Synthesis of Enaminones with Stationary Stereochemistry

Alberto Wisniewski Junior, Alfredo R.M. Oliveira, Carlos Jorge da Cunha, Fabio Simonelli and Francisco A. Marques*

Departamento de Química, Universidade Federal do Paraná, C.P. 19081, 81531-990 Curitiba - PR, Brazil

Five enaminones 4a-e, derived from the reaction of the anion of 2,4,4-trimethyl-2-oxazoline with ethyl acetate, ethyl benzoate, ethyl cyclohexanoate, ethyl hexanoate and ethyl p-methyl benzoate, respectively, were obtained and characterized by 13C-NMR, 1H-NMR, FTIR, and mass spectral analysis. The enaminones 4a and 4b were also analysed by X-ray diffraction. Enaminone 4a crystallized in the monoclinic P2(1)/n space group with a = 9.1450(20) Å, b = 10.5150(20) Å, c = 9.5670(20) Å, \( \beta = 106.21(30)^\circ \), Z = 4. Enaminone 4b crystallized in the monoclinic P2(1)/c space group with a = 16.0520(30) Å, b = 26.0460(50) Å, c = 12.3520 (20) Å, \( \beta = 111.900(30)^\circ \), Z = 4. All five enaminones were found to have an extensive \( \pi \) electron delocalization and to have the same configuration where the double bond is trapped by an internal hydrogen bond between the NH and the C=O.

Keywords: enaminones, 2-oxazolines, intramolecular hydrogen bonding

Introduction

As part of our ongoing work exploring the chemistry of 2-oxazolines\(^1\) we became interested in the preparation of chiral \( \beta \)-hydroxy-2-oxazolines \( \text{II} \) since enantiomerically pure secondary alcohols are useful chiral auxiliaries in organic chemistry both for analytical and synthetic applications\(^2\). In particular the oxazoline moiety of these compounds could easily be converted into other functional groups such as carboxylic acids, alcohols, aldehydes, among others\(^3\), increasing its value as chiral synthons to be applied in organic synthesis.

Chiral secondary alcohols have been mainly obtained from the corresponding ketones by asymmetric hydrogenation\(^4\), by treatment with a hydride reagent modified with a chiral auxiliary\(^4\), or by microbial reduction with baker’s yeast\(^5\) or other microorganisms\(^6,7\). We have chosen to prepare the desired \( \beta \)-hydroxy-2-oxazolines by asymmetric reduction of \( \beta \)-keto-2-oxazolines with baker’s yeast. In an attempt to prepare \( \beta \)-keto-2-oxazolines, we have obtained isomeric enaminones, instead. The present work describes the synthesis and characterization of five such enaminones.

Experimental

General

Nuclear magnetic resonance (NMR) spectra were recorded in CDCl\(_3\) with a Bruker AC-400 or with a Varian...
n-Butyllithium in hexane (13.6 mL, 22 mmol) was added dropwise at -78 °C to a solution of 2,4,4-trimethyl-2-oxazoline (2.486 g, 22 mmol) in dry THF (20 mL), under nitrogen. After stirring for 30 minutes, the resulting solution was added, at -10 °C, to a round bottom flask containing ethyl acetate (3.872 g, 44 mmol) in dry THF (10 mL). The chilling bath was removed and the reaction mixture was stirred for 30 min at room temperature. Water was added to the reaction flask up to the formation of an emulsion, which was dried over anhydrous Na2SO4. After filtration, the solvent was removed under reduced pressure yielding 2.25 g (66%) of enaminone 4a as representative.

Typical procedure for the preparation of enaminone 4a as representative

The cartesian coordinates of molecule 4a were obtained from X-ray data (present work) and converted to a format compatible with Hyperchem8. Mulliken charges9 were calculated using the semi-empirical INDO model10 built in the Hyperchem package8.

Heats of formation

The three isomeric molecules, β-keto-oxazoline 5a, enaminone 4a in configurations Z and E were built and geometry optimized with the AM1 model11 in the Hyperchem program9. The heats of formation of each optimized structures were calculated. The Z configuration of 4a had to be constrained.

