**Electronic supplementary materials** *Mendeleev Commun*., 2010, **20**, 111–112

# Bromination of indomethacin

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## Experimental Section

Proton nuclear magnetic resonance ($^1$H NMR) spectra were recoded on a Varian 400 spectrometer with tetramethylsilane as an internal reference, and all shifts are indicated in ppm. Liquid chromatography and mass spectra (LC-MS) were recorded on Shimadzu HPLC with Waters XBridge $C_{18}$ column, PE SCIEX API 150 EX mass detector and Shimadzu ($\lambda_{max}$ 220 and 254 nm) photometric detector. According to LC-MS spectral data, purity of all samples exceed 98%.

## General procedure for the synthesis of 4- and 6-bromo substituted indomethacins

Indomethacin (30 g, 0.0838 mol) was dissolved in acetic acid (300 ml). *N*-Bromosuccinimide (14.9 g, 0.0838 mol) was added to the solution and the resulting mixture was stirred at room temperature for 12 h. The precipitate was collected by filtration, washed with acetic acid, water, and air dried. A mixture of 4- and 6-bromo substituted indomethacins was obtained in 80% yield. The isomers was separated by column chromatography on silica gel with hexane/ethyl acetate/acetic acid (3:1:0.03) as an eluent.

## 2-[4-Bromo-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid (2)

LC-MS $(M+H)^+$ 436, 438. $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 12.12 (s, 1H), 7.68 (d, *J*=8.2 Hz, 2H), 7.60 (d, *J*=8.2 Hz, 2H), 7.09 (d, *J*=8.9 Hz, 1H), 6.87 (d, *J*=8.9 Hz, 1H), 3.92 (s, 2H), 3.84 (s, 3H), 2.20 (s, 3H). Found (%): C, 52.65; H, 3.68; N, 3.12. Calc. for $C_{19}H_{15}BrClNO_4$ (%): C, 52.26; H, 3.46; N, 3.21.

## 2-[6-Bromo-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid (3)

LC MS $(M+H)^+$ 436, 438. $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 12.37 (s, 1H), 7.69 (d, *J*=7.6 Hz, 2H), 7.66 (d, *J*=7.6 Hz, 2H), 7.38 (c, 1H), 7.24 (c, 1H), 3.86 (s, 3H), 3.70 (s, 2H), 2.12 (s, 3H). Found (%): C, 52.29; H, 3.72; N, 3.13. Calc. for $C_{19}H_{15}BrClNO_4$ (%): C, 52.26; H, 3.46; N, 3.21.

**2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic hypobromous anhydride (4)**

*N*-Bromosuccinimide (0.539 g, 3.08 mmol) was added to a suspension of indomethacin (1 g, 2.8 mmol) in $CCl_4$ (50 ml). After 12 h of stirring at room temperature, the mixture was heated to boiling temperature and insoluble succinimide was filtered off. The solvent was evaporated to dryness under reduced pressure. The residue was crystallized from $CCl_4$ to give hypobromous anhydride **4** (73% yield).

LC-MS $(M+H)^+$ 436, 438. $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 7.64 (d, *J*=8.2 Hz, 2H), δ 7.57 (d, *J*=8.4 Hz, 2H), 7.32 (d, *J*=2.7 Hz, 1H), 6.76 (dd, $J_1$=9.1 Hz, $J_2$=2.6 Hz, 1H) 6.48 (d, *J*=9.1 Hz, 1H), 3.88 (d *J*=17.4 Hz, 1H), 3.78 (s, 3H), 3.76 (d, *J*=17.4 Hz, 1H), 2.07 (s, 3H). Found (%): C, 52.23; H, 3.45; N, 3.01. Calc. for $C_{19}H_{15}BrClNO_4$ (%): C, 52.26; H, 3.46; N, 3.21.

**2-[2-(Bromomethyl)-1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl]acetic acid (5)**

Hypobromite **4** (0.75 g, 1.716 mmol) was dissolved in $CCl_4$ (50 ml) and the solution was heated with stirring at 75 ºC for 1.5 h. After cooling to room temperature the solvent was removed in a vacuum. Obtained acid **5** was used without additional purification.

LC-MS $(M+H)^+$ 436, 438.

**2-[1-(4-Chlorobenzoyl)-2-(hydroxymethyl)-5-methoxy-1*H*-indol-3-yl]acetic acid (6)**

The product is formed upon an attempt of purification of bromide **5** by HPLC, with water – MeCN – 0.05% TFA as a system with 5 to 95% MeCN gradient.

$^1$H NMR (DMSO-$d_6$, 400 MHz) δ 12.37 (s, 1H), 7.66 (m, 4H), 7.10 (d, *J*=2.4 Hz, 1H), 6.90 (d, *J*=9.1 Hz, 1H), 6.77 (dd, $J_1$=9.1 Hz, $J_2$=2.4 Hz, 1H), 4.92 (br, 1H) 4.53 (s, 2H), 3.77 (m, 5H). Calc. for $C_{19}H_{16}ClNO_5$ (%): C, 61.05; H, 4.31; N, 3.75. Found (%): C, 61.41; H, 4.29; N, 3.71.

**9-(4-Chlorobenzoyl)-6-methoxy-4,9-dihydropyrano[3,4-b]indol-3(1*H*)-one (7)**

Compound **6** (100 mg) was dissolved in dry toluene (25 ml) and the solution was refluxed with stirring for 7 h in the presence of molecule sieves (dehydrating agent) and catalytic amount of *p*-toluenesulfonic acid. The cooled mixture was filtred and the solvent removed in a vacuum. The residue was crystallized from acetone to give lactone **7** ( 84% yield).

LC-MS $(M+H)^+$ 356. $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 7.73 (d, *J*=8.4 Hz, 2H), 7.68 (d, *J*=6.4 Hz, 2H), 7.15 (d, *J*=2.4 Hz, 1H), 6.79 (dd, $J_1$=9.1 Hz, $J_2$=2.2 Hz, 1H), 6.72 (d, *J*=9.1 Hz, 1H), 5.53 (s, 2H), 3.85 (s, 2H), 3.78 (s, 3H). Found (%): C, 64.20; H, 4.08; N, 3.73. Calc. for $C_{19}H_{14}ClNO_4$ (%): C, 64.14; H, 3.97; N, 3.94.

**2-[1-(4-Chlorobenzoyl)-2-((dimethylamino)methyl)-5-methoxy-1*H*-indol-3-yl]acetic acid (8)**

To a solution of **5** (0.75 g, 1.72 mmol) in THF (25 ml), dimethylamine (0.232 g, 5.15 mmol, 25% water solution) was added. After five minutes of stirring at room temperature the solvent was evaporated to dryness under reduced pressure. The product **8** was isolated by HPLC.

LC-MS $(M+H)^+$ 401. $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 7.63 (s, 4H), 7.32 (s, 1H), 6.89 (d, *J*=8.8 Hz, 1H), 6.43 (d, *J*=8.8 Hz, 1H), 4.04 (br, 2H), 3.77 (s, 3H), 3.57 (s, 2H), 2.49 (s, 6H), 2.06 (s, 3H). Found (%): C, 63.31; H, 5.54; N, 6.85. Calc. for $C_{21}H_{21}ClN_2O_4$ (%): C, 62.92; H, 5.28; N, 6.99.