Lithiation of Alkoxyalkyl Phenyl Sulfones. New Approach to Acyl Anion Synthesis

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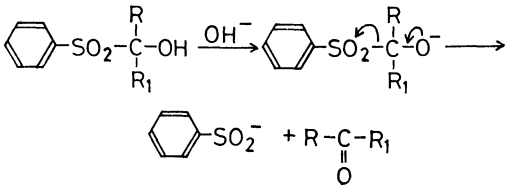
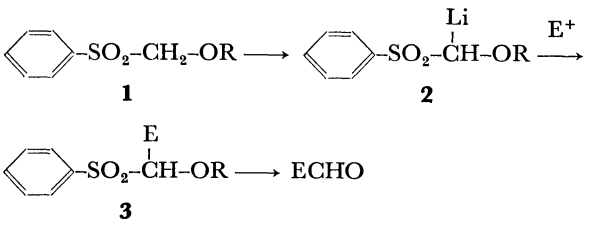
(1-Ethoxyethoxy)methyl and 1-(1-ethoxyethoxy)ethyl phenyl sulfones undergo metalation with LDA in THF in the presence of HMPA. The resulting lithium salts were easily alkylated with various alkyl halides and hydrolyzed under mild conditions to give the corresponding carbonyl compounds. The new synthetic method for the preparation of aldehydes and ketones employing these carbanions has been developed.

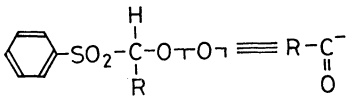
The potential usefulness of sulfur-stabilized carbanions as acyl anion equivalents has been widely recognized.[1] The commonly used "umpolung" reagents include 1,3-dithianes,[2] alkyl alkylthiomethyl sulfoxides,[3,4] vinyl sulfides,[5] dithioesters,[6] and ketene dithioacetals.[7] Few methods exist, however, for the analogous acyl anion equivalents involving an α-sulfonyl carbanion.[8] Recently, Kondo *et al.* and Julia *et al.* reported a route to α,β-unsaturated carbonyl compounds employing the lithium salts of sulfonyl ketone acetals as β-acylvinyl anion equivalents.[9] Most recently, Gokel *et al.* found that the lithio derivative of 4,4-dimethyl-1,3-oxathiolane 3,3-dioxide reacted with alkyl halides to give aldehydes by pyrolysis.[10] An α-hydroxy sulfone, as well as α,β-epoxy sulfones and cyanohydrins, gives readily a carbonyl compounds under basic conditions.[11]



Therefore, the alkylation of the carbanion of α-alkoxy sulfone (**1**) might provide a new method for the syntheses of aldehydes and ketones from alkyl halides.

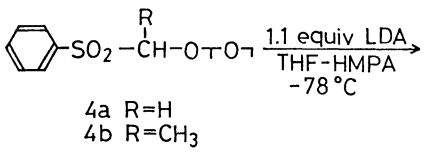


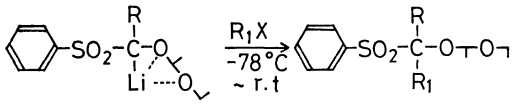
Unfortunately, Magnus and Schank have failed in the alkylation of the carbanion **2** except deuteration and methylation,[8,12] while we have found that the hitherto unknown lithium salts of (1-ethoxyethoxy)methyl phenyl sulfone (**4a**) and 1-(1-ethoxyethoxy)ethyl phenyl sulfone (**4b**) can be successfully generated and are reactive towards alkyl halides. Presumably, the carbanions of **4a** and **4b**, the ethoxyethoxyl group of which was introduced to protect the hydroxyl group, would be advantageously stabilized by the internal lithium chelation.[13] In this report we shall describe the results of our recent work on the use of lithium derivatives (**5a** and **5b**) as acyl anion equivalents.

