The Binary Reagent $(MeO)_3P/Me_3SiCl$ and $(MeO)_3P/CH_3CO_2H$ in 5.0 M Lithium Perchlorate/ Diethyl Ether. An Efficent Route to the Preparation of α-Hydrazinophosphonates and *N*-Hydroxy-α-aminophosphonates

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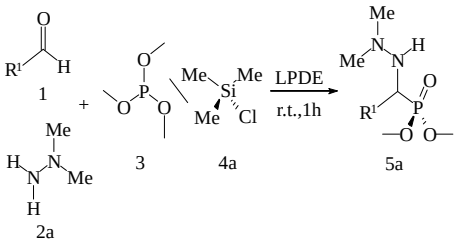
α-Hydrazinophosphonates (*N*-hydroxy-α-aminophosphonates) are generated by lithium perchlorate-catalyzed three-component reaction of aldehydes, *N*,*N*-dimethylhydrazine (phenylhydroxylamine) and trimethylphosphite/trimethylsilyl chloride (acetic acid). The method utilizes cheaply available reagents and hence it is a practical and cost effective strategy, compared to other methods available in the literature.

The development of new methods for the synthesis of α-aminophosphonates derivatives is an important area of synthetic efforts, as can be seen from the number of reports dealing with that subject. As derivatives of α-aminophosphonic acids, α-hydrazinophosphonic acids[1] and *N*-hydroxy-α-aminophosphonates[2] are of considerable interest as compounds with potential biological activity. Several methods are available for the preparation of α-hydrazinophosphonates and have been well documented in the literature: base catalyzed condensation of diethylphosphite with aliphatic aldazones,[3] (this method, however, was not suitable to aryl aldazones), a selective reduction of the α-hydrazonophosphonic acids with $NaBH_3CN$ or BH_3·THF,[4] nucleophilic substitution of 1-sulfonyloxy-alkylphosphonates by hydrazine[5] and nucleophilic substitution of 3-methoxy-1,2,3,6-tetrahydropyridazine derivatives by dimethyl phosphite in the presence of Lewis acids.[6]

In our previous paper[7] dealing with the search of new methods for synthesizing α-hydrazinophosphonates, we reported a new route for obtaining these compounds from aldehydes, *N*,*N*-dimethylhydrazine and dimethyltrimethylsilyl phosphite in 5.0 M lithium perchlorate/diethyl ether (LPDE) solution.[8] In this reaction a hydrazone, formed in situ by the mixture of an aldehyde and *N*,*N*-dimethylhydrazine, is submitted to a nucleophilic attack of dimethyltrimethylsilyl phosphite. In the method developed by us, aliphatic aldehydes were used as substrates for synthesizing dimethyl ester of α-hydrazino phosphonic acids. Unfortunately, the scope of application of this method is limited to α-hydrazinoalkylphosphonic esters. However, aromatic hydrazones are inert to nucleophilic addition of dimethyl trimethylphosphite. In this paper, we wish to report our successful trials on the synthesis of α-hydrazino alkyl (aryl, heterocyclic) phosphonic acids via three-component reaction of aldehydes, *N*,*N*-dimethylhydrazine and trimethylphosphite/ trimethylsilyl chloride in LPDE solution (5.0 M) within 1 h in high yields.[9] Without LPDE solution, no reaction was observed after 4 h.[10] This results are summarized in Scheme 1, which clearly indicate that the present strategy become a general phosphonylation protocol for a variety of alkyl and aryl hydrazones derived from different aldehydes.



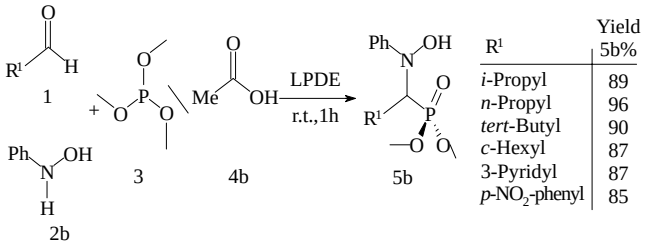
R^1	Yield 5a%
i-Propyl	94
n-Propyl	90
tert-Butyl	94
c-Hexyl	95
2-Furyl	76
p-NO_2-phenyl	86
p-Br-phenyl	89

Scheme 1.

