Gold(III)-Catalyzed Synthesis of Isoxazoles by Cycloisomerization of α,β-Acetylenic Oximes

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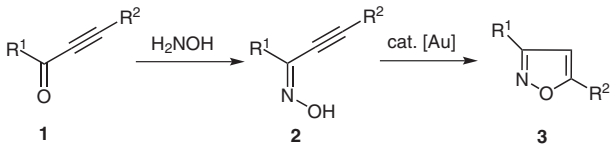
Abstract: Cycloisomerization of α,β-acetylenic oximes leading to substituted isoxazoles was achieved using $AuCl_3$ as catalyst, under moderate reaction conditions. The reaction can be applied to various acetylenic oximes and gives good to excellent yields. The methodology is amenable for the selective synthesis of 3-substituted, 5-substituted or 3,5-disubstituted isoxazoles by simply altering the substituents on the acetylenic oximes.

Key words: α,β-acetylenic oximes, gold(III) chloride, cycloisomerization, isoxazoles

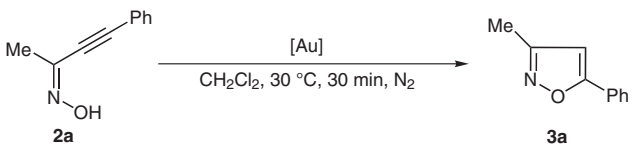
Isoxazoles are an important class of heteroaromatic molecules that are components in a variety of natural products and medicinally useful compounds.[1] Typical biological uses of such compounds include analgesic, antiinflammatory, ulcerogenic, antimicrobial, antifungal, COX-2 inhibitory, antinociceptive and applications as anticancer agents.[2] They also find application in organic synthesis as synthetic intermediates[3] and as chiral ligands.[4] The liquid crystalline properties of isoxazole derivatives, and thus their potential application in optoeletric devices, has also made them attractive synthetic targets.[5] Thus, the development of new methods for the synthesis of the isoxazole skeleton is an area of considerable ongoing interest.[6] In general, the synthetic methods most used to generate isoxazoles involes either the [3+2] cycloaddition of alkenes/alkynes with nitrile oxides, or the reaction of hydroxylamine with a three-carbon component. However, due to their importance as substructures in a broad range of natural and designed products, significant effort continues to be directed toward the development of new isoxazole-based structures and new methods for their construction.[7] However, most of these protocols suffer from the use of strong acids/bases, high reaction temperatures, prolonged reaction time, low yields, tedious workup procedures, stoichiometric reagents or provide poor regioselectivity.

In recent years, gold salts and their complexes have received increasing attention as catalysts for organic transformations.[8] The use of $AuCl_3$ as a homogeneous cycloisomerization catalyst was first reported by Hashmi et al.[9] Recently, few gold-catalyzed protocols for the synthesis of dihydroisoxazoles[10] and the isomeric oxazoles[11] have emerged in the literature. We have studied the application and catalytic effect of gold salts in various heterocycle-forming reactions.[12] Recently, Larock and coworkers reported a novel method for the synthesis of isoxazoles through electrophilic cyclization of 2-alkyn-1-one-*O*-methyl oximes,[7c,d] although this approach was limited by the use of hazardous halogenating reagents. Short et al. reported the K_2CO_3-mediated cyclization of propargyl oximes leading to isoxazoles,[13] although this method suffers from the use of stoichiometric amounts of reagent and long reaction times. To circumvent such limitations in reagent scope, and to establish a mild catalytic protocol, we envisioned the synthesis of α,β-acetylenic oximes (**2**) followed by gold-catalyzed cyclization leading to isoxazoles (**3**; Scheme 1).



Scheme 1 Synthetic approach to isoxazoles

The requisite oximes were easily prepared in good to excellent yields by stirring a mixture of α-acetylenic ketones/aldehydes[14] with hydroxylammonium chloride and 10% $NaHCO_3$ solution in methanol. For substrates where R = H or Me, a 1:1 mixture of *E*/*Z* oximes was formed; when R = Ph, the *Z*-isomer was obtained predominantly. This observation was in complete agreement with results obtained using Larock's procedure.[7c,d] Having established a satisfactory procedure for the preparation of the required oximes, we next set out to investigate the reaction conditions necessary for the synthesis of isoxazoles. Initial studies were conducted using oxime **2a** as a prototype reaction in dichloromethane at 30 °C for 30 minutes (Scheme 2).



