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LETTERS

Studies of π-Diastereofacial Selectivity: Spiro 2-Tetrahydrofuran and 2-Tetrahydrothiophene Ketones

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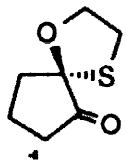
Abstract: The facial influence and synthetic utility of oxygen, sulfur and carbon atoms adjacent to the ketone in the series of α-spiro ketones **2**, **3**, and **4** upon nucleophilic addition has been examined. Addition to the carbonyl group displayed a preference for attack *anti* to the heteroatom in competition with carbon in synthetically useful ratios. Hydride reduction of **2** with chelating reagents ($NaBH_4$, $LiAlH_4$ etc.) reversed this facial preference.

Diastereofacial control of nucleophilic additions to carbonyl groups is affected by many factors particularly stereochemical and electronic effects. A variety of rationalizations have been presented to account for these results but an all encompassing explanation remains elusive.[1-8] In the preceding paper the behaviour of the oxathianyl ketone **1** with various nucleophiles was reported.[9] The addition of methyllithium, methyl magnesium halides, and chelating hydride sources afforded major diastereomers in which the nucleophile had added *syn* to oxygen and *anti* to sulfur. The only exception to this pattern was observed when diisobutylaluminum hydride was used as the reducing reagent. To further probe the origin of these effects and to establish the synthetic potential of these reactions, these studies have been extended to encompass the ketones **2** to **4**.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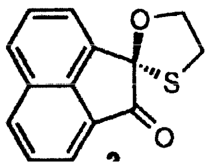
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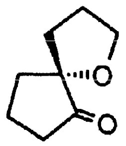
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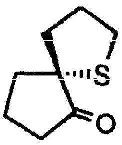
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The naphthalene system **2** is nearly flat and was selected as a substrate for comparison with the cyclopentanone **1**. X-ray analysis[10] plus AM1 and *ab initio* (6-31G*) calculations confirmed that the heterocyclic ring is approximately bisected by the carbonyl group (O=CC-O 50-54° *vs.* O=CC-S 65-68°). The results for several nucleophilic additions are summarized in Table 1. The methyllithium and Grignard reagents added to the carbonyl group in **2** *anti* to sulfur and *syn* to oxygen as observed previously for **1**. Addition of the bulky aluminum reagent methyl aluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) to the reaction prior to the addition of methyllithium caused a reduction in selectivity but not the reversal in facial selectivity encountered previously with conformationally locked cyclohexanones.[11] A similar reversal of facial selectivity was observed upon addition of cerium[12] or ytterbium[13] chlorides to acyl-1,3-oxathianes. However, as Entries h and i indicate, the ratio was not altered significantly with either $MeMgBr/CeCl_3$ or $MeMgBr/YbCl_3$ compared to methyl magnesium bromide itself (Entry e), although addition of $ZnCl_2$ (Entry g) reduced the selectivity slightly relative to the other examples. Unexpectedly, a variety of chelating hydride reducing agents afforded the

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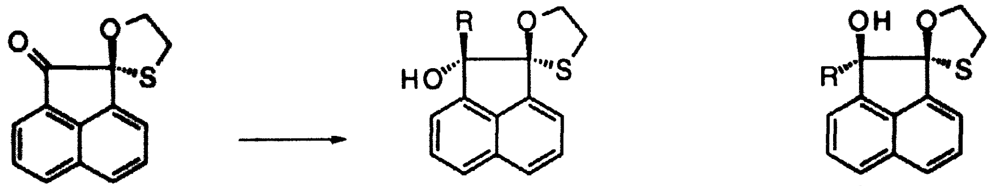
alcohol from a reversal of the direction of attack (*syn* to sulfur, *anti* to oxygen) in **2** compared to **1**. This appears to be the most sterically demanding approach (AM1), although the C-S bond has a larger dipole moment than the C-O bond,[3f,14] and oxygen is more electronegative. Diisobutylaluminum hydride reductions (Entries q to s), in which chelation effects should be reduced, displayed the opposite stereochemical preference compared to Entries j to p and thus parallel the diastereoselective additions with carbon nucleophiles (Entries a to i).

Table 1 Nucleophilic Additions to Naphthalene Ketone 2



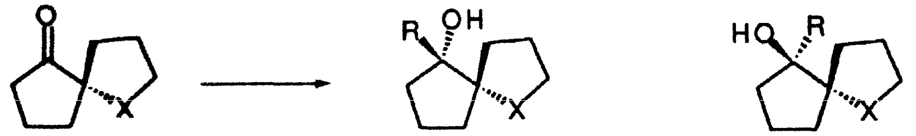
2 **5** R = Me, H **6**

Entry	Reagent[a]	Conditions	%Yield[b]	**5** : **6** %Anti:%Syn[c]
a	MeLi	ether, 0 °C	83	98:2
b	MeLi, $ZnCl_2$	ether, -78 °C	91	78:22
c	MeLi, MAD[d]	toluene, -78 °C	87	87:13
d	MeLi, MAD[e]	toluene, -78 °C	79	77:23
e	MeMgBr	THF, 0 °C	85	76:24
f	MeMgI	ether, 0 °C	82	84:16
g	MeMgBr, $ZnCl_2$	ether, 0 °C	86	63:37
h	MeMgBr, $CeCl_3$	THF, 0 °C	94	77:23
i	MeMgBr, $YbCl_3$	THF, -78 °C	89	72:28
j	$NaBH_4$	MeOH, 22 °C	77	24:76
k	$LiBH_4$	THF, 0 °C	86	31:69
l	$Zn(BH_4)_2$	ether, 0 °C	63	50:50
m	$LiAlH_4$	ether, 0 °C	82	29:71
n	$LiAl(t\text{-}OBu)_3H$	ether, -78 °C	69	11:89
o	$LiB(CHMeEt)_3H$	THF, 0 °C	80	26:74
p	$NaAl[MeO(CH_2)_2O]_2H$	ether, 0 °C	77	9:91
q	$Al(i\text{-}Bu)_2H$	THF, -78 °C	86	83:17
r	$Al(i\text{-}Bu)_2H$	ether, -78 °C	75	88:12
s	$Al(i\text{-}Bu)_2H$	CH_2Cl_2, -78 °C	79	81:19

