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A mild and highly efficient protocol for the one-pot synthesis of primary α-amino phosphonates under solvent-free conditions

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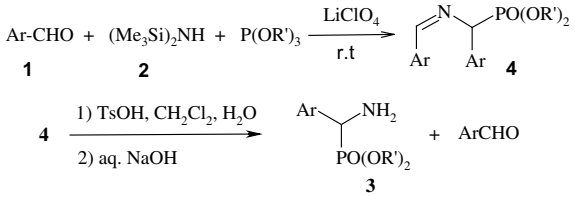
Abstract—Under solvent-free reaction conditions and in the presence of solid $LiClO_4$ a novel and mild protocol for the one-pot, three-component synthesis of primary α-amino phosphonates from an aldehyde, hexamethyldisilazane and a trialkyl phosphite is described giving high yields and having short reaction times. The same products are obtained in very low yields, when the three-component reaction is carried out under microwave irradiation and in the absence of solid $LiClO_4$. Examples of some prepared 1-aryl-*N*,*N*′-bis(arylidene)methanediamines are also described.

1. Introduction

α-Amino phosphonates are an important class of compounds since they can be considered structural analogues of α-amino acids, and their utilities as enzyme inhibitors, antibiotics, pharmacological agents in addition to many other applications are well documented.[1–4] Although many elegant new methods and reagents for the synthesis of secondary and tertiary amino phosphonates have been reported,[5] these approaches are not effective for the synthesis of primary amino phosphonates. These compounds can be obtained by a limited number of synthetic methods,[6–12] but to the best of our knowledge, a one-pot procedure starting from an aldehyde, ammonia and a dialkyl phosphite only gives very low yields even after long reaction times.[12b] Therefore, a successful one pot three-component reaction of an aldehyde, hexamethyldisilazane (HMDS) and a trialkyl phosphite would be an attractive approach for the synthesis of primary α-amino phosphonates under solvent-free conditions.

Recently, there has been increasing interest in solvent-free organic reactions. The solvent-free synthetic method is valuable for ecological and economical reasons. Furthermore, the reported examples have demonstrated that solvent-free reactions are generally faster, give higher selectivity and yields and usually require easier work-up procedures and simpler equipment. Thus, development of solvent-free organic reactions is gaining prominence.[13]

In continuation of our interest in one-pot, three-component syntheses mediated by lithium perchlorate[14] as well as solvent-free organic reactions,[15] we herein describe a simple, new and efficient protocol for the one-pot synthesis of primary α-amino phosphonates using HMDS as a source of amine under solvent-free conditions, Scheme 1. The reaction of benzaldehyde, HMDS and trimethyl phosphite was chosen as a model, and several sets of reaction conditions were examined. The optimized conditions are when the reaction is carried out with benzaldehyde (1.0 equiv), HMDS (1.3 equiv), and trimethyl phosphite (1.2 equiv) in the presence of solid $LiClO_4$ (2.0 equiv). Without $LiClO_4$, the reaction does not take place. To show the generality and scope of the synthesis, the reaction was examined with various structurally diverse aldehydes and trialkyl phosphites, and these results are summarized in Table 1. The intermediate **4**



Scheme 1.

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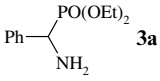
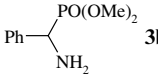
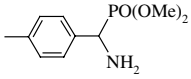
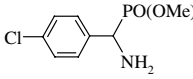
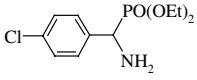
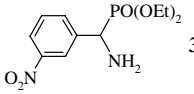
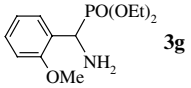
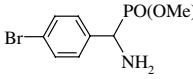
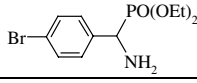
Table 1. Solid $LiClO_4$-promoted synthesis of primary α-amino phosphonates from aldehydes

