



Metal-free synthesis of *E*-vinylphosphonates via photoinduced alkyne hydrophosphonylation and thiol promoted isomerization sequence



Samuele Staderini^a, Alessandro Dondoni^{b,*}, Alberto Marra^{c,*}

^a Dipartimento di Scienze Chimiche e Farmaceutiche, Università di Ferrara, Via Fossato di Mortara 17, 44121 Ferrara, Italy

^b Interdisciplinary Center for the Study of Inflammation, Università di Ferrara, Via Borsari 46, 44100 Ferrara, Italy

^c Institut des Biomolécules Max Mousseron (IBMM), UMR 5247, Ecole Nationale Supérieure de Chimie de Montpellier, 8 Rue de l'Ecole Normale, 34296 Montpellier cedex 5, France

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ABSTRACT

The alkyne hydrophosphonylation is an atom economical method for the synthesis of vinylphosphonates that are compounds of both biological and synthetic relevance. Recent approaches based on the use of metal catalysts have only partially solved the problems of the reaction selectivity as well as of economical and large amount production. We report in this Letter on a metal-free approach that leads to *E*-vinylphosphonates in high yields. The approach is based on a two-step one-pot synthesis, namely: (a) photoinduced anti-Markovnikov addition of a *H*-phosphonate to alkynes to give mixtures of *E*- and *Z*-vinylphosphonates, and (b) cysteine promoted photoinduced conversion of the crude mixtures of adducts into *E*-isomers (58–92% overall yields).

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Introduction

Given that natural products containing carbon-phosphorus bonds (phosphonic and phosphinic acids) have found widespread use in medicine and agriculture, recent years have witnessed an increasing interest in the biochemistry, biology, and synthesis of these compounds and their analogues.¹ Indeed, phosphonates and their parent phosphonic acids have been the target of numerous synthetic efforts.² In particular vinylphosphonates constitute an exceedingly important group of compounds as they are both synthetically versatile³ and biologically active.⁴ While many different synthetic methods leading to vinylphosphonates have been developed,³ the metal-catalyzed addition of dialkyl *H*-phosphonates to terminal alkynes attracted considerable attention. The main problem associated with this approach is the control of the selectivity of the addition mode of the phosphorus–hydrogen bond across the triple bond in order to form a single product among the various possible regio- and stereoisomers (Scheme 1). To address this problem various conditions were applied by the groups led by Tanaka, Han, Beletskaya, and Ananikov.⁵ Nevertheless, the full control of the reaction selectivity remains a major hurdle. The

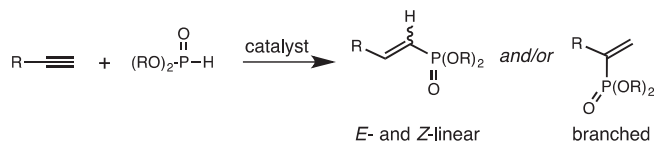
use of expensive metal catalysts such as Pd and Pt and their difficult recovery is another obstacle that precludes the application of this approach to large scale production of vinylphosphonates. Thus, the search of alternative methods for alkyne hydrophosphonylation is highly advisable. In this context we report herein a metal-free photoinduced method leading to anti-Markovnikov *E*- and *Z*-vinylphosphonates and the subsequent almost quantitative conversion of the latter into the former isomers. Overall, the method constitutes a new entry to *E*-vinylphosphonates. This work represents the first example of alkyne hydrophosphonylation under free-radical conditions.

Results and discussion

We have recently reported efficient conditions for the metal-free photoinduced addition of dimethyl *H*-phosphonate (**1**) to *C*-alkenyl sugars (enopyranoses) and a free-radical mechanism initiated by the formation of a phosphonyl radical was suggested.⁶ Thus, we set out to adopting the same conditions for performing the reaction of **1** with the model propargyl *O*-galactoside (**2**) and possibly extend the scope of the approach to other substrates. As in the case of hydrophosphonylation of alkenes to give alkyl phosphonates,⁶ we carried out this reaction at room temperature in glass vials, no care was taken to exclude air and moisture. Moreover, since the optimized conditions leading to a high yield of

* Corresponding authors. Tel.: +33 4 67144345; fax: +33 4 67144344.