In conclusion, we have shown the first example of the successful dimethyltrimethylsilyl phosphite (the formation of dimethyltrimethylsilyl phosphite has been postulsated without real investigation)[11] addition to a wide range of hydrazones which would provide a novel and general method for preparing not only α-hydrazinoalkylphosphonates but also α-hydrazino aryl(heterocyclic)phosphonates via the three-component coupling reactions. Application of this methodology to the chiral α-hydrazino phosphonates is in progress.

On the basis of the good results obtained with different hydrazones it seemed logical to investigate the possibility of extending this methodology to simple alkyl and aryl nitrones, which gave *N*-hydroxy-α-aminophosphonates. The *N*-hydroxy-α-aminophosphonic acids exerting biological activities have been shown to depend on their absolute configuration.[2] To the best of our knowledge, only a few examples of the synthesis of *N*-hydroxy-α-aminophosphonic acids have been reported: addition of phosphite anions and tris(trimethylsilyl)phosphite to chiral *N*-glycosyl-*C*-aryl-nitrones in the presence of Lewis acids,[12] Mitsunobu S_N2-type displacement reaction of the corresponding α-hydroxyphosphonates with *N*-(phenoxy-carbonyl)-*O*-*tert*-butyl-oxycarbonylhydroxylamine[13] and three-component (aldehydes, phenylhydroxylamine and dimethyl-trimethylsilyl phosphite) coupling reactions via $LiClO_4$ catalyzed tandem reaction.[14] Unfortunately there was no observable three-component reactions of aldehydes, phenylhydroxylamine and trimethylphosphite/trimethylsilyl chloride at ambient temperature in LPDE solution (5.0 M). In order to improve the reaction, we examined several reaction conditions and finally found that the desired product was obtained in high yield when acetic acid as co-catalyst was added.[9] Several examples of the synthesis of *N*-hydroxy-α-aminophosphonates are shown in Scheme 2, and in all cases, the desired products were obtained in high yields.

Encouraged by this result, we replaced trimethylsilyl chloride with acetic acid in one-pot three-component hydrazinophosphonylation reaction. No reaction was observed with this reagent, even after 4 h at room temperature. In conclusion, we have presented a new method for the synthesis of *N*-hydroxy-α-



R^1	Yield 5b%
i-Propyl	89
n-Propyl	96
tert-Butyl	90
c-Hexyl	87
3-Pyridyl	87
p-NO_2-phenyl	85

Scheme 2.

aminophosphonates using nitrone-based chemistry.

