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# First example of the Mislow–Braverman–Evans rearrangement retaining the sulfur atom on the original carbon

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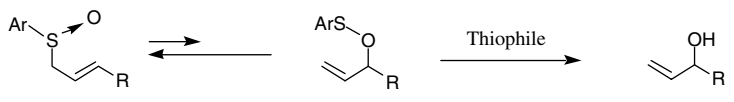
**Abstract**—Treatment of 1-chloro-2-methylalkenyl *p*-tolyl sulfoxides with *N*-lithio 2-piperidone in THF at room temperature resulted in the formation of 1-chloro-2-(hydroxymethyl)alkenyl *p*-tolyl sulfides in good yields. This reaction is the first example of the Mislow–Braverman–Evans rearrangement retaining the sulfur atom on the original carbon.


Rearrangement of allylic sulfoxides to allylic sulfenates was found and developed into a new reaction for the synthesis of allylic alcohols by Mislow,[1] Braverman,[2] and Evans.[3] This reaction is now called the Mislow–Braverman–Evans rearrangement (Scheme 1).[4]

The rearrangement of allylic sulfoxide **1** to allylic sulfenate **2** is a reversible [2,3]-sigmatropic rearrangement and the equilibrium is usually far biased toward the allylic sulfoxide **1**. When this reaction is carried out with a thiophile, such as trimethyl phosphite, the allylic sulfenate **2** is transferred into allylic alcohol **3**.[3] By this treatment, the reaction becomes irreversible to give an allylic alcohol **3**. In this procedure, the sulfur atom of the allylic sulfenate **2** is removed from the compound.

In this decade, we are interested in the use of 1-chlorovinyl *p*-tolyl sulfoxides in organic synthesis.[5] Recently, we found that treatment of the 1-chloro-2-methyl-1-propenyl *p*-tolyl sulfoxide **4** with *N*-lithio 2-piperidone (5 equiv) in THF at room temperature for 3 h resulted in the formation of the vinyl sulfide having a hydroxymethyl group at the β-position **6** in 90% yield as an inseparable mixture of two geometrical isomers ($Z/E = 73/27$).[6,7] Interestingly, 1-(*p*-tolylsulfanyl)piperidin-2-one **7** was obtained as a by-product in a trace amount from the reaction mixture (Scheme 2).

Obviously, this reaction can be recognized to be a unique Mislow–Braverman–Evans rearrangement and a plausible mechanism is as follows (Scheme 3). At first, the vinyl sulfoxide **4** was isomerized to the allylic sulfoxide **A** with a strong base,[8] *N*-lithio 2-piperidone **5** ($pK_a$ value of the hydrogen on the nitrogen of 2-piperidone is 26.4).[9] Then, the sulfoxide–sulfenate rearrangement took place to give allylic sulfenate **B**. The tolylsulfanyl group in **B** was attacked by *N*-lithio 2-piperidone **5** and the sulfanyl group was transferred from the oxygen to the nitrogen to afford 1-(*p*-tolylsulfanyl)piperidin-2-one **7** and alkoxide **C**. Next, the hydrogen on the vinylic carbon bearing the chlorine atom was eliminated by the base **5** to give alkenyl anion **D**, which attacks the sulfanyl group in **7** to afford product **6**. This is the first example of the Mislow–Braverman–Evans rearrangement retaining the sulfur atom on the original carbon.




**1** **2** **3**

**Scheme 1.**

*Keywords*: Sulfoxide; Vinyl sulfoxide; Sulfoxide–sulfenate rearrangement; Mislow–Braverman–Evans rearrangement; Allylic alcohol.
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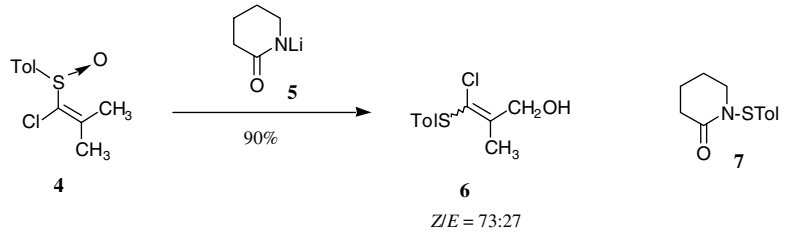
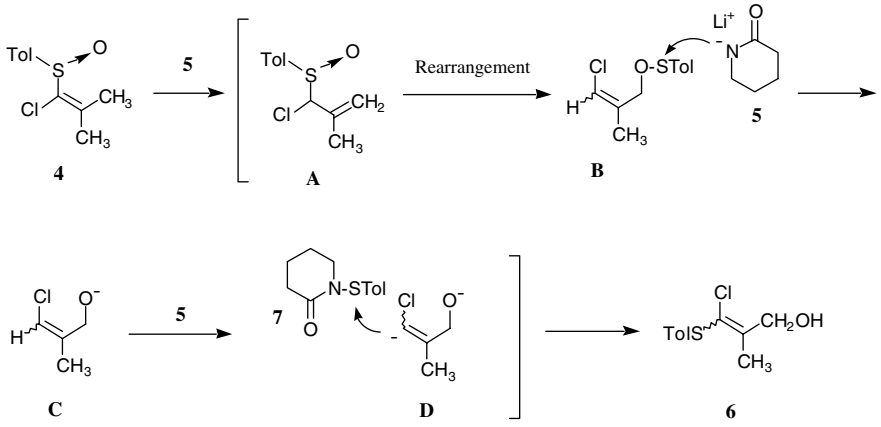


