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On the Reaction of 1-Oxa-4-thiaspiro[4.5]decan-7-one with PhLi. A Reinvestigation

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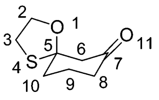
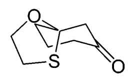
Abstract: Two diastereomeric alcohols are formed from the reaction of 1-oxa-4-thiaspiro[4.5]decan-7-one with PhLi as against the single diastereomer reported earlier. The diastereoselectivity achieved from PhMgBr is significantly higher than with PhLi. The use of Et_2O/hexane = 2:1 as the solvent for the reaction with PhMgBr offered the highest (14:1) diastereocontrol.

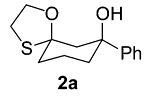
The reaction of 1-oxa-4-thiaspiro[4.5]decan-7-one, **1**, with PhLi was reported to furnish the axial alcohol **2a** in 18% yield after recrystallization.[1] Equilibrium that sterically favored the conformer **1a** over **1b** and the hydrogen bonding of the axial acetal oxygen with O*H* in **2a** were considered as the reasons for single product formation. IR evidence in favor of the said hydrogen bond was presented. This result appeared surprising to us because (a) the energy difference of the two conformers **1a** and **1b** is likely to be small, (b) the equatorial approach of a nucleophile to both **1a** and **1b** would appear to be almost equally favored for the apparently very similar geometries around the carbonyl carbons, and, if so, (c) each of **1a** and **1b** may react individually to furnish eventually a mixture of **2a** and **2b**. We consider only the equatorial approach of nucleophiles because the axial approach is sterically blocked by the acetal function.[2] We, therefore, decided to react **1** with PhLi to determine the product distribution. This has also presented an opportunity to us to react **1** with other nucleophiles such as PhMgBr and selected hydrides in efforts to improve the diastereoselectivity by making use of combination of solvents.



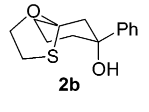
1a



1b



2a



2b

The requisite material **1** was prepared from the condensation of cyclohexane-1,3-dione with 2-mercaptoethanol in benzene under the conditions of azeotropic removal of water following a literature protocol.[1] All the ab initio MO calculations were performed at the HF/6-31G* level of theory using the Gaussian 98 suit of programs.[3] Further geometry improvements were achieved by repeating the calculations at the B3LYP/6-31G* level.[4]

The conformer **1a** is 0.92 kcal mol^{-1} more stable than the conformer **1b**. This is possibly due to the smaller size of the axial acetal oxygen in the former than the axial sulfur in the latter that are involved in 1,3-diaxial interactions with the axial hydrogen on C9 in each. As contemplated above, the dihedral angles O11−C7−C6−C5 and O11−C7−C8−C9 in both **1a** and **1b** are very similar as they are 133.86° and 134.66° in **1a** and 133.22° and 133.92° in **1b**. These very similar dihedral angles serve to ensure very similar geometrical environment around the carbonyl carbon in the ground states of these molecules.

The material **1** was reacted with PhLi in Et_2O, mixtures of Et_2O and hexane, and THF at −70 °C. Indeed, two alcohols were formed. Their ratios and the experimental conditions are collected in Table 1. The ratios of the alcohols were estimated from the relative ^1H integrals of the C*H*$_2$O function of the acetal ring. The alcohols were separated by radial chromatography and characterized. The stereochemical characterization from spectral features alone was difficult and, hence, single-crystal X-ray analyses were performed.[5] The alcohols were indeed **2a** and **2b** as expected from the ground-state conformational distribution of **1** into **1a** and **1b**. The ORTEP plots of **2a** and **2b** are given in the Supporting Information (Figures 1 and 2). In **2a**, the O*H* is close to the acetal oxygen with an interatomic distance of 2.108 Å to allow for hydrogen bonding. On the contrary, the O*H* has moved away from the acetal sulfur in **2b** to indicate the insignificance of hydrogen bonding with sulfur.[6]

The equatorial attack of PhLi to **1a** and **1b** will result in transition states having 1,3-diaxial interactions between OLi and the acetal oxygen and sulfur atoms, respectively. Since, the 1,3-diaxial interactions in the former transition state will be less for the smaller size of the acetal oxygen than the acetal sulfur, the addition to **1a** will be favored.

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TABLE 1. Distribution of 2a and 2b on Reaction of 1 with PhLi in Different Solvents

entry	reaction conditions	yield (%)	**2a/2b**
1	Et_2O, −70 °C	95	1.3:1
2	Et_2O/hexane = 3:1, −70 °C	97	1.5:1
3	Et_2O/hexane = 2:1, −70 °C	97	1.4:1
4	Et_2O/hexane = 1:1, −70 °C	96	1.6:1
5	THF, −70 °C	94	1.7:1

