

Rearrangements of 3-(Methylsulfinyl)quinolinones, 3-(Methylsulfinyl)cinnolinones, 3-(Methylsulfinyl)chromanones and 3-(Methylsulfinyl)chromones with Acetic Anhydride and with Thionyl Chloride

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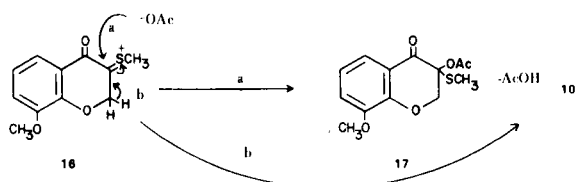
The reaction of 1-methyl-3-(methylsulfinyl)-4(1*H*)quinolinone (1) with acetic anhydride and thionyl chloride gave 3-[[[(acetyloxy)methyl]thio]-1-methyl-4(1*H*)quinolinone (2) and 3-[(chloromethyl)thio]-1-methyl-4(1*H*)quinolinone (3) respectively. 3-(Methylsulfinyl)-4(1*H*)cinnolinone (4) gave the corresponding products when treated under similar conditions. Treatment of 8-methoxy-3-(methylsulfinyl)-4*H*-1-benzopyran-4-one (11) with acetic anhydride and thionyl chloride gave bis addition vinyl Pummerer products 2,3-bis(acetyloxy)-2,3-dihydro-8-methoxy-3-(methylthio)-4*H*-1-benzopyran-4-one (12) and 2,3-dichloro-2,3-dihydro-8-methoxy-3-(methylthio)-4*H*-1-benzopyran-4-one (13), respectively.

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Our continuing interest (1,3) in the utilization of the Pummerer reaction for the synthesis of heterocyclic systems led us to investigate the reactions of 3-methylsulfinyl substituted quinolinones, cinnolinones, chromanones and chromones under various Pummerer conditions. The results are summarized in Table I.

Sulfoxide (1) was conveniently prepared by treating 1-[2-(methylamino)phenyl]-2-(methylsulfinyl)ethanone (4) with triethyl orthoformate and piperidine. It had been prepared previously by a different route (6). Treatment of 1 with acetic anhydride and thionyl chloride gave the expected products [acetate (2) and chloro derivative (3), respectively]. Cinnolinone derivative (4) also gave the expected diacetate (5) and dichloro derivative (6) when treated under similar conditions. Cinnolinone derivative (7) underwent demethylation and rearrangement on reaction with thionyl chloride giving 6. Reaction of 7 with acetic anhydride gave 3-[[[(acetyloxy)methyl]-thio]-1-methyl-4(1*H*)cinnolinone (8).

Treatment of sulfoxide (9) with acetic anhydride gave chromone derivative (10) instead of the normal Pummerer product acetate (17). This results either from neutralization of Pummerer intermediate (16) by elimination of a proton from C₂ (path b) or by elimination of acetic acid from the initially formed 17.

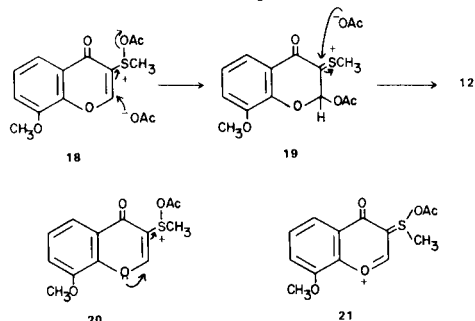


Sulfoxide (11) was prepared either directly by treating 1-(2-hydroxy-3-methoxyphenyl)-2-(methylsulfinyl)ethanone with triethyl orthoformate or by oxidation of 10 with

Table I		
R	I	II
1	2 R-SCH ₂ OAc	3 R-SCH ₂ Cl
4	5	6
7	8 ^a R-SCH ₂ OAc	6
9	10	10 ^b
11	12	13
14	Mixture	15

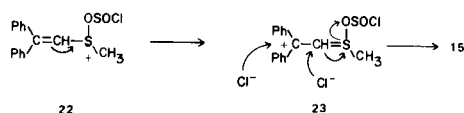
m-chloroperbenzoic acid. Treatment of 11 with acetic anhydride resulted in the production of anomalous Pummerer product diacetate (12). A proposed mechanism for the formation of 12 is shown below. Acetate anion attacks at C₂ of Pummerer intermediate (18) to give

19. Cation (19) is neutralized in the normal way by acetate anion to give 12. Reaction of 11 with thionyl chloride gave the corresponding anomalous product (13). Interaction of the heterocyclic oxygen atom and possible intermediacy of a cation such as 21 may be the reason for the production of anomalous products in these reactions.



