KINETIC AND THERMODYNAMIC SYN DEPROTONATION

OF O-TETRAHYDROPROPYRANYL OXIMES

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Jung and coworkers have reported the preparation and regiospecific alkylation of oxime

dianions.[1] It was demonstrated that primary and secondary (but not tertiary) carbanions of syn

geometry only are formed when oximes are treated with two equivalents of n-butyllithium. Anti

oxime dianions were formed only with difficulty and in low yield. These results were interpreted

as a consequence of the stability of the syn dianion due to chelation of the cation and the

through-space interaction of the 6π-electron system of the syn dianion.[2]

The fact that syn-anti isomerization of the dianions is not observed is synthetically

limiting in that oximes of unsymmetrical ketones are generally obtained as mixtures which are

difficult to separate.[3] Recent reports have indicated that syn-anti mixtures of N,N-dimethyl-

hydrazones are converted to the same monoanion on treatment with lithium diisopropylamide[4] and

Jung has demonstrated that N,N-dimethylhydrazones undergo kinetic anti deprotonation and rapid

isomerization (about the C-N bond) to give the more stable syn anion.[5]

These differences between oxime dianions and N,N-dimethylhydrazones prompted us to in-

vestigate O-alkyl oximes as a potential source of oxime anions capable of isomerization. Spencer[6]

and Fraser[7] have shown that O-methyl oxime anions are alkylated on the syn carbon but no isomeri-

zation of the anion was reported.[8] Since we were interested in the regeneration and further

reactions of the free oxime (from the O-alkyl oxime anion alkylation product), the tetrahydro-

pyranyl (THP) protecting group was chosen for initial study. The required O-THP oximes were

prepared in near quantitative yield as shown in Table 1.
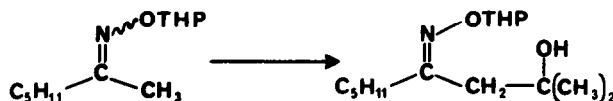
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The O-THP oxime of 2-heptanone (1) was obtained as a 61:39 mixture of E and Z isomers,[9,10] respectively. Treatment of this mixture with 1.1 equivalents of lithium diisopropylamide (LDA) in THF at -50°C for 3 hr followed by the addition of acetone afforded a single product (95% yield) in which alkylation had occurred on the methyl carbon.[11] In this respect, the O-THP oximes behave similarly to N,N-dimethylhydrazones.[4]

Carbonyl compound	Reaction time (hr)[a]	BP, pressure (mp)	Yield	E:Z ratio[b]
cyclohexanone	0.5	93-95°C, 0.5mm	99	---
3-pentanone	0.5	73-75°C, 1.15mm	95	---
pinacalone	2	50-53°C, 0.25mm	95	89:11
2-heptanone	0.5	95-98°C, 0.75mm	94	61:39
camphor	12	100-104°C, 0.5mm	74	c
acetophenone	0.5	117-119°C, 0.4mm	95	68:32
benzophenone	24[d]	(69-71°C)	78	---
propionaldehyde	0.5	87-89°C, 15 mm	99	68:32
isobutyraldehyde	0.5	116-119°C, 25mm	98	75:25
trimethylacetaldehyde	1	97-99°C, 14mm	97	90:10
heptanal	0.5	107-109°C, 0.25mm	93	58:42
benzaldehyde	0.5	106-108°C, 0.5mm	97	e
α-methylcinnamaldehyde	1	164-167°C, 0.4mm	98	e

Table 1. a) Reactions were performed on 100 mmol of carbonyl compound with 1.1 equivalent of THPONH$_2$[12] in 100 ml of benzene at reflux under a Dean-Stark trap until water separation ceased.[13] b) E:Z isomer ratios were determined by nmr integration in C$_6$D$_6$.[10] c) Isomer ratio could not be determined by nmr. d) 0.1 mmole of pTsOH catalyst was added. e) Only one isomer was detected by nmr.

The acetophenone O-THP oxime (2) was obtained as a 68:32 mixture of E and Z isomers, respectively.[14] When this mixture was treated with 1.1 equivalents of LDA at -78° for 1 hr followed by quenching with methanol a 94% recovery of 2 was realized. The recovered mixture was 80% E-2 and 20% Z-2. When the solution was allowed to warm to -50°C for 3 hr prior to quenching with methanol a 95% yield of E-2 was obtained. The Z isomer was not detectable in the crude reaction mixture by nmr. These results are consistent with deprotonation of both the E and Z isomers with equilibration of the anions as shown below.
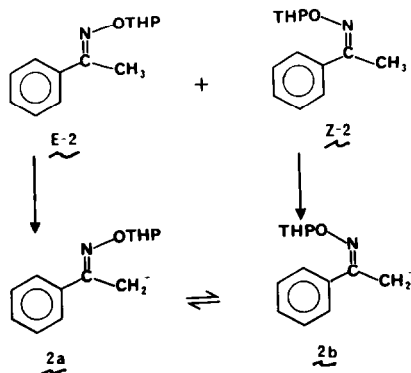
In order to evaluate the relative rates of steps a,a' and b the 68:32 mixture of E-2 and Z-2 was treated with 1.1 equivalents of LDA at -78°C for 30 minutes followed by the addition of excess acetone. The nmr spectrum of the crude reaction mixture showed the presence of 25% Z-2, 10% E-2 and 65% of the E adduct 3.[15] The detection of only one isomer of 3 and the rapid disappearance of E-2 indicates that step a is rapid compared to step a' and that the equilibration of anions 2a and 2b (step b) is rapid and heavily favors the syn anion (2a).

