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Preparation of an α-Aminophosphonate Cation Equivalent and its Reaction with Organoboranes

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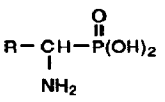
Abstract: Compound **5**, an α-aminophosphonate cation equivalent (**2**), is reacted with organoboranes to yield α-substituted α-aminophosphonic acid derivatives **7**.

Derivatives of α-aminophosphonic acids (**1**), phosphorous analogs of the α-aminocarboxylic acids, have been the focus of numerous recent synthetic studies[1-5] because of their interesting biological activity.



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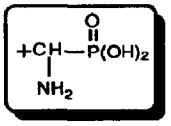

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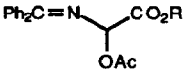

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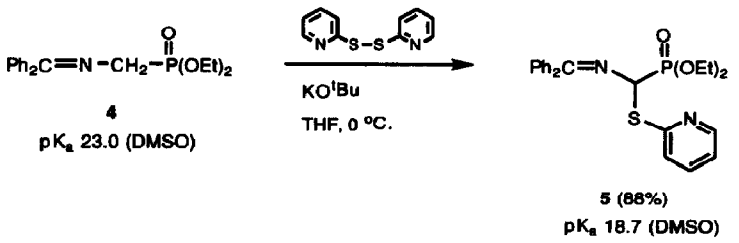
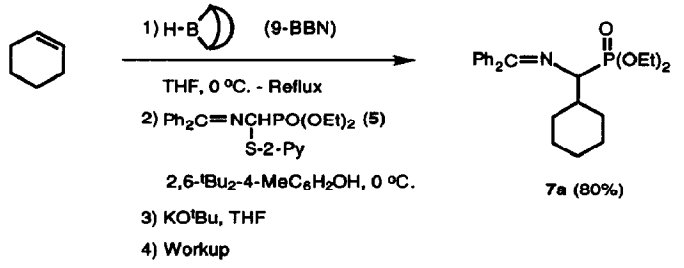
Current methodology is available for construction of compounds **1** by a variety of routes. Thus, in terms of making the final bond to the α-carbon, it is possible to use C-C,[2] C-P,[3] C-N[4] or C-H[5] bond construction. While there are numerous routes involving anionic equivalents of an α-aminophosphonate, there are but few methods for C_α-C_β bond formation using the complimentary α-cationic equivalent **2**.[2e] Studies in our laboratory concerning preparation and reactions of an α-cationic glycine equivalent (**3**)[6] prompted development of a related α-cationic α-aminophosphonate synthon. We report here the preliminary results of these studies.

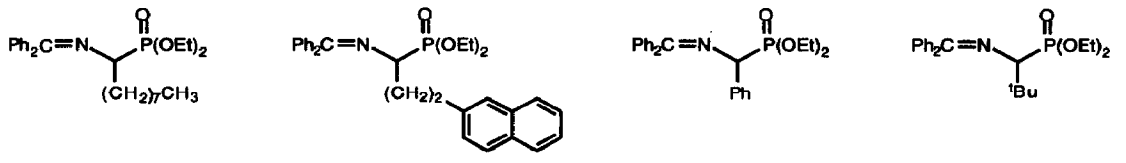
The benzophenone imine was chosen as a versatile protecting group for the primary amine based on our own studies in α-aminocarboxylate chemistry[6-8] as well as its successful implementation with anionic α-aminophosphonates.[2a,d,g,i,j,o] Initial studies focused on the nature of the leaving group to be used in the protected α-aminophosphonates. When attempts to extend use of the acetate group in **3** to the phosphonate series proved unsuccessful, attention was turned to introduction of a sulfur-based leaving group. Thus, treatment of the Schiff base phosphonate **4**[2o,9] with base followed by 2,2'-dipyridyl disulfide resulted in formation of the α-thiopyridyl derivative **5**.[10] Initially, LHMDS was used as base in this synthesis [(a) LHMDS, THF, -78 °C.; (b) $(2\text{-PyrS})_2$, -78 °C to RT] although it was found later that KO^{t}Bu is a more practical base for a single step preparation of **5**.[11,12]



The 2-pyridylthio (2-PyS) group was chosen because it possesses a combination of strong acidifying and good leaving group abilities, together with small steric demands. Introduction of the 2-PyS group into the α-position of **4** (pKa = 23.0) lowers the pKa value (in DMSO) by 4.6 units (statistically corrected for the number of acidic hydrogen atoms), which makes **5** slightly more acidic than $Ph_2C{=}NCH_2CO_2Et$ (**6**) (pKa = 18.7).[13] This increase in acidity is not surprising since the PhS group is known to be strongly acidifying,[14] and the nitrogen atom in the pyridine ring will enhance its acidity.[15] The longer C_α-P and C_α-S bonds in **5** lessen the $A_{1,3}$-allylic type strain[16] in **5** compared to **6** for which introduction of an α-Ph group has been shown to cause a 2.3 pKa unit decrease in acidity[13] (phenyl groups in nonsterically demanding substrates are somewhat more acidifying than PhS groups[14]).

