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# Brønsted Acid-Catalyzed Propargylation/ Cycloisomerization Tandem Reaction: One-Pot Synthesis of Substituted Oxazoles from Propargylic Alcohols and Amides

Ying-ming Pan, Fei-jian Zheng, Hai-xin Lin, and Zhuang-ping Zhan*

*Department of Chemistry, College of Chemistry and Chemical Engineering, and State Key Laboratory for Physical Chemistry of Solid Surfaces, Xiamen University, Xiamen 361005, People's Republic of China*

*zpzhan@xmu.edu.cn*

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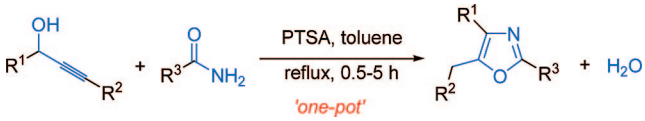
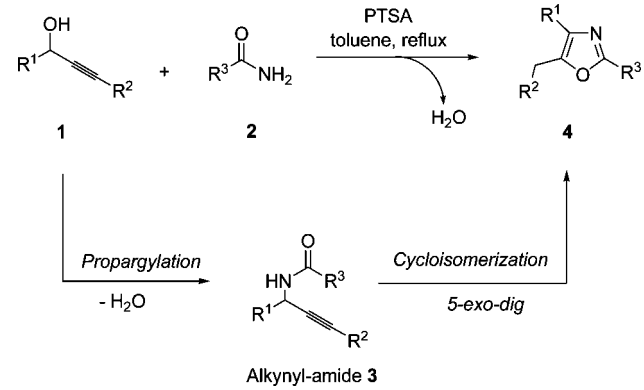



An efficient one-pot propargylation/cycloisomerization tandem process has been developed for the synthesis of substituted oxazole derivatives from propargylic alcohols and amides with use of *p*-toluenesulfonic acid monohydrate (PTSA) as a bifunctional catalyst. This method provides a rapid and efficient access to substituted oxazoles.

Nucleophilic substitution and cyclization are two major reactions of organic chemistry.[1,2] More powerful and useful transformations are possible when these two classes of reactions are combined in a one-pot procedure. Propargylic substitution and subsequent cycloisomerization recently developed in our group are good examples of such transformations.[3]

To further extend the scope of the Lewis acid-catalyzed propargylation/cycloisomerization tandem reaction, we sought to explore the coupling of propargylic alcohols with amides and the subsequent cycloisomerization for the synthesis of substituted oxazoles. In general, substituted oxazoles are accessed via ring derivatization or cyclization of acyclic precursors.[4−6] Among the variety of compounds that can be subjected to cyclization, unsaturated amides are substrates of major interest.[6]

**SCHEME 1. Synthesis of Oxazoles from Propargylic Alcohols and Amides**




However, the one-pot synthesis of substituted oxazoles directly from simple and readily available substrates is much less studied. Recently, efficient propargylation/cycloisomerization sequential reactions of propargylic alcohols with amides in the presence of $[Cp^*RuCl(\mu_2\text{-}SMe)_2RuCp^*Cl]/AuCl_3/NH_4BF_4$[7] or $Zn(OTf)_2/TpRuPPh_3(CH_3CN)_2PF_6$,[8] which led to the synthesis of substituted oxazoles, have been reported. Nevertheless, the previous reports only exemplify terminal propargylic alcohols, and at least two different catalysts are needed. To the best of our knowledge, there is no propargylation/cycloisomerization tandem reaction for the synthesis of substituted oxazoles in the presence of a single catalyst reported in the literature. Herein, we describe a one-pot PTSA-catalyzed propargylation/cycloisomerization tandem reaction. The process is outlined in Scheme 1. PTSA acts as a bifunctional catalyst and effectively catalyzes two reaction processes in a single reaction vessel under the same conditions. The reaction is completed rapidly under mild conditions and is

