhibitors⁷ as well as represents some key structure in a number of biologically active natural products like agrocin 84,⁸

phosmidosine,⁵ and GS-6620.¹⁰ They also form important pharmacophore of many biologically potent compounds e.g. sofosbuvir (FDA approved drug) used for the treatment of hepatitis C virus (HCV),¹¹ evofosfamidum (TH-302) which is in clinical trials for cancer treatment (Fig. 1).¹² Recently, phosphoramidates have also been used in the field of plant hormone as abscisic acid agonists that play role in plant growth regulators.¹³

Owing to their great utility and potential applications in different area of chemistry particularly in pharmaceutical arena, spectacular interest has been paid for the development of new and efficient method for the synthesis of phosphoramidates. A number of classical strategies employed for the synthesis of phosphoramidates, including (i) the reaction of amines with suitable phosphoryl halide,¹⁰ (ii) reaction of amines with phosphoryl chloride generated *in situ* by halogenation of H-phosphonate with carbon tetrachloride,¹⁴ (iii) iodine catalyzed oxidation of phosphite triesters in the presence of excess butyl amine (250 equiv).¹⁵ In addition to above, phosphoramidates were also synthesized through oxidative coupling of amines and H-phosphonates using Cu(I), Ir(III) and I₂ recently¹⁶ (Scheme 1).

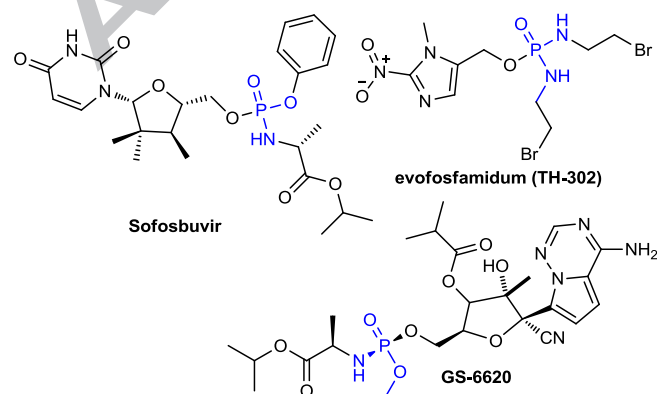
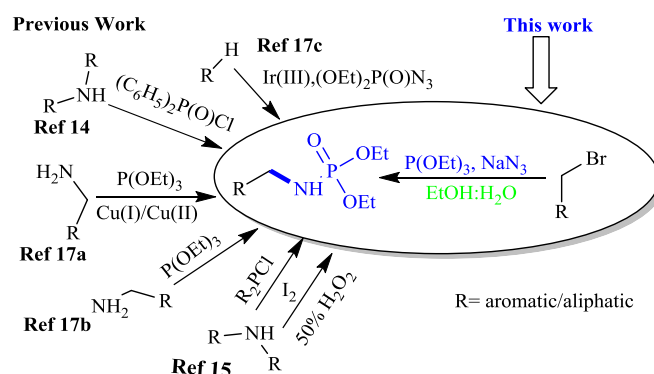


Figure 1. Some representative bioactive phosphoramidates



Scheme 1. Synthesis of phosphoramidates

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2. Result and Discussion

The major limitations associated with existing protocols involve the use and handling of hazardous phosphoryl halides, environmentally harmful organic solvents, toxic metal catalysts, excessive use of reagents, harsh reaction conditions, expensive anhydrous conditions and prolonged reaction time. In an alternative approach, phosphoramidates could be synthesized by coupling trialkyl phosphites and organic azides, which circumvent the above said limitations and environmentally benign nitrogen gas is the only by-product in the reaction. However, this method relies on the preparation and use of unstable and explosive organic azides in health hazardous reaction medium.¹⁷ For economic and environmental concerns, eco-compatible organic methodologies are being developed by avoiding the use of toxic reagents and solvents in excess. Thus, it would be highly desirable to synthesize primary phosphoramidates in one pot under environmental friendly conditions, so that isolation and reaction steps in process can be avoided. Keeping in view the limitations of the earlier methods and our interest in developing new, green and time shorting synthetic methodologies,¹⁸ herein we report a green, mild, metal free and efficient synthesis of primary phosphoramidates from alkyl halides and trialkylphosphites. The method involves in situ generation of organic azides and does not require excess and toxic reagents.

