Phosphorous acid promoted isomerization of propargyl alcohols to α,β-unsaturated carbonyl compounds

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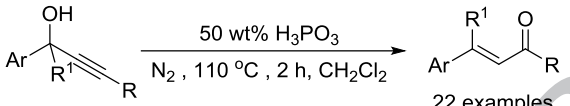

R^1 = Ar or H

22 examples
up to 95% yield

- *metal-free*
- *weak inorganic acid*
- *two-phase system*
- only *E* isomer

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Phosphorous acid promoted isomerization of propargyl alcohols to α,β-unsaturated carbonyl compounds

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ABSTRACT

A metal-free and two-phase protocol for the Meyer-Schuster isomerization of propargyl alcohols to the corresponding α,β-unsaturated carbonyl compounds has been achieved in the presence of stoichiometric phosphorous acid aqueous solution, which produces the desired products in high yields with excellent stereoselectivity. Compared with the traditional methods, the procedure features broad scope of the substrates, mild conditions, and easy separation, providing an appealing alternative to the Meyer-Schuster reaction.

Introduction

As versatile structural building blocks, α,β-unsaturated carbonyl compounds are widely used in the food, agriculture, medicinal industries, and biologically active compounds.[1] This type of compounds has also attracted increasing interest due to their broad applications in organic synthesis.[2] In the past decades, a variety of synthetic strategies toward their synthesis have been developed,[3] such as Heck coupling,[4] Peterson olefinations,[5] formylation,[6] cross-aldol condensations,[7] Saegusa–Ito oxidation reaction,[8] and the oxidation of allylic alcohols,[9] etc.

Among them, the isomerization of readily accessible propargyl alcohols to α,β-unsaturated carbonyl compounds provides a straightforward route to these very valuable raw chemicals with high atom economy.[10] This reaction is named after Meyer and Schuster, which was first reported about 100 years ago. The reaction proceeds under strong Brønsted acids at elevated temperatures, and the scope of the substrate limits to tertiary propargyl alcohols that lack *β*-hydrogen. Over past decades, many improvements have been made by the use of transition metals (Ru, Rh, Mo, V, Pd, Ir, Ti, Ag, Au, and Fe)[11,12] and organic acids.[13] For instances, Douhaibi group developed a $FeCl_3$-promoted isomerization of propargyl alcohols to the corresponding α,β-unsaturated carbonyl compounds in 2011.[12] Next, Hall and coworkers explored a arylboronic acid catalyzed synthesis of such compounds.[13a] Recently, Lee reported *p*-toluenesulfonic acid catalyzed Meyer–Schuster rearrangement of propargyl alcohols into α,β-unsaturated carbonyl compounds.[13b] Despite many advances, the Meyer-Schuster rearrangement has few applications in organic synthesis because it still suffers from harsh reactions, strong acids, limited substrate scope, and/or poor stereoselectivity.[10b] Therefore, facile, efficient, and stereoselective protocols for Meyer-Schuster rearrangement are still highly desired.

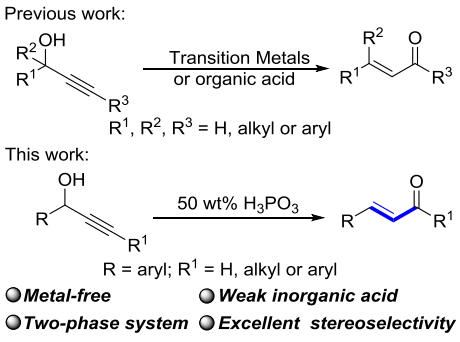

Figure 1. The isomerization of propargyl alcohols.

Herein, we disclose a facile method for Meyer-Schuster rearrangement promoted by phosphorous acid under metal-free condition in two-phase system, and the reaction produces the

‖X.G. and Z.F. contributed equally to this work.

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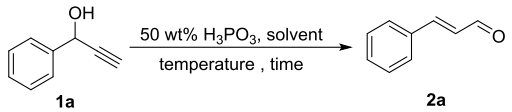
corresponding α,β-unsaturated carbonyl compounds in high yields with high stereoselectivity (Figure 1).[15] H_3PO_3 is an easily accessible, stable, and cheap Brønsted acid with moderate acidity, and it shows unique efficiency in many reactions.[14] The use of H_3PO_3 in this reaction allows broad scope of the substrates, mild conditions, and easy separation.

