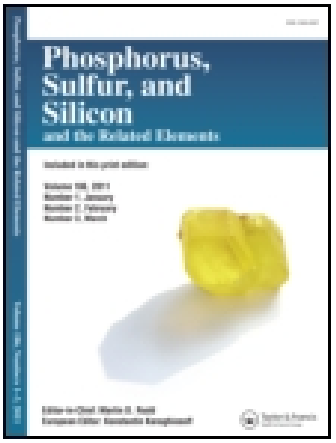


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

The Synthesis and Bioactivity of Dimethyl (2,3- Dihydrobenzo[b] [1,4]Dioxin-6-Yl)(Aryl Amino)Methylphosphonates

Ch. Syama Sundar [a] , N. Bakthavatchala Reddy [a] , S. Siva Prasad [a] , K. Uma Maheswara Rao [a] , S. H. Jaya Prakash [a] & C. Suresh Reddy [a]
[a] Department of Chemistry , Sri Venkateswara University , Tirupati , Andhra Pradesh , India

Accepted author version posted online: 23 Sep 2013.Published online: 12 Mar 2014.

To cite this article: Ch. Syama Sundar , N. Bakthavatchala Reddy , S. Siva Prasad , K. Uma Maheswara Rao , S. H. Jaya Prakash & C. Suresh Reddy (2014) The Synthesis and Bioactivity of Dimethyl (2,3-Dihydrobenzo[b][1,4]Dioxin-6-Yl)(Aryl Amino)Methylphosphonates, Phosphorus, Sulfur, and Silicon and the Related Elements, 189:4, 551-557, DOI: 10.1080/10426507.2013.842998

To link to this article: http://dx.doi.org/10.1080/10426507.2013.842998

Phosphorus, Sulfur, and Silicon, 189:551–557, 2014

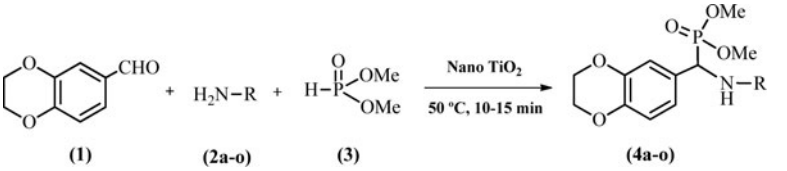
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2013.842998

THE SYNTHESIS AND BIOACTIVITY OF DIMETHYL (2,3-DIHYDROBENZO[B][1,4]DIOXIN-6-YL)(ARYL AMINO)METHYLPHOSPHONATES

Ch. Syama Sundar, N. Bakthavatchala Reddy, S. Siva Prasad, K. Uma Maheswara Rao, S. H. Jaya Prakash, and C. Suresh Reddy

Department of Chemistry, Sri Venkateswara University, Tirupati, Andhra Pradesh, India

GRAPHICAL ABSTRACT



Abstract *A new series of α-aminophosphonates have been synthesized by a one-pot three-component reaction of 2,3-dihydrobenzo[b][1,4]dioxine-6-carbaldehyde, various amines, and dimethyl phosphite by using nano-TiO_2 as a catalyst under solvent-free conditions at 50°C. The major advantages of the present method are high yields, short reaction times, recyclable catalyst, and solvent-free reaction conditions. Among these new structurally diversified set of α-aminophosphonates, dimethyl (2,3-dihydrobenzo[b][1,4]dioxin-6-yl)(3-nitrophenylamino) methylphosphonate and dimethyl (2,3-dihydrobenzo[b][1,4]dioxin-6-yl)(4-fluoro-3-nitrophenyl-amino) methylphosphonate have shown higher antioxidant activity in diphenyl picryl hydrazyl (DPPH) scavenging, reducing power assay, and lipid peroxidation methods.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *for the following free supplemental files: Additional text and figures.]*

Keywords α-Aminophosphonates; nano-TiO_2; solvent-free; antioxidant activity

INTRODUCTION

The synthesis of α-aminophosphonates has gained much interest in recent times due to their structural similarity to the corresponding α-amino acids and role played as transition

Received 10 April 2013; accepted 16 August 2013.