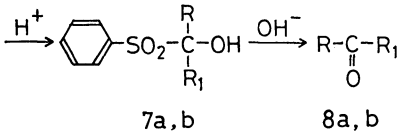


Results and Discussion

Alkylation of Carbanion **5**. Treatment of α-alkoxyalkyl phenyl sulfone (**4**) with lithium diisopropylamide (LDA) in THF at −78 °C in the presence of HMPA produced the yellow solution of carbanion (**5**).







The anion of sulfone (**4**) was efficiently trapped with alkyl halides to provide the monoalkylated product (**6**), which was hydrolyzed to afford aldehydes or ketones in moderate to good isolated yields (Table 1).

Since the elimination of benzenesulfinic acid from the product (**7**) occurs under mild basic conditions and does

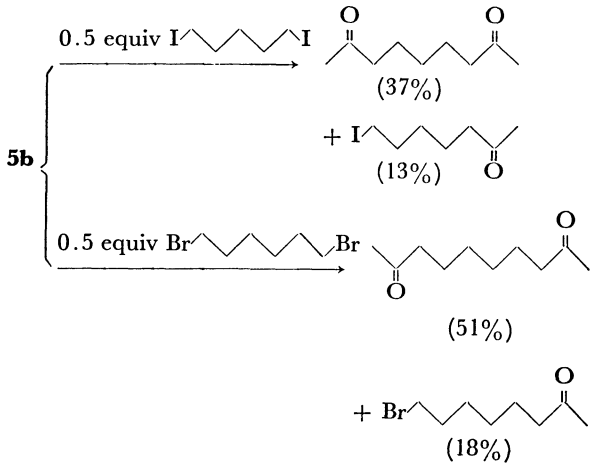


TABLE 1. PREPARATION OF ALDEHYDES AND KETONES FROM CARBANIONS (5) AND ALKYL HALIDES (R_1X)

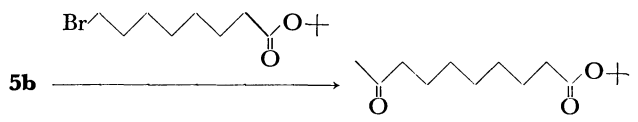
Sulfone (5)	Halide R_1X	Product (8)	Yield %	Bp °C/Torr[a)]	IR cm^{-1}	NMR (CCl_4, ppm)	Found(Calcd) C%	Found(Calcd) H%
5a	1-Iodohexane	$CH_3(CH_2)_5CHO$	71[b)]	72.0/30	1720 (neat)	0.80—1.00 (m, 3H), 1.00—1.76 (m, 8H), 2.35 (t, J=7.0 Hz, 2H), 9.62 (t, J=2.0 Hz, 1H)	73.34 (73.63)	12.59 (12.36)
5a	1-Bromoheptane	$CH_3(CH_2)_6CHO$	54[b)]		1710 (neat)	0.50—1.00 (m, 3H), 1.00—1.80 (m, 10H), 2.05 (t, J=7.0 Hz, 2H), 9.54 (t, J=2.0 Hz, 1H)	74.78 (75.00)	12.61 (12.50)
5a	1-Bromooctane	$CH_3(CH_2)_7CHO$	48[b,c)]	92.0/32	1710 (neat)	0.69—0.90 (m, 3H), 1.00—1.40 (m, 12H), 2.17 (t, J=7.5 Hz, 2H), 9.60 (t, J=2.0 Hz, 1H)	75.74 (76.00)	13.15 (12.76)
5a	1-Bromononane	$CH_3(CH_2)_8CHO$	51[d)]		1720 (neat)	0.76—1.02 (m, 3H), 1.02—1.82 (m, 14H), 2.43 (t, J=7.0 Hz, 2H), 9.70 (t, J=2.0 Hz, 1H)	76.83 (76.92)	12.92 (12.82)
5a	1-Bromodecane	$CH_3(CH_2)_9CHO$	53[b,e)]	78.0/1	1720 (neat)	0.80—1.00 (m, 3H), 1.10—1.60 (m, 16H), 2.35 (t, J=7.0 Hz, 2H), 9.56 (t, J=2.0 Hz, 1H)	77.28 (77.65)	13.19 (12.94)
5b	1-Iodobutane	$CH_3C(=O)(CH_2)_3CH_3$	47[b)]	40.0/32	1720 (neat)	0.80—1.00 (m, 3H), 1.12—1.68 (m, 4H), 2.04 (s, 3H), 2.40 (t, J=7.0 Hz, 2H)	71.73 (71.95)	12.11 (12.08)
5b	1-Iodohexane	$CH_3C(=O)(CH_2)_5CH_3$	53[b)]	56.0/22	1710 (neat)	0.80—1.00 (m, 3H), 1.16—1.64 (m, 8H), 2.04 (s, 3H), 2.35 (t, J=7.5 Hz, 2H)	74.63 (75.00)	12.94 (12.50)
5b	1-Bromohexane	$CH_3C(=O)(CH_2)_5CH_3$	46[b)] (31)[d,f)]					
5b	1-Bromoheptane	$CH_3C(=O)(CH_2)_6CH_3$	55[b)]		1720 (neat)	0.40—1.10 (m, 3H), 1.10—1.80 (m, 10H), 2.04 (s, 3H), 2.35 (t, J=7.0 Hz, 2H)	75.69 (76.06)	12.81 (12.68)
5b	1-Bromooctane	$CH_3C(=O)(CH_2)_7CH_3$	51[b)]	49.5—50.0/4	1720 (neat)	0.80—1.00 (m, 3H), 1.12—1.68 (m, 12H), 2.06 (s, 3H), 2.34 (t, J=7.0 Hz, 2H)	77.05 (76.92)	12.69 (12.82)
5b	1-Bromononane	$CH_3C(=O)(CH_2)_8CH_3$	66[b,d)]	88.0—89.0/10	1720 (neat)	0.70—0.95 (m, 3H), 0.95—1.60 (m, 14H), 2.04 (s, 3H), 2.35 (t, J=8.0 Hz, 2H)	77.69 (77.65)	13.43 (12.94)
5b	1-Bromodecane	$CH_3C(=O)(CH_2)_9CH_3$	51[b)]		1720 (neat)	0.70—1.04 (m, 3H), 1.04—2.00 (m, 16H), 2.04 (s, 3H), 2.24 (t, J=7.5 Hz, 2H)	77.58 (78.26)	13.15 (13.04)

