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Synthesis and Tautomerism of Spiro-Pyrazolines

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Abstract

An experimental study on the synthesis, tautomerism and acid promoted structural changes of spiro-pyrazolines is described. The target was achieved through a [3+2]-dipolar cycloaddition of an alkene with nitrile imines generated *in situ* and was isolated in high yield. The synthesized cycloadduct displayed a tendency to exhibit an imine-enamine type of tautomerism as evidenced by X-ray crystal and NMR studies. Furthermore, addition of an acid resulted in the transformation of an imine tautomer to an enamine. The current report constitutes a first formal observation of this kind of tautomerism observed in spiro-indoline pyrazolines.

Keywords

Spiro-isoxazolines; Spiro-pyrazolines; 1,3-Dipolar Cycloaddition; Tautomerism; Heterocycles; Indolines; Regioselectivity

1. Introduction

Spiro-isoxazolines¹⁻³ and spiro-pyrazolines^{4,5} are of recurring interest to the chemists engaged in the drug-discovery areas of natural product synthesis and heterocyclic methodology development. These compounds incorporate useful isoxazole⁶ or pyrazole⁷ based motifs in their core structures and are junctioned to another carbocyclic/heterocyclic ring at one carbon atom. When compared to spiro-isoxazolines, spiro-pyrazolines, isosterically equivalent to spiro-isoxazolines where the nitrogen replaces the oxygen, are structurally rigid and present the flexibility for possible synthetic and biological property exploration.⁵ In addition to the synthesis of pyrazoles and pyrazoline derivatives, tautomerism is another area of equal interest due to their high application potential in biological systems, chemical reactivity, and molecular recognition.⁸⁻¹⁰ Although, the importance of tautomerism (imine-enamine) has been described very well for pyrazole related ring systems,⁹⁻¹¹ it's rarely observed in analogous spiro-pyrazolines. As of today, only three reports exist on the structural changes observed in spiro-pyrazolines.¹²

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Our long standing interest in this area resulted in the establishment of efficient strategies for the construction of architecturally complex natural product analogues and bioactive heterocycles of synthetic and biological interest.^{5,6d,7g,13,14} In addition to methodology development, we are also equally interested in assessing structural and biological applications for spiro-pyrazolines. Recently, we demonstrated the construction of 1,3,5-trisubstituted pyrazoles on the basis of the 1,3-dipolar cycloaddition protocol, which was then followed by an unforeseen ring fragmentation/elimination.¹⁴ We observed that the placement of an electron-rich or electron-deficient substituents of the aromatic ring at *ortho*-, *meta*-, and *para*-positions is crucial for the identity of the final product (pyrazole or spiro-pyrazoline). Additionally, we also postulated a mechanism based on the occurrence of an imine-enamine type of tautomerism and the factors leading to pyrazole formation rather than the anticipated spiro-pyrazoline (Scheme 1). Based on these observations, we decided to extend the investigation of this protocol for the preparation of a spiro-pyrazoline with an electron rich *para*-methoxy group on the aromatic ring. Herein, we present results from our ongoing research highlighting the first imine-enamine type of tautomerism observed in spiroindoline-pyrazolines.

2. Results and discussion

During our studies toward synthesizing spiro-pyrazolines, we discovered that when 1,3,3-trimethy-2-methylenelindoline (**1**) was used as the dipolarophile, spiro-pyrazoline **6** was the only product isolated. The cycloaddition process^{7g,14-16} leading to the desired spiro-pyrazoline **6**¹⁷ formation occurred with complete regiochemical integrity and in good isolated yield (Scheme 2). While assessing the NMR spectrum of the synthesized spiro-pyrazoline **6**, we observed an inconsistency with respect to the diastereotopic methylene protons. The inconsistency with the methylene protons suggested the need for a detailed NMR study in selected solvents and data comparison of the reported spiro-pyrazolines. The spiro-pyrazoline **6** was subjected to NMR studies in chloroform-*d* and benzene-*d*₆ solvents.¹⁸ The ¹H NMR spectra clearly evidenced the spiro-pyrazoline to exist as imine **6** and enamine tautomer **7** in benzene-*d*₆ and chloroform-*d* solvents respectively. The enamine tautomer **7** (CDCl₃) displayed the enamine (CH=C-NH) proton (multiplet) peak at δ 4.15-4.17 ppm, and the imine tautomer (C₆D₆) **6** displayed the desired diastereotopic proton (C=N-CH₂-) doublets at δ 3.00 and 3.4 ppm (Scheme 3).