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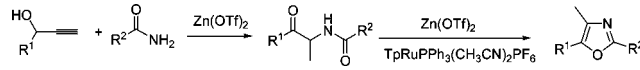
(6) For selected examples, see: (a) Beccalli, E. M.; Borsini, E.; Broggini, G.; Palmisano, G.; Sottocornola, S. *J. Org. Chem.* **2008**, *73*, 4746. (b) Martín, R.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 5521. (c) Schuh, K.; Glorius, F. *Synthesis* **2007**, 2297. (d) Merkul, E.; Müller, T. J. J. *Chem. Commun.* **2006**, 4817. (e) Black, D. A.; Arndtsen, B. A. *Tetrahedron* **2005**, *61*, 11317. (f) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391. (g) Wipf, P.; Aoyama, Y.; Benedum, T. E. *Org. Lett.* **2004**, *6*, 3593. (h) Arcadi, A.; Cacchi, S.; Cascia, L.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2001**, *3*, 2501. (i) Wipf, P.; Rahman, L. T.; Rector, S. R. *J. Org. Chem.* **1998**, *63*, 7132.

(7) Milton, M. D.; Inada, Y.; Nishibayashi, Y.; Uemura, S. *Chem. Commun.* **2004**, 2712.

(8) The zinc(II)-catalyzed propargylic substitution produces α-carbonyl amide. Subsequent cycloisomerization of α-carbonyl amide affords the substituted oxazole.




See: Kumar, M. P.; Liu, R.-S. *J. Org. Chem.* **2006**, *71*, 4951.



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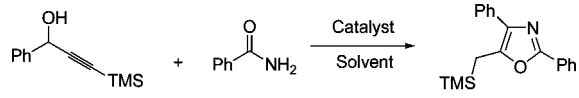
**TABLE 1. Optimization of Formation of Substituted Oxazoles**[a]




**1a** **2a** **4aa**

| entry | catalyst | solvent | time [h] | yield [%][b] |
|---|---|---|---|---|
| 1 | $BiCl_3$ (10 mol %) | toluene | 24 | 35 |
| 2 | $InCl_3$ (10 mol %) | toluene | 24 | 0 |
| 3 | $FeCl_3$ (10 mol %) | toluene | 24 | 36 |
| 4 | $Cu(OTf)_2$ (10 mol %) | toluene | 24 | 57 |
| 5 | $Cu(OTf)_2$ (1 equiv) | toluene | 24 | 59 |
| 6 | PTSA (1 equiv) | toluene | 0.8 | 90 |
| 7 | PTSA (50 mol%) | toluene | 24 | 78 |
| 8 | TFA (1 equiv) | toluene | 4 | 84 |
| 9 | oxalic acid (1 equiv) | toluene | 24 | 0 |
| 10 | HCl (1 equiv)[c] | toluene | 24 | 0 |
| 11 | PTSA (1 equiv) | $CH_3CN$ | 24 | 75 |
| 12 | PTSA (1 equiv) | DCE | 24 | 83 |
| 13 | PTSA (1 equiv) | $CH_3NO_2$ | 24 | 51 |
| 14 | PTSA (1 equiv) | DCM | 24 | 48 |
| 15 | PTSA (1 equiv) | THF | 24 | 0 |

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), and catalyst in solvent (2 mL) at reflux. [b] Isolated yield of pure product based on propargylic alcohol **1a** [c] The concentration of hydrochloric acid is 12 mol/L.

tolerant of air, giving water as the only byproduct. A wide range of secondary propargylic alcohols bearing not only terminal alkyne groups but also internal alkyne groups can effectively be employed, and a number of functional groups, such as TMS, vinyl, bromo, chloro, ester, and methoxy, are tolerated under the reaction conditions. All of the propargylic alcohols used are readily available.

