Mn^{III}-catalyzed Phosphorylation of Vinyl Azides: The synthesis of β-keto phosphine oxides

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PII: S0040-4039(17)30519-1
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.04.069
Reference: TETL 48861

To appear in: *Tetrahedron Letters*

Received Date: 7 April 2017
Revised Date: 15 April 2017
Accepted Date: 21 April 2017

Please cite this article as: Tang, P., Zhang, C., Chen, E., Chen, B., Chen, W., Yu, Y., Mn^{III}-catalyzed Phosphorylation of Vinyl Azides: The synthesis of β-keto phosphine oxides, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.04.069

Graphical Abstract

Mn^{III}-catalyzed Phosphorylation of Vinyl Azides: The synthesis of β-keto phosphine oxides

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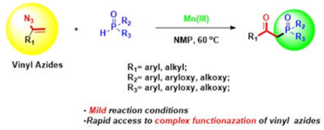

R_1= aryl, alkyl;
R_2= aryl, aryloxy, alkoxy;
R_3= aryl, aryloxy, alkoxy;

- *Mild reaction conditions*
- *Rapid access to complex functionazation of vinyl azides*

Tetrahedron Letters
journal homepage: www.elsevier.com

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Vinyl azides
Radical reaction
Functionalization
Phosphorylation
Mn catalysis

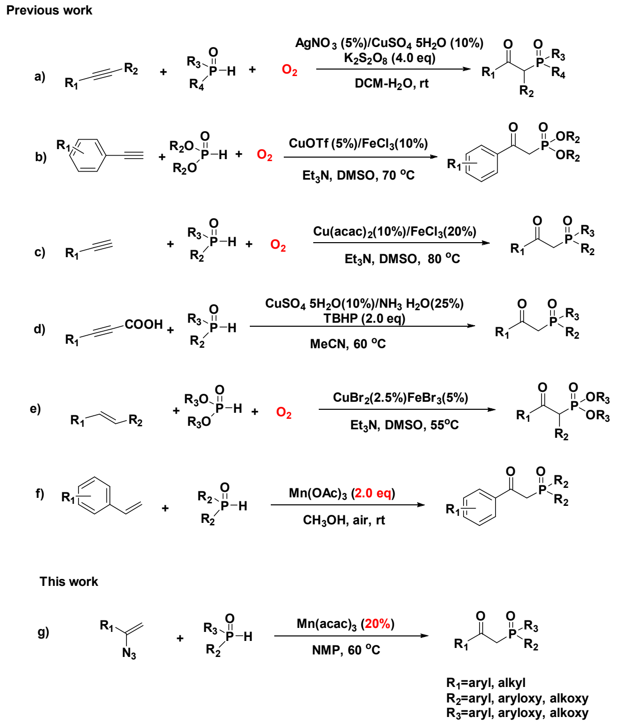
ABSTRACT

Mn^{III}-catalyzed functionalization of vinyl azides via phosphorylation was developed to synthesize various β-keto phosphine oxides in high yields. The transformation is operated in mild conditions and tolerant of a range of functional groups. Control reaction indicates that the reaction mechanism might proceed via the generation of a phosphonated iminyl radical intermediate.

1. Introduction

Organophosphorus compounds play vital role in organic chemistry, pharmaceuticals and material science. [1] Among them, β-keto phosphine oxides are highly valuable and interesting intermediates that facilitate the α, β-unsaturated carbonyl compounds *via* the Horner-Wadsworth-Emmons (HWE) reactions, [2] diversified construction of heterocycles [3] or the synthesis of chiral β-hydroxy phosphonic acids. [4] In recent years, strategies between organophosphorus radicals [5] and radical acceptor have been well developed for affording organophosphorus compounds, especially for the formation of β-keto phosphine oxides. [5a-5f] (**Scheme 1**a-f) However, reported works required O_2 assistance, co-catalyst system or stoichiometric amount of catalyst.