Thus it appears that the heterocyclic system plays no role in the formation of products (2, 3, 5, 6 and 8), but the presence of the heterocyclic oxygen in 11 influences the production of bis addition products (12 and 13). To our knowledge these are the first reported cases of bis addition vinyl Pummerer rearrangements.

The generation of 15 from [2-(methanesulfonyl)-1-phenylethenyl]benzene (14) with thionyl chloride provides another example of a bis addition vinyl Pummerer and again shows how an adjacent group can affect the neutralization pathway of the initially generated cation (22). In this case stabilization of the carbonium ion (23) by the two phenyl groups may be the decisive factor in determining the course of the reaction. Treatment of 14 with acetic anhydride gave a complex mixture.



EXPERIMENTAL

Melting points were measured with a Thomas-Hoover capillary melting point apparatus without correction. Nmr spectra were recorded on a Perkin-Elmer R-12B spectrometer at 60 MHz with TMS as internal standard. Infrared spectra were recorded on a Beckmann DK-1 spectrometer. Mass spectra were obtained with an AEI MS-902 instrument.

1-Methyl-3-(methanesulfonyl)-4(1H)quinolinone (1).

Piperidine (8.5 g., 0.1 mole) was added to a solution of 1-[2-(methanesulfonyl)phenyl]-2-(methanesulfonyl)ethanone (21.1 g., 0.1 mole) in refluxing triethyl orthoformate (200 ml.). The reaction mixture was refluxed under nitrogen for 30 hours, cooled and the product filtered off. Recrystallization from ethyl acetate gave gray crystals (18 g., 81%), m.p. 168-170°; uv: max (ethanol): 246 (19,000), 254 (19,000), 296 (7,000), 322 (11,000) and 377 nm (11,000); ir (nujol): 1630 (CO), and 1050 cm⁻¹ (SO); nmr (DMSO): δ 8.40 to 7.40 (m, 4, ArH), 8.15 (s, 1, C₂H), 4.03 (s, 3, NCH₃), and 2.82 (s, 3, SCH₃).

Anal. Calcd. for C₁₁H₁₁NO₂S: C, 59.71; H, 5.01; N, 6.33; S, 14.49. Found: C, 59.81; H, 5.08; N, 6.12; S, 14.14.

3-[[[(Acetyloxy)methyl]thio]-1-methyl-4(1H)quinolinone (2).

A mixture of 1-methyl-3-(methanesulfonyl)-4(1H)quinolinone (1.0 g., 0.0045 mole) in acetic anhydride (25 ml.) was refluxed under nitrogen for 5 hours, cooled, and poured onto ice-water. The precipitate was filtered off and recrystallized from ethyl acetate to give white crystals (1.1 g., 92%), m.p. 154-155°; uv: max (ethanol): 254 (16,000), 298 (5,500), 328 (10,000) and 336 nm (10,500); ir (nujol): 1775 cm⁻¹ (CO); nmr (deuteriochloroform): δ 8.50 (d, 1, ArH), 7.85 (s, 1, C₂H), 7.80 to 7.20 (m, 3, ArH), 5.40 (s, 2, CH₂), 3.82 (s, 3, NCH₃) and 2.08 (s, 3, CH₃CO).

Anal. Calcd. for C₁₃H₁₃NO₃S: C, 59.30; H, 4.98; N, 5.32; S, 12.18. Found: C, 59.30; H, 5.23; N, 5.23; S, 12.16.

3-[(Chloromethyl)thio]-1-methyl-4(1H)quinolinone (3).

1-Methyl-3-(methanesulfonyl)-4(1H)quinolinone (1.0 g., 0.0045 mole) was slowly added with stirring to thionyl chloride (10 ml.). The solution was stirred at room temperature for 4 hours and poured onto ice-water. The brown precipitate was filtered, washed with water, sucked dry and recrystallized from ethyl acetate to give light brown crystals (420 mg., 39%), m.p. 181-182°; uv: max (ethanol): 254 (16,000), 298 (6,000), 330 (10,000) and 338 nm (10,500); nmr (DMSO): δ 8.42 (s, 1, C₂H), 8.40 to 7.40 (m, 4, ArH), 5.25 (s, 2, CH₂) and 3.82 (s, 3, CH₃).

Anal. Calcd. for C₁₁H₁₀ClNOS: C, 55.11; H, 4.20; N, 5.84; Cl, 14.79; S, 13.37. Found: C, 55.13; H, 4.23; N, 6.26; Cl, 14.61; S, 13.41.

1-Acetyl-3-[[[(acetyloxy)methyl]thio]-4(1H)cinnolinone (5).

