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Synthesis of Diclofenac

YASUMITSU TAMURA,* JUN-ICHI UENISHI, HONG DAE CHOI,
JUN-ICHI HARUTA, and HIROYUKI ISHIBASHI

Faculty of Pharmaceutical Sciences, Osaka University,
1-6 Yamada-oka, Suita, Osaka 565, Japan

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Diclofenac, a potent antiinflammatory agent, was prepared by acid-catalyzed cyclization of *N*-(2,6-dichlorophenyl)- α -(methylsulfinyl)acetanilide or of α -chloro-*N*-(2,6-dichlorophenyl)- α -(methylthio)acetanilide followed by desulfurization and hydrolysis of the resultant 1-(2,6-dichlorophenyl)-3-(methylthio)oxindole.

Keywords—acid-catalyzed cyclization of α -(methylsulfinyl)acetanilide; antiinflammatory agent; diclofenac; Friedel–Crafts cyclization of α -chloro- α -(methylthio)acetanilide; oxindole (indolin-2-one)

In a previous paper,¹⁾ we reported a convenient synthesis of oxindoles by acid-catalyzed cyclization of α -(methylsulfinyl)acetanilides or of α -chloro- α -(methylthio)acetanilides. We now wish to describe an application of the methods to the synthesis of diclofenac (**8**), which is a potent antiinflammatory agent.

N-Acylation of *N*-phenyl-2,6-dichloroaniline (**1**) with α -(methylthio)acetyl chloride gave the α -(methylthio)acetanilide **2** in 87% yield. Oxidation of **2** with *m*-chloroperbenzoic acid (*m*-CPBA) or hydrogen peroxide gave the α -(methylsulfinyl)acetanilide **3** in 91 or 84% yield. The cyclization of **3** by heating in benzene in the presence of *p*-toluenesulfonic acid afforded the 3-(methylthio)oxindole **5** in 84% yield. Compound **5** was also prepared by an alternative route. Thus, chlorination of the sulfide **2** with *N*-chlorosuccinimide (NCS) in CCl₄ followed by cyclization of the resultant α -chlorosulfide **4a** with stannic chloride (SnCl₄) afforded **5** in 89% yield (from **2**). Compound **5** was then desulfurized with zinc dust–acetic acid or Ra-Ni to give the oxindole **6** quantitatively. Compound **6** was hydrolyzed with NaOH solution to give diclofenac (**8**) in 85% yield. Hydrolysis of **5** followed by desulfurization of the resultant amino acid **7** also gave **8**.

Many procedures have been reported for the preparation of diclofenac (**8**). Among them, the route²⁾ through Friedel–Crafts cyclization of *N*-(2,6-dichlorophenyl)- α -chloroacetanilide (**4b**) to **6** seems to be the shortest and best. However, the cyclization of **4b** requires drastic conditions (*ca.* 160 °C). The present sequence of reactions can be carried out under rather mild conditions in high yields, and hence provides a useful synthetic route to diclofenac (**8**).

Experimental

All melting points and boiling points are uncorrected. The infrared (IR) spectra were recorded with a JASCO-IRA-1 spectrophotometer. The proton nuclear magnetic resonance (¹H-NMR) spectra were measured on a Hitachi R-22 spectrometer using tetramethylsilane as an internal standard. High resolution mass spectra (MS) were obtained with a JMS-D-300 instrument at 70 eV.

***N*-(2,6-Dichlorophenyl)- α -(methylthio)acetanilide (**2**)**—A mixture of **1**²⁾ (91.1 g, 0.383 mol) and α -(methylthio)acetyl chloride³⁾ (57.2 g, 0.459 mol) in anhydrous benzene (32.5 ml) was refluxed for 6 h. The solvent and

