Phosphine Induced Dimerization of Propargyl Alcohols Leading to Allyl Propargyl Ethers

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Abstract: A facile method for synthesizing allyl propargyl ethers (APEs) was developed based on the dimerization of propargyl alcohols. The reaction proceeded via an oxaphosphetane intermediate, which was generated without the use of a strong base, thus making this process a pseudo-Wittig reaction under mild reaction conditions. A wide variety of functional groups, including formyl and pyridyl groups were tolerated, thus yielding the corresponding functionalized APEs, which are otherwise not readily prepared via conventional methods. Moreover, a cross-reaction was found to occur when the reaction was conducted in the presence of alcohols that were more acidic than propargyl alcohol, which suggests that the proton transfer from the intermediately formed betaine to the second alcohol is crucial for undergoing the dimerization.

Key words: allyl propargyl ether, oxaphosphetane, pseudo-Wittig reaction, phosphine induced dimerization

1 INTRODUCTION

Phosphines are widely used in organic syntheses because of their high nucleophilicity and oxaphilicity, in addition to their reducing ability. For example, the Wittig reaction is initiated by the nucleophilic attack of a phosphine on a haloalkane, and versatile alkenes are synthesized under basic conditions. In this reaction, an oxaphosphetane serves as a key intermediate, which leads to the formation of a new C–C double bond upon elimination of phosphine oxide. If the oxaphosphetane framework could be generated by an alternative route without the use of a strong base, a novel synthetic method, or a so-called pseudo-Wittig reaction, could be rationalized. For this purpose, alcohols that possess an electrophilic alkyne moiety could be considered suitable reaction partners for a nucleophilic and oxaphilic phosphine. Indeed, trisubstituted allenes were directly synthesized upon treatment of propargyl alcohols with a phosphine¹. This reaction was initiated by the addition of the phosphine to the alkynyl group, and the formed betaine intermediate cyclized to afford an oxaphosphetane intermediate, which led to the corresponding allene upon elimination of the phosphine oxide.

In the course of this study, dimerization of ¹a was observed in some cases to give 4-oxa-1,6-enzyme (allyl propargyl ether; abbreviated as APE hereafter)³a in addition to allene ²a (Scheme 1). This reaction is of interest due to the wide use of APEs as intermediates in the synthesis of natural products, such as salvinoir A², estrogens³ and laurene⁴. In particular, aryl-containing APEs allow for the introduction of an aryl group into alkenalicyclic systems, a transformation which is not readily available by conventional methods. In general, APEs are prepared by the vinyl-

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ation of aromatic aldehydes followed by O-propargylation\textsuperscript{5, 7}; however, vinyl magnesium bromide cannot be easily generated (Scheme 2). Furthermore, the synthesis of arylated APEs suffers from the isomerization to more conjugated styrene derivatives under basic conditions\textsuperscript{8, 9}. These limitations hinder the facile access to APEs, which prompted us to address the dimerization of propargyl alcohols (Scheme 1) in detail by clarifying the reaction mechanism.

2 EXPERIMENTAL PROCEDURES

2.1 General

The melting points were determined on SRS-Optimelt Automated Melting Point System, and were uncorrected. All of the reagents and solvents were obtained from commercial sources, and were used as received. The \(^1\)H NMR spectra were acquired on a Bruker Ascend-400 at 400 MHz with tetramethylsilane as the internal standard. The \(^{13}\)C NMR spectra were acquired on a Bruker Ascend-400 at 100 MHz, and assignments of the signals were performed using DEPT experiments. The high-resolution mass spectra were acquired on an AB SCIEX Triple TOF 4600 and JEOL MS 700N.

2.2 Synthesis of dimer 3, a representative procedure

To a suspension of propargyl alcohol 1a (35 mg, 0.2 mmol) in toluene (2 mL), triphenylphosphine (26 mg, 0.1 mmol) was added. The resultant mixture was heated at 60°C for 1 day. After cooling to room temperature, the solvent was removed in vacuo, and the residue was subjected to silica gel chromatography (hexane/diethyl ether = 8/2, Rf = 0.23) to afford dimer 3a (34 mg, 0.11 mmol, yield 50%) as a pale yellow oil.

