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Ruthenium- and gold-catalysed sequential reactions: a straightforward synthesis of substituted oxazoles from propargylic alcohols and amides

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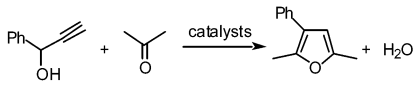
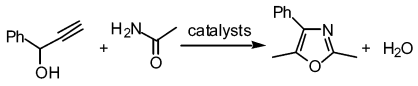
A convenient and straightforward one-pot reaction of propargylic alcohols bearing a terminal alkyne moiety with amides by the sequential action of ruthenium and gold catalysts gives the corresponding substituted oxazoles in good yields with a complete regioselectivity.

Quite recently, we have disclosed that the ruthenium- and platinum-catalysed sequential reactions of propargylic alcohols with ketones or with both ketones and anilines afforded the corresponding tri- and tetra-substituted furans or pyrroles, respectively, in moderate to good yields with a high regioselectivity (eqn. 1).[1] It is noteworthy that, in this catalytic reaction system, both ruthenium and platinum catalysts sequentially promote each catalytic cycle in the same medium.[2] During our continuous study on the sequential reactions catalysed by different catalysts, we have now found the novel reaction of propargylic alcohols with amides catalysed sequentially by ruthenium and gold catalysts to give the corresponding oxazoles in good yields with a complete regioselectivity (eqn. 2). The existing methods for the preparation of oxazoles generally involve multistep synthesis under basic conditions.[3] However, this sequential reaction system provides a simple and one-pot synthetic protocol for a variety of substituted oxazoles under neutral reaction conditions. Preliminary results are described here.



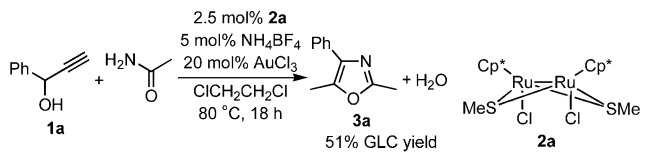
(1)



(2)

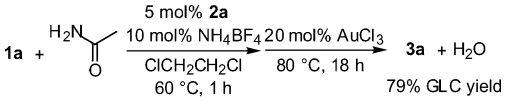
Treatment of 1-phenyl-2-propyn-1-ol (**1a**) with acetamide in the presence of methanethiolate-bridged diruthenium complex (**2a**)[4] (5 mol%), NH_4BF_4 (10 mol%) and $PtCl_2$ (10 mol%) in 1,2-dichloroethane ($ClCH_2CH_2Cl$) at 80 °C for 18 h afforded 2,5-dimethyl-4-phenyloxazole (**3a**) in 8% GLC yield. When $PdCl_2$ was used in place of $PtCl_2$, no oxazole was formed. Interestingly, when $AuCl_3$ (10 mol%) was used as a catalyst in place of $PtCl_2$, **3a** was observed in a significantly better GLC yield of 35%. Although increasing the amount of $AuCl_3$ to 20 mol% improved the yield of **3a** only marginally, reduction of the amount of **2a** (2.5 mol%) increased the yield of **3a** to 51% GLC yield (Scheme 1). A prolonged reaction time did not increase the yield of **3a** under the same reaction conditions.

As a next step, we investigated the one-pot synthesis of the



Scheme 1

oxazole (**3a**) by the stepwise addition[5] of catalysts diruthenium complex (**2a**) and $AuCl_3$ to the reaction medium to obtain higher yield of **3a**. The reaction of **1a** with acetamide in the presence of **2a** (5 mol%) and NH_4BF_4 (10 mol%) in $ClCH_2CH_2Cl$ at 60 °C for 1 h followed by the addition of $AuCl_3$ (10 mol%) and heating the reaction mixture at 80 °C for another 18 h gave **3a** in 69% GLC yield. Increasing the amount of $AuCl_3$ to 20 mol% improved the yield of **3a** to 79% GLC yield (Scheme 2). Although a prolonged reaction time did not increase the yield of **3a**, a shorter reaction time such as 6 h reduced the yield of **3a**. The best results were obtained using 20 mol% of $AuCl_3$, but this catalyst loading was too high and hence we found it more practical to compromise on product yield by the use of 10 mol% $AuCl_3$ for the rest of the reactions.



