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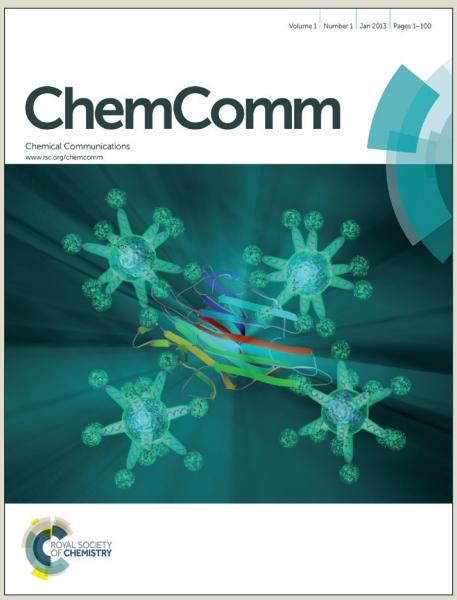

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Mn(III)-Mediated Phosphonation-Azidation of Alkenes: A Facile Synthesis of β-Azidophosphonates

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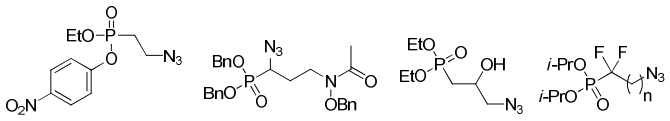
A new and general method for the synthesis of β-azido phosphonates has been achieved through $Mn(OAc)_3$-mediated radical oxidative phosphonation-azidation of alkenes. The starting materials of P(O)-H compounds, alkenes, and azidotrimethylsilane are stable and cheap. This method can be easily adapted to large-scale preparations.

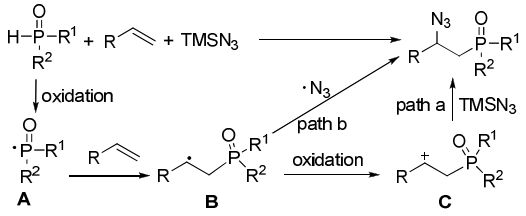
Orangoazides have been widely applied in medicinal chemistry because of their versatile bioactivities.[1] Furthermore, orangoazides are powerful precursors for the generation of a variety of amines, amides, as well as heterocyclic compounds.[2] Therefore, the introduction of an azido group into organic molecules has attracted much attention.[3] Molecules bearing both azido and phosphono groups have extensively been used in pharmaceuticals and fire retardants (Scheme 1).[4] Treatment of azidoalkylphosphonates with terminal alkynes results in the formation of the triazole bridge-connected phosphonates for biotechnology and materials science via the well-known Huisgen-click reaction.[5]



Scheme 1. Biologically active azido-containing phosphonates.

Traditionally, phosphonates with an azido group have been prepared by the nucleophilic substitution of haloalkylphosphonates or α-hydroxyphosphonates with sodium azide under Mitsunobu conditions.[6] Reaction of sulfonyl azides with bisphosphonate esters provides a complementary way to azidoalkylphosphonates.[7] Snider group described reaction of 2-oxoalkylphosphonate with 2-iodoethyl azide in the presence of strong base and phase transfer catalyst.[8] However, these methodologies suffer from multi-step synthesis and limited substrate scope. To develop a simple and efficient approach to β-azidophosphonates from readily available substrates is still highly desired.

Reactions involving organophosphorus radicals have a long history, and are useful reactive species in organic synthetic chemistry.[9] Owing to our continuous interests in the P−C bond formation[10] and the reaction of organophosphorus radicals,[11] we reasoned that generating directly the radical **B** by addition of phosphorous radical **A** onto an alkene would produce cationic intermediate **C** through single-electron oxidation ultimately leading to the formation of β-azidophosphonate via a nucleophilic attack by azidotrimethylsilane(Scheme 2, path a). Alternatively, the radical **B** could be directly trapped by an azido radical to form the desired product (path b).[3b] This transformation allows the direct formation of β-azidophosphonates via tandem phosphonation-azidation of alkenes (Scheme 2).

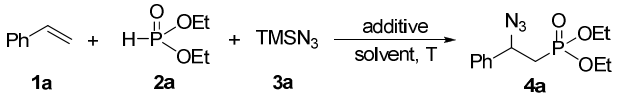


Scheme 2. Possible reaction pathways.

