BRØNSTED ACID–CATALYZED MEYER–SCHUSTER REARRANGEMENT FOR THE SYNTHESIS OF α,β-UNSATURATED CARBONYL COMPOUNDS

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GRAPHICAL ABSTRACT

Abstract An efficient and simple protocol for the Meyer–Schuster rearrangement of propargyl alcohols into α,β-unsaturated carbonyl compounds has been developed using catalytic amounts of p-toluenesulfonic acid in 1,2-dichloroethane.

Keywords α,β-Unsaturated carbonyl compounds; Brønsted acid; Meyer–Schuster rearrangement; p-toluenesulfonic acid; propargyl alcohols

INTRODUCTION

α,β-Unsaturated carbonyl compounds are key structural units for the synthesis of biologically active natural products, pharmaceuticals, and other useful materials.[1] The traditional methods for synthesizing α,β-unsaturated carbonyls—which are based on aldol condensation,[2] Horner–Wadsworth–Emmons reaction,[3] Claisen–Schmidt condensation,[4] etc.—involve multiple steps and exhibit overall poor atom economy. The Meyer–Schuster rearrangement,[5] which involves the rearrangement of propargyl alcohols into α,β-unsaturated carbonyl compounds, is considered a highly efficient reaction because of its high atom economy; however, this reaction...
traditionally requires strongly acidic media and harsh conditions, both of which often result in the formation of a mixture of E and Z stereoisomers. The recently developed synthesis methods catalyzed by transition metals such as Au, Ru, Rh, Ir, Pd, and other metals proceed under mild conditions with high efficiency and selectivity; however, in most cases, expensive catalysts, some of which require preparation and special handling, are required. Recently, we developed the indirect hydration of alkynes catalyzed by FeCl$_2$·4H$_2$O in the presence of methanesulfonic acid and found that 1-phenylprop-2-yn-1-ol reacts smoothly to produce cinnamaldehyde in good yield, via the Mayer–Schuster rearrangement by FeCl$_2$·4H$_2$O in the presence of methanesulfonic acid. Although the results of Meyer–Schuster rearrangement by triflic acid (TfOH) or p-toluenesulfonic acid (PTSA) as a Brønsted acid in tetrahydrofuran (THF) have been reported, the disadvantages were poor yield and poor stereoselectivity. However, when using 1,2-dichloroethane (DCE) as the solvent, 1-phenyl-2-propyn-1-ol readily reacted with catalytic amounts of PTSA to selectively afford E-cinnamaldehyde in good yield. Herein, we describe an efficient PTSA-catalyzed rearrangement of propargyl alcohols into $\alpha,\beta$-unsaturated carbonyl compounds (Scheme 1).

RESULTS AND DISCUSSION

Initially, a variety of Lewis and Brønsted acids were screened using 1-phenyl-2-propyn-1-ol as the model substrate (Table 1). The use of various iron salts as the catalyst was investigated for the formation of a cinnamaldehyde in DCE. Catalytic amounts of FeCl$_3$, FeCl$_2$·4H$_2$O, and Fe(ClO$_4$)$_3$·xH$_2$O were inactive at 60 °C for the Meyer–Schuster rearrangement (entries 1–3). The reaction of 1a and 10 mol% of Fe(OTf)$_3$ gave 2a in 41% yield, exclusively in the E configuration, at 60 °C (entry 4); however, at room temperature, only trace amounts of the product could be detected by $^1$H NMR analysis (entry 5). When using Bi(OTf)$_3$ as the catalyst a relatively poor yield of 2a (44%) was obtained (entry 6), while no reaction occurred when using Sc(OTf)$_3$ (entry 7). The reaction with In(OTf)$_3$ gave a 17:1 mixture of the E and Z stereoisomers, and that too in poor yields (entry 8). Cu(OTf)$_2$ also gave the desired product in poor yield (entry 9).

Next, the effects of various Brønsted acids were investigated for the Meyer–Schuster rearrangement. Bronsted acids such as CSA and TfOH were inefficient in the presence of 30 mol% (entries 10 and 11). However, when using MsOH, 2a was obtained in a moderate yield of 68% (entry 12). To our delight, the $^1$H NMR yield of 2a increased to 89% when using PTSA instead of MsOH (Table 1, entry 13). When the amount of PTSA was decreased to 10 mol%, the yield of 2a decreased to 46% (entry 14). Further, at room temperature, only trace amounts of the product could be detected (entry 15). Then, various solvents were screened to determine the optimal...
solvent for the reaction with PTSA. The use of THF, toluene, CH₃CN, and chlorobenzene resulted in poor yields (entries 16–19); furthermore, no reaction occurred when using EtOH (entry 20).

