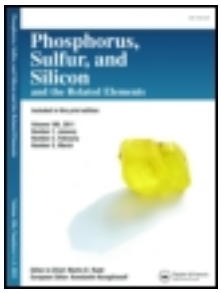

Phosphorus, Sulfur, and Silicon and the Related Elements

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Ultrasound Promoted Synthesis of Biologically Active α-Hydroxyphosphonates/Hydroxyphosphinates using 1,4-Dimethylpiperazine as a Catalyst

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Ultrasound Promoted Synthesis of Biologically Active α-Hydroxyphosphonates/Hydroxyphosphinates using 1,4-Dimethylpiperazine as a Catalyst

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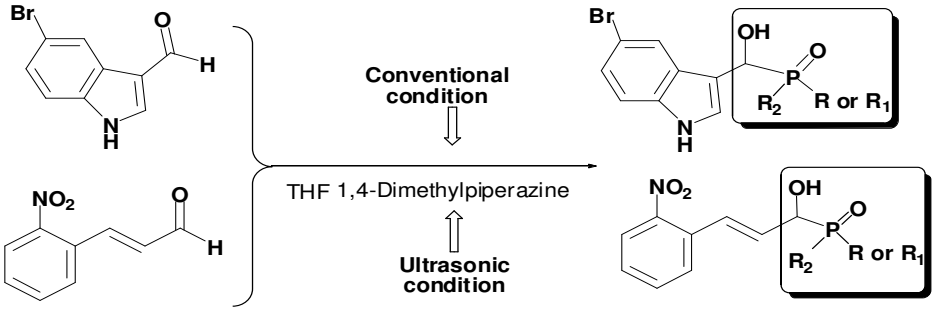
ABSTRACT

A series of new α-hydroxyphosphonates/phosphinates were prepared using 1,4-dimethylpiperazine as a base catalyst under conventional as well as ultrasonic irradiation conditions by the reaction of 5-bromoindole-3-carboxaldehyde/2-nitrocinnamaldehyde with various phosphonates/phosphinates. The high yields of α-hydroxyphosphonates/ hydroxyphosphinates were obtained in less reaction time under ultrasonic irradiation method as compared with the conventional method. The synthesized compounds were screened for their in vitro and in vivo antioxidant activity and the bio-screening data revealed that all the tested compounds exhibited good antioxidant activity. Compound 8e exhibited potent antioxidant activity both in in vitro and in vivo studies.



Keywords: Ultrasound irradiation, 1,4-Dimethylpiperazine, α-Hydroxyphosphonates/hydroxy phosphinates, Antioxidant activity.

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INTRODUCTION

Phosphorus molecules are important scaffolds in organic synthesis to biology. Phosphonates particularly α-hydroxyphosphonates have attained considerable attention since, α-hydroxyphosphonic acids and their esters possesses a broad spectrum of biological and pharmacological activities. It was found that α-hydroxyphosphonates exhibited promising biological activities such as antiviral,1 antivaccina,2 antibacterial,3 anticancer,4 rennin inhibition,5 pesticidal,6 HIV protease inhibitor,7 anti-HIV activity8 and also used as precursors for the synthesis of α-halophosphonates, α-ketophosphonates, α-aminophosphonates, α-thiocyanatophosphonates, α-azidophosphonates and α-carboxyphosphonates.9 Moreover, it was found in the literature that α-hydroxyphosphonates act as potent radical scavengers.10 The versatile biological and synthetic applications of α-hydroxyphosphonates led to considerable attention for the development of new synthetic methodologies and interest to synthesize structurally modified biologically active phosphonates. Several methods have been documented in the literature for the synthesis of α-hydroxyphosphonates in the presence of base catalysts and Lewis acid catalysts, as well as in ultrasonic and microwave irradiation conditions.11-13

Ultrasonication is an important technique and has been used to promote various organic reactions in less time as compared with conventional conditions, and to synthesize bioactive molecules.14-15 Hence, chemists have been focused considerable interest to carry out the reactions under ultrasonication instead of conventional heating. The ultrasound effect on organic reactions is attributed to formation, and growth of acoustic cavitations and impetus collapse of bubbles in the liquid. Bubble collapse provides localized hot-spots with transient temperature of 5000-25000 oK of about 1800 atm and heating cooling rates in excess of 1010 Ks-1.16 The

extreme conditions attained during bubble collapse, favors completion of organic reactions in shorter times.

