Nickel- or Iron-Catalyzed Coupling of Lithiated Methylthiomethyl *p*-Tolyl Sulfone with Lithiated Alkyl Sulfones to Give Methylthioalkenes

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The reaction of methylthiomethyl *p*-tolyl sulfone with alkyl sulfones when lithiated gives regioselectively vinyl sulfides in high yields in the presence of $Ni(acac)_2$ or $Fe(acac)_3$.

The (homo)coupling of metallated alkyl sulfones to give the corresponding symmetrical alkenes has been recently shown to take place efficiently under nickel catalysis.[1] Iron salts can also be used.[2]

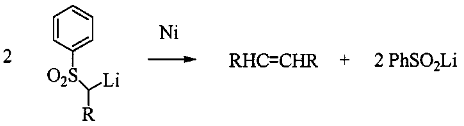

Figure 1

Benzyl sulfones, when metallated, will couple to stilbenes without transition metals.[3a] Saturated or even allylic sulfones do not couple or give only 10−20% yields.[3b] It was assumed that the usually mediocre leaving group ability of the benzenesulfinate anion was enhanced by the metallation[4] of the α-carbon atom.

Unsymmetrical coupling without transition metal catalysis has been observed between alkyl sulfones and alkoxyalkyl sulfones (both metallated) to give efficiently the corresponding alkoxyalkenes (enol ethers)[5]. The leaving group ability of the sulfinate group was considerably enhanced by the alkoxy substitution. Since the alkoxyalkyl sulfones[6] are very readily available, this might be useful as a regioselective route to enol ethers; the *tert*-butyl enol ethers in particular are not so easily prepared.

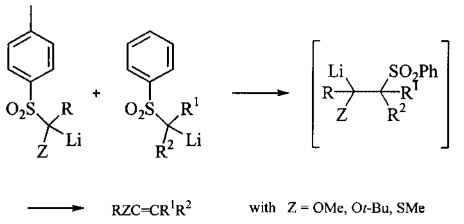

Figure 2

A similar coupling was attempted between sulfones and alkylthioalkyl sulfones. These are readily available by reaction of sulfonyl carbanions with disulfides; the first member of the series methylthiomethyl *p*-tolyl sulfone is commercially available (prepared from dimethyl sulfoxide) and can be readily alkylated.[7] After lithiation, however, they proved less reactive than the metallated alkoxyalkyl sulfones. Prolonged heating in boiling 1,2-dimethoxyethane (DME) was necessary to achieve good conversion, but the yields of vinyl sulfides were high.[5]

In order to bring about this reaction under milder conditions, catalysis with nickel salts was examined. It soon turned out that indeed the reaction can be considerably accelerated. The reaction of alkoxyalkyl sulfones was already so fast, that it did not need acceleration.

A study of the experimental conditions (Table 1), using pentyl phenyl sulfone and methylthiomethyl *p*-tolyl sulfone, showed that the coupling did not proceed at −78°C (run a) or even −30°C (run b); at 0°C the reaction gave a 27% yield of **3** (run c). When the reaction was started at room temperature and allowed to proceed for 15 h the yield was only slightly better (34%, run d).

Carrying out the metallation at 0°C before allowing the mixture to stand at room temperature improved the yield markedly (runs e, f). The best results were obtained when the metallation and the addition of the nickel catalyst were carried out at −78°C before stirring at room temp. for 15 h (run g) or 2 h (run h); the yield was then about 88%. When the time at −78°C was shortened to about 1 min the same yield was obtained after 15 h at room temp. (run i) but not after 2 h (run j). The reaction was very clean, the GLC showed only product **3** with the starting alkyl sulfone, the starting methylthiomethyl sulfone and 1,2-bis(methylthio)ethene.

Very much the same results were obtained when the metallation was performed before the addition of the catalyst or when the base was added to a mixture of sulfones and catalyst.

When the catalyst was first treated with *n*BuLi in THF at −78°C, the sulfones were added and after 1 h of stirring at −78°C the solution was allowed to warm up to room temp. and stirred for another 15 h, a yield of 71% was obtained. This indicates that low-valency nickel species are just as active as Ni^{II}.