The authors express their grateful thanks to Prof. C. D. Reddy, Department of Chemistry, Sri Venkateswara University, Tirupati, for his helpful discussions and also thank DRDO, New Delhi, for providing financial assistance (ERIP/ER/1103894M/ 01/1346). The authors also express their thanks to Prof. Ch. Appa Rao and S. Swapna, Department of Bio-chemistry, S.V. University, Tirupati for conducting antioxidant activity.

Address correspondence to C. Suresh Reddy, Department of Chemistry, Sri Venkateswara University, Tirupati, Andhra Pradesh, India. Tel.: +91-9849694958; Fax: +91877-2289555; E-mail: csrsvu@gmail.com

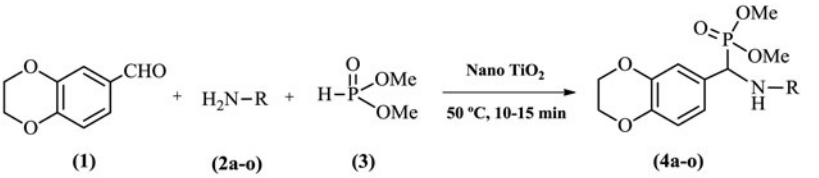
state mimics in peptide hydrolysis.[1,2] Many natural and synthetic α-aminophosphonates and their derivatives have potential applications as anti-HIV, anticancer, and antibiotic agents.[3–8] Furthermore, they are used in agriculture as fungicides, herbicides, and plant growth regulators.[9–11] Consequently different methods have been developed for their synthesis. Of these, nucleophilic addition of phosphites to imines is an established and useful method in which catalysts like $InCl_3$, SmI_2, $ZnCl_2$, $SnCl_4$, $In(OTf)_3$, $Cu(OTf)_2$, $MgClO_4$, and $BF_3.Et_2O$ are conveniently used.[12–19] However, some of these methods are associated with one or more shortcomings such as longer reaction time, use of hazardous and expensive catalysts, low product yields, use of solvents, and harsh reaction conditions. Hence, they do not comply with green chemistry protocols. Due to their valuable role of α-aminophosphonates as versatile building blocks in the synthesis of biologically important compounds, development of an eco-friendly synthesis for them is desirable.

Multicomponent, one-pot synthesis has received considerable attention because of its wide range of applications in pharmaceutical chemistry for the creation of structural diverse combinatorial libraries in drug discovery.[20] Multicomponent reactions are extremely convergent, producing remarkably high increase of molecular complexity in a single step operation.[21] In recent years, much attention has been focused on the design and use of environment-friendly catalysts to increase the product yields and to reduce the amount of toxic waste.[22] Nano-scale metal oxides are found to be highly effective as catalysts for many organic transformations and for the destruction of hazardous chemicals.[23] As a part of our continued interest in the development of synthetic methods for the phosphonate derivatives,[24–27] we found that nano-TiO_2 can be readily used as efficient catalyst in the Kabachnik–Fields reaction for the preparation of α-aminophosphonates under solvent-free conditions. Even though Hosseini–Sarvari reported synthesis of α-aminophosphonates with TiO_2 as catalyst,[28] this reaction requires a large amount of catalyst and long reaction time. Use of nano-TiO_2 reduces this reaction time and catalyst amount. All the synthesized novel α-aminophosphonates **(4a–o)** were screened for antioxidant activity by diphenyl picryl hydrazyl (DPPH) scavenging, reducing power assay, and lipid peroxidation methods.

RESULTS AND DISCUSSION

An efficient and environmentally benign one-pot method was developed for the synthesis of α-aminophosphonates **(4a–o)** by reaction of 2,3-dihydrobenzo[b][1,4]di-oxine-6-carbaldehyde **(1)**, various amines **(2)**, and dimethyl phosphite **(3)** in the presence of nano-TiO_2 as catalyst under solvent-free conditions at 50^oC (Scheme 1).