Scheme 2 Effect of different gold catalysts on the cyclization of acetylinic oxime **2a**

We first tested the reaction of oxime **2a** in the presence of 1 mol% $AuBr_3$ in dichloromethane at room temperature (Table 1). To our delight, the reaction proceeded well and

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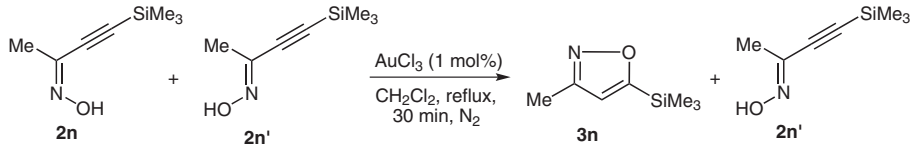


Scheme 3 Reaction of a mixture of oxime-isomers (**2n** and **2n′**) under gold catalysis

the product **3a** was obtained in 72% yield (entry 1). To optimize the reaction conditions, other gold catalysts were explored. Treatment of oxime **2a** with 1 mol% of a range of cationic gold complexes led to product formation in good yields (entries 2, 3 and 4). Gratifyingly, when 1 mol% $AuCl_3$ was used, an excellent yield (93%) of the product was obtained (entry 5). The use of AuCl also led to good yield of the product (entry 6). A control reaction without any catalyst did not led to any product formation, even when the reaction was carried out at reflux temperature. Because the use of 1 mol% $AuCl_3$ at room temperature gave a better yield than with other catalysts for the parent system, the scope of the reaction with this catalyst was tested with a wide range of acetylenic oximes.[15]

Table 1 Screening of Gold Catalysts for the Synthesis of Isoxazole **3a**

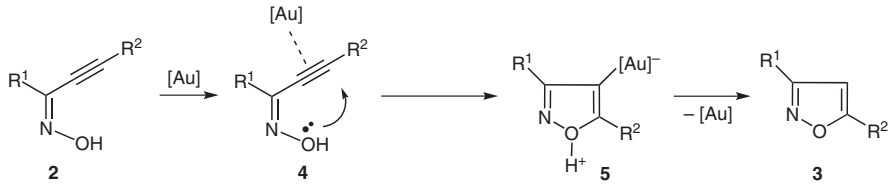
Entry	Catalyst	Yield (%)[a]
1	1 mol% $AuBr_3$	72
2	1 mol% Me_3PAuCl, 2 mol% $AgBF_4$	65
3	1 mol% Ph_3PAuCl, 2 mol% $AgBF_4$	68
4	1 mol% Et_3PAuCl, 2 mol% $AgSbF_6$	60
5	1 mol% $AuCl_3$	93
6	1 mol% AuCl	80
7	no catalyst	–[b]

[a] Isolated yield.
[b] The reaction was carried out at r.t. and at reflux temperature.

Under these optimized conditions, all the substrates tested underwent the reaction completely and resulted in good yields of the product (Table 2). However, the rate of the reaction seems to be dependent on the substituents on the substrates. Oximes having an electron-releasing group on the alkyne residue (entries 1–5, 9, 13 and 15–18) more readily underwent the cyclization than those possessing electron-withdrawing groups (entries 6 and 7). The reaction conditions were also amenable to substituents possessing hydroxy and polyaromatic functionalities, although in these cases the products were formed in more moderate yields (entries 8 and 10). Substrates possessing a silyl group (**2k** and **2n**) underwent cyclization only after heating to reflux for 30 minutes. This may be due to the presence of the electron-withdrawing silyl group, which renders the triple bond more electron-deficient, thus making attack on the triple bond by the nucleophile (=NOH) more difficult. The cycloisomerization of silyl oximes (**2k** and **2n**) by our methodology seems to be superior, since the silyl group was left intact, whereas using the related K_2CO_3 method, desilylated products were obtained.[11] One of the noteworthy advantages of this methodology is the cycloisomerization of oximes possessing a terminal alkyne (**2l**), leading to 3-substituted isoxazole **3l**. A similar type of cyclization has been reported that uses only internal alkynes to lead to the formation of 3,5-disubstituted isoxazoles only.[7c,d] To test the efficacy of the cycloisomerization, when a mixture of *Z* and *E* oximes (**2n** and **2n′**) were tested under the gold-catalyzed cyclization conditions, we found that only the *Z*-isomer underwent the cyclization and the *E*-isomer remained unreacted (Scheme 3).

Formation of the isoxazole-products were characterized by the appearance of a sharp singlet in the ^1H NMR spectrum at δ_H = 6.2–6.8 ppm, which is characteristic of the isoxazolinyl proton. Moreover, all the products exhibited a ^{13}C peak at δ_C = 170.0–170.9 ppm, which is characteristic of the C5 carbon of the isoxazole ring.

A mechanistic proposal for the formation of isoxazole is given in Scheme 4. Thus, π-activation of carbophilic $AuCl_3$ with the triple bond of the oxime **1** leads to π-complex **4**. The latter species undergoes 5-*endo-dig* cyclization to afford the cyclized intermediate **5**, which, upon subsequent protodeauration, results in the formation of isoxazole **3**.