By considering the biological importance of α-hydroxyphosphonates and our continuous research effort focused on ultrasound assisted reactions,17-18 we herein report new method for the synthesis of α-hydroxyphosphonates/hydroxyphosphinates under ultrasound irradiation and conventional conditions using 1,4-dimethylpiperazine as a base catalyst. The antioxidant activity of the title compounds was evaluated.

RESULTS AND DISCUSSION

Chemistry: α-Hydroxyphosphonates/hydroxyphosphinates were prepared easily under ultrasonication conditions using 1,4-dimethylpiperazine as base catalyst was depicted in Scheme 1. To prepare new title compounds, two alkyl phosphinates 3 a-b were synthesized primarily from phenyl phosphinic acid (1) by treating with NaH in THF at 0-5 o C followed by reacting with EtBr/ n-PrBr at 20-30 oC (Scheme S 1 Supplemental Materials).19

[Scheme 1]

To optimize the reaction conditions for the synthesis of α-hydroxyphosphonates/ phosphinates, 5-bromoindole -3-carboxaldehyde (4) and dimethyl phosphite (5a) were selected as models. At first, the model reaction was carried out in THF at 60-65 oC under catalyst free conditions to obtain diethyl (5-bromo-1H-indol-3-yl)(hydroxy)methylphosphonate (6a), even after for long reaction time (16 h) low yield of the product 6a (38%) was observed (Table 1 entry 1). To improve the yield, the model reaction was progressed in different base catalysts, Et3N, piperazine, 1,4-dimethylpiperazine and Lewis acid catalysts, CuCl2, FeCl3, ZnCl2 (Table 1 entry

2-7). The high yield of the product 6a (78%) was observed in a short reaction time (4 h) using 1,4-dimethylpiperazine as a base catalyst (Table 1 entry 3). Further, to examine the solvent effect on the reaction, the model reaction in the presence of 1,4-dimethylpiperazine was tested in different solvents, CH3CN, C6H5CH3, CH2Cl2 and MeOH (Table 1 entry 8-11). Found that good yield of the compound 6a was observed in THF solvent as compared with other used solvents (Table 1 entry 3). To our delight, the effect of the amount of the catalyst was also examined by altering the amount of the catalyst (Table 2 entry 1-5) results revealed that 30 mol% of catalyst, 1,4-dimethylpiperazine is adequate to afford the high yield of the product 6a (Table 2 entry 5). However, the high amount of the catalyst (30 mol%), 1,4-dimethylpiperazine was used to obtain good yield of the product and the catalyst was not reused due to homogeneity of the catalyst. The proposed mechanism for the synthesis of α-hydroxy phosphonates in the presence of 1,4-dimethylpiperazine catalyst was shown in Figure S 1. The generality of the optimized conditions was checked by altering phosphites/synthesized phosphinates, aldehydes and the products were obtained in good yields. The results are tabulated in Table 3.

[Insert Table 1 and Table 2]

In continuation of our endeavor and in search of alternative to conventional heating methods, we attempted to carry out the optimized reaction condition under ultrasonication, interestingly, the reaction was completed in very short reaction time (21 min) and afforded a high yield of the product 6a (88%) at 60 oC in THF. The generality of the reaction was explored and the results are summarized in Table 3.

[Insert Table 3]

The chemical structures of all the synthesized compounds 6 a-e and 8 a-e were characterized by NMR (31P, 1H, 13C), IR, mass spectral data and C, H, N analysis. In 31P NMR spectra, the resonated signals appeared as singlet in the region 18.7-23.9 ppm.21 The P-C-H protons resonated as a doublet due to its coupling with phosphorus atom in the region 4.80-4.64 ppm. In 13C NMR, all the signals were observed in their respective regions. The appearance of characteristic IR stretching absorptions in the regions of 3473-3300 cm-1, 1020-1000 cm-1, 1260-1190 and 785-700 cm-1 confirmed the functionalities, -OH, P-O-C(butyl), P=O, P-C (aliphatic) respectively in the title compounds.22

To avoid the mortality of the animals, an in vitro study was made as preliminary screening method. In vitro non-enzymatic antioxidant activity of title α-hydroxyphosphonates/ phosphinates was evaluated using DPPH23 and superoxide radical scavenging24 methods (Table S 1). Bio-screening data revealed that all the compounds showed potent to moderate antioxidant activity, whereas compounds 6a, 6d, 8d and 8e exhibited potent antioxidant activity in both methods and these results encouraged us to carry out in vivo studies. CATALASE activity25-26 of the title compounds (Figure S 1) was screened and the results indicated that 6a, 6d, 8d and 8e compounds exhibited promising in vivo antioxidant activity. The biological data of the tested compounds disclosed that compounds 6a, 6d, 8d and 8e exhibited promising activity in both enzymatic and non-enzymatic assays. However, compound 8e exhibited scavenged maximum free radicals at both concentrations when compared to the remaining title compounds and the IC50 value of the compound 8e is very near to the standard ascorbic acid.