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References and Notes

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9 A typical experimental procedure: to a mixture of aldehyde (2 mmol) in 5 M LPDE (4 ml) was added *N*,*N*-dimethylhydrazine (phenylhydroxylamine) (2.2 mmol) at room temperature. The mixture was stirred for 15 min and a mixture of trimethylphosphite/trimethylsilyl chloride (acetic acid) (2.2 mmol) was added. After the mixture stirred for 1 h, water (10 ml) was added. The water layer was extracted with CH_2Cl_2 (3 × 30 ml), and the combined organics were washed with a saturated sodium bicarbonate solution (20 ml) and brine (30 ml), dried (Na_2SO_4), and concentrated. The product was purified by flash chromatography (Hexan-Ethylacetate). ^{1}H NMR, ^{13}C NMR, IR, and MS spectra were entirely consistent with the assigned structures. Selected data are as follow: **4a** (R^1 = *p*-NO_2-phenyl) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.3 (m, 2H, Ar-H), 7.7 (m, 2H, Ar-H), 4.55 (d, $^2J_{P\text{-}H}$ = 20 Hz, 1H, H1), 3.7 (d, $^3J_{P\text{-}H}$ = 11 Hz, 3H, OCH_3), 3.69 (d, $^3J_{P\text{-}H}$ = 11 Hz, 3H, OCH_3), 3.1 (bs, 1H, NH), 2.43 (s, 6H, NCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 129.3 (d, $J_{P\text{-}C}$ = 5 Hz, Ar-C), 125.15 (s, Ar-CH), 123.48 (d, $J_{P\text{-}C}$ = 2.5 Hz, Ar-CH), 60.33 (d, $^2J_{P\text{-}C}$ = 145 Hz, C1), 53.76 (d, $^3J_{P\text{-}C}$ = 6.5 Hz, 3H, OCH_3), 53.65 (d, $^3J_{P\text{-}C}$ = 7 Hz, 3H, OCH_3), 47.48 (s, NCH_3); **4a** (R^1 = *p*-Br-phenyl): ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.47 (m, 2H, Ar-H), 4.37 (d, $^2J_{P\text{-}H}$ = 19 Hz, 1H, H1), 3.66 (d, $^3J_{P\text{-}H}$ = 10.6 Hz, 3H, OCH_3), 3.63 (d, $^3J_{P\text{-}H}$ = 10.6 Hz, 3H, OCH_3), 3.0 (bs, 1H, NH), 2.4 (s, 6H, NCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.24 (d, $J_{P\text{-}C}$ = 6.9 Hz, C-Ar), 131.48 (d, $J_{P\text{-}C}$ = 2.6 Hz, CH-Ar), 130.1 (d, $^3J_{P\text{-}C}$ = 6.8 Hz, OCH_3, $J_{P\text{-}C}$ = 5.8 Hz, CH-Ar), 121.77 (d, $J_{P\text{-}C}$ = 4.3 Hz, Ar-C), 60.16 (d, $^2J_{P\text{-}C}$ = 148 Hz, C1, CH), 53.60 (d, $^2J_{P\text{-}C}$ = 7.3 Hz, OCH_3), 53.50 (d, $^2J_{P\text{-}C}$ = 6.7 Hz, OCH_3), 47.65 (s, NCH_3); **5b** (R^1 = *tert*-butyl): ^{1}H NMR (90 MHz, DMSO): δ = 8.1 (bs, OH), 7.2–7.0 (m, 3H, Ar-H), 6.9–6.8 (m, 2H, Ar-H), 3.58 (d, $^3J_{P\text{-}H}$ = 6.3 Hz, 3H, OCH_3), 3.55 (d, $^2J_{P\text{-}H}$ = 5.4 Hz, 1H, H1), 3.46 (d, $^3J_{P\text{-}H}$ = 6.3 Hz, 3H, OCH_3), 1.25 (s, 9H, CH_3); ^{13}C NMR (125 MHz, DMSO): δ = 153.92 (s, Ar-C), 128.40 (s, Ar-CH), 119.72 (s, Ar-CH), 113.73 (s, Ar-CH), 51.68 (d, $^3J_{P\text{-}C}$ = 6.0 Hz, OCH_3), 50.10 (d, $^3J_{P\text{-}C}$ = 7 Hz, OCH_3), 35.37 (d, $^2J_{P\text{-}C}$ = 8.0 Hz, CH, C1), 28.03 (s, CH_3), 27.98 (s, CH_3); **5b** (R^1 = 3-pyridyl): ^{1}H NMR (90 MHz, DMSO): δ = 8.9 (s, 1H, Py-H), 8.4 (m, 1H, Py-H), 8.0 (m, 2H, Py-H), 7.4–6.8 (m, 5H, Ar-H), 5.2 (d, $^2J_{P\text{-}H}$ = 14 Hz, 1H, H1), 3.7 (d, $^3J_{P\text{-}H}$ = 10.8 Hz, 3H, OCH_3), 3.6 (d, $^3J_{P\text{-}H}$ = 10.8 Hz, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO): δ = 149.88 (d, $J_{P\text{-}C}$ = 5.7 Hz, Py-CH), 148.85 (d, $J_{P\text{-}C}$ = 3.4 Hz, Py-CH), 146.71 (d, $J_{P\text{-}C}$ = 16.3 Hz, Py-C), 135.36 (d, $J_{P\text{-}C}$ = 4.8 Hz, Py-CH), 132.73 (s, Ar-C), 128.94 (s, Ar-CH), 123.20 (d, $J_{P\text{-}C}$ = 2.4 Hz, Ar-CH), 117.95 (s, Ar-CH), 113.84 9 (s, Ar-CH), 53.25 (d, $^3J_{P\text{-}C}$ = 6.6 Hz, OCH_3), 52.80 (d, $^3J_{P\text{-}C}$ = 6.8 Hz, OCH_3), 52.42 (d, $^2J_{P\text{-}C}$ = 152 Hz, CH, C1).

10 When a solution of aldehyde and *N*,*N*-dimethylhydrazine was treated with trimethylphosphite/trimethylsilyl chloride in diethyl ether at room temperature for 4 h, the corresponding hydrazone was obtained with high yield.

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