Vinyl azides as attractive and challenging three-atom synthons have drawn much attention for their application for diverse heterocylces construction. [6] The unique properties of the azide group adjacent to an alkene moiety facilitate to tune this functional group into interesting building blocks. Moreover, vinyl azides have been employed as a potential radical acceptor in organic synthesis. [7] For example, formation of pyridines *via* radical reactions of vinyl azides with cyclopropanols, [7b] trifluoromethylation [7c] or perfluoroalkylation [7d] of vinyl azides through iminyl radicals. Recently, our group has reported an efficient synthesis of 5-thiocyano-2-aminothiazoles *via* Fe-catalyzed radical cyclization of vinyl azides. [7e] Thus, in the continue interest in functionalization of vinyl azides, the development of interesting radicals with vinyl azides is still attracting.



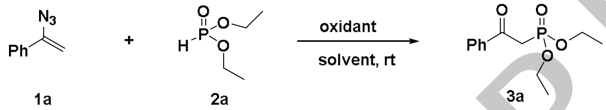
Scheme 1. The formation of β-keto phosphine oxides *via* a P-centered radical.

Here, we disclose a Mn^{III}-catalyzed phosphorylation of vinyl azides with phosphine oxides to afford iminyl radicals. Subsequent conversion of the transient radicals for the βketophosphine oxides. (**Scheme 1**-g) Preliminary mechanistic investigation revealed that the phosphine oxides radical is likely involved in the phosphorylation process.

2. Results and discussion

We envisioned utilizing H-phosphonate (**2a**) as a source of radical. Interesting, a diethyl (2-oxo-2-phenylethyl) phosphonate (**3a**) was isolated in 18% yield by the reaction with vinyl azide (**1a**) using a 50 mol% amount of $Mn(OAc)_3{\cdot}2H_2O$ (Table 1, entry 1). Increasing the amount of $Mn(OAc)_3{\cdot}2H_2O$ to 80 mol% or 100 mol% lead to a slight increase in the yields (25%, Table 1, entries 2-3). While 68% of the product (**3a**) was observed when the reaction was performed with 2.5 equivalents of $Mn(OAc)_3{\cdot}2H_2O$ (Table 1, entry 4). The combined of catalytic amount of Mn (III) and other oxidant such as DDQ resulted in a lower yield (12%, Table 1, entry 5). Other manganese salts such as $Mn(OAc)_2{\cdot}4H_2O$ and $Mn(acac)_3$ were also investigated (Table 1, entries 6-7). Utilization of Mn (III) acetylacetonate [$Mn(acac)_3$] was found to be essential in rendering this reaction with an excellent yield of 70%. Reducing the catalyst loading to 20 mol % could still initiate this reaction with a slightly decreased yield of 60% (Table 1, entry 8). The reaction yields can be improved by elevating the reaction temperature (Table 1, entries 9-10). Next, we intended to explore the relationship of the solvent systems in this reaction. Conducting the reaction in DMSO, DMF and DCE gave the product **3a** in moderate yields (Table 1, entries 11-13), while the reaction conducted in NMP gave **3a** in 92%. Therefore, the best yield of **3a** (92%) was obtained by employing 20 mol% $Mn(acac)_3$ in N-methyl-2-pyrrolidone (NMP) at 60 °C for 6 h.

Table 1. Optimization of the reaction conditions [a]