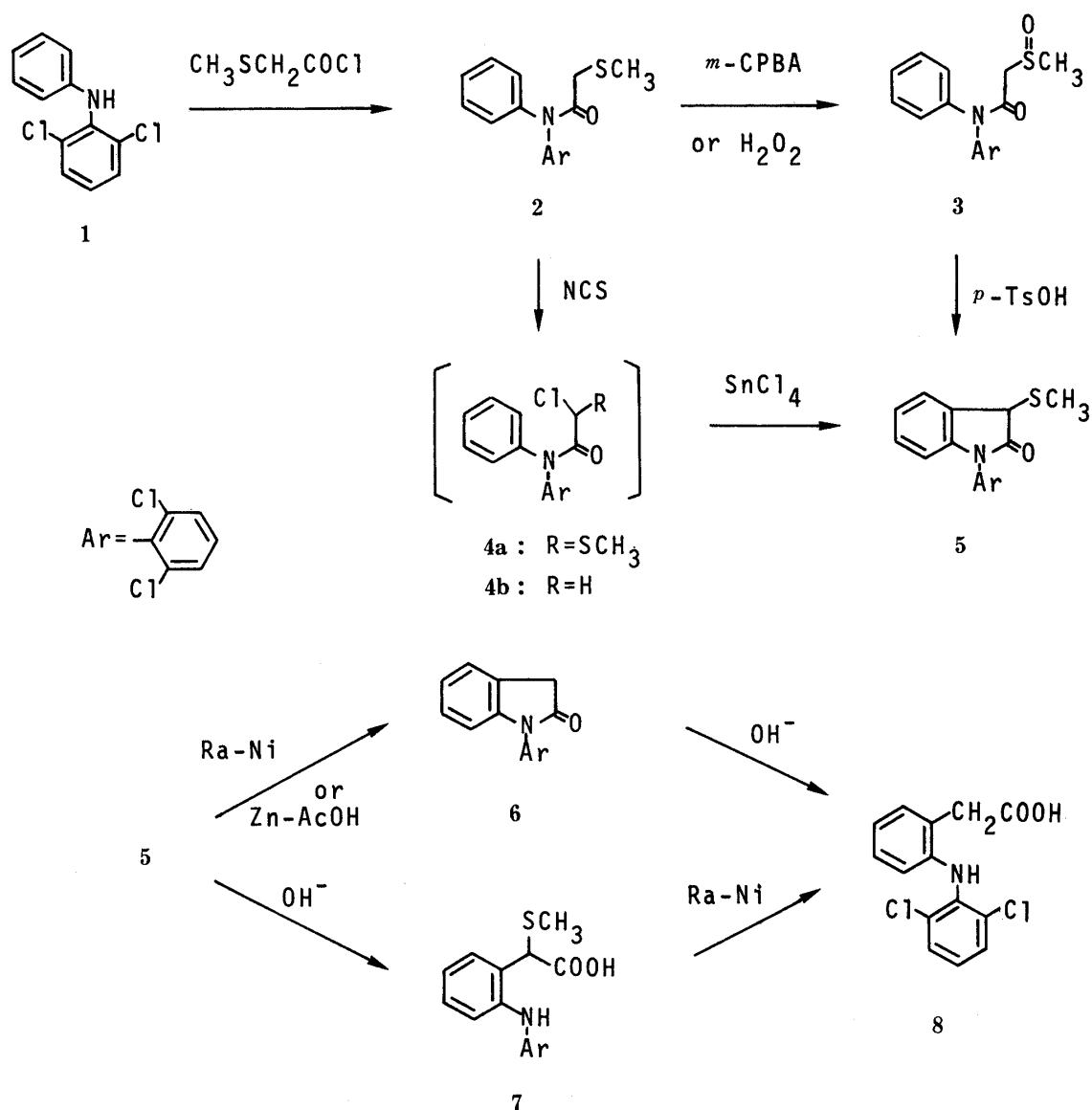


Chart 1

excess acyl chloride were removed *in vacuo* and the residue was distilled to give **2** (115.4 g, 87%), bp 208—211 °C (3 mmHg), mp 43—44.5 °C (from MeOH/H₂O). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1655 (CO). ¹H-NMR (10% solution in CDCl₃) δ : 2.26 (3H, s), 3.16 (1H, br s), 3.36 (1H, br s), and 7.0—7.7 (8H, m). Anal. Calcd for C₁₅H₁₃Cl₂NOS: C, 55.22; H, 4.02; N, 4.29. Found: C, 55.29; H, 3.90; N, 4.40.

When 5 eq of α -(methylthio)acetyl chloride was used in this reaction, the amide **2** was obtained in almost quantitative yield, after evaporation of the solvent and excess acyl chloride.

N-(2,6-Dichlorophenyl)- α -(methylsulfinyl)acetanilide (3)—a) *m*-Chloroperbenzoic acid (83%) (600 mg, 2.88 mmol) was added in small portions to a stirred solution of **2** (924 mg, 2.83 mmol) in CH₂Cl₂ (70 ml) at 0 °C. After being stirred at room temperature for 1 h, the mixture was washed with saturated NaHCO₃ solution and dried over MgSO₄. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel using ethyl acetate as an eluent to give **3** (884 mg, 91%), mp 140—141 °C (from benzene/hexane = 3/2). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1660 (CO) and 1035 (SO). ¹H-NMR (10% solution in CDCl₃) δ : 2.84 (3H, s), 3.53 (3/5H, d, $J=15$ Hz), 3.77 (2/5H, d, $J=14$ Hz), 3.83 (3/5H, d, $J=15$ Hz), 4.08 (2/5H, d, $J=14$ Hz), and 7.1—7.7 (8H, m). Anal. Calcd for C₁₅H₁₃Cl₂NO₂S: C, 52.64; H, 3.83; N, 4.09. Found: C, 52.69; H, 3.66; N, 4.37.

b) Hydrogen peroxide (30%) (16 ml, 0.01 mol) was added dropwise over 5 min to a stirred solution of **2** (3.26 g, 0.01 mol) in methanol (25 ml) at room temperature. The mixture was stirred at the same temperature for 14 h, then water (10 ml) was added to the reaction mixture and the whole was extracted with CHCl₃. The organic layer was washed successively with water and saturated NaCl solution, and then dried over MgSO₄. The solvent was removed *in vacuo* and the residual solid was recrystallized from benzene to give **3** (2.86 g, 84%).

