Isoxazoles via Cycloaddition of Terminal Alkynes and Nitrile Oxides (from Oximes)

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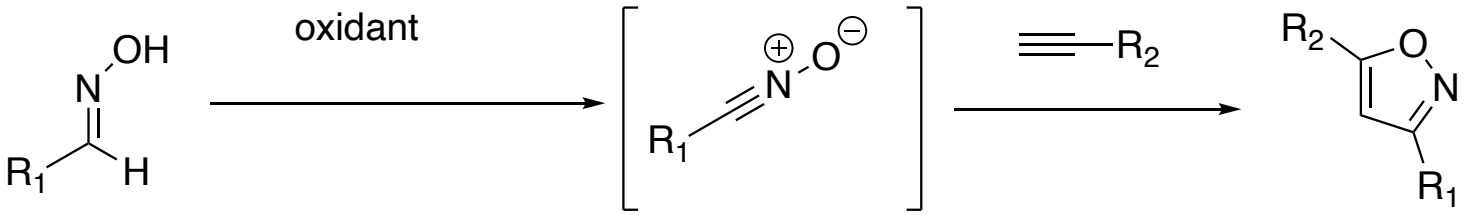
Importance of Isoxazole – Applications[1-3]

- Industry
- Agrochemicals
- Pharmaceuticals
  - Antitumor
  - Antibiotics
  - Prostanoids

Approaches to Isoxazole Formation

- Reaction of 1,3-dicarbonyl compounds with hydroxylamine[4]
- Cyclizationreactions of ynones[5]
- Particular interest - 1,3-dipolar cycloaddition reactions of alkynes with nitrile N-oxides
  - Components readily available
  - Regioselectivity
  - Amenable to establishing structural diversity.

Overall Reaction



Reagents for dipolar cycloaddition

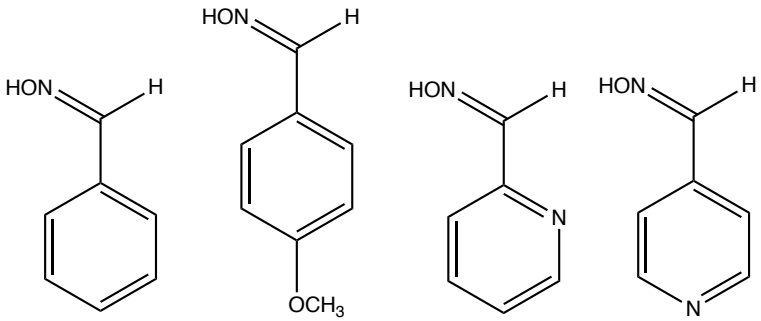
- Copper(I)-catalyzed cycloaddition[6]
- Ruthenium(III)-catalyzed cycloaddition[7]
- Our preference: various oxidizing reagents such as [bis(trifluoroacetoxy) iodo]benzene[8] (PIFA) and iodobenzene diacetate (DIB) catalyzed by TFA.[9]
  - Avoids the use of transition metals that may be problematical in pharmaceutical preparations

Our objective

- Robust method for protocol of dipolar cycloaddition reaction
- Amenable to library syntheses
- Best hypervalent iodide reagent for general synthesis
- Reagents tested
  - (diacetoxy)iodobenzene
  - (diacetoxy)iodobenzene with added TFA
  - Polymer-bound hypervalent iodine reagent[16]
  - Bis(trifluoroacetoxy)iodobenzene – found to be most advantageous

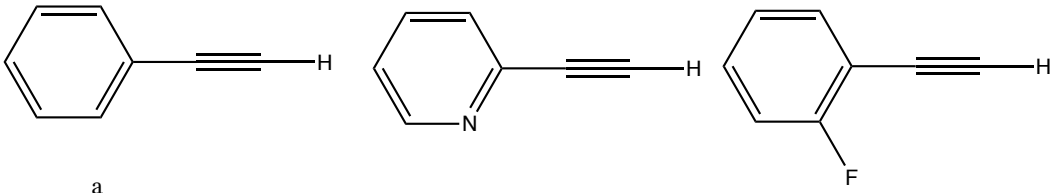
Components of reactions

Oximes



1 2 3 4

Alkynes



a b c

Methods

- Method 1
  - Alkyne and oxime in MeOH/H_2O (5:1), [bis(trifluoroacetoxy)]iodobenzene (1.5 equiv) added. Stirred for 2 days at room temperature, 5 mL of 10% sodium thiosulfate solution added and the mixture was extracted with DCM. The organic layer was dried with and the solvent evaporated. Flash chromatography. Fractions were dried and recrystallized from ether.\
- Method 2
  - Simlar to Method 1 with [bis(trifluoroacetoxy)]iodobenzene added portionwise over two hours and worked up after seven hours