This idea was first examined by using styrene (**1a**), diethyl *H*-phosphonate (**2a**), and azidotrimethylsilane (**3a**) as reaction partners (Table 1). In the beginning, $AgNO_3$ was tested (entry 1),[12] but no desired product was observed. The combined use of Cu(II) and TBHP (tert-butylhydroperoxide) was often used in organophosphorus radical reactions,[13] but the reaction did not work well under these conditions (entries 2 and 3). When $Mn(OAc)_3{\cdot}2H_2O$ was choosen as the oxidant and HOAc as the solvent,[11,14] the product **4a** was obtained in 35% yield at 70 °C under a nitrogen atmosphere (entry 4). Other manganese salts such as $Mn(acac)_3$ and $Mn(OAc)_2/MnO_2$ were also investigated, but no desired product was obtained under these conditions (entries 5 and 6). The solvent systems employed also notably affected the related reaction efficiencies. Conducting the reaction in CH_3CN, DCE, 1,4-

dioxane, toluene, $PhCF_3$, DMF, DMA, and DMSO gave the product **4a** in low yields (entries 7-14), while the reaction conducted in NMP gave **4a** in 73% yield (entry 17).[14b] Further screening indicated that the choice of temperature is also very crucial for the reaction (entries 15-17). The yield of product **4a** decreased when the temperature was raised to 80 °C. However, it remained approximately the same when the temperature was decreased from 70 to 55 °C. The attempt to decrease the amount of $Mn(OAc)_3{\cdot}2H_2O$ was failed. In our reaction, only 19% yield of product was obtained when the reaction was performed in the open air with 0.5 equivalent of $Mn(OAc)_3{\cdot}2H_2O$ (entry 18). A yield of 23% was observed when 2 equivalents of MnO_2 were used as oxidant instead of air (entry 19),[14e] but the combined use catalytic amount of Mn(II or III) and other oxidants such as DTBP, TBHP, dioxygen led to lower yield in this reaction (entries 19-24).

Table 1. Reaction conditions optimization[a]



