An improved facile synthesis of α-amino phosphonates by the reaction of α-amido sulfones with dialkyl trimethyl silyl phosphites catalyzed by Fe (III) chloride

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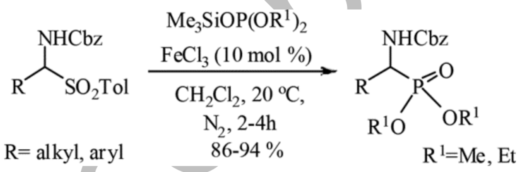
Abstract

An improved efficient synthesis of α-amino phosphonates has been discovered by the reaction of *N*-benzyloxycarbonylamino sulfones with dialkyl trimethyl silyl phosphites in the presence of $FeCl_3$ as a catalyst. The products were formed in high yields (86-94%) within 2-4 h. The catalyst is inexpensive, easily available and highly active. The unreacted dialkyl trimetyl silyl phosphites can easily be removed from the products due to their low boiling points. The sulfones can conveniently be prepared and are generally stable.

Graphical Abstract



KEYWORDS: α-amino phosphonates; *N*-benzyloxycarbonylamino sulfones; stable solids; Dialkyl trimetyl silyl phosphites; $FeCl_3$ catalyst

INTRODUCTION

α-Amino phosphonic acids and their esters are considered [1] structural analogues of α-amino acids. They possess several attractive biological activities including insecticidal, herbicidal and fungicidal properties[2]. They have also been employed as enzyme inhibitors, peptide mimetics, catalytic antibodies and antibiotics [3]. Some of these compounds are used as antirhematic, antioxidant and anti-HIV agents [4]. Thus a number of methods have been developed for the synthesis of α-amino phosphonates, both in racemic and chiral forms [5]. Generally these synthetic methods have been applied to carbonyl compounds and amines or directly to the corresponding imines for hydrophosphonylation. However, several Lewis acids used for catalyze these reactions deactivate or decompose in the presence of amine and water produced during imine formation and many of the imines are unstable. Though methods involving catalyst and solvent free conditions for the synthesis of α-amino phosphonates were developed [6], the serious draw back in such methods is the difficulty in the deprotection of *N*-phenyl group in the products to the corresponding amine under mild conditions. On the other hand, α-amido sulfones, a valuable source of imines, can easily be prepared and generally they are stable solids and can be stored for a long time. Further, unlike in many of the reported methods, the *N*-benzyloxycarbonyl group in the products obtained can easily be demasked to the corresponding primary amine which allows structural modifications. Here we would like to describe the synthesis of α-amino phosphonates using α-amido sulfones in the presence of a catalytic amount of Fe (III) chloride.

In connection with our work [7] on the development of useful synthetic methodologies we have discovered that *N*-benzoyloxycarbonylamino sulfones, when allowed to react with dialkyl trimethyl silyl phosphite using Fe (III) chloride as a catalyst, afforded the protected α-amino phosphonates in high yields (Scheme 1).

RESULTS AND DISCUSSION

The above conversion of *N*-benzoyloxycarbonylamino sulfones into α-amino phosphonates was initially standardized using diethyl trimethyl silyl phosphite and various metal salts. In absence of a catalyst the present conversion did not proceed (Table 1). The transformation was found to be most effective when $FeCl_3$ (10 mol %) and diethyl trimethyl silyl phosphite (1.1 mmol) were allowed to react with sulfone (1.0 mmol) in CH_2Cl_2 at 20 ^oC under N_2 atmosphere (Table 1). The reaction was completed in 2h with 91% yield (Table 1, entry 1). The conversion was less efficient with other catalysts (e.g., $ZnCl_2$, $ZrCl_2$, CuCl and $NiCl_2.6H_2O$) when compared to $FeCl_3$. The catalytic activity of $FeCl_3$ was also better than that of the non-transition metal salt $InCl_3$, as conversions required a longer time with the latter (Table 1). Considering reaction times and yields, $FeCl_3$ was found to be the catalyst of choice. This compound is comparatively inexpensive and easily available.