a) 133.322 Pa. b) Isolated yields. c) $CH_3(CH_2)_7C(=O)(CH_2)_7CH_3$ was isolated in 26% yield. d) GLPC yields. e) $CH_3(CH_2)_9C(=O)(CH_2)_9CH_3$ was isolated in 14% yield. f) Without HMPA.

not require the use of heavy metal, this sequence constitutes a useful preparation of aldehydes and ketones from alkyl halides. However, the overall yields of these syntheses are insufficient for a synthetic method, and secondary and cyclic halides could not be used successfully in these synthesis. It seems to be attributed to the steric hindrance of sulfonyl group.

The ketone synthesis employing **5b** is also applicable to certain α,ω-diketones. For example, 1,5-diiodopentane and 1,6-dibromohexane were converted to 2,8-nonanedione and 2,9-decanedione, respectively.

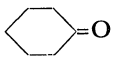
t-Butyl 1-bromooctanoate prepared from *t*-butyl acetate and 1,6-dibromohexane was converted to *t*-butyl 9-oxodecanoate, *i.e.*, a key intermediate of 9-oxodec-(*E*)-2-enoate.[14]



(27%)

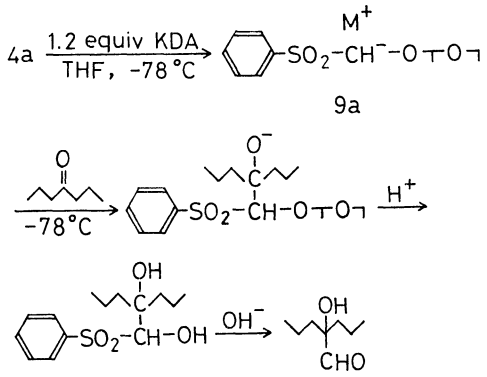
Furthermore, the monoanion **9a** generated by potassium diisopropylamide–lithium *t*-butoxide (KDA)[15] reacted with ketone to afford hydroxy aldehyde,