Crystallographic studies

Each crystal of enaminones 4a and 4b was mounted on the goniometer head of an Enraf-Nonius CAD4 diffractometer and the data were collected at 293(2) K using a highly oriented graphite monochromator and MoKα radiation 0.71073 Å. A summary of data collection and refinement12 can be seen in Table 1. No absorption corrections were made because the absorption coefficients were low in

Theoretical Calculations

Atomic charges

Heats of formation

Crystallographic studies

Each crystal of enaminones 4a and 4b was mounted on the goniometer head of an Enraf-Nonius CAD4 diffractometer and the data were collected at 293(2) K using a highly oriented graphite monochromator and MoKα radiation 0.71073 Å. A summary of data collection and refinement12 can be seen in Table 1. No absorption corrections were made because the absorption coefficients were low in
both cases. The structures were solved by direct methods using the program SHELXS-97\(^{13}\) which revealed the positions of most of the heavy atoms, the remaining heavy atoms were located in successive refinement cycles using the program SHELXL-97\(^{13}\). Drawings were made with the program ZORTEP-II\(^{14}\). The asymmetric unit in the crystal of 4a corresponds to only one enaminone molecule whereas that of 4b is composed of four enaminone molecules (labeled A, B, C and D) and half water molecule of crystallization. The water molecule present in 4b was refined with 50% site occupancy. Hydrogen atoms were added in idealized positions and labeled according to the numbering of the heavy atoms attached to them (Fig. 2). No hydrogen atoms were added to the water oxygen atom. All heavy atoms were refined anisotropically in the last full matrix refinement, and no geometrical constraints were used. The hydrogen atoms were refined using a riding model.

**Results and Discussion**

**Synthesis and spectroscopy**

When anion 3 was allowed to react with an ester, a mixture of two compounds 4 and 5 was obtained, the major one being 4 (>93%) showing the migration of the double bond as determined by \(^1\)H-NMR analysis (Scheme 1).

The intriguing presence of only one signal characteristic of vinylic hydrogen in the \(^1\)H-NMR spectrum of each of the five reaction mixtures indicates that the stereochemistry of the double bond of the enaminones was stabilized in one of the two possible configurations. Also intriguing were the chemical shifts of the two vinylic carbon atoms C(2) and C(8) at around 168 and 75 ppm (Table 2) where the former is less shielded and the latter is more shielded than regular vinylic carbon atoms\(^{15}\). The calculated Mülliken charges (enaminone 4a) of atom C(2) is much more positive than that of C(8) (Table 2) in accordance with the observed \(^13\)C-NMR shifts. This fact suggests that there exists a charge unbalance on these carbon atoms. The more shielded carbon atom must be acquiring an extra charge due to a π conjugation whereas the less shielded one must be losing charge due to inductive effects of the bound nitrogen and oxygen atoms.

The C=O stretching frequency of all five enaminones lies between 1614 and 1637 cm\(^{-1}\) and that of C=C lies between 1532 and 1570 cm\(^{-1}\) and are characteristic of systems with extended π conjugation\(^{16}\).

A peak at around 140 m/z was located in the mass spectra of all five enaminones and was assigned to their common segment left after the loss of the different R

---

**Table 1. Crystallographic data for enaminones 4a and 4b.**

|          | 4a                                      | 4b                                      |
|----------|-----------------------------------------|-----------------------------------------|
| Formula of the asymmetric unit | C\(_8\)H\(_{13}\)NO\(_2\) | (C\(_{13}\)H\(_{15}\)NO\(_2\))\(_4\) 0.5(H\(_2\)O) |
| Crystal system, space group | monoclinic, P 2(1)/n | Monoclinic, P 2(1)/c |
| a (Å)    | 9.145(2) | 16.052(3) |
| b (Å)    | 10.515(2) | 26.646(5) |
| c (Å)    | 9.567(2) | 12.352(2) |
| β (degree) | 106.21(3) | 111.90(3) |
| Volume (Å\(^3\)) | 883.4(3) | 4902.0(15) |
| Z, calculated density | 4, 1.167 g/cm\(^3\) | 4, 1.190 g/cm\(^3\) |
| Reflections collected/unique | 1652 / 1548 [R(int) = 0.0128] | 8737 / 8330 [R(int) = 0.0221] |
| final R indices [I > 2 sigma(I)] | R1 = 0.0495 wR2 = 0.1385 | wR2 = 0.1385 |
| R indices (all data) | R1 = 0.0696 wR2 = 0.1614 |
| Absorption coefficient (mm\(^{-1}\)) | 0.084 | 0.081 |

---

![Scheme 1.](image-url)
substituents. It was observed that for nonaromatic R substituted molecules this peak was much more abundant than for the aromatic ones.

