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SYNTHESIS, DEPROTONATION, AND ALKYLATION OF S-ALLYL SULFOXIMINES

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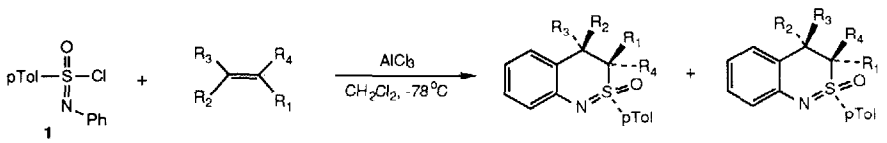
Summary: N-Phenyl-S-(4-methylphenyl)-sulfoximidoyl chloride **1** reacts with allyltrimethylsilane in the presence of aluminum chloride to give benzothiazine **4** in fair yield along with a small amount of S-allyl sulfoximine **3a**. On the other hand, **1** reacts with allyltributyltin to give the S-allyl sulfoximine **3a** almost exclusively. This latter reaction appears to be general. The sulfoximine **3a** is thermally stable and can be deprotonated smoothly with n-BuLi. The anion reacts regioselectively but not stereoselectively with simple alkylating agents. Reactions of the anion with selected aldehydes and enones proceeds with some regiocontrol and, with some exceptions, little stereocontrol.

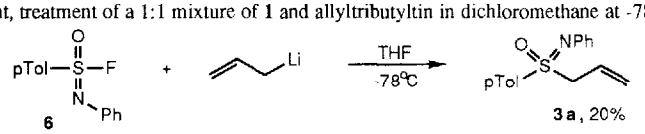
During our study of the Lewis acid mediated reaction of N-phenyl-S-(4-methylphenyl)sulfoximidoyl chloride **1** with alkenes (equation 1),[1] it became of interest to explore the reaction of **1** with alkenes structurally suited to give some indication of the mechanism of this reaction.[2] With this in mind, a solution of **1** and 1.2 equivalents of 3-trimethylsilyl-1-propene in CH_2Cl_2 (-78°C)



Equation 1

was treated with 1.5 equivalents of powdered $AlCl_3$. It was anticipated that the electrofugacity of the trimethylsilyl group and the β-effect would shunt the reaction further toward a stepwise process through carbocation **2**.[3] Elimination of TMS(+) would then result in the formation of S-allyl sulfoximine **3a**. While a small amount of **3a** (27%) was formed in this reaction, the major product of the reaction was benzothiazine **4**, isolated as a 1:1.2 mixture of diastereomers in 47% yield.

We reasoned that the increased electrofugacity of trialkyltin groups relative to the trimethylsilyl group might result in increased yields of **3a**.[4] To our delight, treatment of a 1:1 mixture of **1** and allyltributyltin in dichloromethane at -78°C with 1.5

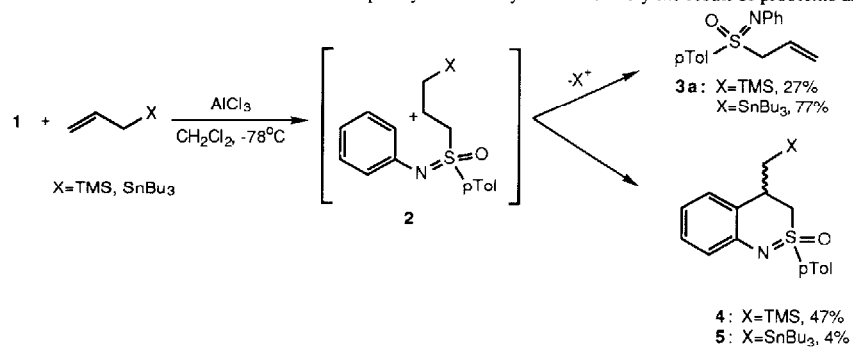


Equation 2

equivalents of finely powdered $AlCl_3$ resulted in the almost exclusive formation of **3** (77%) with only minor amounts of cycloadduct **5**. The structure of **3a** was rigorously established by independent synthesis, albeit in poor yield, as shown in equation 2.[5] Thus, reaction of sulfoximidoyl fluoride **6** with allyllithium in Et_2O at -78°C for 15 minutes gave **3a** in 20% yield after chromatographic purification. Since we anticipated that **3** might readily rearrange to sulfinamide **7** (vide infra), **7** was prepared by two independent routes

and shown to be distinctly different from **3**.[6] In particular, ^{13}C NMR showed a considerable difference between the methylene groups in these two compounds with that of **3a** resonating at 61.57 ppm and that of **7** at 48.50 ppm.

