LETTERS

Gold-Catalyzed Oxime–Oxime Rearrangement

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(5) Supporting Information

ABSTRACT: The gold-catalyzed reaction of pyrrole and indole oximes having a propargyl group attached to the nitrogen atom was studied. The selective 6-endo-dig mode of cyclization was observed for the terminal alkynes giving rise to the formation of pyrazine *N*-oxides in the presence of a gold catalyst. However, the reaction with substituted alkyne



transferred the oxime functionality intramolecularly from one carbon atom to another via the 7-*endo-dig* cyclization process. This transformation is unprecedented in the literature and is named an oxime–oxime rearrangement.

A tom-economical efficient transformations have attracted the attention of researchers as possible methods for environmentally benign syntheses. The Trost research group has made important contributions to this area, developing powerful transition-metal-catalyzed reactions with a wide range of synthetic applications.¹ For such reactions, gold catalysts are considered attractive reagents.² To overcome the difficulties of complex reactions, gold-catalyzed reactions emerged as a powerful tool and were applied in a broad range of reactions, such as nucleophilic addition,³ the Friedel–Crafts reaction,⁴ C– H activation,⁵ and oxidation.⁶

In addition to these reactions, gold derivatives are also capable of catalyzing various rearrangements. For example, gold(I) catalytic cyclization of simple enynes led to the discovery of complex cascade reactions.⁷ Hashmi et al. and other groups demonstrated that gold(III) chloride catalyzes the isomerization of alkynyl epoxides to furans under mild conditions.⁸ Furthermore, a search of the literature reveals that such rearrangements include the formation of homoallylic ketones via hydroxalkoxylation/Claisen rearrangement;^{9a} the formation of homoallenic alcohols via propargyl/Claisen rearrangement;^{9b,c} the transformations of cyclopropyl-, cyclopropenyl-, epoxy-, and aziridinyl-containing molecules into interesting building blocks;^{9d,e} Meyer–Schuster rearrangement;^{9f-h} Cope rearrangement of 1,5-dienes;⁹ⁱ Petasis–Ferrier rearrangement;⁹¹

Recently, we examined the cyclization reaction of a propargyl hydrazone 1^{10} and propargyl amide derivatives 2^{11} formed in situ to give triazepinone and pyrrolopyrazine derivatives (Figure 1).





Furthermore, we researched the gold-catalyzed cyclization reaction of pyrrole-propargyl carboxylic acids **3**. As a continuation of this work, we envisioned the gold-catalyzed reactions of pyrrole- and indole-propargyl oximes. In this context, we discovered a new rearrangement, which we refer to as the *gold-catalyzed oxime—oxime rearrangement* that is unprecedented in the literature.

Oximes are readily available and versatile intermediates in organic synthesis as they can be converted easily to valuable building blocks such as amides. The so-called Beckmann rearrangement has been used for more than a century to generate amides.¹² It generally requires the use of Brønsted or Lewis acids under severe reaction conditions. Recently, some metal catalysts have been used for this transformation.¹³ The first metal-catalyzed Beckmann rearrangement found by Chang et al.¹⁴ shows that the transformation of aldoximes to the corresponding amides can be readily achieved by rhodium catalysis (RhCl-(PPh₃)₃) with high selectivity and efficiency (Scheme 1).

Scheme 1. Transformation of Aldoximes into Amides by Rh Catalyst

Shortly after this publication, a wide range of catalytic systems based on different transition metals such as iridium,¹⁵ ruthenium,¹⁶ palladium,¹⁷ and other catalysts were used for this transformation.¹⁸ Gold-based catalysts have been studied less. Nolan and co-workers¹⁹ reported gold/silver-cocatalyzed conversion of aldoximes into amides at 100 °C in moderate to good yields. Herein, we report the gold-catalyzed reactions of various pyrrole- and indole-derived oximes having a propargyl group.

Received: April 10, 2015

Oximes are usually synthesized by the reaction of hydroxylamine with aldehydes or ketones. The starting materials $6a-c^{10,11}$ were obtained in high yields from the reaction of **5** with propargyl bromide in the presence of NaH as a base (Scheme 2).

Scheme 2. Synthesis of Propargylated Pyrrole and Indole Derivatives



For the incorporation of additional substituents at the terminal acetylene carbon atom, the Sonogashira cross-coupling reaction²⁰ was used to give 7a-c. The synthesis of indole derivatives **9a,b** and **10a,b** was accomplished starting from indolecarbaldehyde **8**²¹ as described above.

