

Facile Synthesis of (E)-Allylic Alcohols by Acid-Catalyzed Modification of the Mislow–Evans Rearrangement of Allylic Sulfoxides

YUKIO MASAKI, KAZUHIKO SAKUMA, and KENJI KAJI

Gifu College of Pharmacy, 5-6-1 Mitahora Higashi, Gifu 502, Japan

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The Mislow–Evans rearrangement of \( \alpha,\beta \)- and \( \alpha,\gamma \)-disubstituted allylic sulfoxides (2) to (E)-allylic alcohols (4) was found to occur under acidic conditions. By combination of this method with a catalytic oxidation of allylic sulfides (1), a novel one-pot transformation of allylic sulfides (1) to 4 was achieved.

**Keywords**—acid-catalyzed Mislow–Evans rearrangement; allylic sulfoxide; (E)-allylic alcohol; catalytic oxidation using selenium dioxide; one-pot synthesis

The Mislow–Evans rearrangement has been widely used for the highly stereoselective 1,3-transposition of allylic sulfoxides (2) and alcohols (4) through intermediary allylic sulenates (3) as a reversible 1,3-charge affinity inversion operation. Usually this process for the conversion of allylic sulfoxides (2) into the (E)-allylic alcohols (4) has been accomplished by use of thiophilic reagents such as trialkyl phosphite \([RO]_3P\), thiaalkoxide \((RS^-)\), and amine in excess. In this note we wish to report a facile acid-catalyzed modification of the Mislow–Evans rearrangement of allylic sulfoxides (2), particularly \( \alpha \)-substituted \( \beta \)-methallylic sulfoxides \((2\ R^2=Me, \ R^3=H)\), leading to \( (E) \)-allylic alcohols \((4a-f)\). The new method seems to be convenient for large-scale operation.

![Chart 1](image)

In the course of a synthetic study on polysisoprenoidquinones, we noticed a minor production of a certain allylic alcohol \((4f)\) during the preparation of an allylic sulfoxide \((2f)\) by oxidation of an allylic sulfide \((1f)\) with 30% \( H_2O_2 \) in glacial acetic acid at room temperature. Detailed investigation of the formation of allylic alcohols \((4)\) from allylic
Table I. Preparation of (E)-Allylic Alcohols (4) from α, β- and α, γ-Disubstituted Allylic Sulfoxides (2) via the Acidic Mislow–Evans Rearrangement

<table>
<thead>
<tr>
<th>Method</th>
<th>4a</th>
<th>4b</th>
<th>4c</th>
<th>4d</th>
<th>4e</th>
<th>4f</th>
<th>4g</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>69</td>
<td>70</td>
<td>72</td>
<td>68</td>
<td>60</td>
<td>74</td>
<td>48(^b)</td>
</tr>
<tr>
<td>B</td>
<td>77</td>
<td>73</td>
<td>78</td>
<td>85</td>
<td>—</td>
<td>—</td>
<td>71</td>
</tr>
<tr>
<td>C</td>
<td>43</td>
<td>61</td>
<td>56</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>61</td>
</tr>
</tbody>
</table>

\(^a\) See the text and experimental section. \(^b\) The corresponding ethyl ether was obtained as a by-product in 37\(^\circ\) yield. \(^c\) Empty columns mean that the reactions have not been tried.

Sulfoxides (2) in acidic media revealed that the following conditions are effective for the requisite transformation: catalytic use of p-toluenesulfonic acid (p-TsOH) (0.1 eq) in EtOH (15–20 °C/15–40 h) (Method A); catalytic use of p-TsOH (0.1 eq) with thiophenol (PhSH) (1.5 eq) or with ethanethiol (EtSH) (excess) in dioxane (15–20 °C/15–40 h) (Method B); use of aqueous 3 n hydrochloric acid in dioxane (15–20 °C/15–40 h) (Method C). The (E)-alcohols (4) were obtained stereoselectively in fair to good yields from various α-substituted β-methallylic sulfoxides (2a–f) and an α,γ-disubstituted one (2g); the results are summarized in the Table I. The (E)-stereochemistry of the allylic alcohols (4) obtained was confirmed by gas liquid chromatography (GLC) and proton nuclear magnetic resonance (\(^1\)H-NMR) analyses of the α,β-unsaturated aldehydes (5a–f) and ketone (5g) derived from 4 by active MnO\(_2\) oxidation,\(^3\) and by comparison with authentic 4 prepared from 2 according to the standard method [(MeO)\(_3\)P–MeOH (20 °C/2 d)].\(^4\)

