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Silylated iminophosphonates: Novel reactive synthons for the preparation of fluorinated aminophosphonates and aminophosphonic acids

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ABSTRACT

A convenient synthetic approach towards previously unknown N- and N,O-silylated α-iminophosphonates bearing fluoroalkyl groups at the imine C atom was developed. The synthetic potential of the compounds was demonstrated by their easy functionalization and the straightforward preparation of biorelevant aminophosphonates and free aminophosphonic acids with heterocyclic residues in the α-position.

Introduction

α-Aminophosphonic acids are phosphorus analogs of the corresponding α-aminocarboxylic acids in which the carboxylic unit is replaced with a bioisosteric phosphonic moiety. The chemistry of α-aminophosphonic derivatives has been extensively developed in recent years, primarily due to their wide spectrum of biological activities, including proteolytic enzyme regulation as mimetics of natural acids,[1–5] inhibitors of AIDS-protease,[1–4] anticancer agents,[5] strong neuromodulators,[2] antibacterial phosphonopeptides,[1–3,6] metal-sequestering drugs, radiopharmaceuticals, NMR imaging agents,[1,2] plant growth regulators and herbicides.[1,2,6]

Most reported methods for the preparation of α-aminophosphonates are based on the addition of phosphites to non-phosphorylated imines as the key step (Pudovik reaction, Scheme 1, route *a*). The three-component Kabachnik-Fields reaction (Scheme 1, route *b*) involves initial synthesis of the C=N bond, followed by subsequent formation of the C—P bond upon the addition of hydrophosphoryl compounds or other phosphorus nucleophiles.[6] In spite of their apparent simplicity, these methods have drawbacks including the purification of final compounds, low reactivity, and limited utility for the preparation of fluoroalkyl substituted aminophosphonates which are particularly promising in drug discovery. Importantly, these methods initially lead to *O*- and/or *N*-substituted derivatives (R', Y ≠ H), and the subsequent removal of protecting groups in highly functionalized aminophosphonates and aminocarboxylates, especially in those bearing electron-withdrawing groups, is often accompanied by C—P bond cleavage. It is worth noting that both free acids and esters show biological activity,[3] which necessitates the development of efficient methods for the synthesis of derivatives containing both protected and unprotected amino and/or phosphonic functionality. In the last decades an alternative general approach for the construction of α-aminophosphonates based on the use of *C*-phosphorylated imines **1** as starting materials (Scheme 1) has been explored by our group.[7]

In particular, the use of unprotected fluorinated NH iminophosphonates **1** (Y = H, R = fluoroalkyl) allows the direct preparation of fluorinated aminophosphonates with a free amino group.[7c,7d,7f] At the same time, our attempts to transform *O*,*O*-dialkyl aminophosphonates bearing the trifluoromethyl group and heterocyclic residues (pyrrol-2-yl, indole-3-yl)[7f] into the corresponding aminophosphonic acids *via* different methods (e.g. acid hydrolysis, use of Me_3SiHal) failed. In all cases the deprotection reaction was accompanied by C—P bond cleavage. We postulated that silylated iminophosphonates could be used to overcome the problem, but such imines were unknown.

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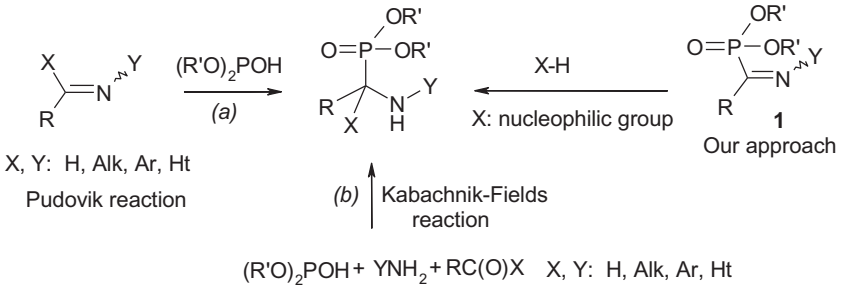


Scheme 1. Methods for the preparation of α-aminophosphonates.

In the present work we disclose the synthesis of previously unknown *N*- and *N,O*-silylated iminophosphonates bearing fluoroalkyl groups at the imine carbon atom and the development of a novel "silyl" strategy for the preparation of biorelevant fluorinated aminophosphonates and aminophosphonic acids.

