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Palladium(0)-mediated cyclization-coupling of β,γ-unsaturated oximes and aryl iodides

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ABSTRACT

The tandem palladium(0)-mediated nucleometalation-cross coupling of β,γ-unsaturated oximes with aryl iodides has been shown to provide the expected 3,5-disubstituted 2-isoxazolines in acceptable yields (11–78%). The addition of a weak base is required for product formation. Some influence on the yield of the reaction is noted in the electronic character of the aryl iodide used in the reaction. Exploration of the substitution patterns on the reactants has led to a proposed mechanism involving a palladium(II)-catalyzed nucleometalation/cyclization followed by reductive elimination of palladium(0) with concomitant coupling to an arene.

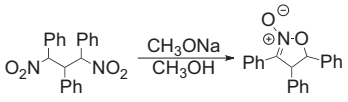
Introduction

The 2-isoxazoline ring system has been studied extensively since its first preparation in the late 1800s. Given the utility of these compounds as precursors for a variety of 1,3-difunctionalized systems,[1,2] bioisosteres for the other systems,[3] and as scaffolds for metal ligands, studies on the various methods for the preparation of the 2-isoxazoline ring system are found throughout the literature.[4–6]

Standard methods for the preparation of this heterocycle include the 1,3-dipolar cycloaddition of a nitrile oxide and an appropriately substituted alkene.[7,8] Although some control of the regio- and stereoselectivity is possible in specific systems,[9] electronic and steric factors of the cycloaddition often dictate the regiochemistry that is observed in the isoxazoline substitution.[10]

The preparation of 2-isoxazolines with regiospecificity in the location of substituents, then, suggests a non-cycloaddition approach to this useful class of heterocycles. Such non-cycloaddition routes to the 2-isoxazoline ring system do exist.[4]

The majority of these alternative routes to the 2-isoxazoline ring system involve the intramolecular construction of the O1–C5 bond or the N2–C3 bond of the isoxazoline as the key cyclization step. The relative ease of formation of the O1–C5 bond by either displacement of a β-leaving group by the oxygen of an oxime or nitronate or addition of an oxime to an internal alkene suggests this as a viable route to this system. For example, the reaction of 1,2,3-triphenyl-1,3-dinitropropane with sodium methoxide in methanol gives rise to the expected 3,4,5-triphenyl-2-isoxazoline N-oxide in 79% yield (Scheme 1).[11] The mechanism of this reaction, the Kohler synthesis, proceeds by nucleophilic displacement of a nitro group by a nitronate intermediate.



Scheme 1. Kohler synthesis.

Our interest in the formation of 3,5-disubstituted isoxazolines via the construction of the O1–C5 bond has revealed the utility of this method.[12–14] In our efforts to further explore the possible use of the cyclized intermediate formed during the initial addition of the hydroxyl group to the unconjugated olefin, we have uncovered an interesting tandem process involving cyclization of a β,γ-unsaturated oxime and its subsequent coupling with an aryl halide. Given the substitution of the oxime starting material, a wide variety of isoxazoline substitution patterns could result.

Results and discussion

A series of the required β,γ-unsaturated oxime starting materials were prepared using a previously published procedure (Scheme 2).[12] For example, treatment of the commercially

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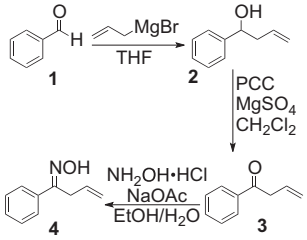
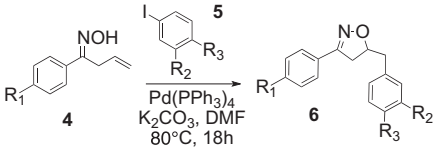


Scheme 2. Synthetic route to β,γ-unsaturated oximes.