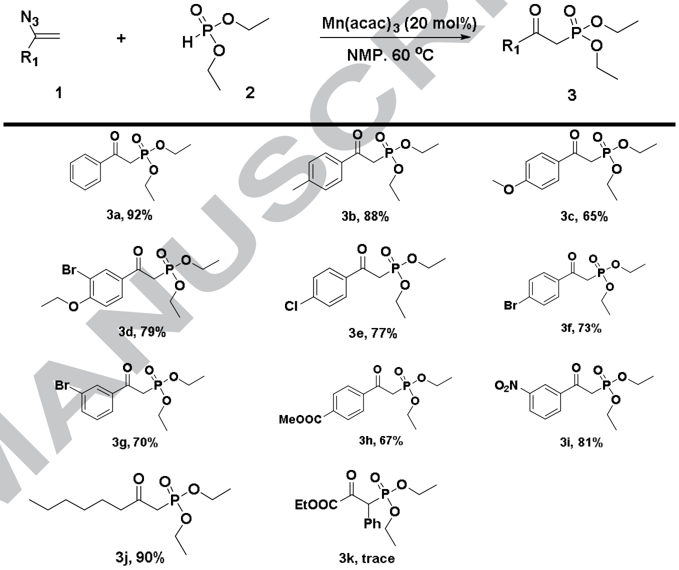


entry	additive (equiv.)	solvent	yield(%)[b]
1	$Mn(OAc)_3{\cdot}2H_2O(0.5)$	NMP	18
2	$Mn(OAc)_3{\cdot}2H_2O(0.8)$	NMP	25
3	$Mn(OAc)_3{\cdot}2H_2O(1.0)$	NMP	25
4	$Mn(OAc)_3{\cdot}2H_2O(2.5)$	NMP	68
5	$Mn(OAc)_3{\cdot}2H_2O(0.5)$+ DDQ(2.0)	NMP	12
6	$Mn(OAc)_2{\cdot}4H_2O(0.5)$	NMP	5
7	$Mn(acac)_3(0.5)$	NMP	70
8	$Mn(acac)_3(0.2)$	NMP	60
9[c]	$Mn(acac)_3(0.2)$	NMP	71
10[d]	$Mn(acac)_3(0.2)$	NMP	92
11[d]	$Mn(acac)_3(0.2)$	DMSO	78
12[d]	$Mn(acac)_3(0.2)$	DMF	70
13[d]	$Mn(acac)_3(0.2)$	DCM	73

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), additive in solvent (1.0 mL containing 18 μL of H_2O) stirring at 25 °C for 6 h. [b]. Yield of the isolated product .[c]. performed at 40 °C [d]. performed at 60 °C

Following the established reaction conditions for the construction of **3a**, the generality of this β-ketophosphonate **3** synthesis was examined using a series of vinyl azides **1**. α-Aryl-substituted vinyl azides were facile to give the corresponding products **3** in good yields (Table 2, **3a**-**3i**). The addition of the phosphonate radical to vinyl azides bearing electron-withdrawing groups (Table 2, **3e**-**3i**) or electron-rich aryl groups (Table 2, **3b**-**3d**) proceed smoothly to give the corresponding β-keto phosphonate in good yields. α-Alkyl-substituted vinyl azide was also capable of coupling with the phosphine oxide radical efficiently (Table 2, **3j**). While trisubstituted vinyl azides having an aryl group at the β-position failed to be employed in this synthesis, probably due to steric hindrance (Table 2, **3k**).

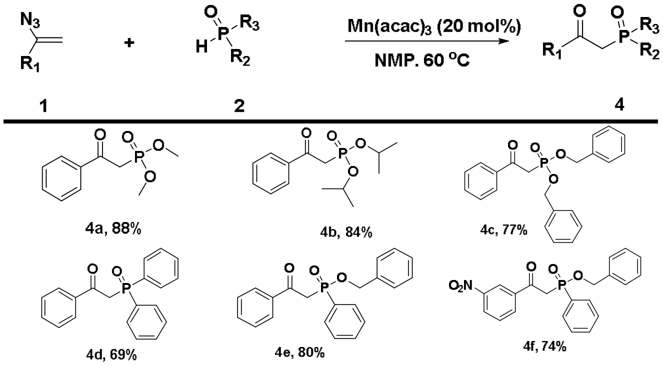
Table 2. Substrate scope of vinyl azides [a]



[a].The reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol, 1.0 equiv.) and $Mn(acac)_3$ (0.2 mmol, 0.2 equiv.) in NMP (2 mL containing 90 μL of H_2O) stirring at 60 °C for 6 h unless otherwise noted.

Next, the generality of phosphine oxides was also examined using α-azidostyrene and 1-(1-azidovinyl)-3-nitrobenzene as shown in Table 3. Not only dialkyl and diaryl H-phosphonates (**4a**-**4c**) but also diarylphosphine oxide (**4d**) and benzyloxyphosphine oxides (**4e**-**4f**) were successfully converted into the corresponding β-keto phosphine oxides **4** with the yields of 69%-88%, thus demonstrating the broad applicability of the present process.