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Table 1. Cross coupling of pentyl phenyl sulfone with methylthiomethyl *p*-tolyl sulfone under $Ni(acac)_2$ catalysis: $PhSO_2CHLiC_4H_9$ (**1**) + *p*-$TolSO_2CHLiSCH_3$ (**2**) → $C_4H_9CH{=}CHSCH_3$ (**3**)

Run	Time at −78°C	Time at other temp.	Time at r.t.	Yield by GLC (%) vinyl sulfide[c] **3**	Yield by GLC (%) side product[a]	Yield by GLC (%) starting material **1**[d]	Yield by GLC (%) starting material **2**[d]
a[b]	1 h	−	−	0	0	58	42
b	1 h	1 h, −30°C	−	< 1	0	57	41
c	1 h	1 h, 0°C	−	27	2	45	26
d	−	−	15 h	34	4	44	14
e	−	1 h, 0°C	15 h	80	1	11	8
f	−	1 min, 0°C	15 h	77	5	11	6
g	1 h	−	15 h	89	1	8	0
h	1 h	−	2 h	88	< 1	8	3
i	1 min	−	15 h	90	2	6	2
j	1 min	−	2 h	79	2	14	3

[a] 1,2-Bis(methylthio)ethene. − [b] After 1 h of stirring at −78°C and quenching. − [c] The (*Z*)/(*E*) ratio was determined by GLC and was about 52:48. − [d] Protonated.

Table 2. Coupling of lithiated pentyl phenyl sulfone with lithiated methylthiomethyl *p*-tolyl sulfone with various metal salts (4 mol-%)[a]: $PhSO_2CHLiC_4H_9$ + *p*-$TolSO_2CHLiSCH_3$ → $C_4H_9CH{=}CHSCH_3$

Run	Catalyst	Yield by GLC (%) (isolated) vinyl sulfide	Yield by GLC (%) (isolated) starting material[b]
A	$Ni(acac)_2$	89 (72)	9
B	$Fe(acac)_3$	75 (66)	15
C	$Co(acac)_2$	32	43
D	$Mn(acac)_2$	20	67
E	$Cu(acac)_2$	18	76
F	$MoO_2(acac)_2$	15	68
G	$Cr(acac)_3$	7	91
H	$Zn(acac)_2$	5	95

[a] See the general procedure in the Experiment Section. − [b] Protonated.

In previous work sometimes notable differences had been observed between aryl and the corresponding *tert*-butyl sulfones. *tert*-Butyl sulfones instead of aryl sulfones were therefore tried in some of cases (R = C_5H_{11} and $C_{12}H_{25}$) and found to behave very much as the corresponding phenyl sulfones.

These results were gratifying in that the new conditions found were indeed much milder than the former ones. In the previous work 2 equivalents of lithiated methylthiomethyl *p*-tolyl sulfone with 1 equivalent of lithiated alkyl phenyl sulfone had to be refluxed in DME for 15 to 30 h in order to achieve good coupling.[5]

A few metal salts (acetylacetonates) were tested under the reaction conditions which had been found best for nickel (Table 2). Other metals can catalyse the reaction, but only iron proved really efficient, although less than nickel.

Next, a number of other sulfones were submitted to the best reaction conditions under nickel or iron catalysis (Table 3): It can be seen that this new regioselective route to vinyl sulfides compares favourably with the previously known ones.[5,9,10]

When higher methylthioalkyl *p*-tolyl sulfones were used under the same reaction conditions, very little vinyl sulfide was obtained, whereas the non-catalyzed reaction had worked well. These lithiated sulfones were consumed very rapidly when treated alone with nickel salts, but very little bis(methylthio)alkene was obtained.

In summary, a more efficient procedure has been found for the coupling of two different sulfones, leading regioselectively to vinyl sulfides. An interesting question is: Why should the unsymmetrical coupling be so much favoured compared to the two symmetrical ones. It is known that the catalyzed coupling of two different alkyl phenyl sulfones leads to a statistical mixture of the three possible alkenes.[1] The mechanistic studies[8,11] do not yet allow a clear answer to that question.

Table 3. Coupling of lithiated sulfones with lithiated methylthiomethyl *p*-tolyl sulfone with $Ni(acac)_2$ and $Fe(acac)_3$ as catalyst[a]: $PhSO_2CLiRR'$ + *p*-$TolSO_2CHLiSCH_3$ → $RR'C{=}CHSCH_3$

Run	R^1	R^2	Yield (%) with Ni by GLC (isolated)	(*E*)/(*Z*)[b]	Yield (%) with Fe by GLC (isolated)	(*E*)/(*Z*)[b]	Ref.
a	C_4H_9	H	83 (72)	51:49	75 (66)	53:47	[9]
b	C_5H_{11}	H	97 (85)	52:48	47 (45)	55:45	[9]
c	C_6H_{13}	H	78 (65)	51:49	50 (47)	55:45	[10]
d	$C_{10}H_{21}$	H	91 (75)	55:45	44 (40)	56:44	[10]
e	C_5H_{11}	CH_3	87 (85)	54:46	72 (68)	58:42	Exp. Sect.
f	C_6H_{13}	CH_3	98 (72)	55:45	55 (54)	57:43	[5]
g	C_7H_{15}	CH_3	91 (83)	55:45	52 (50)	57:43	Exp. Sect.