We have applied this reaction to several other sulfoximidoyl chlorides and found that the reaction proceeds in good to excellent yield. The results are accumulated in Table 1. The poor yield in entry 4 is most likely the result of problems associated with the

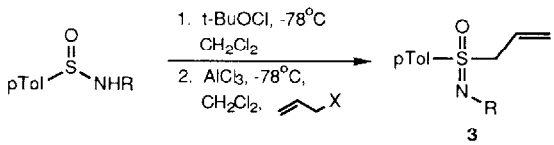


Scheme 1

formation of the sulfoximidoyl chloride itself.

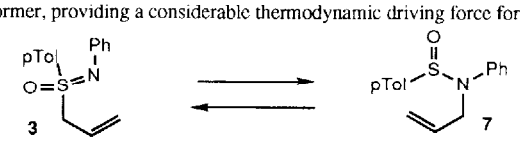
The formation of S-allyl sulfoximines is virtually unprecedented. Johnson and co-workers have reported the preparation of an S-allyl sulfoximine but have also stated that the compound was "...readily subject to rearrangement and/or C-S bond heterolysis under the usual conditions of synthesis."[7] More recently, Gais and co-workers have reported the preparation of a number of stable, enantiomerically pure allylic sulfoximines and have studied their reactions with cuprates in the context of the synthesis of isocarbacyclins.[8]

Table 1. Synthesis of S-allyl sulfoximines.



Entry	R	X	Product	Yield(%)
1	phenyl	TMS	**3a**	23
2	phenyl	$SnBu_3$	**3a**	77
3	o-methylphenyl	$SnBu_3$	**3b**	68
4	o-bromophenyl	$SnBu_3$	**3c**	24
5	benzyl	$SnBu_3$	**3d**	85

We find that **3** is quite stable, surviving intact after reflux in toluene for 20 hours. No evidence was found for the 2,3 sigmatropic rearrangement shown in Equation 3. Interestingly, semi-empirical and ab initio calculations on **8** and **9** indicate that the latter is considerably more stable than the former, providing a considerable thermodynamic driving force for the conversion of the

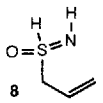


Equation 3

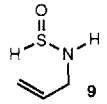
sulfoximine to the sulfinamide.[9] To the extent that this result is applicable to more complex S-allyl sulfoximines, a surprisingly large kinetic barrier to the sigmatropic rearrangement must exist. This is in contrast to at least some allylic sulfilimines, which show a

pronounced tendency to rearrange to sulfenamides.[10]

Although we are just beginning to explore the chemistry of **3a**, we have already shown that treatment of **3** with n-BuLi (THF, -78°C, 15 min.) results in the smooth formation of an anion. This could be alkylated with iodomethane and other simple



8



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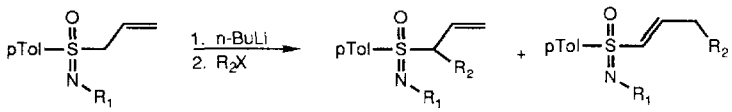
alkylating agents with complete regioselectivity to give **10** as a mixture of diastereomers. These results are summarized in Table 2 (entries 1-3, 6). The lack of stereocontrol is not surprising in view of results obtained in the alkylation of related anions.[11] Reaction of the anion of **3a** with aldehydes is regioselective but not stereoselective as determined by NMR (Table 2, entries 4-5). Further, a complicated reaction mixture is produced with cyclopentenone and cyclohexenone with both alpha and gamma reactivity being observed for the anion via 1,4 addition only. It appears that the adduct resulting from gamma, 1,4 addition to cyclopentenone is diastereomerically pure by ^{1}H and ^{13}C NMR but this is formed in only low yield.[12] It is important to note that in several cases N-phenyl-p-toluenesulfinamide or the corresponding sulfonamide (presumably formed by adventitious oxidation of the sulfiamide) can be isolated from the reaction mixtures. Whether this obtains from α elimination of the anion or β elimintion from alkylation product is not known.

Table 2. Alkylation of S-allyl sulfoximine anions.



3 **10** **11**

Entry	R_1	R_2X	Product(s)	Yield(%)[a]	**10:11** Ratio	Stereoisomer Ratio
1	Ph	CH_3I	**10a**	69[b-d]	100:0	1:1
2	Ph	EtI	**10b**	81[b]	100:0	2:1
3	Ph	CH_2CHCH_2Br	**10c**	54[b-d]	100:0	1.3:1
4	Ph	PhCHO	**10d/11d**	79	5.3:1	f
5	Ph	tBuCHO	**10e/11e**	63[b]	100:0	f
6	$-CH_2Ph$	EtI	**10f**	68	100:0	1:1
7	Ph	cyclopentenone	**10g/11g**	81[b,c]	1.4:1	**11g**: 100:0[e]
8	Ph	cyclohexenone	**10h/11h**	81[c]	1.5:1	f

[a]Yields are for chromatographically purified materials. [b]Small amounts (3-5%) of N-phenyl-p-toluene sulfinamide and/or sulfonamide were formed. [c]Yield based on recovered starting material. [d]Small amounts of dialkylated product were formed. [e]Ratios of other stereoisomers were not rigorously determined. [f]Not determined.