The corresponding oximes were synthesized by the reaction of aldehydes or ketones 6, 7, 9, and 10 with hydroxylamine in ethanol in the presence of anhydrous Na_2CO_3 at 70 °C (Scheme 3). The NMR spectra of the products revealed the formation of

Scheme 3. Synthesis of Oxime Derivatives 11



(*E*)- and (*Z*)-oxime isomers. In some cases, the major product was separated and used for further reaction. In other cases, an (E)/(Z)-oxime-mixture was used. The isomer ratios of the oximes depend on the method of preparation as well as on the bulkiness of the substituents attached to the carbonyl group.²² All the signals of (*Z*)- and (*E*)-isomers differ significantly, up to 0.7 ppm, from each other.^{23b}

As the next step, we turned our attention to the cyclization reaction of oximes 11 with various metal catalysts in chloroform at room temperature. For this purpose, the propargyl oxime 11a was reacted with four different catalysts. Reactions with CuI gave a low yield (45%) of *exo-dig* cyclization product 12a (Table 1 and Scheme 4). AgOTf and L_nAuCl/AgOTf were also screened and gave higher yields, 82% and 92%, respectively. However, AuCl₃ was identified as the optimal choice due to the shorter reaction time, high yield, and easy isolation of the product.

After having obtained the optimal condition for the Aucatalyzed cyclization of oxime 11a, we examined the substrate scope of this reaction. We found that only use of 11a,b and 11g as substrates afforded the cyclization products 12a-c, pyrazine *N*oxide derivatives (Scheme 4). To test the effect of configuration of the oxime derivatives on the mode of the cyclization reaction, Table 1. Yields of 12a with Different Metal Catalysts

catalyst (3 mol %)	yield (%)
AuCl ₃	97
L _n AuCl*/AgOTf ^a	92
AgOTf	82
CuI	45

Scheme 4. Reaction of Oximes 11a,b and 11g with AuCl₃. Synthesis of Pyrazine Oxides



we separated the (E)- and (Z)-isomer of **11a** and submitted them separately to cyclization reactions. Consequently, both isomers smoothly underwent cyclization reactions and gave the product **12a** in almost the same yield. After this finding, in most cases, a mixture of oximes was used for further reactions. Some derivatives of pyrazine *N*-oxide are important pharmaceuticals such as the antibiotic aspergillic acid, the antimicrobial pigment pulcherrimin, and the hypolipidemic synthetic drug acipimox.²³

After finding the optimal conditions for Au-catalyzed cyclization, we attempted to determine the scope and limitation of this transformation. To test our strategy, we reacted oxime derivatives 11c-f and 11h-j having substituted alkynes with AuCl₃ at room temperature to afford the corresponding pyrazine oxides. To our surprise, the reaction of substituted alkynes 11c-f and 11h-j, under the same reaction conditions, underwent a smooth rearrangement to produce 13a-g having isomerized oxime structures in most cases as a mixture of *E*- and *Z*-isomers (Scheme 5). The structures were determined with the help of NMR spectral data.

Scheme 5. Reaction of Oximes 11c–f and 11h,j with AuCl₃. Oxime–Oxime Transformation



To show the exact position of the oxime group, we recorded 2D NMR spectra of **13b**. The presence of aldehyde functionality was established by the resonance signal of the aldehyde proton at 9.56 ppm as a singlet. The exact location of the aldehyde group was determined from the HMBC spectrum, which showed a strong correlation between the aldehyde carbon appearing at 179.4 ppm with two protons of the pyrrole ring, indicating clearly that the aldehyde group is directly connected to the pyrrole ring. On the other hand, the imine carbon, resonating at 157.0 ppm, shows correlation with both methylene protons appearing at 4.64 and 3.29 ppm, as triplets as well as with the α -protons (7.54–7.58 ppm) of the benzene ring clearly show that the oxime

functionality is attached to the benzene ring. Furthermore, to show the presence of a hydroxyl group, the -OH functionality in 13b was transferred into the corresponding acetate 14 (Scheme 6).

Scheme 6. Acetylation Reaction of Oxime 13b with Acetic Anhydride



A chemical proof of the new rearrangement was provided by the independent synthesis of the rearranged product **13c**. For this purpose, the alkyne **7b** was first submitted to a hydration reaction according to a modified literature procedure (Scheme 7).²⁴ A