Entry	Aldehyde	Phosphite	Product	Yield (%)[a]
1	PhCHO	$P(OEt)_3$	 **3a**	88
2	PhCHO	$P(OMe)_3$	 **3b**	92
3	*p*-MeC_6H_4CHO	$P(OMe)_3$	 **3c**	90
4	*p*-ClC_6H_4CHO	$P(OMe)_3$	 **3d**	86
5	*p*-ClC_6H_4CHO	$P(OEt)_3$	 **3e**	82
6	*m*-$O_2NC_6H_4CHO$	$P(OMe)_3$	 **3f**	89
7	*o*-$MeOC_6H_4CHO$	$P(OMe)_3$	 **3g**	80
8	*p*-BrC_6H_4CHO	$P(OMe)_3$	 **3h**	90
9	*p*-BrC_6H_4CHO	$P(OEt)_3$	 **3i**	84

[a] Isolated yields.

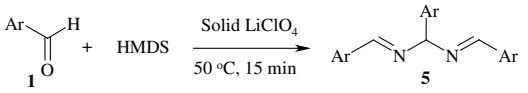
was isolated and characterized from its ^1H NMR spectrum.

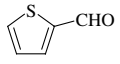
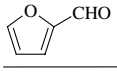
The data in Table 1 shows that different aromatic aldehydes are successfully converted to the corresponding primary α-amino phosphonates in high yields at room temperature under solvent-free conditions. The presence of electron-withdrawing or electron-donating substituents on the aromatic ring did not affect the course of the reaction. Sensitive functionalities such as OMe and NO_2 were tolerated under the mild reaction conditions. Primary α-amino phosphonates were exclusively formed without the formation of any side products such as α-hydroxy phosphonates.

When the three-component reaction between benzaldehyde, HMDS and trimethyl phosphite was attempted under microwave irradiation, in the absence of solid $LiClO_4$ and any solvent, very low yields of the α-amino phosphonates were obtained. The microwave-assisted reaction was carried out in the presence of different Lewis acids, such as $ZnBr_2$, SiO_2, Al_2O_3, and $CoCl_2$, and with different aromatic aldehydes. The highest conversion was found to occur with $ZnBr_2$, after irradiation for 8 min with a yield of 34%.

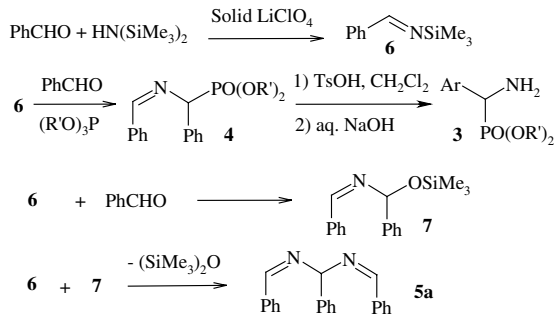
We next investigated the formation of 1-aryl-*N*,*N*′-bis(arylidene)methanediamines, **5**, using benzaldehyde, HMDS and solid lithium perchlorate. The corresponding diamines **5** were obtained in high yields needing only short reaction times at 50 °C, Scheme 2. The resulting derivatives **5** are versatile synthons in organic synthesis, and can be converted into a variety of nitrogen-containing heterocyclic compounds.[12a,16]

Although, a mechanism for the formation of **5** from an aldehyde and HMDS has been described by Soroka,[12] we carried out additional experiments to gain more mechanistic information on this reaction. A mixture of HMDS and anhydrous lithium perchlorate in the absence of benzaldehyde did not produce ammonia and the one-pot reaction of ammonia, benzaldehyde,



Ar	Yield(%)	
Ph	93	**5a**
p-ClC_6H_4	90	**5b**
m-MeC_6H_4	85	**5c**
p-BrC_6H_4	94	**5d**
	90	**5e**
	86	**5f**

Scheme 2.



