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Chiral 6,7-Dihydrooxepin-2(5H)-ones and the Azepinone Analogues: Conformation and Diastereofacial Selectivity in Addition to the Enones

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Abstract: Diastereofacial selectivity in addition to the enones of 6-and 7-substituted dihydrooxepinones was studied. The addition occurred preferentially from the face anti to the substituent and 7-substituted substrates showed higher diastereofacial selectivity than the 6-substituted substrates. An explanation for the observed diastereofacial selectivity is proposed.

Chiral heterocyclic enones are useful intermediates not only for diastereoselective synthesis but also for enantioselective synthesis. Owing to their rigid conformations, they show high diastereofacial selectivity without chelation control which is usually required for acyclic enones such as chiral acrylates. Thus, five- and six-membered heterocyclic compounds such as 5-substituted 2(5H)-furanones,¹ 6-substituted 5,6-dihydro-2(2H)-pyrones,² and 2-substituted 1,3-dioxin-4-ones^{3,4} have been successfully utilized as chiral enones in Michael addition, Diels-Alder reaction, and photo[2+2]addition. The high diastereofacial selectivity has been also observed in enones incorporated in much larger rings such as 9- to 12- membered lactones.⁵ However, the diastereofacial selectivity of chiral heterocyclic enones incorporated in a seven-membered ring has not been extensively studied.^{6,7} Here we report the diastereofacial selectivity of 6- and 7-substituted dihydrooxepinones and 7-substituted dihydroazepinone in addition to the enone moieties.

All chiral oxepinones and azepinone were prepared as racemic mixtures by the method illustrated in Scheme 1,⁸ since in this study only the relative stereochemistry of the stereogenic center in the products was of interest.



4a: R= Me, R'= H, R"= Me 4b: R= H, R'= R"= Me 4c: R= Me, R'= R"= H 4d: R= H, R'= Me, R"= H 4e: R= *tert*-Bu, R'= R"= H 4f: R= H, R'= *tert*-Bu, R"= H

Scheme 1 : a, *m* CPBA, CH₂Ci₂; b, LDA then PhSeBr, THF, -78°C; c, O₃ or H₂O₂, CH₂Cl₂; d, PCI₅, CH₂Cl₂; e, (Boc)₂O, DMAP, benzene; f, CF₃COOH

On catalytic hydrogenation with 10% Pd-C in ethyl acetate, 4,7-dimethyloxepinone (4a) and the azepinone analogue (8) afforded exclusively the *cis*-dimethyl compounds *cis*-2a and *cis*-6 in quantitative yields, respectively, while 4,6-dimethyloxepinone (4b) afforded a mixture of *trans*-2b and *cis*-2b (95% yield) in 1:5 ratio as revealed by ¹H-NMR (500 MHz) spectroscopic study. The assignment of the hydrogenated products was done by comparison of the ¹H-NMR data with those of authentic samples.



Scheme 2

On conjugate addition reaction with methylmagnesium bromide in the presence of CuI and chlorotrimethylsilane at -78 °C, 4c gave *trans*-2a and *cis*-2a in 4:1 ratio, while the *tert*-butyl derivative 4e gave exclusively *trans*-2e. Under the same conditions, 4d gave a mixture of *trans*-2d and *cis*-2d (81% yield) in a ratio of 5:1, and the *tert*-butyl derivative (4f) gave a mixture of *trans*-2g and *cis*-2g (82% yield) with an improved ratio of 10:1.



Scheme 3

The result shows that both 7-substituted oxepinones and the 6-substituted isomers display antiselectivity in catalytic hydrogenation and conjugate addition. Moreover, it has been demonstrated that 7substituted substrates show a higher diastereoafacial selectivity than the 6-substituted isomers, and introduction of the bulkier *tert*-butyl group to the chiral center results in an improved stereoselectivity.

Finally, the diastereofacial selectivity of chiral oxepinones in a cycloaddition reaction was examined. The reaction of 2,4,6-trimethylbenzonitrile *N*-oxide (9) with 4c proceeded under highpressure (10 kbar) for one day at room temperature to afford *anti*-10 as the sole product in 95% yield. The regio- and stereochemistries were determined by X-ray crystallographic analysis (Fig.1).⁹ As expected, this cycloaddition occurred at the face *anti* to the methyl substituent. In contrast, compound 4d exhibited no diastereofacial selectivity in the reaction with 9 affording a 1:1 mixture of *syn*-12 and *anti*-12 as shown by ¹H-NMR analysis of the reaction mixture.