CONCLUSION

In summary, a simple synthetic protocol was developed for the synthesis of α-hydroxyphosphonates/phosphinates under ultrasonication and conventional conditions using 1,4-dimethylpiperazine as a base catalyst. The high yields of α-hydroxyphosphonates/ phosphinates were obtained in lower reaction times under ultrasonication method as compared with conventional method. Further, in vitro and in vivo antioxidant activity was evaluated for the title compounds and all the tested compounds exhibited potent to moderate antioxidant activity. Compounds 6a, 6d, 8d and 8e exhibited promising radical scavenging activity. The variation in scavenging capacity of the tested samples could be attributed to the effect of different substitutions at the α-carbon. The antioxidant activity study of the synthesized compounds provided an additional direction for structural optimization of the compounds for the development of antioxidant nature with improved selectivity and reduced side effects.

EXPERIMENTAL

Thin layer chromatography was performed using silica gel 60 F-254 pre-coated plates (0.25 mm) and visualized by iodine and UV irradiation. Sorbent silica gel (particle size 60-120 mesh) was used for column chromatography for purification of the synthesized compounds. 1H, 13C NMR and 31P NMR spectra were recorded in CDCl3 on a Bruker 400 MHz spectrometer operating at 400 MHz for 1H, 100.25 MHz for 13C and 161.9 for 31P. TMS and 85% H3PO4 were used as internal standards in 1H NMR, 13C NMR and 31P NMR respectively. Mass spectra were recorded in E.S.I Mode on API-3000 mass spectrometer. Elemental analysis was performed on Thermo Finnigan Instrument at University of Hyderabad, Hyderabad.

Sonication was performed using BANDELIN SONOREX® (Germany) with a frequency of 35 kHz and a nominal power 200 W ultrasonic bath for ultrasonic irradiation with inbuilt heating 30-80 (°C), which is thermostatically adjustable. The reaction vessel was placed inside the ultrasonic bath containing water.

Synthesis of dimethyl (5-bromo-1H-indol-3-yl)(hydroxy)methylphosphonate (6a).

Conventional method

5-Bromoindole-3-carboxaldehyde (4) (1 mmol, 223 mg), dimethyl phosphite (5a) (1 mmol, 0.095 mL) and 1,4-dimethylpiperazine (30 mol%) were dissolved in THF (10 mL) in a flask. The reaction mixture was stirred at 60-65oC for 4 h. Progress of the reaction was checked by TLC using n-hexane and ethyl acetate (1:4) as an eluent. After completion of the reaction, the reaction mixture was concentrated using a rota-evaporator and the crude product was purified by column chromatography on silica gel (60–120 mesh) using n-hexane and ethyl acetate (3:1) as an eluent to afford pure dimethyl (5-bromo-1H-indol-3-yl)(hydroxy) methylphosphonate (6a) (84%).

Ultrasonication method

5-Bromoindole-3-carboxaldehyde (4) (1 mmol, 223 mg), dimethyl phosphite (5a) (1 mmol, 0.095 mL) and 1,4-dimethylpiperazine (30 mol%) were dissolved in THF (10 mL) in a flask. The reaction mixture was stirred at 60 oC under ultrasonic irradiation for 21 min. Progress of the reaction was checked by TLC using hexane and ethyl acetate (1:4) as an eluent. After the completion of the reaction, the reaction mixture was concentrated in vacuum to obtain the crude product and it was purified by column chromatography on silica gel (60-120 mesh) using hexane

and ethyl acetate (3:1) as an eluent to afford pure dimethyl (5-bromo-1H-indol-3-yl)(hydroxy)methylphosphonate (6a) (87%). The same experimental procedure was adopted for the preparation of the remaining title compounds 6 b-e and 8 a-e.

Dimethyl (5-bromo-1H-indol-3-yl)(hydroxy)methylphosphonate (6a).

