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# Stereochemical studies of 5-methyl-3-(substituted phenyl)-5-[(substituted phenyl) hydroxy methyl]-2-thiooxazolidin-4-ones

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ABSTRACT

The synthesis and stereochemical aspects of the aldol products, 5-methyl-3-(substituted phenyl)-5-[(substituted phenyl) hydroxy methyl]-2-thiooxazolidin-4-ones, are discussed.



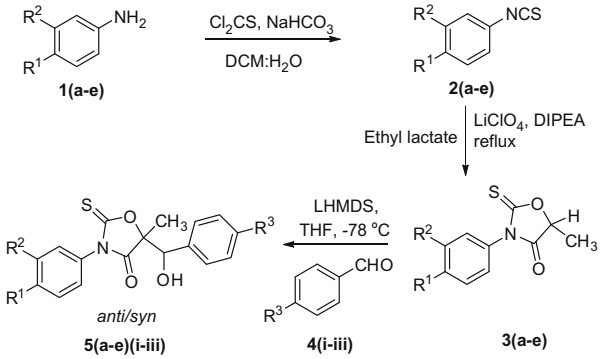
## 1. Introduction

Many drugs/intermediates contain oxazolidinones and thiooxazolidinones as an integral part of their skeleton.[1,2] Thiooxazolidinone scaffolds are known for various biological activities, such as antidiabetics,[2] potassium channel openers,[3] and anticonvulsants.[4] They are also employed as chiral directing agents in asymmetric synthesis.[5,6] Our investigations on these substrates were mainly directed to study the aldol reactions, ascertain the extent of diastereoselectivity, and determine the stereochemical configurations at the newly generated chiral centers.

Aryl isothiocyanates **2**(**a**–**e**), prepared by treating various anilines **1(a–e)** with thiophosgene and sodium hydrogen carbonate in dichloromethane-water medium,[7] were converted into 5-methyl-3-aryl-2-thiooxazolidin-4-ones **3(a–e)** by treating with ethyl lactate and $LiClO_4$ in DIPEA-mediated cyclization.[8] The 3-aryl-2-thiooxazolidin-4-ones were subjected to aldol reactions with 4-halobenzaldehydes **4(i–iii)** by in situ generation of enolates using LHMDS to obtain 5-methyl-3-(substituted phenyl)-5-[(substituted phenyl) hydroxy methyl]-2-thiooxazolidin-4-ones **5**(**a**–**e**)(**i**–**iii**) (Scheme 1).

As a model reaction, 5-methyl-3-(4-fluorophenyl)-2-thiooxazolidin-4-one **3(a)** when subjected to aldol reaction with benzaldehyde **4(iv)** afforded the diastereomers of the aldol product in the ratio of 60:40 as determined from $^1$H NMR by comparing the integration values of characteristic methyl protons.[9] Further examination of the $^1$H NMR spectra of isolated diastereomers revealed that in the case of one diastereomer **5(a)(iv)** the methyl protons at C5 appeared shielded as indicated by the relative upfield signal at 1.54 ppm, whereas for the other isomer **5′**(**a**)(**iv**) the methyl protons were deshielded and appeared downfield at 1.88 ppm (Scheme 2). Therefore it may be assumed that the diastereomer **5(a)(iv)** for which the methyl protons appeared shielded would be the *anti* isomer, where the methyl shares a *syn* relation with the phenyl group and *anti* relation with the hydroxy group, while the diastereomer **5′(a)(iv)** with methyl protons deshielded would be the *syn* isomer with the phenyl and the hydroxy groups oriented *anti* and *syn*, respectively. This assumption was further supported by the observance of spatial interaction between the hydroxy and methyl groups in the *syn* isomer as revealed by the ROESY spectra (Fig. 1) and its absence in the *anti* isomer. A similar difference in chemical shifts of the methyl protons was observed for the *syn* and *anti* diastereomers in the case of other aldol adducts also (Table 1). Thus the aldol reactions of 2-thiooxazolidin-4-ones with 4-halobenzaldehydes afforded *anti* isomer as the major product (Table 2), which is widely the case observed with enolates of cyclic and acyclic systems with *E*-geometry.[9,10]

To obtain a better perspective on the stereochemical orientation, computational studies[11] were carried out. The most stable conformations of the *anti* and *syn* aldol isomers were identified




**Scheme 1.** Synthesis of 5-methyl-3-(substituted phenyl)-5-[(substituted phenyl) hydroxy methyl]-2-thiooxazolidin-4-ones.

