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One pot spiropyrazoline synthesis via intramolecular cyclization/methylation

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ABSTRACT

Regioisomeric spiropyrazolines were synthesized through a tandem intramolecular cyclization/methylation reaction of a functionalized 5,5-disubstituted pyrazoline in one reaction vessel. The 5,5-pyrazolines were constructed through a 1,3-dipolar cycloaddition reaction of aromatic ring containing nitrile imines and a disubstituted geminal alkene. An evaluation of the relative location of the nucleophilic and electrophilic functional groups on the pyrazoline was performed in order to ascertain the best pyrazoline system for the intramolecular cyclization/methylation reaction. Higher spiropyrazoline isolated yields were realized from pyrazolines with the electrophilic ester located further away from the pyrazoline when compared to pyrazolines with a directly bonded ester.

1. Introduction

The spirocyclic molecular framework is a prevalent feature for a number of biologically active heterocyclic natural products,[1,2] and among the FDA approved pharmaceutically relevant heterocycles, the pyrazole and isoxazole moieties are found in the COX II inhibitors, celebrex and bextra.[3,4] Furthermore, as the syntheses of isoxazoles and pyrazoles flourished,[5,6] the corresponding synthetic methodologies targeting spiroisoxazolines and spiropyrazolines were also developing.[7,8] While the major structural feature of a number of biologically active bromotyrosine derived heterocyclic marine natural products is the spiroisoxazoline,[1,2,7] spiropyrazolines have an extra nitrogen, in place of isoxazoline oxygen, and offer the feasibility to construct structurally relevant analogues for the exploration of potential biological activity (Fig. 1). In general spiropyrazolines[8] contain the common basic molecular architecture derived from the corresponding pyrazoline and are characterized by a unique spiro fusion at the C-5 position of a pyrazoline ring. These spiropyrazoline heterocycles are interesting targets for synthesis based upon the interesting spirocyclic skeleton that is often associated with potential bioactive properties.

A variety of methods exist for the synthesis of functionalized spiropyrazolines. General and classical syntheses of pyrazoles and pyrazoline derivatives rely on the 1,3-dipolar cycloaddition[9] of diazoalkanes or nitrile imines with alkynes,[5d,6c–g,j,l–n] alkyne surrogates,[6h,q] or alkenes,[10] closely related [2+3] cycloadditions,[6d,r,11] and other methods.[12] Special attention is warranted toward the synthetic design and development of pyrazoles, pyrazolines, and their derivatives because of their high demand in academic and pharmaceutical sectors. Our recent report on spiroisoxazoline synthesis utilized intramolecular alkylation/methylation of a 5,5-disubstituted isoxazoline as the central spiroisoxazoline synthetic pathway.[13] In this Letter, we extend the application of this practical synthetic methodology toward the synthesis of functionalized unsaturated carbocyclic spiropyrazolines while also determining the best pyrazoline system for the intramolecular cyclization/methylation reaction.

2. Results and discussion

Synthesis of the spiropyrazoline precursor **3a** was initiated by the regioselective 1,3-dipolar cycloaddition of the readily available alkene dipolarophile **1**.[14] The reaction of α-chlorohydrazone **2** with triethylamine results in the in situ generation of the corresponding nitrile imine[6h,i,8a] which combines with **1** in a 1,3-dipolar fashion to afford the highly functionalized 5,5-disubstituted pyrazoline in moderate to good yields as a single regioisomer[15] (Scheme 1). The 1,3-dipolar cycloaddition of **1** with a variety of substituted aromatic nitrile imines was then pursued in order to investigate the scope and limitations of 5,5-disubstituted pyrazolines as precursors to spiropyrazolines via the intramolecular cyclization/methylation synthetic methodology. The 1,3-dipolar cycloaddition results are shown in Scheme 1. All of these cycloadditions occurred with complete regiochemical integrity and in reasonable to good isolated yields.

