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Silver(I) Triflate-Catalyzed Direct Synthesis of *N*-PMP Protected α-Aminopropargylphosphonates from Terminal Alkynes

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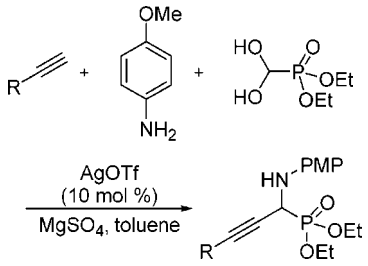
ABSTRACT



***N*-PMP protected α-aminopropargylphosphonates have been synthesized by using a silver(I) triflate-catalyzed one-pot three-component reaction of terminal alkynes, *p*-anisidine, and diethyl formylphosphonate hydrate. Good to excellent yields of the desired products may be obtained with a very simple procedure.**

Since α-aminophosphonate derivatives are structural mimics of α-amino acids, some of these compounds exhibit very high potency in inhibiting the enzymes that are involved in the metabolism of the corresponding amino acids. These compounds have already been found to act as antibacterial agents, neuroactive compounds, anticancer drugs, and pesticides, with some of them already being commercialized.[1] For example, Strater and Lipscomb have reported several L-leucine-phosphonic acid derivatives that are among the most potent low-molecular inhibitors of leucine aminopeptidase.[2] The altered activity of such an enzyme has been associated with HIV infections and several pathological disorders including cancer and cataracts.[3]

Due to their biological significance, many synthetic methods have been developed for these compounds.[1] Among these reported methods, the Mannich-type addition of a phosphorus nucleophile to an imine represents the most efficient way to obtain α-aminophosphonate derivatives.[1,4] Because of our recent interest in the synthesis of α-hydroxyphosphonate[5] and α-aminophosphonate derivatives, we envisaged that α-aminopropargylphosphonates are very good precursors for the synthesis of other α-aminophosphonate derivatives, as the triple bond may be readily elaborated to introduce other functional groups. For example, this bond may be partially or totally saturated through selective

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(3) (a) Umezawa, H. *Recent Results Cancer Res.* **1980**, *75*, 115−125. (b) Taylor, A.; Daims, M. A.; Lee, J.; Surgenor, T. *Curr. Eye Res.* **1982**, *2*, 47−56. (c) Pulido-Cejudo, G.; Conway, B.; Proulx, P.; Brown, R.; Izaguirre, C. A. *Antiviral Res.* **1997**, *36*, 167−177.

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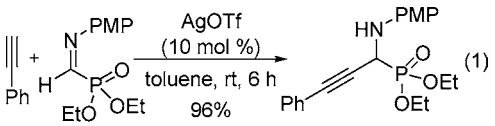
hydrogenation. Furthermore, these compounds may have some interesting biological activities by themselves, although they have never been explored for this purpose. Nevertheless, the synthesis of these interesting compounds was only sporadically mentioned in the literature.[6,7] After a careful literature search, only two related examples were found: In one case, Steglich and co-workers reported an addition of phenylacetylenylmagnesium bromide to a protected α-iminophosphonate to produce the corresponding α-aminopropargylphosphonate in poor yield (20%).[6] In the other case, Maas and co-workers obtained some α-aminopropargylphosphine oxides as side products by reacting phosphane with α-alkynyliminium salts.[7] To the best of our knowledge, no general synthetic method has ever been developed for the synthesis of α-aminopropargylphosphonates.

Metal-catalyzed addition of terminal alkynes to imines, which are either preformed or in situ generated from aldehydes and amines, represents one of the most convenient methods for the synthesis of propargylamines.[8] Recently, this reaction has been successfully applied by Chan's group for the synthesis of α-aminopropargylcarboxylates from α-imino esters.[9] These reports prompted us to study the possibility of synthesizing α-aminopropargylphosphonates through a metal-catalyzed addition of terminal alkynes to α-iminophosphonates. Herein, we wish to report our preliminary results on a silver(I) triflate-catalyzed one-pot three-component reaction for the direct synthesis of *N*-PMP protected α-aminopropargylphosphonates from terminal alkynes.

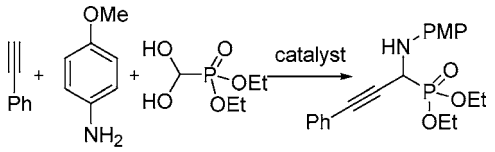
We first studied the silver(I) triflate catalyzed reaction of phenylacetylene (**1a**) and diethyl [(4-methoxyphenyl)imino]-methylphosphonate (**2**).[10] To our pleasure, the desired *N*-PMP-protected[11] α-aminopropargylphosphonate **3a** was obtained in excellent yield (96%, eq 1).