Next, we investigated the scope and limitation of the Meyer–Schuster rearrangement catalyzed by PTSA in DCE, using a variety of propargyl alcohols. The obtained results are shown in Table 2. Electron-rich aromatic propargyl alcohols afforded the desired products in good to excellent yields (entries 2 and 4). However, the use of propargyl alcohol with an ortho-methoxy substituent on the aromatic ring gave the desired product 2c in poor yield (entry 3). When using this substrate, other products were not obtained, but the starting material disappeared within 3 h, probably because of steric hindrance and decomposition. Moreover, substitution of an electron-withdrawing group such as trifluoromethyl, chloro, and bromo on the phenyl ring resulted in reasonable yields of the product (entries 5–8). However, when propargyl alcohol 1i bearing a naphthyl moiety was used, 2i was obtained in only 39% yield (entry 9). We could not obtain other products; however, the starting material disappeared (probably decomposed) within 1 h. The use of 2-phenylbut-3-yn-2-ol 1j resulted in a 1.3:1 mixture of the E and Z stereoisomers in 85% yield, as determined

![Table 1. Optimization of reaction conditions for the rearrangement of propargyl alcohols]

| Entry | Catalyst (mol %) | Solvent | Temp. (°C) | Time (h) | Yield (%) | E/Z ratio |
|-------|-----------------|---------|------------|----------|-----------|-----------|
| 1     | FeCl₃ (10)      | DCE     | 60         | 16       | 0         |           |
| 2     | FeCl₂·4H₂O (10) | DCE     | 60         | 16       | 0         |           |
| 3     | Fe(ClO₄)₃·xH₂O (10) | DCE     | 60         | 16       | 0         |           |
| 4     | Fe(OTf)₃ (10)   | DCE     | 60         | 1        | 41        | (E only)  |
| 5     | Fe(OTf)₃ (10)   | DCE     | 25         | 10       | Trace     | 3:1       |
| 6     | Bi(OTf)₃ (10)   | DCE     | 60         | 1        | 44        | (E only)  |
| 7     | Sc(OTf)₃ (10)   | DCE     | 60         | 10       | 0         |           |
| 8     | In(OTf)₃ (10)   | DCE     | 60         | 6        | 36        | 17:1      |
| 9     | Cu(OTf)₂ (10)   | DCE     | 60         | 3        | 32        | (E only)  |
| 10    | CSA (30)        | DCE     | 60         | 10       | 4         | (E only)  |
| 11    | TiOH (30)       | DCE     | 60         | 3        | Trace     | (E only)  |
| 12    | MsOH (30)       | DCE     | 60         | 5        | 68        | (E only)  |
| 13    | PTSA (30)       | DCE     | 60         | 1        | 89 (84)   | (E only)  |
| 14    | PTSA (10)       | DCE     | 60         | 2.2      | 46        | (E only)  |
| 15    | PTSA (30)       | DCE     | 25         | 10       | Trace     | (E only)  |
| 16    | PTSA (30)       | THF     | 60         | 24       | 21        | (E only)  |
| 17    | PTSA (30)       | Toluene | 60         | 10       | 8         | (E only)  |
| 18    | PTSA (30)       | CH₃CN   | 60         | 10       | 10        | (E only)  |
| 19    | PTSA (30)       | Chlorobenzene | 60     | 8        | 60        | (E only)  |
| 20    | PTSA (30)       | EtOH    | 60         | 10       | 0         |           |

aReaction conditions: 1-phenyl-2-propyn-1-ol (1a, 1.0 mmol), solvent (3.0 mL), in air.
bYields are based on 2a, determined by crude ¹H NMR using dibromomethane as the internal standard.
cAs observed by ¹H NMR.
dIsolated yield.
Table 2. PTSA-catalyzed Meyer–Schuster rearrangement

