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Catalyst free, one pot synthesis of phosphoramidates under environment friendly conditions

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ABSTRACT

An efficient and mild one pot synthesis of phosphoramidates has been reported from simple azide precursors like benzyl, allyl and propargyl halides. The method is simple, metal free giving products in good to excellent yields with wide substrate scope. Benzyl halide derivatives ($Y{-}C_6H_4{-}CH_2{-}X$: X = Cl, Br; Y = p-F, Br, NO_2 & o-Cl, NO_2) reacted with NaN_3 and $P(OR')_3$ at room temperature gave the corresponding phosphoramidates in 86–96% yields, while the reaction with allyl halides ($R1,R_2C = CH{-}CH_2{-}X$: X = Cl, Br, R_1 & R_2 = H, Me) in 60–73% yields. In polar solvents like DMF, DMSO, THF, acetonitrile, methanol moderate yields were obtained (60%–67%) with incomplete substrate conversion. Yields were better in binary polar solvents and water–ethanol was found to be the optimum green solvent in which upto 96% yield was obtained within 4.5 h. It was also observed that triethylphosphite showed better reactivity than trimethylphosphite. Secondary and tertiary halides did not react at all under the optimized conditions. This is the first catalyst free method for the one pot synthesis of phosphoramidates which offers significant green advantages like avoids hazardous organic azides, use of environment friendly ethanol and water as a green reaction medium.

Phosphoramidates have gained considerable interest from few decades since they have found widespread applications in several areas of organic chemistry. They have been used in enantioselective Lewis base-activated catalytic conversions [1] like aldol [2] and allylation reactions [3] and as pro-drug moieties to improve therapeutic potential of a parent drugs [4–6]. N-arylphosphoramidates have been employed for the synthesis of azetidines [7,8], aziridines [9], imines [10] and various heterocycles such as quinazolinediones [11]. In the synthesis of pharmaceutically active peptide-based protease inhibitors, phosphoramidates serve as surrogates for amide bonds since it imitates closely the tetrahedral transition state of reactions of carboxylic acid [12]. The phosphoramidates are also used to synthesize phosphate esters in nucleotides chemistry [13,14] and are present as key structural motifs in a number of biologically active natural products like agrocin 84 [15], phosmidosine [16] and microcin C7 [17]. Moreover, recently phosphoramidates have also found applications in analytical chemistry to improve ionization efficiency and suppress matrix-related ion effects in MALDI-TOF mass spectrometry [18] and as flame retardants [19].

The widespread applications of phosphoramidates have encouraged a numbers of methods for their preparation. Some of the common methods employed for the synthesis of phosphoramidates include (i) the reaction of an amine with a suitable phosphoryl halide [20] (ii) reaction of amines with phosphoryl chloride generated in situ by halogenation of an H-phosphonate with carbon tetrachloride [21] (iii) iodine catalyzed oxidation of phosphite triesters in the presence of excess butyl amine (250 eq.) [22]. More recently Cu (I) salts have been used for oxidative coupling of amines and H-phosphonates to generate phosphoramidates [23]. The major limitations of existing protocols involve the use and handling of hazardous phosphoryl halides, toxic organic solvents, metallic catalysts, excess use of reagents, high temperature and prolonged reaction time. An alternative route for the synthesis of phosphoramidates is provided by the Staudinger phosphite reaction between trialkyl phosphites and organic azides [24]. On one hand the methods involving use of organic azides for the synthesis of phosphoramidates exclude the use of hazardous phosphoryl halides, metallic catalysts, excess reagents to a great extent and environmentally benign nitrogen gas is the only by-product in these reactions. On the other hand organic azides are

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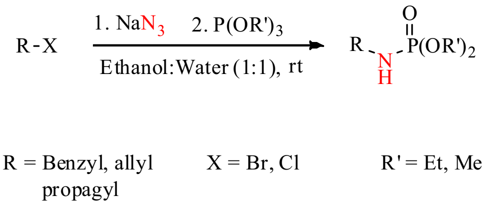


Scheme 1. One pot synthesis of phosphoramidates in different solvent systems.

explosive, unstable and are difficult to isolate particularly for derivatives of low molecular weight [25]. Thus it would be highly desirable to have in situ generation of organic azides. The Hackenberger group has reported a synthetic route for phosphoramidates, in which the in situ formation of azides is used with the phosphite reaction plus an additional rearrangement [26] which follows a previously reported Lewis-acid catalyzed rearrangement protocol [27]. In continuation of our work on green chemistry protocols [28], we herein report an easy, catalyst free, high yielding and a green one pot procedure for the synthesis of phosphoramidates from benzyl, propargyl and allyl halides with commercially available phosphites such as trimethyl or triethylphosphite (Scheme 1).

At the onset of this work, the model reaction of benzyl bromide (1 eq.), sodium azide (1.5 eq.) and triethylphosphite (TEP) (2 eq.) in DMF at room temperature produced the desired product (1a) with 67% yield in 18 h. Encouraged by the catalyst free formation of desired product, optimum reaction conditions were determined to improve the reaction yield and reduce reaction time.