Scheme 3.

and a trialkyl phosphite gave compound **5** in low yields. Finally, a one-pot reaction in the presence of TMSCl gave an α-hydroxy phosphonate as the sole product. With these results in hand, we suggest that the reaction proceeds via an imine **6**, as an intermediate. In the presence of trialkyl phosphite, **6** is converted into **4**, which after hydrolysis under acidic conditions gives α-amino phosphonate **3**. In the absence of trialkyl phosphite, the intermediate **6** reacts with another molecule of aldehyde to form **7**, and finally reaction of **7** and **6** yeilds **5**, as shown in Scheme 3.

In conclusion, in this study we have successfully extended the use of HMDS as a source of ammonia for the one-pot synthesis of α-amino phosphonates in high yields under solvent-free conditions mediated by solid $LiClO_4$. The present procedure provides a novel, very mild and green methodology for the preparation of primary α-amino phosphonates as well as compound **5** under neutral reaction conditions.

Further investigation to broaden the scope and synthetic applications of $LiClO_4$ under solvent-free conditions is underway in our laboratory

2. General procedure for the preparation of α-amino phosphonates 3

A mixture of an aldehyde (5 mmol), HMDS, (7 mmol), trialkyl phosphite (6 mmol) and anhydrous $LiClO_4$ (10 mmol) was stirred at rt for about 15–45 min. The reaction was monitored by TLC. After completion of the reaction, the product was extracted with CH_2Cl_2. Then, *p*-toluenesulfonic acid monohydrate (6 mmol) was added, and the reaction mixture was stirred for 3 h. Water was added and the solution neutralized with NaOH (15%). The organic materials were extracted with CH_2Cl_2 (2×10 mL), and the combined organic layers were washed with water (2×15 mL), dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate, petroleum ether, 10:90) to afford pure α-amino phosphonate. All compounds were characterized on the basis of their spectroscopic data (IR, ^1H NMR, ^{13}C NMR and MS) and by comparison with those reported in the literature.[12,17]

3. General procedure for the preparation of compounds 5

A mixture of aldehyde (10 mmol), HMDS (18 mmol) and $LiClO_4$ (20 mmol) was heated for 15 min at 50 °C, then the reaction mixture was cooled to room temperature to give a solid crude product. $LiClO_4$ was recovered by filtration. The solvent was removed from the filtrate under reduced pressure to give the crude product, which was purified by recrystallization (cyclohexane, petroleum ether or ether). All compounds were characterized on the basis of their spectroscopic data (IR, ^1H NMR, ^{13}C NMR, and MS) and by comparison with those reported in the literature.[12a,16,17]

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17. Selected spectroscopic data: **3a**: Oil. ^{1}H NMR (500 MHz, acetone-d_6): δ 1.20 (m, 6H), 1.94 (br s, NH_2), 3.76–4.10 (m, 4H), 4.23 (d, J = 18.6 Hz, 1H), 7.21–7.50 (m, 5H), IR (CH_2Cl_2): 3360, 1454, 1258 cm^{-1}. **3b**: Oil. ^{1}H NMR (500 MHz, acetone-d_6): δ 2.06 (br, NH_2), 3.48 (d, J = 10.3 Hz, 3H), 3.75 (d, J = 18.1 Hz, 1H), 3.82 (d, J = 9.6 Hz, 3H) 7.22–7.45 (m, 5H), IR (CH_2Cl_2): 3350, 1448, 1250 cm^{-1}. **5a**: mp 101–102 °C; ^{1}H NMR (500 MHz, acetone-d_6): δ 6.08 (s, 1H), 7.34–7.97 (m, 15H), 8.68 (s, 2H); IR, 1660 cm^{-1}. **5e**: mp 112.6–113.8 °C; ^{1}H NMR (500 MHz, acetone-d_6): δ 6.25 (s, 1H), 7.02–7.67 (m, 9H), 8.76 (s, 2H). IR (CH_2Cl_2): 1650 cm^{-1}.