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Short Note

(*E*)-5-[Bromo(phenyl)methylene]-4-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole

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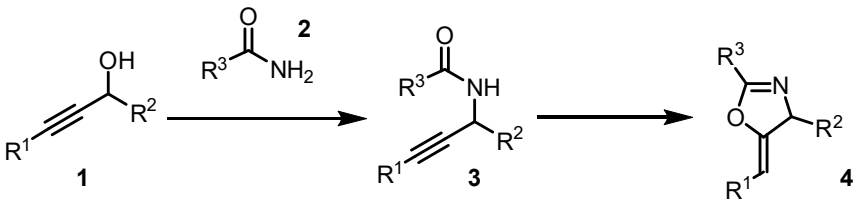
Abstract: One-pot synthesis of (*E*)-5-[bromo(phenyl)methylene]-4-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole (**9**) from propargylic alcohol **5** and *p*-toluamide (**6**) was achieved via gold(III)-catalyzed propargylic substitution, followed by gold(III)-catalyzed bromocyclization. The structure of **9** was confirmed by an X-ray crystallographic analysis.

Keywords: gold catalyst; propargylic substitution; bromocyclization

1. Introduction

Oxazolines are important skeletons found in biologically active natural compounds [1,2], and they have been utilized as useful synthetic intermediates or reagents [3–5]. Therefore, extensive efforts have been made to develop synthetic methods for these compounds over several decades. Most of them are based on cyclization from propargylic amides **3** to oxazolines **4** in the presence of transition metals [6,7] or other reagents [8,9]. However, there were no reports of oxazoline **4** synthesis by propargylic substitution reaction followed by cyclization from propargylic alcohol **1** with amide **2** (Scheme 1).



Scheme 1. Synthesis of functionalized oxazoline.

We have developed efficient synthesis of cyclic compounds (indenes/dihydropyrans/oxazole) from propargylic alcohols through the strategic use of gold catalysts. More recently, we have developed an efficient synthesis of oxazoline **8** via a gold(III)-catalyzed propargylic substitution reaction followed by gold(I)-catalyzed cyclization from propargylic alcohol **5** and amide **6** [10] (Scheme 2, Equation (1)). This is the first example of oxazoline synthesis by sequential reactions (propargylic substitution reaction/cyclization reaction) from propargylic alcohols **5** and amides **6**. In the present study, we planned a gold(III)-catalyzed propargylic substitution reaction followed by halogen-mediated cyclization to obtain halogenated oxazolines **9** from propargylic alcohol **5** with amide **6** (Scheme 2, Equation (2)). Halogenated oxazolines [11,12] are very useful structural motifs because they can be converted to functionalized oxazoles [13,14], which are found as structural parts of natural products and synthetic intermediates [1–5]. Here, we present a one-pot synthesis of (*E*)-5-[bromo(phenyl)methylene]-4-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole

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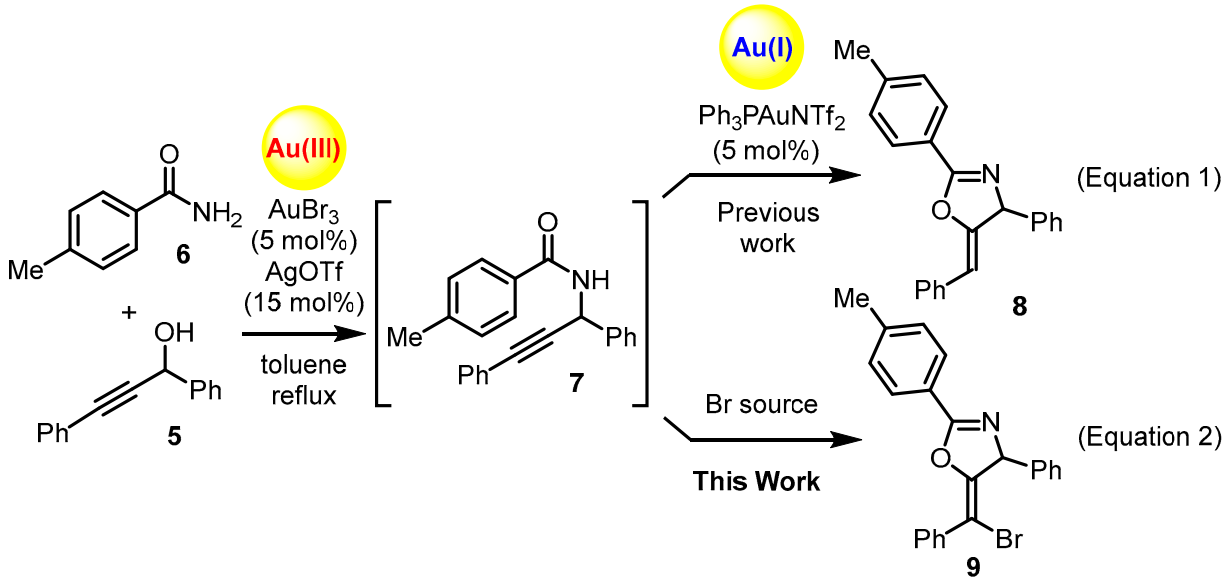
(**9**) from propargylic alcohol **5** and *p*-toluamide (**6**) via a gold(III)-catalyzed propargylic substitution reaction followed by gold(III)-catalyzed bromocyclization.

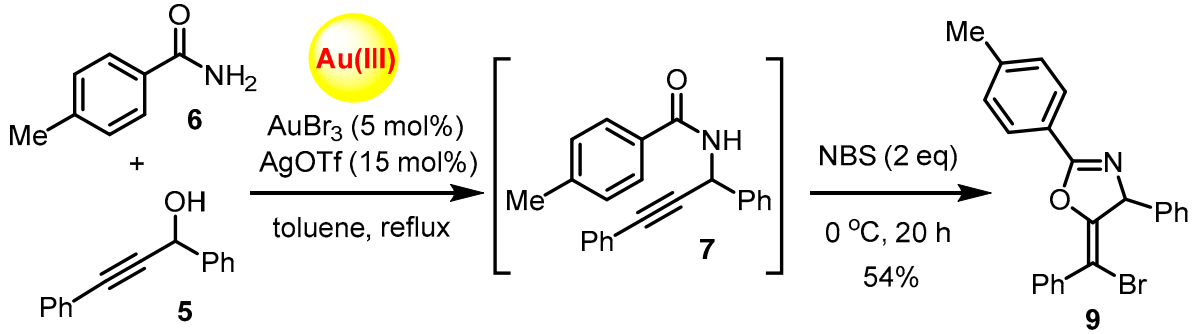


Scheme 2. Equation (1): One-pot synthesis of oxazoline **8** via gold(III)-catalyzed propargylic substitution reaction followed by gold(I)-catalyzed cyclization (previous work); Equation (2): one-pot synthesis of bromooxazoline **9** via gold(III)-catalyzed propargylic substitution reaction followed by gold(III)-catalyzed bromocyclization (this work).

2. Results and Discussion

2.1. Chemistry

The reaction conditions in the initial propargylic substitution reaction of propargylic alcohol **5** and *p*-toluamide (**6**) were those identified in our previous work (5 mol% $AuBr_3$/15 mol% AgOTf in toluene, reflux, 20 min). Various bromine sources (*N*-bromosuccinimide: NBS, 1,3-dibromo-5,5-dimethylhydantoin, and dibromoisocyanuric acid) were investigated for the cyclization of propargylic amide **7** (Scheme 3). When bromocyclization was conducted using either 1,3-dibromo-5,5-dimethylhydantoin or dibromoisocyanuric acid as the bromine source, the yield of product **9** was low in both cases. Finally, treatment of propargylic alcohol **5** with *p*-toluamide (**6**) in the presence of $AuBr_3$ (5 mol%) and AgOTf (15 mol%) in toluene refluxing for 20 min gave propargylic amide **7**, and then addition of NBS (2 eq) resulted in gold(III)-catalyzed bromocyclization [15] to furnish bromooxazoline **9** in 54% yield in one pot. (When the intermediate propargyl amide **7** was isolated and reacted with NBS at 0 °C in toluene without gold catalyst, the bromocyclization did not proceed. Therefore, it is considered that the gold catalyst activated NBS, resulting in the bromocyclization).



