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Synthesis of Hexaprofen [2-(4-Cyclohexylphenyl) propionic Acid]

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Abstract □ A novel preparative method for hexaprofen, which is a potent antiinflammatory agent, is described. Friedel-Crafts reaction of cyclohexylbenzene with ethyl α-chloro-α-(methylthio) acetate **1** and α-chloro-α-(methylthio) acetonitrile **2** afforded ethyl 2-(methylthio)-2-(4-cyclohexylphenyl) acetate **7** and 2-methylthio-2-(4-cyclohexylphenyl) acetonitrile **8**, respectively. Compounds **7** and **8** were converted into the corresponding ethyl 2-methylthio-2-(4-cyclohexylphenyl) propionate **9** and 2-methylthio-2-(4-cyclohexylphenyl) propionitrile **10** by methylation with sodium hydride and methyl iodide. Hexaprofen **13** was prepared by hydrolysis of ethyl 2-(4-cyclohexylphenyl) propionate **11** and of 2-(4-cyclohexylphenyl) propionitrile **12** followed by desulfurization of compounds **9** and **10**.

Keywords □ Hexaprofen, a potent antiinflammatory agent, Friedel-Crafts reation, ethyl α-chloro-α-(methylthio) acetate, α-chloro-α-(methylthio) acetonitrile, methylation, hydrolysis, desulfurization.

The arylakanoic acid class containing the phenylacetic acid moiety has been attracting much attention because of their pharmacological activities as antiinflammatory and analgesic agents. Most of the known synthetic methods for arylalkanoic acid derivatives are dependent on the indirect introduction of an acetic acid group into aromatic nuclei[1].

In the preceding papers[2,3], we have developed a simple and high yield synthetic method for arylacetic esters **5** or arylacetonitriles **6** which involves Friedel-Crafts reaction of aromatic compounds with ethyl α-chloro-α-(methylthio) acetate **1** and α-chloro-α-(methylthio) acetonitrile **2** and successive desulfurization of the resulting products **3** and **4** (Scheme 1).

Recently, we reported the application of this method to the preparation of bufexamac [2-(p-butoxyphenyl) acetohydroxamic acid][4], butibufen [2-(4-isobutylphenyl) butyric acid][5], alminoprofen [2-(p-methylallylaminophenyl) propionic acid][6].

In the present paper, the method is applied to a new synthesis for hexaprofen [2-(4-cyclohexylphenyl) propionic acid][7,8], which is a potent antiinflammatory agent.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorected. The IR spectra were recorded with a Perkin-Elmer 1320 spectrophotometer. The ^{1}H-NMR spectra were recorded on a Hitachi R-1500 (FT; 60 MHz) spectrometer using tetramethylsilane as an internal standard. Mass spectra were measured on a Hewlett-Packard 5970 GC/MS instrument. Column chromatography was carried out with Kieselgel 60 (70-230 mesh, Merck).

***Ethyl 2-methylthio-2-(4-cyclohexylphenyl) acetate* 7**

$SnCl_4$ (774 mg, 2.97 mmole) was added to a stirred solution of **1** (500 mg, 2.97 mmole) and cyclohexylbenzene (476 mg, 2.97 mmole) in CH_2Cl_2 (3 ml) at 0℃ under nitogen atmosphere, and stirring was continued at the same temperature for 30 min. The reaction was quenched by the addition of water and the mixture was extracted with CH_2Cl_2 (10 ml×2), and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel using benzene as an eluent to give **7** (590 mg,

68%) as an oil.

IR (neat) cm^{-1}: 1720 (C=O); ^{1}H-NMR ($CDCl_3$) δ: 1.05-2.68 (m, 11H, cyclohexyl H), 1.25 (t, 3H, CH_2CH_3), 2.07 (s, 3H, SCH_3), 4.20 (q, 2H, CH_2CH_3), 4.45 (s, 1H, CHCOO), 7.03-7.51 (m, 4H, ArH); MS *m/z*: 292 (M^+), 246, 219, 163, 135, 115, 91, 55.

2-Methylthio-2-(4-cyclohexylphenyl) acetonitrile 8

$SnCl_4$ (642 mg, 2.47 mmole) was added to a stirred solution of **2** (300 mg, 2.47 mmole) and cyclohexylbenzene (400 mg, 2.47 mmole) in CH_2Cl_2 (3 m*l*) at 0℃ under nitrogen atmosphere, and stirring was continued at room temperature for 30 min. The reaction was quenched by addition of water and the mixture was extracted with CH_2Cl_2 (10 m*l*×2), and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel (ethyl acetate/n-hexane=1 : 1) to give **8** (405 mg, 67%) as an oil.