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It is clear that the asymmetric induction in these seven-membered enones is not caused by direct steric interaction between the substituent at the chiral center and reagents, as evidenced by the higher asymmetric induction in the 7-substituted substrates in which the steric interaction is less than that in the 6-substituted substrates. To rationalize the above result, compound 8 (mp 93-94 °C) was subjected to X-ray crystallographic analysis. As shown in Fig. 2, this compound has an envelope conformation in which all of the ring atoms except for C_6 are almost in a plane and the 7-methyl group takes *pseudo*-equatorial orientation.⁹ This conformation is very similar to that of oxazepinone derivative $(13)^6$ with a methyl group at the stereogenic center in pseudo-equatorial position. These envelope conformations are originated from the coplanarity of the amide group and the conjugated enone group. Therefore, it is reasonable to assume that 6-and 7-substituted oxepinones take envelope conformations (4a-f) as illustrated in Fig. 2. The alternative envelope conformations (4') are less favorable due to the steric reason. Semi-empirical calculations (MOPAC PM3)¹⁰ suggested that conformations 4a and 4b (minimum energy conformations) are more stable than 4'a and 4'b by 0.67 and 1.98 Kcal/mol, respectively. The calculation also suggested that conformations 4e and 4f are more stable than 4'e and 4'f by 3.41 and 5.88 Kcal/mol, respectively.¹H-NMR (500 MHz) spectroscopic study well supported the conformations of 4a-f as well as 8 in solution as evidenced by the following coupling constants :J_{7Hα-6Hβ} =7.0~9.0 Hz, J_{7Hα-6Hβ}=1.5~2.5 Hz for 4a, c, e and 8; J_{7Hα-6Hβ}=7.0~8.0 Hz, J_{7Hβ-6Hβ}=1.5~2.0 Hz for 4b,d,f; $J_{7HB-6HB}=1.5$ Hz for 4f.



Although the reasons for the above selectivity have not been clearly established, we might assume that the selectivity is caused mostly by steric requirements in the transition state.¹¹ For example, conjugate addition to **4c** and **4e** occurs preferentially at the less hindered bottom face to give stable intermediate **15**. However, the

bottom face attack to 4d and 4f leads to intermediate 17 which is less stable than 15 due to the eclipsing interaction of the R' substituent. For this reason, addition to 4d and 4f occurs selectively at the top face. The improved top face selectivity in the *tert*-butyl derivative 4f supports this assumption. The selectivity in the cycloaddition is rationalized similarly; destabilization of *syn*-12 by the R' substituent allows the attack at both of the faces (Scheme 5).



Scheme 5

In conclusion, we have shown that addition to the enone moiety of 6- and 7-substituted dihydrooxepinones occurs selectively from the face *anti* to the substituent. The diastereofacial selectivity is believed to arise from steric requirements in the transition state.

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REFERENCES AND NOTES

- Feringa, B. L.; Lange de, B.; Jong de, J. C.; Lubben, M.; Faber, W.; Schudde, E. P. Pure and Appl. Chem. 1992, 64, 1865. For nitrogen heterocycles: Romo, D.; Meyers, A. I. Tetrahedron, 1991, 47, 9503. Koot, W.-J.; Hiemstra, H.; Speckamp, W. N. J. Org. Chem., 1992, 57, 1057.
- Pirkle, W. H.; Adams, P. E. J. Org. Chem., 1980, 45, 4117. Takano, S.; Shimazaki, Y.; Sekiguchi, Y.; Ogasawara, K. Synthesis, 1989, 539.
- Kaneko, C.; Sato, M.; Sasaki, J.; Abe, Y. J. Heterocycl. Chem., 1990, 27, 25. Sato, M.; Murakami, M.; Sunami, S.; Kaneko, C.; Furuya, T.; Kurihara, H. J. Am. Chem. Soc., 1995, 117, 4279.
- Demuth, M.; Palomer, A.; Sluma, H.-D.; Dey, A. K.; Kruger, C.; Tsay, Y.-H. Angew. Chem. Int. Ed. Engl., 1986, 25,117. Seebach, D.; Zimmermann, J.; Gysel. U.; Ziegler, R.; Ha, T.-K. J. Am. Chem. Soc., 1988, 110, 4763.
- 5. Still, W. C.; Galynker, I. Tetrahedron, 1981, 37, 3981.
- 6. Sato, M.; Kuroda, H.; Kaneko, C.; Furuya, T. J. Chem. Soc., Chem. Commun., 1994, 687.
- 7. Busque, F.; Cid, P.; March, P.; Figueredo, M.; Font, J. Heterocycles, 1995, 40, 387.
- 8. All new compounds exhibited satisfactory spectroscopic (¹H-NMR and IR) and combustion or high resolution mass spectral analytical data.
- 9. Full details of the crystal structure investigation of 8 and *anti*-10 have been deposited at the Cambridge Crystallographic Data Centre, Lensfield Road, UK.
- 10. MOPAC PM3 was implemended on a Tektronix CAChe workstation.
- A similar rationalization has been proposed for diastereofacial selectivity in addition to chiral 6-membered cyclic enones such as 2-cyclohexen-1-ones and 5,6-dihydro-2(2H)-pyrones. See: Deslongchamp, P.; Stereoeletronic Effects in Organic Chemistry, Pergamon, Oxford, 1983, p.209. Takano, S.; Setoh, M.; Ogasawara, K., Tetrahedron: Asymmetry, 1992, 3, 533.

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