During optimization of the reaction conditions, we found that even a catalytic amount of SeO\(_2\) is enough for oxidation of sulfides (1) to the sulfoxides (2) using the oxidizing reagent system of SeO\(_2\)–H\(_2\)O\(_2\) developed by Mikolajczyk.\(^5\) This finding allowed us to achieve a novel one-pot transformation of allylic sulfides (1) directly to (E)-allylic alcohols (4). Thus, the sulfide (1c) was treated with a catalytic amount of SeO\(_2\) (0.1 eq) and 30\(^\circ\)% H\(_2\)O\(_2\) (1.5 eq) in MeOH at room temperature for 4 h followed by addition of p-TsOH (0.1 eq) to the reaction mixture; stirring for 40 h at room temperature gave the (E)-alcohol (4e) in 69\(^\circ\) yield. The keto alcohol (4e) was also obtained in 51\(^\circ\) yield from the sulfide (1e) by this procedure. This one-pot conversion also occurred in dioxane as a solvent and the (E)-allylic alcohol (4d) was obtained in 58\(^\circ\) yield from 1d.

Experimental

**General**—Reactions were carried out under N\(_2\) atmosphere. Reaction mixtures were worked up in the usual manner, unless otherwise noted: the mixture was taken up with Et\(_2\)O, washed with saturated NaHCO\(_3\) and brine or water, dried over anhyd. MgSO\(_4\), and concentrated to give crude products, which were purified by column chromatography on silica gel (Wakogel C-200) using Et\(_2\)O–hexane as the eluent. Infrared (IR) spectra were taken on a JASCO IRA-1 spectrometer in CHCl\(_3\) solution. Mass spectra (MS) were obtained on a JEOL JMS-D300 instrument at an ionizing potential of 70 eV. \(^1\)H-NMR spectra were recorded on a Hitachi R-20B spectrometer (60 MHz) in CDCl\(_3\) solution. GLC was performed on a JEOL JGC-1100 apparatus (FID) using a stainless steel column (3 mm × 2 m) packed with 2% silicone OV-105 on Chromosorb W-AW-DMCS (80–100 mesh).

**Materials**—Allylic sulfides (1) other than 1b and 1g were prepared from the corresponding isoprenoids via benzenesulfonyl chloride addition for 1c,\(^6\) 1d,\(^4\) and 1f\(^5\) or via allylic chlorination with SO\(_2\)Cl\(_2\) followed by sulfonylation for 1a and 1e.\(^6\) The allylic sulfides 1b\(^7\) and 1g were prepared by base-promoted carbon–carbon bond formation between benzyl bromide and methallyl phenylsulfide or crotyl phenylsulfide, respectively, with BuLi in tetrahydrofuran (THF).

**General Procedure for the Modified Mikolajczyk’s Oxidation of Allylic Sulfides (1) to Provide the Corresponding Sulfoxides (2) Using the SeO\(_2\)–H\(_2\)O\(_2\) Reagent System**—To a mixture of the allylic sulfide (1a) (285 mg, 1.0 mmol)
and SeO₂ (11 mg, 0.1 mmol) in MeOH (5.0 ml) was added dropwise 30% H₂O₂ (150 µl) at room temperature. Stirring was continued for 3 h at room temperature. A usual work-up of the mixture and product isolation by column chromatography gave a diastereomeric mixture of allylic sulfides (2a) (245 mg, 82%) as an oil. ¹H-NMR δ: 1.44, 1.57 (overall 3H, each s, =CH₂), 3.66, 3.80 (overall 3H, each s, OCH₃), 4.60, 4.81, 4.94 (overall 2H, each br s, =CH₂). Other sulfides (2b–g) were prepared in 76–88% yields from the corresponding sulfoxides (1b–g) by this method and used as the diastereomeric mixture in the subsequent rearrangement reactions.