Compounds prepared

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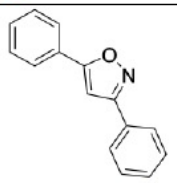
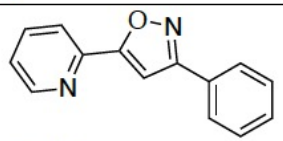
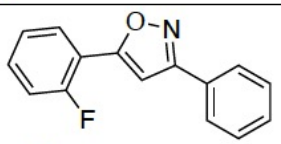
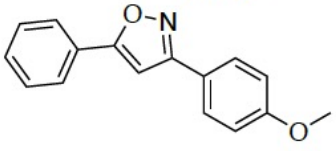
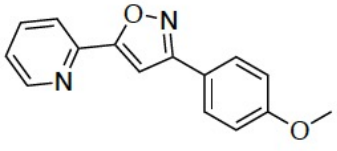
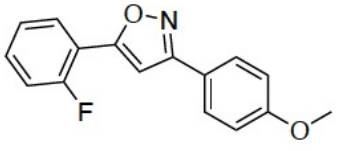
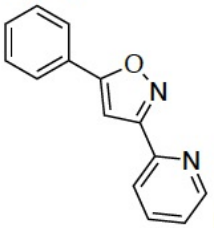
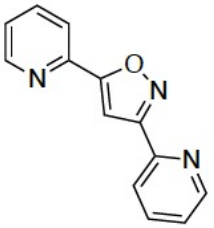
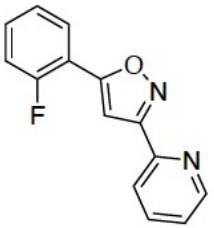
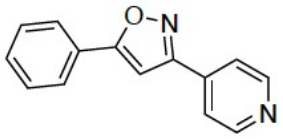
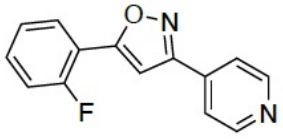
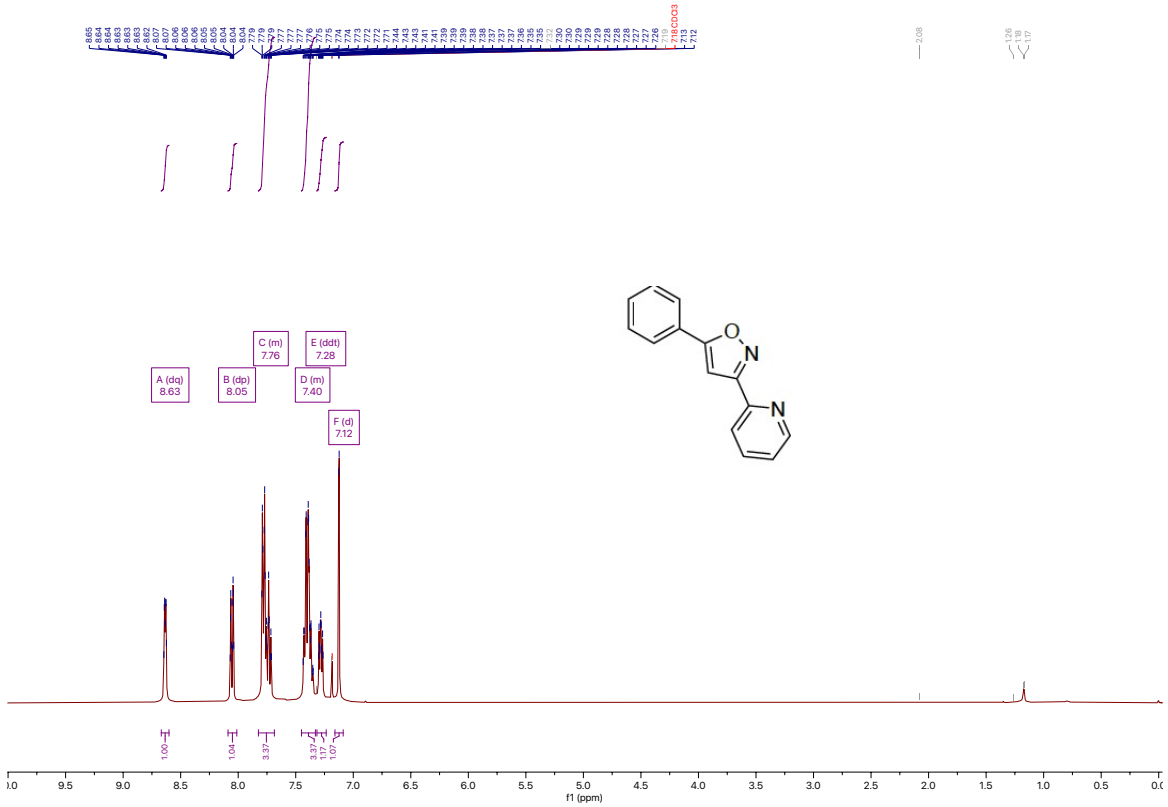
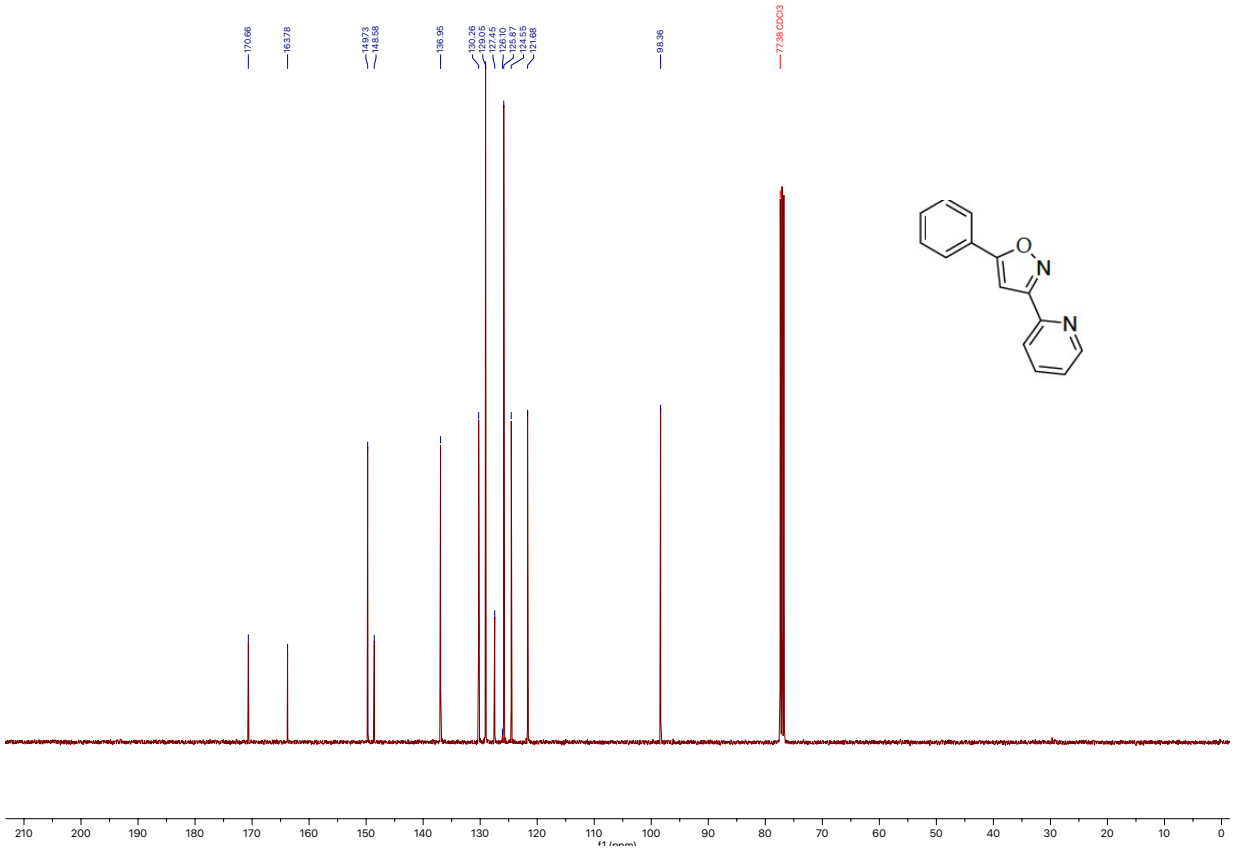
1	 ref 10	 Ref 8	 Ref 11
2	 Ref 11	 Ref 12	
3	 Ref 13	 Ref 15	
4	 Ref 14	Not Characterized	