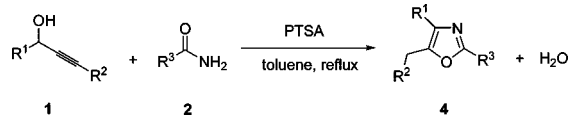
Initially, propargylic alcohol **1a** (0.5 mmol) was treated with benzamide **2a** (0.6 mmol) in the presence of 10 mol % of $BiCl_3$ in toluene at reflux for 24 h and the desired product **4aa** was isolated in 35% yield along with uncyclized alkynyl-amide **3aa** in 56% yield (Table 1, entry 1).[9] With other Lewis acids, such as $Cu(OTf)_2$, $FeCl_3$, and $InCl_3$, the propargylation proceeded smoothly to afford alkynyl-amide **3aa** in high yields, but subsequent intramolecular cycloisomerization led to low yields, or did not afford cyclized product (Table 1, entries 2−4). Furthermore, no improvement in yield could be obtained even in the presence of 1 equiv of $Cu(OTf)_2$ (Table 1, entry 5). We reasoned that the poor catalyst activity of Lewis acids might be ascribed to their weak acidity. Accordingly, we began searching for the appropriate Brønsted acid that would readily catalyze the propargylation/cycloisomerization tandem reaction. Gratifyingly, switching the catalyst to PTSA (1 equiv) furnished the substituted oxazole **4aa** in 90% yield after 0.8 h at reflux (Table 1, entry 6). Notably, a very slow reaction rate was observed when the catalytic amount of PTSA decreased from 1 equiv to 50 mol % (Table 1, entry 7 vs entry 6). With 50 mol % of PTSA, the propargylation proceeded rapidly to afford alkynyl-amide **3aa** in excellent yield, but subsequent intramolecular cycloisomerization was sluggish. The results showed that a stoichiometric amount of PTSA was required to counteract the basicity of the oxazole **4aa** and keep an acidic atmosphere during cycloisomerization. Trifluoroacetic acid (TFA) also effectively promoted the tandem reaction, although a somewhat long reaction time was needed (Table 1, entry 8). Unfortunately, both oxalic acid and hydrochloric acid failed to catalyze the tandem reaction (Table 1, entries 9 and 10). In addition, it was found that the solvent played a crucial role in this tandem reaction (Table 1, entries 6 and 11−15). Acetonitrile and 1,2-dichloroethane as solvents were also able to facilitate the propargylation/cycloisomerization tandem reaction. However, the use of toluene instead of 1,2-dichloroethane and acetonitrile obviously reduced the reaction time from 24 to 0.8 h (Table 1, entry 6 vs. entries 11 and 12). The results of solvents screened showed that the reaction rates were influenced by various factors, such as boiling point, polarity, etc. Among these factors, the boiling point of solvents might be a main factor. However, the detailed mechanism is still not clear.