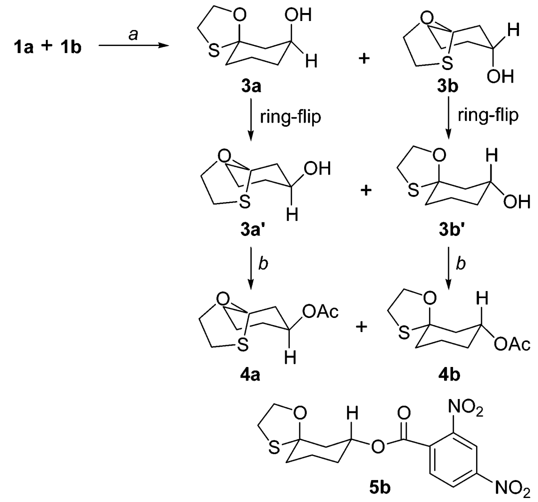
TABLE 2. Distribution of 2a and 2b on Reaction of 1 with PhMgBr

entry	reaction conditions	time (h)	yield (%)	**2a/2b**
1	Et_2O, −70 °C	1	95	5.0:1
2	Et_2O/hexane = 3:1, −70 °C	1	95	6.7:1
3	Et_2O/hexane = 2:1, −70 °C	1	96	14.0:1
4	Et_2O/hexane = 1:1, −70 °C	1	90	4.0:1
5	Et_2O/hexane/HMPA = 6:3:1, −70 °C	1	90	2.3:1

TABLE 3. Distribution of 3a and 3b on Reaction of 1 with Different Hydride Agents

entry	conditions	time (h)	yield (%)	**3a/3b**
1	$NaBH_4$, MeOH, 0 °C	2.5	96	1.4:1
2	$NaCNBH_3$, MeOH, 0 °C, pH 3−4	0.5	95	2.6:1
3	L-Selectride, THF, −70 °C	0.5	92	7.0:1
4	L-Selectride, toluene, −70 °C	0.5	94	2.2:1
5	$LiAlH_4$, Et_2O, 0 °C	2.0	96	2.6:1
6	DIBAL-H, toluene, −70 °C	0.5	90	1.7:1

SCHEME 1. Reaction of 1 with Hydrides[a]



[a] Reagents: (a) $LiAlH_4/Et_2O$ or $NaBH_4$/MeOH, 0 °C; (b) Et_3N, Ac_2O, DMAP, CH_2Cl_2.

The reaction with PhMgBr was more selective than the reaction with PhLi. The results are collected in Table 2. Admixture of hexane caused significant changes in product distribution. It is interesting to note that a reaction in 2:1 mixture of Et_2O and hexane (entry 3) furnished the product **2a** almost exclusively (**2a/2b** = 14:1). Further increase in hexane content (entry 4) had a deteriorating effect insofar as the formation of **2a** was concerned. This is due possibly to the heterogeneous nature of the reaction mixture for the poor solubility of the Grignard reagent. HMPA also affected the selectivity adversely (entry 6, **2a/2b** = 2.3:1).

The reduction of **1** with $LiAlH_4$ in Et_2O at 0 °C (Table 3, entry 5) furnished two inseparable alcohols. These alcohols were transformed into their corresponding acetates (Scheme 1) and separated. The ratio (less polar/more polar)acetate = 1:2.6 was calculated from the relative integrals of C*H*(OAc). The alcohol from the less polar acetate was transformed into 2,4-dinitrobenzoate derivative which was recrystallized from EtOAc−hexanes (mp 105 °C) and its stereostructure confirmed as in **5b** from X-ray analysis. The ORTEP plot of **5b** is given in the Supporting Information (Figure 3). Thus, the less polar acetate was assigned the stereostructure **4b** and the corresponding alcohol **3b′/3b**. The more polar acetate and the corresponding alcohol must then have the stereostructures **4a** and **3a′/3a**, respectively. It is to be noted that the reduction with L-Selectride in THF (7:1, entry 3) was more selective than in toluene (2.2:1, entry 4).

The OAc function in both **4a** and **4b** was equatorial. This was reflected very well from the coupling patterns of C*H*OAc: **4a**, δ 4.83−4.75 (tt, *J* = 10.7 and 4.2 Hz); **4b**, δ 5.00−4.92 (tt, *J* = 10.2, 4.2 Hz). The relatively downfield appearance of the said *H* in **4b** is likely to be due to the anisotropic effect of the axial acetal oxygen.

Similar to Grignard addition, the hydride will be expected to attack the carbonyl function from the equatorial face. However, the resulting axial alcohols, **3a** and **3b**, that suffer from 1,3-diaxial interactions from the acetal function will ring-flip to the more stable equatorial alcohols, **3a′** and **3b′**, respectively. Since the 1,3-diaxial interaction between OH and the acetal sulfur in **3b** is larger than the 1,3-diaxial interaction between OH and the acetal oxygen in **3a**, addition to **1a** will be favored over the addition to **1b**.

From the additions of nucleophiles to 1-oxa-4-thiaspiro[4.5]decan-7-one, we have demonstrated that two alcohols are indeed formed as expected from the ground-state conformational analysis. The previous authors missed the other product during recrystallization. The diastereoselectivity observed from the reaction with PhMgBr was much higher than with PhLi. The combination Et_2O/hexanes = 2:1 as the solvent system exhibited the highest diastereocontrol (14:1) in reaction with PhMgBr. Among the hydrides used, L-Selectride in THF offered the highest diastereoselection which was superior to that achieved from L-Selectride in toluene. The observed solvent effect on diastereoselection is very interesting and deserves attention.

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Supporting Information Available: Experimental details, spectroscopic and analytical data of the product alcohols **2a**, **2b**, **4a**, and **4b**, and ORTEP plots of **2a**, **2b**, and **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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