1,5-Bis (4-nitrophenyl) -4-oxahept-6-ene-1-yne (3b)
Yellow oil. IR (ATR, cm\(^{-1}\)) 1518, 1345; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 8.22 (d, \(J = 8.4\) Hz, 2H), 8.18 (d, \(J = 8.4\) Hz, 2H), 7.57 (d, \(J = 8.4\) Hz, 4H), 5.89 (ddd, \(J = 17.2, 10.0, 7.2\) Hz, 1H), 5.43 (d, \(J = 17.2\) Hz, 1H), 5.40 (d, \(J = 10.0\) Hz, 1H), 5.13 (d, \(J = 7.2\) Hz, 1H), 4.46 (s, 2H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 147.6 (C), 147.4 (C), 147.3 (C), 136.4 (CH), 132.5 (CH), 129.2 (C), 127.6 (CH), 123.7 (CH), 123.5 (CH), 119.2 (CH2), 89.9 (C), 84.7 (C), 80.9 (CH), 56.4 (CH\(_2\)); HRMS (ESI-TOF) \(m/z\) [M + Na\(^+\)] \(\text{Calcd for C}_{20}\text{H}_{16}\text{O}_{3} 304.1099;\) found 304.1100.

Scheme 2 Conventional method for preparation of arylated APEs.
Dimerization of Propargyl Alcohol

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1H NMR (CDCl3, 400 MHz) δ 8.21 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 9.2 Hz, 2H), 6.78 (d, J = 9.2 Hz, 2H), 6.03 (dd, J = 16.8, 6.4 Hz, 1H), 5.59 (d, J = 16.8 Hz, 1H), 5.31 (d, J = 10.4 Hz, 1H), 3.74 (s, 3H), 13C NMR (CDCl3, 100 MHz) δ 154.5 (C), 151.3 (C), 147.7 (C), 147.5 (C), 136.9 (CH), 127.4 (CH), 123.8 (CH), 117.8 (CH2), 117.5 (CH), 114.6 (CH), 81.1 (CH), 55.6 (CH2); HRMS (EI-double focusing) m/z Calcd for C16H15NO4 285.1003; found 285.1003.

3- (4-Nitrophenyl)-4-oxahept-1-ene-6-yne (4c)

Pale yellow oil. 1H NMR (CDCl3, 400 MHz) δ 8.21 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 8.82 (dd, J = 17.2, 10.0, 7.2 Hz, 1H), 5.40 (d, J = 17.2 Hz, 1H), 5.36 (d, J = 10.0 Hz, 1H), 5.12 (d, J = 7.2 Hz, 1H), 4.21 (d, J = 2.0 Hz, 2H), 2.45 (dd, J = 2.0, 2.0 Hz, 1H); 13C NMR (CDCl3, 100 MHz) δ 147.57 (C), 147.55 (C), 136.4 (CH), 127.6 (CH), 123.6 (CH), 119.2 (CH2), 80.2 (CH), 79.1 (C), 74.9 (CH), 55.6 (CH2); HRMS (EI-double focusing) m/z Calcd for C12H13NO3 219.0895; found 219.0896.

3- (4-Methoxyphenyl)oxy-3- (4-nitrophenyl)-1-propene (4d)

Pale yellow oil. 1H NMR (CDCl3, 400 MHz) δ 8.21 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 9.2 Hz, 2H), 6.78 (d, J = 9.2 Hz, 2H), 6.03 (dd, J = 16.8, 10.4, 6.4 Hz, 1H), 5.59 (d, J = 16.8 Hz, 1H), 5.31 (d, J = 10.4 Hz, 1H), 3.74 (s, 3H); 13C NMR (CDCl3, 100 MHz) δ 154.5 (C), 151.3 (C), 147.7 (C), 147.5 (C), 136.9 (CH), 127.4 (CH), 123.8 (CH), 117.8 (CH2), 117.5 (CH), 114.6 (CH), 81.1 (CH), 55.6 (CH2); HRMS (EI-double focusing) m/z Calcd for C16H15NO4 285.1003; found 285.1003.

3 RESULTS AND DISCUSSION

3.1 Dimerization of propargyl alcohol 1a

When 3- (4-nitrophenyl)propyn-1-ol (1a) was heated at 60 °C for 24 h in toluene in the presence of tributylphosphine, dimerization afforded APE 3a in 14% yield (Table 1, Entry 1). In the 1H NMR spectrum of 3a, four signals between 5 and 6 ppm were assigned to the allyl group, in addition to a singlet, which was assigned to the methylene of the propargyl group, indicating the formation of APE framework. In addition, a couple of signals for sp carbons and signals of vinyl group were observed in the 13C NMR spectrum. Other spectral data also supported the structure of the product to be APE 3a.