With these optimal conditions in hand, we examined the scope of this tandem reaction. Typical results are shown in Table 2. To our delight, all the secondary propargylic alcohols **1** bearing not only terminal alkyne groups but also internal alkyne groups participated well in the tandem reaction, producing the propargylation/cycloisomerization products in good yields with complete regioselectivity. Among the benzylic-propargylic alcohols **1a**−**d** that were examined, propargylic alcohol **1a** ($R^2$ = TMS) gave the most desirable result, providing the substituted oxazole in excellent yield (Table 2, entry 1). Propargylic alcohol **1h** possessing an electron-donating group at the aryl ring ($R^1$ = 4-$MeOC_6H_4$) reacted smoothly with amide **2a** affording the oxazole **4ha** in 94% yield (Table 2, entry 8). Moreover, substrates **1i** and **1j** possessing electron-withdrawing groups (bromo and ester functionalities) at the aryl ring were also successfully employed in the tandem reaction to give the oxazoles **4ia** and **4ja** in 89% and 78% yields, respectively (Table 2, entries 9 and 10). Obviously, electron-rich propargylic alcohols provided the desired products in higher yields than electron-poor propargylic alcohols. Internal propargylic alcohols **1c** and **1d** ($R^2$ = *n*-Bu, Ph) also gave good results (Table 2, entries 3 and 4). The reaction of terminal propargylic alcohol **1b** ($R^2$ = H) with benzamide afforded the oxazole **4ba** in good yield after a somewhat long reaction time (Table 2, entry 2). Additionally, propargylic alcohols **1e**−**g** ($R^1$ = 1-naphthyl) readily underwent propargylation/cycloisomerization tandem reaction to afford the substituted oxazoles **4ea**−**ga** in high yields with complete regioselectivity (Table 2, entries 5−7). However, the aliphatic propargylic alcohols, such as 3-phenylprop-2-yn-1-ol ($R^1$ = H; $R^2$ = Ph) and 4-phenylbut-3-yn-2-ol ($R^1$ = $CH_3$; $R^2$ = Ph), failed to afford the substituted oxazoles. The results suggested that the propargylation proceeded through a propargylic cation intermediate. Instability of the propargylic cation intermediate made the tandem reaction less favorable. For the aromatic propargylic alcohols, the reaction is completed rapidly under mild conditions and is tolerant of air, giving water as the only byproduct. This is in sharp contrast to the Ru/Au-catalyzed sequential reaction[7] where the reactions were performed under $N_2$ atmosphere and the substrates were limited to propargylic alcohols bearing terminal alkyne groups. It should be noted that functional groups such as TMS, bromo, ester, and methoxy in the propargylic alcohols were readily carried through the tandem reaction, allowing for the subsequent elaboration of the products.

A variety of amides **2** were also employed to examine the generality of the method. Both aromatic amides and aliphatic amides could be efficiently incorporated into the oxazole framework. The tandem reaction proceeded smoothly when the aryl groups of the aromatic amides were substituted with

(9) We have reported that the $BiCl_3$-catalyzed nucleophilic substitution of propargylic alcohols with benzamide affords the alkynyl-amides in good yields, see ref 3d.

