Arch. Pharm. Res. Vol. 16, No. 4, pp. 343-346, 1993

Note

Synthesis of 7-[p-(Methylthio)benzoyl]-5-benzofuranacetic Acid

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(Received October 11, 1993)

A new method was described for the preparation of 7-[p-(methylthio)benzoyl]-5-benzofuranacetic acid **6**, which is an analgesic agent. Methyl 5-(2,3-di-hydrobenzofuran)acetate **3** was obtained by Friedel-Crafts reaction of 2,3-dihydrobenzofuran with methyl α-chloro-α-(methylthio)actate **1** and desulfurization of **2**. Tifurac **6** was synthesized from acylation of 3 with p-(methylthio)benzoyl chloride followed by bromination of **4**, dehydrohalogenation, and hydrolysis of **5**.

Key words: 7-[p-(Methylthio)benzoyl]-5-benzofuranacetic acid, Analgesic agent, Methyl 5-(2,3-dihydrobenzofuran)acetate, Friedel-Crafts reaction, Methyl α-chloro-α-(methylthio)acetate

INTRODUCTION

The arylalkanoic acid derivatives with an acetic acid group or a propionic acid group have been widely used as nonsteroidal antiinflammatory and analgesic agents. Several synthetic routes for preparation of the agents have been developed, but most synthetic work in this area is the indirect introduction of an acetic acid group into aromatic nuclei (Lednicer and Mitscher, 1980; Roth and kleeman, 1988).

In previous paper (Tamura *et al.*, 1982), we reported a novel preparative method for ethyl arylacetates by Friedel-Crafts reaction of aromatic compounds with ethyl α-chloro-α-(methylthio)acetate and successive desulfurization of the resulting ethyl α-(methylthio)arylacetates. The method was recently applied to syntheses of hexaprofen (Choi *et al.*, 1992) and tolmetin (Choi and Ma, 1992) as antiinflammatory agents.

The present paper describes its application to a convenient synthesis of sodium 7-[p-(methylthio)benzoyl]-5-benzofuranacetate.hydrate, which is apotent analgesic agent (Fig. 1).

MATERIALS AND METHODS

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

Methyl α-chloro-α-(methylthio)acetate 1

N-Chlorosuccinimide (4.71 g, 0.035 mol) was added to a stirred solution of methyl α-(methylthio)acetate (4.2 g, 0.035 mol) in CCl_4 (20 ml) in small portions at 0℃ and the stirring was continued at room temperature for 10 hr. The precipitated succinimide was filtered off and the solvent was removed in vacuo. The residue was distilled at 42-43℃/2 mmHg [lit. 82-83℃/14 mmHg, (Bohme and Krack, 1977)] to give **1** (4.4 g, 81%) as an oil.

IR (neat) cm $^{-1}$: 1725(CO); 1H-NMR (CDCl3) δ: 2.32 (3H, s, SCH_3), 3.84(3H, s, $COOCH_3$), 5.37(1H, s, Cl-CH-COO).

Methyl α-(methylthio)acetate was synthesized according to literature (H-erriot and Picker, 1975). Thus, methylmercaptan sodium salt (15% in water; 34.6 g, 0.072 mol), methyl bromoacetate (9.18 g, 0.06 mol), benzene (30 ml), and trioctylmethylammonium chloride (100 mg) were combined. The reaction mixture was stirred vigorously at room temperature for 2 hr. The organic layer was separated, washed with water (10 ml × 2), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was distilled at 29-30℃/3 mmHg to give methyl α-(methylthio)acetate (5.62 g, 78%).

IR (neat) cm $^{-1}$: 1720(CO); ^{1}H-NMR ($CDCl_3$) δ: 2.22 (3H, s, SCH_3), 3.20(2H, s, CH_2COO), 3.75(3H, s, $COOCH_3$).