Scheme 2

Reactions of a variety of propargylic alcohols with various amides were carried out by the stepwise addition of diruthenium complex **2a** (5 mol%) and $AuCl_3$ (10 mol%).[6] Typical results are shown in Table 1. The reactions of various propargylic alcohols (**1**) with isobutyramide gave the expected 2-isopropyl-5-methyloxazoles in good to high isolated yields (Table 1; Entries 1–4). No other regioisomers were observed in all cases. However, the reaction of 1,1-diphenyl-1-penten-4-yn-3-ol (**1e**) gave only 20% isolated yield of **3f** (Table 1; Entry 5). Unfortunately, no reaction of alkyl-substituted propargylic alcohols proceeded at all. On the other hand, both alkyl and aryl amides are available as substrates (Table 1; Entries 6–11). As expected, no reaction occurred when *N*-methylacetamide, 2-pyrrolidone, and methanesulfonamide were used as substrates. In addition, our attempts to obtain the thiazoles by the reactions of propargylic alcohol (**1a**) with thiobenzamide and thioacetamide were unsuccessful.

In order to obtain some information on the reaction mechanism, we monitored the transformation of propargylic amide (**4a**) to the corresponding oxazole (**3a**) in the presence of $AuCl_3$ (5 mol%) in CD_2Cl_2 at room temperature by ^1H NMR. The complete conversion of propargylic amide (**4a**) into the corresponding allenamide[7] (**5a**) was observed, and **5a** was then converted into the oxazole (**3a**) catalysed by $AuCl_3$. In fact, the transformation of **4a** into **3a** was confirmed in the presence of $AuCl_3$ (5 mol%) in $ClCH_2CH_2Cl$ at 80 °C for 18 h, **3a** being obtained in 91% GLC yield (eqn. 3). Separately, we carried out the propargylic substitution reaction of **1a** with acetamide in the presence of **2a** (5 mol%) in $ClCH_2CH_2Cl$ at 60 °C for 1 h to give **4a** in 73% isolated yield (eqn. 4).[8] These results suggest Scheme 3 for this catalytic transformation. At first, **1a** is transformed rapidly into propargylic amide **4a** by the catalysis of **2a**. Then, isomerization from **4a** into **5a** occurs by the catalysis of $AuCl_3$. Finally, intramolecular cyclization of **5a** gives **3a** also by the catalysis of $AuCl_3$. Intramolecular cyclisation of **4a** after coordination of an

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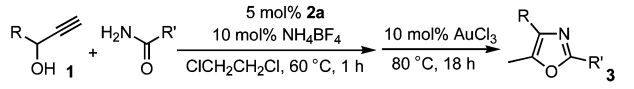
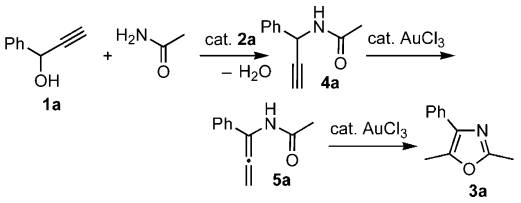
Table 1 Ru- and Au-catalysed sequential reactions of propargylic alcohols **1** with amides to give the corresponding substituted oxazoles **3**[a]



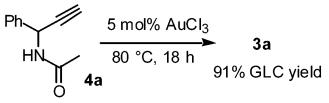
Entry	Propargylic alcohol (**1**)	Amide	Oxazole (**3**)	Yield (%)[b]
1	R = Ph	**1a** R′ = ^{i}Pr	**3b**	88
2	R = *p*-MeC_6H_4	**1b** R′ = ^{i}Pr	**3c**	62
3	R = *p*-ClC_6H_4	**1c** R′ = ^{i}Pr	**3d**	59
4	R = 2-naphthyl	**1d** R′ = ^{i}Pr	**3e**	61
5	R = Ph_2C=CH	**1e** R′ = ^{i}Pr	**3f**	20
6	R = Ph	**1a** R′ = Me	**3a**	59 (69)[c]
7	R = Ph	**1a** R′ = vinyl	**3g**	52
8	R = Ph	**1a** R′ = CH_2=CMe	**3h**	80
9	R = Ph	**1a** R′ = Ph	**3i**	83
10	R = Ph	**1a** R′ = *p*-MeC_6H_4	**3j**	84
11	R = Ph	**1a** R′ = *p*-ClC_6H_4	**3k**	65

[a] All the reactions of propargylic alcohol **1** (0.60 mmol) with amide (3.00 mmol) were carried out in the presence of **2a** (0.03 mmol) and NH_4BF_4 (0.06 mmol) in $ClCH_2CH_2Cl$ (10 ml) at 60 °C for 1 h followed by the addition of $AuCl_3$ (0.06 mmol) and $ClCH_2CH_2Cl$ (20 ml) and heating the reaction mixture at 80 °C for 18 h. [b] Isolated yield. [c] GLC yield.

