Non-Steroidal Antiinflammatory Agents. 1. A Novel Synthesis of 1-Methyl-5-*p*-tolylpyrrole-2-acetic Acid (Tolmetin)

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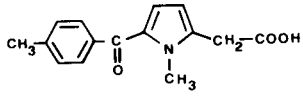
Received June 7, 1982

A four-step preparation of 1-methyl-5-*p*-tolylpyrrole-2-acetic acid (Tolmetin) is reported starting from 1-methyl-2-*p*-tolylpyrrole. Formylation of this compound followed by condensation with methyl(methylthio)-methyl sulfoxide furnished 1-(methylsulfinyl)-1-methylthio-2-(1-methyl-5-*p*-tolyl-2-pyrrolyl)ethylene. Pummerer rearrangement of the latter compound gave ethyl 1-methyl-5-*p*-tolylpyrrole-2-acetate, which was hydrolyzed in alkaline medium to afford Tolmetin.

J. Heterocyclic Chem., **19**, 1493 (1982).

Tolmetin **1** is an useful therapeutic agent belonging to the non-steroidal antiinflammatory class.

The first synthesis of this compound was described by Carson and coworkers in 1971 (2).



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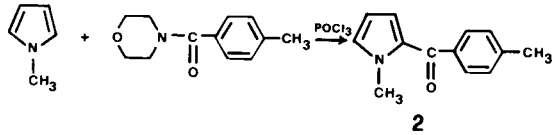
The fundamental step of Carson's procedure was the aroylation by the Friedel-Crafts method of 1-methyl-2-pyrroleacetonitrile, but the low yield in preparing this compound (3) and formation of two aroylated isomers (2) dramatically abated the overall yield of Tolmetin to 3.7% considering 1-methylpyrrole as the starting material.

Later (1979), Carson patented the above synthesis with a modification in aroylation procedure (4) without giving yield data.

In 1978 another five-step synthesis of Tolmetin from the non-commercially available 1-methyl-2-oxymethyl-5-chloropyrrole was patented by Calzada Badia (5).

We report now a new procedure starting from 1-methyl-2-*p*-tolylpyrrole **2**, which was obtained as the only product when 1-methylpyrrole was treated with the morpholide of *p*-toluic acid in the presence of phosphorus oxychloride according to Vilsmeier-Haack reaction (Scheme 1) (6).

SCHEME 1



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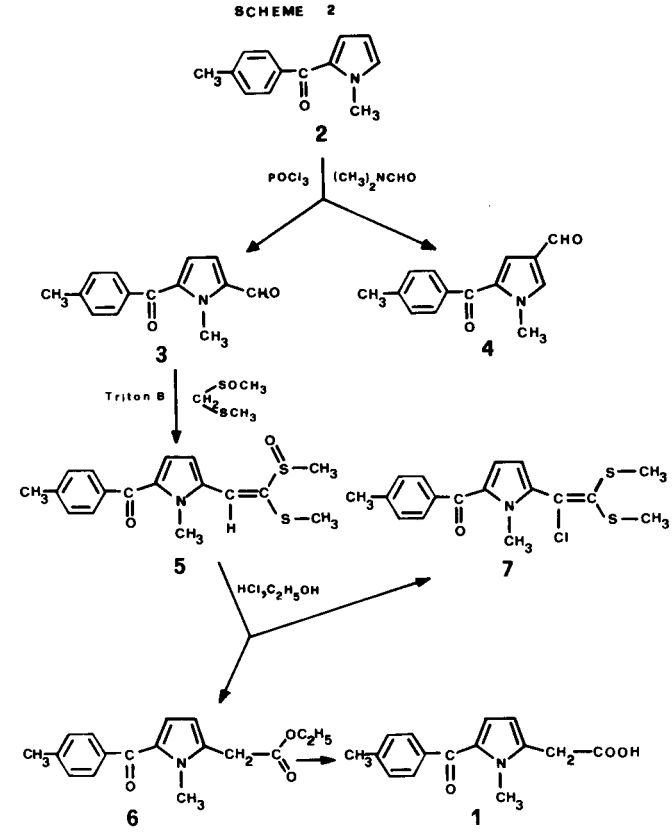
The introduction of the acetic moiety in **2** was achieved as follows. Formylation of **2** with the *N,N*-dimethylformamide-phosphorus oxychloride complex led to the formation of two isomeric products, 1-methyl-5-*p*-tolylpyrrole-2-carbaldehyde **3** and 1-methyl-5-*p*-tolylpyrrole-3-carbaldehyde **4**, respectively. The former compound was then subjected to condensation with methyl(methylthio)methyl sulfoxide in the presence of Triton B to afford 1-methylsulfinyl-1-methylthio-2-(1-methyl-5-*p*-tolyl-2-pyrrolyl)ethylene **5** (7).