At present, these results do not bode well for the utilization of these anions in asymmetric synthesis. However, given the current interest in chiral allylic and benzylic anions[13] and the structural versatility of the sulfoximine functional group,[14] enantiomerically pure analogues of **3** may yet prove useful in the synthesis of allylic amines and chiral, non-racemic compounds.[8] We are currently exploring this possibility.[15]

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6. Data on **3**: ^{1}H NMR ($CDCl_3$, 300 MHz) 7.77 (d, 2H, J=8.3), 7.28 (d, 2H, J=8.0), 7.17-7.09 (m, 2H), 7.07-7.02 (m, 2H), 6.87 (tt, 1H, J=7.2,1.3), 5.84 (ddt, 1H, J=17.1,10.0,7.4), 5.30 (d, 1H, J=10.3), 5.07 (dd, 1H, J=17.1, 1.2), 4.00 (d, 2H, J=7.4) 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) 145.23, 144.10, 134.03, 129.80, 129.68, 128.91, 125.27, 124.32, 123.42, 121.52, 61.57, 21.52; IR (neat) 3079m, 3059m, 3028m, 2995w(sh), 2981w, 2959w(sh), 2922m, 2871w, 1925w, 1653w, 1638w, 1595s, 1572m, 1487s, 1457m(sh), 1448m, 1421m, 1399m, 1380w(sh), 1304s(sh), 1292s(br), 1267s, 1213s(sh), 1204s, 1186s, 1180s, 1153w(sh), 1116m(sh), 1095s, 1074m, 1038s, 1022m(sh), 1013s, 995s, 935m(br), 891w(sh), 876m, 817m, 801m, 778m(sh), 757s, 695s, 668m, 646s, 626s, 610s, 600s; MS (70 eV) 271(M+, 22), 230(43), 214(14), 183(16), 182(100), 181(14), 180(12), 168(14), 167(85), 139(38), 132(18), 123(17), 92(14), 91(33), 77(20), 69(13), 65(19), 51(10). Anal. Calcd for $C_{16}H_{17}NOS$: 271.1031. Found: 271.1010.

Sulfinamide **7** was prepared by treatment of allyl phenyl amine with p-toluenesulfinyl chloride (CH_2Cl_2, 48%) or the the alkylation of N-phenyl-p-toluenesulfinamide with allyl bromide (acetone, K_2CO_3, reflux, 60%). Data on **7**: ^{1}H NMR ($CDCl_3$, 300 MHz) 7.56 (d, 2H, J=8.2), 7.35-7.23 (m, 6H), 7.13 (tt, 1H, J=7.1,1.4), 5.62 (ddt, 1H, J=7.2,10.3,6.0), 5.04 (ddd, 1H, J=10.5, 2.8, 1.4), 5.00 (dd, 1H, J=3.4, 1.5), 4.02 (ddt, 1H, J=15.9,6.2,1.3), 3.91 (ddt, 1H, J=15.9, 5.8, 1.5), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 143.59, 141.53, 140.59, 133.91, 129.56, 129.04, 125.89, 124.89, 123.54, 118.11, 48.50, 21.39; IR (CCl_4) 3028w(sh), 3059w, 3040w, 3025w, 2985w, 2952w, 2924w, 2866w, 1643w, 1597s, 1492s, 1455m, 1418w, 1343w, 1322w, 1301m, 1292m, 1277m, 1232m, 1223m, 1210m(sh), 1177m, 1143m, 1097s, 1075s, 1051m, 1032m, 1018m, 1009m, 994m, 923m, 834m. Anal. Calcd for $C_{16}H_{17}NOS$: 271.1031. Found: 271.1024.

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9. MNDO MOPAC (Version 5.0) The heats of formation of **8** and **9** were 118 and 32 kcal/mol, respectively.

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15. Compounds **3a-3d**, **4-7**, **10a-c**, **10d**, **11d** and **11g** exhibited acceptable ^{1}H and ^{13}C NMR and IR spectra as well as satisfactory combustion analysis or exact mass data. Other compounds were characterized by spectroscopic means as an inseparable mixture of diastereomers. All yields are for chromatographically purified materials.

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