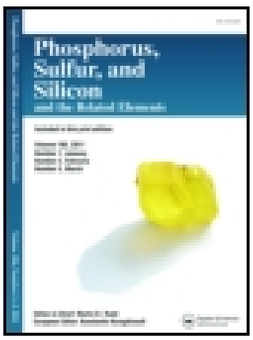

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A SIMPLE PROTOCOL FOR THE SYNTHESIS OF *α*--SUBSTITUTED PHOSPHONATES

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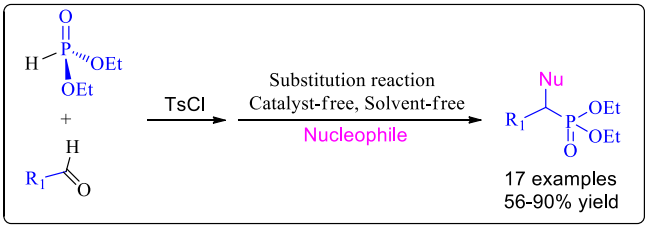
Abstract

An efficient, easy-to-handle and mild substitution reaction approach has been developed for the synthesis of phosphonate derivatives, which are very important in the field of industrial, agricultural, and medicinal chemistry. A large number of nucleophiles, including arylamines, alkylamines, heteroarylamines, primary amines and secondary amines, sulfides, and carbides were attempted to react with α-tosyloxyphosphonate **1**. The reaction proceeded under catalyst-free and neat conditions and the corresponding phosphonates **2** were afforded in good yields.



Keywords

α-substituted phosphonate, p-toluenesulfonyl chloride, catalyst-free, substitution reaction.

INTRODUCTION

α-Aminophosphonate, *α*-phosphoryl sulfide, and related derivatives have caught considerable attention on account of their structural and biological analogy to *α*-amino acids.[1] These phosphonates are very important in the fields of industrial, agricultural, and medicinal chemistry since they can be used as enzyme inhibitors,[2] antibacterial agent,[3] herbicide,[4] antiviral agent,[5] antitumor agent.[6]

Specifically, a number of methods for the synthesis of *α*-aminophosphonate have been reported during past two decades. Among these, the conventional Kabachnik--Fields three-component reaction or Pudovik reaction is predominantly employed, and mostly catalyzed by an inorganic Lewis acid, such as $BF_3 \cdot Et_2O$,[7] $Mg(ClO_4)_2$,[8] $Al(OTf)_3$,[9] $AlCl_3$,[10] $InCl_3$,[11] $In(OTf)_3$,[12] $SnCl_4$,[13] $BiCl_3$,[14] TiO_2,[15] $TiCl_4$,[16] $FeCl_3$,[17] CuI,[18] $CuCl_2$,[19] $Yb(OTf)_3$,[20] $YbCl_3$,[21] $CeCl_3 \cdot 7H_2O$,[22] $ZrOCl_2 \cdot 8H_2O$ and $ZrO(ClO_4)_2 \cdot 6H_2O$.[23] Besides, organic compounds or organometallic complexes are also important, such as tetramethylguanidine,[24] trimethylchlorosilane,[25] *p*-toluenesulfonic acid,[26] acetic acid,[27] trifluoromethanesulfonic acid,[28] cupreine-derived catalyst,[29] and tetra(tert-butyl) phthalocyanine aluminum chloride,[30] and zirconocene bis(perfluorobutanesulfonate).[31] Next to these homogeneous catalysts, recyclable immobilized or solid acid catalysts appeared more attractive recently, such as $SbCl_3/Al_2O_3$,[32] $NaHSO_4/SiO_2$,[33]

polyacrylic acid/SiO_2,[34] Al(phthalocyanine) complex/SiO_2,[35] BF_3/SiO_2,[36] amberlyst 15,[37] $H_2Ti_3O_7$ nanotubes,[38] graphene oxide,[39] and L-cysteine functionalized magnetic nanoparticles (LCMNP).[40] Moreover, another type of reusable catalyst so called ionic liquids were also applied and demonstrated interesting results.[41]