Pale yellow solid, mp: 67-69 oC. 31P NMR (CDCl3, 161.9 MHz): δ 19.1 ppm; 1H NMR (CDCl3, 400 MHz): δ 3.86 (s, 6H), 4.49 (d, 1H, J = 7.3 Hz, P-C-H), 6.02 (s, -OH), 7.18 (s, 1H, Ar-H), 7.78 (s, 1H, Ar-H), 7.30 (d, 1H, J = 4.8 Hz, Ar-H), 7.32 (d, J = 4.4 Hz, 1H, Ar-H), 8.17 (s, 1H, NH) ppm; IR (KBr) (vmax cm-1): 723 (P-C), 1022 (P-O-C(aliphatic)), 1195 (P=O), 3474 (-OH); E.S.I. mass m/z (%): 334 (100) [M+.], 336 (98) [M+.+2], 319 (55); Anal. cald. for C11H13BrNO4P: C: 39.54, H: 3.92, N: 4.19. Found: C: 39.50, H: 3.89, N: 4.13.

(E)-Dimethyl 1-hydroxy-3-(2-nitrophenyl)allylphosphonate (8a).

Pale orange solid, mp: 84-86oC. 31P NMR (CDCl3, 161.9 MHz): δ 22.6 ppm; 1H NMR (CDCl3, 400 MHz): δ 3.90 (s, 6H), 4.60 (d, 1H, J = 6.3 Hz, P-C-H), 5.20 (s, -OH), 6.40-6.50 (dd, 1H, J = 15.8, 7.0 Hz), 6.70 (d, 1H , J = 15.9 Hz), 7.30 - 7.60 (m, 3H), 8.00 (d, 1H , J = 14.0 Hz) ppm; IR (KBr) (vmax, cm-1): 740 (P-C), 1016 (P-O-C(aliphatic)), 1220 (P=O), 3460 (-OH); E.S.I. mass m/z (%): 287 (100) [M+.], 257 (38), 179 (20), 135 (30); Anal. cald. for C11H14NO6P: C: 46.00; H: 4.91; N: 4.88; Found: C: 46.10; H: 4.88; N: 4.91.

The Supplemental Materials contains additional characterization data for compounds 6b-e and 8b-eand sample spectra for compound 8d (Figures S 3 – S 5).

BIOLOGICAL ACTIVITY:

The in vitro antioxidant activity of the newly synthesized compounds 6 a-e and 8 a-e was screened using DPPH, superoxide radical scavenging methods. The biological data revealed that

all the compounds exhibited potent to moderate antioxidant activity. These results encouraged to investigate in vivo antioxidant activity of the title compounds on catalase, which was carried out after the examination of the acute toxicity of the title compounds. The results are summarized in Table S 1 and Figure S 1 (See Supplemental Materials).

STATISTICAL ANALYSIS

All the values expressed as mean ± SD and data were analyzed by one-way ANOVA, using Graph pad INSTAT. The post-hock analysis was carried out by Dunnet's multiple comparison tests to estimate the significance of difference between individual groups.

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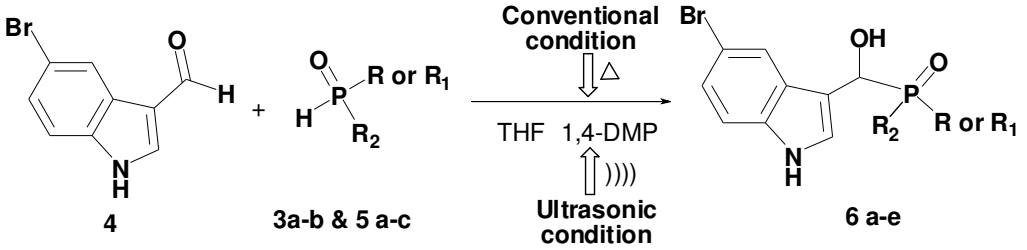
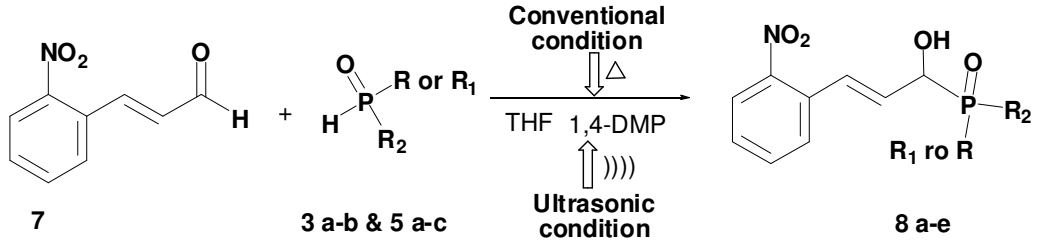




S. No	R	R_1	R_2	Phosphinate/phosphite	Product
1		OMe	OMe	5a	**6a**
2		OEt	OEt	5b	**6b**
3		OBut	OBut	5c	**6c**
4	OEt		Ph	3a	**6d**
5	OPri		Ph	3b	**6e**
6		OMe	OMe	5a	**8a**
7		OEt	OEt	5b	**8b**
8		OBut	OBt	5c	**8c**
9	OEt		Ph	3a	**8d**
10	OPri		Ph	3b	**8e**

Scheme 1. Synthesis of α-hydroxyphosphonates/phosphinates under conventional and ultra-sonication conditions.

