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Efficient synthesis of di- and trisubstituted 2-aryloxazoles via ytterbium(III) triflate catalyzed cyclization of tertiary propargylic alcohols with aryl amides

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ABSTRACT

An efficient synthetic method to prepare di- and trisubstituted 2-aryloxazoles based on $Yb(OTf)_3$ catalyzed cyclization of trisubstituted propargylic alcohols with aryl amides is described. The reaction was accomplished in moderate to excellent product yields and with complete regioselective control. The mechanism is suggested to involve activation of the starting alcohol by the metal catalyst that results in its ionization. Subsequent cyclization of this newly generated carbocationic species with the aryl amide then affords the oxazole. In view of the mild conditions along with the low cost, commercially availability of $Yb(OTf)_3$ and its high tolerance to air and moisture, the present synthetic approach offers an operationally simplistic and convenient route to this important aromatic heterocycle.

1. Introduction

Oxazoles constitute an immensely important member of the aromatic heterocycle family due to their presence in a myriad of bioactive natural products, role as privileged pharmacophores and ability to serve as versatile building blocks in organic synthesis [1–12]. Accordingly, this has led to numerous synthetic methods for constructing this aromatic heterocycle and the continued pursuit of ever more efficient and flexible approaches [1–12]. Recently, this has hitherto included works describing oxazole synthesis via cyclization of propargylic alcohols as pro-electrophiles [13–41,44,47] with amides [10–12]. First reported by Uemura and co-workers, oxazole formation from reaction of these substrates was found be possible by employing a dual diruthenium (II,III) and gold(III) catalytic system [10]. Following this work, Liu and Kumar demonstrated a dual ruthenium(III) and zinc(II) catalyst combination could also mediate the cyclization of propargylic alcohols with amides that afforded the oxazole product in excellent yields [11]. More recently, Zhan and co-workers described a Brønsted acid mediated version of this ring forming reaction could be achieved in the presence of a stoichiometric amount of *p*-$TsOH\cdot H_2O$ [12]. Although shown to be highly efficient, generating H_2O as potentially the only byproduct, a drawback in these respective synthetic approaches was the need for two metal catalysts, one to achieve alkyne propargylation and another for subsequent cyclization of the resulting propargylated intermediate, or a stoichiometric amount of the Brønsted acid. Added to this is the cost of the catalysts and a substrate scope limited to terminal propargylic alcohols in reactions catalyzed by the dual metal systems. In this regard, we envisioned ytterbium(III) triflate would hold promise as a catalyst for cyclization of tertiary propargylic alcohols with aryl amides. A low cost and commercially available metal salt that has a high tolerance to air and moisture, $Yb(OTf)_3$ is one prominent member of the family of lanthanide salts that has been shown to be versatile in mediating a wide variety of organic transformations that make use of alcohol pro-electrophiles in excellent yields and with high selectivity [19–27]. For example, we recently reported $Yb(OTf)_3$ to be an efficient catalyst for the regioselective formation of indenols based on tandem Friedel–Crafts arylation/hydroarylation of propargylic alcohols with phenols [19]. As part of an ongoing program examining the utility of alcohol pro-electrophiles in organic synthesis [19,22,28–39], we report herein the use of $Yb(OTf)_3$ for tandem allenation/cycloisomerization of tertiary propargylic alcohols with aryl amides (Scheme 1). The di- and trisubstituted 2-aryloxazole products were obtained in moderate to excellent yields and as

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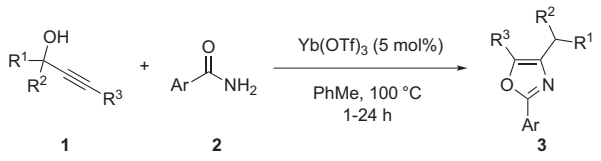


R^1, R^2 = aryl
R^3 = H, alkyl, aryl, heteroaryl

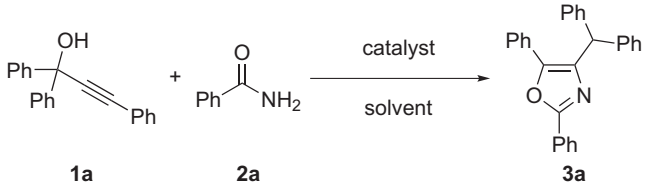
Scheme 1. Synthesis of di- and tri substituted 2-aryloxazoles based on $Yb(OTf)_3$ catalyzed cyclization of tertiary propargylic alcohols with aryl amides.

a single isomer with regiochemistry opposite to those reported for the closely related dual metal and Brønsted acid promoted synthetic methods [10–12].