[a] See general procedure in the Experimental Section. − [b] Determined by GLC.

Experimental Section

General: Methylthiomethyl *p*-tolyl sulfone and the catalysts are commercially available. The alkyl phenyl sulfones and the alkyl *tert*-butyl sulfones were prepared according to ref.[1] − IR: Perkin-Elmer 1420. − NMR: Cameca 250 and Bruker AM 400. The chemical shifts are expressed in ppm downfield from TMS or referenced to residual chloroform (δ = 7.27). − HRMS: AEI-Kratos SM 50. − GLC: Girdel 30 gas chromatograph using a non-polar capillary column.

General Procedure for the Coupling Reaction of Methylthiomethyl *p*-Toly Sulfone with Alkyl Phenyl Sulfones Under Ni(acac)$_2$ or Fe(acac)$_3$ Catalysis: The reactions were carried out under argon. Methylthiomethyl *p*-tolyl sulfone (1 mmol) and the alkyl phenyl sulfone (1 mmol) were dissolved in 10 mL of freshly distilled THF and 4% Ni(acac)$_2$ (10 mg) or Fe(acac)$_3$ (14 mg) was added. The solution was degassed and at −78°C *n*BuLi (2.2 mmol, 1.6 M, in hexane, 1.4 mL) was added dropwise to give a yellow-brown solution. The solution was stirred at −78°C for 1 h and then warmed to room temp. and stirred for 15 h. A light precipitate was observed at the end of the reaction. The reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ (50 mL), extracted with ether (3 × 50 mL), and dried with $MgSO_4$. After evaporation of the solvent, the residual brown oil was purified by flash chromatography on silica gel (pentane/ether, 90:10).

2-Methyl-1-(methylthio)hept-1-ene: 87% by GLC, (*Z*)/(*E*) = 54:46, 85% (135 mg) isolated. − IR (CCl_4): $\tilde{\nu}$ [$^{-1}$] = 2956, 2926, 2858, 1611, 1437, 1375, 1308, 1172, 1104, 1030, 814. − ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, 3 H, $-CH_2-CH_3$), 1.23−1.50 (m, 6 H,$-CH_2-$), 1.72 (s) and 1.76 (s) [3 H, $=C(R)-CH_3$], 2.06 (t, J = 7.4 Hz) and 2.16 (t, J = 7.5 Hz) [2 H, $=C(CH_3)-CH_2-$], 2.24 (s) and 2.27 (s) (3 H, $-SCH_3$), 5.60 [s, 1 H, $=CH(SCH_3)$]. − ^{13}C NMR ($CDCl_3$): δ = 14.0, 17.2, 17.3, 22.3, 22.4, 22.5, 22.8, 26.9, 27.4, 31.3, 31.5, 33.5, 39.1, 119.6, 119.9, 137.4. − HR MS; *m/z*: 158.11299; calcd. for $C_9H_{18}S$ 158.112923.

2-Methyl-1-(methylthio)non-1-ene: 91% by GLC, (*Z*)/(*E*) = 55:45, 83% (155 mg) isolated. − IR (CCl_4): $\tilde{\nu}$ [$^{-1}$] = 2963, 2926, 2851, 2734, 1628, 1462, 1381, 1314, 1178, 1116, 1036, 807. − ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, 3 H, $-CH_2-CH_3$), 1.22−1.40 (m, 10 H, $-CH_2-$), 1.75 (s) and 1.78 (s) [3 H, $=C(R)-CH_3$], 2.04 (t, J = 7.5 Hz) and 2.14 (t, J = 7.5 Hz) [2 H, $=C(CH_3)-CH_2-$], 2.25 (s) and 2.26 (s) (3 H, $-SCH_3$), 5.59 [s, 1 H, $=CH(SCH_3)$]. − ^{13}C NMR ($CDCl_3$): δ = 13.9, 17.1, 17.5, 22.5, 27.6, 28.9, 31.6, 33.4, 40.0, 119.5, 119.9, 136.6, 137.2. − HR MS; *m/z*: 186.144286; calcd. for $C_{11}H_{22}S$ 186.144223.

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