IR (neat) cm^{-1}: 2220 (CN); ^{1}H-NMR ($CDCl_3$) δ: 0.84-2.78 (m, 11H, cyclohexyl H), 2.23 (s, 3H, SCH_3), 4.73 (s, 1H, CHCN), 7.07-7.53 (m, 4H, ArH); MS *m/z*: 245 (M^+), 198, 171, 142, 116, 89, 41.

Ethyl 2-methylthio-2-(4-cyclohexylphenyl) propionate 9

A solution of **7** (500 mg, 1.71 mmole) in dimethylformamide (5 m*l*) was added to a suspension of sodium hydride (60% dispersion in mineral oil) (76 mg, 1.9 mmole) in dimethylformamide (2 m*l*) at 0℃ under nitrogen atmosphere, and the mixture was stirred at the same temperature until the evolution of hydrogen ceased. Methyl iodide (296 mg, 2.0 mmole) was then added and the mixture was stirred at 0℃ for 30 min and at room temperature for 40 min. The reaction mixture was poured into a solution of 5% NH_4Cl (10 m*l*) and extracted with Et_2O (10 m*l*×2). The extract was washed with water and dried ($MgSO_4$). The solvent was evaporated off. The residue was chromatographed on silica gel (benzene) to give **9** (431 mg, 82%) as an oil.

IR (neat) cm^{-1}: 1715 (C=O); ^{1}H-NMR ($CDCl_3$) δ: 1.0-2.78 (m, 11H, cyclohexyl H), 1.27 (t, 3H, CH_2CH_3), 1.77 (s, 3H, CCH_3), 1.99 (s, 3H, SCH_3), 4.25 (q, 2H, CH_2CH_3), 7.0-7.57 (m, 4H, ArH); MS *m/z*: 306 (M^+), 233, 203, 185, 131, 103, 43.

2-Methylthio-2-(4-cyclohexylphenyl) propionitrile 10

By the same procedure as described above for the preparation of **9**, compound **10** was obtained from **8** (808 mg, 3.3 mmole) in 60% yield (512 mg).

1, 2 **3, 4** **5, 6**

1,3,5: R=COOEt **2,4,6**: R=CN

Scheme 1

mp.: 89-90℃ (from n-hexane); IR (KBr) cm^{-1}: 2220 (CN); ^{1}H-NMR ($CDCl_3$) δ: 0.9-2.71 (m, 11H, cyclohexyl H), 1.93 (s, 3H, CCH_3), 2.07 (s, 3H, SCH_3), 7.08-7.67 (m, 4H, ArH); MS *m/z*: 259 (M^+), 182, 156, 130, 103, 77, 41.

Ethyl 2-(4-cyclohexylphenyl) propionate 11

(a) Zinc dust (1.34g) was added to a solution of **9** (500 mg, 1.63 mmole) in acetic acid (3 m*l*), and the resultant mixture was refluxed for 1h, then cooled. Water (5 m*l*) and $CHCl_3$ (15 m*l*) were added to the reaction mixture and the inorganic materials were filtered off. The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (10 m*l*×2). The combined organic layer dried ($MgSO_4$) and the solvent was evaporated off. The residue was chromatographed on silica gel using benzene as an eluent to give **11** (374 mg, 89%) as an oil.

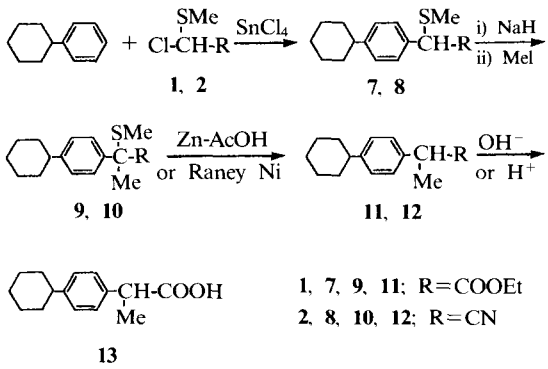
IR (neat) cm^{-1}: 1725 (C=O); ^{1}H-NMR ($CDCl_3$) δ: 0.98-2.76 (m, 11H, cyclohexyl H), 1.20 (t, 3H, CH_2CH_3), 1.47 (d, 3H, $CHCH_3$), 3.66 (q, 1H, $CHCH_3$), 4.11 (q, 2H, CH_2CH_3), 6.98-7.42 (m, 4H, ArH); MS *m/z*: 260 (M^+), 201, 167, 131, 105, 91, 41.

(b) Raney nickel (W-2, 2g) was added to a solution of **9** (424 mg, 1.38 mmole) in ethanol (20 m*l*) and the mixture was refluxed for 3h. The Raney nickel was filtered off and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel using benzene as an eluent to give **11** (338 mg, 95%) as an oil.

2-(4-Cyclohexylphenyl) propionitrile 12

By the same procedure as described above for the preparation of **11**, compound **12** was obtained from **10** (480 mg, 1.84 mmole) and zinc dust (1.65g) in 81% yield (317 mg) as an oil.