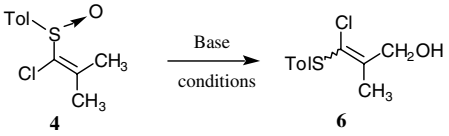

**Scheme 2.**

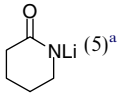
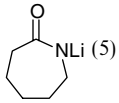
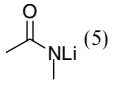
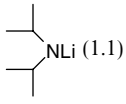



**Scheme 3.** A plausible mechanism for the Mislow–Braverman–Evans rearrangement retaining the sulfur atom on the original carbon.

We then investigated the proper base for this reaction and the results are summarized in Table 1. Entry 1 shows the result described above. *N*-Lithio caprolactam showed a similar result as *N*-lithio 2-piperidone **5**; however, the yield was diminished somewhat. *N*-Lithio *N*-methylacetamide gave markedly diminished yield of **6**. The reaction with lithium diisopropylamide gave only a complex mixture even when the reaction was conducted at −78 °C for 10 min (entry 4).

**Table 1.** Treatment of 1-chlorovinyl *p*-tolyl sulfoxide **4** with bases




| Entry | Base (equiv) | Temperature | Time | Yield of **6** (%) |
|---|---|---|---|---|
| 1 |  (5)[a] | Room temperature | 3 h | 90 |
| 2 |  (5) | Room temperature | 3 h | 75 |
| 3 |  (5) | Room temperature | 3 h | 30 |
| 4 |  (1.1) | −78 °C | 10 min | Complex mixture |

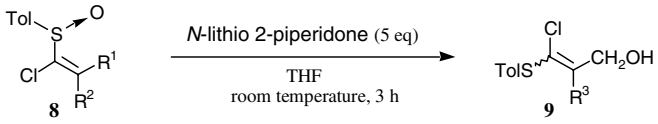
[a] When this reaction was carried out with less amount of the base, some amount of the starting material **4** remained.

From the results in Table 1, it became obvious that the reaction proceeds smoothly when the base having appropriate basicity was used. A base having stronger basicity, lithium diisopropylamide, resulted in decomposition of **4**. It is also interesting that *N*-lithio cyclic amide gave better yields (compare entries 1 and 2 with 3).

In order to know the generality and the characteristics of this reaction, various kinds of 1-chloroalkenyl *p*-tolyl sulfoxides **8** were synthesized from ketones and aldehydes, and treated with *N*-lithio 2-piperidone. The results are summarized in Table 2. Entries 1 and 2 show the results of 1-chloro-2-methyl-1-heptenyl *p*-tolyl sulfoxide **8a**, which was synthesized from 2-heptanone. Both geometrical isomers, **8a**-***E*** and **8a**-***Z***, gave a similar yield of the allylic alcohols and it was found that the ratio of the isomers of the allylic alcohols was the same.