Then the reaction was optimised further by the reaction of sulfones with different phosphites (e.g., $Me_3SiOP(OEt)_2$, $H(O)P(OEt)_2$ and $P(OEt)_3$) using $FeCl_3$ as catalyst (Table 2). It has also been observed that the reaction times were shorter and the yields were higher when the conversions were conducted using $FeCl_3$ and dialkyl trimethyl silyl phosphites instead of other phosphonating agents (Table 2) as had been done earlier when $InCl_3$ was used as the catalyst [8]. The reaction of α-amido sulfones with dialkyl trimethyl silyl phosphites in the presence of $InCl_3$ also took longer reaction times to afford the products in lower yields (Table 1).

The experimental procedure of the present conversion is also convenient as a dialkyl trimethyl phosphite (having lower b.p.) can easily be removed from the reaction mixture by simple evaporation under vacuum. On the other hand, a trialkyl phosphite (having higher b.p.) is difficult to remove from the reaction mixture. Thus the treatment of *N*-benzoyloxycarbonylamino sulfones with dialkyl trimethyl silyl phosphite catalyzed by $FeCl_3$ constitutes an improved method for the synthesis of α-amino phosphonates (Scheme 1). Recently another method involving the reaction of *N*-benzoyloxycarbonylamino sulfones and dialkyl phosphites in the presence of a phase transfer catalyst and a base has been reported [9]. However, the reaction time was long (60 h) and the sulfones derived from aromatic aldehydes were not utilized.

A series of α-amino phosphonates have successfully been prepared from *N*-benzoyloxycarbonylamino sulfones generated[10] from different aldehydes (aromatic, hetero-aromatic and aliphatic). Sulfones containing electron-donating as well as electron-withdrawing groups in the aromatic ring underwent the conversion smoothly. Both dimethyl trimethyl silyl phosphite and diethyl trimethyl silyl phosphite were used to prepare the α-amino phosphonates (Table 3). The *N*-Cbz group of the products can easily be deprotected and the free amine group may be utilized to prepare their different analogues [11].

The reaction was conducted at 20^0C because at higher temperatures the silyl reagent decomposed to some extent. The conversion was completed within 2-4 h and the yields were impressive (86-94%). Different functional groups such as hydroxyl, ether, halogen and nitro remained intact. The structures of the products were confirmed from their spectral (IR, ^{1}H, ^{13}C NMR, ESIMS and HRMS) properties. The products **2a**-**2f** are new compounds. The spectral data of the products **2g-2r** are fully in agreement with the reported data [7].

It is known that α-amido sulfones on treatment with a suitable Lewis acid can be converted into the corresponding protected imines containing a positively charged nitrogen [11]. Here *N*-benzoyloxycarbonylamino sulfones **1** are converted first in the presence of $FeCl_3$ into the imines **A** which then undergo phosphonylation with dialkyl trimethyl silyl phosphite to form the corresponding protected α-amino phosphonates **2** (Scheme 2).

CONCLUSION

In conclusion, we have developed an improved efficient and general method for the synthesis of protected α-amino phosphonates by treatment of *N*-benzoyloxycarbonylamino sulfones with dialkyl trimethyl silyl phosphites in the presence of $FeCl_3$ as a catalyst. The application of an easily available, inexpensive and highly active catalyst has made the process simple, improved and practical. The *N*-Cbz group of the products can easily be deprotected and the free amine group can be utilized to prepare their different analogues.