Pummerer rearrangement of **5** by treatment with hydrogen chloride in dry ethanol according to Ogura and coworkers (8) gave, after chromatographic partition on silicagel, two main products, the ethyl ester of 1-methyl-5-*p*-tolylpyrrole-2-acetic acid **6** and the 1,1-bis-methylthio-2-chloro-2-(1-methyl-5-*p*-tolyl-2-pyrrolyl)ethylene **7**, respectively.

When the ester **6** was subjected to hydrolysis in alkaline medium 1-methyl-5-*p*-tolylpyrrole-2-acetic acid **1** was ob-

SCHEME 2



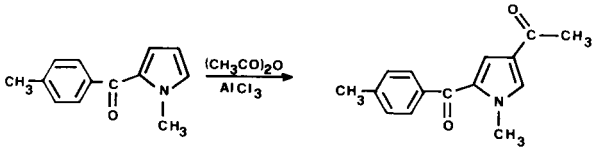
tained (9), identical with a sample prepared according to Carson (2).

All these reactions are depicted in Scheme 2.

The structure of **7**, the product accompanying the required ester **6**, was established on the basis of the following evidence. Molecular formula $C_{17}H_{18}ClNOS_2$ was confirmed by its mass spectrum (parent peak m/e 351.1 and base peak m/e 119) and by elemental analysis; besides, examination of the nmr spectrum indicated the absence of ethyl groups and the presence of four methyl groups, four benzene protons and two doublets attributable to the pyrrole protons at the β-positions. The ir spectrum confirmed the absence of carbonyl bands typical of ethyl esters and, finally, absence of ethylenic protons in the nmr spectrum indicated undoubtedly the position of chlorine atom (10) in the molecule of **7**.

The conversion of aryl methyl ketones to arylacetic acids recently described by Myrboh and coworkers (11) could offer a further example of a simple synthetic approach to Tolmetin. However, attempts to prepare the required 1-methyltolyl-2-pyrrolylmethyl ketone by acetylation of **2** were unsuccessful, the only material recovered being the isomeric 1-methyl-5-*p*-tolyl-3-pyrrolyl methyl ketone **8** (Scheme 3). Furthermore, when this compound was treated with boron trifluoride etherate and lead(IV)

SCHEME 3



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acetate no reaction took place under the conditions reported by the above cited authors (11).

All of the new products were identified by elemental analyses, ir and nmr spectra and, when reported, the mass spectra.

EXPERIMENTAL

All melting points were taken on a Fisher-Johns apparatus and are uncorrected. Infrared spectra (nujol mulls) were run on a Perkin-Elmer model 297 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian EM-390 instrument (TMS internal standard). The mass spectra were recorded on a Hewlett-Packard 5908-A mass spectrometer. Merck according to Brockmann alumina, florisil and silica gel 60 were used for chromatographic purifications. Elemental analyses were performed by A. Pietrogrande, Padova, Italy.

1-Methyl-2-*p*-tolylpyrrole (**2**).

To 41.00 g (0.2 mole) of *N*-(*p*-tolyl)morpholine, 66.2 g (0.43 mole) of phosphorus oxychloride was added and the resulting mixture was maintained under stirring at room temperature for 4 hours. Then a solution of 16.2 g (0.2 mole) of 1-methylpyrrole in 400 ml of 1,2-dichloroethane was added in one portion to the mixture and stirring was continued for an additional 40 hours. The solution formed was added to 450 ml of 10% sodium carbonate, the mixture was allowed to stand at room temperature for 15 minutes and then refluxed for 45 minutes. After cooling the organic layer was separated, washed with water and then dried over anhydrous sodium sulphate. The residual oil obtained on removing the solvent *in vacuo* was dissolved in benzene and passed through an alumina column. The benzene eluates after evaporation furnished 25.9 g (65%) of 1-methyl-2-*p*-tolylpyrrole as an oil, bp 175° at 0.1-1 mm; ir: 1630 cm^{-1} (CO).

