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THE MECHANISM OF HYDROXYLATION OF ORGANOMETALLIC REAGENTS BY 2-SULFONYLOXAZIRIDINES

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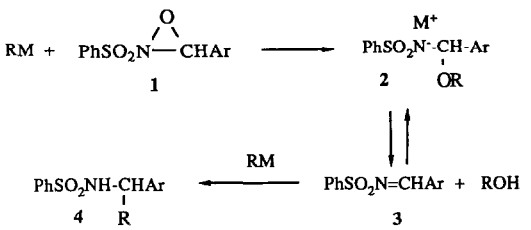
Summary: The hydroxylation of organometallic reagents (RM) by 2-sulfonyloxaziridines **1** is shown to involve a hemiaminal intermediate **2**, whose stability is apparently related to the nucleophilicity of the hydroxylated product (ROH).

There is considerable recent interest in the synthesis of alcohols, phenols and α-hydroxy carbonyl compounds by direct hydroxylation of organometallic reagents and metal enolates.[1-5] Prominent among the oxidizing reagents that have been used for this purpose are Vedejs' MoOPH (MoO_5·HMPA·pyridine) reagent[2] and 2-sulfonyloxaziridines **1**.[3,4] Both MoOPH and **1** are members of the same class of oxidizing reagents in that they have their active site oxygens as part of a three-membered ring. We, as well as others, have suggested that these reagents transfer oxygen to neutral substrates by a similar S_N2 reaction mechanism.[6] A kinetic investigation of the oxidation of sulfoxides to sulfones and the epoxidation of alkenes by **1** revealed that only a minor amount of negative charge developed on the oxaziridine carbon and nitrogen atoms in the transition state.[6] A transition state with negative charge residing on the oxaziridine nitrogen atom has been suggested by Knipe and co-workers for the oxidation of I^- to I_2 by **1**; i.e. **2** (R=I).[7]

SCHEME



a) Ar= p-Tolyl, b) Phenyl, c) 2-Chloro-5-nitrophenyl

Much less is known about the mechanism of oxygen-transfer by MoOPH and **1** to substrates that are anionic. Such information is particularly important in maximizing the efficiencies of these reagents. For example, the oxidation of lithium and Grignard reagents by **1** is accompanied by the sulfonimine addition product **4** (Scheme).[4] While good to excellent yields of α-hydroxy

carbonyl compounds are obtained on oxidation of sodium and potassium enolates with **1**, lithium enolates give complex mixtures of products which include the aldol adduct **4** (R=enolate).[3a,8] The formation of **4** in these transformations results in low yields and difficult separations.

In our original studies of the hydroxylation of lithium and Grignard reagents by **1** it was suggested that oxidation involves a stepwise S_N2 mechanism with the formation of hemiaminal intermediate **2** which collapses to ROH and sulfonimine **3** (Scheme).[4a] Evidence for or against the existence of **2** was not presented. However, the fact that excess sodium or potassium enolates are oxidized by **1** to give high yields of α-hydroxy carbonyl compounds accompanied by only minor amounts of the aldol addition product **4** was proposed as evidence for **2**.[3a,8] Evans and co-workers further suggest that **2** is counterion dependent, based on the fact that lithium enolates gave approximately 1:1 mixtures of the hydroxylated and aldol products.[8]

In this letter we present the first direct evidence for the involvement of a relatively stable hemiaminal intermediate **2** in the oxidation of lithium and Grignard reagents by **1**. Furthermore, the stability of **2** appears to be dependent on the nucleophilicity of the product.

Typically, hydroxylations were carried out by dropwise addition of **1** in 5 mL of THF to 1.5 equivalents (0.6 mmoles) of the organometallic reagent (RM) at -78 °C. Alternatively, RM (0.6 mmoles) was added to a THF solution of **1** cooled to -78 °C (*reverse addition*). After stirring for 30 minutes the reaction was warmed to 0 °C and quenched by addition of 2 mL of saturated NH_4Cl solution. Products were analyzed by GLC by comparison with standard solutions of authentic materials. The sulfonimine addition products, **4** were prepared in 52-80% isolated yield by reaction of RM with the sulfonimine **3**.[9]

In general, oxidation of lithium and Grignard reagents (RM) by 2-sulfonyloxaziridines **1** affords useful levels of alcohols and phenols (ROH) in addition to the unwanted adduct **4** (Table). Regardless of the counterion (MgBr, MgCl, Li, Cu, Na) the aryl organometallic reagents gives substantial amounts of **4** compared to the alkyl Grignards. Note that PhMgI affords *only* iodobenzene on oxidation with **1b** (entry 12). Reverse addition has little effect on the yield of **4** for the aryl organometallic reagents, but reduces **4** to low levels for the alkyl Grignard reagents (Table: compare entries 1, 3, 5, 14, 21 with 2, 4, 6, 15, 22).