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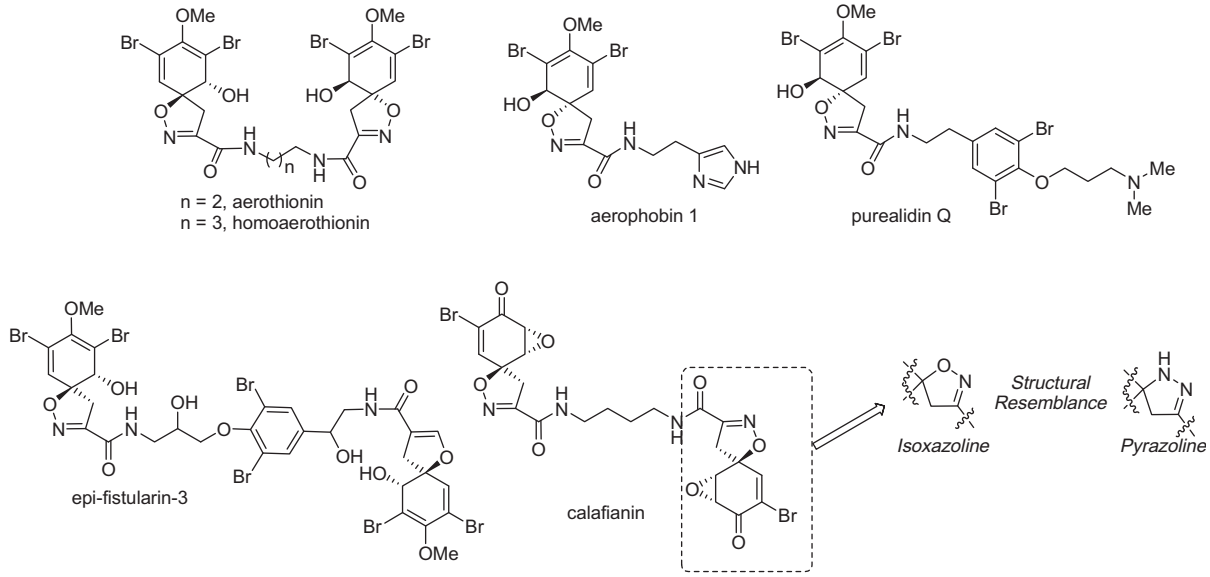
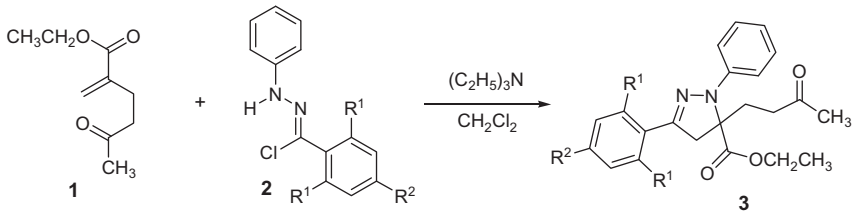


Figure 1. Naturally occurring spiroisoxazolines and spiropyrazoline structural resemblance.



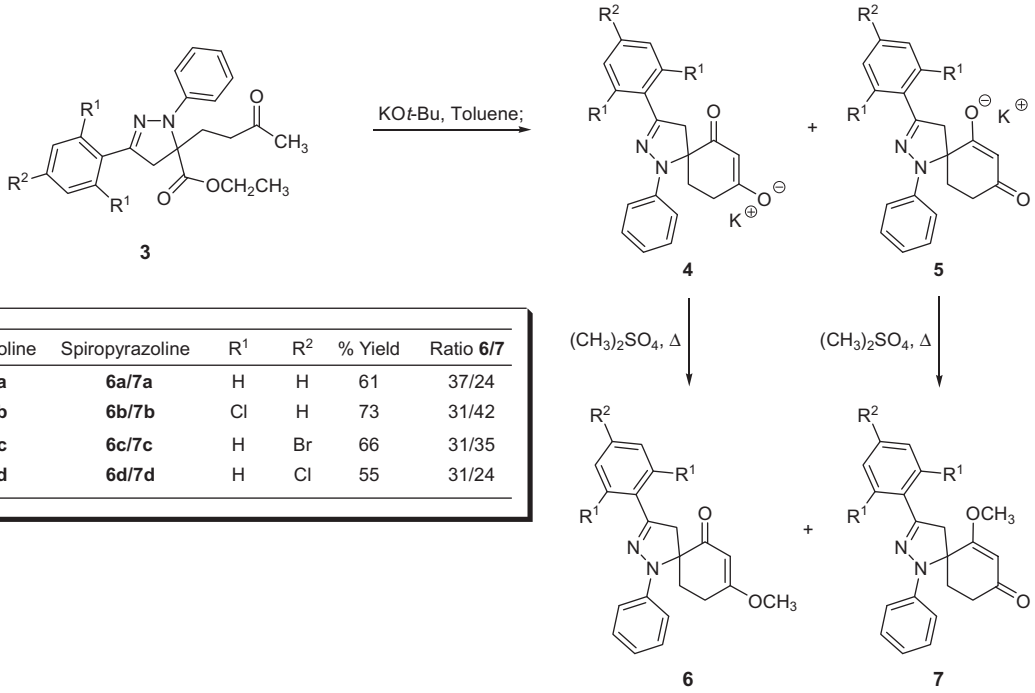
Entry	Pyrazoline	R^1	R^2	% Yield
1	**3a**	H	H	67
2	**3b**	Cl	H	73
3	**3c**	H	Br	85
4	**3d**	H	Cl	77

