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Radical Reaction of Sodium Hypophosphite with Terminal Alkynes: Synthesis of 1,1-Bis-*H*-phosphinates

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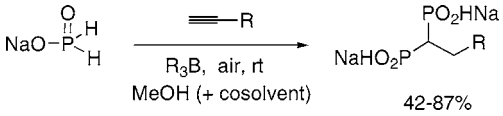
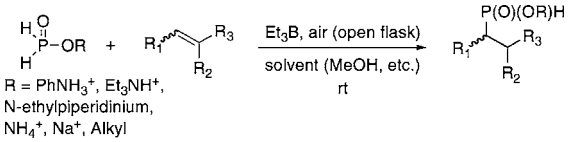
ABSTRACT



The room-temperature radical addition of sodium hypophosphite to terminal alkynes produces the previously unknown 1-alkyl-1,1-bis-*H*-phosphinates in moderate yield. The reaction is initiated by R_3B and air and proceeds under mild conditions in an open container. The bissodium salts precipitate spontaneously from the reaction mixtures, thus providing a simple purification procedure and the opportunity for multigram synthesis. The 1,1-bis-*H*-phosphinate products are novel precursors of the biologically important 1,1-bisphosphonates.

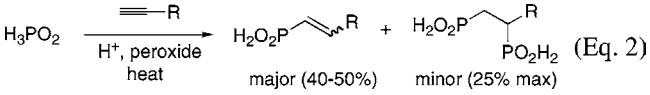
We recently reported a novel and general approach toward *H*-phosphinate derivatives based on the room-temperature radical addition of hypophosphorous compounds to alkenes (eq 1).[1] Since then, we have studied the reactions of alkynes



(Eq. 1)

with sodium hypophosphite under similar conditions and discovered the formation of a new class of compounds: 1-alkyl-1,1-bis-*H*-phosphinates.[2] We now report the results of this study.

The thermal, peroxide-initiated radical reaction of hypophosphorous acid with alkynes has been studied by Nifant'ev and co-workers.[3] Several products were identified depending on the conditions employed (eq 2). A mixture of *trans*- and *cis*-alkenyl-*H*-phosphinic acids was produced as the major



(Eq. 2)

component, along with minor amounts of disubstituted 1,2-bis-*H*-phosphinic acids. Nifant'ev had also investigated alkenes under the same conditions.[4] Previously, we found that our milder reaction conditions considerably expanded the scope of *H*-phosphinates, which could be produced in terms of both functional group tolerance on the alkene and the hypophosphorous reagent employed.[1] These differences prompted the study of alkynes as substrates under our R_3B/air and room-temperature conditions.

As a model study, the reaction of sodium hypophosphite with 1-hexyne was investigated using Et_3B/air to promote radical formation. The results are summarized in Table 1. Methanol was initially selected as solvent because sodium

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(2) Montchamp, J.-L.; Deprèle, S. U.S. Patent Number US 6,781,011 B2, 2004.
(3) (a) Nifant'ev, E. E.; Solovetskaya, L. A.; Maslennikova, V. I.; Magdeeva, R. K.; Sergeev, N. M. *J. Gen. Chem. USSR* **1986**, *56*, 680. (b) Nifant'ev, E. E.; Magdeeva, R. K.; Solovetskaya, L. A.; Sergeev, N. M. *J. Gen. Chem. USSR* **1984**, *54*, 630.
(4) (a) Nifant'ev, E. E.; Magdeeva, R. K.; Shchepet'eva, N. P. *J. Gen. Chem. USSR* **1980**, *50*, 1416. (b) Karanewsky, D. S.; Badia, M. C.; Cushman, D. W.; DeForrest, J. M.; Dejneka, T.; Loots, M. J.; Perri, M. G.; Petrillo, E. W., Jr.; Powell, J. R. *J. Med. Chem.* **1988**, *31*, 204.

