Lithium-Chlorine Exchange Reaction of α-Chloro α-Sulfonyl Ketones

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Lithium-chlorine exchange of α -chloro α -sulfonyl ketones, easily prepared from 1-chloroalkyl aryl sulfoxides and aldehydes in good yields, with *n*-butyllithium gave α -sulfonyl ketones in high yields. Some trials to trap the enolate intermediate were carried out.

Lithium-halogen exchange reactions are well known for the preparation of functionalized and/or unstable alkyl-, vinyl-, and aryllithium reagents. 1) The mechanism 2) and application of these reactions to new synthetic methodology 3) have been widely studied. Although the lithium-halogen exchange takes place with alkyl, vinyl, and aryl iodides and bromides, a lithium-chlorine exchange is rare. 4)

Recently, α -halogenated sulfur compounds (α -halosulfides,⁵) α -halosulfoxides,⁶) and α -halosulfones⁷) have received much attention in organic chemistry. They are now frequently used in the development of new synthetic methods by several research groups.⁵⁻⁷) We recently focused our attention on the chemistry of α -chlorosulfones and found that the reaction of α -chloro α -sulfonyl ketones with alkyllithium resulted in high yields of lithium-chlorine exchange (Scheme 1).

ArSCHX
$$\xrightarrow{1) \text{LDA/R}^2\text{CHO}}$$
 ArSO₂C-C-R² $\xrightarrow{R^1 \text{ O}}$ $\xrightarrow{N-\text{BuLi}}$ $\xrightarrow{R^2 \text{ OLi}}$ $\xrightarrow{R^2 \text{ ArSO}_2\text{C-C-R}^2}$ $\xrightarrow{R^2 \text{ ArSO}_2\text{C-C-R}^2}$ $\xrightarrow{N-\text{BuLi}}$ $\xrightarrow{R^2 \text{ ArSO}_2\text{ R}^2}$ $\xrightarrow{R^2 \text{ ArSO}_2\text{C-HCR}^2}$ $\xrightarrow{N-\text{BuLi}}$ $\xrightarrow{R^2 \text{ ArSO}_2\text{C-C-R}^2}$ $\xrightarrow{R^2 \text{ ArSO}_2\text{C-HCR}^2}$ $\xrightarrow{R^2 \text{ ArSO}_2\text{C-HCR}^2}$ $\xrightarrow{R^1 \text{ ArSO}_2\text{C-HCR}^2}$

A typical experiment is reported starting from 1-chloroethyl p-tolyl sulfoxide 1 (Ar=Tol, R¹=Me, X=Cl: see Table 1) and m-anisaldehyde. Treatment of 1a with 1.2 equiv. of LDA in THF at -60 °C followed by m-anisaldehyde gave the adduct (a

mixture of two diastereomers) in 96% yield. The adduct was oxidized with 3-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2 at room temperature to afford a mixture of sulfones in 97% yield. Swern oxidation⁸) of the hydroxyl group of the sulfone gave α -chloro α -sulfonyl ketone 2a quantitatively. All other α -halo α -sulfonyl ketones used in this study were synthesized in the same way in high overall yields.

 α -Chloro α -sulfonyl ketone 2a was reacted with n-BuLi (1.1 equiv.) in THF at -60 °C and after quenching with aqueous NH4Cl, 4a (Ar=Tol, R¹=Me, R²=m-methoxyphenyl)⁹⁾ was obtained in 85% yield. No product from the reaction of n-BuLi with the carbonyl carbon of 2a was detected. Obviously, this reaction is a lithium-chlorine exchange. The reaction with some other α -halo α -sulfonyl ketones was carried out and the results are summarized in Table 1.

Table 1. Lithium-halogen Exchange Reaction of α-Halo α-Sulfonyl Ketones 2 with Alkyllithium