Characterization – HNMR, CNMR, GC/MS see Supplemental information – HNMR for 3a



CNMR 3a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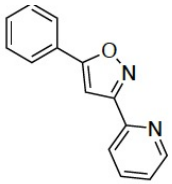
GC/MS 3a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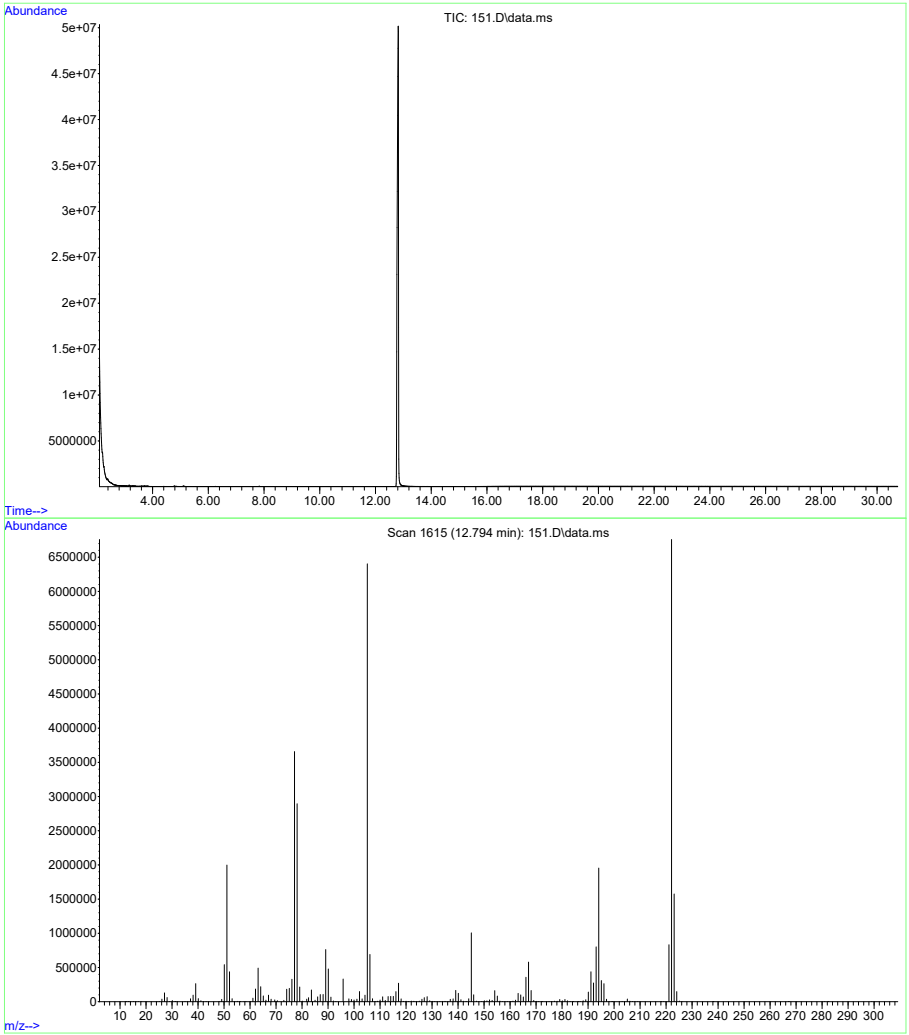
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m/z-->

Side products

- Nitrile from oxime (dehydration)
- Methyl ester from oxime (hydrolysis, oxidation, esterification by methanol)
- Easily separated by flash chromatography (exception ester in case 2c)

Conclusions, Future work, Acknowledgement

- A general method for isoxazole formation has been developed
- Method 2 is a superior approach to the general synthesis
- Hydroxylic solvents are necessary for a practical reaction

- Future – Other reagents in attempt to avoid chromatography step

- Support by Miami University Chemistry Department is acknowledged

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