While the use of triphenylphosphine considerably increased the yield of 3a (Table 1, Entry 2), no reaction was observed in the presence of a nitrogen nucleophile, DABCO (Table 1, Entry 3). In order to increase the conversion, a higher temperature was employed; however, the yield of 3a decreased (Table 1, Entry 4) and the formation of a complex reaction mixture was noted. Next, when the amount of phosphine was varied, (Table 1, Entries 5 and 6), almost no effect on the yield of APE 3a was noted. 0.5 equivalents of triphenylphosphine were found to be sufficient to induce the dimerization, without the concomitant formation of any by-product (Table 1, Entries 5 and 6). Subsequently, the effects of various solvents were evaluated, and among the tested solvents, toluene was found to be the most suitable (Table 1, Entries 6–9). Notably, when the reaction was conducted in ethanol, ethyl ether 4a was obtained as the major product in 41% yield (Table 1, Entry 9). In spite of considerable efforts, the yield of 3a con-

Table 1 Optimization of reaction conditions.

| Entry | Temp. (°C) | Solv. | Nucleophile (equiv) | Yield (%) | Recovery of 1a (%) |
|-------|------------|-------|--------------------|-----------|-------------------|
| 1     | 60         | Toluene | PBu3 (1)           | 14        | 64                |
| 2     | 60         | Toluene | PPPh3 (1)          | 52        | 36                |
| 3     | 60         | Toluene | DABCO (1)          | 0         | Quant.            |
| 4     | 80         | Toluene | PPPh3 (1)          | 24        | 22                |
| 5     | 60         | Toluene | PPPh3 (2)          | 54        | 17                |
| 6     | 60         | Toluene | PPPh3 (0.5)        | 50        | 50                |
| 7     | 60         | Cyclohexane | PPPh3 (0.5) | 22        | 47                |
| 8     | 60         | Acetonitrile | PPPh3 (0.5) | 7         | 88                |
| 9     | 60         | Ethanol  | PPPh3 (0.5)        | 41        | 17                |
| 10    | 60         | Toluene  | PPPh3 (0.5)        | 0         | Quant.            |

* Determined by 1H NMR. b 1,4-Diazabicyclo[2.2.2]octane. C Ph妞O (1 equiv.) was added.
verged at approximately 50%, which suggested that half the amount of propargyl alcohol 1a was deactivated during the reaction, most likely due to phosphine oxide as evidenced by the fact that no reaction took place when 1 equivalent of triphenylphosphine oxide was added to the reaction mixture (Table 1, Entry 10). Interaction between 1a and phosphine oxide was also confirmed by 1H, 13C, and 31P NMR spectroscopy (Scheme 3). For example, when phosphine oxide was added to a solution of 1a in C6D6, the signal for the propargylic proton shifted downfield in the 1H NMR spectrum. This spectral change suggested that the adjacent hydroxyl group interacted with phosphine oxide, which could prevent further reaction.

3.2 Scope, limitation, and mechanistic rationale

Cross-adduct 4a was formed in the reaction using ethanol as a solvent (Table 1, Entry 9). This result prompted us to apply the present protocol for the synthesis of other allyl ethers (Table 2). Although no crossed product 4a was observed in the reaction of 1a with an equimolar amount of ethanol, 23% of 4a was obtained when 5 equivalents of ethanol were used (Table 2, Entries 1 and 2). While only a small amount of cross-adducts 4b was formed from allyl alcohol 6b, a more efficient crossed reaction was noted for propargyl alcohol 6c (Table 2, Entries 3 and 4). The difference in reactivity could be attributed the acidity of 6. Indeed, phenol 6d also underwent the cross reaction leading to 4d in a similar yield; however, more acidic acetic acid 6e diminished the yield of 4e10, which might be attributed to the low nucleophilicity of the acetate ion (Table 2, Entries 5 and 6).

To further probe the scope of this reaction, other propargyl alcohols were employed11. Propargyl alcohols that possessed electron-deficient aromatic groups, such as 1b and 1c, efficiently underwent the reaction to afford the corresponding dimers 3b and 3c in 35% and 37% yields, respectively (Scheme 4). These results revealed that enhanced electrophilicity at the alkyne moiety was required. Since no reaction took place even at 100°C when propargyl ether 7 was used instead of 1a in the presence of propargyl alcohol 6d, the hydroxy group was considered to be a crucial factor in the present reaction (Scheme 5).