In addition to the C–P bond formation strategy through the hydrophosphorylation of imines, alternative methods were available to produce *α*-aminophosphonates. For example, C−C bond formation through addition reaction[42] or C−H bond formation through catalytic hydrogenation of enamido phosphonate[43] were also fairly useful mainly for the synthesis of asymmetric *α*-aminophosphonates. Another representative approach is direct formation of C-N bond through nucleophilic substitution reaction of a nucleophilic zincate and *O*-acylhydroxylamine in the presence of copper catalyst (Scheme 1).[44] Similarly, a simple protocol where the electrophilic *α*-tosyloxyphosphonate **1** reacts with amine to generate an *α*-aminophosphonate without metal catalyst seems more attractive and convenient (Scheme 1). Moreover, a changeable nucleophile would render this route extremely versatile. Actually, this strategy has produced numerous useful *α*-substituted phosphonates **2**, such as azidobenzylphosphonates[45], *α*-sulfanylphosphonates[46] and bisphosphonates[47]. However, reactions of **1** with amine, aryl sulfide or carbide have not been reported yet. Consequently, in this paper we report the systematic study of this synthetic route to obtain *α*-substituted phosphonates.

RESULTS AND DISCUSSION

In view of the strong electron–withdrawing ability of the phosphonate group in **1a**, *p*-tosyloxyl as leaving group (LG) was chosen to promote the process of the substitution reaction.[48] Optimized reaction conditions were explored through the reaction of **1a** and aniline as model substrate. The obtained results are given in Table 1. Reflux of **1a** and aniline (1:1.2) was carried out in different solvents including dichloromethane, ethyl acetate, tetrahydrofuran, acetonitrile, toluene, methanol, ethanol, and DMF (Table 1, entries 1-8). Unfortunately, the percentage yield of **2a** was rather low (< 25%), which is presumably due to the strong C–OTs bond in **1a** even with *p*-tosyloxyl as the leaving group. The solvent-free approach (35%) evidenced to be better reaction conditions compared with reactions carried out in solvent (Table 1, entry 9). The results clearly indicate that 80°C was the most suitable reaction temperature under solvent-free conditions, since the yield did not increase and by-product appeared when the reaction was performed at higher temperature (Table 1, entries 11-14). Surprisingly, the influence of molar ratio on the yield of **2a** was highly important. The yield increased about 12% when one more equivalent of aniline was added (Table 1, entries 15-20). The optimum stoichiometric ratio of **1a** and aniline was 1:5, and higher dosage did not give higher conversion. The apparent growth may come from the catalytic action of aniline, which facilitated the deprotonation step of protonated **2a** and eventually enhanced the reaction rate (Scheme 2). To verify this hypothesis, one experiment was conducted by adding 1.2 equivalent K_2CO_3 to the mixture (Table 1, entry 10). Unex-

pectedly, the substitution reaction did not result in a substantial higher yield compared to entry 9 (Table 1, entry 10). Hence, the assumption that an excess of amine act as catalyst was incorrect, therefore an equilibrium-controlled reaction is more tenable.

In order to examine the scope and the limitation of this method, different nucleophiles were combined with **1a** under optimal conditions, and the obtained data are disclosed in Table 2. It is obvious that the reaction using substituted aniline bearing an electron-withdrawing group displayed higher yields of the desired products **2** (Table 2, entries 1-3). We conjectured that the relative advantageous deprotonation step after substitution should be responsible for this phenomenon (Scheme 2). Moreover, with the increase of the steric hindrance of the aniline the overall reaction rate decreased dramatically (Table 2, entries 4-8), which is in accordance with the characteristics of a bimolecular nucleophilic substitution (S_N2) reaction. Nevertheless, five equivalent *n*-butylamine (Table 2, entry 9) did not react smoothly with **1a** unless a large excessive of amine was added. Heteroarylamines were also tested to examine the application scope of this method, such as 2-benzothiazolamine, 2-aminopyridine and pyrrole, but unfortunately unfavorable results were obtained. Interestingly, sodium thiophenolate (1.2 equiv, table 2, entry 10) can react with **1a** easily at room temperature in THF, which is attributed to its strong nucleophilic ability. Other nucleophiles were investigated, such as potassium phthalimide, $(EtOOC)_2CH^-Na^+$ and $Me_3SiC{\equiv}C^-Li^+$, but the desired products were not obtained presumably due to the weak nucleophilicity or strong basicity.