E-mail addresses: adn@unife.it (A. Dondoni), Alberto.Marra@univ-montp2.fr (A. Marra).

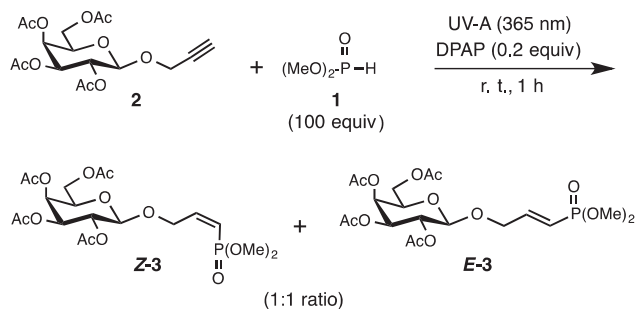


Scheme 1. Possible products from alkyne hydrophosphonylation.

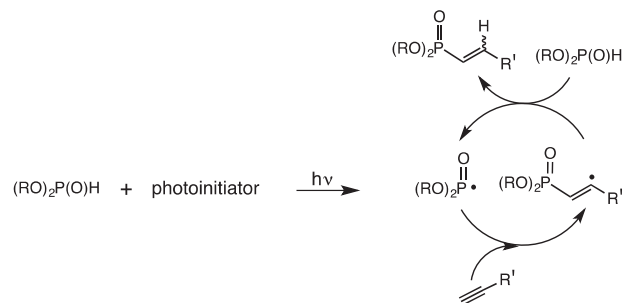
sugar-based alkyl phosphonates were established using a very large excess of **1**,⁶ the hydrophosphonylation of the sugar alkynes was performed in the presence of the same excess of dimethyl *H*-phosphonate (**1**) that in fact was used as a solvent. Thus, a stirred solution of alkynyl sugar **2** and 0.2 equiv of 2,2-dimethoxy-2-phenylacetophenone (DPAP) as initiator in freshly distilled phosphonate **1** (100 equiv) was irradiated with a household UV-A lamp (λ_{max} 365 nm) at room temperature for 1 h and then submitted to distillation under reduced pressure to recover the excess of **1**. The ¹H NMR spectrum of the crude mixture showed the absence of the signal at 2.48 ppm (t, 1H, ⁴*J* = 2.3 Hz) corresponding to the propargylic proton and the presence of signals showing the formation of a mixture of anti-Markovnikov galactosyl *Z*- and *E*-vinylphosphonates **Z-3** and **E-3**, respectively, in a ca. 1:1 ratio (Scheme 2). The two isomers were easily detected since **Z-3** showed a ³*J*_{cis} of 13.6 Hz whereas **E-3** displayed a larger vicinal constant (³*J*_{trans} = 17.6 Hz) for the alkene protons. Individual compounds **Z-3** and **E-3** were isolated by column chromatography on silica gel and fully characterized (see Supplementary material).

Thus, it may be concluded that unlike the free-radical hydrothiolation of alkynes that is known to proceed with a double addition mode to give dithioethers,⁷ the photoinduced hydrophosphonylation terminated at the stage of monoadduct formation. As a free-radical mechanism is very likely to be followed by this reaction as well by virtue of the experimental conditions that were employed and its suppression by the presence of a radical trap such as γ -terpinene,⁸ the following scheme may be outlined (Scheme 3). As in the alkene hydrophosphonylation,⁶ this should involve the photoinduced generation of a phosphonyl radical that adds to the terminal carbon of the alkyne **2** to give a β -phosphanyl-substituted vinyl radical. This intermediate by abstraction of a hydrogen radical from the unreacted *H*-phosphonate **1**, would lead to the final vinylphosphonate and a new phosphonyl radical, thus propagating the radical chain. Evidently, the last step lacks stereoselectivity as shown by the formation *E*- and *Z*-products in equal amounts.