A mixture of 3-(methanesulfonyl)-4(1H)cinnolinone (2.0 g., 0.0096 mole) in acetic anhydride (25 ml.) was refluxed for 4 hours, cooled, and poured onto ice-water. The precipitate was filtered, sucked dry and recrystallized from methanol to give light brown crystals (1.82 g., 65%), m.p. 125-126°; uv: max (ethanol): 256 (23,000), 262 (21,000) and 360 nm (11,000); ir (nujol): 1765, 1735 and 1650 cm⁻¹ (CO); nmr (deuteriochloroform): δ 9.05 (d, 1, ArH), 8.25 (d, 1, ArH), 8.00 to 7.20 (m, 2, ArH), 5.67 (s, 2, CH₂), 2.81 (s, 3, NCOCH₃) and 2.08 (s, 3, OCOCH₃).

Anal. Calcd. for C₁₃H₁₂N₂O₄S: C, 53.42; H, 4.14; N, 9.58; S, 10.97. Found: C, 53.35; H, 4.20; N, 9.71; S, 11.16.

4-Chloro-3-[(chloromethyl)thio]cinnoline (6).

A mixture of 3-(methanesulfonyl)-4(1H)cinnolinone (5.0 g., 0.024 mole) in thionyl chloride (30 ml.) was refluxed for 6 hours, cooled, and poured onto ice-water. The precipitate was filtered, washed with water, sucked dry, and recrystallized from ethyl acetate to give light brown crystals (5.42 g., 92%), m.p. 139-140°; uv: max (ethanol): 252 (24,000) and 360 nm (2,000); nmr (deuteriochloroform): δ 8.70 to 7.70 (m, 4, ArH) and 5.68 (s, 2, CH₂).

Anal. Calcd. for C₉H₆Cl₂N₂S: C, 44.10; H, 2.47; N, 11.43; Cl, 28.94; S, 13.08. Found: C, 44.06; H, 2.44; N, 11.63; Cl, 28.67; S, 13.23.

2,3-Dihydro-8-methoxy-3-(methanesulfonyl)-4H-1-benzopyran-4-one (9).

A mixture of 1-(2-hydroxy-3-methoxyphenyl)-2-(methanesulfonyl)ethanone (45.6 g., 0.2 mole), 36% aqueous formaldehyde (16.66 g., 0.2 mole) and piperidine (1 ml.) in methanol (500 ml.) was refluxed under nitrogen for 15 minutes. The solvents were removed under reduced pressure to give a solid residue. Recrystallization from ethyl acetate gave white crystals (36 g., 75%), m.p. 119-121°; uv: max 272 (9,000) and 344 nm (2,000); ir (nujol): 1675 cm⁻¹ (CO); nmr (deuteriochloroform): δ 7.60 to 6.90 (m, 3, ArH), 5.20 (dd, 1, J = 5 Hz, J = 15 Hz, C₂H), 4.75 (dd, 1,

$J = 5$ Hz, $J = 15$ Hz, C_2H), 3.90 (s, 3, OCH_3), 3.70 (t, 1, $J = 5$ Hz, C_3H) and 2.80 (s, 3, SCH_3).

Anal. Calcd. for $C_{11}H_{12}O_4S$: C, 54.99; H, 5.03; S, 13.34. Found: C, 55.02; H, 4.99; S, 13.38.

8-Methoxy-3-(methylthio)-4*H*-1-benzopyran-4-one (10).

A mixture of 2,3-dihydro-8-methoxy-4*H*-1-benzopyran-4-one (16.0 g., 0.072 mole) in acetic anhydride (75 ml.) was heated at 100° under nitrogen for 4 hours, cooled, and poured onto ice-water. The precipitate was filtered, washed with water, sucked dry, and recrystallized from methanol to give white crystals (12.5 g., 85%), m.p. 114-115°; uv: max 252 (22,400) and 320 nm (4,400); ir (nujol): 1650 cm^{-1} (CO); nmr (deuteriochloroform): δ 8.10 (s, 1, C_2H), 7.83 (d, 1, ArH), 7.50 to 7.00 (m, 2, ArH), 4.00 (s, 3, OCH_3) and 2.43 (s, 3, SCH_3).

Anal. Calcd. for $C_{11}H_{10}O_3S$: C, 59.44; H, 4.54; S, 14.43. Found: C, 59.23; H, 4.58; S, 14.48.

8-Methoxy-3-(methylsulfinyl)-4*H*-1-benzopyran-4-one (11).

