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Alkyne Cycloadditions Mediated by Tetrabutylammonium Fluoride: A Unified and Diversifiable Route to Isoxazolines and Pyrazolines

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Abstract

A versatile approach to isoxazolines and pyrazolines by the cyclization of alkyne substrates using tetrabutylammonium fluoride (TBAF) is described. The reported diheteroatom cycles were produced under mild reaction conditions and with broad product scope. Evidence is also provided for a vinyl anion intermediate produced under unusually mild conditions, which was trapped in situ as part of a tandem cyclization/aldehyde addition sequence. Finally, a deprotection/functionalization method is described, leading to a substituted pyrazoline in good diastereoselectivity.

Graphical Abstract

Studies involving partially unsaturated diheteroatom heterocycles abound in the medicinal chemistry literature. For instance, isoxazolines have been exploited as inhibitors of human macrophage migration inhibitory factor (MIF).¹ This same heterocyclic scaffold has also shown immunopotentiating activity² and antitumor properties (Figure 1).³ Pyrazolines have also been at the center of numerous medicinal chemistry investigations⁴ including the development of selective inhibitors of B-Raf,⁵ carbonic anhydrase,⁶ and aurora kinases A and B for anti-tumor therapy.⁷ This compound class also shows promise as pesticides⁸ and antifungal agents.⁹

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ASSOCIATED CONTENT

Supporting Information

Characterization data for all new compounds and experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Not surprisingly, a variety of synthesis routes to these heterocycles have emerged to enable further medicinal discovery. Their synthesis is generally achieved through [3+2] cycloadditions.¹⁰ While important headway with this reaction has recently been made by Bharate¹¹ and Kittakoop,¹² these mainly racemic approaches are largely limited to aryl-substituted oximes to stabilize nitrile oxide formation. Intramolecular cyclizations leading to isoxazolines resolve the problem of regioselectivity. Using this strategy, allyloximes have been efficiently converted to isoxazolines catalyzed by palladium¹³ and copper.¹⁴ Mukherjee describes a mild organocatalytic asymmetric approach to both isoxazolines and pyrazolines involving a 5-exo-trig mechanism (Scheme 1).¹⁵ A similar mechanistic approach was used by Kokotos;¹⁶ however, in both cases, product scope is limited due to the presence of the exocyclic fragment required to activate the system for ring closure. List reported the development of an asymmetric electrocyclization of α,β -unsaturated hydrazones catalyzed by a chiral phosphoric acid.¹⁷ While the approach by List stands out for its efficiency and enantioselectivity, it remains limited to pyrazolines bearing two aryl substituents. Using a similar Brønsted acid catalyst, Rueping developed an asymmetric cycloaddition between alkenes and N-benzoylhydrazones to afford fused bicyclic pyrazoline derivatives.¹⁸ Overall, the aforementioned approaches to isoxazolines and pyrazolines are either limited to the production of only one of these heterocycles or suffer from limited product scope. Given the growing importance of these heterocycles, the search for unified and more general methods to their synthesis continues to be a worthy goal.

We previously reported a novel route to pyrazolines using mild, non-metal mediated conditions.¹⁹ Our follow-up efforts with this reaction were focused on elucidating the reaction mechanism, which we have recently shown to involve a unique cation- π interaction between a tetraalkylammonium ion and carbon-carbon triple bond present in the substrate.²⁰ During these and subsequent studies, we discovered that our ammonium-mediated reaction could also be used to access isoxazolines.

In the present communication, we describe our expansion of this unified approach to produce these diheteroatom heterocycles with good product generality. We also put forward additional evidence for a 5-endo-dig mechanism that proceeds through a vinyl anion intermediate despite the exceptionally mild conditions (Scheme 1). Finally, we reveal a one-pot deprotection/functionalization approach to prepare highly functionalized pyrazolines.

