Tetrahedron Letters No. 18, pp 1439 - 1442, 1976. Pergamon Press. Printed in Great Britain.

REACTIONS OF OXIME DIANIONS: STEREOSPECIFICITY IN ALKYLATION

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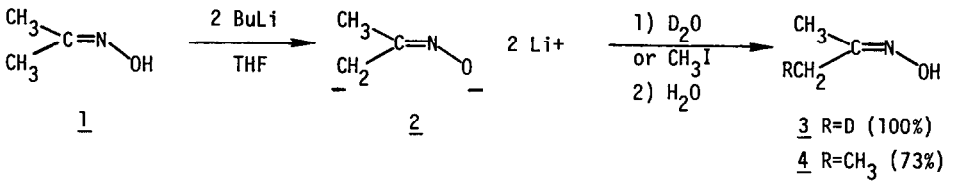
(Received in USA 22 January 1976; received in UK for publication 23 March 1976)

Several years ago Hauser observed that treatment of aromatic ketoximes with two equivalents of strong base resulted in the formation of dianions which could be successfully alkylated on carbon.[2] However, no information on the stereochemistry of the alkylated products was ever reported. We now wish to report total stereospecificity in the formation and alkylation of the α-carbon, oxygen-dianions of aliphatic ketoximes.

Treatment of acetoxime 1 with two equivalents of n-BuLi in THF at 0°C for 15 minutes resulted in the formation of exclusively the syn dianion 2, which upon deuteration afforded cleanly compound 3.[3] That the deuteration had occurred only on the syn methyl group was shown clearly by the NMR spectrum of 3 in benzene which exhibited a multiplet for the syn methyl group (δ 1.70, 2H) and

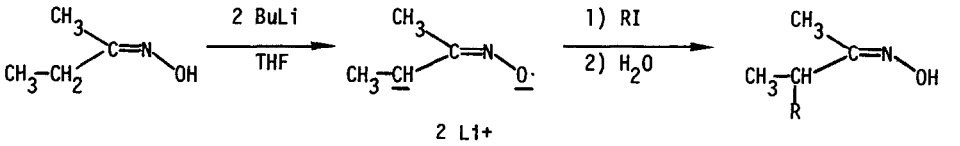


1 2 3 R=D (100%) 4 R=CH_3 (73%)

a singlet for the anti methyl group (δ 1.61, 3H). Addition of methyl iodide to a solution of 2 afforded only the syn ethyl methyl ketoxime 4 in 73% yield. The NMR spectrum of 4 in benzene was identical to that reported by Karabatsos for this compound, which could be prepared only as the minor isomer (26%) of the syn-anti mixture from the oximination of ethyl methyl ketone.[4]

The ketoxime 4 was converted exclusively into the syn dianion 5 upon treatment with two equivalents of n-BuLi in THF at 0°C for 15 minutes. This is an indication of the remarkable energy difference in favor of the syn dianion since this deprotonation involves forming a secondary carbanion (syn) in preference to normally-favored primary carbanion (anti). Addition of an equivalent of methyl iodide to 5 provided in 81% yield the alkylated product 6, the structure of which was again proven by the identity of its NMR spectrum to that reported by Karabatsos for the minor isomer (9%) from the oximination of methyl isopropyl ketone.[4] VPC analysis of the product showed

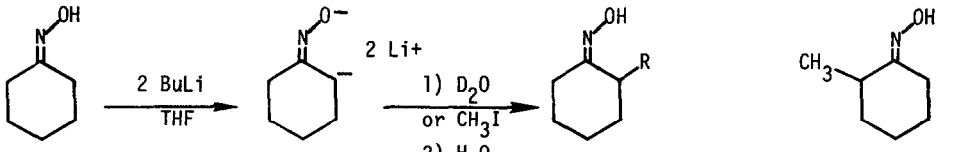
that none of the isomeric 3-pentanone oxime was present by comparison to an authentic sample. By the use of n-propyl iodide or isopropyl iodide, the corresponding alkylation products, 7 and 8, could be prepared, in yields of 53% and 46%, respectively.