Scheme 3. Palladium(0) catalyzed cyclization-coupling of unsaturated oximes (**4**) and aryl iodides (**5**).

available substituted benzaldehyde (**1**) with allylmagnesium bromide provided nearly quantitative yield of the expected 1-phenyl-3-buten-1-ol (**2**). Oxidation of **2** using pyridinium chlorochromate (PCC) in dichloromethane with magnesium sulfate added as a support phase gave the expected ketone as the major component of the product mixture. A minor component (~10%) was determined to be the starting benzaldehyde presumably arising via an acid-catalyzed retro-Cope rearrangement of the unsaturated alcohol. Attempts to eliminate this byproduct through addition of sodium acetate, sodium carbonate, and other mild bases were unsuccessful. Purification of **2**, however, was necessary by column chromatography before continuation of the synthesis. Interestingly, no rearrangement of the alkene into conjugation was observed under the conditions employed during the oxidation or subsequent oximation reactions. The resulting ketone (**3**) was then treated with hydroxylamine hydrochloride and sodium acetate in refluxing aqueous ethanol to afford the desired β,γ-unsaturated oxime in good yield as a mixture of syn and anti isomers (**4**) that were not individually isolated before use in the title reaction.

A variety of catalysts potentially suitable for mediation of the tandem cyclization-coupling reaction were explored.[15] Specifically, attempts to effect cyclization of the unsaturated oxime with coupling to another compound included the use of aluminum, boron, titanium(IV), tin(II), lead(II), zinc(II), mercury(II), gold(I), gold(III), palladium(0), and palladium(II). The utility of each mediator was explored using both catalytic (10% by mol) and stoichiometric quantities with a variety of ligands. Spectroscopic examination of the reaction mixtures indicated that only gold(I), mercury(II), and palladium(II) effected the formation of a 2-isoxazoline ring system under the conditions attempted. Specifically, the isoxazoline ring was observed in the proton NMR spectrum of the crude reaction mixture with the use of both catalytic and stoichiometric quantities of these metals. Characteristic signals (as doublet of doublets) for protons on C4 and the benzylic position suggested the formation of the isoxazoline ring and coupling to the arene.

Attempts to isolate the trace amount of isoxazoline-containing product from the gold(I)-mediated reaction using a variety of chromatographic methods were unsuccessful. However, isolation of the isoxazoline product from the mercury(II)- and palladium(II)-mediated cyclization was accomplished as expected. Yields for the palladium(II)-mediated product were unsatisfactory and the method was not pursued further; however, mercury(II)-mediated cyclization of the unsaturated oxime gave rise to an isolable di-(2-isoxazolinyl)-mercury(II) complex in moderate yield (40%). Both NMR and XRF (X-ray fluorescence) were consistent with the formation of the dimer. That reaction and further exploration of the use of mercury in the formation of substituted isoxazoline products is currently being explored in more detail and will be presented in due time.

The use of catalytic quantities of palladium(0) in the tandem cyclization-coupling reaction of β,γ-unsaturated oximes (**4**) gave rise to the coupled isoxazoline product (**6**) in yields ranging from 11% to 78% (Scheme 3). Specifically, 5 mol equiv of a substituted aryl iodide (**5**), 5 mol equiv of potassium carbonate, and 10% mol equiv of $Pd(PPh_3)_4$ (tetrakis-(triphenylphosphine)palladium(0)) were added to a stirred solution of 1 mol equiv of the substituted β,γ-unsaturated oxime (**4**) in dimethylformamide. The reaction was stirred at 80 °C over an 18 h period. Extractive isolation with diethyl ether gave rise to the product mixture. Observation of the product in the crude product mixture was possible using HNMR spectroscopy. The presence of the 2-isoxazoline coupled to the aryl group was noted by the presence of four doublet-of-doublets near 3 ppm and the complex signal near 5 ppm.