**Crystal structure**

In order to assign the stereochemistry of the double bond, it was decided to determine the crystal structures of enaminones 4a and 4b whose single crystals were obtained by dropwise addition of hexane to a warm solution of these compounds in ethyl acetate.

To follow the discussion below please refer to Tables 1 and 3 and to Fig. 2. The asymmetric unit of the single crystal of 4b has four enaminone molecules (labeled A, B, C and D) whereas that of 4a has only one. The intermolecular dihedral angle between the phenyl and the heterocyclic ring planes is 28.99(0.16), 20.15(0.12), 9.44(0.34) and 18.12(0.33) degrees for enaminone 4b molecules A, B, C and D, respectively. Despite this dihedral angle differences the other structural parameters are quite similar for all four molecules. These packing characteristics are responsible for the high cell volume exhibited by the crystal of 4b as compared to that of 4a.

Enaminones 4a and 4b have configuration E that is favored over the Z due to the intermolecular hydrogen bonding N(3)-H(3)---O(10). From the bond order assignments\textsuperscript{17,18} given in Table 3 one can infer that the lone electron pairs of the nitrogen and oxygen atoms are conjugated with the adjacent π system that extends over atoms N(3), C(2), O(1), C(8), C(9) and O(10).

The torsion angle formed by N(3)-C(2)-C(8)-C(9) is less than 6°, in both structures, revealing that this part of the molecule is almost flat in accordance with the proposed extended π delocalization.

In crystals 4a and 4b there are also intermolecular hydrogen bondings between the H(3) and O(10). In 4a this intermolecular contact is 2.13 Å whereas in 4b it ranges from 2.17 to 2.28 Å. In 4a the intermolecular hydrogen bonding distance is shorter than the intramolecular one indicating that this kind of interaction plays an important role in the crystal packing.

![Figure 2](image-url). Ortep drawing of enaminones 4a and 4b (molecule A). Thermal ellipsoids are drawn to the 50% level. Hydrogen labels are not shown, except H(3). The dashed lines indicate the intramolecular hydrogen bonding.
Relative thermodynamic stability

The methyl substituted system 4a was selected as a representative of the series for the estimation of the relative stability of isomers β-keto-2-oxazoline and enamino in configurations E and Z.

The calculated heat of formation of enamino 4a in the E configuration is 23.3 kJ/mole lower than that for the β-keto-2-oxazoline 5a in accordance with their relative abundance in solution as observed in the 1H-NMR spectrum. The calculated heat of formation of the E isomer of 4a is 26.4 kJ/mole lower than that for the Z isomer suggesting that the former is thermodynamically favored, as observed in the crystal structure of enamino 4a.

Conclusion

In an attempt to prepare five β-keto-2-oxazolines by the reaction of 2,4,4-trimethyl-2-oxazoline anion with five esters we have obtained the isomeric enamino instead. The reaction of 2,4,4-trimethyl-2-oxazoline anion with five esters was analysed by single crystal X-ray diffraction and one of them was subjected to theoretical calculations.

The common segment of two enamino molecules have quite similar crystal structural parameters and correspond to the E configuration of the double bond. The NMR shifts of the carbon and hydrogen atoms of the common segment of the five enamino are also alike. These two analyses allowed us to conclude that the common segment has similar electronic structure and that the double bond is in the E configuration in all five enamino.

The double bond is stabilized in the configuration E due to the internal hydrogen bond, N-H---O=C, either in the solid state or in a non polar solvent such as chloroform. Analogous compounds were reported to show this behavior. The calculated heat of formation of the enamino E is lower than those of enamino Z and β-keto-2-oxazoline molecules, in agreement with the experimental evidence.