**TABLE 2. Synthesis of Substituted Oxazoles 4 from Propargylic Alcohols 1 and Amides 2**[a]

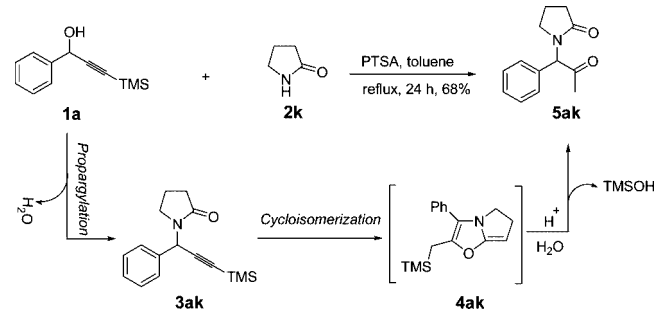



1 2 4

| Entry | Propargylic alcohol | Amide | Product | Time [h] | Yield [%]b |
|---|---|---|---|---|---|
| 1 | **1a:** $R^1$ = Ph; $R^2$ = TMS | **2a:** $R^3$ = Ph | **4aa** | 0.8 | 90 |
| 2 | **1b:** $R^1$ = Ph; $R^2$ = H | **2a:** $R^3$ = Ph | **4ba** | 5 | 76 |
| 3 | **1c:** $R^1$ = Ph; $R^2$ = *n*-Bu | **2a:** $R^3$ = Ph | **4ca** | 4 | 82 |
| 4 | **1d:** $R^1$ = Ph; $R^2$ = Ph | **2a:** $R^3$ = Ph | **4da** | 4 | 85 |
| 5 | **1e:** $R^1$ = 1-Naphthyl; $R^2$ = TMS | **2a:** $R^3$ = Ph | **4ea** | 0.8 | 91 |
| 6 | **1f:** $R^1$ = 1-Naphthyl; $R^2$ = H | **2a:** $R^3$ = Ph | **4fa** | 5 | 77 |
| 7 | **1g:** $R^1$ = 1-Naphthyl; $R^2$ = *n*-Bu | **2a:** $R^3$ = Ph | **4ga** | 4 | 84 |
| 8 | **1h:** $R^1$ = 4-$MeOC_6H_4$; $R^2$ = TMS | **2a:** $R^3$ = Ph | **4ha** | 0.5 | 94 |
| 9 | **1i:** $R^1$ = 4-$BrC_6H_4$; $R^2$ = TMS | **2a:** $R^3$ = Ph | **4ia** | 1 | 89 |
| 10 | **1j:** $R^1$ = 4-$MeOOCC_6H_4$; $R^2$ = TMS | **2a:** $R^3$ = Ph | **4ja** | 2 | 78 |
| 11 | **1a:** $R^1$ = Ph; $R^2$ = TMS | **2b:** $R^3$ = 4-$MeOC_6H_4$ | **4ab** | 0.7 | 93 |
| 12 | **1a:** $R^1$ = Ph; $R^2$ = TMS | **2c:** $R^3$ = 2-$HOC_6H_4$ | **4ac** | 0.7 | 92 |
| 13 | **1a:** $R^1$ = Ph; $R^2$ = TMS | **2d:** $R^3$ = 4-$MeC_6H_4$ | **4ad** | 0.8 | 91 |
| 14 | **1a:** $R^1$ = Ph; $R^2$ = TMS | **2e:** $R^3$ = 4-$ClC_6H_4$ | **4ae** | 0.8 | 87 |
| 15 | **1a:** $R^1$ = Ph; $R^2$ = TMS | **2f:** $R^3$ = 4-$O_2NC_6H_4$ | **4af** | 2 | 75 |
| 16 | **1a:** $R^1$ = Ph; $R^2$ = TMS | **2g:** $R^3$ = Me | **4ag** | 3.5 | 82 |
| 17 | **1a:** $R^1$ = Ph; $R^2$ = TMS | **2h:** $R^3$ = Vinyl | **4ah** | 1 | 88 |
| 18 | **1a:** $R^1$ = Ph; $R^2$ = TMS | **2i:** $R^3$ = *n*-Pr | **4ai** | 1 | 81 |
| 19 | **1a:** $R^1$ = Ph; $R^2$ = TMS | **2j:** $R^3$ = *i*-Pr | **4aj** | 1 | 78 |

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), and PTSA (0.5 mmol) in toluene (2 mL) at reflux. See the Supporting Information for details. [b] Isolated yield of pure product based on propargylic alcohol **1**.

**SCHEME 2. Synthesis of Keto-amide 5ak from Propargylic Alcohol 1a and 2-Pyrrolidinone 2k**




electron-donating (Table 2, entries 11 and 12) and electron-withdrawing groups (Table 2, entries 14 and 15). Electron-rich groups are beneficial to the tandem reaction. Aliphatic amides required slightly longer reaction times, but maintained high yields (Table 2, entries 16−19). Interestingly, attempted propargylation/cycloisomerization of propargylic alcohol **1a** with 2-pyrrolidinone **2k** led not to the expected product **4ak**, but to the keto-amide **5ak** in 68% yield (Scheme 2).[10] We propose that the intramolecular cycloisomerization of alkynyl-amide **3ak** affords the cyclized product **4ak**, and the instability of **4ak** makes the ring-opening reaction possible to afford keto-amide **5ak** through the attack of water in the presence of proton acid.

The crystal structure of oxazole **4ja** (Table 2, entry 10) has been determined by X-ray diffraction and is shown in Figure 1. The X-ray crystal structure reveals that the dihedral angle between plane 1 (defined by atoms C5−C10) and plane 2 (O1, N1, and C1−C3) is 2.43 (0.2)°, and the dihedral angle between plane 2 (O1, N1, and C1−C3) and plane 3 (C12−C17) is 6.56 (0.2)°. The planarity and the bond lengths (see the Supporting Information for details) are consistent with the $\pi$ system delocalization that is extended over the whole molecule. We reasoned that these synthetic compounds would have good photophysical properties, especially substituted oxazoles with long conjugation lengths. Synthesis and the potential optoelectronic applications of analogous oligomers by the PTSA-catalyzed propargylation/cycloisomerization tandem reaction are currently going on in our laboratory.