In order to standardize the operating reaction conditions, the reaction among 2,3-dihydrobenzo[b][1,4]dioxine-6-carbaldehyde, aniline, and dimethyl phosphite was run as a model. At room temperature there is minimal formation of the corresponding α-aminophosphonates in the presence of nano-TiO_2 catalyst even after 6 h of reaction time under solvent-free conditions (Table 1, Entry 1). Increase of the reaction temperature from 30^oC to 50^oC led to the formation of α-aminophosphonates up to 94% yield. Further increase in the temperature did not show any improvement in the yield. No formation of product was observed in the absence of nano-TiO_2 even after 6 h of the reaction time (Table 1, Entry 6). This shows that nano-TiO_2 is absolutely essential to drive the reaction to completion. The reusability of the nano-TiO_2 as a catalyst was also examined. After each run, the product was filtered and the catalyst residue was washed with CH_2Cl_2, dried, and reused. It was found that the catalyst can be used for three cycles in the synthesis of



Entry	R	Entry	R	Entry	R
2a & 4a		2f & 4f		2k & 4k	
2b & 4b		2g & 4g		2l & 4l	
2c & 4c		2h & 4h		2m & 4m	
2d & 4d		2i & 4i		2n & 4n	
2e & 4e		2j & 4j		2o & 4o	

Scheme 1

compound **4a** and in each case it gave 94%, 94%, 93% yield of the product, respectively (Table 1, Entry 3).

After optimization of experimental conditions with aniline, we extended this three-component coupling reaction with several other amines keeping 2,3-dihydrobenzo[b][1,4]dioxine-6-carbaldehyde and dimethyl phosphite as constant substrates and nano-TiO_2 as the catalyst.

In all the cases, the reactions were completed within 10–15 min and gave the corresponding α-aminophosphonates in 86%–96% yield. In these reactions, initial formation of imine intermediate is the key step for which further addition of dimethyl phosphite

Table 1 Optimization of reaction conditions for synthesis of **4a**

Entry	Temperature (°C)	Nano TiO_2 (mol%)	Time (min/h)	Yield (%)[a]
1	30/RT	5	6 h	48
2	40	5	15 min	72
3[b]	50	5	10 min	94,94,93
4	60	5	10 min	94
5	70	5	10 min	94
6	50	0	6 h	—

[a]Isolated yield.
[b]Catalyst was reused three times.

Table 2 Physical characteristics of α-aminophosphonates (**4a–o**)

Product (4)	Time (min)	Yield (%)[a]	mp[b] (°C)
4a	10	94	184–186
4b	12	90	171–173
4c	12	89	175–176
4d	10	96	142–144
4e	12	95	197–199
4f	15	86	131–133
4g	15	87	142–144
4h	12	91	128–130
4i	14	89	101–103
4j	10	91	125–127
4k	12	87	135–137
4l	14	88	138–140
4m	12	90	161–163
4n	15	89	125–127
4o	15	90	141–143

[a]Isolated yield.
[b]Melting point.

occurs to form α-aminophosphonates. Analysis of the data (Table 2) reveals that the amine substrates with electron donating groups (-Me, -OMe) gave high yields when compared with those having electron withdrawing groups (-NO_2, -F, -Cl). Electron donating group increases the nucleophilicity of N-atom facilitates its bonding with electrophilic carbonyl carbon of the aldehyde during the formation of imine intermediate. The proposed chemical structures for the synthesized compounds **4a–o** were confirmed by IR, ^{1}H, ^{13}C, ^{31}P, and mass spectrometry and elemental analyses.

CONCLUSION

An efficient one-pot synthesis of α-aminophosphonates by the reaction of aldehyde, amine, and dimethyl phosphite in the presence of nano-TiO_2 as catalyst under solvent-free conditions in excellent yields is accomplished. The advantages of this method are mild reaction conditions, use of eco-friendly reusable catalyst, easy workup, and high yields. Being an effective and green procedure, this may serve as the method of choice for commercial production of α-aminophosphonates. Their antioxidant activity as evaluated by DPPH scavenging, reducing power assay, and lipid peroxidation methods for the compounds **4f**, **4g**, **4i**, and **4k** shown them to have higher antioxidant activity when compared with that of the standard Ascorbic acid antioxidant.

EXPERIMENTAL

All reagents were purchased from Sigma-Aldrich, Hyderabad, India, and used without further purification. IR spectra were recorded in KBr pellets on a Perkin-Elmer 683 spectrophotometer (California, USA). ^{1}H, ^{13}C, ^{31}P NMR spectra were taken on Jeol JNM ECP 400 NMR instrument (Tokyo) at room temperature in DMSO-d_6 or $CDCl_3$ using tetramethylsilane (TMS) as internal standard. ^{31}P NMR (161.7 MHz) was taken in DMSO-d_6 using 85% H_3PO_4 as external standard with broadband ^{1}H decoupling. EI-Mass spectra

were obtained on JEOL GCMATE II GC-MS spectrometer (Tokyo) at SAIF IIT-Madras, Chennai. Melting points were determined on Guna Mel-Temp apparatus (Tempo Instruments and Equip., Mumbai, India) and were uncorrected.