Several α-tosyloxyphosphonates **1** were prepared to verify this statement. When *iso*-butyraldehyde was employed as raw material, it is reasonable that the substitution tendency between aniline and **1b** was much lower than that of benzyl-type *p*-TsOCHPh[$PO(OEt)_2$] **1a** (Table 3, entry 1). When different substituted benzaldehydes were used, including electron–donating and electron–withdrawing group on benzene ring, 70-85% yield of **2** was achieved (Table 3, entries 2-6).

The structure of **2p** was confirmed by single crystal X-ray diffraction as shown in Figure 1. The most important structural feature is the existence of two N1-H···O3 hydrogen bonds [H-bond length: 2.303 Å; H-bond angle: 137.4(2)°] between two secondary amine molecules. A similar configuration was also described by Kapoor[32] in which **3** possesses a N--H···O distance of 2.053 Å and a N--H···O angle of 168.1(2)°. The formative H-bonded dimer stabilizes these compounds, increases their melting point and render them solid at ambient conditions. Although other H-acceptors (F1, O1 and O2) are present in **2p**, they are not used for H-bond formation. For α-aminophosphonates **2h** and **2i** with tertiary amine moiety, intermolecular H-bonds are not formed and as a consequence they exist as liquids. X-ray data collection parameters are presented in Table S 1 (Supplemental Materials) and bond lengths and angles in Tables S 2 and S 3.

CONCLUSION

In conclusion, a simple protocol to synthesize α-substituted phosphonates via a substitution reaction of **1** and different nucleophiles was developed. The versatile procedure benefits from numerous nucleophilic reagents and avoids the use of sensitive metal compounds and harsh reaction conditions. The nucleophilicity and dosage of the nucleophiles are highly important for the reaction outcome. Sodium thiophenolate can react with **1a** smoothly in favorable proceeding conditions with 86% yield. Further application of this method toward the synthesis of biologically active molecules is in progress in our group.

EXPERIMENTAL

All chemicals and solvents were purchased from Aladdin and Sinopharm Chemical Reagent Co., Ltd, and were directly used for the synthesis. All reactions were carried out in sealed vial, and no special precautions were taken. ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR, and ^{19}F-NMR were recorded on a Bruker Avance HD III 500NMR spectrometer in $CDCl_3$ using TMS as internal standard. Chemical shifts were reported in parts per million (ppm). Coupling constants (J) were reported in Hz and refer to apparent peak multiplicity. IR spectra were recorded on Bruker-Vertex 80V Vacuum infrared spectrometer. The Supplemental Materials contains complete characterization data for the products and sample ^{1}H, ^{13}C and ^{31}P NMR spectra are presented in Figures S 1 -- S 69. CCDC 1448386 contains the supplementary crystallographic data for this paper. These data

can be obtained free of charge via www.ccdc.cam.ac.uk/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, B2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

General Procedure for Synthesis of 1：A solution of aldehyde (10 mmol), diethyl phosphite (10 mmol), and triethylamine (7 mL) in DCM (20 mL) was stirred at room temperature for 4 h. Subsequently, *p*-toluenesulfonyl chloride (12 mmol) was added, and the mixture was stirred continuously at room temperature overnight. Saturated NH_4Cl solution was added, and the crude product was extracted by DCM (3×10 mL), washed with brine, and dried over anhydrous Na_2SO_4. The volatiles were removed *in vacuo* to offer a yellowish-brown crude product, which was purified by column chromatography using silica gel, producing the desired product (78-93% yield).

General Procedure for Synthesis of 2: Nucleophiles (10.0 mmol) and **1** (2.0 mmol) were stirred in an oil bath at 80°C for 6-48 h (detection using TLC). The reaction mixture was separated directly on silica gel column, providing the corresponding product (56-90% yield).

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Table 1 Effects of solvent, temperature and stoichiometric ratio on the reaction of **1a** and aniline[a].

