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A SYNTHESIS OF (\pm)-FUROIIXIOLAL

RAMESH C. ANAND* and VIBHA SINGH

Department of Chemistry, Indian Institute of Technology, Hauz Khas, New Delhi 110 016, India

ABSTRACT.—The sesquiterpenoid furanoaldehyde furoixiolal [**1**] has been synthesized in 7 steps from 3-(*p*-tolyl)butanal. The key step is a Pummerer rearrangement of **5**, which leads via **6** to the furan **7**. The synthesis confirms the structure of **1**.

Furoixiolal, a sesquiterpenoid furanoaldehyde, was isolated from the aerial parts of *Ixiolaea leptolepis*. It has been assigned structure **1** on the basis of spectroscopic studies (1). In the present paper we report an unambiguous synthesis of furoixiolal [**1**] to confirm its structure and to have the natural product in reasonable amount for studying its conversion to other *p*-curcumene type sesquiterpenoids. The synthesis is delineated in Scheme 1.

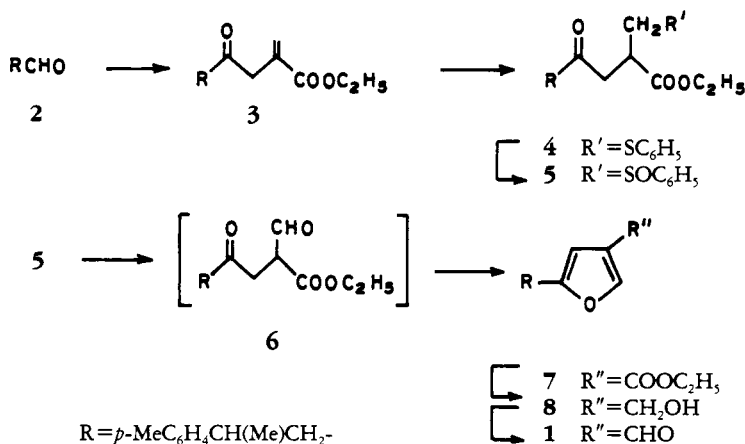
The starting compound, 3-*p*-tolylbutanal [**2**] (2), was reacted with ethyl 2-bromomethyl-2-propenoate in aqueous saturated NH_4Cl /THF system in the presence of Zn dust (3) to form the corresponding hydroxyester, which without isolation was oxidized with Jones' reagent in Me_2CO to ketoester **3** in 72% yield. Conjugate addition of thiophenol to unsaturated ester **3** proceeded smoothly in 89% yield using NaOC_2H_5 in EtOH to

yield the sulfide **4**. Sodium metaperiodate oxidation of **4** was carried out in MeOH to afford sulfoxide **5** in 87% yield. The sulfoxide **5** was stirred with trifluoroacetic anhydride in Ac_2O followed by basic hydrolysis of the crude resulting product in the presence of HgCl_2 to give an oil **6**. This was stirred with H_2SO_4 to yield 3-(3'-*p*-tolylbutyl)-4-ethoxycarbonylfuran [**7**] in 62% yield. LAH reduction of **7** to the corresponding carbinol **8** followed by PDC oxidation furnished 3-(3'-*p*-tolylbutyl)-4-formylfuran [**1**], whose ir and ^1H -nmr spectral data were identical with those shown by Lehmann *et al.* (1).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—General procedures were as previously described (4).

ETHYL 4-KETO-2-METHENYL-6-*p*-TOLYLHEPTANOATE [3].—A mixture of saturated NH_4Cl solution (35 ml), THF (7 ml), 3-*p*-tolylbutanal [**2**]