At the onset of this work, the model reaction was performed with benzyl bromide (1 eq), sodium azide (1.5 eq) and triethylphosphite (1 eq) in DMF at room temperature produced the desired product **1a** with 67% yield in 20 h (Table 1, entry 4). Encouraged by the catalyst free formation of desired product, reaction conditions were optimized to improve yield in minimum reaction time.

Table 1. Screening of various solvents for synthesis of phosphoramidates

Reaction scheme: Benzyl bromide + NaN_3 , $\text{P}(\text{OEt})_3$ / Solvent/s, rt $\rightarrow$ **1a**

Entry	Solvent/s	Yield (%) ^b	Time(h)
1	Benzene	43	48
2	Toluene	51	48
3	Xylene	54	48
4	DMF	67	20
5	DMSO	60	12
6	THF	67	12
7	MeCN	61	24
8	MeOH	67	12
9	DMF - H ₂ O (1:1)	89	4.5
10	DMSO - H ₂ O (1:1)	93	4.5
11	THF - H ₂ O (1:1)	92	4.5
12	MeCN - H ₂ O(1:1)	87	6
13	MeOH - H ₂ O (1:1)	91	5
14	EtOH - H₂O (1:1)	94	4.5
15	Acetone - H ₂ O (1:1)	94	4.5
16	<i>t</i> -BuOH - H ₂ O (1:1)	93	5
17	EtOH - H ₂ O (1:3)	90	4.5
18	EtOH - H₂O (3:1)	94	4.5
19	EtOH	67	4.5
20	H ₂ O	57	24

^aAll the reactions were carried out using 1 eq of benzyl bromide, 1.5 eq of NaN_3 and 1 eq of triethylphosphite in 10 mL of solvent/s.

^bIsolated yield of the product.

A series of solvents were screened for the model reaction and interestingly, it was observed that rate of conversion completely depends on the nature of solvents (Table 1). In non polar solvents like benzene, toluene and xylene, poor yields were obtained with incomplete substrate conversion even after a long reaction time (48 h or more) at room temperature (Table 1, entries 1-3). In polar solvents like DMF, DMSO, THF, acetonitrile and methanol moderate yields were obtained (60-67%) with incomplete substrate conversion even if reaction time was extended at room temperature (Table 1, entries 4-8). In case of DMF and DMSO side products were formed due to prolonged reaction time as reported in the literature.¹⁹ Further these solvents require higher temperature for complete substrate conversion because of poor solubility of sodium azide, but at high temperature alkyl bromides are known to undergo an Arbuzov type reaction²⁰ to form phosphonates without forming our desired product. The literature supports various reactions involving NaN_3 can be performed in water as a reaction medium,²¹ so we contemplate that mixture of water miscible solvents could be a better reaction medium and at the same time perform the reaction in two steps/one pot manner to avoid the side reactions. In view of this, various combinations of miscible polar solvents (1:1) like DMF-H₂O, DMSO-H₂O, THF-H₂O, CH₃CN-H₂O, MeOH-H₂O, EtOH-H₂O, acetone-H₂O, and *t*-BuOH-H₂O (Table 1, entries 9-16) were examined and interestingly, the reaction proceed smoothly with complete substrate conversion to give the desired product in excellent yields in each solvent mixture with much shorter reaction time at room temperature. Fascinatingly, the aqueous solvents proved better for compensation of high temperature and prolonged reaction time. Among the 50% aqueous alcohols, EtOH: water was chosen as better reaction medium because of lesser reaction time (4.5 h), better yield (94%) and ecofriendly. The solvent effect was further confirmed by executing the reaction using different proportion of ethanol: water i.e. EtOH: water (1:3), EtOH: water (3:1) as well as only EtOH and water separately (Table 1, entries 17-20). The use of water alone as reaction medium produced poor yield even after employing a prolonged reaction time due to very poor solubility of benzyl halide (Table 1, entry 20) while in case of ethanol yield comparatively equal to methanol with reduction in reaction duration. Both the reaction rate and the yield were increased gradually as the proportion of water increased upto the ratio of ethanol : water (1:1). Therefore aqueous ethanol (1:1) was chosen as the effective composition involving minimum use of organic solvent with 94% overall yield of the desired product **1a** in 4.5 h of reaction time at room temperature (entry 14). By this methodology desired products were obtained with clean and complete conversion without any side product.