Scheme 1. Synthesis of highly functionalized pyrazoline **3**.

Suitable bases for the intramolecular cyclization process were evaluated in conjunction with solvent compatibility and temperature. Optimal reaction conditions were realized for the intramolecular cyclization/methylation reaction by employing potassium *t*-butoxide as the base in anhydrous toluene.[16] The intramolecular cyclization/methylation was achieved in one reaction vessel, and each step was monitored via TLC through the consumption of the starting materials. Spiropyrazoline **6a** was isolated in 37% yield, and its regioisomer, **7a**, was isolated in 24% yield (Scheme 2). The isolation of the two spiropyrazoline regioisomers results from the O-methylation of both spiropyrazoline enolates (Scheme 2).

Based upon the positive results obtained from the intramolecular cyclization/methylation of **3a**, the application of this synthetic methodology was applied toward a variety of pyrazoline derivatives for spiropyrazoline construction. The isolated yields of various spiropyrazolines arising from pyrazoline intramolecular cyclization/methylation are shown in Scheme 2. The overall yields for the isolation of the spiropyrazoline regioisomers range from 55% to 73% for the two-step one pot process. Each spirocyclic regioisomer was identified based upon the unique nature of the ^{13}C chemical shift of the quaternary carbon of the pyrazoline. Generally, when the pyrazoline quaternary carbon is located alpha to the carbonyl, as found in compound **6**, the ^{13}C chemical shift is greater than 70 ppm. However, due to the non availability of carbonyl's deshielding effect, the pyrazoline quaternary carbon of the alternate regioisomer, such as compound **7**, gives rise to a ^{13}C chemical shift that is less than 70 ppm. These spectroscopic observations are in correlation with previous results reported from our research laboratories.[13] Even though the isolated yields for the aforementioned spiropyrazolines were good, we decided to investigate the potential of improving the intramolecular cyclization/methylation yields by repositioning the electrophilic ester to a more remote location relative to the pyrazoline ring thereby potentially decreasing the steric environment of the ester.

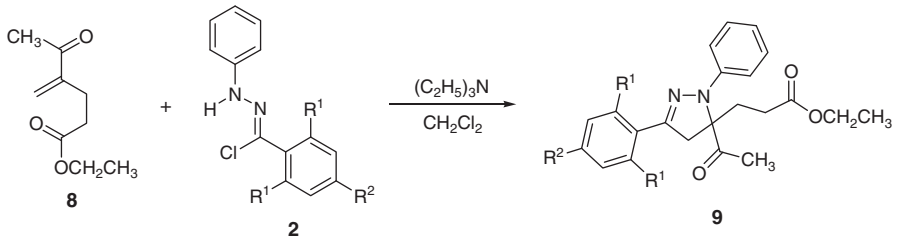
The cycloaddition of the nitrile imine arising from **2a** with **8**[17] affords functionalized 5,5-disubstituted pyrazoline **9a** in high yield as a single regioisomer. Scheme 3 illustrates the products and the isolated yields of the pyrazolines derived from 1,3-dipolar cycloaddition reactions of **8** with the corresponding α-chloro hydrazone precursor. Intramolecular cyclization/methylation of **9a** was achieved to afford spiropyrazolines **6a** and **7a** in 36% and 39% respective isolated yields which represents an overall 15% increase for the isolation of **6a** and **7a** arising from pyrazoline **3a**.[16] Improved overall isolated yields were realized for the syntheses of both regioisomers for other spiropyrazolines as shown in Scheme 4. Higher isolated yields for these spiropyrazolines likely result from decreasing the steric environment of the pyrazoline ester.[13b]



