ORGANIC LETTERS

2006
Vol. 8, No. 19
4283−4285

Phosphine-Catalyzed α-*P*-Addition on Activated Alkynes: A New Route to P–C–P Backbones

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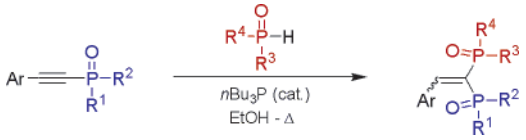
Received June 28, 2006

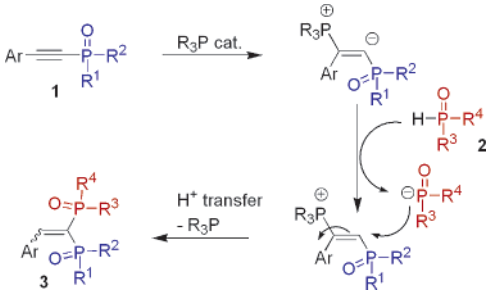
ABSTRACT



***n*-Tributylphosphine was found to efficiently catalyze the α-*P* addition of *H*-phosphonates, *H*-phosphinates, and *H*-phosphine oxide pronucleophiles on alkynes bearing phosphane oxide activating moieties. The reaction leads to 2-aryl-1-vinyl-1,1-diphosphane dioxide derivatives in good yields affording a new route to P–C–P backbones. The products of this reaction are easily converted to biologically important 1,1-bis-phosphonates analogues.**

Catalysis employing tertiary phosphines has proven to be useful for a series of transformations of electron-deficient alkynes.[1] In these reactions, the phosphine catalyst allows redirection of the regioselectivity of the addition of nucleophiles to these Michael acceptors from the classical β-addition mode to an α or γ addition. Although phosphines-catalyzed γ-addition reactions has been widely described,[2] the α-addition has been explored only with nitrogen[3] or oxygen[4] pronucleophiles. In connection with our efforts to extend the α-addition reaction,[5] we now report our investigations concerning the reaction of *P*-centered pronucleophiles to alkynes activated by a phosphane oxide moiety. This reaction should generate 1-vinyl-1,1-diphosphane dioxide derivatives **3**, whose preparation has only been sporadically reported,[6] and provide a new access to P−C−P backbones (Scheme 1).

Scheme 1. Proposed Route to *gem*-Bis-phosphane Dioxide Vinyl Derivatives **3**



According to the postulated mechanism (Scheme 1), the nucleophilic tertiary phosphine adds first to the triple bond

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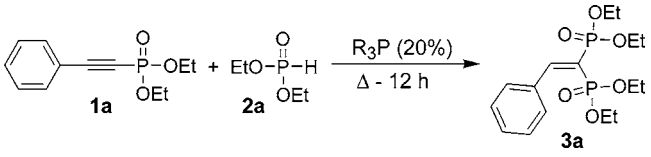
10.1021/ol061589v CCC: $33.50
Published on Web 08/23/2006

of the electron-deficient alkyne **1**, generating an active phosphonium intermediate which then could undergo nucleophilic α-*P*-addition of the *H*-phosphane oxide pronucleophile **2** followed by elimination of the phosphine catalyst. Several parameters including the nature of the phosphine catalyst and the pK_a of the pronucleophile **2** might therefore influence the efficiency of the reaction.

As a model reaction, we investigated the α-*P*-addition of diethyl phosphite **2a** to alkynylphosphonate **1a** using various phosphines as catalysts. The results, summarized in Table 1, showed that the yield of the expected product **3a** depends

Table 1. Optimization of the Reaction Conditions[a]



entry	R_3P	solvent	yield[b] (%)
1	Ph_3P	toluene	5
2	Ph_2PMe	toluene	10
3	*n*-Bu_3P	toluene	42
4	Et_3P	toluene	65
5	*n*-Bu_3P	dioxane	34
6	*n*-Bu_3P	Et_2O	20
7	*n*-Bu_3P	EtOH	**98**
8	*n*-Bu_3P	DMF	18
9	*n*-Bu_3P	DMSO	2