EXPERIMENTAL

All commercially available reagents were used directly without further purification unless otherwise stated. The solvents used were all of AR grade and were distilled under a dry N_2 atmosphere where necessary. All reactions were performed in pre-dried apparatus unless otherwise stated. The progress of the reactions was monitored by analytical thin-layer chromatography (TLC) performed on *Merck* Silica Gel 60 F_{254} plates. Column chromatography (CC) was carried out using silica gel 60 – 120 mesh (*Qingdao Marine Chemical*, China). Melting points of the final compounds were recorded on a *Buchi-510* instrument. IR spectra were recorded on a *Perkin-Elmer IR-683* spectrophotometer with KBr optics (values were reported in cm^{-1}). ^1H & ^{13}C-NMR spectra were recorded on a *Gemini 200* MHz, *Bruker 300* MHz and *Inova 500* MHz spectrometers with TMS as internal standard in $CDCl_3$. The chemical shifts are expressed as δ values in ppm and the coupling constants (J) are given in Hz. ESI-MS were recorded with *VG-Autospec micromass* and HRMS with *QSTAR XL,* Hybrid MS system (Applied Biosystems). Yields were of purified compounds unless otherwise stated.

General Experimental Procedure For The Synthesis Of A-Amino Phosphonates (2a-2o)

To a stirred mixture of α-amido sulfone, **1** (1 mmol) and $FeCl_3$ (10 mol %) in dry CH_2Cl_2 (5 ml) dialkyl trimethyl silyl phosphate (1.2 mmol) was added under N_2 at 20 ^{0}C. The reaction was monitored by TLC. After completion, the reaction mixture was diluted with CH_2Cl_2 (10 ml) and washed with water (2x10 ml). The organic portion was separated, dried over anhydrous Na_2SO_4 and concentrated. The residue was subjected to column chromatography (silica gel, hexane-EtOAc) to obtain pure protected α-amino phosphonate **2**. The spectral data of some of the representative products are given below.

Spectral Data For The Selected Compounds benzyl (dimethoxyphosphoryl)(phenyl)methylcarbamate (2a)

White solid. m.p. 118-119 ^{0}C; IR: 3325, 1714, 1551, 1458, 1255. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50-7.41 (*m*, 2 H); 7.38-7.21 (*m*, 8 H); 6.40 (*dd*, *J* = 10.0, 4.0, 1 H); 5.21-4.99 (*m*, 3 H); 3.70 (*d*, *J* = 10.0, 3 H); 3.41 (*d*, *J* = 10.0, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 156.0 (*d*, *J* = 9.0); 136.2; 135.1; 128.9; 128.3; 128.0; 67.2; 53.9 (*d*, *J* = 6.5); 53.5 (*d*, *J* = 6.0); 52.2 (*d*, *J* = 154.4). ESI-MS: $[M + H]^+$ = 350, $[M + Na]^+$ = 372; HRMS (ESI) Calcd for $[C_{17}H_{20}NO_5P+Na]^+$ = 372.0976, found = 372.0995.

Benzyl (Dimethoxyphosphoryl)(Furan-2-Yl)Methylcarbamate (2e)

White solid; m.p. 69-72 ^{0}C; IR: 3243, 1718, 1533, 1458, 1262; ^{1}H NMR (200MHz, $CDCl_3$): 7.40 (*brs*, 1 H), 7.30 (*brs*, 5 H), 6.41 (*brs*, 1 H), 6.33 (*m*, 1 H), 5.59 (*brd*, *J* = 10.0, 1 H), 5.29 (*dd*, *J* = 24.0, 10.0, 1 H), 5.14 (*d*, *J* = 12.0, 1 H), 5.07 (*d*, *J* = 12.0, 1 H), 3.72 (*d*, J = 10.0, 3 H), 3.63 (*d*, *J* = 10.0, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$):155.7 (*d*, *J* = 9.0), 148.0, 143.0, 136.2, 128.6, 128.2, 111.1, 109.1, 67.3, 53.8 (*d*, *J* = 6.0), 53.2 (*d*, *J* = 6.2), 46.1 (*d*, *J* = 155.0); ESIMS: $[M + H]^+$ = 340, $[M + Na]^+$= 362; HRMS (ESI): Calcd for $[C_{15}H_{18}NO_6P+H]^+$ =340.0950, found = 340.0955.