Scheme 3. One-pot synthesis of bromooxazoline **9** via gold(III)-catalyzed propargylic substitution reaction followed by gold(III)-catalyzed bromocyclization.

The NMR spectroscopic data supported the formation of bromooxazoline **9**, and the expected structure was confirmed by means of X-ray crystallographic analysis [16]. The *E* configuration of the double bond could be verified by the X-ray crystal structure data of compound **9**.

2.2. X-ray Structure Analysis

X-ray analysis of a single crystal of bromooxazoline **9** grown via slow diffusion of dichloromethane solvent at room temperature revealed a monoclinic crystal structure and a $P2_1/c$ space group (Table 1). The torsional angle between the *p*-tolyl ring and the oxazoline ring is 5.99°, and that between the oxazoline ring and the phenyl ring is 13.85°, indicating that three rings are slightly twisted in bromooxazoline **9** (Figure 1A). The crystal packing was driven by the combination of the intermolecular π–π stacking interaction (3.4 Å) (Figure 1B red line) between the oxazoline ring and the tolyl group and the intermolecular CH–N interactions (2.5 Å) (Figure 1B green line) between the C–H of the phenyl group and the nitrogen atom of the oxazoline ring. Very interestingly, the intermolecular two CH–Br interactions between the bromine atom and hydrogen atom of the phenyl group (3.0 Å) and the bromine atom and hydrogen atom of the tolyl group (3.0 Å) were observed (Figure 1C blue line) [17,18].

Table 1. Summary of the crystallographic data and refinement statistics for bromooxazoline **9**.

Parameter	Data
Identification	$C_{23}H_{18}BrNO$
Formula weight	404.29
Temperature/K	293(2)
Crystal system	monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a/Å 10.0295(2) α/° 90 b/Å 22.6360(5) β/° 99.839(2) c/Å 8.09410(10) γ/° 90
Volume/Å^3	1810.56(6)
Z	8
$D_{calc.}$/g cm^{-3}	1.483
μ/mm^{-1}	3.172
F(000)	824.0
Crystal size/mm^{-1}	0.22 × 0.15 × 0.12
Radiation	CuK_α (λ = 1.54184)
2Θ range for data collection/°	3.906 to 77.142
Index range	$-12 \leq h \leq 12$, $-26 \leq k \leq 27$, $-7 \leq l \leq 9$
Reflections collected	13,128
Independent reflections	3560 [R_{int} = 0.0265, R_{sigma} = 0.0242]
Data/restrains/parameters	3560/0/236
Goodness-of-fit on F^2	1.179
Final R indexes (I)	R_1 = 0.0380, wR_2 = 0.1053
Final R indexes (all data)	R_1 = 0.0385, wR_2 = 0.1056
Largest diff. peak/hole/e Å^{-3}	1.309/−0.460

We compared the X-ray crystal structure diagrams of the previously reported compound, (*Z*)-5-benzyline-4-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole (**8**, magenta; see Equation (1), Scheme 2) [13], and the newly synthesized (*E*)-5-[bromo(phenyl)methylene]-4-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole (**9**, yellow) in Figure 2. The tolyl-oxazoline-phenyl rings of oxazoline **8** are nearly co-planar. That is, the torsion angles of the tolyl-oxazoline and oxazoline-phenyl rings are 0.30 and 0.01 degrees, respectively. In contrast, the torsion angle of the oxazoline-phenyl rings in bromoxazoline **9** is 0.01 degrees, while the torsional angle of the oxazoline-phenyl rings in **9** is 13.85 degrees. The major difference between oxazoline **8** and bromoxazoline **9** is the torsion angle between the oxazole and phenyl rings. That is, bromoxazoline **9** is slightly more twisted than oxazoline **8**.