4 5

6 R=CH_3 81%
7 R=nPr 53%
8 R=iPr 46%

In like manner cyclohexanone oxime 9 could be converted into the stereospecifically substituted compounds 11 and 12, via the syn dianion 10, by deuteration (100%) and methylation (74%) respectively. The structures were determined from the NMR spectra of these compounds.[5] Compound 12 was previously unknown since oximination of 2-methylcyclohexanone yields only the anti isomer 13.[6]

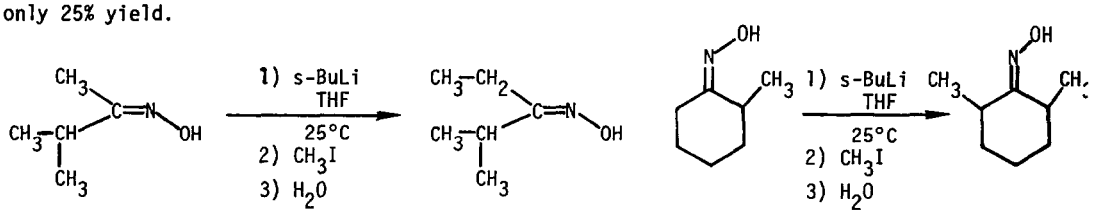


9 10

11 R=D (100%)
12 R=CH_3 (74%)

13

In contrast to the very clean stereospecific syn alkylation described above, oximes in which the syn carbon is disubstituted, e.g., 6 or 12, could not be cleanly alkylated at all. Metalation of the monoanion with s-BuLi in THF at 0°C was extremely slow and was in fact incomplete after several hours at room temperature. Addition of methyl iodide gave along with a large amount of starting material, the anti methylation product (14 or 15) as the only observed alkylated product in only 25% yield.



6 25% 14 12 23% 15

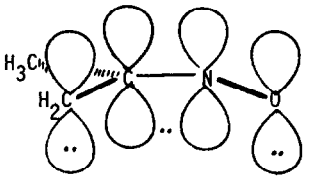
This great disparity in the rates of deprotonation of 4 and 6 is unusual and indicates a large difference in the kinetic acidity of the syn and anti protons. The anti anion (even though primary) is formed extremely slowly under the same conditions which cause rapid formation of the syn anion (primary or secondary). The fact that the anti dianions of the oximes 6 and 12 could not be formed in high yield even under forcing conditions suggests a large difference in the thermodynamic acidity of the protons as well.

The results of our investigation indicate total stereospecificity in proton abstraction. We have observed no syn-anti equilibration or isomerization of the dianions, even at room temperature or above (e.g., 5 is stable towards equilibration in THF at room temperature for 7 hours, or at reflux for 1 hour). All of these oxime dianions are remarkably stable substances which can be handled even at room temperature without significant decomposition. This is in sharp contrast to the α-monoanions of oxime methyl ethers which are reported by Spencer to decompose at 0°C.[7]

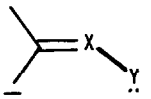
The reasons for this remarkable stereospecificity for syn dianion geometry are not immediately obvious. Several factors may be involved,[8] but the most likely are the greater inherent stability of the syn dianion versus the anti and strong chelation of alkali metal salts by the syn dianion. In an attempt to evaluate the importance of chelation, we have conducted the alkylation experiments in the presence of possible lithium chelating agents such as tetramethylethylenediamine (TMEDA), hexamethylphosphoramide (HMPA), and proton sponge. In all cases the same stereospecificity was observed.[9] We are now investigating the use of a stronger lithium chelating agent, e.g., a cryptate, in these reactions.

We believe that part of the explanation must lie in the electronic structure of the syn dianion, e.g., 2. In 2 there is a 6 π-electron system which permits an attractive through-space nonbonded interaction between the α-C and the O, which should stabilize the compound.[10] This interaction is not present in the anti dianion. This type of reasoning was first expressed by Epiotis[11] to explain why cis-1,2-difluoroethylene was more stable than trans. We propose that this is a general argument which can help account for a large number of similar observations of stereospecificity. For example, the mono- and dianions 16a-d have shown similar stereospecificity in alkylations, that is, when alkylation occurs γ to the Y function, only the cis olefin isomer is formed. We suggest that this is due to the fact that all possess this favorable 6 π-electron system.

We are currently attempting to extend this regiospecific alkylation technique to other systems. A typical experimental procedure follows: To a solution of the oxime 4 (0.96 g, 11 mmol) in 40 ml dry THF at -78°C was added 8.9 ml (2.4 M, 22 mmol) of n-butyl lithium in hexane over



2



16

	X	Y	Reference
a	C	OR	12
b	C	S^-	13
c	N	^-NTs	14
d	N	OR	7

10 min. The resulting mixture was warmed in an ice bath for 20 min., recooled to -78°C, and methyl iodide (0.96 ml, 11 mmol) added. The mixture was warmed to 25°C and stirred for 45 min. Aqueous workup gave 0.91 g of syn methyl isopropyl ketoxime 6 (81%).

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