General Procedure for the Mislow–Evans Rearrangement of the Allylic Sulfides (2) Leading to the (E)-Allylic Alcohols (4) in Acidic Media — Method A: A mixture of 2a (150 mg, 0.5 mmol) and p-TsOH·H₂O (10 mg, 0.05 mmol) in MeOH (6.0 ml) was stirred for 40 h at room temperature. A usual work-up of the mixture and product isolation gave the oily terminal allylic alcohol (4a) (66 mg, 69%). IR cm⁻¹: 3550, 3400, 1600, 1585, 1490, 1460, 1430. MS m/e: 192 (M⁺, 44%), 174 (24%), 161 (100%), 159 (37%), 120 (31%), 90 (69%). ¹H-NMR δ: 1.71 (3H, s, =CH₂), 2.38 (1H, s, OH), 3.33 (2H, d, J = 7.0 Hz, Ar-CH₂CH₂ =), 3.79 (3H, s, OCH₃), 3.91 (2H, s, =CH₂OH), 5.53 (1H, brt, J = 7.0 Hz, Ar-CH₂CH =), 6.64–7.78 (4H, m, arom-H). Anal. Calc. for C₁₂H₁₆O₂; C, 74.97; H, 8.39. Found: C, 74.69; H, 8.45.

Method B: A mixture of 2a (150 mg, 0.5 mmol), thiophenol (PhSH) (83 mg, 0.75 mmol), and p-TsOH·H₂O (10 mg, 0.05 mmol) in dioxane (3.0 ml) was stirred for 20 h at room temperature. A usual work-up of the mixture and product isolation gave 4a (74% yield, 77%). Under these conditions, thiophenol may be replaced by ethanethiol (ca. 5 eq).

Method C: A mixture of 2a (150 mg, 0.5 mmol) and 3 N HCl (2.0 ml) was stirred for 20 h at room temperature. A usual work-up of the mixture and product isolation gave 4a (41 mg, 43%).

Results for other sulfoxides (2) are summarized in Table I, and the (E)-allylic alcohols (4c, d, f) obtained were confirmed to be identical with the corresponding authentic samples by chromatographic and spectral comparisons.

Data for other (E)-allylic alcohols follow:
4b: Oil. IR cm⁻¹: 3540, 3400, 1600, 1490, 1450. MS m/e: 162 (M⁺, 17%), 160 (14%), 144 (26%), 130 (100%), 128 (46%), 90 (92%). ¹H-NMR δ: 1.68 (3H, br s, =CH₂), 3.03 (1H, s, OH), 3.34 (2H, d, J = 7.0 Hz, Ph-CH₂CH₂ =), 3.89 (2H, s, =CH₂OH). m/z 5.54 (1H, brt, J = 7.0 Hz, Ph-CH₂CH =), 7.12 (5H, s, arom-H).
4c: Oil. IR cm⁻¹: 3550, 3400, 1705, 1350. MS m/e: 142 (M⁺, 5%), 124 (91%), 108 (30%), 83 (100%), 80 (72%). ¹H-NMR δ: 1.64 (3H, s, =CH₂), 2.09 (3H, s, CH₂CO). 2.10–2.62 (4H, m, CH₂CH₂). 3.02 (1H, s, OH). 3.88 (2H, s, =CH₂OH). m/z 5.30 (1H, brt, J = 6.5 Hz, =CH).
4d: Oil. IR cm⁻¹: 3550, 3400, 1660, 1600, 1490, 1445. MS m/e: 162 (M⁺, 6%), 160 (39%), 144 (27%), 117 (76%), 103 (62%), 90 (100%). ¹H-NMR δ: 1.17 (3H, d, J = 7.0 Hz, 2.62 (1H, s, OH). 3.32 (2H, d, J = 5.0 Hz, Ph-CH₂CH =). 3.93–4.42 (1H, m, CH(OH)). 5.31–6.01 (2H, m, CH = CH). 7.17 (5H, s, arom-H).

One-Pot Synthesis of 2-Methyl-6-p-toly1-2(E)-hepten-1-ol, [(±)-(E)-Nuclericol] (4e)¹ from 2-Methyl-3-phenylthio-6-p-tolyl-1-heptene (1c) — A 30% H₂O₂ solution (150 µl) was added dropwise to a mixture of the allylic sulfide (1c) (310 mg, 1.0 mmol) and SeO₂ (11 mg, 0.1 mmol) in MeOH (5.0 ml) at room temperature, and stirring was continued for 4 h at the same temperature. Then, p-TsOH·H₂O (19 mg, 0.1 mmol) was added to the mixture. Stirring was continued for 40 h at room temperature. A usual work-up of the mixture and product isolation gave the oily (E)-allylic alcohol (4e)² (150 mg, 69%).

The keto alcohol, 2-methyl-6-oxo-2(E)-hepten-1-ol (4f) was obtained in 51% yield from 2-methyl-3-phenylthio-1-heptene-1-one (1e) by the same procedure as described for 4c.