Results and discussion

We commenced our studies with the reaction of a commercially available propargyl alcohol **1a** (0.2 mmol) and H_3PO_3 50 wt% aqueous solution (0.2 mmol, 1.0 equiv) in CH_2Cl_2 under nitrogen at 80 °C for 12 h, the desired product cinnamaldehyde **2a** was obtained in 70% GC yield with 100% *E* isomer (Table 1, entry 1). A brief examination of temperature and time (Table 1, entries 1–6) indicated that the reaction time could be shortened from 12 h to 2 h and the cinnamaldehyde (**2a**) was obtained in 85% yield (Table 1, entry 4) while raising the temperature up to 110 °C. Increasing the loading of H_3PO_3 aqueous solution to 1.5 eq. could lead to higher yield (90%, Table 1, entry 8; entries 7–9). Then, the screen of different concentration of H_3PO_3 aqueous solution demonstrated that the 50 wt% H_3PO_3 aqueous solution was best (Table 1, entries 10 and 11 *vs* entry 8). Investigation of solvents showed that ethyl acetate (EA), $CHCl_3$, ethyl alcohol (EtOH), tetrahydrofuran (THF), toluene, and H_2O were inferior to CH_2Cl_2 (Table 1, entries 12–17 and entry 8). Furthermore, a series of acids (HNO_3, H_2SO_4, H_3PO_2, H_3PO_4, CH_3COOH, TsOH) were also screened (Table 1, entries 18–23), the results suggested that H_3PO_3 was more suitable for this system (Table 1, entry 8). The reaction also proceeded smoothly under air, and produced the desired product in 80% yield (Table 1, entry 24), which was slightly lower than those in inert condition.

Table 1 Optimization of reaction conditions[a]



1a **2a**

Entry	H_3PO_3/equiv	Solvent	T/°C	t/h	Yield[b](%)
1	1.0	CH_2Cl_2	80	12	70
2	1.0	CH_2Cl_2	100	12	83
3	1.0	CH_2Cl_2	100	2	79
4	1.0	CH_2Cl_2	110	2	85
5	1.0	CH_2Cl_2	120	2	87
6	1.0	CH_2Cl_2	110	1	80
7	1.3	CH_2Cl_2	110	2	87
8	1.5	CH_2Cl_2	110	2	90(81)[c]
9	1.7	CH_2Cl_2	110	2	88
10[d]	1.5	CH_2Cl_2	110	2	70
11[e]	1.5	CH_2Cl_2	110	2	78
12	1.5	EA	110	2	59
13	1.5	$CHCl_3$	110	2	79
14	1.5	EtOH	110	2	none
15	1.5	THF	110	2	none
16	1.5	Toluene	110	2	41
17	1.5	H_2O	110	2	none
18[f]	HNO_3	CH_2Cl_2	110	2	none
19[f]	H_2SO_4	CH_2Cl_2	110	2	59
20[f]	H_3PO_2	CH_2Cl_2	110	2	20
21[f]	H_3PO_4	CH_2Cl_2	110	2	85
22[f]	CH_3COOH	CH_2Cl_2	110	2	none
23[f]	TsOH	CH_2Cl_2	110	2	71
24[g]	1.5	CH_2Cl_2	110	2	80

[a]Reaction conditions: **1a** (0.2 mmol), H_3PO_3 50 wt% aqueous solution, N_2 atmosphere, solvents (0.5 mL).

[b]GC yield.

[c]Isolated yield.

[d]30 wt % H_3PO_3 aqueous solution.

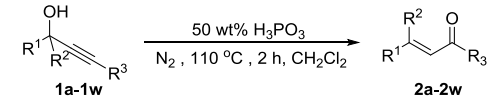
[e]70 wt % H_3PO_3 aqueous solution.

[f]Other 50 wt% acid aqueous solutions instead of H_3PO_3.