SCHEME 1

(4.76 g, 0.029 mol), ethyl 2-bromomethyl-2-propenoate (6.0 g, 0.031 mol), and Zn dust (2.6 g, 0.04 mol) was stirred at 60°, and progress of the reaction was monitored on tlc. After most of the aldehyde had reacted (4 h), the mixture was cooled and Et₂O (50 ml) was added. The Et₂O layer was separated and the aqueous layer re-extracted with Et₂O (40 ml×3). The combined organic phase was washed with brine (50 ml×3) and dried. The solvent was removed, and the residue (6.99 g) was dissolved in Me₂CO (65 ml). To this stirred solution at 0–5° was added Jones' reagent (11 ml). The mixture was stirred for 0.5 h, diluted with H₂O (150 ml), and extracted with Et₂O (60 ml×3). The aqueous layer was saturated with NaCl and again extracted with Et₂O. The combined ethereal layers were washed with brine and dried. The solvent was removed, and the residue was chromatographed on Si gel (300 g). The pure ketoester **3** (5.55 g, 72%) was obtained with *n*-C₆H₁₄-C₆H₆ (50:50) as the eluent: *ir* ν max (film) cm⁻¹ 3080, 1723, 1712, 1633, 1525, 931, 818; ¹H nmr (CDCl₃) δ 1.21–1.42 (6H, m), 2.38 (3H, s), 2.68 (2H, d, *J*=8 Hz), 3.05–3.68 (3H, m), 4.32 (2H, q, *J*=7 Hz), 5.42–5.60 (1H, m), 6.11–6.52 (1H, m), 7.21 (4H, s). *Anal.* calcd for C₁₇H₂₂O₃: C 74.42, H 8.00. Found C 74.58, H 8.25.

ETHYL 4-KETO-2-PHENYLTHIOMETHYL-6-*p*-TOLYLHEPTANONE [4].—To a stirred solution of NaSC₆H₅, prepared from Na (0.78 g, 0.034 mol) in absolute EtOH (60 ml) and C₆H₅SH (13.94 ml, 0.136 mol), was added ketoester **3** (8.9 g, 0.034 mol) in EtOH (20 ml), and the stirring was continued for 4 h. The mixture was poured into cold H₂O (160 ml) and extracted with CH₂Cl₂ (100 ml×3). The combined organic extracts were washed with H₂O and dried. The solvent was removed and the residue was chromatographed on Si gel (325 g). The desired compound **4** was eluted with *n*-C₆H₁₄-EtOAc (90:10) (13.04 g, 89%): *ir* ν max (film) cm⁻¹ 3038, 1744, 1712, 1580, 820, 745; ¹H nmr (CDCl₃) δ 1.22–1.42 (6H, m), 2.36 (3H, s), 2.68–3.20 (8H, m), 4.12 (2H, q, *J*=7 Hz), 7.08–7.30 (9H, m). *Anal.* calcd for C₂₃H₂₈O₃S: C 71.89, H 7.34. Found C 72.11, H 7.62.

ETHYL 4-KETO-2-PHENYLSULFINYLMETHYL-6-*p*-TOLYLHEPTANOATE [5].—To a stirred solution of sulfide (IV) (8.0 g, 0.032 mol) in MeOH (600 ml) at 0–5° was added sodium metaperiodate (9.28, 0.043 mol) in H₂O (40 ml). After 1 h, the solution was stirred at room temperature for 14 h. It was filtered, and the residue was washed with MeOH (60 ml×3). The combined filtrate and washings were concentrated at 30° to attain sulfoxide **5** (7.25 g, 87%); *ir* (film) ν max cm⁻¹ 1745, 1715, 1580, 1315, 1200, 1150, 1078, 1028, 812, 755; ¹H nmr (CDCl₃) δ 1.22–1.44 (6H, m), 2.32 (3H, s), 2.68–3.40 (8H, m), 4.18 (2H, q, *J*=7 Hz), 7.20 (4H, s), 7.33–7.68 (5H, m).