Piperidine (8.5 g., 0.1 mole) was added to a solution of 1-(2-hydroxy-3-methoxyphenyl)-2-(methylsulfinyl)ethanone (22.8 g., 0.1 mole) in refluxing triethyl orthoformate (200 ml.). The reaction mixture was refluxed for 40 minutes. The solvents were evaporated under reduced pressure to give a red semicrystalline mass. Recrystallization from ethanol gave white crystals (7.5 g., 32%), m.p. 158-160°; uv: max 240 (17,000) and 312 nm (4,000); ir (nujol): 1650, 1630 (CO) and 1050 cm^{-1} (SO); nmr (deuteriochloroform): δ 8.30 (s, 1, C_2H), 7.80 (d, 1, ArH), 7.70 to 7.20 (m, 2, ArH), 4.10 (s, 3, OCH_3) and 2.95 (s, 3, SCH_3).

Anal. Calcd. for $C_{11}H_{10}O_4S$: C, 55.45; H, 4.23; S, 13.46. Found: C, 55.52; H, 4.18; S, 13.41.

8-Methoxy-3-(methylsulfinyl)-4*H*-1-benzopyran-4-one (11) from (10).

A mixture of 8-methoxy-3-(methylthio)-4*H*-1-benzopyran-4-one (5.5 g., 0.025 mole) and *m*-chloroperbenzoic acid (5.0 g., 0.029 mole) in dichloromethane (200 ml.) was stirred at room temperature for 4 hours. The solvent was removed under reduced pressure to give a white solid. The solid was washed with ethanol and recrystallized from ethanol to give white crystals (4.2 g., 71%), m.p. 158-160°. The analytical and spectral data were identical to those described above.

2,3-bis(Acetyloxy)-2,3-dihydro-8-methoxy-3-(methylthio)-4*H*-1-benzopyran-4-one (12).

A mixture of 8-methoxy-3-(methylsulfinyl)-4*H*-1-benzopyran-4-one (5.0 g., 0.021 mole) in acetic anhydride (25 ml.) was refluxed under nitrogen for 10 hours, cooled, and poured onto ice-water. The precipitate was filtered off and recrystallized from

ethyl acetate to give white crystals (4.47 g., 63%), m.p. 181-182°; uv: max 264 (9,000) and 330 nm (2,000); ir (nujol): 1775, 1755 and 1700 cm^{-1} (CO); nmr (deuteriochloroform): δ 7.80 to 7.70 (m, 4, ArH and C_2H), 3.90 (s, 3, OCH_3), 2.32 (s, 3, SCH_3), 2.20 (s, 3, $COCH_3$) and 2.09 (s, 3, $COCH_3$).

Anal. Calcd. for $C_{15}H_{16}O_7S$: C, 52.94; H, 4.74; S, 9.42. Found: C, 52.86; H, 4.84; S, 9.45.

2,3-Dichloro-2,3-dihydro-8-methoxy-3-(methylthio)-4*H*-1-benzopyran-4-one (13).

A mixture of 8-methoxy-3-(methylsulfinyl)-4*H*-1-benzopyran-4-one (5.0 g., 0.021 mole) in thionyl chloride (45 ml.) was stirred at room temperature for 3 hours and poured onto ice-water. The precipitate was filtered, washed with water and recrystallized from methanol to give pale yellow crystals (6.0 g., 97%), m.p. 75-77°; uv: max 264 (8,000) and 330 nm (2,000); ir (nujol): 1720 cm^{-1} (CO); nmr (deuteriochloroform): δ 7.80 to 7.10 (m, 3, ArH), 6.52 (s, 1, C_2H), 3.95 (s, 3, OCH_3) and 2.45 (s, 3, SCH_3).

Anal. Calcd. for $C_{11}H_{10}Cl_2O_3S$: C, 45.07; H, 3.68; Cl, 24.19; S, 10.94. Found: C, 45.05; H, 3.60; Cl, 23.97; S, 11.08.

[1,2-Dichloro-2-(methylthio)-1-phenylethyl]benzene (15).

A mixture of [2-(methylsulfinyl)-1-phenylethenyl]benzene (7) (25.0 g., 0.1 mole) in thionyl chloride (170 ml.) was stirred at room temperature for 3 hours and poured onto ice-water. The precipitate was filtered, washed with water and recrystallized from hexane to give white crystals (8.2 g., 26%), m.p. 79-81°; nmr (deuteriochloroform): δ 7.90-7.20 (m, 10, ArH), 5.95 (s, 1, CH) and 2.31 (s, 3, CH_3).

Anal. Calcd. for $C_{15}H_{14}Cl_2S$: C, 60.61; H, 4.75; Cl, 23.85; S, 10.79. Found: C, 60.65; H, 4.75; Cl, 23.89; S, 10.96.

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