Tetrahedron Letters 52 (2011) 4768-4770

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of β -hydroxyphosphonates by iron-catalyzed oxidative addition of phosphonyl radicals to alkenes

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ARTICLE INFO

ABSTRACT

Article history: Received 3 June 2011 Revised 1 July 2011 Accepted 6 July 2011 Available online 19 July 2011

Keywords: Iron catalysis Radical reactions Oxygenation Phosphonates

Phosphorus-centered radicals are useful reactive species in organic synthetic chemistry.¹ Phosphites or thiophosphites can be substituted for toxic organotin reagents as radical mediators.¹ Furthermore, these compounds cause hydrophosphonation with alkenes or alkynes under suitable radical conditions to give corresponding organophosphorus compounds.^{1,2} Ingeniously designed radical reactions using various phosphorus compounds bearing a P-X bond (X = halides, selenide, metals, etc.) are also known.^{1,3} Recently, we reported new methods for generation of aryl, alkoxycarbonyl, or sulfonyl radicals from corresponding hydrazine compounds in the presence of an iron catalyst and molecular oxygen.⁴ In these reactions, addition of generated radicals to alkenes and subsequent aerobic oxidation takes place to give corresponding β-hydroxyesters,^{4a} β-hydroxysulfones,^{4b} or 2-arylperoxides.^{4c} In radical reactions using hydrazides as radical precursors, reactions are initiated by iron-catalyzed aerobic oxidation of hydrazides **2** to give diazenes **C** via supposed intermediates A and B. Generated radicals E from diazenes C with release of molecular nitrogen cause addition reaction to alkenes, and sequent trapping of radical intermediates **F** by oxygen gives β -hydroxy compounds via intermediates G, H, and I (Scheme 1). Herein, we wish to report iron-catalyzed generation of phosphonyl radicals from phosphorohydrazidates and oxidative addition to alkenes under aerobic conditions to give β-hydroxyphosphonate compounds.⁵ β-Hydroxyphosphonate compounds are valuable compounds because they are known as bioisosteres of carboxylic acid

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derivatives and their potential biological properties have attracted broad interest. 6,7

Phosphorohydrazidates have been shown to work as radical precursors by iron-catalyzed aerobic oxida-

tion to generate corresponding phosphonyl radicals. Generated radicals cause intermolecular addition to

various alkenes in the presence of molecular oxygen to give β -hydroxyphosphonate compounds in good

Treatment of α -methylstyrene (**1a**) with 2.5 equiv of diethyl phosphorohydrazidate (**2b**) in the presence of a catalytic amount of iron (III) chloride (FeCl₃) (10 mol %) and air in heating THF gave β -hydroxyphosphonate compound **3b** in 18% yield (Table 1, Entry 1). Iron (III) oxide (Fe₂O₃) was an ineffective catalyst (Entry 2), whereas the use of iron (II) phthalocyanine [Fe(Pc)] significantly improved in the yield of the product (Entry 3).⁸ The reaction under oxygen atmosphere gave a similar yield (Entry 4). When the amount of the iron catalyst was reduced to half, a large decrease in yield of the product was observed (Entry 5). The reaction hardly proceeded in the absence of an iron catalyst (Entry 6).

Several variations of the alkoxy moiety of phosphorohydrazidates were examined (Scheme 2). First, the reaction of dimethyl phosphorohydrazidate (**2a**) did not gave a product due to its insolubility in THF, but addition of MeOH as a co-solvent to the reaction mixture caused a desired reaction to give β -hydroxyphosphonate compound **3a** in good yield. On the other hand, when phosphorohydrazidates **2c** and **d** having secondary or aromatic alkoxy groups were employed in this reaction, sluggish reactions were observed and yields of products **3c** and **d** were low. In the case of diphenyl phosphorohydrazidate (**2d**), the presence of electronwithdrawing phenoxy groups might interfere in the generation of the corresponding phosphonyl radical, but the reasonable reason of lower reactivity of **2c** and **d** is unclear at present.

Results of radical reactions of various alkenes are summarized in Table 2. Since our preliminary experiments indicated that the use of O_2 gave better results than air in many cases, suitable atmosphere for the reaction was different depending on each substrate.





