[Chem. Pharm. Bull. 33(6)2531—2534(1985)]

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

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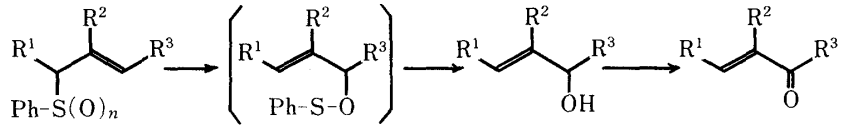
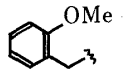
(Received September 7, 1984)

The Mislow–Evans rearrangement of α,β- and α,γ-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.

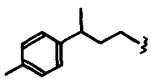
Keywords——acid-catalyzed Mislow–Evans rearrangement; allylic sulfoxide; (*E*)-allylic alcohol; catalytic oxidation using selenium dioxide; one-pot synthesis

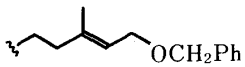
The Mislow–Evans rearrangement has been widely used for the highly stereoselective 1,3-transposition of allylic sulfoxides (**2**) and alcohols (**4**) through intermediary allylic sulfenates (**3**) as a reversible 1,3-charge affinity inversion operation.[1] Usually this process for the conversion of allylic sulfoxides (**2**) into the (*E*)-allylic alcohols (**4**) has been accomplished by use of thiophilic reagents such as trialkyl phosphite [$(RO)_3P$], thioalkoxide (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 α-substituted β-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.

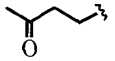


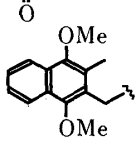
a : $R^1=$  $R^2=Me$, $R^3=H$

b : $R^1=$ CH_2Ph $R^2=Me$, $R^3=H$

c : $R^1=$  $R^2=Me$, $R^3=H$

d : $R^1=$  $R^2=Me$, $R^3=H$

e : $R^1=$  $R^2=Me$, $R^3=H$

f : $R^1=$  $R^2=Me$, $R^3=H$

g : $R^1=$ CH_2Ph $R^2=H$, $R^3=Me$

Chart 1

In the course of a synthetic study on polyisoprenoidquinones,[2] 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 tempefature. 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

Method[a]	Yield (%) of (*E*)-allylic alcohol						
	4a	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**
A	69	70	72	68	60	74	48[b]
B	77	73	78	85	—[c]	—	71
C	43	61	56	—	—	—	61

a) See the text and experimental section. *b*) The corresponding ethyl ether was obtained as a by-product in 37% 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 [$(MeO)_3P$–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_2O_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% H_2O_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 (**4c**) in 69% yield. The keto alcohol (**4e**) was also obtained in 51% 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% 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_2O, 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_2O–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 CCl_4 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* benzenesulfenyl chloride addition for **1c**,[4] **1d**,[4] and **1f**[2] or *via* allylic chlorination with SO_2Cl_2 followed by sulfenylation 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_2O_2 Reagent System——To a mixture of the allylic sulfide (**1a**) (285 mg, 1.0 mmol)

and SeO_2 (11 mg, 0.1 mmol) in MeOH (5.0 ml) was added dropwise 30% H_2O_2 (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 sulfoxides (**2a**) (245 mg, 82%) as an oil. ^{1}H-NMR δ: 1.44, 1.57 (overall 3H, each s, $=CCH_3$), 3.66, 3.80 (overall 3H, each s, OCH_3), 4.60, 4.81, 4.94 (overall 2H, each br s, $=CH_2$). Other sulfoxides (**2b**—**g**) were prepared in 76—88% yields from the corresponding sulfides (**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 Sulfoxides (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·H_2O (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%). ^{1}H-NMR δ: 1.71 (3H, s, $=CCH_3$), 2.38 (1H, s, OH), 3.33 (2H, d, J=7.0 Hz, Ar-C$\underline{H}_2$CH=), 3.79 (3H, s, OCH_3), 3.91 (2H, s, $=CC\underline{H}_2OH$), 5.53 (1H, br t, J=7.0 Hz, Ar-$CH_2C\underline{H}$=), 6.64—7.78 (4H, m, arom-H). *Anal.* Calcd for $C_{12}H_{16}O_2$: 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·H_2O (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 mg, 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) in dioxane (4.0 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[2,4] 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%). ^{1}H-NMR δ: 1.68 (3H, br s, $=CCH_3$), 3.03 (1H, s, OH), 3.34 (2H, d, J=7.0 Hz, Ph-C$\underline{H}_2$CH=), 3.89 (2H, s, $=CC\underline{H}_2OH$), 5.54 (1H, br t, J=7.0 Hz, Ph-$CH_2C\underline{H}$=), 7.12 (5H, s, arom-H).

4e: Oil. IR cm^{-1}: 3550, 3400, 1705, 1350. MS *m/e*: 142 (M^+, 5%), 124 (91%), 108 (30%), 83 (100%), 80 (72%). ^{1}H-NMR δ: 1.64 (3H, s, $=CCH_3$), 2.09 (3H, s, CH_3C(O)), 2.10—2.62 (4H, m, CH_2CH_2), 3.02 (1H, s, OH), 3.88 (2H, s, $=CC\underline{H}_2OH$), 5.30 (1H, br t, J=6.5 Hz, =CH).