1a **2** PMP = *p*-MeOC$_6$H$_4$ **3a**

In view that the imine **2** has to be prepared every time freshly from *p*-anisidine (**4**) and the corresponding α-formylphosphonate hydrate (**5**),[10] a one-pot three-component reaction with the in situ formation of **2** would be more convenient. Thus, by using **4**, **5**, and **1a** as the substrates, we screened several transition metal catalysts, which are known[8,9] for their ability in activating the terminal alkynes, in an effort to develop an efficient one-pot synthesis. The results are summarized in Table 1.

Table 1. Optimization of Catalyst and Reaction Conditions[a]



1a **4** **5** **3a**

entry	catalyst	solvent	yield (%)[b]
1	$Zn(OTf)_2$, $In(OTf)_3$, AgOAc	toluene	0
2	$CuBr_2$, CuX (X = Br, Cl, I), $AgNO_3$, AgI	toluene	<10
3	$Sc(OTf)_3$	toluene	16
4	$Cu(OTf)_2$	toluene	36
5	$(CuOTf)_2 \cdot C_6H_5CH_3$	toluene	30
6	AgOTf	toluene	62
7	AgOTf	hexane	22
8	AgOTf	CH_2Cl_2	32
9	AgOTf	dioxane	41
10	AgOTf	CH_3CN	36
11[c,d]	AgOTf	toluene	78
12[c,e]	AgOTf	toluene	72
13[c,f]	AgOTf	toluene	94

[a] Unless otherwise indicated, all reactions were carried out with phenylacetylene (0.75 mmol), *p*-anisidine (0.50 mmol), diethyl α-formylphosphonate hydrate (0.50 mmol), and the catalyst (0.05 mmol, 10 mol %) at rt in the specified solvent (6.0 mL) for 12 h. [b] Yield of isolated product after chromatography. [c] Reactions were carried out at rt for 6 h. [d] MS (4 Å) (300 mg) was used as the additive. [e] Na_2SO_4 (2.5 mmol) was used as the additive. [f] $MgSO_4$ (2.5 mmol) was used as the additive.

As shown in Table 1, Zn(II) triflate, In(III) triflate, and Ag(I) acetate do not catalyze the desired reaction (entry 1). Similarly, copper(II) bromide, copper(I) halides, silver(I) nitrate, and silver(I) iodide prove to be poor catalysts for this reaction (entry 2). In contrast, scandium(III) and copper-(II) triflates as well as the toluene complex of copper(I) triflate do catalyze the desired reaction, albeit in low efficiency (entries 3 to 5). Silver(I) triflate turned out still the best catalyst for the in situ mode, as the highest yield of **3a** (62%) was obtained (entry 6). Among the common organic solvents, toluene proved to be the best one for this reaction, whereas hexane (entry 7), dichloromethane (entry 8), dioxane (entry 9), and acetonitrile (entry 10) all gave inferior yields. Nonetheless, even under these optimized conditions (entry 6), the yield was not yet comparable to that of the isolate imine (eq 1). We speculated that the

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(7) Reisser, M.; Maas, G. *J. Org. Chem.* **2004**, *69*, 4913−4924.
(8) For examples, see: (a) Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319−4321; (b) Li, C.-J.; Wei, C. *Chem. Commun.* **2002**, 268−269. (c) Wei, C.; Li, C.-J. *Green Chem.* **2002**, *4*, 39−41. (d) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638−5639. (e) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584−9585. (f) Wei, C.; Li, Z.; Li, C.-J. *Org. Lett.* **2003**, *5*, 4473−4475. (g) Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497. (h) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107−1110. (i) Benaglia, M.; Negri, D.; Dell'Anna, G. *Tetrahedron Lett.* **2004**, *45*, 8705−8708. (j) Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472−1483. (k) Wei, C.; Mague, J. T.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5749−5754. (l) Li, Z.; Wei, C.; Chen, L.; Varma, R. S.; Li, C.-J. *Tetrahedron Lett.* **2004**, *45*, 2443−2446. (m) Ju, Y.; Li, C.-J.; Varma, R. S. *QSAR Comb. Sci.* **2004**, *23*, 891−894. (n) Bisai, A.; Singh, V. K. *Org. Lett.* **2006**, *8*, 2405−2408. (o) Huang, B.; Yao, X.; Li, C.-J. *Adv. Synth. Catal.* **2006**, *348*, 1528−1532.
(9) (a) Ji, J.-X.; Au-Yeung, T. T.-L.; Wu, J.; Yip, C. W.; Chan, A. S. C. *Adv. Synth. Catal.* **2004**, *346*, 42−44. (b) Ji, J.-X.; Wu, J.; Chan, A. S. C. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 11196−11200.
(10) Compounds **2** and **5** were prepared by using a modified procedure originally reported by Hamilton and co-workers, see: Hamilton, R.; McKervey, M. A.; Rafferty, M. D.; Walker, B. J. *J. Chem. Soc., Chem. Commun.* **1994**, 37−38.
(11) The PMP group may be readily deprotected, see: (a) Marin, S. D. L.; Martens, T.; Mioskowski, C.; Royer, J. *J. Org. Chem.* **2005**, *70*, 10592−10595. (b) Reference 9b.