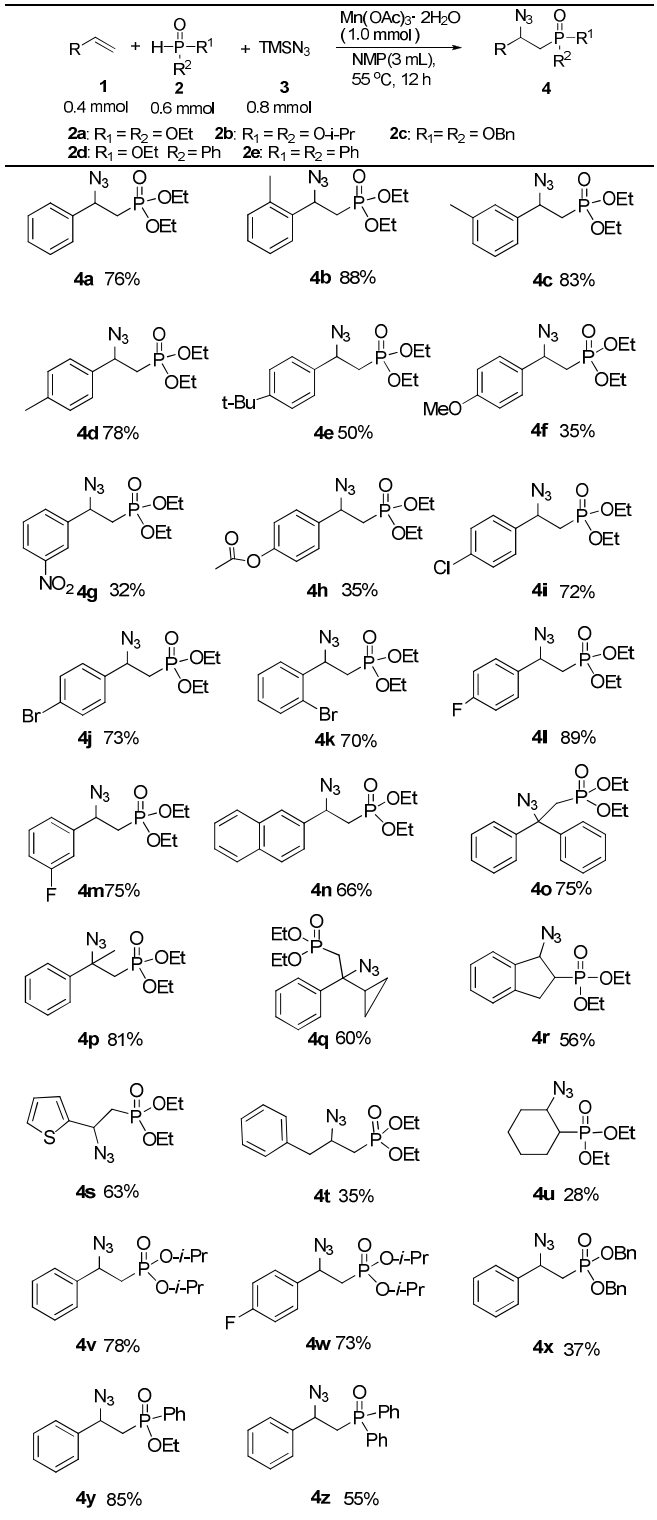
1a 2a 3a 4a

Entry	Additive (equiv)	Solvent	T[°C]	Yield [%]
1	$AgNO_3$(0.2)+$K_2S_2O_8$(2)	CH_3CN	100	0
2	$CuCl_2$ (0.2)+TBHP (3)	CH_3CN	100	0
3	$CuSO_4$ (0.2)+TBHP (3)	CH_3CN	60	0
4	$Mn(OAc)_3{\cdot}2H_2O$ (3)	HOAc	70	35
5	$Mn(acac)_3$	HOAc	100	0
6	$Mn(OAc)_2{\cdot}$(1)+ MnO_2(4)	NMP	100	15
7	$Mn(OAc)_3{\cdot}2H_2O$ (3)	CH_3CN	70	23
8	$Mn(OAc)_3{\cdot}2H_2O$ (3)	DCE	70	0
9	$Mn(OAc)_3{\cdot}2H_2O$ (3)	Dioxane	70	32
10	$Mn(OAc)_3{\cdot}2H_2O$ (3)	Toluene	70	43
11	$Mn(OAc)_3{\cdot}2H_2O$ (3)	$PhCF_3$	70	65
12	$Mn(OAc)_3{\cdot}2H_2O$ (3)	DMF	70	54
13	$Mn(OAc)_3{\cdot}2H_2O$ (3)	DMA	70	67
14	$Mn(OAc)_3{\cdot}2H_2O$ (3)	DMSO	70	60
15	$Mn(OAc)_3{\cdot}2H_2O$ (3)	NMP	70	73
16	$Mn(OAc)_3{\cdot}2H_2O$ (3)	NMP	80	65
17	**$Mn(OAc)_3{\cdot}2H_2O$ (2.5)**	**NMP**	**55**	**75**
18[b]	$Mn(OAc)_3{\cdot}2H_2O$ (0.5)	NMP	55	19
19	$Mn(OAc)_3{\cdot}2H_2O$ (0.5) + MnO_2(2)	NMP	55	23
20	$Mn(OAc)_3{\cdot}2H_2O$ (0.1) + DTBP(2)	NMP	55	0
21	$Mn(OAc)_3{\cdot}2H_2O$ (0.1) + TBHP(2)	NMP	55	13
22	$Mn(OAc)_3{\cdot}2H_2O$ (0.1) + Air	NMP	55	0
23[c]	$Mn(OAc)_3{\cdot}2H_2O$ (0.1) + O_2	NMP	55	0
24[c]	$MnCl_2$ (0.1) + O_2	NMP	55	0

[a] *Reaction conditions:* **1a** (0.4 mmol), **2a** (0.6 mmol), **3a** (0.8 mmol), additive in solvent (3 mL) stirring under nitrogen for 12 h. Oil bath temperature. Yield of the isolated product. [b] Under air. [c] Under O_2 (balloon).