General Procedure for α-Aminophosphonates (4a–o)

A mixture of aldehyde (1 mmol), amine (1 mmol), dimethylphosphite (1 mmol), and nano-TiO_2 (5 mol%) was stirred at 50°C. The completion of the reaction was confirmed by thin layer chromatography (TLC). CH_2Cl_2 (10 mL) was added, stirred and filtered the mixture to separate the catalyst that was dried under vacuum and reused. The filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product obtained was subsequently purified by silica gel column chromatography using 30% ethyl acetate: *n*-hexane as an eluent. This procedure was successfully applied for the preparation of all title products (Table 2). The supplemental material contains complete characterization data for the new compounds and selected spectra for **4a**, **4b**, and **4l** (Figures S4–S12).

Physical, Analytical, and Spectral Data for Selected Compounds 4a, 4b, and 4l

Dimethyl (2,3-Dihydrobenzo[b][1,4]Dioxin-6-yl)(Phenylamino) Methyl Phosphonate (4a). Brown solid, Yield: 94%, mp: 184°C–186°C. IR (KBr) (ν_{max}, cm^{-1}): 3296 (NH), 1235 (P = O), 751 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.53 (3H, d, J = 12 Hz, P-OCH_3), 3.77 (3H, d, J = 8 Hz, P-OCH_3), 4.21 (4H, s, OCH_2CH_2O), 4.68 (1H, d, J = 20 Hz, P-CH), 4.73 (1H, s, NH), 6.58–7.13 (8H, m, Ar-H). ^{13}C NMR (100.5 MHz, DMSO-d_6) δ: 53.8 (d, J = 12 Hz, 2 X P-OCH_3), 54.9 (d, J = 152 Hz, P-CH), 64.2 (C-4 & C-5), 113.8 (C-2^1 & C-6^1), 116.6 (C-6), 117.5 (C-3), 118.5 (C-2), 120.7 (C-4^1), 128.5 (C-1), 129.1 (C-3^1 & C-5^1), 143.3 (C-7), 143.7 (C-8), 146.0 (C-1^1). ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 20.0. EI-MS (*m/z*, %): 350 (M+1, 20), 349 (M+•, 100). Anal. Calcd. for $C_{17}H_{20}NO_5P$: C, 58.45; H, 5.77; N, 4.01. Found: C, 58.35; H, 5.67; N, 3.95.

Dimethyl (2,3-Dihydrobenzo[b][1,4]Dioxin-6-yl)(4-Fluorophenylamino) Methyl Phosphonate (4b). Red solid, Yield: 90%, mp: 171°C–173°C. IR (KBr) (ν_{max}, cm^{-1}): 3298 (NH), 1246 (P = O), 749 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.48 (3H, d, J = 12 Hz, P-OCH_3), 3.66 (3H, d, J = 12 Hz, P-OCH_3), 4.19 (4H, s, OCH_2CH_2O), 4.95 (1H, dd, J = 12 Hz, J = 28 Hz, P-CH), 6.23–6.26 (1H, m, NH), 6.76–7.02 (7H, m, Ar-H). ^{13}C NMR (100.5 MHz, DMSO-d_6) δ: 52.9 (d, J = 7 Hz, P-OCH_3), 53.3 (d, J = 6 Hz, P-OCH_3), 52.9 (d, J = 153 Hz, P-CH), 63.9 (C-4 & C-5), 114.4 (C-3^1 & C-5^1), 114.8 (C-6), 115.0 (C-2^1 & C-6^1), 116.8 (C-3), 121.2 (C-2), 129.3 (C-1), 142.7 (C-7), 142.9 (C-8), 143.6 (C-1^1), 154.8 (C-F, d, J = 203 Hz,). ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 22.2. EI-MS (*m/z*, %): 368 (M+1, 18), 367 (M+•, 100). Anal. Calcd. for $C_{17}H_{19}FNO_5P$: C, 55.59; H, 5.21; N, 3.81. Found: C, 55.49; H, 5.16; N, 3.75.

