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Radical Induced Allylations of Functionalized α-Haloalkylphenyl Sulfones.

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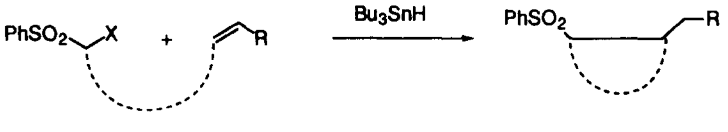
Abstract: α-Haloalkylphenyl sulfones are efficiently allylated using allyltributyltin in benzene at reflux in the presence of AIBN. Several functional groups (e.g. ester, keto, amino, nitro etc.) are tolerated by these conditions that ultimately allow the chemoselective allylation of phenylsulfones at α position.

The enhanced aptitude of the phenylsulfonyl group in stabilizing carbanions at α position is the major basis of its widespread use in organic synthesis.[1] Alkylphenylsulfonyl carbanions can be easily generated by using strong bases as BuLi, LDA etc. owing to the low acidity of these α hydrogens (pK_a about 29 in DMSO).[2] The generation of such carbanionic species often entails a limitation on the nature of the functional groups present in the molecular framework . Indeed, a chemoselective deprotonation of α-alkylphenylsulfonyl hydrogen in the presence of other readily enolizable group (carbonyls, nitro etc.), is frequently a hard question to work out. In this context, α alkylsulfonyl radicals represent an attractive option to the use of the parent carbanions in carbon-carbon bonding procedures. Such radical species have found a consistent utilization in the construction of five membered ring structures,[3] although it has been demonstrated that the sulfonyl moiety offers little or no stabilization to the radical entity.[4] On the contrary the electron withdrawing effect exerted by the sulfonyl group, makes α alkylsulfonyl radicals rather electrophilic species and therefore they would require electron rich alkenes to give additions in intermolecular processes (Scheme 1).

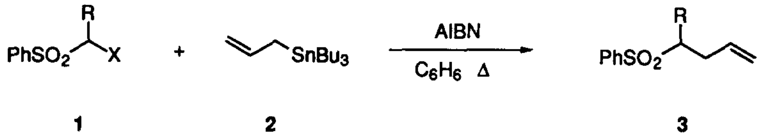


X = Cl, Br R = Ph, Alkyl, NR_2

Scheme 1

The reductive alkylation of various enamines using chloromethyl *p*-tolylsulfone in the presence of tributyltin hydride has been carried out by Renaud *et al.*, and is limited to the use of unsubstituted arenesulfonylmethyl radicals.[5] The utilization of substituted radical sources and/or less reactive olefins is probably foiled by a direct reduction of the halosulfone precursor as already underlined in some intramolecular ring closures.[3b,e]

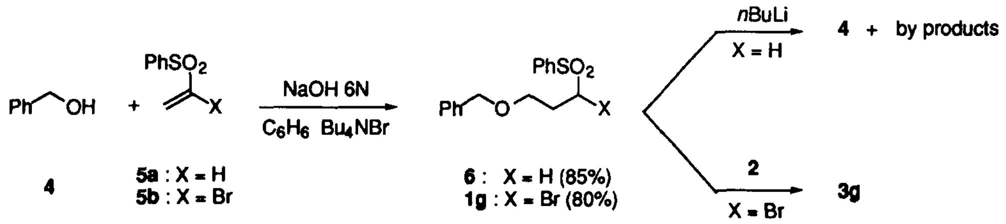
For this reason we decided to test allyltributyltin as a source of chain-elongable carbon framework, since it is known that these tin derivatives are almost 10-fold more reactives than ordinary alkenes.[6] α-Haloalkylphenyl sulfones are allylated through a S_H2' process that implies addition of the corresponding α-alkylsulfonyl radical to the allyltin derivative **2**, followed by a fragmentation of the carbon-tin bond (Scheme 2).



X = Cl, Br

Scheme 2

Reaction of 1-bromo-1-phenylsulfonyl cyclohexane **1a** with allyltributylstannane **2** in benzene at reflux gave the corresponding allyl derivative in good yield (table), showing that this procedure is rather unaffected by the steric hindrance at the radical centre. A significative number of electrophilic functions has been included in these substrates in order to check their behaviour in the radical process. As expected, keto and ester functions are fully compatible with our conditions as displayed by the allylation of compounds **1b**[7] and **1c**.[3a] Albeit β-hydroxysulfone dianions are easily alkylated at the α position,[8] the corresponding *O*-protected anions usually suffer a facile β-elimination. We have verified this behaviour treating benzyloxy sulfone **6** with BuLi in THF at -78°C (Scheme 3). After 30 minutes at -78°C about 30% of the starting sulfone **6** was decomposed into benzyl alcohol and other by products.[9] Benzyloxy-α-bromo sulfone **1g** is cleanly converted (85% yield) into allylsulfone **3g** without any of the above cited drawbacks.