With this preliminary result in hand, the generality of the method was explored under the optimized conditions [alkene (0.4 mmol), P(O)-H (0.6 mmol), $TMSN_3$ (0.8 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (1.0 mmol), in NMP (3 mL) at 55 °C under nitrogen for 12 h], and the results are summarized in Table 2. In general, most of the functional groups were tolerated under the present conditions. The methyl substituted styrenes, such as *ortho*-methyl, *meta*-methyl, and *para*-methyl groups on the aryl ring, reacted efficiently and gave the desired products **4b-4d** in high yields. Various aromatic alkenes with electron-donating (*t*-butyl and methoxyl) groups or electron-

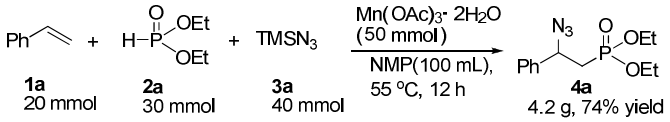
Table 2. Phosphonation-azidation of alkenes



withdrawing (COOEt and NO_2) groups on the benzene ring were investigated, and the corresponding products were obtained in lower yields (**4e-4h**). These examples imply that the reaction involves radical and cationic intermediates. Halogen atoms such as fluoro, chloro, and bromo on the aromatic ring were unaffected under the present reaction conditions to afford the corresponding products **4i-4m** in good yields, which could allow for further synthetic transformations. More bulky substrates such as 2-vinylnaphthalene and ethene-1,1-diyldibenzene also smoothly converted into product **4n** and **4o** in 66% and 75% yields. When prop-1-en-2-ylbenzene and (1-cyclopropylvinyl)benzene were used, they reacted smoothly to result in products **4p** and **4q** in 81% and 60% yield, respectively. Moreover, cyclic aromatic alkene also reacted smoothly, leading to the desired product **4r** in 56% yield. In addition, 2-vinylthiophene could also provide the expected product **4s** in 63% yield. Aliphatic alkenes were also examined. Unfortunately, only low yields of the desired products were obtained (**4t** and **4u**).

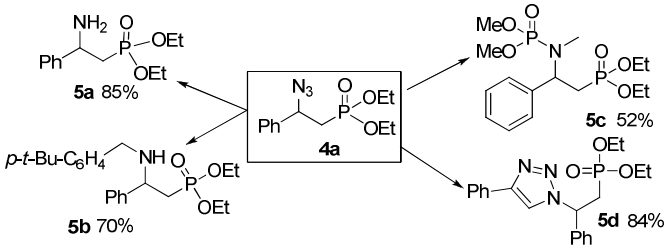
Diisopropyl *H*–phosphonate (**2b**) was also used in the β-azidophosphonation of alkenes process, and led to the formation of products **4v** and **4w** in 78 and 73% yields. Dibenzyl *H*–phosphonate (**2c**) gave a low yield of product **4x**. Treatment of ethyl phenylphosphinate (**2d**) with styrene and azidotrimethylsilane afforded the desired product **4y** in 85% yield. Diphenylphosphine oxide produced the desired product **4z** in only 55% yield.

In order to demonstrate the practical application of this method, styrene (**1a**, 20 mmol) was employed in a gram-scale reaction and delivered **4a** in 74% yield (Scheme 3).



Scheme 3. Gram-scale preparation of **4a**.

It is noteworthy that the β-azidophosphonates could be widely applied in direct and efficient synthesis of many bioactive molecules as useful building blocks (Scheme 4). With the gram-scale **4a** in hand, we next prepared β-aminophosphonate **5a** in good yield. Furthermore, **5b** was obtained via the reduction of the azide and subsequent reductive alkylation process with 4-tert-butylbenzaldehyde. Biphosphonate **5c** was easily obtained via the reduction of the azide and phosphonation-rearrangement process. Undoubtedly, click reaction was employed to yield triazole bridge-connected phosphonate **5d.**



Scheme 4. Further transformations of β-azidophosphonates.

In conclusion, we have successfully developed a highly efficient and general method for the preparation of β-azidophosphonates through $Mn(OAc)_3$-mediated radical oxidative phosphonation-azidation of alkenes under relatively mild reaction conditions. This method is highly efficient and provides rapid access to a broad spectrum of β-azidophosphonates in moderate to good yields. Moreover, this reaction can be effectively scaled up and the product can be conveniently obtained in a one-pot process.

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Notes and references

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Electronic Supplementary Information (ESI) available: Experimental procedures for the synthesis, spectral data and NMR spectra of compounds **4a-4z**. See DOI: 10.1039/c000000x/

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