IR (neat) cm^{-1}: 2230 (CN); ^{1}H-NMR ($CDCl_3$) δ: 0.87-2.86 (m, 11H, cyclohexyl H), 1.62 (d, 3H, $CHCH_3$), 3.85 (q, 1H, $CHCH_3$), 7.24 (s, 4H, ArH); MS *m/z*: 213 (M^+), 170, 157, 142, 116, 91, 55, 41.



Scheme 2

Hexaprofen* [*2-(4-Cyclohexylphenyl) propionic acid*] *13

(a) Compound **11** (400 mg, 1.57 mmole) was added to a solution of potassium hydoxide (440 mg) in water (3 m*l*) and methanol (4 m*l*) and the mixture was heated at 60-70℃ for 3h, then cooled. Water was added to the mixture and the solution was washed with CH_2Cl_2. The aqueous layer was acidified to pH 1 with concentrated hydrochloric acid and extracted with Et_2O (10 m*l*×2), and dried ($MgSO_4$). The solvent was evaporated off. The residual solid was recrystallized from n-hexane to give **13** (332 mg, 91%) as a solid.

mp.: 111-112℃ (lit.[7] 112-113℃); IR (KBr) cm^{-1}: 3400-2740 (OH), 1680 (C=O); ^{1}H-NMR ($CDCl_3$) δ: 1.05-2.80 (m, 11H, cyclohexyl H), 1.48 (d, 3H, $CHCH_3$), 3.68 (q, 1H, $CHCH_3$), 7.19 (s, 4H, ArH), 10.21 (br.s, 1H, COOH).

(b) Compound **12** (333 mg, 1.56 mmole) was added to a solution of water (3 m*l*) and concentrated sulfuric acid (2 m*l*) and the mixture was refluxed for 5h, then cooled. The mixture was poured into ice water and extracted with Et_2O (10 m*l*×2), and dried ($MgSO_4$). The solvent was evaporated off. The residual solid was recrytallized from n-hexane to give **13** (300 mg, 82%) as a solid.

RESULTS AND DISCUSSION

Friedel-Crafts reaction of cyclohexylbenzene with **1** in the presence of stannic chloride gave ethyl 2-methylthio-2-(4-cyclohexylphenyl) acetate **7** in 68% yield. Methylation of **7** by treatment with sodum hydride and then methyl iodide in dimethylformamide afforded ethyl 2-methylthio-2-(4-cyclohexylphenyl) propionate **9** in 82% yield. ^{1}H-NMR spectrum of **9** confirmed the presence of new CH_3 group (δ 1.77 ppm) and disappearance of CH group (δ 4.45 ppm) appeared in **7**. This means selective methylation on carbon atom of benzylic position adjacent to ester group.

Compound **9** was desulfurized with zinc dust in acetic acid or Raney nickel in ethanol to give ethyl 2-(4-cyclohexylphenyl) propionate **11** in 89% and 95 % yield. ^{1}H-NMR spectrum **11** displayed signals for new CH group (δ 3.66 ppm) and disappearance of SCH_3 group (δ 1.99 ppm) appeared in **9**. Saponification of **11** with potassium hydroxide in aqueous methanol afforded hexaprofen **13** in 91% yield, which was also prepared by an alternative route.

Thus, cyclohexylbenzene reacted with **2** in the presence of stannic chloride to give 2-methylthio-2-(4-cycloxylphenyl) acetonitrile **8** in 67% yield. Methylation of **8** by treatment with sodium hydride and then methyl iodide in dimethylformamide afforded 2-methylthio-2-(4-cyclohexylphenyl) propionitrile **10** in 60% yield. ^{1}H-NMR spectrum of **10** confirmed the presence of new CH_3 group (δ 1.93 ppm) and disappearance of CH group (δ 4.73 ppm) appeared in **8**.

Compound **10** was desulfurization with zinc dust in acetic acid to give 2-(4-cyclohexylphenyl) propionitrile **12** in 81% yield. ^{1}H-NMR spectrum of **12** showed signals for new CH group (δ 3.85 ppm) and disappearance of SCH_3 group (δ 2.07 ppm) appearaned in **10**. Hexaprofen **13** could also be obtained in 82% yield by acid hydrolysis of **12** with concentrated sulfuric acid.

The synthetic route for **13** is outlined in Scheme 2. The structural assignment of the newly synthesized compounds **7-12** was based on IR, ^{1}H-NMR, mass spectroscopy.

In summary, hexaprofen **13** was synthesized by two efficient routes. The reaction steps were shortened in comparision with the method reported by Carenini *et al.*[7] The present sequence of reactions can be carried out under rather mild conditions in high yields, and hence provides a useful synthetic route to hexaprofen **13**.

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