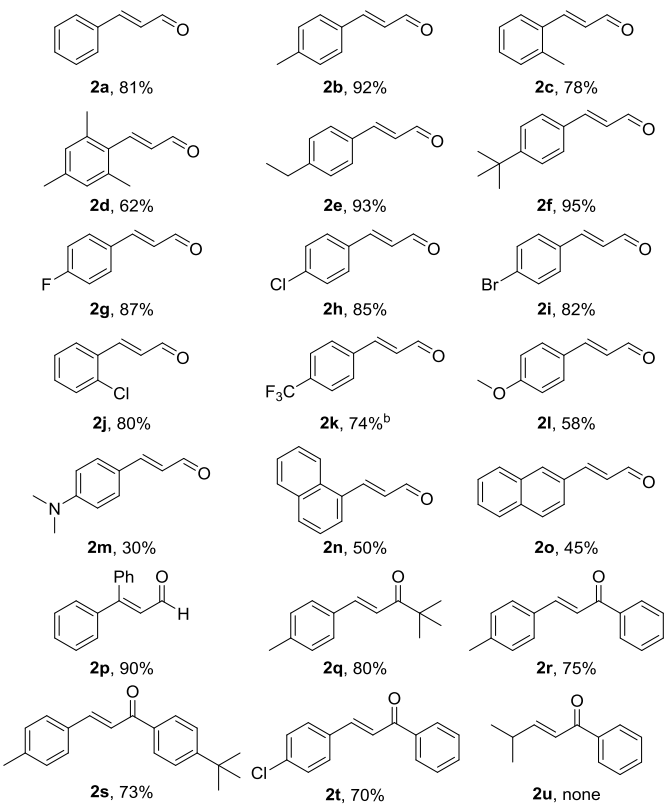
[g]Air.

With the optimized conditions in hand, we next investigated the scope and generality of the reaction. As shown in Table 2, this phosphorous acid promoted isomerization reaction worked well for a wide variety of substrates with outstanding functional group tolerance, producing various (*E*)-α,β-unsaturated aldehydes in good to high yields with excellent stereoselectivity. Propargyl alcohols substituted with alkyl (**2b**–**2f**), halogen (**2g**–**2j**), and trifluoromethyl (**2k**) worked well to give the corresponding (*E*)-α,β-unsaturated aldehydes in 62–95% yields. The trans-geometry of the α,β-unsaturated aldehyde was ascertained by the high coupling constant of the vinyl protons ($J \approx 15.6$–16.4 Hz) in the ^1H NMR spectra. The electron effect of substituents played important roles in the reaction. The electron-donating groups in the phenyl ring, which favor the formation of propargyl cation **A** (vide infra), resulted in higher yields of the desired products [**2b** (92%), **2e** (93%), and **2f** (95%) *vs* **2g** (87%), **2h** (85%), **2i** (82%), and **2k** (74%)]. The steric hindrance of substituents was

Table 2 Substrate scope of α,β-unsaturated carbonyl compounds[a]



1a-1w **2a-2w**



[a]Reaction conditions: propargylic alcohol (0.2 mmol), H_3PO_3 50 wt% aqueous solution (0.3 mmol), N_2 atmosphere, 110 °C, 2 h, CH_2Cl_2 (0.5 mL), isolated yield.

[b]10h.

detrimental to the reaction [**2c** (78%) and **2d** (62%) *vs* **2b** (92%); **2j** (80%) *vs* **2h** (85%)]. In addition, the attachment of methoxy (**2l**), and *N*,*N*-dimethylamino (**2m**) that might be protonated by Brønsted acids resulted in lower yields (58% and 30%, respectively). Notably, the high efficiency (80–85%) of the formation of the halogenated products **2h**–**2j** may be applied for further functionalization toward more complex targets via stepwise coupling reactions. Treating sterically hindered 1-(naphthalen-2-yl)prop-2-yn-1-ol (**1n**) and 1-(naphthalen-1-yl)prop-2-yn-1-ol (**2o**) with H_3PO_3 50 wt% aqueous solution gave the corresponding products in moderate yields (50% and 45% yield, respectively). In addition, tertiary propargylic alcohol 1,1-diphenyl-2-propyn-1-ol was also compatible with this reaction system, and the corresponding product (3,3-diphenylacrylaldehyde **2p**) was produced in excellent yield (90%) with 100% *E* isomer. Furthermore, the α,β-unsaturated ketones also could be obtained in good yields under the optimized conditions when terminal alkyne substituted with alkyl or aryl groups (**2q**–**2t**). Unfortunately, the isomerization of the substrate 4-methyl-1-phenylpent-1-yn-3-ol (**1u**) did not occur due to instability of its propargyl cation.

Interestingly, the propargylic alcohol (**1v**, 1-ethynylcyclohexan-1-ol) with hydrogens in *beta*-position to the alcohol proceeded a Rupe rearrangement in this reaction system, and produced the corresponding enone product (**2v**) in 85% yield (Figure 2).