In our previous studies, we only examined hydrazine substrates bearing both an alkyl and ester unit at the propargyl position. These room temperature reactions gave pyrazoline products in five minutes in the presence of tetrabutylammonium fluoride (TBAF) in acetonitrile.²⁰ To explore the role of alkyl-only propargyl substituents on the rate of cyclization, we prepared a series of hydrazine and oxamine derivatives without the ester unit. We were delighted to discover that these compounds were also converted to pyrazolines and isoxazolines (products **2** – **12**) with TBAF in acetonitrile (Scheme 2). Without a propargyl ester group, the reactions were noticeably slower; however, heating to 70 °C afforded good yields in 1 h. Based on these results, we believe the rate enhancing effect of the ester unit in the substrate used in our previous studies to be due to inductive activation of the triple bond. We considered an alternative explanation based on a Thorpe-Ingold effect; however,

substrate **4**, bearing two alkyl substituents at the propargyl position, was no more reactive than other alkyl-only substrates.

Besides being able to produce both pyrazolines and isoxazolines under the same conditions, the scope of this reaction is relatively broad leading to all alkyl-substituted heterocycles as well as those with aryl and alkyl groups. It is important to note that, to our knowledge, this is only the second²¹ example of the synthesis of 2,5-dihydroisoxazoles from terminal alkynes (compounds **8** and **9**). Traditional cyclization approaches for hydroamination of alkynes utilize strong π -acids, which are incompatible with terminal alkynes.²² One limitation of the present method appears to be with substrates bearing an aryl group as the only propargyl substituent. These failed to give the expected product (such as **13**).

To assess the importance of heteroatom substitution at the propargyl position, substrates **14** and **15** were prepared (Scheme 3). These substrates failed to cyclize even with extended reaction times and increased temperatures. Compounds **16** and **17** were of interest since they contain a diheteroatom unit at the homopropargyl position, which we considered might be important for cyclization. Here again, no cyclization was observed in the presence of TBAF even under refluxing conditions in acetonitrile. In the presence of TBAF, substrate **18** gave pyrazoline product **19** presumably after a decarboxylation (Scheme 3). However, no cyclization product resulting from the attack of the hydroxyl oxygen on the alkyne was observed. This selectivity further suggested that a propargyl diheteroatom plays an essential role in the present reaction. Given these considerations, we believe that the observed 5-endo-dig cyclization is likely promoted by the inductive electron withdrawing effect of the propargyl heteroatom. In their computational analysis, Alabugin and co-workers recently showed that a 5-endo-dig-cyclization of a related system was unusually favored due to an in-plane aromatic transition state.²³

Cyclitve attack on non-conjugated carbon-carbon triple bonds without the aid of a transition metal has rarely appeared in the literature. One mechanistic consequence is that a vinyl anion intermediate is formed. These are typically high-energy species in the absence of stabilizing interactions with transition metals. Vinyl anion intermediates have rarely been invoked under similar conditions.²⁴ We envisioned that, in our reaction, the vinyl anion is immediately quenched by a proton source especially since partial deuterium incorporation was observed in the product of reactions performed in deuterated acetonitrile (MeCN-d₃). However, we sought further proof of a vinyl anion intermediate by attempting to trap the putative anion with an aldehyde. We were pleased to discover that cyclization followed by vinyl anion trapping was successful in the presence of excess p-Cl-benzaldehyde in nitrobenzene as solvent (Scheme 4). Due to the presence of water in TBAF,²⁵ the reaction was performed with TBAB and sodium phenoxide as base leading to product **21** in modest isolated yield (50%). We note that the added base (NaOPh) was entirely soluble in this reaction and thus TBAB was not required as a phase transfer agent in this reaction. As we highlighted in our previous mechanistic investigation, the ammonium cation engages the carbon-carbon triple bond in a cation- π interaction, which seems connected with its rate enhancing effect on this reaction.²⁰ The vinyl anion was also successfully trapped by other electron deficient aromatic aldehydes though in lower yields.