Table 1. Optimization of the catalyst and solvent for the synthesis of α-hydroxyphosphonates/phosphinates.a

Entry	Catalyst	Solvent	Temperature (oC)	Time (h)	Yield (%)
1	No catalyst	THF	60-65	16.0	38
2	Et3N (25 mol%)	THF	60-65	7.0	49
3	1,4-Dimethylpiperazine (25 mol%)	THF	60-65	4.0	78
4	Piperazine (25%)	THF	60-65	4.0	75
5	CuCl2 (25 mol%)	THF	60-65	4.0	69
6	FeCl3 (25 mol%)	THF	60-65	4.0	71
7	ZnCl2 (25 mol%)	THF	60-65	4.0	71
8	1,4-Dimethylpiperazine (25 mol%)	CH3CN	75-80	4.0	69
9	1,4-Dimethylpiperazine (25 mol%)	C6H5CH3	80-90	4.0	70
10	1,4-Dimethylpiperazine (25 mol%)	DCM	30-40	4.0	65
11	1,4-Dimethylpiperazine (25 mol%)	EtOH	60-65	4.0	68

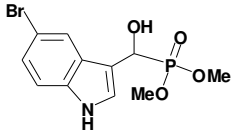
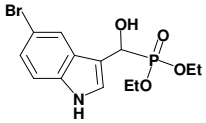
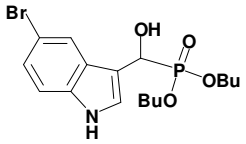
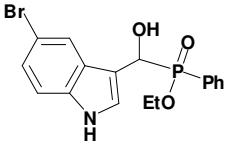
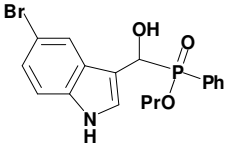
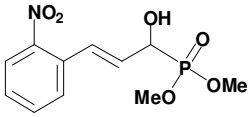
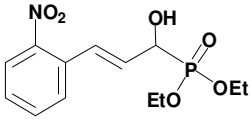
aThe model reaction was carried out using 5-bromoindole -3-carboxaldehyde (4) (1 mmol) and dimethyl phosphite (5a).

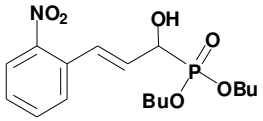
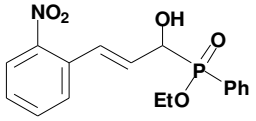
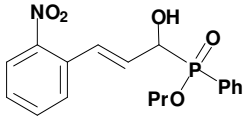
Table 2. Amount of catalyst, 1,4-dimethylpiperazine effect on the synthesis of α-hydroxy phosphonates/phosphinates.a

Entry	Catalyst mol (%)	Time	Yield (%)b
1	2.5	4.0 h	46
2	5	4.0 h	53
3	10	4.0 h	58
4	20	4.0 h	65
5	30	4.0 h	84
6	40	4.0 h	84
7c	30	21 minc	88

aThe model reaction was carried out using 5-bromoindole -3-carboxaldehyde (4) (1 mmol) and dimethyl phosphite (1 mmol) (5a). bIsolated yields. cThe model reaction was carried out in ultra-sonication using 30 mol% of 1,4-dimethyl piperazine as a catalyst.

Table 3 Synthesis of α-hydroxyphosphonates/phosphinates under conventional and ultra-sonication using 30 mol% of DMP catalyst.

Compd	Structure	Timea (h)/ b (min)	Yielda/b (%)
6a		4.0/21	84/88
6b		4.0/21	86/90
6c		4.5/21	86/86
6d		5.0/21	83/87
6e		5.0/21	85/85
8a		4.5/21	80/85
8b		4.5/21	81/87

8c		5.0/21	81/87
8d		5.0/21	82/83
8e		5.0/21	79/84

aTime and isolated yields of the reaction was carried out under conventional conditions. bTime and isolated yields of the reaction was carried out under ultra-sonication conditions.