Entry	2					4	
	Ar	R ¹	R^2	X	RLi ^{a)} (equiv.)	Yield/% ^{b)}	
a	Tol	Me	m-CH ₃ OC ₆ H ₄	Cl	<i>n</i> -BuLi (1.1)	4a	85
b	Tol	Me	$Ph(CH_2)_2$	Cl	MeLi (1.1)	4 b	58(88) ^{c)}
c	Tol	Me	$Ph(CH_2)_2$	Cl	<i>n</i> -BuLi (1.1)	4 b	95
d	Tol	Me	$CH_3(CH_2)_5$	Cl	<i>n</i> -BuLi (1.1)	4 d	99
e	Tol	ⁱ Pr	$Ph(CH_2)_2$	Cl	<i>n</i> -BuLi (1.1)	4 e	69(98) ^c
f	Tol	ⁱ Pr	$CH_3(CH_2)_5$	Cl	<i>n</i> -BuLi (1.1)	4 f	71(97) ^{c)}
g	Ph	$CH_3(CH_2)_6$	$Ph(CH_2)_2$	Cl	MeLi (1.1)	4 g	56(75) ^{c)}
h	Ph	$CH_3(CH_2)_6$	$Ph(CH_2)_2$	Cl	<i>n</i> -BuLi (1.1)	4 g	90
i	Ph	$CH_3(CH_2)_6$	$CH_3(CH_2)_5$	Cl	<i>n</i> -BuLi (1.1)	4 i	92
j	Tol	Me	$Ph(CH_2)_2$	$Br^{d)}$	<i>n</i> -BuLi (3.0)	4 b	94
k	Ph	Me	$Ph(CH_2)_2$	F ^{e)}	<i>n</i> -BuLi (2.1)	5 ^{f)}	53

a) All reactions were carried out in dry THF at -60 °C. b) Isolated yield. All α -sulfonyl ketones 4, and 5 are colorless oily compound.

c) Conversion yield. d) 1-Bromoethyl *p*-tolyl sulfoxide was prepared according to the method by Iriuchijima (Ref. 11). e) 1-Fluoroethyl phenyl sulfoxide was prepared according to the method by Wunk (Ref. 12).

As shown in Table 1, this lithium-chlorine exchange reaction of α -chloro α -sulfonyl ketones is effective with both MeLi and n-BuLi; however, n-BuLi gave much higher yields. Lithium-bromine exchange 10) of α -bromo α -sulfonyl ketone also gave a good result (entry j). Lithium-fluorine exchange did not take place with α -fluoro α -sulfonyl ketone (entry k); this reaction gave alkylated product 5 in a moderate yield.

Metal-chlorine exchange of α -chloro α -sulfonyl ketones was also studied with Grignard reagents. For example, treatment of 2d with MeMgBr in THF only gave methylated product 6. The use of EtMgBr in THF gave a reduced alcohol 7. Reaction of 2a with EtMgBr also gave the alcohol 8 in a high yield and no magnesium-chlorine exchange was detected.

$$ToISO_{2}C(CH_{3})C(CH_{2})_{5}CH_{3} \xrightarrow{MeMgBr} ToISO_{2}C(CH_{3})C(CH_{2})_{5}CH_{3}$$

$$CI \qquad CI \qquad CH_{3} \qquad 6 \qquad (75\%)$$

$$OH \qquad OH \qquad I$$

$$ToISO_{2}C(CH_{3})CH(CH_{2})_{5}CH_{3}$$

$$CI \qquad CH_{3} \qquad 6 \qquad (75\%)$$

$$OH \qquad I$$

$$CI \qquad 7 \qquad (67\%)$$

$$OH \qquad OH \qquad I$$

$$CI \qquad 7 \qquad (67\%)$$

$$OH \qquad OH \qquad I$$

$$CI \qquad OCH_{3} \qquad EtMgBr \qquad ToISO_{2}C(CH_{3})C \qquad OH \qquad I$$

$$CI \qquad H \qquad OCH_{3} \qquad 8 \qquad (92\%)$$

The lithium-chlorine exchange of α -chloro α -sulfonyl ketones 2 was thought to take place through an enolate 3. Actually, the reaction of 2a with 1.1 equiv. of n-BuLi at -60 °C followed by tert-butyldimethylsilyl chloride (TBDMS-Cl) and triethylamine gave silyl enol ether 9 (determined by 1 H NMR), which was then hydrolyzed on silica gel to afford β -ketosulfone 4a. Treatment of the enolate intermediate 3a with ethyl chloroformate gave the enol carbonate 10 in 29% yield with 4a (53%). Treatment of the enolate intermediate 3a with acetaldehyde gave the alcohol 11 in 35% yield with 4a (64%).

ToISO₂ OTBDMS ToISO₂ OCO₂C₂H₅ O ToISO₂C(CH₃)C CH(OH)CH₃ OCH₃
$$CH_3O$$
 CH_3O CH_3O

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- 9) 1-(3-Methoxyphenyl)-2-(p-tolylsulfonyl)-1-propanone **4a**: colorless oil; IR (neat) 1690 (CO), 1150 (SO₂) cm⁻¹; ¹H NMR δ 1.55 (3H, d, J=7 Hz), 2.42 (3H, s), 3.83 (3H, 3H, s), 5.10 (1H, q, J=7 Hz), 7.0-7.8 (8H, m); MS m/z (%) 318 (M⁺, 19), 135 (100).
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