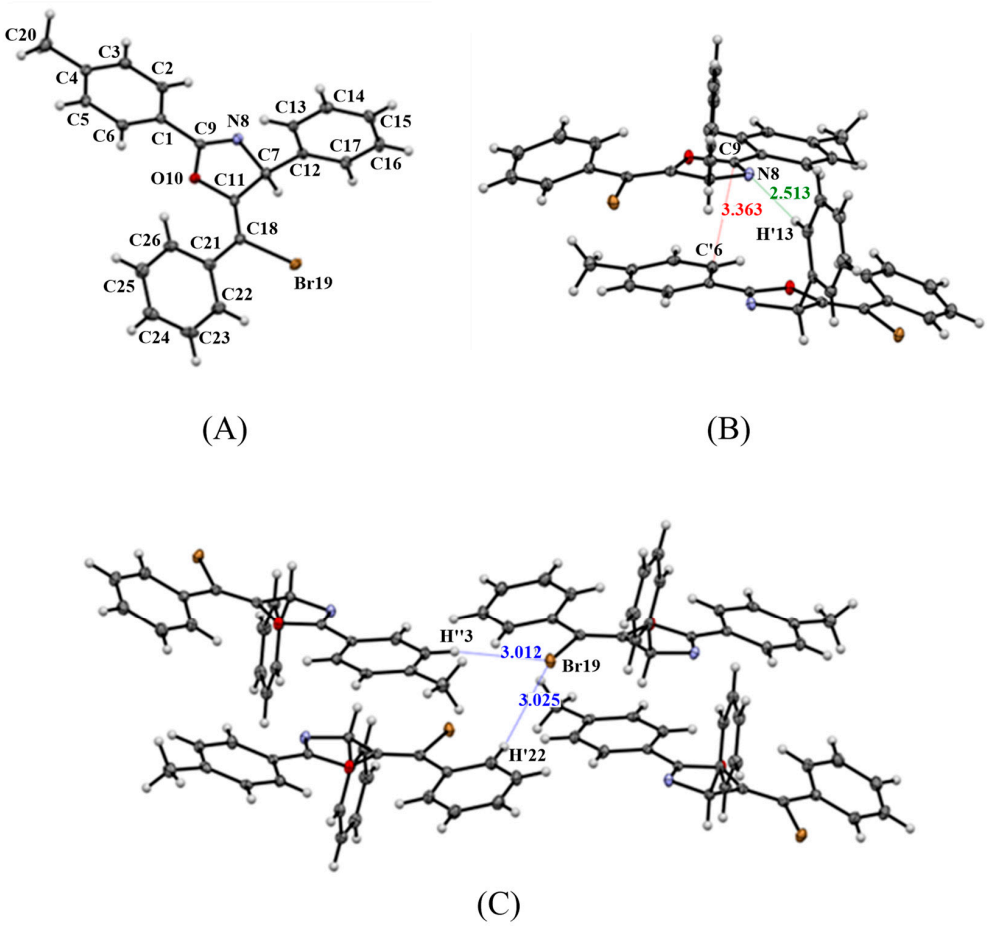


Figure 1. (**A**) ORTEP diagram of (*E*)-5-[bromo(phenyl)methylene]-4-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole (**9**) with thermal ellipsoids at the 50% probability level. (**B**,**C**) Packing diagram of **9** for interaction. (a) Blue = nitrogen; (b) white = hydrogen; (c) red = oxygen; (d) grey = carbon; and (e) orange = bromide. Interaction colors: (f) red line = π–π stacking interaction; (g) green line = CH–N interaction; and (g) blue line = CH–Br interaction.

