Synthesis of 3-(2′-methoxy,5′-bromophenyl)-2,3-epoxy Phenyl Propanone, A Novel Epoxidated Chalcone Derivative

An Undergraduate Organic Chemistry Experiment

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Over the years a multitude of chalcone derivatives have been synthesized because of their promise as antimicrobial agents (*1–7*). Various chalcones have been reported as having bacteriostatic (*8*), tuberculostatic (*9*), and insecticidal (*1*) activity.

This paper describes the synthesis of the novel chalcone 3-(2′-methoxy,5′-bromo phenyl)-1-phenyl-prop-2-enone and its subsequent epoxidation to the title compound as a simple and informative undergraduate organic chemistry experiment. The three-step synthesis (Fig. 1) has a number of educational merits: (1) compound **2** is an analogue of several biologically active molecules; (2) students can examine the mass spectra of compounds **1, 2,** and **3** to observe the isotopic effect of the bromine substituent (Fig. 2); (3) the progress of the epoxidation step can be monitored by observing changes in the PMR spectra (Fig. 3); and (4) three crystalline products (**1, 2,** and **3**) can be obtained in high yield within 3 h.

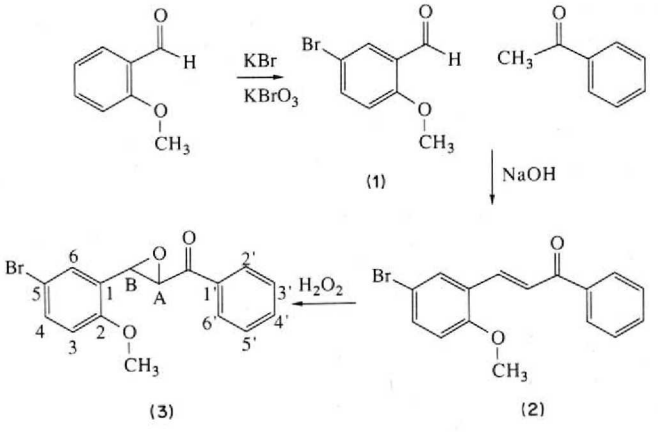

Figure 1. The reaction sequence.

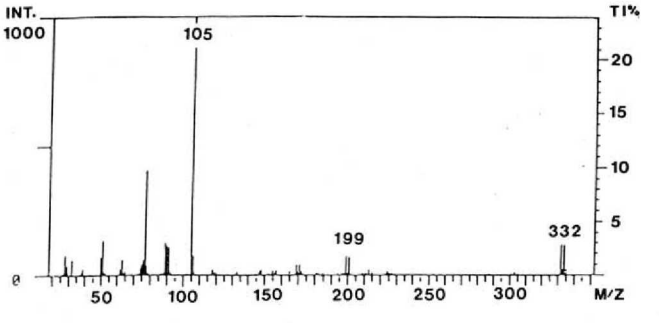

Figure 2. The mass spectrum of compound **3** recorded on a Jeol JMX DX-300 double-focusing instrument at 70 eV. The characteristic 1:1 ratio of peaks at M and M + 2 for compounds containing one bromine atom is well represented for compound **3**, with peaks at m/z 332 and m/z 334.

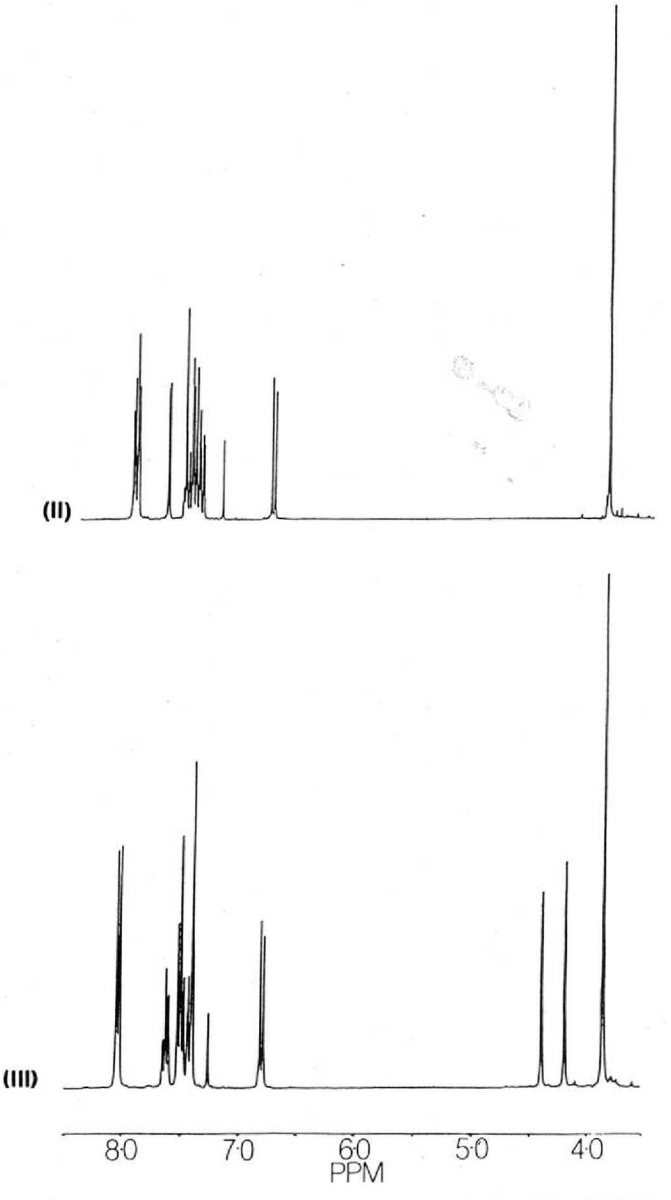

Figure 3. Partial 300 MHz PMR spectrum of compounds **2** and **3** in 1% TMS $CDCl_3$.