In summary, we have developed a highly efficient method for the synthesis of the substituted oxazoles via PTSA-catalyzed propargylation/cycloisomerization tandem reaction. PTSA, working as a bifunctional catalyst, catalyzes two mechanistically distinct processes in a single-pot under the same reaction

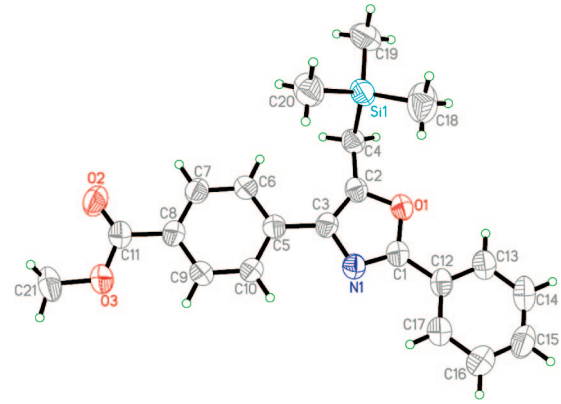



**FIGURE 1.** X-ray crystal structure of oxazole **4ja**. The thermal ellipsoids are at the 50% probability level.

conditions. The reaction is completed rapidly under mild conditions and is tolerant of air, giving water as the only byproduct. Propargylic alcohols bearing terminal or internal alkyne groups are readily available. This facile methodology allows rapid access to a variety of substituted oxazoles.

## Experimental Section

A typical experimental procedure for the reaction of 1-phenyl-3-(trimethylsilyl)prop-2-yn-1-ol (**1a**) with benzamide (**2a**) catalyzed by 1 equiv of PTSA is described below: to a 5-mL flask were successively added 1-phenyl-3-(trimethylsilyl)prop-2-yn-1-ol (**1a**) (102 mg, 0.5 mmol), benzamide (**2a**) (72.6 mg, 0.6 mmol), toluene (2.0 mL), and *p*-toluenesulfonic acid monohydrate (PTSA, 95 mg, 0.5 mmol). The reaction mixture was stirred at reflux and monitored periodically by TLC. Upon completion, the toluene was removed under reduced pressure by an aspirator, and then the residue was purified by silica gel column chromatography (EtOAc/hexane) to afford 2,4-diphenyl-5-((trimethylsilyl)methyl)oxazole (**4aa**) as a yellow oil (138 mg, 90% yield). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.14 (s, 9H), 2.41 (s, 2H), 7.27−7.32 (m, 1H), 7.41−7.45 (m, 5H), 7.72−7.75 (m, 2H), 8.04−8.06 (m, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ −1.1, 16.4, 125.9, 126.7, 126.9, 127.8, 128.5, 128.7, 129.7, 132.9, 134.3, 147.2, 158.6; IR (film) 3061, 2954, 1595, 1494, 1448, 1250 cm$^{-1}$; ESI-MS *m*/*z* (%) 308 (100) [M + H$^+$], 330 (21) [M + Na$^+$]. Anal. Calcd for $C_{19}H_{21}NOSi$: C, 74.22; H, 6.88; N, 4.56. Found: C,74.09; H, 7.11; N, 4.31.

(10) The trimethylsilyl group might not be tolerated under the acidic condition (e.g., *p*-toluenesulfonic acid, $InCl_3$) for a long time and fell off during workup. See: (a) Feng, X.-B.; Tan, Z.; Chen, D.; Shen, Y.-M.; Guo, C.-C.; Xiang, J.-N.; Zhu, C.-L. *Tetrahedron Lett.* **2008**, *49*, 4110. (b) Reference 3a.

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**Supporting Information Available:** Experimental procedures and spectra data for all compounds, and X-ray data for compound **4ja**. This material is available free of charge via the Internet at http://pubs.acs.org.

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