Scheme 7. Independent Synthesis of the Oxime-Oxime Rearranged Product 13c



solution of 7b in a mixture of AcOH, acetone, and MeOH was reacted with a catalytic amount of HgSO₄ in the presence of H₂SO₄. The hydration process proceeded rapidly to give the desired ketoaldehyde 15 in quantitative yield. For the chemoselective protection of aldehyde functionality, the ketoaldehyde 15 was treated with 1,2-ethanedithiol in the presence of SnCl₂. H_2O^{25} (10 mol %) to give the thicketal 16 in 71% yield. The reaction of thioketal with hydroxylamine in ethanol in the presence of anhydrous Na₂CO₃ at 70 °C formed the desired isomeric oximes 17 in almost quantitative yield ((E)-isomer 86%; (Z)-isomer 14%). Finally, the thioketal 17 was subjected to hydrolysis using $HgCl_2-HgO^{26}$ in aqueous methanol to give the desired product 13c. Comparison of the NMR spectral data of those compounds obtained by AuCl₃-catalyzed reaction of 11e and HgCl₂-HgO-catalyzed hydrolysis reaction of 17 showed that these compounds were identical. With this experiment, the structure 13c formed by an unprecedented oxime-oxime rearrangement was proved by chemicals methods.

These experiments led to our discovery of a new rearrangement, which we refer to as the *oxime–oxime rearrangement*. Based on all this information obtained, we propose the following goldcatalyzed cyclization reaction mechanism (Scheme 8).

The proposed catalytic cycle was initiated by the activation of the triple bond by $AuCl_3$ to form the intermediate **B**, which enables a nucleophilic attack by the nitrogen atom of oxime to the alkyne functionality to give the intermediates **C** and **D**, which lead to the formation of the final products **J** and **H** through **I** and **E**–**G**, respectively.

The electronic nature of the substituents attached to the triple bond determines the mode of the nucleophilic attack. To gain more insight into the chemoselectivity, we conducted some Scheme 8. Proposed Reaction Mechanism for the Formation of Pyrazine Oxides and Oxime–Oxime Rearrangement



calculations to understand the formation of the products arising from 7-endo-dig as well as 6-exo-dig cyclization processes.²⁷ Geometry optimizations and frequency calculations of complexes **11g** and **11i** with AuCl₃ were performed using the B3LYP (Becke-3-parameter-Lee–Yang–Parr) hybrid level within 6-31G(d,p) and LANL2DZ (Au) basis set. Natural bond orbital (NBO) analysis was performed at the same level of theory to obtain the charge distribution of the structures.

We found that in the case of 11g AuCl₃ is much closer to the terminal alkyne carbon atom and the positive charge is localized on internal alkyne carbon C-2 so that the oxime nitrogen atom attacks exclusively this carbon atom giving rise to the formation of *6-exo-dig* cyclization products **12c** (Figure 2). However, if the



Figure 2. Geometry optimized structures of $11g + AuCl_3$ and $11i + AuCl_3$ complexes; NBO charges and distances (in Å).

terminal group of alkyne is substituted by a phenyl group, in the $AuCl_3$ complex, the gold unit has a stronger interaction with the C-2 carbon atom and the positive charge is localized on C-1 because of the better stabilization by the aromatic ring or a methyl group. The shorter bond length between the Au atom and C-2 (2.18 Å) compared to the other bond, between Au and C-1 (2.67 Å), supports our finding. Therefore, the nitrogen atom attacks in the case of **11i** exclusively the alkyne carbon atom substituted by a phenyl group forming an intermediate having the structure **D**. The water present in the reaction media attacks the iminium ion to form **F**, which undergoes a ring-opening process where oxime functionality is transferred to the carbon atom connected to the benzene ring. The overall reaction is the intramolecular transfer of an oxime functionality from one carbon atom to another via the formation of a seven-membered ring as the intermediate **E**.

In this paper, we described an efficient gold(III)-catalyzed reaction of various N-atom propargylated pyrrole and indole

oximes. Terminal alkynes underwent a 6-exo-dig cyclization reaction giving rise to the formation of pyrazine N-oxides. This synthetic strategy represents a reasonable methodology for the construction of hitherto unknown skeletons. However, in the case of substituted alkynes, the reaction proceeded in a completely different way forming an intermediate with a sevenmembered ring, which transfers the oxime functionality intramolecularly from one carbon to another. This type of rearrangement has not been previously observed and represents a new rearrangement, the oxime–oxime rearrangement.

ASSOCIATED CONTENT

Supporting Information

Experimental conditions, spectroscopic data (1D and 2D NMR spectra) of the products, Cartesian coordinates for the optimized structures. This material is available free of charge via the Internet at http://pubsacs.org.The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/ acs.orglett.Sb01041.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from the Scientific and Technological Research Council of Turkey (TUBITAK, Grant No. TBAG-112 T360), the Turkish Academy of Sciences (TUBA), and Middle East Technical University (METU) is gratefully acknowledged. We also thank Research Assistant Ozlem Sari (METU) for her help with calculations.

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