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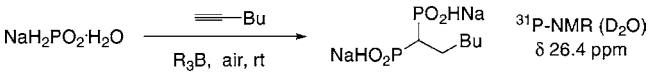
Table 1. Influence of Reaction Conditions with 1-Hexyne[a]



entry	NaH_2PO_2 equiv	solvent	isolated yield[b]
1	2.5	MeOH	13
2[c]	2.5[c]	MeOH[c]	0[c]
3	2.5	MeOH/acetone (5:1)	44
4	6.0	MeOH	52
5	6.0	MeOH/H_2O (5:1)	23
6	6.0	MeOH/CH_3CN (5:1)	27
7	6.0	MeOH/acetone (5:1)	57
8	6.0	MeOH/DMF (5:1)	67
9	6.0	MeOH/dioxane (5:1)	67
10	6.0	THF/H_2O (2:1)	0
11	10.0	MeOH	62
12	10.0	MeOH/dioxane (5:1)	65

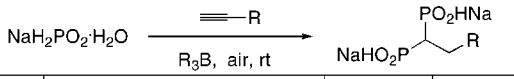
[a] Reactions were conducted in a flask open to air at room temperature, using Et_3B (1 equiv) in hexane (1 M) in reagent-grade solvent. Unless otherwise noted, the concentration of 1-hexyne before addition of Et_3B was 0.2 M. [b] All yields are isolated after filtration and washing with cold methanol. [c] Concentration was 0.1 M.

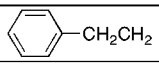
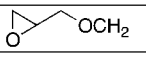
hypophosphite has no significant solubility in other common organic solvents at room temperature. Interestingly, the novel 1,1-bis-*H*-phosphinate was always obtained as the major product (the remaining filtrate contains some unreacted alkyne, along with small amounts of the 1,2-disubstituted isomer and, in some cases, traces of the alkenyl intermediate). Additionally, the 1,1-bis-*H*-phosphinate disodium salt precipitated spontaneously from the reaction mixture, thereby allowing easy isolation. The only 1,1-bis-*H*-phosphinate derivatives reported in the literature are the unsubstituted ethyl and isopropyl esters of the parent acid,[5] which were obtained from $Cl_2PCH_2PCl_2$.[6]

Under the conditions we used with alkenes,[1] only a small amount of precipitate formed (entry 1). As expected, decreasing the concentration lowered the yield further (entry 2) because of both a less-efficient chain reaction and an increased solubility of the product which impedes its recovery. Addition of a cosolvent significantly increases the yield (entry 3). Because 2.5 equiv of NaH_2PO_2 was optimum for reaction with olefins and because bis addition is required with alkynes, increased amounts of hypophosphite were tried. Not surprisingly, this resulted in significant improvements (compare entry 11 with entry 4 and entry 1). Various cosolvents were also tried. Water (entry 5) and acetonitrile (entry 6) were unsatisfactory, whereas acetone (entry 7), DMF (entry 8), or dioxane (entry 9) afforded good yields of 1,1-bis-*H*-phosphinate. At this point, further increasing the amount of sodium hypophosphite had little effect (entry 12 vs 9). Therefore, the conditions in entry 9 appeared nearly ideal.

Next, the scope of the reaction was studied on a variety of terminal alkyne substrates (Table 2). All alkynes react to give the corresponding 1,1-bis-*H*-phosphinate which always precipitated out of the reaction mixture. Initially, the addition was investigated using unoptimized conditions (method A, Table 2). Reaction in methanol generally afforded lower yields than when dioxane was employed as a cosolvent (method B, Table 2, entry a vs b). Polar alkynes also give better yields possibly because of their higher solubility in methanol. A variety of functional groups are tolerated. Although the yields were sometimes low, the reaction is convenient to run even on a large scale and does not require particular precautions. Gas chromatographic analysis of the filtrate after low-yielding reactions shows that the alkyne starting material remains in significant quantity. Thus, a "recycling" strategy was developed to increase conversion: after the first run, the filtrate is concentrated, taken up in the solvent, and more NaH_2PO_2 and Et_3B are added. For example, using this method, 4-phenyl-1-butyne (Table 2, entry 11b) yields the bisphosphinate in 21% yield in the first run and in 35% yield in the second run, for a 56% overall yield (method C, Table 2).