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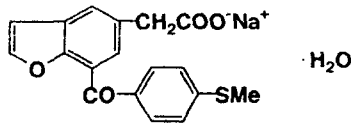


Tifurac sodium

Fig. 1.

Methyl α-methylthio-5-(2,3-dihydrobenzofuran)acetate 2

$TiCl_4$ (505 mg, 2.66 mmol) was added to a stirred solution of 2,3-dihydrobenzofuran (320 mg, 2.66 mmol) and **1** (411 mg, 2.66 mmol) in CH_2Cl_2 (5 ml) at 0℃ under nitrogen atmosphere, and the stirring was continued at the same temperature for 20 min. The reacton was quenched by the addition of water, then the mixture was extracted with CH_2Cl_2 (10 ml ×2), and the extract was dried over anhydrous $MgSO_4$. The solvent was removed in vacuo. The residue was chromatographed on silica gel using n-hexane/ethylacetate (4/1) as eluent and further purified by crystallization from n-hexane to give **2** (513 mg, 81%) as white crystals.

mp.: 62-63℃; IR (KBr) cm^{-1}: 1725 (CO); ^{1}H-NMR ($CDCl_3$) δ: 2.08(3H, s, SCH_3), 3.19(2H, s, J=8.8 Hz, C3-H on dihydrobenzofuran), 3.74(3H, s, $COOCH_3$), 4.44(1H, s, CHCOO), 4.57(2H, t, J=8.8 Hz, C_2-H on dihydrobenzofuran), 6.48-7.51(3H, m, arom); MS m/e: 238[M^+], 191, 163, 131, 91, 77, 51.

Methyl 5-(2,3-dihydrobenzofuran)acetate 3

Zinc dust (1.42 g) was added to a solution of **2** (400 mg, 1.68 mmol) in acetic acid (3 ml), and the mixture was refluxed with vigorous stirring for 1 hr, then cooled. Water (10 ml) and CH_2Cl_2 (10 ml) were added to the reaction mixture and the inorganic materials filtered off. The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (10 ml ×2). The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated off. The residue was chromatographed on silica gel using benzene as an eluent to give **3** (288 mg, 89%) as a colorless oil.

IR (neat) cm^{-1}: 1720(CO); ^{1}H-NMR($CDCl_3$) δ: 3.17(2H, t, J=8.8 Hz, C_3-H on dihydrobenzofuran), 3.53(2H, s, CH_2COO), 3.68(3H, s, $COOCH_3$), 4.55(2H, t, J=8.8 Hz, C_2-H on dihydrobenzofuran), 6.53-7.40(3H, m, arom); MS m/e: 192[M^+], 133, 131, 105, 77, 65, 51.

Methyl 7-[p-(methylthio)benzoyl]-5-(2,3-dihydrobenzofuran)acetate 4

$SnCl_4$ (475 mg, 1.82 mmol) was added to a stirred solution of **3** (350 mg, 1.82 mmol) and p-(methylthio) benzoyl chloride (340 mg, 1.82 mmol) in CH_2Cl_2 (4 ml) at room temperature under nitrogen atmosphere, and the stirring was continued at the same temperature for 3 hr. The reaction was quenched by the addition of water,the mixture was extracted with CH_2Cl_2 (10 ml ×2), and the extract was dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was chromatographed on silica gel using n-hexane/ethylacetate (1/1) as eluent to give **4** (436 mg, 70%) as white crystals.

mp.: 107-108℃ (from n-hexane:ethylacetate=1 : 1); IR (KBr) cm^{-1}: 1720(CO); ^{1}H-NMR($CDCl_3$) δ: 2.52 (3H, s, SCH_3), 3.22(2H, t, J=8.8 Hz, C_3-H on d-ihydrobenzofuran), 3.56(2H, s, CH_2COO), 3.70(3H, s, $COOCH_3$), 4.58(2H, t, J=8.8 Hz, C_2-H on dihydrobenzofuran), 7.06-7.92(6H, m, arom); MS m/e: 342[M^+], 283, 236, 219, 159, 142, 77, 45.