Although we were well aware about the scarce reactivity of the internal C=C double bonds of 1,2-disubstituted alkenes toward thiols under free-radical conditions,⁹ we decided to explore the possibility of introducing a sugar residue via thiol-ene coupling (TEC)¹⁰ in either **Z-3** and **E-3** and obtaining in this way doubly glycosylated alkyl phosphonates. To this aim, a mixture constituted of



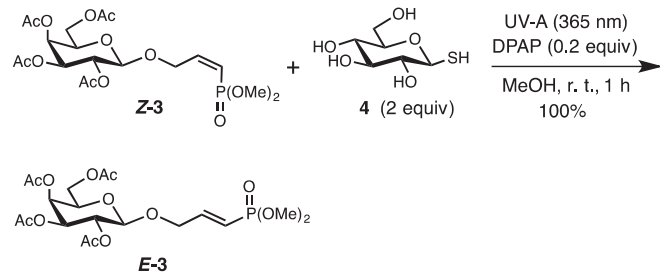
Scheme 2. Hydrophosphonylation of alkyne **2** to give vinylphosphonates **Z-3** and **E-3**.



Scheme 3. Plausible mechanism of free-radical alkyne hydrophosphonylation.

the vinylphosphonate **E-3**, DPAP (0.2 equiv), and glucosyl thiol **4** (2 equiv) in MeOH was irradiated for 1 h at room temperature. This system did not provide any product whereas unaltered phosphonate **E-3** was totally recovered. On the other hand, performing the same reaction using the vinylphosphonate **Z-3** resulted in the total isomerization of the latter to give the thermodynamically more stable isomer **E-3** in quantitative yield (Scheme 4). The isomerization was successfully performed with an identical result using the crude mixture of *Z* and *E* isomers obtained from the addition of the *H*-phosphonate **1** to the sugar alkyne **2**. This reaction was totally inhibited by the presence of γ -terpinene and did not proceed when the UV-A irradiation was carried out in the absence of thiol **4**, with or without the photoinitiator DPAP. Nevertheless, these results were not surprising because *cis*–*trans* isomerization of 1,2-disubstituted alkenes by addition–elimination sequence of the PhS[•] radical is a well known process and an established methodology in fine chemical synthesis.^{11,12} Therefore, we considered this result in a positive way because the combination of the hydrophosphonylation reaction and the subsequent isomerization process provided a new and efficient synthetic route to *E*-vinylphosphonates.

Given the above observations, the use of a commercially available thiol as the isomerization catalyst was explored. While simple thiols, such as ethanethiol and thiophenol, were uneffective, probably due to their fast oxidation to the corresponding disulfides, the one that turned out to be suitable for our purposes was *L*-cysteine, an odorless and inexpensive compound. The results from the application of this thiol to the transformation of alkynes **2**, **5**, **7**, **9**, **11**, and **13** into the corresponding *E*-vinylphosphonates **3**, **6**, **8**, **10**, **12**, and **14** are collected in Table 1. All hydrophosphonylations were carried out as outlined in the equation at the top of Table 1 and, with the exception of the reaction of entry 4, the crude mixtures of vinylphosphonates were subjected to the photoinduced isomerization after removal of excess dimethyl *H*-phosphonate (**1**) under high vacuum. While the anomeric (**2** and **5**) and non-anomeric (**7**) *O*-propargyl sugars gave the corresponding *E*-vinylphosphonates in good yields and selectivity (entries 1–3), the ethynyl *C*-glucoside **9** (entry 4) did not undergo a quantitative hydrophosphonylation. Therefore, the unreacted alkyne **9** (20%)



Scheme 4. Thiol promoted isomerization of vinylphosphonate **Z-3** into **E-3**.

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