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Ortho-Substituted Aryl Sulfoxides Designed for Highly Diastereoselective Radical Reactions

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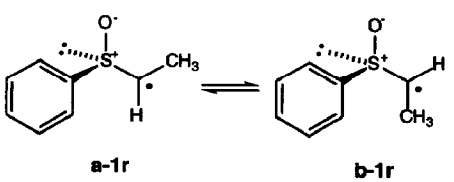
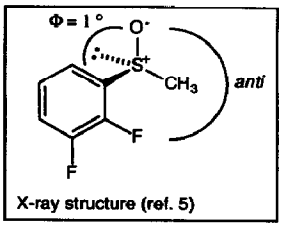
Abstract: Radical allylation of 1-arenesulfinylethyl radicals has been examined for different *ortho*-substituted aryl groups. High level of diastereoselectivity (up to 95 % ds) has been achieved with the *o*-chlorobenzenesulfinyl group. Rationalization of the results based on ground state conformation of the radicals is presented.

Recent work of our group[1,2] and others[3] has demonstrated that 1-(arylsulfinyl)alkyl radicals react with low level of diastereoselectivity. In the preceeding[2] paper we examined the allylation of 1-(phenylsulfinyl)ethyl radical (**1r**), the lack of stereoselectivity being attributed to the existence of two radical conformers of similar energy **a-1r** and **b-1r** leading to products of opposite relative configuration. Based on the assumption that a greater energy difference between the two conformers is needed in order to obtain high diastereoselectivities,[4] we decided to investigated the replacement of the phenyl group by a substituted aryl group. *Ab initio* calculations have shown that the energy profile for rotation around the C_{ar}-S bond presents one minimum corresponding to the situation where the S-O bond is eclipsed with the phenyl ring.[5] When one electron withdrawing ortho substituent X is present, the most stable conformation is the one in which the S-O bond is coplanar with the ring and *anti* with respect to the substituent X. X-ray structural analysis of 2,3-difluorophenyl methyl sulfoxide shows that such a conformation (Φ = 1°) is also predominant in the solid state.[5]

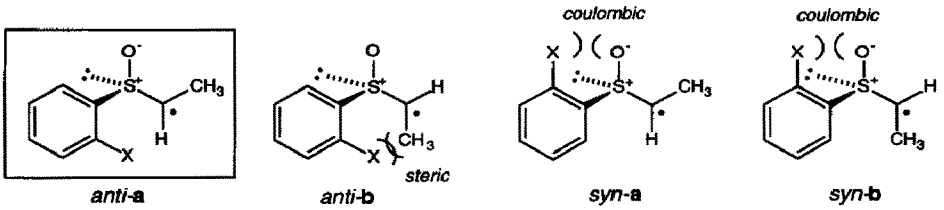


a-1r **b-1r**



X-ray structure (ref. 5)

Therefore, our basic idea is to destabilized the *anti*-**b** conformation of the radical relative to the *anti*-**a** by repulsive steric interactions between the methyl group and a substituent X in the ortho position of the phenyl ring. The two other possible conformers *syn*-**a** and *syn*-**b** were expected to be destabilized relative to the others by repulsive coulombic interactions between the group X and the negatively charged oxygen atom of the sulfoxide.



The racemic radical precursors **2-11** have been prepared and subjected to allylation reactions. The reactions of *o*-oxygenated derivatives were investigated first. Introduction of a free hydroxy group (**2**) induced no diastereoselectivity enhancement (entry 2, 65 % ds) relative to the phenyl sulfoxide **1** (entry 1, 66 % ds). The diastereoselectivity of the reaction was enhanced when the *o*-hydroxy group was protected with a tetrahydropyranyl group (entry 3, 79 % ds), a methoxymethyl group (entry 4, 82 % ds) and a *n*-propyl group (entry 5, 81 % ds). This last result indicates that the second oxygen of the acetal moiety in **3** and **4** is not necessary for the stereoselectivity enhancement. Sterically bulky groups such as pivalyl (**6**) and *t*-butyldimethylsilyl (**7**) are inefficient (entry 6 and 7, 71 % and 68 % ds respectively). More interestingly, the tosylate **8** reacted with 81 % ds (entry 8) and the two diastereoisomers were cristalline and extremely easy to separate by flash chromatography.

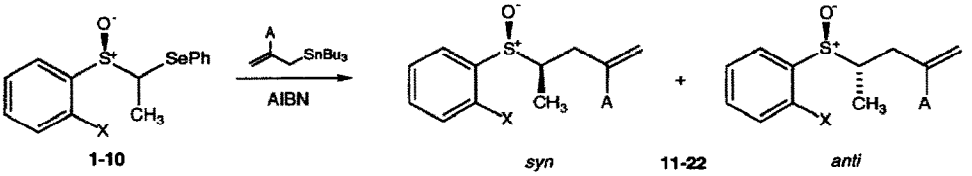


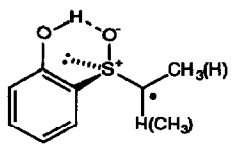
Table. Radical allylation of sulfoxides **1-10** at 10 °C in benzene.[6]

Entry	Radical precusor	X	A	Product	Yield[a)]	*syn/anti*
1	**1**	H	TMS	**11**	80 %	66 : 34[2]
2	**2**	OH	TMS	**12**	50 %	65 : 35
3	**3**	OTHP	TMS	**13**	55 %[b)]	79 : 21
4	**4**	OMOM	TMS	**14**	60 %	82 : 18
5	**5**	O*n*-Pr	TMS	**15**	70 %	81 : 19
6	**6**	OPiv	TMS	**16**	65 %	71 : 29
7	**7**	OTBDMS	TMS	**17**	62 %	68 : 32
8	**8**	OTs	TMS	**18**	65 %[c)]	81 : 19
9	**9**	Cl	TMS	**19**	60 %	90 : 10
10	**9**	Cl	TMS	**19**	20 %[d)]	95 : 5
11	**9**	Cl	H	**20**	54 %	88 : 12
12	**9**	Cl	COOMe	**21**	66 %	80 : 20
13	**10**	Br	TMS	**22**	47 %	90 : 10

