

## Ligand Exchange Reaction of Sulfoxides in Organic Synthesis: A New Method for Generation of Magnesium Enolates of $\alpha$ - Chloro Carboxylic Acids and Their Derivatives

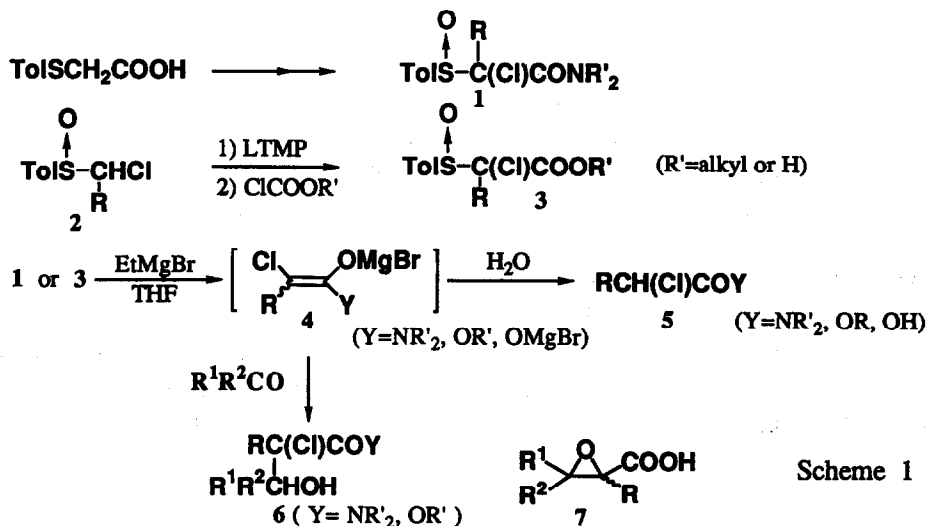
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*Abstract:* Treatment of  $\alpha$ -chloro  $\alpha$ -sulfinyl carboxylic acid derivatives with EtMgBr in THF at low temperature gave magnesium enolates of the  $\alpha$ -chloro carboxylic acid derivatives. The enolates reacted with ketones and aldehydes to afford aldol compounds (or  $\alpha,\beta$ -epoxy acids) in good yields.

Enolates are one of the most fundamental and versatile intermediates in organic synthesis with carbonyl compounds.<sup>1</sup> The enolates of carbonyl compounds are now easily prepared using bases containing various metals (Li, Mg, Zn, B, Al, etc.). On the other hand, generation of enolates from carboxylic acids and their derivatives is somewhat more difficult than from carbonyl compounds. The enolates of carboxylic acid derivatives are generated by lithium amides or by the Reformatsky reaction<sup>2</sup> (zinc enolate) from  $\alpha$ -bromo esters. Direct formation of magnesium enolates of carboxylic esters are usually difficult unless  $\alpha$ -position is activated with an electron-withdrawing group.<sup>3</sup>




Scheme 1

We recently reported new synthetic methods from 1-haloalkyl aryl sulfoxide and carbonyl compounds<sup>4</sup> via ligand exchange reaction of sulfoxides.<sup>5</sup> Specifically, on treatment with EtMgBr,  $\alpha$ -halo  $\alpha$ -sulfinyl ketones gave magnesium enolates accompanied with a reductive elimination of the sulfinyl group.<sup>6</sup> In continuation of our studies on the ligand exchange reaction of sulfoxides in organic synthesis, here we report a novel method for generation of the magnesium enolate of  $\alpha$ -chlorocarboxylic acids and their derivatives 4, and trapping the enolates with carbonyl compounds (Scheme 1).

$\alpha$ -Chloro  $\alpha$ -sulfinylamides 1 were easily prepared from *p*-tolylthioacetic acid.<sup>7</sup>  $\alpha$ -Chloro  $\alpha$ -sulfinylesters and acids 3 were conveniently obtained from 1-chloroalkyl *p*-tolyl sulfoxides 2<sup>8</sup> and alkyl chloroformate using lithium 2,2,6,6-tetramethylpiperidide (LTMP) as a base.

Treatment of  $\alpha$ -chloro  $\alpha$ -sulfinylamide 1a (see Table 1) with 1.3-equiv. of EtMgBr in THF at -78 °C for 10 min followed by quenching with aqueous NH<sub>4</sub>Cl, gave cleanly the desulfinylated  $\alpha$ -chloroamide 5a in 78% yield. Similar treatment of the  $\alpha$ -chloro  $\alpha$ -sulfinylesters (3e and 3f) gave  $\alpha$ -chloroesters 5e and 5f with better yields. Quite interestingly, even  $\alpha$ -chloro  $\alpha$ -sulfinylcarboxylic acid 3g gave  $\alpha$ -chloropropionic acid 5g in good yield (entry g). Moreover, the amides 1b-1d, prepared from primary amines or ammonia, required three-equivalent of EtMgBr for completion of the reaction. It is thought that the acidic NH hydrogen of the amides consumes one-equivalent of EtMgBr.