| Entry | Substrate | Product | Time (h) | Yield\(^ b\) (%) |
|-------|-----------|---------|----------|-------------------|
| 1     | \(\text{Ph}-\text{CHOH} \quad 1\text{a} \quad \text{Ph}-\text{CH=O} \quad 2\text{a}\) | 1       | 84       |
| 2     | \(\text{H}_2\text{O}-\text{CHOH} \quad 1\text{b} \quad \text{CH}_3-\text{CH=O} \quad 2\text{b}\) | 2       | 96       |
| 3     | \(\text{OMe}-\text{CHOH} \quad 1\text{c} \quad \text{OMe}-\text{CH=O} \quad 2\text{c}\) | 3       | 32       |
| 4     | \(\text{MeO}-\text{CHOH} \quad 1\text{d} \quad \text{MeO}-\text{CH=O} \quad 2\text{d}\) | 2       | 82       |
| 5     | \(\text{CF}_3-\text{CHOH} \quad 1\text{e} \quad \text{CF}_3-\text{CH=O} \quad 2\text{e}\) | 5       | 50       |
| 6     | \(\text{Cl}-\text{CHOH} \quad 1\text{f} \quad \text{Cl}-\text{CH=O} \quad 2\text{f}\) | 2       | 67       |
| 7     | \(\text{Cl}-\text{CHOH} \quad 1\text{g} \quad \text{Cl}-\text{CH=O} \quad 2\text{g}\) | 1       | 83       |
| 8     | \(\text{Br}-\text{CHOH} \quad 1\text{h} \quad \text{Br}-\text{CH=O} \quad 2\text{h}\) | 2       | 65       |
| 9     | \(\text{CHOH} \quad 1\text{i} \quad \text{CH=O} \quad 2\text{i}\) | 1       | 39       |
| 10    | \(\text{H}_2\text{CH(OH)} \quad 1\text{j} \quad \text{Ph}-\text{CH(O=O)} \quad 2\text{j}\) | 8       | 85 \((E/Z = 1.3:1)\) |
| 11    | \(\text{Ph}-\text{CHOH} \quad 1\text{k} \quad \text{Ph}-\text{CH(O=O)} \quad 2\text{k}\) | 6       | 83       |
| 12    | \(\text{OAc}-\text{CHOH} \quad 1\text{l} \quad \text{Ph}-\text{CH(O=O)} \quad 2\text{l}\) | 1       | 70       |

\(^a\)Reaction conditions: propargyl alcohols (1.0 mmol), PTSA (30 mol%), DCE (3.0 mL), in air.
\(^b\)Isolated yields.
by $^1$H NMR analysis of the crude mixture before column chromatography (entry 10). Rearrangement of the internal alkynyl alcohol proceeded efficiently to give the corresponding $\alpha,\beta$-unsaturated ketone $2k$ in good yield, although this reaction required a longer time to complete as compared to those with terminal alkynes (entry 11). 1-Phenylprop-2-ynyl acetate $1l$, too, reacted smoothly to produce cinnamaldehyde $2a$ in good yield (entry 12). Finally, we tested 2°-aliphatic propargyl alcohols such as undec-1-yn-3-ol and 5-phenylpent-1-yn-3-ol, but no reaction was observed. Moreover, internal propargyl alcohols such as 3-phenyl-1-p-tolylprop-2-yn-1-ol did not afford the desired product but gave the dimeric ether.$^{[14]}$

**CONCLUSIONS**

In conclusion, we have demonstrated that PTSA is a very effective catalyst that promotes the Meyer–Schuster rearrangement. Various propargyl alcohols were tolerated in this reaction, which was applicable to internal alkynyl alcohols as well. This reported catalytic procedure for the synthesis of $\alpha,\beta$-unsaturated carbonyl compounds is a very simple, efficient, and selective methodology involving readily available propargyl alcohols as precursors and proceeding in an atom-economical manner.

**EXPERIMENTAL**

$^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a Bruker Avance III 400 NMR spectrometer. Deuterated chloroform was used as the solvent, and chemical shift values ($\delta$) are reported in parts per million relative to the residual signals of this solvent ($\delta$ 7.26 for $^1$H and $\delta$ 77.0 for $^{13}$C). 1,2-Dichloroethane was distilled from CaCl$_2$. Commercially available reagents were used without purification. Propargyl alcohols were prepared by Grignard addition to aldehyde.

**General Procedure for the Synthesis of $\alpha,\beta$-Unsaturated Carbonyl Compounds from Aryl Propargyl Alcohols**

1-Phenyl-2-propyn-1-ol (66.08 mg, 0.5 mmol) was added to a suspension of $p$-toluenesulfonic acid (98%, Alfa Aesar, 28.35 mg, 30 mol%) in dry 1,2-dichloroethane (3.0 mL). The stirred solution was heated at 60°C for 1 h. Then, the solvent was removed at reduced pressure and the residue was purified by column chromatography with n-Hex/EtOAc (7/1) as the eluent to give cinnamaldehyde ($2a$, 55.70 mg, 84%) as a yellow color oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.70 (d, $J = 7.7$ Hz, 1H), 7.58–7.55 (m, 1H), 7.45–7.43 (m, 4H), 6.72 (dd, $J = 16.0$, 7.7 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 193.6, 152.6, 133.9, 131.1, 129.0, 128.5, 128.4.

All products reported in this article are known compounds, and their full data can be obtained from the reported literature.

**FUNDING**

This work was supported by the 2013 Research Grant from the Kangwon National University (No. 120131489) and by the “Leaders Industry–University Cooperation” Project, supported by the Ministry of Education, Science, and Technology (MEST).
SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

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