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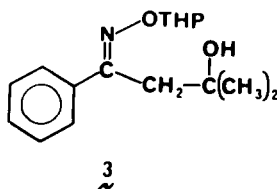
These results indicate that formation of the syn O-THP oxime anion is both kinetically and thermodynamically favored whereas with N,N-dimethylhydrazones the anti anion is kinetically favored[5] and the syn anion is thermodynamically favored.[2,5]

This change in kinetic preference in deprotonation is probably due to the ability of the THP oxygen to compete more effectively than the dimethylamine moiety (of N,N-dimethylhydra-zones) with THF in coordination with the lithium cation. Coordination of the THP oxygen with the lithium cation positions the base near the syn alkyl group and facilitates proton abstraction. Thus in N,N-dimethylhydrazones steric effects control the site of kinetic deprotonation, and in O-THP oximes (and probably oxime monoanions and O-alkyl oximes) coordination of the lithium amide directs kinetic deprotonation. In both cases the thermodynamic product is the same.

Acknowledgements

References

1. M. E. Jung, P. A. Blair, and J. A. Lowe, Tetrahedron Lett., 1439 (1976).

2. The factors which thermodynamically favor the syn anion have been discussed. See N. D. Epiotis, J. Amer. Chem. Soc., 95, 3087 (1973); R. A. Fraser and K. L. Dhawan, J. Chem. Soc., Chem. Commun., 674 (1976); W. G. Kofron and M. K. Yeh, J. Org. Chem., 41, 439 (1976).

3. G. J. Karabatsos and R. A. Taller, Tetrahedron, 24, 3347 (1968).

4. The mixture of N,N-dimethylhydrazones of 2-pentanone gives 98% deprotonation on the methyl carbon when treated with LDA; E. J. Corey and D. Enders, Tetrahedron Lett., 11 (1976).

5. M. E. Jung and T. T. Shaw, Tetrahedron Lett., 3305 (1977).

6. T. A. Spencer and C. W. Leong, Tetrahedron Lett. 3889 (1975).

7. R. A. Fraser and K. L. Dhawan, J. Chem. Soc., Chem. Commun., 674 (1976).

8. Fraser reported that Z-trans-2-methyl-4-t-butylcyclohexanone O-methyl oxime (i) could not be metalated. (See ref. 7)
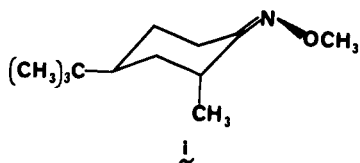
9. All new compounds were characterized by spectral analysis (nmr, ir, and mass spectra) and elemental analysis of homogeneous samples.

10. The methyl proton resonance (1.65 δ for E isomer, 1.60 δ for Z isomer in benzene d$_6$) were assigned by analogy to the differences observed in the chemical shifts of syn and anti alkyl protons of O-methyl oximes. See G. J. Karabatsos and N. Hsi, Tetrahedron, 23, 1079 (1967).

11. NMR spectrum (CDCl$_3$) δ 5.13 (m, 1H, OCHO), 3.9-3.3 (m, 2H, OCH$_2$), 3.15 (s, 1H, OH), 2.56 and 2.44 (AB q, J=13Hz, 2 H, N=C - CH$_2$), 2.25 (t, J=8Hz, 2H, N=C - CH$_2$), 1.88 - 1.0 (m, 12H), 1.21 (s, 6H, O-C-CH$_3$), 0.88 (t, J=6Hz, CH$_3$).

12. R. N. Warrener and E. N. Cain, Angew. Chem. Int. Ed., 5, 511 (1966); also see T. Oguri, T. Shiori, and S. Yamada, Chem. Pharm. Bull., 23, 167 (1975).

13. With aldehydes and unhindered ketones the reactions can be performed under much milder conditions. For example, heptanal (50 mmol) and THPONH2 (55 mmol) in 50 ml of benzene shows immediate separation of water. The solution was stirred at 25°C for 30 minutes and the organic layer was separated and the solvent was evaporated to afford a 95% yield of the O-THP oxime.

14. Methyl proton resonances 2.10 δ for E isomer, 2.02 δ for Z isomer in benzene d$_6$; see ref. 10.

15. NMR of 3 (CDCl$_3$) δ 7.61 - 7.4 (m, 2H, ArH), 7.3 - 7.1 (m, 3H, ArH), 5.3 (m, 1H, OCHO), 3.93 - 3.37 (m, 2H, OCH$_2$), 3.12 and 2.91 (AB q, J=12Hz, N=C-CH$_2$), 2.69 (s , 1H, OH), 1.97 - 1.35 (m, 6H), 1.2 (s, 3H, CH$_3$), 1.19 (s, 3H, CH$_3$).