1-Chloroalkenyl *p*-tolyl sulfoxide derived from methyl vinyl ketone (**8b**-***E*** and **8b**-***Z***) gave a mixture of allylic alcohols in 66% and 52% yield and again the ratio of the isomers was completely the same (entries 3 and 4). 1-Chloroalkenyl *p*-tolyl sulfoxide derived from acetophenone (**8c**-***E*** and **8c**-***Z***) gave a mixture of allylic alcohols in better yield and again the ratio of the isomers was completely the same (entries 5 and 6). The results shown in entries 7 and 8 implied that this reaction is compatible with esters. 1-Chloroalkenyl *p*-tolyl sulfoxide derived from acetaldehyde **8e**-***Z*** gave 3-chloro-3-(*p*-tolyl-

**Table 2.** Treatment of 1-chlorovinyl *p*-tolyl sulfoxides **8** with *N*-lithio 2-piperidone




| Entry | 8 | | | 9 | | |
|---|---|---|---|---|---|---|
| | | $R^1$ | $R^2$ | $R^3$ | Yield (%) | Diastereomeric ratio (*Z*:*E*)[a] |
| 1 | **8a-*E*** | $(CH_2)_4CH_3$ | $CH_3$ | $(CH_2)_4CH_3$ | 53 | 75:25 |
| 2 | **8a-*Z*** | $CH_3$ | $(CH_2)_4CH_3$ | $(CH_2)_4CH_3$ | 55 | 75:25 |
| 3 | **8b-*E*** | $CH{=}CH_2$ | $CH_3$ | $CH{=}CH_2$ | 66 | 86:14 |
| 4 | **8b-*Z*** | $CH_3$ | $CH{=}CH_2$ | $CH{=}CH_2$ | 52 | 86:14 |
| 5 | **8c-*E*** | Ph | $CH_3$ | Ph | 86 | 32:68 |
| 6 | **8c-*Z*** | $CH_3$ | Ph | Ph | 83 | 31:69 |
| 7 | **8d-*E*** | $(CH_2)_5COOC(CH_3)_3$ | $CH_3$ | $(CH_2)_5COOC(CH_3)_3$ | 50 | 77:23 |
| 8 | **8d-*Z*** | $CH_3$ | $(CH_2)_5COOC(CH_3)_3$ | $(CH_2)_5COOC(CH_3)_3$ | 58 | 75:25 |
| 9 | **8e-*Z*** | H | $CH_3$ | H | 81 | 96:4 |
| 10 | **8f** | $CH_2CH_3$ | $CH_2CH_3$ | | No reaction | |
| 11 | **8g** | | $-(CH_2)_{14}-$ | | No reaction | |
| 12 | **8h** | $(CH_2)_5CH_3$ | H | | No reaction | |

[a] The ratio of the isomers was determined from $^1$H NMR.

sulfanyl)-2-propenol in 81% yield and the *Z*-isomer was obtained predominantly in this case (entry 9).

The results shown in entries 10–12 are very interesting. No reaction was observed on treatment of alkenyl sulfoxides **8f–h** (these were synthesized from 3-pentanone, cyclopentadecanone, and heptanal) with *N*-lithio 2-piperidone. Even forcing conditions with *N*-lithio 2-piperidone, **8f–h** were completely recovered and found to be quite stable with this base.

From these results, at this point, these unique Mislow–Braverman–Evans rearrangements take place so far only when the 1-chloroalkenyl *p*-tolyl sulfoxides have at least one methyl group at the β-position. We are continuing our investigation to find the conditions for this unique rearrangement to other 1-chloroalkenyl *p*-tolyl sulfoxides.

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6. To a flame-dried flask under argon atmosphere at room temperature were added dry THF (40 mL) followed by 2-piperidone (5 mmol). *n*-BuLi (5 mmol) was added to the reaction mixture and the solution was stirred for 10 min. A solution of **4** (222 mg, 1 mmol) in dry THF was added to the reaction mixture and the whole mixture was stirred at room temperature for 3 h. The reaction was quenched by adding saturated aqueous $NH_4Cl$ and the product was purified by silica gel column chromatography to give **6** (colorless oil; 200 mg; 90%) as an inseparable mixture of two geometrical isomers. IR (neat) 3338 (OH), 2920, 1491, 1015, 804 $cm^{-1}$; MS *m*/*z* (%) 228 ($M^+$, 75), 230 (29), 124 (100), 92 (17), 91 (49). Calcd for $C_{11}H_{13}ClOS$: M, 228.0374. Found: *m*/*z* 228.0366. $^1$H NMR: ***Z*-6**, 1.69 (1H, t, $J = 6.0$ Hz, OH), 2.20 (3H, s), 2.34 (3H, s), 4.41 (2H, d, $J = 6.4$ Hz), 7.15 (2H, d, $J = 8.0$ Hz), 7.25 (2H, d, $J = 8$ Hz). ***E*-6**, 1.69 (1H, t, $J = 6.0$ Hz, OH), 2.10 (3H, s), 2.34 (3H, s), 4.52 (2H, d, $J = 6.1$ Hz), 7.15 (2H, d, $J = 8.0$ Hz), 7.26 (2H, d, $J = 8$ Hz).
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