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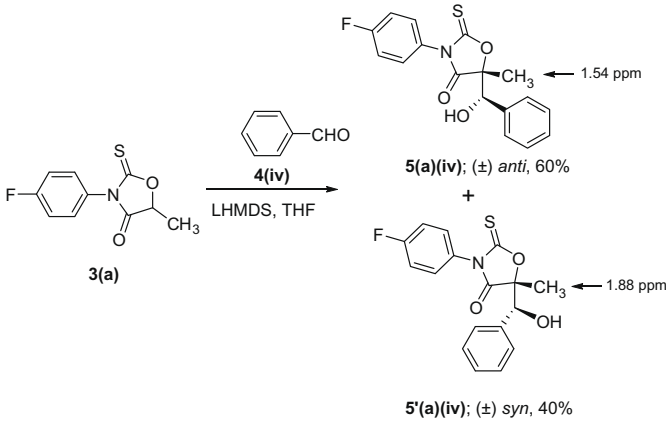



**Scheme 2.** *Anti* and *syn* isomers of 5-methyl-3-(4-fluorophenyl)-5-(phenyl hydroxy methyl)-2-thiooxazolidine-4-one.

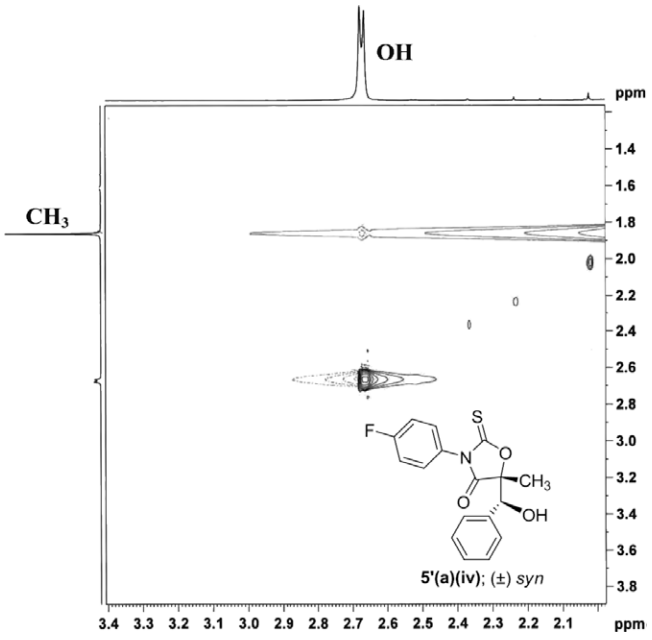



**Figure 1.** Expanded ROESY spectrum of **5′**(**a**)(**iv**) indicating hydroxy and methyl interactions.

(Fig. 2), and transition state models[12] corresponding to these conformers were proposed as illustrated in Figure 3. In the transition state **TS-I**, the phenyl and methyl groups are in a diequatorial conformation and this is possible only if they are *trans* to each other. Energetically this would be the most stable conformation, and the diaxial *trans* conformer would be much less favored. The transition state **TS-II** with the methyl group oriented axial and the phenyl group disposed equatorial represents the *cis* isomer and is less stable when compared to the diequatorial *trans* conformer. The most stable diequatorial conformation would thus lead to an *anti* diastereoselectivity in product formation. An assignment of the stereochemistry would indicate that the transition state **TS-I** would lead to (*S*,*R*) configurations at C5 and C6 for the *anti* aldol and (*R*,*S*) for its enantiomer, whereas the *syn* aldol arising from the transition state **TS-II** will have the configurations (*R*,*R*), and (*S*,*S*) for its enantiomer. To prove our assumptions and further to determine the stereochemistry, the *anti* aldol of **5(a)(i)** was chosen and chiral derivatization method was employed to separate the two enantiomers from the racemic mixture.[13,14]