Additional DEPT-135 studies in benzene-*d*₆ solvent concluded the methylene peak at δ 39.8 ppm facing downward demonstrating the occurrence of spiro-pyrazoline as the imine **6**. Furthermore, the observed methylene peak was absent when the study was repeated in chloroform-*d*. This type of observed tautomerism is the first of its kind and to our knowledge, only Toth's research group has documented similar results exhibited by spirochromone-pyrazolines.¹² The existence of a spiro-pyrazoline as imine **6** and enamine **7** tautomers in chloroform and benzene solvents is depicted in Figure 1 where the imine tautomer is slightly yellow in C₆D₆. However, the enamine tautomer exists as a reddish-pink colored compound in CDCl₃.

Gratifyingly, the existence of spiro-pyrazoline **6** as a crystalline solid enabled us to perform X-ray studies to reveal compound's regio-structural features.¹⁹⁻²¹ Compound **6**

(C₂₆H₂₇N₃O) was unambiguously confirmed by the X-ray structural analysis and revealed the presence of –CH₂–group at C15 carbon position, which provided the necessary evidence to show that the compound exists in the form of an imine (CH₂–C=N) tautomer as a major conformer in the solid state. The ORTEP rendition of the crystal structure of **6** is as shown in Figure 2.

Our next idea was to spectroscopically observe any structural changes that the spiro-pyrazoline would undergo from imine to enamine, or enamine to imine, in the presence of a proton source. We hypothesized that an acidic environment would provide a proton source in C₆D₆ that would change the favored tautomer from the imine to the analogous enamine. Previous reports described the addition of an trifluoroacetic acid (TFA) resulted in structural changes and indicated the transformation from an imine to an enamine.^{12c} On the basis of this information, we decided to introduce TFA to the aforementioned NMR study in order to determine whether TFA would trigger any structural changes of spiro-pyrazoline **6** in chloroform-*d* and benzene-*d*₆ solvents.²² Upon addition of TFA, the desired structural changes were observed and clearly the anticipated transformation from imine **6** to enamine **7**, that is in accordance with literature precedent, was observed.²³ The two characteristic doublets at δ 3.00 and 3.4 ppm that were characteristic of the diastereotopic protons (C=N–CH₂–) observed before TFA addition completely disappeared, and an extra peak toward NH proton appeared at δ 1.59 ppm. However, no potential change in tautomerism was observed when TFA was added to sample **7** that was dissolved in chloroform-*d*. The most likely reason for the aforementioned behavior is attributed to the relative stability and extended conjugation of one tautomer over the other under acidic conditions. However, the acidic nature of CDCl₃ or commercial trifluoroacetic acid that served as a proton source to bring the anticipated transformation remains inconclusive at this stage. The acid promoted imine-enamine tautomerism of the spiro-pyrazoline is shown in Scheme 4.

3. Conclusions

In summary, the *p*-methoxyphenyl spiro-pyrazoline was synthesized via [3+2]-dipolar cycloaddition of the indoline dipolarophile with the corresponding hydrazonyl chloride. The synthesized spiro-pyrazolines exhibited imine-enamine type of tautomerism as evidenced by Xray crystal and NMR studies. Furthermore, evidence of the imine-enamine tautomerism in our spiro-pyrazolines provides credence for the tautomerism based mechanistic postulation for the spiro-pyrazoline ring fragmentation that leads to the corresponding pyrazole.

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References

1. (a) Berquist, PR.; Wells, RJ. Chemotaxonomy of the Porifera: The Development and Current Status of the Field. In: Scheuer, PJ., editor. Marine Natural Products: Chemical and Biological

