Ultrasound-Promoted Synthesis of Aceclofenac

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An efficient synthesis of Aceclofenac under ultrasound irradiation is described. This method provides several advantages such as excellent yield and a simple workup procedure. Compared with traditional method, this method is more convenient and can be easily controlled.

Keywords: Aceclofenac, ultrasound irradiation.

Introduction
Aceclofenac 1 is 2-[(2,6-dichlorophenyl) amino] phenylacetoxyacetic acid is a phenyl acetic acid derivative that shows analgesic and inflammatory activities. It is indicated for long term management of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It is also widely used in condition of mild to moderate pain and post-operative pain, dysmenorrhoea, musculoskeletal trauma and gonalgia. The property of aceclofenac is similar to diclofenac as non-steroidal anti-inflammatory drug (NSAID). NSAIDs possess anti-inflammatory properties as well as they reduce elevated body temperature and antiplatelet activity to varying degree and are non-addicting. The gastrointestinal tolerability of aceclofenac is better than that of diclofenac and other NSAIDs and it has a faster onset of action. The incidence of treatment related diarrhoea is less with aceclofenac (1%) than the diclofenac (6.6%). It is an alternative NSAID to diclofenac in the treatment of osteoarthritis. It is rapidly and efficiently absorbed after oral administration but has short half-life of 4h. The anti-inflammatory effect of aceclofenac is stronger than paracetamol and has good tolerability profile in a variety of painful conditions and is also used in soft tissue injuries. Several methods have been developed for synthesis of this compound under different conditions. These methods take long reaction time. Ultrasound assisted organic synthesis has attracted attention in recent years, due to enhanced reaction rates, high yields, improved selectivity and eco-friendly reaction conditions. The present study reports a mild, rapid and efficient procedure for synthesis of aceclofenac under ultrasound irradiation (UI).

Materials and Methods
Melting points were determined in open capillary method and uncorrected. Progress of reaction was monitored by TLC using toluene-ethylacetate-methanol-glacial acetic acid (20:30:10:2.5). Experiment under ultrasound irradiation was carried out in ultrasonic bath model UC-55 (Analab Scientific Instruments Pvt. Ltd., Vadodara, India) having maximum power output of 120W and 30 KHz operating frequency.

Synthesis of Aceclofenac by ultrasound irradiation
Disopropylethylamine 5.8ml (0.0337mol) was added to a solution of 10g (0.0337mol) diclofenac in tetrahydrofuran (30ml) in a 100ml flask. Then 5.5ml (0.0377mol) tert-butyl-bromoacetate was added. The mixture was sonicated in the water bath of an ultrasonic cleaner at 35-40°C. After the completion of the reaction (4 hours; monitored by TLC), the reaction mixture was basified with 6ml 30% (w/w) sodium hydroxide solution. The organic layer was concentrated in vacuo to remove the solvent. After removal of solvent, 18ml formic acid was added and the mixture sonicated at 35-40°C. After completion of the reaction (6 hours; monitored by TLC), the reaction mixture was cooled to room temperature and diluted with 70ml water. The product was filtered and washed with 50ml water, thus obtaining 11.25g (94%) of aceclofenac having melting point of 149-150°C (lit. m.p.149-150°C), Rf0.58 [toluene:ethylacetate:methanol:glacial acetic

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Results and Discussion

UI of diclofenac 2 with diisopropylethylamine 3 and tert-butylbromoacetate 4 in tetrahydrofuran followed by basification with 30% (w/w) sodium hydroxide solution and removal of organic solvent gave tert-butyl-2-[(2,6-dichlorophenyl)amino]phenylacetic acid 5.

The crude product without further purification was again subjected to UI in presence of formic acid giving aceclofenac 1 (Scheme). Overall yield of aceclofenac, starting from diclofenac, involving UI was 94% compared to 42% and 87% by conventional method\(^7,8\) (heating).

Conclusion

Non-steroidal anti-inflammatory and analgesic drug aceclofenac has been synthesised from diclofenac in a rapid and clean method under ultrasound irradiation.

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