Benzyl 3-(Diethoxyphosphoryl)(3,4,5-Trimethoxyphenyl)Methylcarbamate (2g)

White solid; m.p. 109-111^{0}C; IR: 3238, 1712, 1594, 1234; ^{1}H NMR (200 MHz, $CDCl_3$) 7.36-7.22 (*m*, 5 H), 6.63 (*s*, 2 H), 5.84 (*brs*, 1 H), 5.12 (*d*, *J* = 12.0, 1 H), 5.07 (*d*, *J* = 12.0, 1 H), 5.01 (*d*, *J* = 24.0, 10.0, 1 H), 4.14-4.01 (*m*, 2 H), 3.95 (*m*, 1 H), 3.85 (*s*, 6H), 3.81 (*s*, 3 H), 3.70 (*m*, 1 H), 1.28 (*t*, *J* = 7.0, 3 H), 1.12 (*t*, *J* = 7.0, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$):155.7, 153.3, 136.1, 130.8, 128.5, 128.3, 117.1, 116.1, 105.1, 105.0, 67.4, 63.4 (*d*, *J* = 6.2), 63.1 (*d*, *J* = 6.2),60.8, 56.1, 52.1 (*d*, *J* = 155.5), 16.4 (*d*, *J* = 6.0), 16.3 (*d*, *J* = 6.0); ESIMS: $[M + H]^+$ = 468; HRMS (ESI): Calcd for $[C_{22}H_{30}NO_8P+H]^+$ = 468.1782, found = 468.1784.

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The authors thank CSIR, New Delhi for financial assistance.

SUPPORTING INFORMATION

The scanned copies of ^{1}H-NMR, ^{13}C-NMR and HRMS spectra for new compounds **2a-2f** and for known compounds **2g-2h** are provided. This material can be found via the "Supplementary Content" section of this article's webpage.

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Catal. **2008**, 350, 1195-1208; p) J. P. Abell, H. Yamamoto, *J. Am. Chem. Soc.*, **2008**, 130, 10521-10523; q) B. Das, P. Balasubramanyam, M. Krishnaiah, B. Veeranjaneyulu, G. Chinna Reddy, *J. Org. Chem*. **2009**, 74, 4393-4395; r) B. Das, G. Satyalakshmi, K. Suneel, K. Damodar, *J. Org. Chem.*, **2009**, 74, 8400-8402; s) Y. Gao, Z. Huang, R. Zhuang, J. Xu, P. Zhang, G. Tang, Y. Zhao, *Org. Lett.*, **2013**, 15, 4214-4217.

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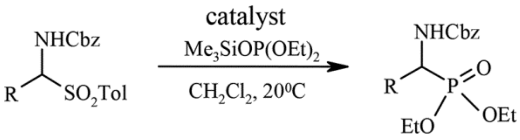
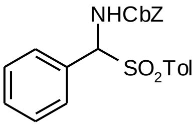
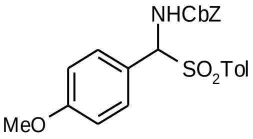
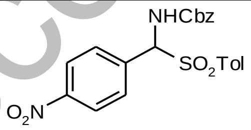
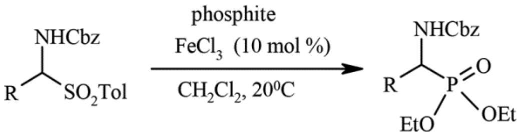
Table 1. Studies on activity of different catalysts for the synthesis of α-amino phosphonates by reaction of α-amido sulfones with diethyl trimethyl silyl phosphate.[a]

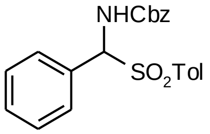
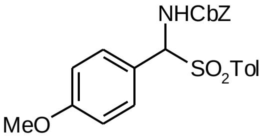
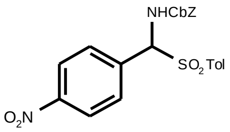