**Table 1**
Chemical shift (ppm) comparison of aldol diastereomers

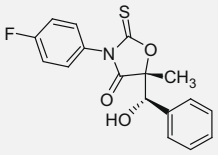
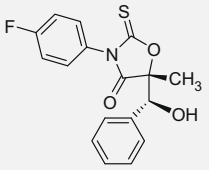
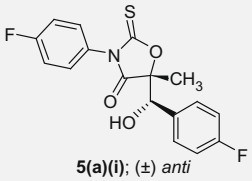
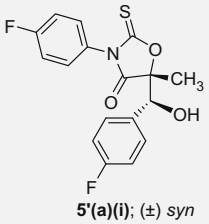
| Entry | Product | Me |
|---|---|---|
| 1 |  **5(a)(iv)**; (±) *anti* | 1.54 |
| 2 |  **5'(a)(iv)**; (±) *syn* | 1.88 |
| 3 |  **5(a)(i)**; (±) *anti* | 1.52 |
| 4 |  **5'(a)(i)**; (±) *syn* | 1.83 |

**Table 2**
Synthesis of 5-methyl-3-(substituted phenyl)-5-[(substituted phenyl) hydroxy methyl]-2-thiooxazolidin-4-ones

| Entry | $R^1$ | $R^2$ | $R^3$ | Isolated yield[a] (**5**) (%) | *Anti*/*syn* ratio[b] (**5**) (%) |
|---|---|---|---|---|---|
| 1 | F | H | F | 65 | 90:10 |
| 2 | F | H | Cl | 63 | 82:18 |
| 3 | F | H | Br | 67 | 85:15 |
| 4 | Cl | H | F | 70 | 85:15 |
| 5 | Cl | H | Cl | 75 | 86:14 |
| 6 | Cl | H | Br | 62 | 88:12 |
| 7 | F | Cl | F | 59 | 69:31 |
| 8 | F | Cl | Cl | 55 | 66:34 |
| 9 | F | Cl | Br | 58 | 67:33 |
| 10 | Cl | $CF_3$ | F | 56 | 74:26 |
| 11 | Cl | $CF_3$ | Cl | 54 | 66:34 |
| 12 | Cl | $CF_3$ | Br | 59 | 71:29 |
| 13 | Me | H | F | 70 | 80:20 |
| 14 | Me | H | Cl | 68 | 77:23 |
| 15 | Me | H | Br | 66 | 92:08 |

[a] The isolated yield is given as a total of *anti* and *syn* isomers after chromatographic purification.
[b] The *anti*/*syn* ratio was determined from $^1$H NMR of the crude product.