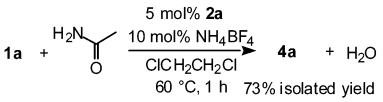


Scheme 3

alkyne moiety to the gold catalyst followed by tautomerisation may also be considered as another pathway for this catalytic reaction.



(3)



(4)

In summary, an elegant route for the synthesis of a variety of substituted oxazoles in good yields with a complete regioselectivity was achieved by the sequential action of ruthenium and gold catalysts from simple and readily available starting materials such as propargylic alcohols and amides. Further investigations involving the elucidation of the detailed reaction mechanism and broadening the scope of this sequential catalytic system are currently in progress.

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5 For recent examples, see (*a*) P. A. Evans and J. E. Robinson, *J. Am. Chem. Soc.*, 2001, **123**, 4609; (*b*) B. M. Choudary, N. S. Chowdari, S. Madhi and M. L. Kantam, *Angew. Chem., Int. Ed.*, 2001, **40**, 4620; (*c*) J. L. Christopher, W. Bielawski and R. H. Grubbs, *J. Am. Chem. Soc.*, 2001, **123**, 11312; (*d*) T. Shimada, K. Mukaide, A. Shinohara, J. W. Han and T. Hayashi, *J. Am. Chem. Soc.*, 2002, **124**, 1584; (*e*) J. Tian, N. Yamagiwa, S. Matsunaga and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2002, **41**, 3636; (*f*) S. U. Son, K. H. Park and Y. K. Chung, *J. Am. Chem. Soc.*, 2002, **124**, 6838; (*g*) B. M. Trost and M. R. Machacek, *Angew. Chem., Int. Ed.*, 2002, **41**, 4693; (*h*) A. E. Sutton, B. A. Seigal, D. F. Finnegan and M. L. Snapper, *J. Am. Chem. Soc.*, 2002, **124**, 13390.

6 A typical experimental procedure for the reaction of 1-phenyl-2-propyn-1-ol (**1a**) with isobutyramide catalysed by [Cp*RuCl(μ_2-SMe)$_2$RuCp*Cl] (**2a**) and $AuCl_3$ is described below. Complex **2a** (19 mg, 0.03 mmol) and NH_4BF_4 (6 mg, 0.06 mmol) were placed in a 50 mL flask under N_2 to which anhydrous $ClCH_2CH_2Cl$ (10 mL), **1a** (79.2 mg, 0.6 mmol) and isobutyramide (261.4 mg, 3.0 mmol) were added and then the mixture was magnetically stirred at 60 °C for 1 h. Then, $AuCl_3$ (18.2 mg, 0.06 mmol) and anhydrous $ClCH_2CH_2Cl$ (20 mL) were added and the reaction was heated for another 18 h at 80 °C. The solvent was concentrated under reduced pressure by an aspirator, and then the residue was purified by TLC (SiO_2) with EtOAc–*n*-hexane (1 : 99) to give 2-isopropyl-5-methyl-4-phenyloxazole (**3b**) as a yellow oil (106.5 mg, 0.53 mmol, 88% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (d, 6 H, J = 7.2 Hz), 2.38 (s, 3 H), 2.95 (sept., 1 H, J = 7.2 Hz), 7.15 (t, 1 H, J = 7.6 Hz), 7.28 (t, 2 H, J = 7.6 Hz), 7.53 (d, 2 H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7, 20.5, 28.4, 126.5, 126.8, 128.3, 132.5, 133.8, 142.7, 166.4 ppm; HRMS Calcd for $C_{13}H_{15}NO$ [M] 201.1154. Found 201.1152.

7 Selected ^{1}H NMR data for **5a**. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 2.10 (s, 3 H), 4.14 (d, 1 H, J = 2.4 Hz), 4.70 (t, 1 H, J = 2.4 Hz), 5.49 (br, 1 H).

8 Detailed results of propargylic amidation along with the reaction mechanism will be published elsewhere. See reference 4.