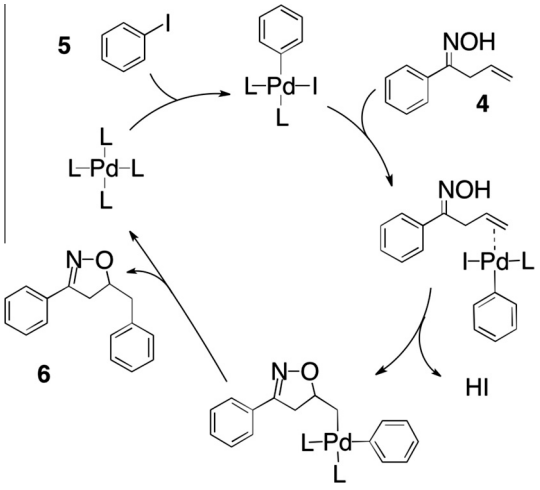
Separation of the product from the reaction mixture using low pressure column chromatography resulted in the isolation of the title compounds as white solids. Compound identity was confirmed by spectroscopic methods and the specific correlations of each atom to its signal in the NMR spectra were determined. Table 1 lists the specific compounds prepared by this method and their isolated yield. In many cases, the isolated yield of the product was significantly less than would have been predicted by examination of the crude product mixture by HNMR spectroscopy. This was likely due to the decomposition of the product on the silica gel during chromatography.

Examination of the yields of the palladium(0)-mediated reaction led to a proposed mechanism for the reaction. In that mechanism, the palladium(0) first undergoes oxidative insertion in the aryl iodide bond.[16,17] The resulting palladium(II) complex then forms an η^2-complex with the β,γ-unsaturated system, activating the internal carbon of the alkene functional group for nucleophilic attack of the oxime hydroxyl group. Then, addition to the alkene and formation of the 2-isoxazoline ring system gives rise to the σ-palladium complex. During this process, the loss of the iodide ligand and deprotonation of the isoxazoline oxygen occurs. This results in the formal production of HI during the reaction and is the cause of the use of potassium carbonate in the reaction mixture. In the absence of the carbonate, the yield of the reaction is significantly reduced, likely due to the buildup of HI in the

Table 1
2-Isoxazolines prepared by Scheme 3

Compound	R_1	R_2	R_3	Yield[a] %
6a	H	H	H	53
6b	H	H	CH_3	39
6c	H	H	OCH_3	28
6d	H	OCH_3	H	58
6e	CH_3	H	H	53
6f	CH_3	H	CH_3	78
6g	CH_3	H	OCH_3	39
6h	CH_3	OCH_3	H	57
6i	OCH_3	H	H	29
6j	OCH_3	H	CH_3	29
6k	OCH_3	H	OCH_3	57
6l	OCH_3	OCH_3	H	65
6m	F	H	H	58
6n	F	H	CH_3	22
6o	F	H	OCH_3	11
6p	F	OCH_3	H	nd[b]

[a] The yield is of the isolated and purified product.
[b] The expected product was not detected in the reaction mixture.



Scheme 4. Proposed mechanism for the title reaction.

reaction mixture. Such a buildup would inhibit the cyclization and likely aid ring-opening of any formed isoxazoline. Finally, reductive elimination of the σ-palladium(II) complex would result in coupling of the aryl group to the 5-methylene carbon of the isoxazoline to give compound **6** and would allow re-formation of the palladium(0) complex (Scheme 4).

Based on the proposed mechanism, electron-donating groups on the β,γ-unsaturated oxime would, through a resonance effect, increase the electron density at the oxime nitrogen. This would result in a more nucleophilic oxime oxygen and a predicted increase in the yield of the reaction. Similarly, electron-withdrawing groups placed on the aryl iodide would be expected to decrease electron density at the palladium center making the complex more associative with the β,γ-unsaturated oxime. Again, such an arrangement would be expected to increase the yield of the reaction. This is, in fact, what is generally observed in the actual yields of the reaction (see Table 1), though further evaluation of the reaction is necessary to confirm these observations.

Conclusion

The reaction of β,γ-unsaturated oximes with aryl iodides can be mediated by catalytic amounts of palladium(0). The yield of the reaction is somewhat dependent upon the electronic effects of substitution on both starting materials. This methodology provides a route to the formation of the 2-isoxazoline by ring closure of the O1–C5 bond and results in the formation of a new carbon–carbon bond to an aryl substituent. The products are easily identifiable in the proton NMR spectrum due to the presence of the four doublet-of-doublets characteristic of the methylene units around the isoxazoline ring junction.

Acknowledgments

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Supplementary data

Supplementary data (the general procedure for the title reaction and spectroscopic data for each of the compounds prepared by this method) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.01.076. These data include MOL files and InChiKeys of the most important compounds described in this article.

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