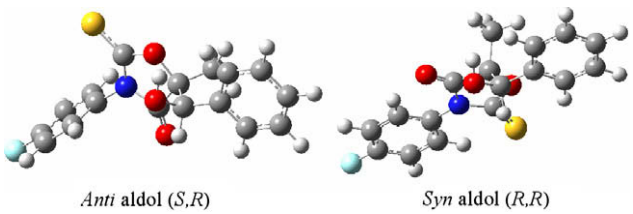



**Figure 2.** Most stable conformations of the *anti* and *syn* aldols.

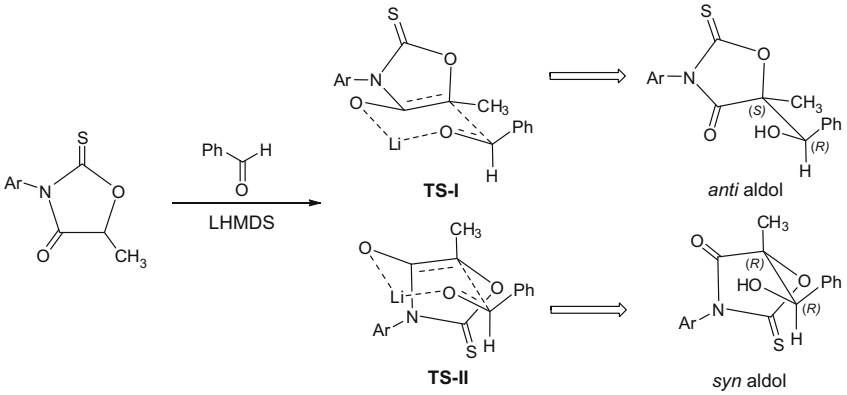
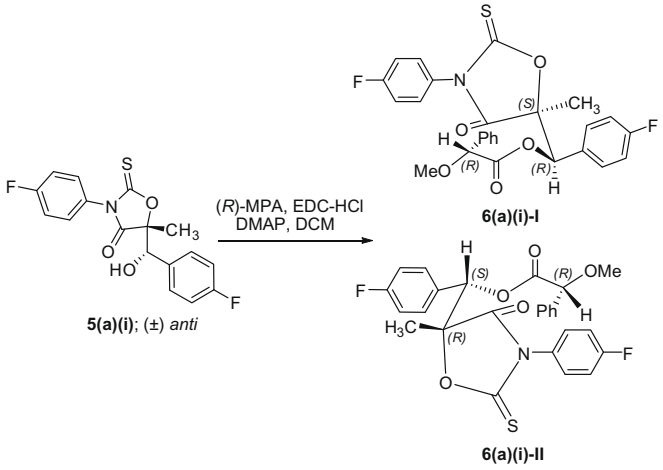



**Figure 3.** Transition state models for the formation of *anti* and *syn* aldol diastereomers.




**Scheme 3.** Chiral derivatization of secondary alcohol with (*R*)-MPA.

The compound **5(a)(i)** was subjected to reaction with (*R*)-α-methoxyphenylacetic acid (MPA) using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl) and DMAP in DCM (Scheme 3), and a third chiral center of known and fixed configuration was incorporated thereby converting the two enantiomers into diastereomers **6(a)(i)-I** ($R_f$ 0.53; EtOAc/hexane, 3:7; mp 78–81 °C) and **6(a)(i)-II** ($R_f$ 0.40; EtOAc/hexane, 3:7; mp 72–75 °C), which were conveniently separated using preparative thin layer chromatography and characterized by $^1$H NMR.

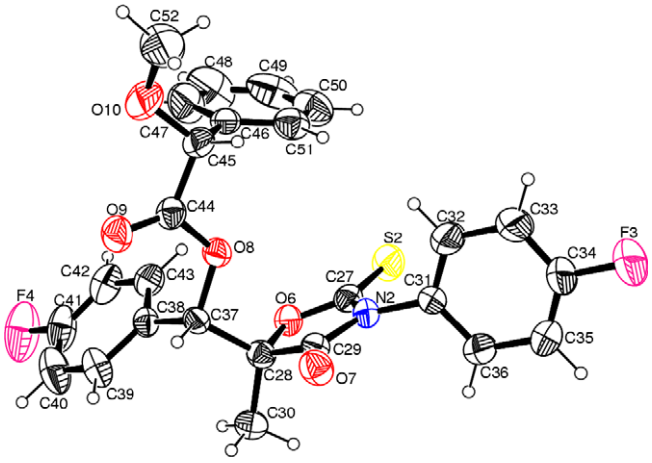


**Figure 4.** ORTEP diagram of the diastereomer **6**(**a**)(**i**)-**II**.

A suitable crystal of **6(a)(i)-II** was subjected to single crystal X-ray analysis[15] and a perspective view of the diastereomer with the atom numbering is given in Figure 4. The crystal structure shows that the stereochemistry at C5 and C6 is (*R,S*) for the diastereomer 6(**a**)(**i**)-**II** of the *anti* aldol MPA ester, which validates the stereochemistry predicted. Consequently the diastereomer **6(a)(i)-I** should have the opposite configuration (*S,R*) at the chiral centers; it being the other enantiomer of the *anti* aldol.

To conclude, we have described herein the aldol reactions of 5-methyl-3-(substituted phenyl)-2-thiooxazolidin-4-ones which gave the *anti* aldol isomer as the major product. The stereochemistry at the two chiral centers was predicted with the help of transition state models and further confirmed by single crystal X-ray diffraction study.