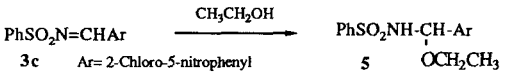
Competitive rate experiments, involving the reaction of equivalent amounts of **1** and **3** with RM, reveal that the organometallic reagents are oxidized 1-3 times faster than addition to **3**.[10] Thus if the life-time of hemiaminal **2** is long, adduct **4** would be formed in low yield. Conversely, if the life-time of **2** is short, then substantial amounts of adduct **4** would be formed. As can be seen from the results summarized in the Table the life-time of **2** is shorter for aryl organometallic reagents and longer for the alkyl organometallic reagents. This would appear to be related to the nucleophilicity of the leaving group ArO^- vs RO^-.

Hemiaminal **2** (R=Et, M=H) can be detected in the NMR by quenching the reaction of ethyl magnesium bromide with **1a-b** at -78 °C with NH_4Cl. Hemiaminal **5** was prepared in greater than 83 percent isolated yield by heating **3c** with ethanol.[11] Attempts to prepare **2a-b** (R=Et, M=H) in a similar manner resulted in hydrolysis of the sulfonimine to $ArCH(OEt)_2$ and $PhSO_2NH_2$.

Table: Oxidation of Organometallic Reagents (RM) by 2-Sulfonyloxaziridines (**1**) at -78 °C in THF.

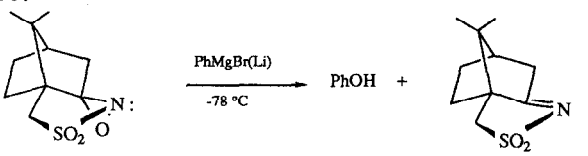
entry	RM[a]	Oxaziridine (**1**) Ar=	% Yield of Products[b] ROH	PhSO$_2$NHCH(R)Ar (**4**)
1	PhMgBr	p-Tolyl	84	51
2			90[c]	53
3	PhMgCl	p-Tolyl	38	28
4			33[c]	16
5	PhLi	p-Tolyl	55	38
6			62[c]	40
7			55[d]	44
8	p-MeOPhMgBr	p-Tolyl	29	24
9	Ph$_2$CuLi	p-Tolyl	28	7
10	PhMgBr	2-Cl-5-NO$_2$-Ph	49[c]	70
11	PhNa	Ph	56	78
12	PhMgI	Ph	O	PhI (84%)
13	o-MeOPhLi		70	78
14	CH$_3$(CH$_2$)$_6$CH$_2$MgBr	Ph	77	32
15			81[c]	2
16	CH$_3$(CH$_2$)$_5$CH(MgCl)CH$_3$	Ph	41	11
17			43[c]	6
18			86[c,d]	trace
19	C$_6$H$_{11}$MgBr	Ph	47	10
20			42[c]	8
21	C$_6$H$_{11}$MgCl	Ph	95	15
22			72[c]	8

a) Ratio of RM to **1** 1.5:1. b) Products were analyzed by gas chromatography on a 6 ft. x 1/8 " 3% OV-17 on 80/100 Supelcoport column. The analyses were determined by comparison of peak areas with standard solutions of the reaction products. c) Addition of RM to oxaziridine. d) Ratio of RM to **1**, 3:1.



3c Ar= 2-Chloro-5-nitrophenyl **5**

To eliminate the addition product **4**, an oxaziridine that affords on oxidation a sulfonimine resistant to addition by the organometallic reagent is used. In this regard oxidation of (+)-(camphorylsulfonyl)oxaziridine (**6**)[3b] with PhMgBr and PhLi gave phenol, 96% and 41 %, respectively, with recovery of the camphorsulfonimine **7** in >95% yield. Indeed PhM (MgCl, Li) failed to react with **7**. It is for this reason that the isolated chemical yields for oxidation of lithium enolates to α-hydroxy carbonyl compounds (50-86%) by (+)-**6** (50-95% ee)[3b,c] are so much better than with **1b**.[3a,8]



(+)-6 7

Previously we suggested that the oxygen-transfer reactions of oxaziridine are a useful model system for the metal peroxides and dioxiranes which are less easily studied.[6,12] If this is correct then it seems reasonable that intermediates similar to **2** may be involved in the oxygen-transfer reactions of these reagents to anionic substrates.

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9. Satisfactory elemental analysis were obtained for all new compounds. The sulfonimine addition products, **4** were characterized by a D_2O exchangable proton at δ 5.15-5.58 (d, 1H NH) and the benzilic proton at 4.25-6.0 ppm; **4a** (R=Ph) mp 153-4 °C; **4c** (R=Ph) mp 159-61 °C; **4a** (R=o-MeOPh) mp 121-2 °C; **4b** (R=n-octyl) mp 73-4 °C; **4b**(R=s-octyl) mp 78-9 °C; **4b** (R=cyclohexyl) mp 179-180 °C.
10. PhMgCl oxidized **1a** 2.3 times faster than addition to **3a**; PhLi oxidizes **1a** at about the same rate as addition to **3a**; n-$CH_3(CH_2)_7MgBr$ oxidizes **1a** 3 times faster than addition to **3a**.
11. Compound **5** (R=Et) had the following properties; mp 108-110 °C; NMR ($CDCl_3$) δ 1.08 (t, 3H, Me); 3.34-3.73 (m, 2H; diastereotopic methylene group); 5.65 (d, 1H, NH, J= 9.1 Hz); 5.98 (d, 1H, J= 9.1 Hz); 7.4-8.3 (m, 8H).
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