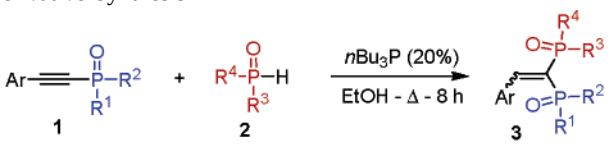
[a] Reactions conducted in refluxing solvent (or 110 °C for DMF and DMSO) under argon; the concentration of the substrates was 0.1 M. [b] Yields of **3a** were determined by HPLC.

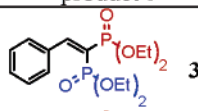
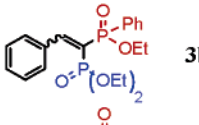
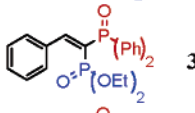
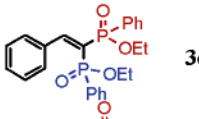
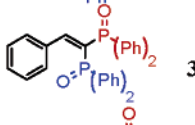
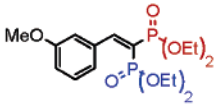
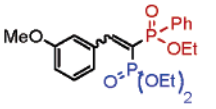
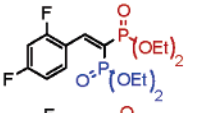
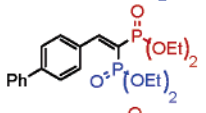
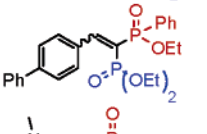
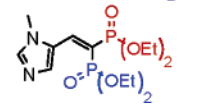
on the nature of the phosphine and the solvent. As expected, the requirement of a highly nucleophilic trialkylphosphine is clearly illustrated by the reactivity order of the tested phosphines (entries 1−4, Table 1). The use of ethanol as solvent was also found essential to achieve complete conversion of the substrate into the desired product (entry 7, Table 1). Previous findings showed that alcohols might act as cocatalysts in phosphine-catalyzed isomerization of alkynoates.[7]

To explore the scope and limitation of the reaction, we then carried out a series of α-*P*-additions using the optimized conditions. Different *P*-pronucleophiles **2** were thus refluxed in ethanol with arylalkynes **1** activated by a phosphonate, phosphinate, or phosphine oxide group in the presence of *n*Bu_3P. Whatever the combinations, the corresponding products were successfully obtained in moderate to high yields (Table 2). The products bearing two different phosphane oxide groups were isolated as a mixture of stereoisomers.

Compounds **3** are evident precursors of *gem*-bis-phosphonates analogues which are now recognized as an important class of therapeutically active molecules for several human pathologies, such as osteoporosis,[8] rheumatoid arthritis,[9] and cancer.[10] In this context, the presented method might be a

Table 2. Phosphine-Catalyzed *gem*-Bis(phosphane oxide)vinyl Derivative Synthesis[a]



entry	product **3**		yield (%)[b]	ratio *Z*/*E*
1		**3a**	95	-
2		**3b**	90	75/25
3		**3c**	64	100/0
4		**3d**	63	-
5		**3e**	53	-
6		**3f**	95	-
7		**3g**	92	75/25
8		**3h**	80	-
9		**3i**	81	70/30
10		**3j**	83	-
11		**3k**	79	75/25
12		**3l**	97	-

[a] Reaction conditions: alkyne **1** (0.5 mmol), *P*-pronucleophile **2** (0.55 mmol), *n*-Bu_3P (0.1 mmol), EtOH reflux under Ar. [b] Isolated yields.

valuable new route for the synthesis as well as the labeling of these important biologically active compounds. As an example, the preparation of the heterocyclic bisphosphonate **4** was easily carried out in 4 steps (47% global yield) using the presented reaction as a key step; the possibility of labeling was also confirmed (Scheme 2). Compound **4** is an analogue