One of the benefits of the present route to pyrazolines and isoxazolines is that the starting propargyl substrates are readily accessible in non-racemic form. We have previously produced these materials through the catalytic asymmetric addition of silyl allenes to an azidodicarboxylates.¹⁹ However, these starting materials can also be prepared by taking advantage of the extensive literature on catalytic asymmetric alkyne additions to aldehydes.²⁶ To demonstrate this accessibility to non-racemic heterocyclic products, we converted commercially available (S)-1-octyn-3-ol (99% ee) to propargyl hydrazine **22** in one step (Scheme 5). A subsequent cyclization afforded the corresponding pyrazoline **23** with no erosion of enantiomeric purity.

Transformations involving isoxazolines and pyrazolines have usually focused on cleaving the N-N or N-O bonds. However, in the present work, we sought to further elaborate these ring systems in novel ways to build more complex frameworks.

In this vein, we envisioned that the tert-butyloxycarbonyl (Boc) group on the enamine nitrogen in each heterocycle could be removed under acidic conditions. Accordingly, we attempted a selective removal of this group and were pleased to observe the formation of 2-pyrazoline products **24** and **25** (Scheme 6). We note that compound **25** is a novel azaproline derivative and contains an orthogonally protected carboxylic acid and amine group, which can be conveniently exploited in peptide synthesis. These reactions worked best with trifluoroacetic acid (TFA) in the presence of activated molecular sieves. Under the same conditions, isoxazoline **26** was also produced in excellent yields. Intrigued by this result, we explored the use of a Lewis acid²⁷ to promote the addition of an aldehyde to the C₄-carbon of **6a** together with selective Boc removal. To our delight, the functionalization attempt yielded addition product **27** in good yield and reasonable diastereoselectivity (6:1). Others have deprotected enamine-type systems using hydroxide²⁸ or palladium²⁹ with concomitant addition. However, similar transformations under Lewis acidic conditions leading to products such as **27** is unprecedented.³⁰

The relative stereochemistry between centers C₃ and C₄ of product **27** was determined to be exclusively *trans*. Crystallography studies indicate that the configurational variability is at the exocyclic position (C₆). The *trans* selectivity between C₃ and C₄ can be understood as resulting from the steric hindrance offered by the alkyl substituent at C₃ that favors a Re-face attack (Figure 2). Importantly, this substituent also constrains the Boc group on the adjacent nitrogen to assume a relative *trans* orientation (N₂ to C₃). Based on this N₂ configuration, we argue that an *exo*-like attack of the Sc(OTf)₃-ethylglyoxylate complex is favored. Finally, the major diastereomer of **27** can be rationalized as the result of minimizing steric interactions between the glyoxylate and the N₂ Boc group (Figure 2).

In conclusion, we have developed a unified method to synthesize pyrazolines and isoxazolines using mild, non-metal mediated conditions. These studies also allowed for a further exploration of the reaction mechanism. The cyclization reaction proceeded through a vinyl anion intermediate, produced under exceptionally mild conditions, which underwent addition to an aldehyde. This method is also ideally suited to the nonracemic synthesis of these diheteroatom heterocycles starting from easily accessible propargyl substrates. Finally, our initial efforts to further functionalize these heterocycles with simultaneous selective

deprotection led to promising diastereoselectivity. Attempts to develop an asymmetric version of this Lewis acid-mediated method are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Representative bioactive molecules

Figure 2.
Rationale for observed stereoselectivity

Current Approaches

Mukherjee

List

Present Work

Scheme 1.

Intramolecular cyclization approaches

Scheme 2. Isoxazoline and pyrazoline substrate scope^a

^aAll reactions were performed at 0.1 M concentration of propargyl hydrazine or oxyamine and TBAF (1.5 equiv) with near-refluxing temperatures (60 - 70 °C); ^b Reaction proceeded very slowly at rt; however, heating to 70 °C for 12 h led to full conversion; ^c Reaction required heating to 80 °C.

Scheme 3.
Role of the propargyl heteroatom

^aProduct **19** was isolated along with unreacted starting material.

Scheme 4.
Tandem cyclization and vinyl anion trapping

Scheme 5.
Synthesis of non-racemic pyrazolines

Selective removal of Boc group

Deprotection with concomitant aldehyde addition

Scheme 6.
Selective deprotection and aldehyde addition