Synthesis of Dienol Ethers Using the Phosphine-Catalyzed Alkyne Isomerization Reaction

Michael Yunyi Fu, Jiawen Guo, Patrick H. Toy*

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, P. R. of China Fax +85228571586; E-mail: phtoy@hku.hk Received 8 November 2010

Abstract: A series of δ -alkoxy-substituted electron-deficient alkynes were isomerized to the corresponding dienol ethers using phosphine catalysis. Both Ph₃P and a polymer-supported phosphine were found to be useful in this context. This methodology represents a general procedure for the synthesis of 'push-pull' δ -alkoxy dienones.

Key words: organocatalysis, polymer-supported catalyst, alkyne isomerization, dienes, enol ethers, triphenylphosphine

Nearly two decades ago, and virtually simultaneously, the groups of Lu¹ and Trost² reported the stereoselective Ph_3P -catalyzed isomerization of alkynones into the corresponding *E*,*E*-dienones (Scheme 1).³ Shortly thereafter Rychnovsky and Kim reported that the use of PhOH as a weakly acidic co-catalyst allowed less activated alkynoates to be similarly isomerized.⁴ Since then such isomerization reactions have been used in a variety of contexts,⁵ especially natural product synthesis.⁶



We recently reported a bifunctional polymer bearing both phosphine and phenol groups and its use as a catalyst for Morita-Baylis-Hillman reactions.⁷ This material was subsequently used to catalyze the isomerization of a variety of alkynoates to the corresponding 2E, 4E-dienoates, 8,9and during the course of this later work it occurred to us that the reported substrate scope for such isomerization reactions was rather limited. All of the alkynone and alkynoate substrates described in the literature possessed alkyl substituents at the δ -position (R¹ in Scheme 1). To the best of our knowledge, no examples of isomerization substrates bearing heteroatom substituents at this position have been described in the literature. Furthermore, we noted the great synthetic utility of Zincke aldehydes (Scheme 2) recently reported by Vanderwal and co-workers,10 and wondered if analogous 'push-pull' dienol ethers could be prepared via isomerization of the corresponding δ -alkoxy-substituted electron-withdrawing-group-acti-

SYNLETT 2011, No. 7, pp 0989–0991 Advanced online publication: 08.03.2011 DOI: 10.1055/s-0030-1259700; Art ID: W01510ST © Georg Thieme Verlag Stuttgart · New York vated alkynes. A survey of the literature indicated that while KOH has been used instead of a secondary amine to open a pyridinium salt to form the glutaconaldehyde potassium salt, such dienol ethers are relatively rare, and it appears that no general procedure exists for their stereoselective synthesis.^{11,12} Importantly, our strategy would allow for the synthesis of both dienones and dienoates since alkynones and alkynonates are suitable substrates for the isomerization reaction. Thus, if our concept proved feasible, it could be used to efficiently prepare a range of potentially useful building blocks for organic synthesis in an organocatalytic and highly stereoselective manner (Scheme 2).



Scheme 2

In order to test our hypothesis, we set out to synthesize a series of substrates of the general structure **1** in a straightforward manner. As a starting point we treated $2a^{13}$ with *n*-BuLi (1.2 equiv) at low temperature to generate the corresponding acetylide ion, which was reacted directly with a range of aldehydes (1.2 equiv) to afford the corresponding propargyl alcohols. These were in turn oxidized using PDC (2.5 equiv) at room temperature to afford the desired ketones **1a–f** (Scheme 3).¹⁴ Additionally, aryl ether **2b**¹⁵ and allyl ether **2c**¹⁶ were prepared according to literature procedures and converted into **1g** and **1h**, respectively, using similar methodology (Scheme 4). Thus a range of δ -benzyloxy, -phenoxy, and -allyloxy alkynones was prepared in short order.

Once the synthesis of substrates 1a-h was complete, we examined the isomerization of 1a using both triphenylphosphine (Ph₃P) and JandaJel-triphenylphosphine



Scheme 3 Synthesis of isomerization substrates 1a-f



Scheme 4 Synthesis of isomerization substrates 1g-h

(JJ-PPh₃),¹⁷⁻²⁰ a heterogeneous polymer-supported phosphine that we have previously reported. Gratifyingly, our initial studies were successful, and we were able to quickly identify optimal reaction conditions for the formation of 3a from 1a as being the use of 0.2 equivalents of phosphine catalyst in hot toluene (1 M, 80 °C; Table 1, entry 1). In this reaction the use of Ph₃P and JJ-PPh₃ afforded essentially the same yield of isolated product (90% vs. 86%, respectively), with the later having the advantage that it could be separated from **3a** by simple filtration.²¹ We then applied these reaction conditions to substrates **1b-h** using both Ph₃P and JJ-PPh₃ as the catalyst. As before, in all cases these nucleophilic phosphine catalysts afforded similar yields of the corresponding dienol ether products **3b-h** (entries 2–8). It should be noted that the isomerization of phenyl ether 1g to 3g was stopped after three hours in order to minimize byproduct formation. Despite the shorter reaction time for these experiments, high yield of **3g** was obtained in both cases. For the reactions catalyzed by Ph₃P, the products were purified by silica gel chromatography. When the reactions were performed using JJ-PPh₃, the phosphine catalyst was removed by filtration, and then further purification was performed if necessary.

In summary, we have developed a short synthesis of 5alkoxy-2E,4E-dienones based on the phosphine-catalyzed isomerization of electron-deficient alkynes. This represents the first general, organocatalytic, and stereoselective method for the synthesis of such dienol ether compounds, and we are currently examining their synthetic utility in the context of complex molecule synthesis.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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Isomerization of **1a-h** to **3a-h** Using Ph₃P and JJ-PPh₃ Table 1



^a Isolated yield of 1.0 mmol scale reactions with 0.2 mmol catalyst (Ph₃P or JJ-PPh₃) in toluene (1 M, 80 °C) for 18 h. ^b Reaction time: 3 h.

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- (21) General Reaction Procedure To a solution of 1 (1.0 mmol) in toluene (1 mL) was added Ph₃P or JJ-PPh₃ (0.2 mmol). The reaction vial was then shaken at 80 °C for 18 h. At this time, the reaction mixture was either concentrated and purified by silica gel chromatography (for Ph₃P) or filtered and concentrated in vacuo (for JJ-PPh₃). All products 3 were characterized by ¹H NMR and ¹³C NMR spectroscopy.

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