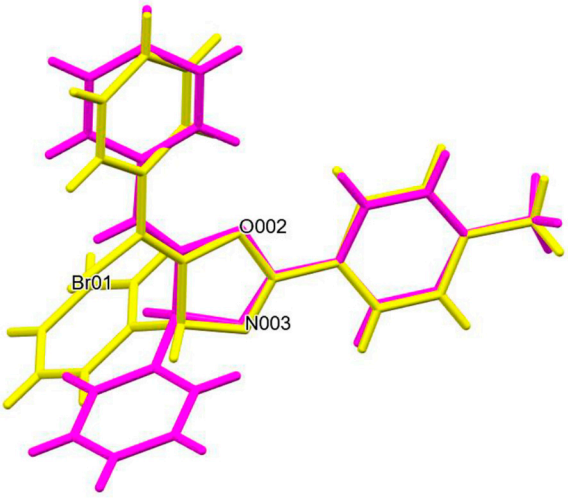


Figure 2. Comparison between bromooxazoline **9** and oxazoline **8** (see, Equation (1), Scheme 2) [16]. Yellow: (*E*)-5-[bromo(phenyl)methylene]-4-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole (**9**). Magenta: (*Z*)-5-benzyline-4-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole (**8**).

3. Materials and Methods

3.1. General Information

^{1}H and ^{13}C NMR spectra were recorded using a BRUKER AV-300 spectrometer in $CDCl_3$. Chemical shifts (δ) were reported in parts per million (ppm) on an internal standard (tetramethylsilane, 0.0 ppm for ^{1}H, $CDCl_3$, 77.0 ppm for ^{13}C). Infrared (IR) spectra were recorded with a Shimadzu FTIR-8200A. Mass spectra were recorded on JEOL JMS-700 spectrometers. Single crystal X-ray crystallography data were recorded on Rigaku XtaLAB SynergyCustom. Melting points were recorded at BUCHI melting point M-565. Merck silica gel 60 (1.09385) and Merck silica gel 60 F254 were used for column chromatography and thin layer chromatography (TLC), respectively.

*3.2. Synthesis of (E)-5-[Bromo(phenyl)methylene]-4-phenyl-2-(p-tolyl)-4,5-dihydrooxazole (**9**)*

$AuBr_3$ (4.8 mg, 0.011 mmol, 5 mol%) and AgOTf (8.3 mg, 0.032 mmol, 15 mol%) were added at room temperature to a solution of 1,3-diphenylprop-2-yn-1-ol (**5**) (45 mg, 0.22 mmol) and *p*-toluamide (**6**) (32 mg, 0.24 mmol) in toluene (5 mL), and the mixture was heated at reflux for 20 min. After confirming consumption of the starting alcohol **5** and the production of propargylic amide **7**, *N*-bromosuccinimide (77 mg, 0.43 mmol) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 20 h. The crude product was subjected to column chromatography on silica gel (hexane:AcOEt = 5:1) to give bromooxazoline **9** (47 mg, 54%).

Mp. 141–140 °C (CH_2Cl_2); IR (KBr) 3751, 3649, 1670, 1638, 1319, 1304 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.1 Hz), 7.76 (2H, d, *J* = 8.1 Hz), 7.43–7.30 (8H, m), 7.25–7.22 (2H, m), 6.01 (1H, s), 2.39 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.9, 152.7, 142.8, 137.8, 135.9, 129.3, 128.7, 128.6, 128.3, 128.1, 128.0, 123.2, 101.5, 76.3, 21.6; HRMS (EI) *m*/*z* calcd for $C_{23}H_{18}{}^{79}BrNO$ $[M]^+$ 403.0572, found 403.0574. The supporting ^{1}H-NMR, ^{13}C-NMR, IR, and mass spectra are presented in the Supplementary Material Files.

4. Conclusions

We were able to synthesize (*E*)-5-[bromo(phenyl)methylene]-4-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole (**9**) by gold(III)-catalyzed propargylic substitution reaction followed by gold(III)-catalyzed bromocyclization in one pot from propargyl alcohol **5** and amide **6**. We are currently examining the application of this method to the synthesis of various (*E*)-5-[bromo(phenyl)methylene]-4-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole derivatives.

Supplementary Materials: ^{1}H, ^{13}C-NMR, IR, HRMS and X-ray data (CCDC-2321720) of (*E*)-5-[bromo(phenyl)methylene]-4-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole (**9**).

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Data Availability Statement: Data are contained within the article and Supplementary Materials.

Conflicts of Interest: The authors declare no conflicts of interest.

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