Table 2. Preparation of symmetrical ketones from dianions (**10**) and alkyl halides (R_1X)

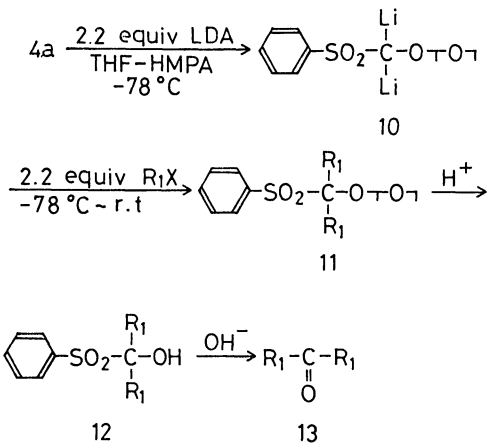
Halide R_1X	Product (**12**)	Yield %	Mp(Bp) °C(°C/Torr[a])	IR cm^{-1}	NMR (CCl_4, ppm)	Found(Calcd) C%	Found(Calcd) H%
1-Bromobutane	$CH_3(CH_2)_3C(CH_2)_3CH_3$ ‖ O	52[b]	(78.0/30)	1720 (neat)	0.64—0.96 (m, 6H), 1.08—1.64 (m, 8H), 2.30 (t, J=7.5 Hz, 4H)	76.32 (76.06)	12.77 (12.68)
1-Bromohexane	$CH_3(CH_2)_5C(CH_2)_5CH_3$ ‖ O	55[b]	31.5	1720 (KBr)	0.70—1.00 (m, 6H), 1.00—2.10 (m, 16H), 2.28 (t, J=7.0 Hz, 4H)	78.52 (78.79)	13.38 (13.13)
1-Bromoheptane	$CH_3(CH_2)_6C(CH_2)_6CH_3$ ‖ O	72[b]	40.0—40.5	1710 (KBr)	0.70—1.10 (m, 6H), 1.10—1.80 (m, 20H), 2.32 (t, J=7.0 Hz, 4H)	79.83 (79.65)	13.15 (13.27)
1-Bromooctane	$CH_3(CH_2)_7C(CH_2)_7CH_3$ ‖ O	52[b]	52.0—53.0	1710 (KBr)	0.80—1.00 (m, 6H), 1.00—1.80 (m, 24H), 2.30 (t, J=7.0 Hz, 4H)	80.02 (80.31)	13.47 (13.39)
1-Bromodecane	$CH_3(CH_2)_9C(CH_2)_9CH_3$ ‖ O	72[b]	61.0—62.0	1710 (KBr)	0.80—1.00 (m, 6H), 1.16—1.72 (m, 32H), 2.28 (t, J=7.5 Hz, 4H)	80.88 (81.29)	13.71 (13.55)
1,5-Dibromopentane		70[b]	(65.0/36)	1700 (neat)	1.50—2.10 (m, 6H), 2.20—2.50 (m, 4H)	73.27 (73.47)	10.12 (10.20)

a) 133.322 Pa. b) Isolated yields.

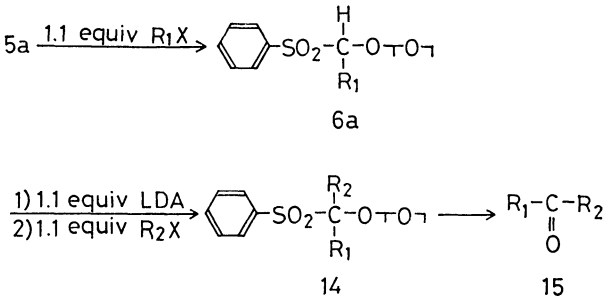
whereas the monoanion **5a** generated by LDA could not be used successfully in the reaction. For example, treatment of **9a** with 4-heptanone in THF produced 2-hydroxy-2-propylpentanal in 63% yield.