## 2. X-ray crystallographic data

Crystallographic data for compound **6(a)(i)-II** have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 761988. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.027.

## References and notes

1. Walker, R. B.; Fitz, L. D.; Williams, L. M.; Linton, H.; Smith, C. C. *Gen. Pharmacol.: Vasc. Syst.* **1993**, *24*, 669.
2. Momose, Y.; Maekawa, T.; Yamano, T.; Kawada, M.; Odaka, H.; Ikeda, H.; Sohda, T. *J. Med. Chem.* **2002**, *45*, 1518.
3. Liang, P.-H.; Hsin, L.-W.; Cheng, C.-Y. *Bioorg. Med. Chem.* **2002**, *10*, 3267.
4. Shapiro, S. L.; Rose, I. M.; Testa, F. C.; Roskin, E.; Freedman, L. *J. Am. Chem. Soc.* **1959**, *81*, 6498.
5. Lin, G. Q.; Li, Y. M.; Chan, A. S. C. Principles and Applications of Asymmetric Synthesis; Wiley Interscience: New York, 2001. p. 135.
6. Aitken, R. A.; Kilenyi, S. N. Asymmetric Synthesis; Blackie Academic & Professional: London, 1992. p. 83.
7. Nair, V. A.; Mustafa, S. M.; Mohler, M. L.; Dalton, J. T.; Miller, D. D. *Tetrahedron Lett.* **2006**, *47*, 3953.

8. (a) Kumar, V.; Nair, V. A. *Tetrahedron Lett.* **2010**, *51*, 966; (b) Khatik, G. L.; Pal, A.; Apsunde, T. D.; Nair, V. A. *J. Heterocycl. Chem.* **2010**. doi:10.1002/jhet.369.
9. (a) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066; (b) Ishihara, T.; Ichihara, K.; Yamanaka, H. *Tetrahedron Lett.* **1995**, *36*, 8267; (c) Ghosh, A. K.; Fidanze, S.; Onishi, M.; Hussain, K. A. *Tetrahedron Lett.* **1997**, *38*, 7171.
10. (a) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310; (b) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920; (c) Mateos, A. F.; Coca, G. P.; Alonso, J. J. P.; Gonzalez, R. R.; Hernandez, C. T. *Tetrahedron Lett.* **1995**, *36*, 961; (d) Majewski, M.; Gleave, D. M. *Tetrahedron Lett.* **1989**, *30*, 5681; (e) Brunner, M.; Koskinen, A. M. P. *Tetrahedron Lett.* **2004**, *45*, 3063; (f) Hayashi, T. *Tetrahedron Lett.* **1991**, *32*, 5369.
11. (a) Calculations were performed using GAMESS Interface program by semi-empirical method PM3 on Chem3D Ultra 10.0 (CambridgeSoft).; (b) Matsugi, M.; Itoh, K.; Nojima, M.; Hagimoto, Y.; Kita, Y. *Tetrahedron Lett.* **2001**, *42*, 6903.
12. (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1; (b) Heathcock, C. H.. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; p 111; (c) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3684; (d) Allinger, N. L.; Tribble, M. T.; Miller, M. A.; Wertz, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 1637; (e) Manoharan, M.; Eliel, E. L. *Tetrahedron Lett.* **1983**, *24*, 453; (f) Booth, H.; Grindley, T. B. *J. Chem. Soc., Chem. Commun.* **1983**, 1013; (g) Gawley, R. E.; Aubé, J.. *Principles of Asymmetric Synthesis*. In *Tetrahedron Organic Chemistry Series*; Elsevier (Pergamon imprint): Oxford, 1996; Vol. 14. p. 161.
13. (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512; (b) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.
14. (a) Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1995**, *60*, 504; (b) Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2000**, *11*, 2781; (c) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17.
15. (a) Sheldrick, G. M. SHELXS-97. Program for the Solution of Crystal Structures, University of Göttingen, Germany.; (b) Sheldrick, G. M. SHELXL-97. Program for the Refinement of Crystal Structures, University of Göttingen, Germany.