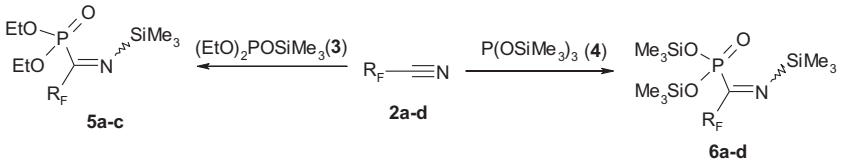
Results and discussion

A convenient and experimentally simple method for the synthesis of *N*- and *N,O*-silylated iminophosphonates based on reaction of highly electrophilic fluorinated nitriles **2** with (diethyl)trimethylsilylphosphite **3** or tris(trimethylsilyl)phosphite **4**, respectively, was developed (Scheme 2). Virtually pure iminophosphonates **5** and **6** were obtained almost in quantitative yields upon mixing the reagents at low temperature in an autoclave (for gaseous nitriles **2a,b**) or in a flask (for nitriles **2c,d**) and gradual warming to room temperature (see Table). Compounds **5** and **6** are moisture sensitive, but stable at room temperature under an anhydrous atmosphere. However, upon heating they undergo partial dissociation to the starting compounds.

Recently, we reported that mixed fluoro(chloro) acetonitriles react with hydrophosphoryl compounds, $(RO)_2P(O)H$, *via* two competitive pathways: (i) formation of NH iminophosphonates and (ii) reductive dehalogenation of nitriles.[8] In contrast, silylated phosphites **3** and **4** reacted chemoselectively with all of the studied haloacetonitriles **2a-d** (Scheme 2).

Formation of the P—C bond was confirmed by ^{13}C NMR spectroscopy of compounds **5** and **6**, in which an imine carbon atom signal (δ 158–169 ppm) with a large direct C—P coupling constant ($^1J_{CP}$ 171–221 Hz, $^3J_{CF}$ 30–35 Hz) was observed. According to ^1H, ^{13}C, ^{19}F, and ^{31}P NMR data, *N,O*-silylated trifluoroacetimidoyl phosphonate **6a** exists in C_6D_6 as a mixture of *E,Z* isomers (*E*/*Z* ~ 3:1). For all other compounds only one set of signals was observed in the NMR spectra (see Table).

Compounds **5** and **6** are the first representatives of *C*-phosphorylated imines bearing silyl functionality at the nitrogen atom,[9] and can be used in synthesis without purification. Upon treatment with methanol (1 equiv.) silylated imines **5a-c** were quantitatively transformed into the parent NH iminophosphonates **7a–c** (Scheme 3), which were previously synthesized *via* the reaction of nitriles **2** with diethyl phosphite.[7c,7f,8] This represents an advantageous method for the synthesis of mixed chloro(fluoro) NH iminophosphonates **7b,c**; alternative methods based on the reactions of nitriles **2b,c** with diethyl phosphite are of limited utility due to low chemoselectivity.[8] The reaction of *N*-silylated iminophosphonate **5b** with CD_3OD represents a simple approach to previously unknown *N*-deuterated iminophosphonate **8**.



Scheme 2. Synthesis of *N*- and *N,O*-silylated iminophosphonates.

Table
Synthesis and selected spectral data of *N*- and *N,O*-silylated iminophosphonates.

Compound	R_F	Reaction conditions	Yield (%)	δ_P (ppm)	$^1J_{C\text{-}P}$ (Hz)	δ_F (ppm)
5a	CF_3	−80 °C → r.t. 7 d	98	−1.2	188.8	−71.9
5b	CF_2Cl	−50 °C → r.t. 10 h	100	−3.6	207.7	−60.0
5c	$CFCl_2$	−5 °C → r.t. 10 h	100	−3.2	205.1	−61.4
6a	CF_3	−80 °C → r.t. 7 d	100	−20.8 (*E*) −23.6 (*Z*)	202.5 171.6	−70.6 (*E*) −69.5 (*Z*)
6b	CF_2Cl	−50 °C → r.t. 10 h	100	−21.5	205.3	−57.8
6c	$CFCl_2$	−5 °C → r.t. 2 h	100	−22.8	220.5	−60.0
6d	$PhCF_2$	−5 °C → r.t. 3 d	100	−18.3	208.3	−93.3