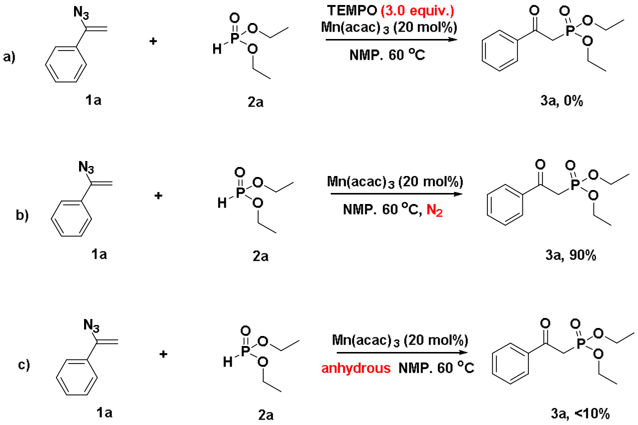
Table 3. Substrate scope of $R_2P(O)H$ compounds [a]



[a].The reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol, 1.0 equiv.)

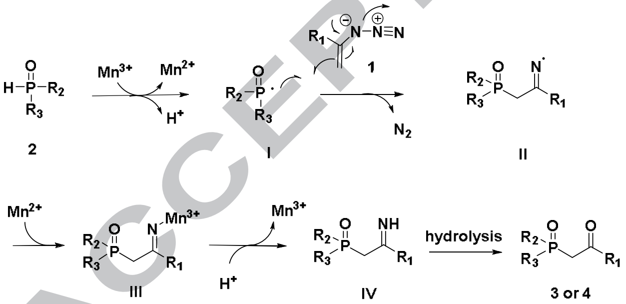
and $Mn(acac)_3$ (0.2 mmol, 0.2 equiv.) in NMP (2 mL containing 90 µL of H_2O) stirring at 60 °C for 6 h unless otherwise noted.

To gain insight into the reaction mechanism for the formation of **3a**, control experiments were subsequently carried out (**Scheme 2**). When TEMPO (2, 2, 6, 6-tetramethyl-1-piperidinyloxy), a widely used radical scavenger, was added into the reaction system, the formation of **3a** was completely inhibited. When the reaction was performed under N_2, the desired product **3a** was obtained. While product **3a** failed to afford in anhydrous NMP. This findings imply that the reaction involves a radical process and the keto group comes from water in solvents.



Scheme 2. Control reaction

Based on these observations, a possible reaction mechanism for the formation of **3** or **4** is proposed in **Scheme 3**. The reaction might be initiated by the addition of phosphine oxide radical **I**, generated by one-electron oxidation of **2** by Mn (III), to vinyl azide **1**, affording iminyl radical **II** with elimination of dinitrogen. Consecutively, the generated iminyl radical **II** was reduced by the resulting Mn (II) species and subsequently protonated to afford imine intermediate **IV** and regenerated Mn(III) species. The hydrolysis of **IV** would give the desired β-keto phosphonate **3** or β-keto phosphine oxides **4**.



Scheme 3. A possible reaction mechanism

3. Conclusion

In summary, we have developed Mn (III)-catalyzed radical phosphorylation of vinyl azides using phosphine oxides. Further investigation of the reaction mechanism showed that this reaction probably proceed through an oxidant radical pathway. Moreover, the reaction process features an operation with functional-group tolerance and high yields.

Acknowledgements

This work was supported from the National Natural Science Foundation of China (No. 81273356 and 81473074), National Science & Technology Major Projects for "Major New Drugs Innovation and Development" of China (2014ZX09304002-007) and Arthritis & Chronic Pain Research Institute, USA to Y. Yu; National Natural Science Foundation of China (No. 81402778) to W. Chen.

Supporting Information

Supplementary data (Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra for all products) associated with this article can be found in the online version, at http://dx.doi.org/

Note

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Highlights:

1. Mn^{III}-catalyzed functionalization of vinyl azides via phosphorylation.
2. The transformation is operated in mild conditions and tolerant of a range of functional groups.
3. The procedure afforded the β-keto phosphine oxides in high yields.