Dimethyl ((2,3-Dihydrobenzo[b][1,4]Dioxin-6-yl)(Pyridin-4-Ylamino)Methyl) Phosphonate (4l). Green solid, Yield: 88%, mp: 138°C–140°C. IR (KBr) (ν_{max}, cm^{-1}): 3301 (NH), 1262 (P=O), 749 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.75 (3H, d, J = 8 Hz, P-OCH_3), 3.91 (3H, d, J = 8 Hz, P-OCH_3), 4.20 (4H, s, OCH_2CH_2O), 4.63 (1H, d, J = 24, P-CH), 6.89–6.93 (1H, m, NH), 7.26–8.20 (7H, m, Ar-H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 52.9 (d, J = 6.2 Hz, P-OCH_3), 53.3 (d, J = 6.2 Hz, P-OCH_3), 54.9 (d, J = 154.3 Hz, P-CH), 63.4 (C-4 & C-5), 114.5 (C-6), 114.7 (C-2^1 & C-5^1), 116.5 (C-3), 121.0 (C-2), 129.9 (C-1), 142.6 (C-7), 142.8 (C-8), 143.4 (C-3^1 & C-4^1), 155.8 (C-1^1). ^{31}P

NMR (161.7 MHz, DMSO-d_6) δ: 20.5. EI-MS (*m/z*, %): 351 (M+1, 21), 350 (M+•, 100). Anal. Calcd. for $C_{16}H_{19}N_2O_5P$: C, 54.86; H, 5.47; N, 8.00. Found: C, 54.76; H, 5.41; N, 7.94.

Biology

Antioxidant Activity. According to our prediction, the α-aminophosphonates (**4a–o**) have the ability to scavenge the DPPH radical by donating one electron. Since phosphorus has affinity toward oxygen, it can easily bind and scavenge reactive oxygen species (ROS) effectively. The compounds **(4a–o)** containing phosphorus, oxygen, and nitrogen atoms are expected to be more active due to the presence of nonbonded electron pairs containing hetero atoms that serve as binding sites in the bio-matrix. **4f, 4g, 4i,** and **4k** displayed appreciable antioxidant activity. **4i** showed the highest activity because both fluorine and $-NO_2$ substituents helps homolytic cleavage of α-methylene C-H bond to form corresponding free radicals which in turn reacts with ROS radical and scavenge them. The α-C-H bond in **4i** has to take place since the resulting phosphoryl free radical is more stable due to the extensive delocalization of the free radicals over the conjugated aromatic phosphoryl system.

Diphenyl Picryl Hydrazyl (DPPH) Radical Scavenging Activity. The free radical scavenging activity of α-aminophosphonates against DPPH radical was performed in accordance with Choi et al.[29] and results are summarized in Figure S1.

Reducing Power Assay. The reducing power of synthesized compounds was determined according to the method of Oyaizu et al.[30] and results are summarized in Figure S2 (supplemental materials).

Lipid Peroxidation Assay. It was determined using a modified method of Ohkawa et al.[31] and results are summarized in Figure S3 (supplemental materials).