[a] Reactions were performed with 1.1 equivalent of reagent. [b] Combined yield of isolated diastereomers. [c] Determined by GC-MS. [d] MAD: methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide). [e] 2 equivalents of MAD used.

In an effort to understand and interpret these results cyclopentanones **3** and **4** were synthesized.[15] In these cases one heteroatom has been removed so the competition is between carbon and oxygen or sulfur. For this series the nucleophile can avoid the electron density associated with the lone pairs of the heteroatom and a competition between heteroatom complexation sites no longer exists. The strong preference observed for attack *syn* to carbon and *anti* to the heteroatom for both spiro systems is summarized in Table 2. However, there is negligible discrimination with zinc borohydride in either series (Entries e and l).[16] Thus a range of hydrides including DIBAL-H, which lacks a metal counterion, displayed the same, consistent, facial preference in contrast to the results for the oxathiolane ketone 1. In total, these combined results are inconsistent with the Cram chelate model,[17] and do not satisfy the Felkin-Ahn transition state,[18] nor the hyperconjugation theory (Cieplak model).[4] In addition, our calculations and examination of the electrostatic potential surfaces were of limited predictive value except in the case of 3 which possessed an asymmetric surface.

Table 2 Nucleophilic Additions to Spiro Ketones 3 and 4



3 X = O
4 X = S

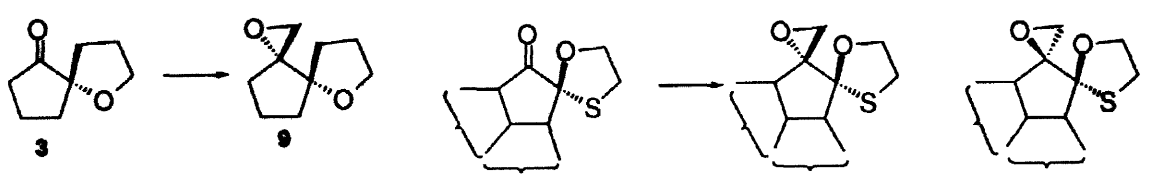
7

R = Me, H

8

Entry	Substrate	Reagent[a]	Conditions	%Yield[b]	**7 : 8** %Anti:%Syn[c]
a	**3**	MeLi	ether, 0 °C	90	100:0
b	**3**	MeMgBr	ether, 0 °C	93	100:0
c	**3**	$NaBH_4$	MeOH, 22 °C	89	94:6
d	**3**	$LiBH_4$	THF, 22 °C	94	84:16
e	**3**	$Zn(BH_4)_2$	ether, 22 °C	85	50:50
f	**3**	$LiAlH_4$	ether, 0 °C	84	86:14
g	**3**	Al(*i*-Bu)$_2$H	CH_2Cl_2, -78 °C	92	80:20
h	**4**	MeLi	ether, 0 °C	80	100:0
i	**4**	MeMgBr	ether, 0 °C	87	100:0
j	**4**	$NaBH_4$	MeOH, 22 °C	89	89:11
k	**4**	$LiBH_4$	THF, 22 °C	94	84:16
l	**4**	$Zn(BH_4)_2$	ether, 22 °C	86	50:50
m	**4**	$LiAlH_4$	ether, 0 °C	81	100:0
n	**4**	Al(*i*-Bu)$_2$H	CH_2Cl_2, -78 °C	81	95:5

[a]Reactions were performed with 1.1 equivalent of reagent. [b] Combined yield of isolated diastereomers. [c]Determined by GC-MS.



3 **9** **1 or 2**

From **1**, 92 8
From **2**, 94 6

In order to further probe these effects and reduce the chelating ability of the reagent ketones **1-3** were epoxidized with dimethylsulfoxonium methylide at 0 °C in THF. Ketone **3** afforded the single diastereomer **9** (93%) from addition *anti* to oxygen as in the cases above. In a similar manner ketones **1** and **2** gave the oxiranes from addition *anti* to sulfur (>90%) which corresponded to the major pathway with the methyl and hydride reagents.

The perturbations introduced by heteroatoms adjacent to carbonyl groups in cyclic ketones are subtle. The facial preference is a consequence of the interplay of the reagent, the preferred angle of attack, the tendency for chelation, torsion angle and steric effects as well as the electronegativity of the atoms and the polarity of the adjacent bonds.[3] In general the nucleophile seeks to avoid interaction with the lone pair of the heteroatom and reduce the torsional strain when the alternative face contains carbon. With sulfur present the steric effect is increased and generally *anti* attack is enhanced. This tendency is altered in the naphthyl series due to the presence of the metal ions present in ionic hydrides. Recently charge density studies,[18] frontier molecular orbital calculations[19] and the assessment of electrostatic interactions[20] have helped our understanding of various carbonyl systems. Fraser *et al.*[3f] demonstrated the importance of electrostatic effects for the interpretation of the directive influence of stereodependent substituents. The results above may be rationalized by consideration of the electrostatic consequences that arise from through-bond and through-space interactions in the transition state.

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