Table 1. Yield of the Desulfinylation of 1 or 3


Entry	1 or 3		EtMgBr (eq.) <sup>a)</sup>	<u>5</u> Yield(%) <sup>c)</sup>
	R	NR' <sub>2</sub> or OR'		
a	1a	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> —N 	1.3	5a(78)
b	1b		3.0	5b(73) <sup>d)</sup>
c	1c		3.0	5c(80) <sup>d)</sup>
d	1d	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> —NH <sub>2</sub>	3.0	5d(78)
e	3e		2.0 <sup>b)</sup>	5e(91)
f	3f		2.0 <sup>b)</sup>	5f(93)
g	3g	CH <sub>3</sub> —OH	2.5	5g(67)

a) To a solution of EtMgBr in THF was added dropwise a solution of 1 or 3 in dry THF at -78°C. b) To a solution of 1 or 3 in dry THF at -78°C was added dropwise a solution of EtMgBr. c) Isolated yield. d) Conversion yield.

This desulfinylation was assumed to be a ligand exchange reaction of sulfoxide<sup>9</sup> and the product would be a magnesium enolate 4. To confirm this expectation and to develop this reaction to new synthetic method, the reaction was quenched with carbonyl compounds (Scheme 1, Table 2). For example, treatment of 1a with EtMgBr in THF at -78 °C for 10 min, followed by addition of slight excess of cyclohexanone, gave the desired aldol 6a in 69%

yield. Similar treatment of  $\alpha$ -chloro  $\alpha$ -sulfinylesters **3e** and **3f** gave the aldol products **6l** and **6m** in good yields. Other examples are shown in Table 2. When hindered ketone and easily enolizable ketone were used in this reaction, no adduct but  $\alpha$ -chloroamide **5a** was obtained in low to moderate yield (entry d and e).

Table 2. Synthesis of  $\alpha$ -Chloro  $\beta$ -Hydroxy Esters and Amides **6** from **1** and **3** with Carbonyl Compounds via the Ethylmagnesium Bromide Promoted Desulfinylation

Entry	1 or 3		Carbonyl Compounds		6 Yield(%) <sup>a)</sup>
	R	Y	R <sup>1</sup>	R <sup>2</sup>	
a	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub>		—(CH <sub>2</sub> ) <sub>5</sub> —	—	6a(69)
b			Ph	H	6b(72)
c			m-MeOC <sub>6</sub> H <sub>4</sub>	H	6c(63)
d			Ph	Ph	6d(0) <sup>b)</sup>
e			PhCH <sub>2</sub>	CH <sub>3</sub> CH <sub>2</sub>	6e(0) <sup>b)</sup>
f		—NHCH <sub>2</sub> Ph	—(CH <sub>2</sub> ) <sub>5</sub> —	—	6f(72)
g			Ph	H	6g(68)
h			Ph(CH <sub>2</sub> ) <sub>2</sub>	H	6h(66)
i		—NH(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	—(CH <sub>2</sub> ) <sub>5</sub> —	—	6i(61)
j			Ph	H	6j(81)
k		—NH <sub>2</sub>	—(CH <sub>2</sub> ) <sub>5</sub> —	—	6k(76)
l	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub>	—OEt	—(CH <sub>2</sub> ) <sub>5</sub> —	—	6l(80)
m		—O <sup>t</sup> Bu	Ph(CH <sub>2</sub> ) <sub>2</sub>	H	6m(64)

a) Isolated yield. b) This reaction gave  $\alpha$ -chloroamide **5a** via the desulfinylation of **1a**.

This reaction of  $\alpha$ -chloro  $\alpha$ -sulfinyl acid **3g** gave somewhat different results. For example, treatment of **3g** with three-equivalent of EtMgBr for 10 min, followed by quenching with 3-phenylpropanal gave  $\alpha,\beta$ -epoxy carboxylic acid **7a** in 55% yield after the usual workup for isolation of carboxylic acid (basic extraction). Other results are shown in Table 3. It is worth noting that this is a novel Darzen's condensation of  $\alpha$ -chlorocarboxylic acid. The Darzen's condensation<sup>10</sup> usually is carried out with  $\alpha$ -halo esters.

We are continuing to study the scope and limitation, and the synthetic uses of this procedure.

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Table 3. Synthesis of  $\alpha,\beta$ - Epoxy Carboxylic Acid **7** from **3g** and Carbonyl Compounds *via* the Ethylmagnesium Bromide Promoted Desulfinylation

Entry	$R^1R^2CO$		7 Yield(%) <sup>a)</sup>
	$R^1$	$R^2$	
a	Ph(CH <sub>2</sub> ) <sub>2</sub>	H	7a(55)
b	Ph	H	7b(68)
c	Ph	CH <sub>3</sub>	7c(73)
d	Ph	Ph	7d(81)

a) Isolated yield.

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7. *p*-Tolythioacetic acid was treated with SOCl<sub>2</sub> followed by an amine to give an amide, which was chlorinated with NCS. Then the resulting  $\alpha$ -chlorosulfide was oxidized with MCPBA to give  $\alpha$ -chloro  $\alpha$ -sulfinylacetic acid amide. Alkylation of the amide with LDA and iodoalkane gave **1** in high overall yield.
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