Table 2. Scope of Alkyne Radical Hydrophosphinylation

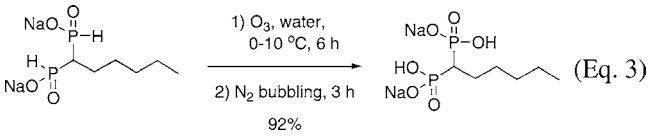


entry	R	method[a]	isolated yield (%)[b]
1a	CH_2OH	A	20
1b		B	52
2a	$CH_2CH_2CH_2OH$	A	25
2b		B	64
3a		A	46
3b		B	78
4a		A	39
4b		B	87
5a	Me_3Si	A	33
5b		B	41
6a	Oct	A	48
6b		B	64
7a	*t*-Bu	A	39
7b		B	46
8a	CO_2Et	A	40
8b		B	60
9a	CH_2OCH_3	A	51
9b		B	47
10	$CH_2CH_2CO_2H$	B	69
11a		B	21
11b		C	56
12	$CH_2NH_2.HCl$[c]	B[c]	42[c]
13a	$CBZ_2NCH_2CH_2$	A	22
13b		B	48
14a		A	24
14b		B	41

[a] Reactions were conducted in a flask open to air at room temperature, using reagent-grade solvent(s) with NaH_2PO_2 (6 equiv) and Et_3B (1 equiv, 1 M in hexane). Method A: MeOH. Method B: MeOH/dioxane (5:1). Method C: after a run conducted, as in Method B, the filtrate is concentrated and redissolved in the solvent mixture along with NaH_2PO_2 (6 equiv), and Et_3B is added. The yield corresponds to the combined yield after both runs. For additional details, see the Supporting Information. [b] 1,1-Bis-*H*-phosphinates were isolated by simple filtration after washing with cold methanol in >95% purity. [c] 2 equiv of Et_3B were used.

(5) Novikova, Z. S.; Odinets, I. L.; Lutsenko, I. F. *J. Gen. Chem. USSR* **1987**, *57*, 459.
(6) Hietkamp, S.; Sommer, H.; Stelzer, O. *Chem. Ber.* **1984**, *117*, 3400.

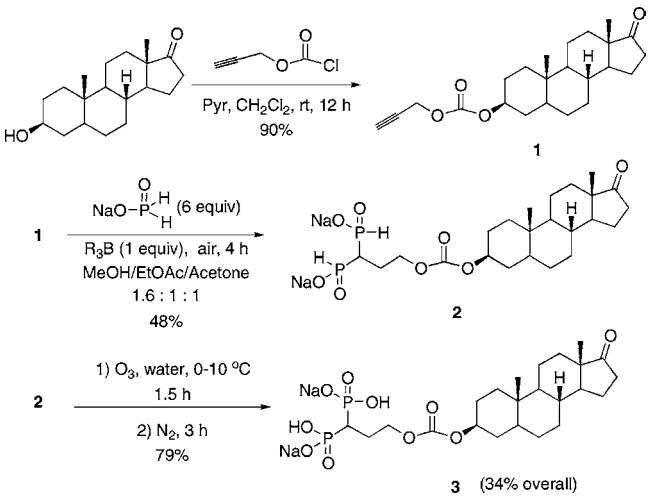
Bisphosphonates are an important class of biologically active compounds, used, for example, in the treatment of bone diseases such as osteoporosis[7] or to prepare conjugates with high bone affinity.[8] Thus, the oxidative conversion of 1,1-bis-*H*-phosphinates into the corresponding bisphosphonates was investigated. *H*-Phosphinic acids have been converted into phosphonates through a variety of methods.[9] The acids are more reactive toward oxidation than the corresponding neutral salts because the P(V)−P(III) tautomerism of the phosphinylidene group is catalyzed by non-neutral conditions. However, we found ozonolysis to be a practical method to directly convert the 1,1-bis-*H*-phosphinate disodium salt into the corresponding phosphonate (eq 3). The same bisphosphonate was recently shown by Szajnman and co-workers to have significant activity on *Trypanosoma cruzi* farnesyl pyrophosphate synthase (K_i = 0.47 μM; IC_{50} = 5.67 μM).[10] Other reagents can also be employed (H_2O_2, NaOCl, Br_2), but ozonolysis was generally found to be more convenient.[11]