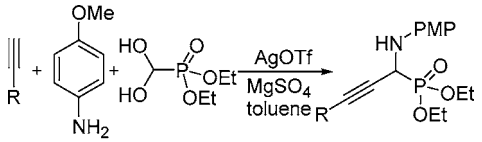
differences in the reaction efficiency between this in situ generated and the preformed α-iminophosphonate (**2**) were due to the inevitable production of water under the in situ conditions, as water may cause the formed **2** to hydrolyze back to the starting formylphosphonate (**5**) under the action of the catalyst, which is also a Lewis acid. On the basis of this assumption, we intentionally added some drying agents into the reaction mixture in an attempt to remove the water. To our pleasure, the yield of **3a** was indeed increased to 78% when 4 Å molecular sieves were added (entry 11). Moreover, the reaction time was shortened to 6 h from 12 h. A similar yield may also be achieved with sodium sulfate (entry 12). The most efficient combination proved to be silver(I) triflate and magnesium sulfate, as an excellent yield of 94% of the product may be obtained (entry 13). This result is similar to that of the preformed α-iminophosphonate.

To understand the scope of this new reaction, various terminal alkynes were studied as the substrates and the results are summarized in Table 2. As is evident from Table 2, besides phenylacetylene (entry 1), other aryl-substituted alkynes are also good substrates for this reaction. For example, all monohalogenated phenylacetylenes produce excellent yields (≥81%) of the desired aminopropargylphosphonates (entries 2−5). Interestingly, acetylenes with both electron-withdrawing groups (entries 2−6) and electron-donating groups (entries 7−9) on the phenyl ring give the expected products in good yields, with the exception of the 3,5-difluorophenyl derivative, which generates the product (**3j**) in slightly lower yield (entry 10). 1-Ethynylnaphthalene also participates in this reaction, and the desired product (**3k**) was isolated in 61% yield (entry 11).

Nonetheless, aliphatic terminal alkynes react very slowly under these one-pot conditions and lead to lower yields. These products are better synthesized with the preformed imine **2**. In this way, a 72% yield may be obtained for the product (**3*l***) of 1-heptyne. The products of 4-phenyl-1-butyne (**1m**) and an acetyl-protected α-hydroxyalkyne (**1n**) were similarly obtained (entries 13 and 14).

In summary, we have developed the first general method for the synthesis of *N*-PMP-protected α-aminopropargylphosphonates by using a silver(I) triflate-catalyzed one-pot three-component reaction of terminal alkynes with aromatic substituents, *p*-anisidine, and diethyl formylphosphonate hydrate. For aliphatic alkynes, the imine needs to be preformed. Good to excellent yields of the desired product may be obtained with a very simple operation procedure.

Table 2. Silver(I) Triflate-Catalyzed One-Pot Synthesis of *N*-PMP Protected α-Aminopropargylphosphonates[a]



1 **4** **5** **3**

entry	R	product	yield (%)[b]
1	Ph	**3a**	94
2	4-BrC_6H_4	**3b**	84
3	2-BrC_6H_4	**3c**	86
4	4-ClC_6H_4	**3d**	83
5	4-FC_6H_4	**3e**	81
6	4-$CF_3C_6H_4$	**3f**	78
7	4-$CH_3C_6H_4$	**3g**	89
8	3-$CH_3C_6H_4$	**3h**	90
9	4-$CH_3OC_6H_4$	**3i**	80
10	3,5-$F_2C_6H_3$	**3j**	69
11	naphth-1-yl	**3k**	61
12[c]	$CH_3(CH_2)_3CH_2$	**3l**	72
13[c]	$PhCH_2CH_2$	**3m**	64
14[c]	$AcO(CH_3)_2C$	**3n**	55

[a] Unless otherwise specified, all reactions were conducted with the alkyne (0.75 mmol), *p*-anisidine (0.50 mmol), diethyl α-formylphosphonate hydrate (0.50 mmol), anhydrous $MgSO_4$ (2.50 mmol), and AgOTf (0.05 mmol, 10 mol %) in anhydrous toluene (6.0 mL) at rt for 6 h. [b] Yield of isolated product after chromatography. [c] The preformed imine **2** (0.50 mmol) was slowly added to a toluene solution (2.0 mL) of the alkyne (0.75 mmol) and AgOTf (0.05 mmol), and the reaction mixture was stirred at rt for 24 h.

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Supporting Information Available: Detailed experimental procedures and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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