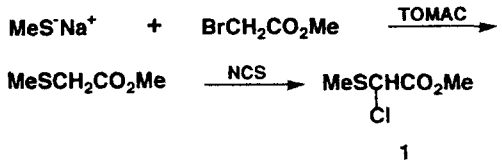
Methyl 7-[p-(methylthio)benzoyl]-5-benzofuranacetate 5

N-Bromosuccinimide (229 mg, 1.29 mmol) and benzoyl peroxide (15 mg) were added to a solution of **4** (400 mg, 1.17 mmol) in CCl_4 (5 ml), and the mixture was refluxed for 4 hr, then cooled. The precipitated succinimide was filtered off. The filtrate was washed with a solution of 5% NaOH (3 ml), and dried over anhydrous $MgSO_4$. Triethylamine (2 ml) was added to the above filtrate, and the mixture was refluxed for 2 hr, then cooled. The reaction was quenched by the addition of water, the mixture was extracted with CH_2Cl_2 (7 ml ×2), and the extract was dried over anhydrous $MgSO_4$. The solvent and excess triethylamine were removed in vacuo. The residue was chromatographed on silica gel using n-hexane/ethylacetate (1/1) as eluent and further purified by crystallization from isopropyl alcohol to give **5** (211 mg, 53%) as yellow crystals.

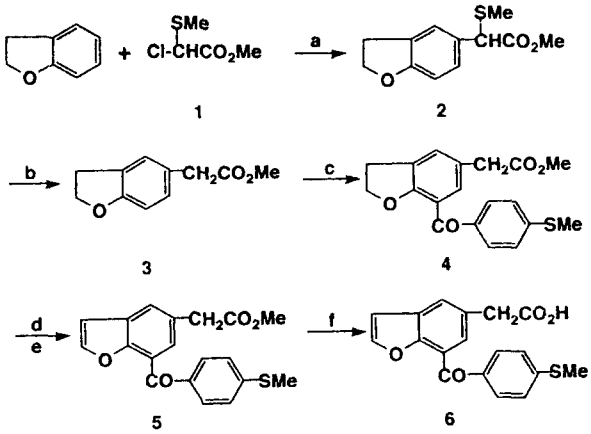
mp.: 121-122℃; IR (KBr) cm^{-1}: 1730(CO), 1640(CO); ^{1}H-NMR ($CDCl_3$) δ: 2.53(3H, s, SCH_3), 3.71(3H, s, $COOCH_3$), 3.75(2H, s, CH_2COO), 6.80(1H, d, C_2-H on benzofuran), 7.13-8.20(7H, m, C_3-H on benzofuran and arom); MS m/e: 340[M^+], 281, 217, 151, 102, 79, 32.

7-[p-(Methylthio)benzoyl]-5-benzofuranacetic acid [Tifurac] 6

Compound **5** (300 mg, 0.88 mmol) was added to a solution of KOH (250 mg) in water (5 ml) and methanol (3 ml),and the mixture was heated at 70-80℃ for 3 hr, then cooled. Water (5 ml) was added to the mixture, and solution was washed with CH_2Cl_2 (10 ml). The aqueous layer was acidified to pH 1 with concentrated HCl, extracted with ethyl ether (10 ml ×2), and dried over anhydrous MgSO4. The solvent was evaporated off. The residue was recrystallized from isopropyl alcohol to give **6** (261 mg, 91%) as pale yellow crystals.



Scheme 1



a: $TiCl_4$; b: Zn, AcOH; c: p-(methylthio)benzoyl chloride,$SnCl_4$; d: N-bromosuccinimide, benzoyl peroxide; e: triethylamine; f: KOH, MeOH, H_2O.

