Diclofenac Synthesis

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Diclofenac is an NSAID, Non-Steroidal Anti-Inflammatory Drugs, widely used clinically in the treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, and has been available in the United States since 1988 (Banks et al. 1995). Diclofenac can cause hepatotoxicity, and despite the rare nature of these events, affects a large number of people due to its widespread usage. It is one of the most common drugs associated with idiosyncratic hepatic injury (Daly et al. 2007). From November 1988 to June 1991 the FDA received 180 cases of diclofenac-induced adverse hepatic injury of which 79% were female, 71% were elderly patients (above the age of 60), and 77% of the patients had osteoarthritis. In most of the cases the liver injury was characterized by hepatocellular damage or mixed hepatocellular injury, and there were some cases of cholestasis (Banks et al. 1995). The incidence of diclofenac hepatotoxicity has been reported to be 6.3 per 100 000 patients (DeAbajo et al. 2004). Bioactivation to reactive intermediates, their disposition, the production of oxidative stress, mitochondrial damage, and immune-mediated mechanisms have been suggested to play a role in diclofenac-mediated liver toxicity.¹

1 Synthesis

Diclofenac (**1.5**), 2-[(2,6-dichlorophenyl)-amino]-phenylacetic acid, is synthesized from 2-chlorobenzoic acid and 2,6-dichloroaniline. The reaction of these in the presence of sodium hydroxide and copper gives N-(2,6-dichlorophenyl)anthranilic acid (**1.1**), the carboxylic group of which undergoes reduction by lithium aluminum hydride. The resulting 2-[(2,6-dichlorophenyl)-amino]-benzyl alcohol (**1.2**) undergoes further chlorination by thionyl chloride into 2-[(2,6-dichlorophenyl)-amino]-benzylchloride (**1.3**) and further, upon reaction with sodium cyanide converts into 2-[(2,6-dichlorophenyl)-amino]benzyl cyanide (**1.4**). Hydrolysis of the nitrile group leads to diclofenac (**1.5**)²

is treated with Thionyl chloride SOCl₂ which is an inorganic compound, it is a moderately volatile colourless liquid with an unpleasant acid odour. Thionyl chloride is primarily used as a chlorinating reagent so that hydroxide group of (1.2) will be converted into Chlorine leading to a new product (1.3). The 2-[(2,6-dichlorophenyl)-amino]-benzylchloride (1.3) reacts with sodium Cyanide (Cyanide anion) NaCN throw a Nucleophilic substitution SN₂ reaction mechanism (We have a primary substrate, a very good leaving group and a strong nucleophile) leading to the 2-[(2,6-dichlorophenyl)-amino]benzyl cyanide (1.4), Alkaline Hydrolysis of which using sodium hydroxide leads to a carboxylate salt which reacts with water (Hydron) so that a carboxylic acid will be formed leading the final product: Diclofenac (1.5).

2 Types of Chemical Reactions

The reaction between 2-chlorobenzoic acid and 2,6-dichloroaniline is an aromatic nucleophilic substitution called ipso substitution (addition-elimination) so that the product (1.1) is obtained. Lithium aluminium hydrate LiAlH₄ commonly abbreviated to LAH, is an inorganic compound is used as a reducing agent in organic synthesis, especially for the reduction of esters, carboxylic acids, and amides, so carboxylic acid of (1.1) will be converted into primary alcohol and a new product will appear (1.2), the resulting primary alcohol (1.2)

3 Detailed Mechanism

The mechanism of diclofenac is detailed in **Fig.2, 3rd page**, for the first reaction, which is an ipso aromatic nucleophilic substitution, it's a C—N coupling, the catalyst used is copper in presence of potassium hydroxyde, as this reaction proceeds well with an electron-rich aryl, it's the **Ullmann-type coupling reactions**³, having observed the improvement using ultrasound in the cross-coupling of o-halobenzoic acids and substituted benzoamines with copper, or Cu/Zn under probe sonication³, Galy and co-workers successfully synthesized acridine derivatives using this method. In order to replace dry organic solvents with more environmentally benign ones, Pellón et al. extended the synthesis of halobenzoic acid and alkylamine in the presence of water as a solvent with copper under

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Fig. 1 Synthesis of Diclofenac

probe sonication³. In most cases, the yields were 20% greater than those resulting from classic heating.

From (1.4) to (1.5), there is an enol-ketone Tautomerization equilibrium leading to a carboxylate salt.

4 Conclusion

Diclofenac is a widely prescribed nonsteroidal antiinflammatory drug and, after flucloxacillin and amoxicillin–clavulanate, is among the most common drugs causing idiosyncratic DILI. It has been estimated that diclofenac-related DILI (**Drug Induced Liver Injury**) occurs in 4 in every 100,000 people prescribed this drug⁴. Susceptibility to diclofenac-related DILI does not appear to relate to HLA genotype⁴. Instead, it has been suggested that reactive metabolites may bind to hepatocyte proteins triggering local damage and inflammation.

References

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Fig. 2 Mechanism of Diclofenac Synthesis