- Perspectives. Vol. 5. Academic Press; New York: 1993. p. 1-50.(b) Faulkner DJ. Nat Prod Rep. 1998;113. [PubMed: 9586223]
2. (a) Berquist, PR.; Wells, RJ. Marine Natural Products. Scheuer, PJ., editor. Vol. V. Academic Press; New York: 1983. Chapter 1(b) Smietana M, Gouverneur V, Mioskowski C. Tetrahedron Lett. 1999; 40:1291.
3. (a) Adamo MFA, Chimichi S, De Sio F, Donati D, Sarti-Fantoni P. Tetrahedron Lett. 2002; 43:4157.(c) Harburn JJ, Rath NP, Spilling CD. J Org Chem. 2005; 70:6398. [PubMed: 16050702] (d) Adamo MFA, Donati D, Duffy EF, Sarti-Fantoni P. J Org Chem. 2005; 70:8395. [PubMed: 16209583] (e) Savage GP. Curr Org Chem. 2010; 14:1478.(f) Dadiboyena S. Curr Org Synth. 2013; 13:661.(g) Marsini MA, Huang Y, Van De Water R, Pettus TRR. Org Lett. 2007; 9:3229. [PubMed: 17645344] (h) Wasserman HH, Wang J. J Org Chem. 1998; 63:5581.(i) Boehlow TR, Harburn JJ, Spilling CD. J Org Chem. 2001; 66:3111. [PubMed: 11325276] (j) Forrester AR, Thomson RH, Woo SO. Liebigs Ann Chem. 1978;66.(k) Murakata M, Yamada K, Hoshino O. J Chem Soc, Chem Commun. 1994;443.(l) Singh V, Yadav GP, Maulik PR, Batra S. Tetrahedron. 2008; 64:2979.
4. (a) Singh A, Roth GP. Organic Lett. 2011; 13:2118.(b) Dawood KM, Fuchigami T. J Org Chem. 2005; 70:7537. [PubMed: 16149781] (c) Singh V, Singh V, Batra S. Eur J Org Chem. 2008;5446. (d) Dawood K. Tetrahedron. 2005; 61:5229.(d) Dadiboyena S. Eur J Med Chem. 2013; 63:347. [PubMed: 23517727] (e) Kerbel A, Vebrel J, Roche M, Laude B. Tetrahedron Lett. 1990; 31:4145. (f) Jedlovska E, Levai A, Toth G, Balazs B, Fisera L. J Heterocycl Chem. 1999; 36:1087.
5. Dadiboyena S, Hamme AT II. Tetrahedron Lett. 2011; 52:2536. [PubMed: 21686095]
6. For isoxazoles, see: Waldo JP, Larock RC. Org Lett. 2005; 23:5203. [PubMed: 16268538] Grecian S, Fokin VV. Angew Chem, Int Ed. 2008; 47:8285.Crossley JA, Browne DL. J Org Chem. 2010; 75:5414. [PubMed: 20608670] Dadiboyena S, Xu J, Hamme AT II. Tetrahedron Lett. 2007; 48:1295. [PubMed: 18265873] Dadiboyena S, Nefzi A. Tetrahedron Lett. 2012; 53:2096. [PubMed: 22715296] Dadiboyena S, Nefzi A. Eur J Med Chem. 2010; 45:4697. [PubMed: 20724040] Lee CC, Fitzmaurice RJ, Caddick S. Org Biomol Chem. 2009; 7:4349. [PubMed: 19830280]
7. For pyrazoles, see: Browne DL, Helm MD, Plant A, Harrity JPA. Angew Chem Int Ed. 2007; 46:8656.Browne, DL; Viva, JF.; Plant, A.; Gomez-Bengoa, E.; Harrity, JPA. J Am Chem Soc. 2009; 131:7762. [PubMed: 19449876] Deng X, Mani NS. Org Lett. 2008; 10:1307. [PubMed: 18302402] Dadiboyena S, Hamme AT II. Curr Org Chem. 2012; 16:1390.Dadiboyena S, Nefzi A. Eur J Med Chem. 2011; 46:5258. [PubMed: 21978837] Janin YL. Chem Rev. 2012; 112:3924. [PubMed: 22548590] Dadiboyena S, Valente EJ, Hamme AT II. Tetrahedron Lett. 2010; 51:1341. [PubMed: 20161634] Browne DL, Harrity JPA. Tetrahedron. 2010; 66:553.Oh L. Tetrahedron Lett. 2006; 47:7943.
8. (a) Zheng Z, Yu Z, Luo N, Han X. J Org Chem. 2006; 71:9695. [PubMed: 17168587] (b) Dardonville C, Elguero J, Rozas I, Fernandez-Castano C, Foces-Foces C, Sobrados I. New J Chem. 1998;1421.(c) Kwiakowsky JS, Pullman B. Adv Heterocycl Chem. 1975; 18:199.
9. (a) Sanguinet L, Pozzo J. J Phy Chem B. 2005; 109:11139.(b) Guimon C, Pfister-Guillouzo G, Begtrup M. Can J Chem. 1983; 61:1197.(c) Abdel-Wahab BF, Dawood KM. Arkivoc. 2012:491.
10. Elguero, J.; Marzin, C.; Katrizky, AR.; Linda, P. The Tautomerism of Heterocycles. Academic Press; New York: 1976.
11. Hadda TB, Ali MA, Masand V, Gharby S, Fergoung T, Warad I. Med Chem Res. 2013; 22:1438.
12. (a) Toth G, Levai A, Dinya Z, Snatzke G. Tetrahedron. 1991; 47:8119.(b) Toth G, Levai A, Szollosy A, Duddeck H. Tetrahedron. 1993; 49:863.(c) Toth G, Levai A, Duddeck H. Mag Res Chem. 1992; 30:235.
13. (a) Ellis ED, Xu J, Valente EJ, Hamme AT II. Tetrahedron Lett. 2009; 50:5516. [PubMed: 20160942] (b) McClendon E, Omollo AO, Valente EJ, Hamme AT II. Tetrahedron Lett. 2009; 50:533. [PubMed: 20140060] (c) Dadiboyena S, Hamme AT II. Eur J Org Chem. 2013:7567.
14. Dadiboyena S, Valente EJ, Hamme AT. Tetrahedron Lett. 2009; 50:291. [PubMed: 20098488]
15. (a) Huisgen R. Angew Chem, Int Ed Engl. 1963; 2:565.(b) Huisgen R. Angew Chem, Int Ed Engl. 1963; 2:633.
16. *General Procedures for the 1,3-Dipolar Cycloaddition:* A solution of the 1,3,3-trimethy-2-methylenelindoline (3 mmol) and the hydrazonyl chloride (3 mmol) in 10 mL of either dry chloroform or dichloromethane was treated with triethylamine (334 mg, 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, a minimum amount of silica gel was added, and the solvent was evaporated under reduced pressure. The crude products were purified by flash column chromatography over silica gel using hexanes-ethyl acetate (8:2) ratio as an eluant system.