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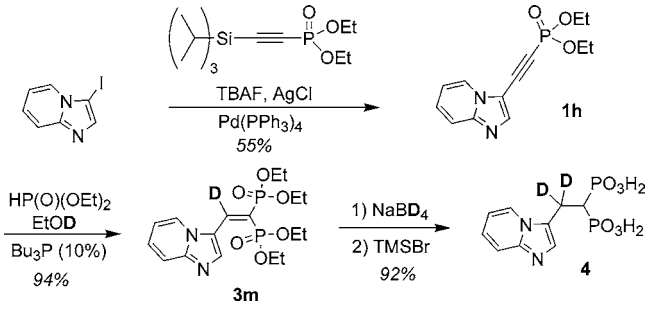
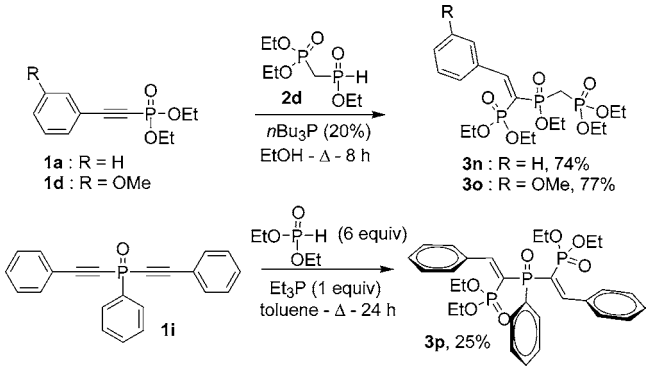
Scheme 2. Synthesis of Labeled Minodronate Analogue **4**



Scheme 3. Formation of P−C−P−C−P Backbones



to minodronate (also known as YM529), a member of the third-generation of biologically active bisphosphonates.[11]

Finally, we have undertaken the preparation of P−C−P−C−P backbones using the *n*-Bu_3P mediated α-*P*-addition reaction. The reaction of *H*-phosphonylphosphonate **2d** with alkynyl phosphonates **1a** and **1d** proceeded smoothly to afford, after chromatographic purification, the corresponding vinylic triphosphane trioxides P(O)−C−P(O)−C−P(O) **3n** and **3o** as pure *Z* isomers in good yields. Double α-*P*-addition reaction of diethyl phosphite **2a** was also achieved on bis-alkynyl phosphine oxide **1i**. The reaction conducted to the expected product **3p** as pure *Z*,*Z* isomer but required the use of a less hindered phosphine (Et_3P) and drastic conditions which conducted to poor yield (Scheme 3).

In conclusion, we have developed a simple and practical method for the preparation of 2-aryl-1-vinyl-1,1-diphosphane dioxide derivatives. These products can be easily converted into 1,1-bis-phosphonates which are important biologically active drugs. The reported methodology allows the control of the nature of the two phosphane oxide groups, which constitutes an undeniable advantage compared to classical methods.[12] An interesting possibility would be the synthesis and biological evaluation of the phosphinates analogues of the 1,1-bis-phosphonates currently used as therapeutic agents. This structural modification should indeed decrease the highly charged nature of these drugs and therefore increase their uptake. From an organic synthesis point of view, the present methodology offers a new route to compounds bearing P(O)−C−P(O) moiety which are common precursors of vinyl phosphane oxides[13] and of ligands for catalysis.[14]

The presented reaction can also be successfully used for the straightforward synthesis of compounds bearing P−C−P−C−P backbones. Further investigations to prepare various biochemically stable triphosphate analogues using this methodology are currently underway.

Acknowledgment. This work was supported by the "Nuclear Toxicology" program of the CEA for which grateful acknowledgment is made. We also thank E. Zekri and D. Buisson (CEA) for experimental assistance with MS and LC/MS measurements.

Supporting Information Available: Experimental procedures for synthesis and full characterization for compounds; ^1H NMR and ^{31}P NMR spectra of products **3a**−**p** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For example, benzylidenebisphosphine oxide **3e** is easily reduced by LAH to the corresponding saturated bisphosphine, data not shown.