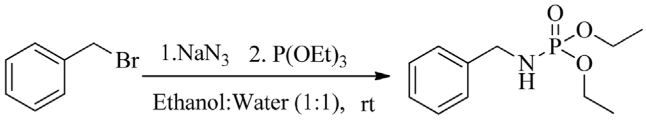
A series of solvents were screened for the model reaction to improve the yield of the reaction. In non polar solvents like benzene, toluene and xylene, poor yields were obtained with incomplete substrate conversion even after a long reaction time (48 h) or more at room temperature (Table 1, entries 6–8). In polar solvents like DMF, DMSO, THF, acetonitrile, methanol moderate yields were obtained (60%–67%) with incomplete substrate conversion even if long reaction time was employed at room temperature (Table 1, entries 1–5). In case of DMF and DMSO due to prolonged reaction time side products were formed which was in accordance with the literature [29]. These solvents thus demand higher temperatures for complete substrate conversion mainly due the poor solubility of sodium azide. But higher temperatures could not be applied for this one pot conversion, since at high temperature alkyl bromides may lead to formation of a phosphonates from the phosphite in an Arbuzov type reaction and desired product cannot be formed. To overcome the solubility problem of NaN_3, the reaction was conducted in water, but poor yields were obtained even after a long reaction time (Table 1, entry 17) due to very low solubility of benzyl halides. Subsequently, we decided to perform the one-pot reaction in a sequential manner using water (in combination with other miscible organic solvents) as a reaction medium to achieve complete conversion in shorter reaction time. In view of this, various combinations of solvents like DMF–water, THF–water, methanol–water, acetonitrile–water, acetone–water, ethanol–water, t-butanol–water, DMSO–water (Table 1, entries 9–16) were examined. We were pleased to achieve complete conversion of the benzyl bromide to the corresponding azide in every solvent combination with shorter but varying reaction times at room temperature. Upon addition of triethylphosphite (TEP), the reaction proceeded cleanly to afford the desired product (corresponding phosphoramidate) with good to excellent yields without any side product (Table 1, entries 9–16), except in case of DMF, where traces of side products were also formed. It is always desirable to have, cleaner, safer, and eco-friendly protocols, in this connection we examined various green organic solvents in combination with water and finally ethanol–water (1:1) proved to be the best green medium giving complete conversion of benzyl bromide to benzyl azide and upon addition of TEP, the desired phosphoramidate (1a) was obtained in an excellent overall yield of 96% in 4.5 h of reaction time at room temperature (Scheme 2). Further we observed that when the reaction time for the model reaction is extended particularly after the addition of TEP, formation of side products takes place. Therefore, to achieve clean and complete conversion, optimum way was to carry out the reaction in a domino one pot manner at room temperature, under catalyst free conditions and stop reaction immediately after completion.

After optimization of the reaction conditions, scope of the one-pot protocol was investigated for variety of benzyl halides. First, the influence of the substitution pattern at the benzyl bromide was studied. It was noticed in all cases, that the reaction proceeds cleanly and the desired products are formed in excellent yields with varying reaction times (Table 2, entries 2–7). Benzyl halides with electron withdrawing substituent reacted faster than those having electron donating substituent (Table 2, entries 2–15). Ortho substituted benzyl halides were found to react sluggishly and needed slightly longer reaction time. In contrast, para and meta substituted benzyl halides reacted faster. It was also observed that benzyl bromides reacted faster than the corresponding chlorides since bromide is a good leaving group. We further extended the developed protocol for other substrates like allyl, propargyl and alkyl halides and were pleased to observe that in case of allyl and propargyl halides, the reaction proceeds smoothly to produce the desired products in excellent yields, but slightly longer reaction time was required (Table 2, entries 14–18). However, in case of normal primary bromides, the desired phosphoramidates were not formed; this may be attributed to their lesser reactivity. Secondary and tertiary halides did not react at all under the optimized conditions. It was also observed that triethylphosphite showed better reactivity than trimethylphosphite.

Table 1
Screening of various solvents for one pot synthesis of phosphoramidates.[a]

Entry	Solvent system	Yield (%)[b]	Time (h)
1	DMF	67	18
2	DMSO	61	18
3	THF	67	18
4	Acetonitrile	63	20
5	Methanol	60	12
6	Benzene	43	48
7	Toluene	51	48
8	Xylene	54	48
9	DMF–water	89	4.5
10	DMSO–water	93	4.5
11	THF–water	92	4.5
12	Acetonitrile–water	87	6
13	Methanol–water	96	4.5
14	Ethanol–water	96	4.5
15	Acetone–water	96	4.5
16	t-Butanol–water	92	5
17	Water	57	24

[a] All the reactions were carried out using 1 eq. of benzyl bromide, 1.5 eq. of NaN_3 and 2 eq. of tri ethylphosphite in 10 ml of solvent.
[b] Isolated yield.



1a

Scheme 2. One pot synthesis of phosphoramidates with different substrates.