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.21; H, 6.51; N, 7.15.

Formylation of 1-Methyl-2-*p*-tolylpyrrole.

To a solution of 7.3 g (0.1 mole) of *N,N*-dimethylformamide in 30 ml of 1,2-dichloroethane 15.3 g (0.1 mole) of phosphorus oxychloride were added by dropping while stirring. The solution was then heated at reflux for 30 minutes, then cooled to 50° and a solution of 19.9 g (0.1 mole) of 1-methyl-2-*p*-tolylpyrrole **2** in 50 ml of 1,2-dichloroethane was added dropwise. The mixture was heated at 50-60° for 2 hours, cooled to room temperature, treated with a 5% sodium acetate solution (120 ml) and refluxed for 15 minutes. After cooling the organic layer was separated, washed with water, dried over anhydrous sodium sulphate, then evaporated to give a brownish oil which was chromatographed on silica-gel column. Elution with benzene followed by evaporation *in vacuo* of the collected eluates afforded 11.45 g (50%) of 1-methyl-5-*p*-tolylpyrrole-2-carbaldehyde **3**, mp 100-103° after recrystallization from cyclohexane; ir: 1675 cm^{-1} (CHO), 1630 cm^{-1} (CO); nmr (deuteriochloroform): δ 2.4 (s, 3, CH_3 *p*-tolyl group), 4.26 (s, 3, N-CH_3), 6.65 and 6.85 (two doublets, 2, pyrrole β-protons), 7.3 and 7.8 (two doublets, 4, benzene protons), 9.8 ppm (s, 1, CHO).

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.84; H, 5.68; N, 6.25.

Further elution of the above chromatographic column with chloroform furnished 3.4 g (15%) of 1-methyl-5-*p*-tolylpyrrole-3-carbaldehyde **4**, mp 146-148° after recrystallization from carbon tetrachloride; ir: 1670 cm^{-1} (CHO), 1630 cm^{-1} (CO); nmr (deuteriochloroform): δ 2.4 (s, 3, CH_3 *p*-tolyl group), 4.05 (s, 3, CH_3-N), 7.18 (s, 1, pyrrole α-H), 7.3 (d, 2, benzene protons near CH_3), 7.6 (s, 1, pyrrole β-H), 7.8 (d, 2, benzene protons near CO), 9.85 ppm (s, 1, CHO).

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.82; H, 5.52; N, 6.19.

1-(Methylsulfinyl)-1-methylthio-2-(1-methyl-5-*p*-tolyl-2-pyrrolyl)ethylene (**5**).

To a solution of 2.27 g (0.01 mole) of 1-methyl-5-*p*-tolylpyrrole-2-carbaldehyde **3** in THF (5 ml) were added Triton B (1 ml) and 1.24 g (0.01 mole) of methyl(methylthio)methyl sulfoxide and the mixture was refluxed for 4 hours. The solution was then evaporated *in vacuo* to small volume, treated with crushed ice, acidified by adding concentrated hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water, then dried on anhydrous sodium sulphate and finally evaporated *in vacuo*. The oily residue was dissolved in a mixture of benzene-chloroform (1:1) and passed through a silica-gel column. The eluates were collected and evaporated under reduced pressure to afford 2.0 g (60%) of 1-(methylsulfinyl)-1-methylthio-2-(1-methyl-5-*p*-tolyl-2-pyrrolyl)-ethylene **5**, mp 108-110° (from cyclohexane); ir: 1620 cm^{-1} (CO), 1055 cm^{-1} (SO); nmr (carbon tetrachloride): δ 2.3 (s, 3, CH_3-S), 2.4 (s, 3, CH_3 *p*-tolyl group), 2.6 (s, 3, CH_3-SO), 4.05 (s, 3, CH_3-N), 6.65 (d, 1, pyrrole β-H), 7.1-7.3 (superimposed peaks, 3, pyrrole β-H and benzene protons near CH_3), 7.6-7.8 ppm (superimposed peaks, 3, CH=C< and benzene protons near CO).