After optimization, scope of the developed protocol was investigated for regioselective phosphoramidate synthesis of various benzyl halides. First, the influence of the substitution pattern at the benzyl bromide was studied. It was noticed that all performed reactions were neat and clean affording the desired products in excellent yields within reaction time limit (Table 2, entries 1-7). The developed protocol was found compatible with various substituted benzyl halide (Cl and Br) functionalities such as Cl, Br, F, OCH_3 and NO_2 . Benzyl bromides with electron withdrawing substituents were found more reactive than electron donating substituents (Table 2, entries 1-15). Reaction was also carried out with bromo methyl substituted triazoles (Table 2, entries 15-17) and afforded desired products in excellent yield. *o*-Substituted benzyl halides (Table 2, entries 3, 4 and 6) were found to react sluggishly and slightly lowered the yield in contrast to *p*- and *m*- substituted benzyl halides. Beside this, it

was also observed that benzyl bromides reacted faster than the corresponding chlorides since bromide is a good leaving group.

Table 2. Synthesis of various phosphoramidate (**1a-1o**)

$\text{Ar-CH}_2\text{Br} \xrightarrow[\text{EtOH:H}_2\text{O (1:1), RT, 4-6 h}]{\text{NaN}_3, \text{P(OR)}_3} \text{Ar-CH}_2\text{NHP(OR)}_2 \quad \text{R}_1 = \text{Et or Me}$			
Entry	Substrate	Product	Yield (%) ^a
1			94
2			96
3			87
4			91
5			89
6			91
7			92
8			87
9			90
10			93
11			89
12			88
13			86

14			85
15			92
16			90
17			93

^aIsolated yield of the product.

Efforts were made for further extension of the developed protocol using allyl and propargyl halides (Table 3). In case of allyl and propargyl halides the reaction proceeded smoothly and the desired products were formed in excellent yields (Table 3, entries 1-7), but required slightly longer reaction time. However, in case of alkyl bromides the desired phosphoramidates were formed at higher temperature with relatively lower yields (Table 2, entries 6 & 7). Triethylphosphite showed slightly better reactivity than the corresponding trimethylphosphite.

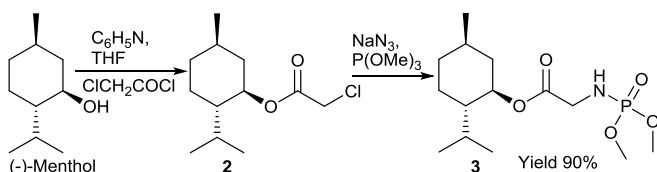
Table 3. Synthesis of various phosphoramidate of aliphatic halides (**1p-1u**)

$\text{R-CH}_2\text{Br} \xrightarrow[\text{EtOH:H}_2\text{O (1:1), RT, 4-6 h}]{\text{NaN}_3, \text{P(OR)}_3} \text{R-CH}_2\text{NHP(OR)}_2 \quad \text{R = alkyl/allyl/propargyl; R}_1 = \text{Et or Me}$			
Entry	Substrate	Product	Yield (%) ^a
1			71
2			73
3			70
4			63
5			60
6			55
7			52

^aIsolated yield of the product.

4. General experimental procedure:

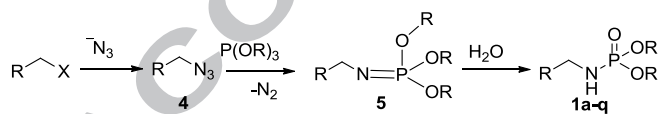
Keeping in mind the applications of phosphoramidates in various fields like pharmaceuticals and agro-pharmaceuticals, the developed methodology was applied on natural products for being our area of interest to carry out structural modification of bioactive natural products for better potency with least toxicity.²² Natural product (NP) (-)-menthol was taken as a model substrate for preparation of its phosphoramidate **3** through formation of intermediate **2** of the parent molecule (Scheme 2).²³ In view of this, the reaction of intermediate **2** under optimized conditions afforded the desired phosphoramidate **3** with excellent yield (90%). The result of this reaction recommends that the present methodology can be used for preparation of biological active natural product derived phosphoramidates.