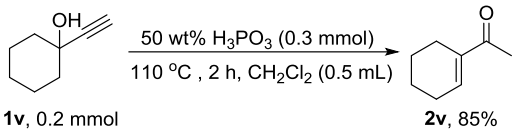


Figure 2. Phosphorous acid promoted Rupe-rearrangement.

To further extend the practicability of this reaction, the isomerization of propargyl alcohols **1a** was carried out on much larger scale (10 mmol). The reaction proceeded smoothly in the two-phase system, and comparable yield (1.028 g, 78%) of the desired product was observed. It is worth noted that this reaction is the first report of two-phase Meyer-Schuster rearrangement, which allowed easy separation of the product by simple extraction and concentration, demonstrating the synthetic value of the procedure in organic synthesis (Figure 3).

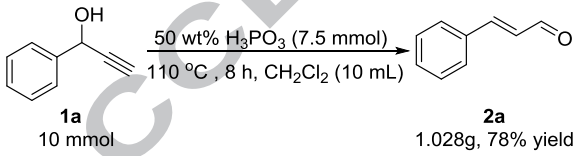


Figure 3. Preparation of cinnamaldehyde at 10 mmol scale.

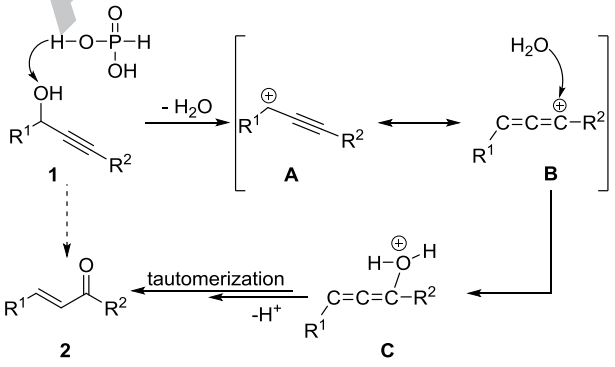


Figure 4. Possible reaction mechanism.

The mechanism of acid-promoted the Meyer-Schuster rearrangement was well-accepted,[16] which involves formal 1,3-hydroxyl shift and tautomerization. Firstly, propargyl alcohol **1** is translated into oxonium salt via rapid protonation step, then takes off a water molecule to generate propargyl cation **A**, which followed by a formal 1,3-cation shift to form the allene cation **B**. Finally, attack of a water molecule on the carbocation and deprotonation is followed by tautomerization to give the α,β-unsaturated carbonyl compound **2** (Figure 4).

Conclusions

In summary, by the use of relatively weak inorganic acid, we developed a facile, efficient, and stereoselective procedure for Meyer-Schuster rearrangement. The reaction proceed under metal free conditions in two-phase system, which produces a variety of α,β-unsaturated carbonyl compounds in high yields with excellent stereoselectivity. The merits of the procedure such as mild conditions, high yields, excellent stereoselectivity, and easy separation allow it as an appealing alternative to the Meyer-Schuster reaction.

Experimental Section

Typical procedure: propargyl alcohols (0.2 mmol), H_3PO_3 50 wt% aqueous solution (0.3 mmol), CH_2Cl_2 (0.5 mL) were placed in 10 mL sealed Schlenk tube under N_2 atmosphere, then stirred at 110 °C for 2 h and monitored by GC or GC-MS or TLC. After completion of the reaction, the mixture was cooled to room temperature, washed with saturated Na_2CO_3 solution, then extracted three times with CH_2Cl_2. The combined organic layer was dried with anhydrous Na_2SO_4, subjected to filtration, and concentrated in vacuo. The residue was purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate to afford the pure products.

Acknowledgments

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Supplementary data

Supplementary data (general information and experimental procedures, assigned ^{1}H, ^{13}C NMR spectral data in table form, copies of ^{1}H, and ^{13}C NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.xxxx.

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Highlights

- Metal-free Meyer-Schuster rearrangement
- Two-phase system using weak inorganic acid phosphorous acid as promoter
- High yields and excellent stereoselectivity
- Scalable synthesis and easy separation

17.
18.

Phosphorous acid promoted isomerization of propargyl alcohols to α,β-unsaturated carbonyl compounds

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