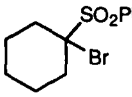
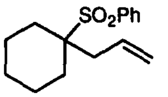
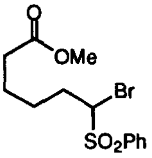
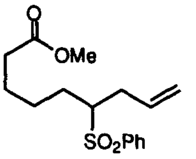
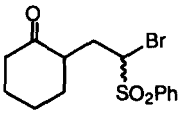
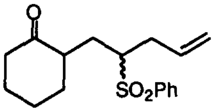
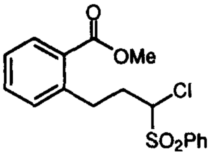
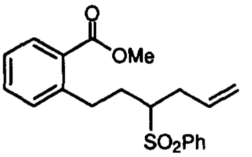
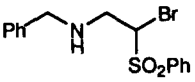
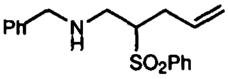
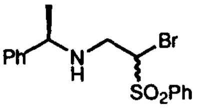
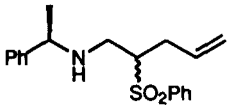
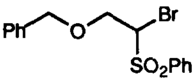
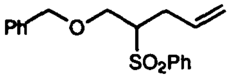
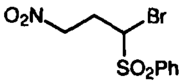
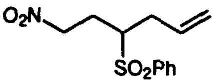


Scheme 3

Nitronate anions are readily attacked by electrophilic agents, but primary nitro groups are rather insensitive to radical cleavages.[10] Therefore, they can be profitably included in our substrates as shown for the allylation of 3-nitro-1-bromopropylphenyl sulfone **1h**.

In conclusion, α-haloalkylphenyl sulfones can be efficiently allylated in the presence of other readily enolisable groups in the molecule. Ester, keto, nitro and amino groups are unaffected by the reaction with allyltributyltin in benzene at reflux. The carbanionic version of such functionalization would create some chemoselectivity troubles that could be overcame only with extreme difficulty . Further studies on synthetic applications of this procedure are currently in progress in our laboratory.

Table. Allylation of α-Haloalkylphenyl Sulfones with Allyltributiltin in Benzene at Reflux

Entry	Substrate 1	Allyl derivative 3[11]	Reaction Time (h)	Yield %[a]
a			2	85
b			2	75
c			3	90[b]
d			2	82
e			4	70
f			4	72[b]
g			2	85
h			3	70

a : Yield of isolated, pure compounds   b : Isolated as 3:2 mixture of diastereomers.

Allylation of α-haloalkylphenyl sulfones : general procedure.

α-Haloalkylphenyl sulfone **1** (2 mmol) was dissolved in dry benzene (12 mL) and then allyltributyltin (1.32g, 4 mmol) and AIBN (0.065g, 0.4 mmol) were added. The mixture was refluxed for the appropriate time (see table) and the solvent was removed under reduced pressure. The oily residue was dissolved in ether (30 mL) and washed with 10% KF solution (3x5 mL). The organic phase was dried over sodium sulfate and, after removal of the solvent at reduced pressure, the residue was purified by flash chromatography.

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9. Decomposition of **6** was complete after 2h at -78°C. The same experiment was carried out at 0°C and the starting material was completely destroyed after 30 minutes. Reaction progress was monitored by gas chromatographic analysis.
10. Secondary, tertiary as well as activated nitroalkanes quickly react with alkyltin radicals to afford cleavage products : a) ref 6a; b) Ono, N. *Nitro Compounds : Recent Advances in Synthesis and Reactivity* Feuer, H.; Nielsen, A. T.; Eds. VCH; Weinheim, 1990, p.1.
11. Representative data for some new compounds follows: **3b**: oil, I.R. (cm^{-1}, neat): 1735 ,1640, 1320, 1145; ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm : 1.30-1.95 (m, 6H), 2.21-2.42 (m, 3H), 2.50-2.78 (m,1H), 2.95-3.15 (m, 1H), 3.64 (s,3H), 4.95-5.10 (m, 2H), 5.61-5.75 (m, 1H), 7.53-7.70 (m, 3H), 7.85-7.95 (m, 2H). **3d** : oil, I.R.: 1705, 1315, 1145; ^{1}H-NMR δ : 1.85-2.03 (m, 1H), 2.05-2.22 (m, 1H), 2.35-2.50 (m,1H), 2.58-2.73 (m, 1H), 3.00-3.25 (m, 2H), 3.83 (s, 3H), 5.05-5.15 (m 2H), 5.68-5.89 (m, 1H), 7.15-7.30 (m, 2H), 7.35-7.45 (m, 1H), 7.52-7.80 (m, 3H), 7.85-7.95 (m, 3H). **3e** : oil, I.R.: 3340, 1310, 1140 ^{1}H-NMR δ : 2.15 (s, 1H), 2.20-2.35 (m, 1H), 2.50-2.68 (m, 1H), 2.85-3.05 (m, 2H), 3.15-3.28 (m, 1H), 3.73 (d,1H, *J* 13.5 Hz), 3.76 (d, 1H, *J* 13.5 Hz), 5.00-5.13 (m, 2H), 5.58-5.80 (m, 1H), 7.20-7.38 (m, 4H), 7.48-7.70 (m, 4H), 7.80-7.88 (m, 2H). **3g** : oil, I.R. 1640, 1310, 1140; ^{1}H-NMR δ : 2.36-2.55 (m, 1H), 2.70-2.85 (m, 1H), 3.22-3.34 (m 1H), 3.76 (d, 1H, *J* 1.9 Hz), 3.79 (d, 1H, *J* 1.6 Hz), 4.36 (d, 1H, *J* 11.9 Hz), 4.37 (d, 1H, *J* 11.9 Hz), 5.05-5.15 (m, 2H), 5.65-5.88 (m,1H), 7.07-7.15 (m, 2H), 7.22-7.31 (m, 2H), 7.45-7.65 (m, 4H), 7.84-7.92 (m, 2H).

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