(Eq. 3)

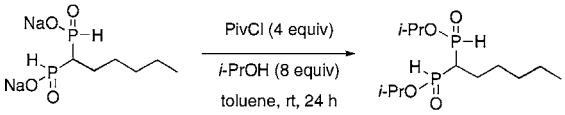
The unique potential of 1,1-bis-*H*-phosphinates to function as precursors of bisphosphonates was then realized with the preparation of a steroid conjugate (Scheme 1). Bisphosphonate−steroid conjugates[12] have been proposed as a method to direct hormones to the bone for the treatment of osteoporosis and to decrease the well-known problems associated with hormone replacement therapy. Epiandrosterone was reacted with propargyl chlorofomate to form the corresponding carbonate **1** in nearly quantitative yield. Because of the solubility profile of the steroid, a ternary solvent mixture was employed for the radical reaction with NaH_2PO_2, which then afforded 1,1-bis-*H*-phosphinate **2** as a white solid. Finally, oxidation with ozone produced the bisphosphonate−steroid conjugate **3**. Thus, the present reaction can be used for the expeditious synthesis of bisphosphonates. Literature syntheses of steroid−bisphosphonate conjugates require time-consuming multistep sequences, whereas our synthesis of **3** can be conducted quickly with a reasonable overall yield.[13]

Scheme 1. Preparation of a Steroid−Bisphosphonate Conjugate



The present reaction has obvious potential for the preparation of bisphosphonate libraries from terminal alkyne precursors. Additionally, it avoids the cumbersome and sometimes problematic[8g,12a] protection−deprotection strategies associated with the alkylation of methylenebisphosphonate esters.

Finally, the esterification of a 1,1-bis-*H*-phosphinate was studied. It was found that a direct esterification of the sodium salt with PivCl/*i*-PrOH delivered the corresponding ester as a mixture of stereoisomers in good yield (eq 4).



(Eq. 4)

In conclusion, we have developed a simple and practical approach to a new class of organophosphorus compounds.

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(8) Bisphosphonate conjugates for bone targeting: (a) [methotrexate] Sturtz, G.; Appéré, G.; Breistol, K.; Fodstad, O.; Schwartsmann, G.; Hendriks, H. R. *Eur. J. Med. Chem.* **1992**, *27*, 825. (b) [doxorubicin] Fabulet, O.; Sturtz, G. *Phosphorus, Sulfur Silicon* **1995**, *101*, 225. (c) [protein] Uludag, H.; Gao, T.; Wohl, G. R.; Kantoci, D.; Zernicke, R. F. *Biotechnol. Prog.* **2000**, *16*, 1115. (d) [protein] Uludag, H.; Kousinioris, N.; Gao, T.; Kantoci, D. *Biotechnol. Prog.* **2000**, *16*, 258. (e) [fluoroquinolones] Herczegh, P.; Buxton, T. B.; McPherson, J. C., III.; Kovacs-Kulyassa, A.; Brewer, P. D.; Sztaricskai, F.; Stroebel, G. G.; Plowman, K. M.; Farcasiu, D.; Hartmann, J. F. *J. Med. Chem.* **2002**, *45*, 2338. (f) [carboranes] Kultyshev, R. G.; Liu, J.; Liu, S.; Tjarks, W.; Soloway, A. H.; Shore, S. G. *J. Am. Chem. Soc.* **2002**, *124*, 2614. (g) [prostaglandin E_2 conjugate] Gil, L.; Han, Y.; Opas, E. E.; Rodan, G. A.; Ruel, R. J.; Seedor, J. G.; Tyler, P. C.; Young, R. N. *Bioorg. Med. Chem.* **1999**, *7*, 901.