Scheme 4 Proposed mechanism for the gold(III)-catalyzed cycloisomerization of acetylenic oximes

Table 2 Gold-Catalyzed Synthesis of Isoxazoles by Cycloisomerization of α,β-Acetylenic Oximes[a]

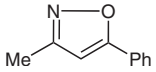
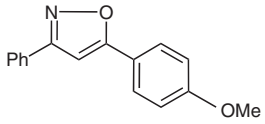
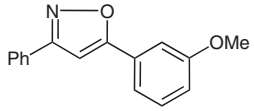
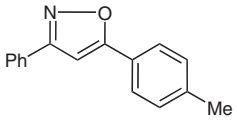
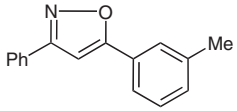
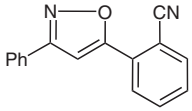
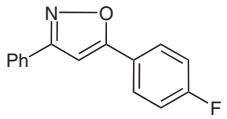
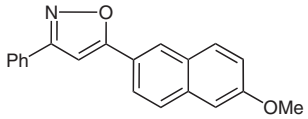
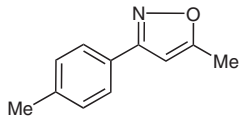
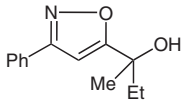
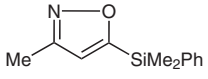
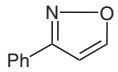
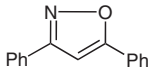
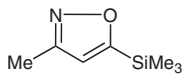
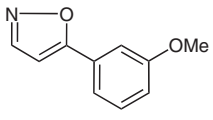
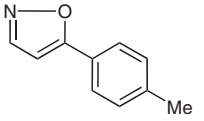
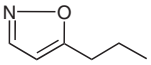
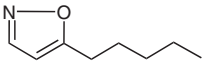
Entry	Acetylenic oxime **2**			Isoxazole **3**[b]		Time (min)	Yield (%)[c]
		R^1	R^2				
1	**2a**	Me	Ph	**3a**		10	92
2	**2b**	Ph	4-$MeOC_6H_4$	**3b**		10	94
3	**2c**	Ph	3-$MeOC_6H_4$	**3c**		10	91
4	**2d**	Ph	4-MeC_6H_4	**3d**		10	95
5	**2e**	Ph	3-MeC_6H_4	**3e**		10	93
6	**2f**	Ph	2-NCC_6H_4	**3f**		20	82
7	**2g**	Ph	4-FC_6H_4	**3g**		20	83
8	**2h**	Ph	6-methoxy-2-naphthyl	**3h**		15	81
9	**2i**	4-MeC_6H_4	Me	**3i**		10	90
10	**2j**	Ph	2-hydroxybutyl	**3j**		25	78
11	**2k**	Ph	$SiPhMe_2$	**3k**		30	75[d]
12	**2l**	Ph	H	**3l**		25	80
13	**2m**	Me	Ph	**3m**		10	93
14	**2n**	Me	$SiMe_3$	**3n**		30	79[d]
15	**2o**	H	3-$MeOC_6H_4$	**3o**		10	92

Table 2 Gold-Catalyzed Synthesis of Isoxazoles by Cycloisomerization of α,β-Acetylenic Oximes[a] (continued)

Entry	Acetylenic oxime **2**			Isoxazole **3**[b]		Time (min)	Yield (%)[c]
		R^1	R^2				
16	**2p**	H	4-MeC_6H_4	**3p**		10	95
17	**2q**	H	*n*-Pr	**3q**		10	89
18	**2r**	H	*n*-Pent	**3r**		10	88

[a] All reactions were carried out at 30 °C in CH_2Cl_2 using 1 mol% $AuCl_3$ under a nitrogen atmosphere.
[b] All products were characterized by IR, ^1H NMR, ^{13}C NMR and MS.
[c] Isolated yield.
[d] Reaction was carried out at reflux.

In summary, we have shown that gold(III) chloride efficiently catalyzes the cycloisomerization of various α,β-acetylenic oximes, leading to the formation of isoxazoles in excellent yields. Further studies to extend the scope, synthetic utility and application of the method to natural product synthesis are in progress.

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(15) **Synthesis of 3-Methyl-5-trimethylsilylisoxazole (3); Typical Procedure**: To a solution of oxime **2n** (500 mg, 3.22 mmol) in anhydrous CH_2Cl_2, was added $AuCl_3$ (9.76 mg, 0.0321 mmol) under an N_2 atmosphere and the solution was stirred for the specified time (Table 2) at 30 °C. After completion of the reaction (as indicated by TLC), the reaction mixture was concentrated under reduced pressure and purified by column chromatography over silica gel (100–200 mesh) to afford pure product, 3-methyl-5-trimethylsilylisoxazole (**3n**) as a yellow oil; IR (neat): 3302, 2912, 1604, 1419, 1338, 1085, 885, 757 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.29 [s, 9 H, $Si(CH_3)_3$], 2.29 (s, 3 H, CH_3), 6.24 (s, 1 H, isoxazolinyl-*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ = –1.8, 10.8, 113.5, 157.7, 177.8. MS (EI): *m*/*z* = 172 $[M]^+$. Anal. Calcd for $C_7H_{13}NOSi$: C, 54.15; H, 8.44; N, 9.02. Found: C, 53.95; H, 8.47; N, 9.15.