Scheme 2. Synthesis of Phosphoramidate of (-)-menthol

A comparison with existing methodologies, the developed method offers a better alternative for the synthesis of benzyl, allyl, alkyl, and propargyl phosphoramidates in terms of yield, reaction time and eco-compatibility.²⁴ Additionally, various allylic phosphoramidates synthesized by this route could be subjected to thermal [3, 3]-sigmatropic intra-molecular rearrangement, leading to the selective N–C bond formation to synthesize different types of products depending upon the proper choice of substituents on the substrates.²⁵ Further, the standardized procedure offers significant green advantages, avoiding purification and handling of hazardous organic azides involving their in-situ formation. Use of eco-friendly and biodegradable aqueous as a reaction medium makes the protocol more attractive by avoiding the use of toxic organic solvents.

Based on the previous mechanistic reports and controlled experiment,²⁶ the first step may involve the nucleophilic attack of (-N₃) on halide to form azide **4** which upon reaction with trialkyl phosphite losses N₂ to form phosphorimidate **5** which finally rearranges to final products **1a-u** (Scheme 3).



Scheme 3. Plausible mechanism for the synthesis of phosphoramidates

3. Conclusion

An eco-friendly and efficient synthesis has been developed for the synthesis of primary phosphoramidates using simple azide precursors like benzyl, allyl, alkyl and propargyl halides in EtOH-H₂O (1:1) as a green reaction medium. Operational simplicity, metal free, in situ generation of organic azides and environmental benign conditions are the features of the developed protocol. This reaction has a wide substrates scope and offers the possibility of synthesizing phosphoramidates in good yield under mild conditions. Furthermore, this protocol can also be used for synthesis of valuable phosphoramidates of APIs, natural products or their derivatives as prodrugs.

In a typical procedure, the substrate benzyl halide (1 mmol) and NaN₃ (1.5 mmol) were taken in round bottom flask containing ethanol-water (1:1) (10 mL). The resulting solution was stirred at room temperature till the starting material was completely consumed (monitored by TLC). Trialkyl phosphite (1 mmol) was added to the flask and further stirred till the completion of reaction as monitored by TLC. After completion of reaction, Ethanol was evaporated in the reaction mixture and diluted with water. Aqueous reaction mixture was extracted with EtOAc. Combined organic layer was concentrated on rotavapour under reduced pressure, crude reaction mixture was purified on silica gel (60-120) column chromatography using chloroform and methanol as eluting solvents. The purified compounds were characterised by spectroscopic techniques i.e. ¹H NMR, ¹³C NMR, IR and HRMS. Spectroscopic data of all the synthesised products along with ¹H NMR, ¹³C NMR spectra are provided in supporting information while the data of compound **3** is given below.

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl-2-((dimethoxy phosphoryl)amino) acetate (3); Colour less oil; IR (cm⁻¹, CHCl₃ soln): 3384, 2955, 2927, 1746, 1458, 1255, 1035 and 834; ¹H NMR (400 MHz, CDCl₃) δ 4.66 (m, 1H), 3.57-3.66 (m, 8H), 3.35 (m, 1H), 1.90 (d, *J* = 11.2 Hz, 1H), 1.80 – 1.69 (m, 1H), 1.60 (d, *J* = 11.3 Hz, 2H), 1.40 (bs, 1H), 1.30 (t, *J* = 11.3 Hz, 1H), 0.94 (dt, *J* = 38.7, 13.4 Hz, 2H), 0.84 (d, *J* = 16.4 Hz, 6H), 0.67 (m, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 169.41 (d, *J* = 6.4 Hz), 74.02, 51.83 (2x OCH₃), 45.74, 41.72, 39.58, 32.91, 30.15, 24.99, 22.20, 20.72, 19.45, 15.06. ³¹P NMR (160 MHz, CDCl₃) δ 10.57; HRESIMS *m/z* calcd for C₁₄H₂₈NO₅P [M+H]⁺ 322.0147, found 322.0154.

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Supplementary Material

Complete experimental details and characterization data for all products. This material is available free of charge via the Internet

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Research highlights

Efficient synthesis of primary
phosphoramidates.

Aqueous ethanol as a green reaction
medium

The methodology was applied on natural
products to carry out structural .