Entry	Solvent[b]	Yield [%][c]	Entry	Molar ratio	Temperature [°C]	Yield [%][c]
1	DCM	< 5	11	1:1.2	60	15
2	EA	< 5	12	1:1.2	70	21
3	THF	8	13	1:1.2	90	35
4	CH_3CN	9	14	1:1.2	100	34
5	Toluene	13	15	1:2	80	40
6	MeOH	14	16	1:3	80	53
7	EtOH	19	17	1:4	80	65
8	DMF	23	18	1:5	80	77
9	Sol-	35	19	1:6	80	77
10	Sol-	37	20	1:7	80	76

[a]Reaction conditions: **1a** (1.0 mmol), $PhNH_2$ (1.2 mmol), 6 h under reflux. [b]5 ml solvent. [c]Isolated yield. [d]Reaction temperature: 80°C. [e]1.2 equivalent K_2CO_3 was added.

Table 2 Synthesis of *α*-substituted phosphonates **2** from **1a**.[a]

En-try	Nucleophiles	**2**	t/h	Yield [%][b]	Refer-ence
1		**2b**	6	85	[49]
2		**2c**	6	80	[50]
3		**2d**	6	90	[11]
4		**2e**	10	60	[51]
5		**2f**	48	67	-
6		**2g**	48	60	-
7		**2h**	9	56	[17]

8			9	70	-
9[c]		**2j**	6	73	[52]
10[d]		**2k**	3	86	[53]

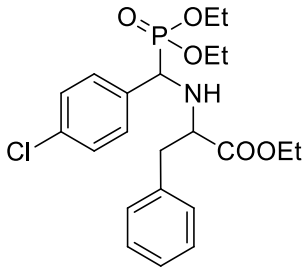
[a]Reaction conditions: **1a** (2.0 mmol), nucleophiles (10.0 mmol) under neat conditions at 80°C.

[b]Isolated yield. [c]5 ml *n*-butylamine was added. [d]1.2 equivalent sodium thiophenolate and 5 ml THF was added, room temperature.

Table 3 Synthesis of *α*-aminophosphonates **2** by using aniline as nucleophile.[a]

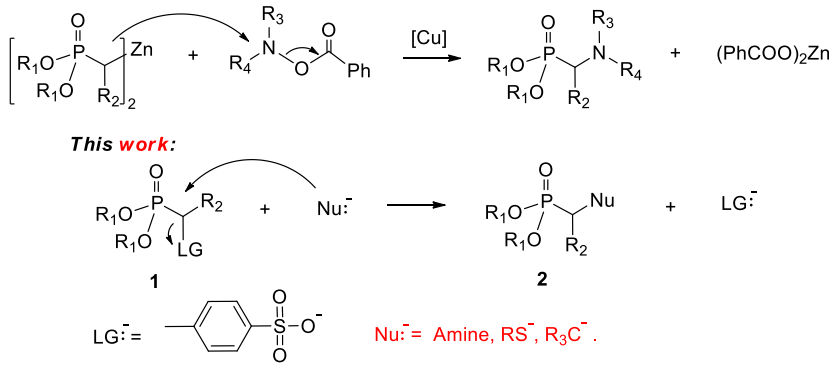
En-try	Nucleophiles	**2**	t/h	Yield[%][b]	Refer-ence
1	**1b**	**2l**	12	<5	[52]
2	**1c**	**2m**	8	80	[15a]
3	**1d**	**2n**	10	76	[54]
4	**1e**	**2o**	9	78	-
5[c]	**1e**	**2p**	6	85	-
6	**1f**	**2q**	12	70	[15a]

[a]Reaction conditions: **1** (2.0 mmol), aniline (10.0 mmol) under neat conditions at 80°C. [b]Isolated yield. [c]3-fluoroaniline was used as nucleophile.

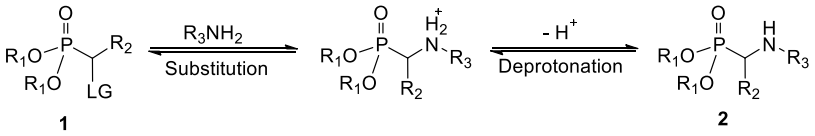


3

Figure 1 ORTEP diagram and the labeling of atoms for the crystal structure of *α*-aminophosphonate **2p** (left). H-bonds between phosphonate oxygen (O3) and the hydrogen attached to nitrogen (N1) (right).



Scheme 1 Synthetic route to *α*-substituted phosphonates **2** through nucleophilic substitution reaction.



Scheme 2 Substitution and deprotonation steps during formation of α-substituted phosphonates **2**.