Scheme 2

mp.: 149-151°C [lit. 153-4°C, (Syntex, Inc., 1989)]; IR(KBr) cm^{-1}: 3300-2600(OH), 1680(CO), 1630(CO); ^{1}H-MNR ($CDCl_3$) δ: 2.52(3H, s, SCH_3), 3.79 (2H, s, CH_2 COO), 6.80(1H, d, C_2-H on benzofuran), 7.12-8.26(7H, m, C_3-H on benzofuran and arom), 10.21(1H, s, br s, COOH).

RESULTS AND DISCUSSION

By means of the phase-transfer synthesis of sulfides, methyl α-(methylthio)acetate was obtained from methylmercaptan sodium salt and methyl bromoacetate in the presence of trioctylmethylammonium chloride (TOMAC). Methyl α-chloro-α-(methylthio)acetate **1** was prepared from methyl α-(methylthio)acetate by chlorination with N-chlorosuccinimide (NCS) according to the procedure described by Bohme and Krack (1977) (Scheme 1).

Friedel-Crafts reaction of one equimolar amount of 2,3-dihydrobenzofuran with **1** in the presence of $TiCl_4$ afforded methyl α-methylthio-5-(2,3-dihydrobenzofuran)acetate **2** in 81% yield. When the reaction was carried out with $SnCl_4$, 2,3-dihydrobenzofuran gave **2** in 63% yield.

Desulfurization of **2** with zinc dust in hot acetic acid could easily be accomplished to give methyl 5-(2,3-dihydrobenzofuran)acetate **3** in 89% yield. Compound **4** was prepared by acylation of **3** with p-(methylthio) benzoyl chloride in the presence of $SnCl_4$ in 70% yield.

As the procedure for methyl 7-[p-(methylthio)benzoyl]-5-benzofuranacetate **5** by bromination of benzylic position on dihydrobenzofuran ring of **4** and successive dehydrohalogenation, the treatment of **4** with N-bromosuccinimide and benzoyl peroxide afforded bromo compound, which was refluxed with triethylamine to give **5**. ^{1}H-NMR spectrum of **5** revealed the presence of signals at δ 6.80 ppm (1H, d, C_2-H on benzofuran), δ 7.13-8.20 ppm (7H, m, C_3-H on benzofuran and phenyl protons) and the disappearance of signals at δ 3.22 ppm (2H, t, J=8.8 Hz, C_3-H on dihydrobenzofuran), δ 4.58 ppm (2H, t, J=8.8 Hz, C_2-H on dihydrobenzofuran) appeared in **4**. Finally alkaline hydrolysis of **5** with KOH afforded **6** in 91% yield.

The synthetic route for tifurac is outlined in Scheme 2. The structural assignment of newly synthesized compounds **2-5** was based on IR, ^{1}H-NMR, MS spectroscopy.

Ethyl 5-(2,3-dihydrobenzofuran)acetate, which is a key intermediate for preparation of tifurac, was previously synthesized from the procedure through acylation of 2,3-dihydrobenzofuran with acetyl chloride and Willgerodt-Kindler reaction of 5-acetyl-2,3-dihydrobenzofuran, followed by hydrolysis of 2-(2,3-dihydrobenzofuran-5-yl)thioacetic acid morpholide and esterification of 2-(2,3-dihydrobenzofuran-5-yl)acetic acid (Syntex, 1989).

In conclusion, compound **3** could be obtained by a two-step sequence. Friedel-Crafts reaction of 2,3-dihydrobenzofuran with **1** gave **2**, which was readily converted into **3** by reductive desulfurization. Compound **4** was synthesized from acylation of **3** with p-(methylthio)benzoyl chloride. Tifurac **6** was successfully prepared by bromination of **4**, dehydrohalogenation of the resulting bromo compound, and hydrolysis of **5**, good-yield process.

ACKNOWLEDGEMENT

We thank Mr. W. K. Lee of Public Health and Environment Institute of Pusan for measuring GC-MS.

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