3 **4** **5** **6** **7**

Entry	Pyrazoline	Spiropyrazoline	R^1	R^2	% Yield	Ratio **6/7**
1	**3a**	**6a/7a**	H	H	61	37/24
2	**3b**	**6b/7b**	Cl	H	73	31/42
3	**3c**	**6c/7c**	H	Br	66	31/35
4	**3d**	**6d/7d**	H	Cl	55	31/24

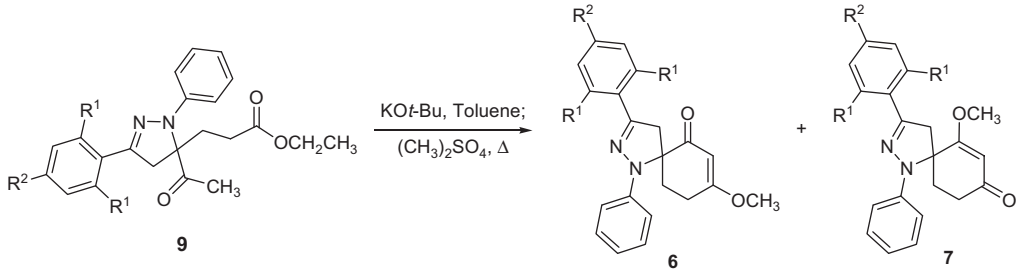
Scheme 2. Synthesis of spiropyrazoline regioisomers **6** and **7**.



8 **2** **9**

Entry	Pyrazoline	R^1	R^2	% Yield
1	**9a**	H	H	71
2	**9b**	Cl	H	76
3	**9c**	H	Br	78

Scheme 3. 5,5-Disubstituted pyrazolines isolated from the 1,3-dipolar cycloaddition reaction.



9 **6** **7**

Entry	Pyrazoline	Spiropyrazoline	R^1	R^2	% Yield	Ratio **6/7**
1	**9a**	**6a/7a**	H	H	75	36/39
2	**9b**	**6b/7b**	Cl	H	78	36/42
3	**9c**	**6c/7c**	H	Br	80	37/43

Scheme 4. Spiropyrazoline regioisomers **6** and **7** arising from the intramolecular cyclization/methylation reactions of **9**.

3. Conclusions

In conclusion, we have developed a synthetic methodology to construct unsaturated spiropyrazolines through an intramolecular cyclization/methylation process. 1,3-Dipolar cycloaddition of the functionalized alkene with nitrile imines led to the formation of the 5,5-disubstituted pyrazolines. The latter was used as the precursor to prepare the corresponding spiropyrazolines as two regioisomers through sequential intramolecular cyclization/methylation reactions. Future studies directed toward the synthesis of spiropyrazoline derivatives and other natural product analogues through intramolecular cyclization/methylation are currently in progress.

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15. *General procedure for the synthesis of [2+3]-cycloaddition products*: A solution of the functionalized alkene (3.0 mmol) and the hydrazonyl chloride (3.0 mmol) in 10 mL of either dry chloroform or dichloromethane was treated with triethylamine (0.463 mL, 3.3 mmol). The reaction mixture was stirred at rt until the disappearance of the starting materials, as evidenced by TLC. After the reaction was complete, the crude reaction mixture was concentrated, and the solvent was evaporated under reduced pressure. The crude products were purified by flash column chromatography over silica gel by using the appropriate hexanes–ethyl acetate ratio as an eluant system.
16. *General procedure for the intramolecular cyclization/alkylation*: To a solution of the cycloaddition product (1.0 mmol) in 15 mL of anhydrous toluene was added potassium *tert*-butoxide (6–8 mmol). The reaction mixture was then allowed to stir under anhydrous conditions until the disappearance of the starting materials, as evidenced by TLC. To this mixture was added 2 equiv of dimethyl sulfate (2 mmol, 0.186 mL), and the reaction mixture was heated to reflux temperature for 8 h under anhydrous conditions. The reaction mixture was later quenched with saturated ammonium chloride and extracted with EtOAc. The crude reaction mixture was concentrated, and the solvent was evaporated under reduced pressure. The crude products were purified by flash column chromatography over silica gel by using the appropriate hexanes–ethyl acetate ratio as an eluant system.
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