17. *Representative NMR data of 5'-(4-methoxyphenyl)-1,3,3-trimethyl-2'-phenyl-2',4'-dihydrospiro[indoline-2,3'-pyrazole] (6)*: After column chromatography, this compound was obtained as light purple solid (Yield: 68%, 0.81g), mp 112-115°C; IR (CaF₂, CCl₄) ν 2969, 2933, 1603, 1514, 1428 cm⁻¹. ¹H NMR (imine form **6**, C₆D₆): δ 1.10 (s, 3H), 1.29 (s, 3H), 2.25 (s, 3H), 3.03 (d, *J* = 18.2 Hz, 1H), 3.32 (s, 3H), 3.40 (d, *J* = 18.2 Hz, 1H), 6.09 (d, *J* = 7.6 Hz, 1H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.76-6.94 (m, 4H), 7.03-7.22 (m, 5H), 7.72 (d, *J* = 8.8 Hz, 2H); ¹³C NMR: δ 29.1, 31.3, 39.8, 55.1, 100.6, 104.8, 114.6, 118.6, 118.8, 120.8, 121.8, 126.2, 127.5, 129.8, 141.8, 147.3, 150.8, 153.2, 160.8; (Enamine form **7**, CDCl₃): δ 1.67 (s, 6H), 2.70 (d, *J* = 5Hz, 3H), 3.85 (s, 3H), 4.14 (br s, 1H), 6.39 (t, *J* = 7.8Hz, 1H), 6.51 (d, *J* = 8Hz, 1H), 6.66 (d, *J* = 8 Hz, 1H), 6.72 (s, 1H), 6.79 (d, *J* = 7.8 Hz, 2H), 6.93-7.21 (m, 6H), 7.82 (d, *J* = 8.8 Hz, 2H); ¹³C NMR: δ 28.9, 31.1, 38.1, 55.6, 100.6, 110.7, 114.3, 116.7, 125.9, 126.1, 127.2, 128.1, 128.2, 128.2, 128.7, 129.5, 140.4, 147.3, 150.7, 152.8, 159.8; HRMS (EI): *m/z* calcd for C₂₆H₂₇N₃O (MNa⁺): 420.2046; found: 420.2040.
18. NMR study: ~4-5mg of spiro-pyrazoline was dissolved in 0.5mL of the selected solvent.
19. Sheldrick, GM. SHELXS86. Crystallographic Computing 3. Sheldrick, GM.; Kruger, C.; Goddard, R., editors. Oxford University Press; 1985. p. 175-189.
20. Sheldrick, GM. SHELX97 [Includes SHELXS97, SHELXL97, CIFTAB]. Programs for Crystal Structure Analysis (Release 97-2). Institut für Anorganische Chemie der Universität; Tammanstrasse 4, D-3400 Göttingen, Germany: 1998.
21. Structural information for spiro-pyrazoline (**6**) has been deposited with the CCDC as 701051, available free of charge from www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033).
22. The study was carried out in NMR tubes. Commercial TFA and NMR solvents were utilized without any purification.
23. When 2-3 drops of commercial TFA was added dropwise to chloroform-*d* and benzene-*d*₆ samples containing the spiro-pyrazoline, the tautomerism from imine **6** to enamine **7** was clearly observed in benzene-*d*₆. Admixtures of C₆D₆ and CDCl₃ weren't performed as part of this study.

Figure 1.
Spiro-pyrazoline existence as imine (left: benzene) and enamine (right: chloroform) tautomer.

Figure 2.
Thermal ellipsoid plot of spiro-pyrazoline **6**.

Scheme 1. Pyrazole synthesis from the spiro-pyrazoline intermediate **3**.

Scheme 2.

Spiro-pyrazoline isolated from 1,3-dipolar cycloaddition.

Scheme 3.

Enamine-imine tautomerism exhibited by spiro-pyrazoline in chloroform-*d* and benzene-*d*₆ solvents.

Scheme 4.

TFA promoted structural transformation of spiro-pyrazoline **6** in benzene- d_6 and chloroform- d solvents.