One-pot conversion of 8-benzylxoxo-2,6-dimethyl-3-phenylthio-1,6(E)-octadiene (1d) into 8-benzylxoxo-2,6-dimethyl-2(E),6(E)-octadien-1-ol (4d)³ was also carried out in 58% yield under similar conditions described above except for the use of dioxane as the solvent and the addition of 5 mol eq of PhSH in the rearrangement step.

General Procedure for Oxidation of the Allylic Alcohols (4) with Active MnO₂ Providing the α,β-Unsaturated Carbonyl Compounds (5) — A mixture of the allylic alcohol (4a) (100 mg, 0.5 mmol) and active MnO₂ (500 mg) in CH₂Cl₂ (10 ml) was stirred for 3 h at room temperature, then the mixture was diluted with Et₂O and filtered. Evaporation of the solvent and purification of the residue by column chromatography gave the oily aldehyde (5a) (58 mg, 61%). IR cm⁻¹: 1760, 1630, 1595, 1480, 1450. MS m/e: 190 (M⁺, 100%). 173 (47%), 161 (45%), 120 (35%), 90 (56%). ¹H-NMR δ: 1.84 (3H, s, =CH₂), 3.65 (2H, d, J = 7.0 Hz, Ar-CH₂CH =), 3.86 (3H, s, OCH₃), 6.54 (1H, brt, J = 7.0 Hz, Ar-CH₂CH =), 6.73–7.38 (4H, m, arom-H), 9.38 (1H, s, CHO).

The (E)-α,β-unsaturated aldehydes (5c) and (5d) obtained were shown to be identical with the corresponding authentic samples by spectral comparison. Spectral data for other aldehydes (5) and the ketone (5g) follow:

5b: IR cm⁻¹: 1760, 1635, 1600, 1480. MS m/e: 160 (M⁺, 67%), 145 (46%), 131 (57%), 90 (100%). ¹H-NMR δ: 1.83 (3H, s, =CH₂), 3.65 (2H, d, J = 7.5 Hz, Ph-CH₂CH =), 6.54 (1H, brt, J = 7.5 Hz, Ph-CH₂CH =), 6.97–7.37 (5H, m, arom-H), 9.38 (1H, s, CHO).

5e: IR cm⁻¹: 1710, 1670, 1630. MS m/e: 141 [(M⁺+1)⁺], 140 (M⁺, 8%), 122 (29%), 112 (28%), 97 (100%). ¹H-NMR δ: 1.74 (3H, s, =CH₂), 2.14 (3H, s, CH₂CO), 2.52–2.70 (4H, m, CH₂CH₂), 6.39 (1H, brt, J = 7.0 Hz, =CH), 9.34 (1H, s, CHO).

5f: IR cm⁻¹: 1670, 1630, 1590. MS m/e: 284 (M⁺, 100%), 269 (31%), 209 (21%), 187 (24%). ¹H-NMR δ: 1.97 (3H, s, =CH₂), 2.36 (3H, s, Ar-CH₂), 3.88, 3.90 (each 3H, s, OCH₃), 3.90 (2H, d, J = 7.0 Hz, Ar-CH₂CH =).
(1H, br t, \( J = 7.0 \text{ Hz} \), Ar-CH\(_2\)CH\(=\)CH, 7.43—7.65, 7.95—8.23 (each 2H, m, arom-H), 9.44 (1H, s, CHO).

5g: IR cm\(^{-1}\): 1670, 1630, 1590, 1490, 1450. MS m/e: 160 (M\(^+\), 52\%), 145 (29\%), 127 (31\%), 117 (100\%), 115 (40\%). \(^1\)H-NMR \( \delta \): 2.16 (3H, s, CH\(_3\)C(O)), 3.56 (2H, dd, \( J = 6.5 \) and 1.5 Hz, Ph-CH\(_2\)CH=CH), 6.02 (1H, dt, \( J = 16.0 \) and 1.5 Hz, Ph-CH\(_2\)CH=CHC(O)), 6.85 (1H, dt, \( J = 16.0 \) and 6.5 Hz, Ph-CH\(_2\)CH=CH), 7.05—7.43 (5H, m, arom-H).

References


3) No double bond isomerization has generally been observed in the oxidation of allylic alcohols with active MnO\(_2\): A. J. Fatiadi, Synthesis, 1976, 65. For the aldehydes (5 \( R^1 = \)H), no aldehyde proton signal corresponding to (Z)-\( \alpha, \beta \)-unsaturated aldehyde, which generally appears at the range of \( \delta \): 9.95—10.20, was observed in the \(^1\)H-NMR.