*Formation and Alkylation of Dianion **10**.* The dianion of (1-ethoxyethoxy)methyl phenyl sulfone (**4a**) was successfully generated on treatment with 2.2 equiv. of LDA in THF in the presence of HMPA. The dianion thus formed reacted with alkyl halides to give symmetrical ketones **13** in good yields (Table 2).



Since it was expected that **4a** is alkylated stepwise with the different kinds of alkyl halides, the unsymmetrical ketone synthesis from **4a** was carried out according to the following route.



The use of 1-bromohexane as R_1X and bromoethane as R_2X afforded a mixture of ethyl hexyl ketone (14%), diethyl ketone (14%) and dihexyl ketone (37%). The low yield of the desired ketone **15** may be attributable to a predominant deprotonation of **6a** with **5a** followed by alkylation with R_1X.

Experimental

Melting points were determined with a Yanagimoto melting point apparatus and are uncorrected. Boiling points were determined during distillation and are uncorrected, Infrared data were obtained using a Hitachi Model 215 spectrophotometer. The proton magnetic resonance spectra were determined on a JEOL PS-100 spectrometer. Chemical shifts are given in δ units, part per million relative to tetramethylsilane as an internal standard.

*(1-Ethoxyethoxy)methyl Phenyl Sulfone (**4a**).* Hydroxymethyl phenyl sulfone was prepared from formaldehyde and benzenesulfinic acid by the reported procedure.[16] To a solution of hydroxymethyl phenyl sulfone (68.0 g, 0.40 mol) in the presence of *p*-toluenesulfonic acid (0.40 g) in 200 ml of dichloromethane at 0 °C was added dropwise a solution of ethyl vinyl ether (0.53 mol) in 100 ml of dichloromethane. The reaction mixture was stirred at 0 °C for 3 h and extracted

with dichloromethane. The combined organic layers were washed successively with water, saturated aqueous solution of sodium hydrogencarbonate, and water, and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a yellow oil (90.0 g, 92%). Purification by alumina (Woelm B-Super 1) column chromatography (benzene) gave **4a** (50.8 g, 52%) as a colorless oil; IR (neat): 1070, 1140, and 1300 cm^{-1}. ^1H-NMR (CCl_4): δ 1.08 (t, J=6.8 Hz, 3H), 1.20 (*d*, J=6.8 Hz, 3H), 3.20—3.70 (m, 2H), 4.50 (s, 2H), 4.90 (q, J=6.8 Hz, 1H), 7.40—8.00 (aromatic, 5H). Found: C, 54.32; H, 6.69%. Calcd for $C_{11}H_{16}O_4S$: C, 54.08; H, 6.60%.

1-(1-Ethoxyethoxy)ethyl Phenyl Sulfone (4b). 1-Hydroxyethyl phenyl sulfone was prepared by stirring an ethereal solution of benzenesulfinic acid with excess acetaldehyde at 0 °C for 9 h. A solution of ethyl vinyl ether (18.5 g, 0.26 mol) in dichrolomethane (20 ml) was added to a solution 1-hydroxyethyl phenyl sulfone (37.2 g, 0.20 mol) in the same solvent (100 ml) in the presence of catalytic amount of *p*-toluenesulfonic acid (0.20 g). The reaction mixture was stirred at 0 °C for 3 h and extracted with dichloromethane. The subsequent work-up was carried out by the same procedure as described in the preparation of **4a** to give a yellow oil. Purification by alumina (Woelm B-Super 1) column chromatography (benzene) gave **4b** (30.0 g, 60%) as a pale yellow oil; IR (neat): 1300, 1140, and 1080 cm^{-1}. ^1H-NMR (CCl_4): δ 1.12 (t, J=6.8 Hz, 3H), 1.32 (d, J=6.7 Hz, 6H), 3.30—4.00 (m, 2H), 4.38 (q, J=6.7 Hz, 1H), 4.90 (q, J=6.7 Hz, 1H), 7.30—7.90 (aromatic, 5H). Found: C, 55.53; H, 6.44%. Calcd for $C_{12}H_{18}O_4S$: C, 55.82; H, 6.98%