Experimental

Step 1

o-Methoxybenzaldehyde (6.8 g, 0.05 mol) was dissolved in glacial acetic acid (50 mL), and to this solution was added potassium bromide (6.0 g, 0.05 mol), potassium bromate (4.3 g, 0.025 mol), and distilled water (10 mL). The solution was refluxed for 30 min, in which time bromine was liberated up the condenser. The yellow solution was cooled slowly, and the resulting white needles were filtered off, washed with water, and recrystallized from aqueous ethanol to give 2-methoxy,5-bromo benzaldehyde (1) as white needles (8.9 g, 83%), mp 117 °C lit (*10*) 116.4 °C.

PMR (1% TMS in $CDCl_3/d_6$ DMSO 1:1) δ 2.49, s, 3H, OCH_3; 7.08, d, 1H, H3, J 8.7 Hz; 7.67, dd, 1H, H4, J 2.3 Hz, 8.7 Hz; 7.72, d, 1H, H6, J 2.2 Hz; 10.3, s, 1H, CHO.

CMR (1% TMS in $CDCl_3$) 55.9 (OCH_3), 113.45 (C5), 113.74 (C3), 126.75 (C1), 131.01 (C6), 139.27 (C4), 160.75 (C2), 168.32 (CHO). *m/z* 215 ($M^+ + 2$, 11%), 213 (M^+, 11%), 74 (30), 63 (100).

Step 2

Acetophenone (0.6 g, 5 mmol), ethanol (15 mL), and 2 M sodium hydroxide solution (12 mL) was stirred at room temperature for 5 min. 2-Methoxy, 5-bromobenzaldehyde (1.05 g, 5 mmol) was then added and the resulting solution stirred at room temperature for 15 min. The yellow product was filtered, washed with cold water, and recrystallized from aqueous ethanol to give the chalcone derivative 3-(2′-methoxy, 5′-bromophenyl)-1-phenylprop-2-enone (**2**) (1.43 g, 90%), mp 49–50 °C. (Found: C, 60.9; H, 4.2; O, 10.2; $C_{16}H_{13}BrO_2$ requires C, 60.6; H, 4.2; O, 10.1%). ν cm^{-1} 3490, 1668, 1606, 1482, 1254, 1012, 684 cm^{-1}.

PMR (1% TMS in $CDCl_3$) δ 3.88, s, 3H, OCH_3; 6.81, d, 1H, H3, J 8.7 Hz; 7.42, d, 1H, H_A, J 2.58 Hz; 7.48, dd, 1H, H4, J 8.3 Hz, 2.6 Hz; 7.52, dd, 2H, H3′, H5′, J 10.1 Hz, 6.36 Hz; 7.58, d, 1H, H6, J 2.40 Hz; 7.72, 1H, d, H_B, J 2.45 Hz; 8.0, dd, 2H, H2′, H6′, J 10.7 Hz, 3.6 Hz; 8.02, m, 1H, H4′.

CMR (1% TMS in $CDCl_3$) δ 55.8 (OCH_3), 113.0 (C3), 113.0 (C5), 123.62 (C_A), 125.95 (C1), 128.58 (C2′C6′), 128.58 (C3′C5′), 131.15 (C4), 132.76 (C6), 134.0 (C4′), 138.46 (C_B), 157.4 (C2), 191.8 (C=O). *m/z* 317 (M^+ 2, 5%), 315 (M^+, 5%), 286(11), 284(11), 105(28), 89(28), 77(100).

Step 3

To a solution of 3-(2′-methoxy, 5′-bromophenyl-1-phenylprop-2-enone (1.0 g, 3.15 mmol) and ethanol (30 mL) was added 2 M sodium hydroxide (3 mL), and the solution was stirred for 5 min. An excess of 28% w/w hydrogen peroxide (1 mL) was then added dropwise and the resulting solution stirred at 5 °C for 10 min. Distilled water (3 mL) was added to the solution to assist precipitation of the epoxide as a white solid, which was then recrystallized from aqueous ethanol to give the epoxide, **3**, as fine white crystals (0.97 g, 92%), mp 105–106 °C. (Found: C, 57.8; H, 3.9; O, 14.2; $C_{16}H_{13}BrO_3$ requires C, 57.7; H, 3.9; O, 14.4%).

ν_{max} 3490, 1682, 1490, 1402, 1260, 1122, 1014, 806, 690 cm^{-1}.

PMR (1% TMS in $CDCl_3$) 3.81, s, 3H, OCH_3; 4.13, s, 1H, H_A; 4.34, s, 1H, H_B; 6.77, d, 1H, H3, J 8.4 Hz; 7.39, d, 1H, H6, J 1.89 Hz; 7.40, dd, 1H, H4, J 1.89 Hz, 9.3 Hz; 7.49, dd, 2H, H3′, H5′, J 7.56 Hz; 7.60, m, 1H, H4′, J 7.0 Hz; 8.02, dd, 2H, H2′H6′, J 7.29 Hz.

CMR (1% TMS in $CDCl_3$) δ 54.93 (OCH_3), 55.6 (C_A), 60.3 (C_B), 112.12 (C3), 113.19 (C5), 128.29 (C1), 128.38 (C3′, C5′), 128.38 (C2′, C6′), 128.82 (C4), 132.32 (C6), 133.93 (C4′), 157.23 (C2), 193.12 (C=O). *m/z* 334 (M^+ + 2, 125), 332 (M^+, 125), 201(7), 199(7), 105(100), 77(40).

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