In analogy with earlier studies with compound **3**,[6c] the 2-pyridylthio-substituted aminophosphonate **5** is readily α-alkylated with organoboranes.[17] Thus, preparation of the organoborane from cyclohexene and 9-BBN followed by addition of **5**, a sterically hindered phenol and then KO^{t}Bu yielded, following oxidative workup, the alkylated derivative **7a**.[12,18] Similarly, compounds **7b** and **7c** were prepared starting from the alkenes, 1-octene and 2-vinylnaphthalene, respectively. Compounds **7d** and **7e**, in which a phenyl or t-butyl group has been added to **5**, are prepared from the organoboranes derived from phenyl or t-butyl lithium and 9-MeOBBN. Derivatives **7**





can be readily deprotected to yield either the corresponding α-substituted α-aminophosphonates or phosphonic acids.[2d,g,i,j,o]

Overall, this chemistry provides the possibility of "appending" the α-aminophosphonate unit onto functionality that can easily be converted into organoboranes. In many cases (e.g. **7a**, **7c**, **7d** and **7e**) such products are difficult to prepare by the corresponding alkylative routes because of problems with elimination or nucleophilic aromatic substitution.

Further studies to expand the scope of these cationic α-aminophosphonic acid derivatives are in progress.

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10. For a similar preparation in the α-aminocarboxylate series, see reference 6a.
11. Preparation of **5**: A solution of KO^{t}Bu in THF (1M, 11 mL, 11 mmol) was added dropwise with stirring over fifteen minutes to a precooled (ice bath) solution of Schiff base **4**[20,9] (3.31 g, 10 mmol) and 2,2'-dipyridyl disulfide (2.2 g, 10 mmol) in dry THF (25 mL) under argon. During the slow addition of the base the appearance and disappearance of an orange color was observed as well as the formation of a white precipitate that accumulates. Following the addition, stirring was continued for 30 minutes at 4 °C. and then 30 minutes at room temperature. The reaction mixture was quenched with H_2O (25 mL), diluted with EtOAc (25 mL) and the phases were separated. The aqueous layer was extracted with EtOAc (15 mL), the organic layers were combined and washed with 5% aqueous Na_2CO_3 (25 mL), H_2O (25 mL) and brine (50 mL), dried (Na_2SO_4), filtered and evaporated using a rotary evaporator. The crude yellow product was ground up and then dispersed in a minimum of hot ether. The volume of the solution was reduced on a rotary evaporator to about 30 mL, hexane (70 mL) was added and the mixture was heated to reflux. The mixture was then kept at room temperature for five hours followed by overnight in the freezer. The resulting crystals were filtered, washed with cold hexane and then dried *in vacuo* (0.1 mm Hg) for five hours to give pure **5** (3.89 g, 88%), mp = 94-95° C.
12. Starting substrate **5** and all products **7** gave satisfactory elemental analyses or high resolution mass spectra as well as NMR spectra consistent with the assigned structures.
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18. Preparation of **7a**: Freshly distilled cyclohexene (0.11 mL, 1.1 mmol) was added dropwise with stirring to an ice-cooled solution of 9-BBN (134 mg, 1.1 mmol) in dry THF (4 mL) under argon. The ice bath was removed and stirring was continued for 15 minutes at room temperature and then for one hour at reflux. The solution was cooled to room temperature and Schiff base **5** (440 mg, 1 mmol) followed by 2,6-di-tert-butyl-4-methylphenol (264 mg, 1.2 mmol) were added. The reaction mixture was cooled in an ice bath and a solution of KO^{t}Bu in THF (1M, 1.25 mL, 1.25 mmol) was added dropwise at which time the solution became deep red color in color. The ice bath was removed and stirring was continued overnight (after five minutes a white precipitate started to accumulate). The yellow reaction mixture was diluted with EtOAc (10 mL) and H_2O (10 mL), the phases were separated and the organic phase was washed with 5% aqueous $NaHCO_3$ (2 X 10 mL). The organic phase was then cooled in an ice bath and 1N aqueous NaOH (5 mL) and 30% aqueous H_2O_2 (0.5 mL) were added dropwise with stirring. After stirring an additional four hours at 4 °C., the layers were separated and the organic layer was dried (Na_2SO_4), filtered and evaporated using a rotary evaporator. The crude product was purified by flash chromatography using silica gel with hexane/EtOAc (1:1) as eluent to give pure **7a** (330 mg, 80%), mp = 92-93° C.

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