General Procedure. Reaction of the Carbanion 5a with 1-Iodohexane: To a solution of LDA (22 mmol) in a mixture of 80 ml of THF and 4 ml of HMPA at −78 °C was added dropwise under nitrogen a solution of **4a** (20 mmol) in 10 ml of dry THF. After stirring for 1 h, a solution of 1-iodohexane (30 mmol) in 10 ml of dry THF was added dropwise. The reaction mixture was stirred at −78 °C for 2 h and at room temperature for 16 h. After quenching with methanol, the reaction mixture was treated with 2 mol dm^{-3} hydrochloric acid (150 ml) for 1 h and extracted with ether. The combined ethereal layers were treated with an aqueous sodium hydrogencarbonate solution (40 mmol) for 4 h and dried (Na_2SO_4). Removal of the solvent and distillation under reduced pressure gave 1.62 g (71%) of heptanal.

2,9-Decanedione: Mp 57.0—57.5 °C. IR (KBr): 1710 cm^{-1}. ^1H-NMR (CCl_4): δ 1.10—1.70 (m, 8H), 2.06 (s, 6H), 2.36 (t, J=7.8 Hz, 4H). Found: C, 70.31; H, 10.77%. Calcd for $C_{10}H_{18}O_2$: C, 70.59; H, 10.59%.

2,8-Nonanedione: Mp 47.5—48.0 °C. IR (KBr): 1720 cm^{-1}. ^1H-NMR (CCl_4): δ 1.00—1.70 (m, 6H), 2.08 (s, 6H), 2.38 (t, J=7.0 Hz, 4H).

t-*Butyl 9-Oxodecanoate*: Bp 97.0—98.0 °C/146.7 Pa. IR (neat): 1720 cm^{-1}. ^1H-NMR (CCl_4): δ 1.10—1.70 (m, 19H), 2.00 (s, 3H), 2.16 (t, J=7.0 Hz, 2H), 3.34 (t, J=7.0 Hz, 2H). Found: C, 69.17; H, 11.08%. Calcd for $C_{14}H_{26}O_3$: C, 69.42; H, 10.74%.

2-Hydroxy-2-propylpentanal: To a solution of potassium *t*-butoxide (2.52 g, 22 mmol) and diisopropylamine (3.1 ml, 22 mmol) in dry THF (60 ml) at −78 °C under nitrogen was added butyllithium (18 mmol). The mixture was stirred for 10 min at −78 °C, and a solution of **4a** (3.66 g, 15 mmol) in dry THF (10 ml) was added. After stirring at −78 °C for 10 min, a solution of 4-heptanone (2.57 g, 22 mmol) in dry THF (5 ml) was added, and the mixture was maintained at −78 °C for 1 h. The reaction was quenched with methanol (50 ml). The subsequent aqueous work-up was carried out by the same procedure as described previously to give a yellow oil. Chromatography on silica-gel column (hexane–benzene, 1 : 1, v/v) gave 1.36 g (63%) of 2-hydroxy-2-propylpentanal as a colorless oil; IR (neat): 3450 and 1720 cm^{-1}. ^1H-NMR (CCl_4): δ 0.60—1.90 (m, 14H), 3.45 (s, 1H), 9.40 (s, 1H). Found: C, 67.02; H, 10.90%. Calcd for $C_8H_{16}O_2$: C, 66.67; H, 11.11%.

Dihexyl Ketone: To a solution of LDA (44 mmol) in 80 ml of dry THF in the presence of HMPA (8 ml) at −78 °C was added dropwise under nitrogen a solution of **4a** (20 mmol) in 10 ml of dry THF. After stirring for 1 h, a solution of 1-bromohexane (44 mmol) in 10 ml of dry THF was added dropwise and the reaction mixture was stirred at −78 °C for 2 h and at room temperature for 16 h. The subsequent work-up was carried out by the same procedure to give yellow crystals. Recrystallization from ethanol gave 2.18 g (55%) of pure dihexyl ketone as white needles.

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