2. Results and discussion

At the start of the study, we chose to examine the cyclization of 1,1,3-triphenylprop-2-yn-1-ol **1a** with benzamide **2a** by a variety of Lewis acids to establish the reaction conditions (Table 1). This revealed subjecting 1 equiv of **1a** with 2 equiv of **2a** in the presence of 5 mol% of $Yb(OTf)_3$ in toluene at 100 °C for 24 h gave the best result (entry 1). Under these conditions, 4-benzhydryl-2,5-diphenyloxazole **3a** was furnished in 88% yield (Table 1, entry 1), comparable to those obtained for the closely related dual metal and Brønsted acid mediated reactions [10–12]. The structure and regiochemistry of the oxazole product was determined on the basis of ^1H NMR measurements and X-ray crystallographic analysis (Fig. 1, Appendix). A comparable product yield was afforded on replacing toluene with 1,2-dichloroethane as the solvent or decreasing the amount of **2a** from 2 to 1.2 equiv (Table 1, entries 2, 3). In contrast, markedly lower product yields were obtained when the reaction was repeated in MeCN or $MeNO_2$ in place of toluene as solvent (Table 1, entries 4, 5). Low product yields were also found on switching the Lewis acidic catalyst from $Yb(OTf)_3$ to either AgOTf, CuBr or $FeCl_3.6H_2O$ (Table 1, entries 6–8). Moreover, a low product yield of 54% furnished from a control experiment with TfOH as the catalyst provided evidence that, in the presence of potential TfOH formed *in situ*, the cationic Yb(III) complex is the catalytically active species (Table 1, entry 9).

Table 1
Optimization of reaction conditions[a]



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Entry	Catalyst	Solvent	Yield (%)[b]
1	$Yb(OTf)_3$	PhMe	88
2[c]	$Yb(OTf)_3$	PhMe	86
3[d]	$Yb(OTf)_3$	$(CH_2Cl)_2$	85
4[d]	$Yb(OTf)_3$	MeCN	53
5	$Yb(OTf)_3$	$MeNO_2$	76
6	AgOTf	$MeNO_2$	60
7	CuBr	$MeNO_2$	56
8	$FeCl_3 \cdot 6H_2O$	$MeNO_2$	40
9	TfOH	$MeNO_2$	54

[a] All reactions were performed at 100 °C for 24 h with catalyst/**1**/**2** ratio = 1:20:40.
[b] Isolated yield.
[c] Reaction conducted with 1.2 equiv of **2a**.
[d] Reaction conducted at reflux temperature.

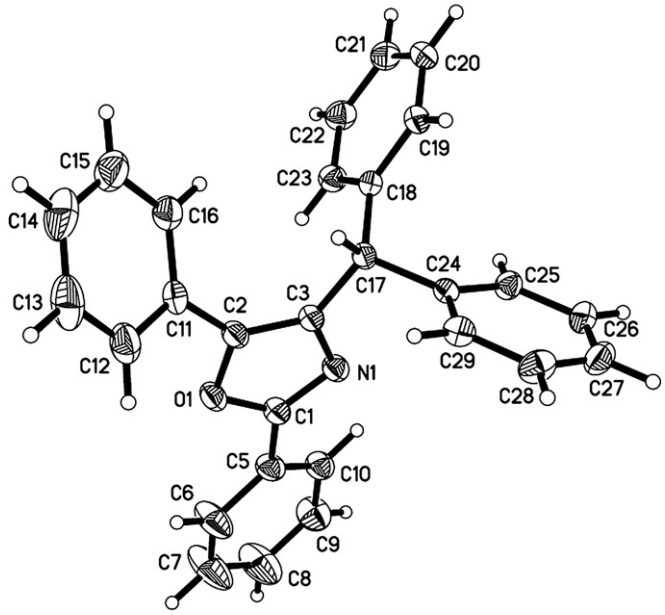

Fig. 1. ORTEP drawing of 2-aryloxazole **3a** with thermal ellipsoids at 50% probability levels (Appendix).

With the optimum conditions established, we next explored the scope of the present reaction by examining a series of propargylic alcohols **1b**–**q** and amides **2a**–**l** (Table 2). This showed that reactions of **2a** with propargylic alcohols bearing an electron-withdrawing group on the carbinol or alkyne carbon gave the corresponding 2-aryloxazoles in good to excellent yields (Table 2, entries 1–7). Similarly, the analogous reactions of **2a** with propargylic alcohols where the carbinol or alkyne carbon contained a pendant electron-donating group afforded the corresponding 2-aryloxazoles in good to excellent yields (Table 2, entries 8–10). Cyclizations of **2a** with starting alcohols where the identity of R^3 was either an alkyl or heterocycle functional group or a terminal alkyne moiety were also found to proceed well and afford **3l**–**3n** in 51–88% yield (Table 2, entries 11–13). In contrast, reactions of **2a** with propargylic alcohols where either or both R^1 and R^2 was a methyl functional group, as in **1o** and **1p**, gave either a mixture of side products that could not be identified by ^1H NMR analysis or near quantitative recovery of the substrates (Table 2, entries 14, 15). Similarly, reaction of **2a** with the secondary alcohol **1q** led to the preferential formation of the corresponding *N*-propargylation adduct **4** in 31% yield in addition to recovery of the substrate in 31% yield (entry 16). An examination of reactions of **1a** with different aryl amides, on the other hand, gave the corresponding 2-aryloxazole adducts **3o**–**t** in moderate to excellent yields (Table 2, entries 17–22). Under the standard conditions, reactions of **1a** with the alkyl amides **2i**–**k** and urea **2l** were the only instances that resulted in the recovery of the starting alcohol in near quantitative yields (entries 24–27). In addition, treating **1a** with the cyclic amide **2h** was found to afford the ketoamide **5**, structure of which was confirmed by X-ray crystallography (Fig. 2, Appendix), as the sole product in 69% yield (entry 23). A similar outcome in product chemoselectivity leading to preferential formation of the ketoamide adduct from reaction of a secondary propargylic alcohol with cyclic amide **2h** has also been reported for the analogous *p*-$TsOH \cdot H_2O$-mediated approach [12].