4-ETHOXYCARBONYL-2-(2'-*p*-TOLYL-PROPYL)FURAN [7].—To a cooled (0–5°) and stirred solution of (CF₃CO)₂O (8.0 g, 0.038 mol) in (Ac₂O) (34 ml) was added NaOAc (3.12 g, 0.038 mol) followed by sulfoxide **5** (4.64 g, 0.0116 mol). The mixture was stirred at 0–5° for 3 h and then 14 h at room temperature. The solvent was removed under vacuum, and the crude residue was taken up in Et₂O (150 ml). The Et₂O was washed with H₂O, and the solvent was removed. The residue was refluxed with stirring in MeCN-H₂O (4:1) (200 ml) containing CaCO₃ (6.0 g) and HgCl₂ (3.40 g) for 3 h. The mixture was filtered through Celite, solvent was removed from the filtrate, and the aqueous layer was extracted with Et₂O (50 ml×3). The combined ethereal solutions were washed with H₂O and brine and dried. The solvent was removed, and the residue was chromatographed on Si gel (150 g). The ketoaldehyde **6** was obtained with *n*-C₆H₁₄-EtOAc (90:10) as the eluent (1.52 g, 45%). To this stirred ice cold liquid **6** (1.52 g, 0.0052 mol) was added H₂SO₄ (1 ml) dropwise. The mixture was stirred at 50° for 5 min, added to H₂O (100 ml) at 0–5°, and extracted with Et₂O (60 ml×3). The combined ethereal layers were washed with H₂O, NaHCO₃ (5%), and H₂O and dried. The solvent was removed, and the residue was chromatographed on Si gel (150 g) to furnish the furoic ester **7** (0.863 g, 62%) using *n*-C₆H₁₄-C₆H₆ (80:20) as the eluent: *ir* ν max (film) cm⁻¹ 1725, 1543, 1516, 1455, 1200, 1145, 1100, 810, 795, 755; ¹H nmr (CDCl₃) δ 1.12–1.34 (6H, m), 2.28 (3H, s), 2.72–2.94 (2H, m), 3.02–3.33 (1H, m), 4.26 (2H, q, *J*=7 Hz), 6.20 (1H, s), 7.19 (4H, s), 7.83 (1H, s). *Anal.* calcd for C₁₇H₂₀O₃: C 74.97, H 7.40. Found C 75.23, H 7.64.

4-FORMYL-2-(2'-*p*-TOLYLPROPYL)FURAN (FUROIOLAL) [1].—To a suspension of LAH (0.19 g, 0.005 mol) in Et₂O (15 ml) was added dropwise ester **7** (1.35 g, 0.005 mol) in Et₂O (10 ml). The mixture was refluxed for 6 h and then cooled to 0°. A cold (10°) solution of Na₂SO₄ (10 ml) was added to quench the reaction. The Et₂O layer was separated, and the aqueous layer was extracted with Et₂O (20 ml×3). The combined ethereal layers were washed with brine (20 ml×2) and dried. The solvent was removed to yield the alcohol **8** (0.906 g, 79.5%): *ir* ν max (film) cm⁻¹ 3375, 1555, 1512, 1462, 1030, 910, 818, 735; ¹H nmr (CDCl₃) δ 1.25 (3H, d, *J*=8 Hz), 1.80 (1H, br, exchangeable with D₂O), 2.25 (3H, s), 2.78–2.98 (2H, m), 3.02–3.33 (1H, m), 4.28 (2H, s), 5.96 (1H, s), 7.12 (4H, s), 7.26 (1H, s). *Anal.* calcd for C₁₅H₁₈O₂: C 78.28, H 7.82. Found C 78.36, H 7.86.

To a stirred suspension of PDC (1.676 g, 0.006 mol) in CH₂Cl₂ (20 ml) was added the above alcohol **8** (0.90 g, 0.0039 mol) in CH₂Cl₂ (5 ml), and the mixture was stirred to 10 h. Dry Et₂O (100 ml) was added to the reaction mixture, the organic

layer was decanted, and the residue was triturated with Et₂O (50 ml×4). The combined ethereal solutions were passed through Si gel (100 g). The column was eluted with Et₂O (150 ml), and the combined solvent was removed. The residue was rechromatographed on Si gel (75 g). The aldehyde, which was obtained using *n*-C₆H₁₄-C₆H₆ (90:10) as the eluent, was distilled under reduced pressure to give **1** (0.705 g, 79%): bp 151–155° (bath)/3–4 mm; ir ν max (film) cm⁻¹ 2956–2866, 2720, 1687, 1534, 1507, 1453, 1399, 1372, 1354, 1272, 1265, 1135, 1100, 1000, 1029, 935, 883, 865, 818, 775, 755; ¹H nmr (CDCl₃) δ 1.26 (3H, d, *J*=8 Hz), 2.28 (3H, s), 2.78–2.88 (2H, m), 2.98–3.22 (1H, m), 6.26 (1H, s), 7.06 (4H, s), 7.88 (1H, s), 9.81 (1H, s).

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