1-(2,6-Dichlorophenyl)-3-(methylthio)oxindole (5)—a) Compound **3** (4.89 g, 14.3 mmol) was heated under reflux in dry benzene (50 ml) containing anhydrous *p*-toluenesulfonic acid (7.38 g, 42.9 mmol) for 30 min. After cooling to room temperature, the mixture was washed with water and dried over MgSO_4 . The solvent was removed *in vacuo* and the residual solid was recrystallized from benzene/hexane (3/10) to give **5** (3.88 g, 84%), mp 131–132 °C. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1725 (CO). $^1\text{H-NMR}$ (10% solution in CDCl_3) δ : 2.19 (3H, s), 4.49 (1H, s), 6.2–6.4 (1H, m), and 7.0–7.6 (6H, m). *Anal.* Calcd for $\text{C}_{15}\text{H}_{11}\text{Cl}_2\text{NOS}$: C, 55.57; H, 3.42; N, 4.32. Found: C, 55.25; H, 3.37; N, 4.20.

b) *N*-Chlorosuccinimide (7.3 g, 0.055 mol) was added in small portions to a stirred solution of **2** (16.3 g, 0.05 mol) in CCl_4 (100 ml) at 0 °C and the mixture was stirred at room temperature for 1 h. The reaction mixture was cooled to 0 °C and the precipitated succinimide was filtered off, then stannic chloride (23.4 g, 0.09 mol) was added to the filtrate at room temperature. The mixture was stirred at the same temperature for 50 min and the reaction was quenched by addition of water (50 ml) and CH_2Cl_2 (50 ml). The organic layer was separated and washed successively with dil. HCl, water, saturated NaHCO_3 , and water, then dried over MgSO_4 . The solvent was removed *in vacuo* and the residual solid was recrystallized from benzene/hexane (3/10) to give **5** (13.9 g, 85%).

1-(2,6-Dichlorophenyl)oxindole (6)—a) Compound **5** (620 mg, 1.91 mmol) was heated under reflux in ethanol (200 ml) containing Raney nickel (W-2, 2 g) for 70 min. The Raney nickel was removed by filtration and the solvent was evaporated off. The residual solid was recrystallized from benzene/hexane (2/3) to give **6** (490 mg, 92%), mp 126–126.5 °C, lit.²⁾ 126–127 °C. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1720 (CO). $^1\text{H-NMR}$ (10% solution in CDCl_3) δ : 3.76 (2H, s), 6.2–6.5 (1H, m), and 6.9–7.6 (6H, m).

b) Compound **5** (16.2 g, 0.05 mol) was heated with vigorous stirring under reflux in acetic acid (100 ml) containing zinc dust (13.3 g, 0.2 mol) for 4 h. A solution of NaHCO_3 (150 g) in water (500 ml) was added to the reaction mixture and the whole was extracted with CH_2Cl_2 (500 ml). The organic layer was washed with water and dried over MgSO_4 . The solvent was removed *in vacuo* to give **6** (14.5 g, 97%) in almost pure form, mp 126–126.5 °C (from benzene/hexane).

2-[(2,6-Dichlorophenyl)amino]- α -(methylthio)phenylacetic Acid (7)—A solution of **5** (780 mg, 2.4 mol) in 2N NaOH (6 ml) and ethanol (6 ml) was refluxed for 48 h, then cooled. Ice-water (30 ml) was added and the whole was extracted with ethyl ether. The aqueous layer was acidified to pH 1 with concentrated hydrochloric acid and extracted with ethyl ether. The organic layer was washed with water and dried over MgSO_4 . The solvent was evaporated off and the residue was chromatographed on silica gel with benzene/ethyl acetate (1/1) as an eluent to give **7** (750 mg, 91%), mp 136.5–138 °C (from benzene/hexane = 1/1). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1700 (COOH). $^1\text{H-NMR}$ (10% solution in CDCl_3) δ : 2.08 (3H, s), 5.01 (1H, s), 6.4–7.6 (7H, m), and 8.72 (2H, br s). High resolution MS Calcd for $\text{C}_{15}\text{H}_{13}\text{NO}_2\text{S}$: 341.0041. Found: 341.0039.

Diclofenac (8)—a) A solution of **6** (648 mg, 2 mmol) in 20% NaOH (7 ml) and ethanol (5 ml) was refluxed for 3 h, then the reaction mixture was cooled to 0 °C. The precipitates were collected by filtration and washed with water, then recrystallized from water to give the sodium salt of diclofenac (**8**) (630 mg, 85%), mp 283–285 °C (dec), lit.²⁾ 283–285 °C.

b) Compound **7** (295 mg, 0.91 mmol) was heated under reflux in ethanol (15 ml) containing Raney nickel (W-2, 2 g). The Raney nickel was removed by filtration and the solvent was evaporated off to give **8** (218 mg, 85%), mp 156–158 °C (from ethyl ether/petr. ether), lit.²⁾ 156–158 °C.

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