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Bromination of indomethacin

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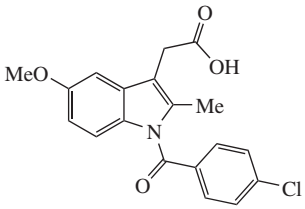
Treatment of indomethacin with *N*-bromosuccinimide in AcOH results in bromination in aromatic positions 4 and 6, while the use of tetrachloromethane allows ultimate bromination at the C(2) Me group of the indole moiety to proceed.

Indomethacin (2-methyl-5-methoxy-[1-(4-chlorobenzoyl)-1*H*-indol-3-yl]acetic acid) **1**, which relates to 3-indolylacetic acid type, is one of the most active nonsteroidal anti-inflammatory drugs. Discovered in 1963,[1,2] it is used for treatment of rheumatoid arthritis, periarthritises, ankylosing spondylitis, osteoarthrosis, gout, inflammatory diseases of connective tissue and musculoskeletal system, thrombophlebitis and other diseases accompanied by inflammation. It is also used in curing of neurotic syndrome. Indomethacin is a non-selective inhibitor of cyclooxygenases 1 and 2, strong blocker of enzymes participating in prostaglandin synthesis and possesses analgesic activity.[3–6] Surprisingly, despite its broad application, its chemistry is not studied sufficiently.



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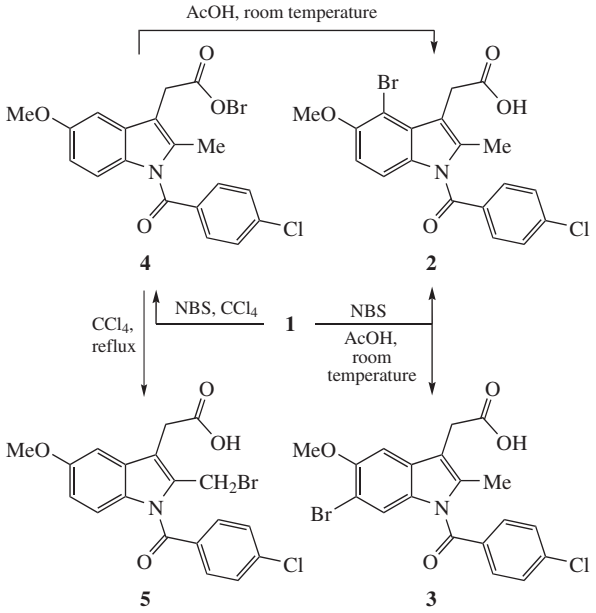
Here, we have investigated bromination of indomethacin, since introduction of bromine atom into a molecule allows one to succeed in further diversity of derivatization.

In principle, bromination of compound **1** may occur either at the benzene ring or at the methyl group at position 2. Preliminary experiments using tetrabutylammonium or pyridinium tribromide and molecular bromine gave dibromo or polybromo-substituted products. The use of *N*-bromosuccinimide (NBS) provided selective monobromination depending on reaction conditions. Reaction in AcOH at room temperature occurred as aromatic electrophilic substitution and gave 4- and 6-bromo derivatives **2** and **3** (Scheme 1), with their ratio being dependent on the concentration of indomethacin. Unfortunately, this method did not provide good selectivity. Use of carbon tetrachloride as the solvent resulted in the formation of 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetyl hypobromite **4**. In the ^{1}H NMR spectrum of compound **4**, the signals of all aromatic and aliphatic protons are clearly observed, while the carboxylic proton is absent. In the LC-MS spectra, there are two molecular ions of similar intensity with a *m*/*z* difference of two units typical of isotopic cluster for monobromo compounds. Elemental analysis data also agree with the proposed molecular formula.

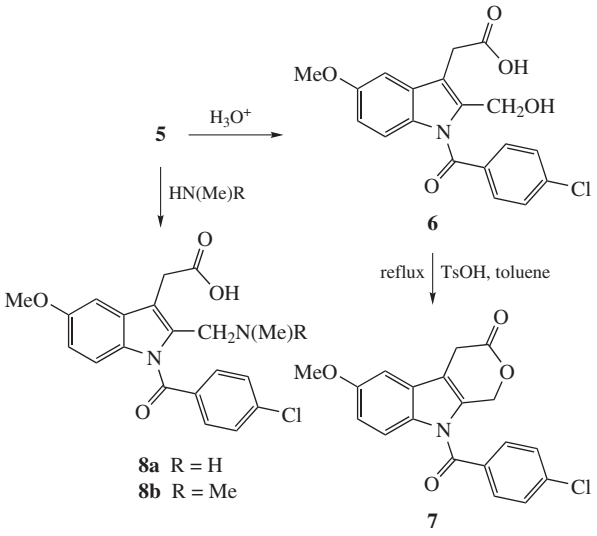


Scheme 1

Acyl hypohalites are usually unstable (synthesis and extraction of acetyl hypobromite from solution was first described in 1974[7]). Such compounds are used as brominating agents and donors of bromine cation.[8] Hypobromite **4** obtained is surprisingly relatively stable and could be recrystallized from carbon tetrachloride.

We have discovered that keeping hypobromite **4** in acetic acid at room temperature results in migration of bromine into position 4 of the indole ring. ^{1}H NMR spectrum of the product **2** thus obtained contains signal of the carboxylic proton at 12.37 ppm, while only two aromatic doublets at 7.09 and 6.87 ppm with *J* 8.9 Hz are present. This two-step protocol allows selective preparation of 4-bromo indole derivative **2** to be carried out. On the other hand, refluxing hypobromite **4** in CCl_4 gave 2-bromomethyl-1*H*-indole **5**, the product of bromine migration to the methyl group. We failed in isolating compound **5** in the pure form and made assignment of its structure based on the structures of its further transformation products **6**–**8** (Scheme 2). These products contain substituted benzylic methylene group.

Similar phenomena were described by Gopalakrishnan and Hogg.[9] In polar solvent, a heterolysis of O–Br bond and electro-



Scheme 2

philic attack of bromine cation at the nearest position of benzene ring occurred. In non-polar solvent, its homolysis induced intramolecular radical mechanism.

The bromine in derivatives **2**, **3** and **5** can be easily replaced by various functional groups to give promising indomethacin derivatives.

Hydrolysis of compound **5** in dilute trifluoroacetic acid resulted in hydroxymethyl derivative **6**. Alcohol **6** thus obtained easily cyclizes into pyranoindolone **7** during reflux in toluene in the presence of catalytic amount of TsOH. Benzylic bromine atom in compound **5** can be readily replaced with various nucleophiles. For example, amino derivatives **8a**,**b** were prepared by addition of anhydrous solutions of amines to a solution of bromide **5** in THF.

The structure of the obtained compounds **2**–**8** were confirmed by LC-MS and ^{1}H NMR spectroscopy;† molecular ions of the products under LC-MS conditions conform to their molecular masses, and values of proton chemical shifts in ^{1}H NMR spectra are identical to literature data.

In summary, we have developed convenient selective and efficient procedures for the bromination of indomethacin at position 4 or at C(2) Me group of the indole moiety. The intermediate, the corresponding acyl hypobromite, turned out to be a relatively stable compound. The results obtained may be of interest for both medicinal combinatorial and fundamental organic chemistry.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2010.03.016.

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† For the full NMR data, see Online Supplementary Materials.