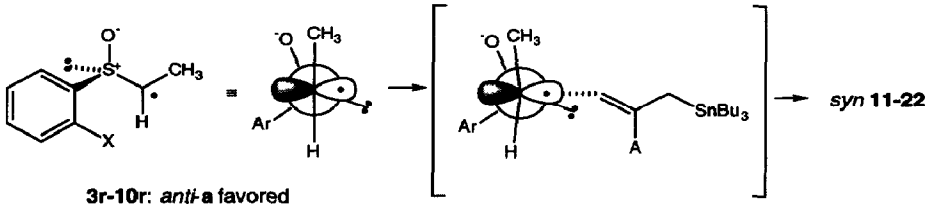
a) Isolated yield of pure material, not optimized. Starting material (up to 30 %) was recovered. b) After removal of the THP group (CF_3COOH). c) *Anti* isomer (9 %) was also isolated. d) Toluene, -70 °C, 60 % of **9** was recovered.

The best selectivities were obtained with the *o*-halogenated sulfoxides. The *o*-chloro and *o*-bromo derivatives **9** and **10** were both allylated at 10 °C with 90 % ds (entries 9 and 13).[7] The stereoselectivity was even enhanced by runing the reaction at lower temperature (entry 10, 95 % ds at -70 °C).[8] The nature of the allylstannane also had an influence on the stereoselectivity. Slightly lower selectivity was observed with allyltributylstannane (entry 11, 88 % ds). This effect was more pronounced for [2-(methoxycarbonyl)propen-1-yl]tributylstannane (entry 12, 80 % ds). The relative configuration of **22** was proved by debromination (Bu_3SnH/AIBN) to give **11** whose relative configuration was already known from our previous work.[2] For all the other products, the structure were attributed based on analogy of ^{1}H-NMR spectra.[9]

Our assumption that the radical conformation is the major factor affecting the stereoselectivity is confirmed by our results. For instance, the presence of an *o*-hydroxy group favors the *syn*-**a** and *syn*-**b** conformations of **2r** because of a hydrogen bond which leaves the conformational equilibium around the S-C• bond unchanged relative to the original phenyl case (**1r**). As expected, halogen atoms favors the *anti*-**a** conformation, the same conformation is favored (to a lower extend) by the presence of OTs, OTHP, OMOM and O*n*-Bu groups. Reactions from the less hindered face of the *anti*-**a** conformer lead to the *syn* compounds. The low selectivity observed with very large groups such as OPiv and OTBDMS is not understood.



2r: *syn*-**a** and *syn*-**b** favored
(**a**/**b** ratio similar to **1r**)



3r-10r: *anti*-**a** favored

In conclusion, we have demonstrated that by proper substitution of the aromatic ring, it is possible to obtain highly stereoselective reactions from (arylsulfinyl)alkyl radicals. For practical reasons, we believe that the o-chlorophenyl sulfoxide derivatives which are easy to prepare from *o*-chlorothiophenol will find numerous applications in the control of the stereoselectivity of radical and eventually of non-radical processes.

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References and Notes

(1) Renaud, P. *Tetrahedron Lett.* **1990**, *31*, 4601-4604.

(2) Renaud, P.; Carrupt, P.-A.; Gerster, M.; Schenk, K. *Tetrahedron Lett.* preceeding paper.

(3) Tsai, Y.-M.; Ke, B.-W.; Lin, C.-H. *Tetrahedron Lett.* **1990**, *31*, 6047-6050.

(4) Radical addition to olefins are usually characterized by an early transition state, this allows us to assume that they are reactant-like. Dewar, M. J. S.; Olivella, S. *J. Am. Chem. Soc.* **1978**, *100*, 5290-5295.

(5) Ianelli, S.; Musatti, A.; Nardelli, M.; Benassi, R.; Folli, U.; Taddei, F. *J. Chem. Soc.* **1992**, 49-58.

(6) Typical procedure: A solution of the radical precursor (1 mmol), allylstannane (1.5 mmol) and AIBN (10 mg) in degassed benzene (4 ml) was irradiated with a 300 W sunlamp at 10-15 °C for 12 h. Every 4 h, AIBN (10 mg) was added to the reaction mixture. Crude products (suitable for ^{1}H-NMR ds determination) were isolated by filtration through silicagel (AcOEt/petroleum ether) and were further purified by flash chromatography.

(7) All new compounds have been characterized by ^{1}H-NMR, ^{13}C-NMR, MS, IR and elemental analysis. ^{1}H-NMR data (200 MHz, $CDCl_3$): *syn*-**19**: 0.09 (*s*, 9H); 0.85 (d, J = 6.7, 3H); 2.35 (*dd*, J = 14.2, 9.4, 1H); 2.82 (*ddm*, J = 14.3, 5.9, 1H); 3.15 (*ddq*, J = 9.4, 5.9, 6.7, 1H); 5.49 (*d*, J = 2.4, 1H); 5.70 (*dm*; J = 2.4); 7.30-7.50 (*m*, 3H); 7.73-7.80 (*m*, 1H). *anti*-**19**: 1.35 (d, J = 7.0, 3H).

(8) At this temperature, the formation of some vinyl sulfoxide has been observed.

(9) Methyl signal (doublet) of the *syn* diastereoisomers appears at a higher field (0.8-1.0 ppm) than the one of the *anti* isomers (1.3-1.4 ppm).

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