REFERENCES

1. Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991,** 63, 193-215.
2. Thirumurugan, P.; Nandakumar, A.; Priya, N. S.; Muralidaran, D.; Perumal, P. T. *Tetrahedron Lett.* **2010,** 51, 5708-5712.
3. Tibhe, G. D.; Lagunas-Rivera, S.; Vargas-Diaz, E.; Garcia-Barradas, O.; Ordonez, M. *Eur. J. Org. Chem.* **2010,** 2010, 6573-6581.
4. Boukallaba, K.; Elachqar, A.; Hallaoui, A. E.; Alami, A.; Hajji, S. E.; Labriti, B.; Martinez, J.; Rolland, V. *Phosphorus, Sulfur Silicon Relat. Elem.* **2006,** 181, 819-823.
5. Ravinder, K.; Reddy, A. V.; Krishnaiah, P.; Venkataramana, G.; Reddy, V. L. N.; Venkateswarlu, Y. *Synth. Commun.* **2004,** 34, 1677-1683.
6. Dake, S. A.; Raut, D. S.; Kharat, K. R.; Mhaske, R. S.; Deshmukh, S. U.; Pawar, R. P. *Bioorg. Med. Chem. Lett.* **2011,** 21, 2527-2532.
7. Lavielle, G.; Hautefaye, P.; Schaeffer, C.; Boutin, J. A.; Cudennec, C. A.; Pierre, A. *J. Med. Chem.* **1991,** 34, 1998-2003.
8. Xu, Y.; Yan, K.; Song, B.; Xu, G.; Yang, S.; Xue, W.; Hu, D.; Lu, P.; Ouyang, G.; Jin, L.; Chen, Z. *Molecules* **2006,** 11, 666-676.
9. Maier, L; Diel, P. J. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991,** 57, 57-64.
10. Kozolowski, H.; Pusino, A.; Swiatek, J.; Spychala, J.; Glowiak, T.; Micera, G.; Gessa, C. *J. Agric. Food Chem.* **1990,** 38, 1989-1992.
11. Nska, H.; Bonarska, D.; Bielecki, K., Sarapuk, J. *Cell. Mol. Biol. Lett.* **2002,** 7, 929-935.
12. Ranu, B. C.; Hajra, A.; Jana, U. *Org. Lett.* **1999,** 1, 1141-1143.

13. Xu, F.; Luo, Y. Q.; Deng, M. Y.; Shen, Q. *Eur. J. Org. Chem.* **2003,** 4728-4730.
14. Zon, J. *Pol. J. Chem.* **1981,** 55, 643-646.
15. Laschat, S.; Kunz, H. *Synthesis*. **1992,** 90-94.
16. Ghosh, R.; Maiti, S.; Chakraborty, A.; Maiti, D. K. *J. Mol. Catal. A: Chem.* **2004,** 210, 53-57.
17. Paraskar, A. S.; Sudalai, A. *Arkivoc*. **2006,** x, 183-189.
18. Bhagat, S.; Chakraborti, A. K. *J. Org. Chem.* **2007,** 72, 1263-1270.
19. Ha, H. J.; Nam, G. S. *Synth. Commun*. **1992,** 1143-1148.
20. Subba Reddy, B. V.; Reddy, M. R.; Narasimhulu, G.; Yadav, J. S. *Tetrahedron Lett*. **2010,** 51, 5677-5679.
21. Jiang, B.; Rajale, T.; Wever, W.; Tu, S. J.; Li, G. *Chem. Asian J*. **2010,** 5, 2318-2335.
22. Mukhopadhyay, C.; Ray, S. *Tetrahedron* **2011,** 67, 7936-7945.
23. Karmakar, B.; Banerji, J. *Tetrahedron Lett*. **2011,** 52, 4957-4960.
24. Syama Sundar, Ch.; Srinivasulu, D.; Nayak S. K.; Suresh Reddy, C. *Phosphorus, Sulfur Silicon Relat. Elem.* **2012,** 187, 523-534.
25. Bakthavatchala Reddy, N.; Uma Maheswara Rao, K.; Syama Sundar, Ch.; Siva Prasad, S.; Nayak, S. K.; Suresh Reddy, C. *Org. Commun*. **2012,** 5, 171-178.
26. Santhi Sudha, S.; Syama Sundar, Ch.; Bakthavatchala Reddy, N.; Uma Maheswara Rao, K.; Jaya Prakash, S. H.; Suresh Reddy, C. *Phosphorus, Sulfur Silicon Relat. Elem.* **2012,** 188, 1402-1411.
27. Narayana Reddy, M. V.; Siva Kumar, B.; Balakrishna, A.; Suresh Reddy, C.; Nayak, S. K.; Reddy, C. D. *Arkivoc*. **2007,** xv, 246-254.
28. Hosseini–Sarvari, M. *Tetrahedron* **2008,** 64, 5459-5466.
29. Choi, C. W.; Kim, S. C.; Hwang, S. S.; Choi, B. K.; Ahn, H. J.; Lee, M. Y.; Park, S. H.; Kim, S. K.; *Plant Sci*. **2002,** 153, 1161-1168.
30. Oyaizu, M. *Jpn. J. Nutr.* **1986,** 44, 307-315.
31. Ohkawa, N.; Ohishi, K.; Yagi, K. *Anal. Biochem.* **1979,** 95, 351-358.