On the basis of the above results, a plausible mechanism for the dimerization was proposed (Scheme 6). The reaction was initiated by the addition of the phosphine to the alkyne moiety of 1 and was accompanied by deprotonation of the hydroxy group to afford betaine 8. This intermediate was stabilized by the coordination with another molecule of propargyl alcohol 1, and the subsequent addition of the alcohol gave the dimeric ylide 9. When the reaction was
conducted in the presence of an acidic alcohol, a similar addition proceeded to afford the crossed adduct 4. Betaine 10 resulted from the intramolecular proton transfer, and underwent cyclization to produce oxaphosphetane 11, which in turn yielded dimer 3 upon elimination of phosphine oxide.

4 CONCLUSION
A direct method for synthesis of APEs 3 was developed via the phosphine-induced dimerization of propargyl alcohols 1. In this reaction, functional groups such as formyl and pyridyl moieties were well tolerated and required no protection. Furthermore, it was found that the phosphine oxide, an elimination product from the oxaphosphetane intermediate 11, led to the deactivation of unreacted propargyl alcohol 1. Thus, although the yield of the reaction converged at 50%, the yield based on the conversion of the starting material is quite high. In addition, the cross reaction was also found to occur when the reaction was conducted in the presence of acidic alcohols. This procedure and the mechanistic insights will be of considerable value to researchers in the field of synthetic and phosphine chemistry.

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References
1) Iwai, K.; Yokoyama, S.; Asahara, H.; Nishiwaki, N. A direct synthesis of trisubstituted allenes from propargyl alcohols via oxaphosphetane intermediates. Bull. Chem. Soc. Jpn. 91, 337-342 (2018).
2) Lanfranchi, A.D.; Bour, C.; Hanquet, G. Enantioselective access to key intermediates for salvinorin A and analogues. *Eur. J. Org. Chem.* **15**, 2818-2826 (2011).

3) Mikami, K.; Takahashi, K.; Nakai, T.; Uchimaru, T. Asymmetric tandem Claisen-Ene strategy for convergent synthesis of (+)-9(11)-dehydroestrone methyl ether: Stereochemical studies on the ene cyclization and cyclic enol ether Claisen rearrangement for steroid total synthesis. *J. Am. Chem. Soc.* **116**, 10948-10954 (1994).

4) Oh, H.C.; Han, W.J.; Kim, S.J.; Um, Y.S.; Jung, H.H.; Jang, H.W.; Won, S.H. A short synthesis of (+)-laurone: Mechanistic reinvestigation in palladium-catalyzed cycloreductions of 1,6-enynes. *Tetrahedron Lett.* **41**, 8365-8369 (2000).

5) Yu, S.; Wu, C.; Ge, S. Cobalt-catalyzed asymmetric hydroboration/cyclization of 1,6-enynes with pinacolborane. *J. Am. Chem. Soc.* **139**, 6526-6529 (2017).

6) Kim, E.D.; Kwak, J.; Kim, S.I.; Jeong, N. Kinetic resolutions by enantioselective Pauson–Khand-type reaction. *Adv. Synth. Catal.* **351**, 97-102 (2009).

7) Candito, D.; Lautens, M. Stereoselective nickel-catalyzed [2+2+2]cycloaddition of enynes and arynes. *Synlett* 1987-1992 (2011).

8) Martinez-Errro, S.; Sanz-Marco, A.; Bermejo G.A.; Vazquez-Romero, A.; Ahlquist, M.S. G.; Martin-Matute, B. Base-catalyzed stereospecific isomerization of electron-deficient allylic alcohols and ethers through ion-pairing. *J. Am. Chem. Soc.* **138**, 13408-13414 (2016).

9) Murakami, M.; Minamikawa, H.; Mukaiyama, T. Trityl salt-catalyzed aldol-type reaction of alkyl enol ethers with acetals. *Chem. Lett.* **16**, 1051-1052 (1987).

10) Marion, N.; Gealageas, R.; Nolan, S.P. [(NHC)AuI]-Catalyzed rearrangement of allylic acetates. *Org. Lett.* **9**, 2653-2656 (2007).

11) Aridoss, G.; Sarca, V.D.; Ponder, J.F.Jr.; Crowe, J.; Laali, K.K. Electrophilic chemistry of propargylic alcohols in imidazolium ionic liquids: Propargylation of arenes and synthesis of propargylic ethers catalyzed by metallic triflates [Bi(OTf)₃, Sc(OTf)₃, Yb(OTf)₃], TIOF, or B(C₆F₅)₃. *Org. Biomol. Chem.* **9**, 2518-2529 (2011).