4g: 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%). ^{1}H-NMR δ: 1.17 (3H, d, J=7.0 Hz, 2.62 (1H, s, OH), 3.32 (2H, d, J=5.0 Hz, Ph-C$\underline{H}_2$CH=), 3.93—4.42 (1H, m, C$\underline{H}$(OH)), 5.31—6.01 (2H, m, CH=CH), 7.17 (5H, s, arom-H).

One-Pot Synthesis of 2-Methyl-6-*p*-tolyl-2(*E*)-hepten-1-ol, [(±)-(*E*)-Nuciferol] (4c)[4] from 2-Methyl-3-phenylthio-6-*p*-tolyl-1-heptene (1c)——A 30% H_2O_2 solution (150 μl) was added dropwise to a mixture of the allylic sulfide (**1c**) (310 mg, 1.0 mmol) and SeO_2 (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·H_2O (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 (**4c**)[4] (150 mg, 69%).

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

One-pot conversion of 8-benzyloxy-2,6-dimethyl-3-phenylthio-1,6(*E*)-octadiene (**1d**) into 8-benzyloxy-2,6-dimethyl-2(*E*),6(*E*)-octadien-1-ol (**4d**)[4] was also carried out in 58% yield under the same conditions as 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 MnO_2 Providing the α,β-Unsaturated Carbonyl Compounds (5)——A mixture of the allylic alcohol (**4a**) (100 mg, 0.5 mmol) and active MnO_2 (500 mg) in CH_2Cl_2 (10 ml) was stirred for 3 h at room temperature, then the mixture was diluted with Et_2O 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}: 1670, 1630, 1595, 1480, 1450. MS *m/e*: 190 (M^+, 100%), 173 (47%), 161 (45%), 120 (35%), 90 (65%). ^{1}H-NMR δ: 1.84 (3H, s, $=CCH_3$), 3.65 (2H, d, J=7.0 Hz, Ar-C$\underline{H}_2$CH=), 3.86 (3H, s, OCH_3), 6.54 (1H, br t, J=7.0 Hz, Ar-$CH_2C\underline{H}$=), 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[4] by spectral comparison. Spectral data for other aldehydes (**5**) and the ketone (**5g**) follow:

5b: IR cm^{-1}: 1670, 1635, 1600, 1480. MS *m/e*: 160 (M^+, 67%), 145 (46%), 131 (57%), 90 (100%). ^{1}H-NMR δ: 1.83 (3H, s, $=CCH_3$), 3.65 (2H, d, J=7.5 Hz, Ph-C$\underline{H}_2$CH=), 6.54 (1H, br t, J=7.5 Hz, Ph-$CH_2C\underline{H}$=), 6.97—7.37 (5H, br, arom-H), 9.38 (1H, s, CHO).

5e: IR cm^{-1}: 1710, 1670, 1630. MS *m/e*: 141 [$(M+1)^+$, 16%], 140 (M^+, 8%), 122 (29%), 112 (28%), 97 (100%). ^{1}H-NMR δ: 1.74 (3H, s, $=CCH_3$), 2.14 (3H, s, CH_3C(O)), 2.52—2.70 (4H, m, CH_2CH_2), 6.39 (1H, br t, 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%). ^{1}H-NMR δ: 1.97 (3H, s, $=CCH_3$), 2.36 (3H, s, Ar-CH_3), 3.88, 3.90 (each 3H, s, OCH_3), 3.90 (2H, d, J=7.0 Hz, Ar-C$\underline{H}_2$CH=), 6.51

(1H, br t, $J=7.0$ Hz, Ar-$CH_2C\underline{H}=$), 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 δ: 2.16 (3H, s, $CH_3C(O)$), 3.56 (2H, dd, $J=6.5$ and 1.5 Hz, Ph-$C\underline{H}_2CH=CH$), 6.02 (1H, dt, $J=16.0$ and 1.5 Hz, Ph-$CH_2CH=C\underline{H}C(O)$), 6.85 (1H, dt, $J=16.0$ and 6.5 Hz, Ph-$CH_2C\underline{H}=CH$), 7.05—7.43 (5H, m, arom-H).

References

1) P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislow, *J. Am. Chem. Soc.*, **90**, 4869 (1968); R. Tang and K. Mislow, *ibid.*, **92**, 2100 (1970); D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974).
2) Y. Masaki, K. Hashimoto, K. Sakuma, and K. Kaji, *Chem. Pharm. Bull.*, **32**, 3952 (1984).
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** $R^3=H$), no aldehyde proton signal corresponding to (*Z*)-α,β-unsaturated aldehyde, which generally appears at the range of δ: 9.95—10.20, was observed in the ^{1}H-NMR.
4) Y. Masaki, K. Hashimoto, and K. Kaji, *Tetrahedron Lett.*, **1978**, 4539, 5123; *idem, Tetrahedron*, **40**, 3481(1984). Y. Masaki, K. Hashimoto, K. Sakuma, and K. Kaji, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 1289.
5) J. Drabowicz and M. Mikolajczyk, *Synthesis*, **1978**, 758.
6) Y. Masaki, K. Sakuma, K. Hashimoto, and K. Kaji, *Chem. Lett.*, **1981**, 1283.
7) Y. Masaki, K. Sakuma, and K. Kaji, *J. Chem. Soc., Perkin Trans. 1*, **1985**, in press.