(9) Oxidation of *H*-phosphinates: [H_2O_2] (a) Barton, D. H. R.; Vonder Embse, R. A. *Tetrahedron* **1998**, *54*, 12475. (b) Kehler, J.; Hansen, H. I.; Sanchez, C. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2547. [Br_2] (c) Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin. Trans 1* **1984**, 2845. (d) Fastrez, J.; Jespers, L.; Lison, D.; Renard, M.; Sonveaux, E. *Tetrahedron Lett.* **1989**, *30*, 6861. (e) Hamilton, R.; Walker, B.; Walker, B. J. *Tetrahedron Lett.* **1995**, *36*, 4451. (f) Drag, M.; Grembecka, J.; Kafarski, P. *Phosphorus, Sulfur Silicon* **2002**, *177*, 1591. [$NaIO_4$] (g) Vitharana, D.; France, J. E.; Scarpetti, D.; Bonneville, G. W.; Majer, P.; Tsukamoto, T. *Tetrahedron: Asymmetry* **2002**, *13*, 1609. [I_2] (h) Albouy, D.; Brun, A.; Munoz, A.; Etemad-Moghadam, G. *J. Org. Chem.* **1998**, *63*, 7223.

(10) Szajnman, S. H.; Montalvetti, A.; Wang, Y.; Docampo, R.; Rodriguez, J. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3231.

(11) Depending on the substrate and oxidizer, variable amounts of phosphate can also form through P−C bond cleavage. Details will be provided in the full paper.

(12) (a) Page, P. C. B.; McKenzie, M. J.; Gallagher, J. A. *J. Org. Chem.* **2001**, *66*, 3704. (b) Page, P. C. B.; Moore, J. P. G.; Mansfield, I.; McKenzie, M. J.; Bowlerb, W. B.; Gallagher, J. A. *Tetrahedron* **2001**, *57*, 1837.

(13) A compound related to **3** with an ester tether in place of our carbonate tether was prepared from $Cl_2P(O)CH_2P(O)Cl_2$ in five steps and 61% overall yield. However, one of the steps requires a 5 day reaction time. Circumventing this step results in a five-step sequence with a 26% overall yield. See ref 12a.

Through oxidation, these 1,1-bis-*H*-phosphinates can be converted into 1,1-bisphosphonates which are biologically important compounds. An intriguing possibility which remains for further studies would be if in vivo oxidation of the 1,1-bis-*H*-phosphinates can take place[14] because these compounds would then act as novel bisphosphonate prodrugs.[15] Further investigations to study the reactivity of the 1,1-bis-*H*-phosphinates and to prepare various conjugates are currently underway and will be reported in a full account.

Acknowledgment. We thank the National Institute of General Medical Sciences/NIH (R01 GM067610) for the support of this research.

Supporting Information Available: Representative experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) There is some evidence for the oxidation of *H*-phosphinates into phosphonates in vivo: Froestl, W.; Mickel, S. J.; Hall, R. G.; von Sprecher, G.; Diel, P. J.; Strub, D.; Baumann, P. A.; Brugger, F.; Gentsch, C.; Jaekel, J.; Olpe, H.-R.; Rihs, G.; Vassout, A.; Waldmeier, P. C.; Bittiger, H. *J. Med. Chem.* **1995**, *38*, 3297. P(III) compounds such as Et_3P have also been shown to undergo oxidation in vivo: Shaw, C. F., III. *Chem. Rev.* **1999**, *99*, 2589.

(15) The highly-charged nature of bisphosphonates decreases uptake and causes the rapid excretion of these compounds. For examples of bisphosphonate prodrugs, see: (a) Ezra, A.; Hoffman, A.; Breuer, E.; Alferiev, I. S.; Mönkkönen, J.; Hanany-Rozen, N. E.; Weiss, G.; Stepensky, D.; Gati, I.; Cohen, H.; Törmälehto, S.; Amidon, G. L.; Golomb, G. *J. Med. Chem.* **2000**, *43*, 3641. (b) Niemi, R.; Vepsäläinen, J.; Taipale, H.; Järvinen, T. *J. Med. Chem.* **1999**, *42*, 5053. (c) Ahlmark, M.; Vepsäläinen, J.; Taipale, H.; Niemi, R.; Järvinen, T. *J. Med. Chem.* **1999**, *42*, 1473.