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Table 2

Reactions of various alkenes



Scheme 1. Iron-catalyzed radical generation and oxidative addition to alkenes.



Optimizations of reaction conditions

	Ļ	O (EtO) ₂ PNHNH ₂ 2b (2.5 equiv) [Fe] catalyst	но Д	DEt
	Ph 1a	THF, 65 °C 24 h	Ph ' ' ' ' 3b	DEt
Entry	Fe catalyst		Atmosphere	Yield% ^a
1	FeCl ₃ (10 mol %)		Air	18
2	Fe ₂ O ₃ (10 mol %)		Air	5
3	Fe(Pc) (10 mol %)		Air	84
4	Fe(Pc) (10 mol %)		02	85
5	Fe(Pc) (5 mol %)		Air	25
6	None		• ·	2

^a Yield of isolated product.





^b THF-MeOH (2:1) was used as solvent.

Since additions of phosphorus-centered radicals to alkenes are suggested to be reversible,^{1a} high concentration of oxygen might be required for the efficient trapping of the resultant carbon-centered radical by oxygen depending on the radical instability. Various styrene-type alkenes **1b-h** underwent oxidative additions of the phosphonyl radical to give corresponding β -hydroxyphosphonate compounds **4b-h** (Entries 2–8).⁹ Of these entries, *p*-nitro derivative **4d** showed a moderate reactivity (Entry 4). The difference in stability of benzyl-position radical intermediates generated by addition of the phosphonyl radical might affect the reactivity. In the case of styrene (**4e**) (Entry 5), a small amount of a



β-ketophosphonate derivative [PhCOCH₂P(O)(OEt)₂] was detected along with β-hydroxyphosphonate **4e** by ¹H NMR analysis of the crude material. Enyne **1i** could be used as substrates and corresponding β-hydroxyphosphonate compounds **4i** were obtained in reasonable yields (Entry 9).¹⁰ As shown in reactions of aliphatic alkenes **1j** and **k**, the generality of reactions using nonconjugated alkenes is unlikely to be high (Entries 10 and 11).

When vinyl ether **11** was subjected to the present radical reaction, a reaction involving over oxidation occurred to give diethylphosphonoacetate **4I** in moderate yield (Entry 12).¹¹ Radical addition to α , β -unsaturated ester bearing an electron-deficient alkene **1m** also proceeded to give corresponding β -hydroxyphosphonate compounds **4m** (Entry 13).

In conclusion, we have developed a new method for synthesis of β -hydroxyphosphonate derivatives using a radical methodology. Our present work includes several unique points compared with known synthetic methods using phosphorus-centered radicals, such as the use of phosphorohydrazidates as radical precursors and the sequence of the process involving addition of phosphonyl radicals and oxygenation of alkenes to produce of β -hydroxyphosphonate derivatives. We would also like to emphasize the simplicity and safety of the experimental procedure using an inexpensive and nontoxic iron catalyst and molecular oxygen.¹²

Acknowledgments

This research was supported by a Grant-in-Aid for Young Scientists (B) (23790008) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.026.

References and notes

- 1. Review: (a) Studer, A.; Amrein, S. *Synthesis* **2002**, 835; (b) Leca, D.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Chem. Soc. Rev.* **2005**, 34, 858.
- Recent examples: (a) Jessop, C. M.; Parsons, A. F.; Routledge, A.; Irvine, D. J. Tetrahedron Lett. 2004, 45, 5095; (b) Antczak, M. I.; Montchamp, J.-L. Synthesis 2006, 3, 3080; (c) Hirai, T.; Han, L-B. Org. Lett. 2007, 9, 53.
- Recent examples: (a) Sato, A.; Yorimitsu, H.; Oshima, K. J. Am. Chem. Soc. 2006, 128, 4240; (b) Carta, P.; Puljic, N.; Robert, C.; Dhimane, A.-L.; Fensterbank, L.; Lacôte, E.; Malacria, M. Org. Lett. 2007, 9, 1061; (c) Vaillard, S. E.; Mück-Lichtenfeld, C.; Grimme, S.; Studer, A. Angew. Chem., Int. Ed. 2007, 46, 6533; (d)

Bruch, A.; Ambrosius, A.; Fröhlich, R.; Studer, A.; Guthrie, D. B.; Zhang, H.; Curran, D. P. *J. Am. Chem. Soc.* **2010**, *132*, 11452; (e) Lamas, M.-C.; Studer, A. Org. *Lett.* **2011**, *13*, 2236.