Anal. Calcd. for $C_{17}H_{19}NO_2S_2$: C, 61.25; H, 5.75; N, 4.20; S, 19.20. Found: C, 61.48; H, 5.90; N, 4.39; S, 18.98.

Pummerer Rearrangement of **5**.

To a solution of 1.7 g (0.0051 mole) of 1-(methylsulfinyl)-1-methylthio-2-(1-methyl-5-*p*-tolyl-2-pyrrolyl)ethylene **5** in 25 ml of absolute ethanol were added 2.2 ml of a saturated ethanolic solution of hydrogen chloride and

the resulting solution was maintained with stirring at room temperature for 70 hours. After evaporation *in vacuo*, the oily residue was passed through a florisil column (benzene as eluent) to afford 1.6 g of a pale yellow oil, which was then subjected to column chromatography on silica-gel [benzene-cyclohexane (1:1) as eluent]. The eluates, after evaporation *in vacuo*, furnished 0.8 g (45.5%) of 1,1-bismethylthio-2-chloro-2-(1-methyl-5-*p*-tolyl-2-pyrrolyl)ethylene **7**, mp 100-102° (from light petroleum ether); ir: 1620 cm^{-1} (CO); nmr (carbon tetrachloride): δ 2.25, 2.35 and 2.4 (three singlets, 9, attributable to methyl protons of S-CH_3 and CH_3 *p*-tolyl groups), 3.85 (s, 3, N-CH_3), 6.1 and 6.6 (two doublets, 2, pyrrole β-H), 7.2 and 7.7 ppm (two doublets, 4, attributable to benzene ring H; ms: (25 eV) m/e (relative intensity) 351 (M^+, 13.5), 119 ($C_8H_7O^+$, 100), 91 ($C_7H_7^+$, 14.8).

Anal. Calcd. for $C_{17}H_{18}ClNOS_2$: C, 58.04; H, 5.12; Cl, 10.08; N, 3.98; S, 18.23. Found: C, 57.90; H, 5.18; Cl, 10.00; N, 3.85; S, 18.01.

Further elution of the above column with chloroform as eluent afforded 0.5 g (35% of calculated) of ethyl 1-methyl-5-*p*-tolylpyrrole-2-acetate **6**, mp 74-75° (from cyclohexane); ir: 1740 cm^{-1} ($COOC_2H_5$), 1620 cm^{-1} (CO); nmr (deuteriochloroform): δ 1.2 (t, 3, CH_3-CH_2), 2.4 (s, 3, *p*-tolyl group CH_3 protons), 3.7 (s, 2, $CH_2COOC_2H_5$), 3.98 (s, 3, N-CH_3), 4.2 (q, 2, CH_3-CH_2), 6.1-6.7 (two doublets, 2, pyrrole β-H), 7.25 and 7.72 (two doublets, 4, benzene-ring H); ms: (70 eV) m/e (relative intensity) 285 (M^+, 37), 270 ($C_{16}H_{16}NO_3^+$, 14), 212 ($C_{14}H_{14}^+$, 100), 119 ($C_8H_7O^+$, 15), 91 ($C_7H_7^+$, 12).

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.48; H, 6.80; N, 4.87.

1-Methyl-5-*p*-tolylpyrrole-2-acetic Acid (**1**).

A suspension of 0.7 g ($2.4.10^{-3}$ mole) of ethyl 1-methyl-5-*p*-tolylpyrrole-2-acetate **6** in 2.1 ml of 10% aqueous sodium hydroxide was refluxed for 30 minutes, then diluted to 30 ml with water and acidified with concentrated hydrochloric acid. The precipitate was filtered off and recrystallized from toluene to afford 0.6 g (95.2% of yield) of 1-methyl-5-*p*-tolylpyrrole-2-acetic acid **1**, mp 158-160° (lit (2) mp 155-157°).

1-Methyl-2-*p*-tolyl-4-acetylpyrrole (**8**).