Entry	Sulfone	Catalyst	t (h)	Yield (%) [b]
1		$FeCl_3$	2	91
		$InCl_3$	9	74
		$ZnCl_2$	16	65
		$ZrCl_4$	16	69
		CuCl	16	59 [c]
		$NiCl_2.6H_2O$	16	62 [c]
		No Catalyst	24	NR [d]
2		$FeCl_3$	2	94
		$InCl_3$	9	76
		$ZnCl_2$	16	68
		$ZrCl_4$	16	71
		CuCl	16	62 [c]
		$NiCl_2.6H_2O$	16	66 [c]
		No Catalyst	24	NR [d]
3		$FeCl_3$	4	86
		$InCl_3$	12	64
		$ZnCl_2$	16	51
		$ZrCl_4$	16	54
		CuCl	20	48 [c]
		$NiCl_2.6H_2O$	20	53 [c]
		No Catalyst	24	NR [d]

[a] Reaction conditions: Sulfone (1 mmol), phosphite (1.2 mmol) and $FeCl_3$ (10 mol %) were used. [b] Yields of isolated, pure compounds after column chromatography. [c] Catalyst (20 mol %) was used. [d] No Reaction.

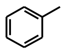
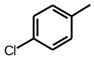
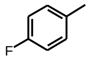
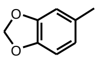
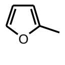
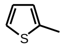
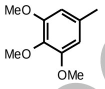
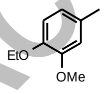
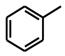
Table 2. Reactivity of various phosphites on treatment with α-amido sulfones in the presence of $FeCl_3$ catalyst at 20°C.[a]

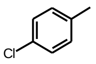
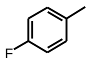
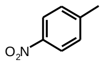
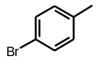
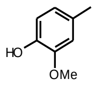
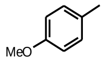
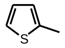


Entry	Sulfone	Phosphite	t (h)	Yield (%) [b]
1		$Me_3SiOP(OEt)_2$ $H(O)P(OEt)_2$ $P(OEt)_3$	2 12 10	91c) 15 74
2		$Me_3SiOP(OEt)_2$ $H(O)P(OEt)_2$ $P(OEt)_3$	2 12 10	94[c] 20 76
3		$Me_3SiOP(OEt)_2$ $H(O)P(OEt)_2$ $P(OEt)_3$	4 12 10	86[c] Trace 42

[a]Reaction conditions: Sulfone (1 mmol), phosphite (1.2 mmol) and $FeCl_3$ (10 mol %) were used. [b] Yields of isolated, pure compounds after column chromatography. [c] Reaction conducted at 20°C.

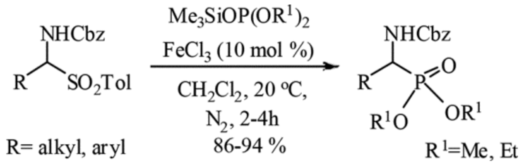
Table 3. $FeCl_3$-catalyzed synthesis of α-amino phosphonates by the reaction of α-amido sulfones with dialkyl trimethyl silyl phosphites (Scheme 1)[a]

Entry	R	R^1	Product[b] **2**	Time (h)	Yield (%)[c]
1		Me	**2a**	2	90
2		Me	**2b**	2.5	87
3		Me	**2c**	2.5	86
4		Me	**2d**	2	91
5		Me	**2e**	3	87
6		Me	**2f**	2.5	90
7		Et	**2g**	2	94
8		Et	**2h**	2	92
9		Et	**2i**	2	91

10		Et	**2j**	2.5	90
11		Et	**2k**	2.5	89
12		Et	**2l**	4	86
13		Et	**2m**	2.5	89
14		Et	**2n**	2	92
15		Et	**2o**	2	94
16		Et	**2p**	2	88
17	*n* Butyl	Et	**2q**	3	86
18	*n* Hexyl	Et	**2r**	3.5	87

[a]Reaction conditions: Sulfone (1 mmol), phosphite (1.2 mmol) and $FeCl_3$ (10 mol %) were used. [b]All the products were fully characterized by usual spectroscopic techniques. [c] Yields of isolated, pure compounds after column chromatography.

Scheme 1. Conversion of α-amido sulfones into α-amino phosphonates.



Scheme 2. Proposed mechanism for the synthesis of α-amino phosphonates from α-amido sulfones.