- (a) Taniguchi, T.; Sugiura, Y.; Zaimoku, H.; Ishibashi, H. Angew. Chem., Int. Ed. 2010, 49, 10154; (b) Taniguchi, T.; Idota, A.; Ishibashi, H. Org. Biomol. Chem. 2011, 9, 3151; (c) Taniguchi, T.; Zaimoku, H.; Ishibashi, H. Chem. Eur. J. 2011, 17, 4307.
- Recent examples of phosphorus centered radical reactions under oxidative conditions: (a) Kagayama, T.; Nakano, A.; Sakaguchi, S.; Ishii, Y. Org. Lett. 2006, 8, 407; (b) Mu, X.-J.; Zou, J.-P.; Qian, Q.-F.; Zhang, W. Org. Lett. 2006, 8, 5291; (c) Elamparuthi, E.; Linker, T. Angew. Chem., Int. Ed. 2009, 48, 1853; (d) Xu, W.; Zou, J.-P.; Zhang, W. Tetrahedron Lett. 2010, 51, 2639; (e) Zhou, J.; Zhang, G.-L.; Zou, J.-P.; Zhang, W. Eur. J. Org. Chem. 2011, 3412; (f) Pan, Z.-Q.; Wang, L.; Zou, J.-P.; Zhang, W. Chem. Commun. 2011, 47, 7875.
- Recent reports on biological properties of β-hydroxyphosphonate compounds:
 (a) Cui, P.; Tomsig, J. L.; McCalmont, W. F.; Lee, S.; Becker, C. J.; Lynch, K. R.; Macdonald, T. L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1634; (b) Macchiarulo, A.; Pellicciari, R. *J. Mol. Graphics Modell.* **2007**, *26*, 728; (c) Woodyer, R. D.; Li, G.; Zhao, H.; van der Donk, W. A. *Chem. Commun.* **2007**, 359.
- Recent examples of synthesis of β-hydroxyphosphonate compounds: (a) Orsini, F.; Caselli, A. *Tetrahedron Lett.* **2002**, 43, 7255; (b) Yamagishi, T.; Fujii, K.; Shibuya, S.; Yokomatsu, T. *Tetrahedron* **2006**, 62, 54; (c) Vargas, S.; Suárez, A.; Álvarez, E.; Pizzano, A. *Chem. Eur. J.* **2008**, 14, 9856; (d) Sobhani, S.; Vafaee, A. *Tetrahedron* **2009**, 65, 7691.
- 8. Typical procedure: A mixture of α -methylstyrene (1a) (50.0 mg, 0.423 mmol), diethyl phosphorohydrazidate (2b) (178 mg, 1.06 mmol) and Fe(Pc) (24.0 mg, 0.0423 mmol) in THF (2.1 ml) was heated at 65 °C (reflux). After cooling to room temperature, the resulting suspension was diluted with Et₂O and filtered. After removal of solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane/EtOAc, 1:1) to give **3b** (97 mg, 84%) as a colorless oil.
- 9. In the reaction of vinylcyclopropane **1h**, opening of the cyclopropane ring was not observed due to the stability of the resultant benzyl radical. The similar discussion has been described in our previous manuscript, see Ref. 4c.
- 10. Two resonance contributions of a propargyl radical and a allenyl radical could be considered about the radical generated from enyne 1i, but no allene product was observed. Formation of alkyne-type products has been experimentally shown to be favored in the case of substituted propargyl radicals, see: Fantazier, R. M.; Poutsma, M. L. J. Am. Chem. Soc. 1968, 90, 5490.
- A example of oxidative addition of phosphonyl radicals to enol ethers: Mochizuki, T.; Hayakawa, S.; Narasaka, K. Bull. Chem. Soc. Jpn. 1996, 69, 2317.
- Iron Catalysis in Organic Chemistry; Plietker, B., Ed.; Wiley-VCH: Weinheim, 2008.