To a suspension of 10.7 g (0.08 mole) of aluminum trichloride in 50 ml of carbon disulfide were added 2 ml (0.02 mole) of acetic anhydride and the mixture was stirred for 10 minutes. Then a solution of 3.98 g (0.02 mole) of 1-methyl-2-*p*-tolylpyrrole **2** in 20 ml of carbon disulfide was dropped onto the mixture while stirring during 10 minutes. After refluxing for 30 minutes the mixture was treated with crushed ice, acidified with concentrated hydrochloric acid and kept under stirring for 1 hour. The mixture was then extracted with chloroform and the organic layer was washed with 5% sodium bicarbonate, then with water and finally dried on anhydrous sodium sulphate. Removal of the solvent *in vacuo* furnished an oily product, which was chromatographed on silica-gel column, benzene:chloroform (1:1) as eluent. Eluates were collected and evaporated under reduced pressure to afford 3.5 g (60%) of 1-methyl-2-*p*-tolyl-4-acetylpyrrole **8**, mp 106-108° (from cyclohexane); ir: 1670 cm^{-1} ($COCH_3$), 1620 cm^{-1} ($COC_6H_4CH_3$); nmr (deuteriochloroform): δ 2.3 and 2.35 (two singlets, 6H, attributable to CH_3 protons of acetyl and *p*-tolyl groups), 4.0 (s, 3, N-CH_3), 7.05 (s, 1, pyrrole β-H), 7.2 (d, 2, benzene-ring H near methyl group), 7.4 (s, 1, pyrrole α-H), 7.7 ppm (d, 2, benzene-ring H near CO group); ms: (70 eV) m/e (relative intensity) 241 (M^+, 24), 226 (M^+-CH_3, 100), 119 ($C_8H_7O^+$, 10), 91 ($C_7H_7^+$, 12).

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.59; H, 6.31; N, 5.93.

Acknowledgment.

We are grateful to the Italian C. N. R. (Consiglio Nazionale delle Ricerche) for financial support of this study.

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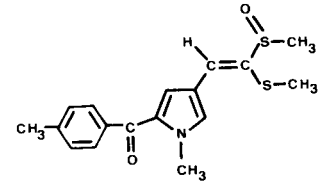
(5) J. M. Calzada Badia (Laboratorio Estedi S. L.) Spanish Patent 456,334, 16 Jan 1978, Appl 26 Feb 1977; *Chem. Abstr.*, **89**, 179850q (1978).

(6) The use of *N,N*-dimethyl-*p*-tolylamide in this reaction under various experimental conditions always gave unsatisfactory results due to the difficulty encountered in the separation of the required product from isomeric mixtures; *cf.*, J. White and G. McGillivray, *J. Org. Chem.*, **42**, 4248 (1977).

(7) The aldehyde **4** also reacted with methyl (methylthio)methyl sulfoxide giving 1-methylsulfinyl-1-methylthio-2-(1-methyl-5-*p*-tolyl-3-pyrrolyl)ethylene **9**, mp 148-150° from ethyl acetate (yield, 54%); ir: 1625 cm^{-1}



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(CO), 1050 cm^{-1} (SO). Satisfactory elemental data were obtained for this compound.

(8) K. Ogura, Y. Ito and G. Tsuchihashi, *Bull. Chem. Soc. Japan*, **52**, 2013 (1979); K. Ogura, S. Mitamura, K. Kishi and G. Tsuchihashi, *Synthesis*, 880 (1979); K. Ogura, Y. Ito and G. Tsuchihashi, *ibid.*, 736 (1980); K. Ogura and G. Tsuchihashi, *Tetrahedron Letters*, 1383 (1972).

(9) The overall yield of Tolmetin referred to 1-methylpyrrole was finally 6.5%, larger than the overall yield of Carson's procedure (2) amounting to 3.7%.

(10) Formation of unsaturated chlorosulfide by substitution at the β-vinyl carbon atom has been described in the Pummerer rearrangement of unsaturated sulfoxide when treated with thionyl chloride; *cf.*, G. A. Russel and G. J. Mikol, "Pummerer and Polonovski Reactions", in the "Mechanisms of Molecular Migrations", Vol 1, p 172, reference 24, B. S. Thyagarajan, ed, Interscience Publishers, J. Wiley and Sons, Inc., New York, 1968.

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