From the analysis of bond orders (based on bond lengths), 13C chemical shifts, and C=O, C=C stretching frequencies, it was possible to detect an extensive delocalization of the lone electron pairs of the enamino nitrogen and oxygen atoms over the adjacent vinyl and carbonyl π system.

Considering that the enamino and the β-keto-2-oxazoline forms could be in equilibrium in solution it might be possible to reduce them with baker’s yeast to the β-hydroxy-2-oxazoline form. This possibility is currently being tested.

Supplementary Material

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic data Center as supplementary publication CCDC, 116080 (enamino 4a), 116081 (enamino 4b).

Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax + 44 1223 336033) or e-mail deposit@ccdc.cam.ac.uk

Acknowledgments

We thank FUNPAR, CNPq/PADCT for financial support, to Prof. Ivo Vencato, Analytical Center of UFSC for the collection and interpretation of crystal data. We also thank Prof. J.D. da Motta from DQUI-UFPR for his support in theoretical calculations.

References

1. a) Simonelli, F.; Oliveira, A.R.M.; Marques, F.A.; Gomes, A.L.; Echterhoff, M.R.F.; Santos, A.A. Abstracts of the 18th Annual Meeting of the Brazilian Society of Chemistry 1995, QQ 086; b) Oliveira, A.R. M.; Marques, F.A.; Simonelli, F.; Santos, A.A.; Abstracts of 8th Brazilian Meeting on Organic Synthesis 1998, PS-031, p 78.
2. Morrison, J.D. Asymmetric Synthesis: Academic Press: 1984.
3. Frump, J.A. Chem. Rev. 1971, 71, 483.
4. Nogradi, M. Stereoselective Synthesis: VCH: 1986. Chapt. 2 and 3.
5. a) Servi, S. Synthesis 1990, 1; b) Csink, R.; Glanzer, B.I. Chem. Rev. 1991, 91, 49.
6. a) Akita, H.; Furuichi, A.; Koshiji, K.; Oishi, T. Tetrahedron Lett. 1982, 23, 4051; b) Horikoshi, K.; Furuki, A.; Koshiji, K., Akita, H.; Oishi, T. Agric. Biol. Chem. 1983, 47, 435.
7. Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P.; Poli, S.; Gardini, F.; Guerzoni, M.E. Tetrahedron: Asymmetry 1991, 2, 243.
8. Hyperchem Program Version 4.5, Hypercube Inc., Gainesville, Florida, USA.
9. Szabo, A.; Ostlund, N.S. In Modern Quantum Chemistry McGraw Hill, 1st Edition, 1989.
10. Pople, J.A.; Beveridge, D.; Dobosh, P. J. Chem. Phys. 1967, 47, 2026.
11. Dewar, M.J.S.; Zoebish, E.G.; Healy, E.F. J. Am. Chem. Soc., 1985, 107, 3902.
12. Enraf-Nonius. CAD-4 Express Software. Version1.1. Enraf-Nonius, Delft, The Netherlands, 1993.
13. Sheldrick, G.M. SHELX-97. Program for the Refinement and Solution of Crystal Structures. Univ. of Göttingen.
14. Zsolnai, L. ZORTEP. An Interactive ORTEP Program; University of Heidelberg, Germany.
15. Breitmaier, E.; Voelter, W. In *Carbon-13 NMR Spectroscopy: High Resolution Methods and Applications in Organic Chemistry and Biochemistry*; VCH: Weinheim, 3rd Edition, 1987.

16. Silverstein, R.M.; Bassler, G.C.; Morrill, T.C. In *Spectrometric Identification of Organic Compounds*, John Wiley & Sons, 5th Edition, 1991.

17. Cunha, C.J. da; Fielder, S.S.; Stynes, D.V.; Masui, H.; Auburn, P.R.; Lever, A.B.P. *Inorg. Chim. Acta* **1996** 242, 293.

18. Wycoff, R.W.G. In *Crystal Structures*; John Wiley & Sons; 2nd Edition, 1969.

19. Dixit, A.N.; Reddy, K.V.; Deshmukh, A.R.A.S.; Rajappa, S.; Ganguly, B.; Chandrasekhar, J. *Tetrahedron* **1995**, 51, 1437 and references cited therein.

*Received: March 26, 1999*