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## Research Paper

### Innovative Recycling of Undesired Enantiomer of Naproxen<sup>#</sup>

Prashanth Reddy.G<sup>1</sup>, Kagga Mukkanti<sup>2</sup>, Sandeep Mohanty<sup>1</sup>, Rakeshwar Bandichhor<sup>1\*</sup>

<sup>1</sup> API R&D, Integrated Product Development, Innovation Plaza, Dr. Reddy's Laboratories Ltd, Bachupally, Qutubullapur, Hyderabad-500072, A.P., India

<sup>2</sup>Center for Environment, Institute of Science and Technology, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad 500072, A.P., India

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**Key words:** Racemization, undesired enantiomer, hydrolysis, nitrile intermediate, one pot process

**Abstract:** Synthesis of **1** involves hydrolysis of nitrile intermediate and efficient resolution of racemic naproxen followed by recycling of undesired enantiomer in two discrete steps. Herein, we disclose one pot racemization and hydrolysis of nitrile intermediate based manufacturing process of **1**.

## Introduction

Naproxen **1** as shown in [Fig. 1] is a nonsteroidal anti-inflammatory drug (NSAID) meant for the treatment of pain, fever and inflammation. Naproxen **1** is currently available in the market as a nonsteroidal anti-inflammatory drug [1] under the various brand names viz Aleve, Anaprox, Antalgin, Feminax Ultra, Flanax, Inza, Midol, Miranax, Naposin, Napreelan, Naprogesic, Naprosyn, Narocin, Proxen, Synflex, Xenobid. Although, there are myriad of approaches [2-22] that have been developed for **1** however, we optimized the slightly modified synthesis that consists of six steps as shown in Scheme 1 [23].

The synthesis commences with the Friedal-Crafts acylation of 2-methoxynaphthalene to obtain **5** followed -

by Darzen's condensation that affords intermediate **6**, hydrolysis and decarboxylation to get naphthyl acetaldehyde intermediate **7**. Thereafter, intermediate **7** was condensed with hydroxyl amine followed by dehydration to afford *in situ* nitrile intermediate **2** and hydrolysis of it afforded racemic naproxen **3**.

Subsequently, resolution of **3** by employing *N*-octyl glucamine yields enantiomerically pure naproxen **1**. Mother liquor contains mainly undesired enantiomer **4** which was racemized back to racemic naproxen **3**. As shown in [Fig. 2]. This process suffers from several disadvantages such as (a) discrete reaction stages for nitrile hydrolysis to get racemic naproxen followed by resolution and racemization of (*R*)-enantiomer, (b) Racemization in pressure vessel in presence of large quantity of base, (c) An additional set of equipment for racemization. In our continued endeavor

Corresponding Author\* Tel.: +91 4044346117; Fax: +91 40446285; E-mail: [rakeshwarb@drreddys.com](mailto:rakeshwarb@drreddys.com)

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for process improvements, we developed an efficient one pot process for hydrolysis and racemization which has been accomplished by modifying the original process.

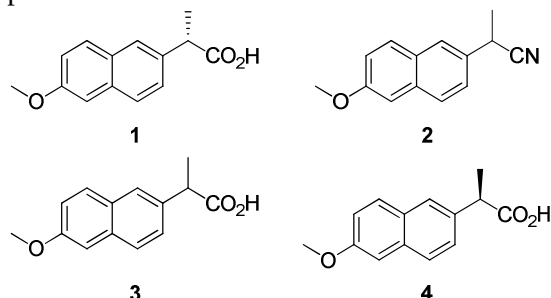


**Figure 1:** Naproxen framework

## Results and Discussion

Our objective was to carry out two steps process; racemization of (*R*)-naproxen **4** and hydrolysis of nitrile intermediate **2** in single reactor as shown in [Fig.3].

Operationally, the mother liquor (toluene), after separation of the salt **9**, found to contain approximately 15 to 20% of the salt **9** and 80 to 85% of the undesired salt **10**. The mother liquor was washed with water at < pH 2 to remove the *N*-octyl glucamine.

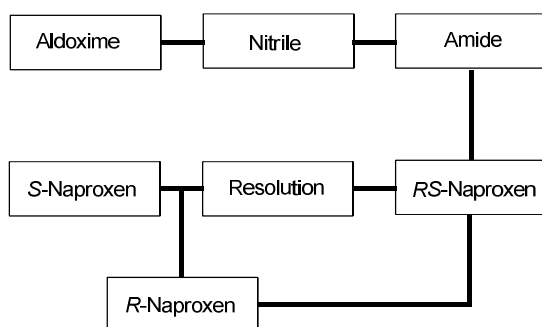
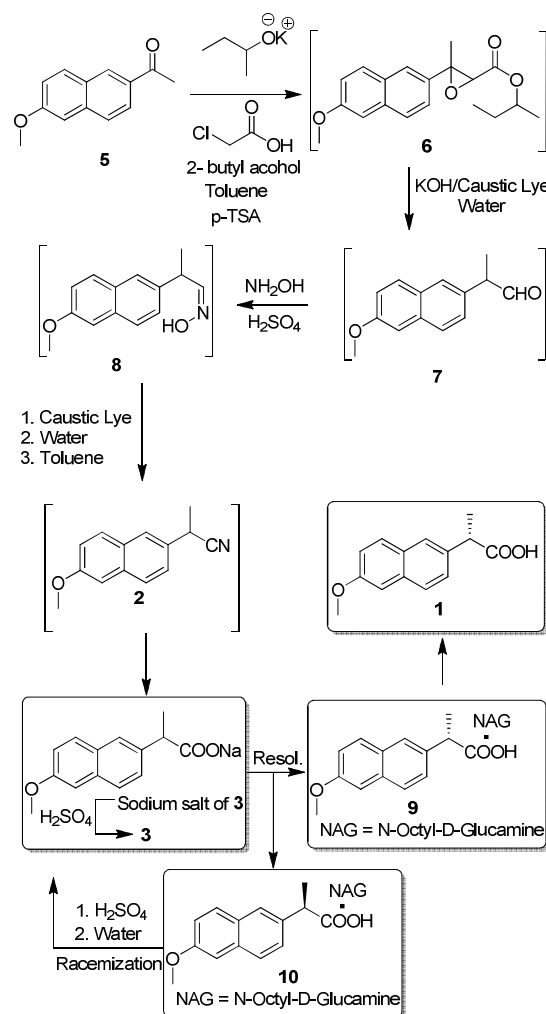


**Figure 2:** Process flow for manufacturing of the naproxen



**Scheme 1:** Precedent process for **1**

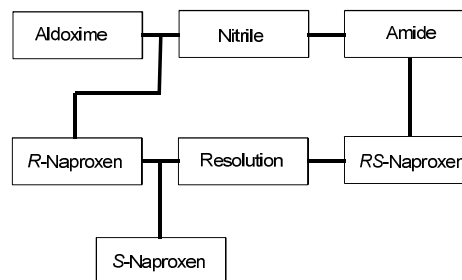


**Figure 3:** Improved process flow for manufacturing of the naproxen

The separated organic phase (toluene) which contains majorly **4** was subjected to simultaneous distillation of solvent and addition of residue to the reaction mass of

nitrile hydrolysis, which is in caustic lye solution.

The reaction mass containing both the nitrile intermediate and the undesired (*R*)-isomer was heated to reflux (125 to 135 °C) and maintained for 10 to 12 h. The reaction mixture was further diluted with water followed by washing the reaction mass with toluene to remove impurities. The aq. layer allowed to cool to 25 °C and acidified with sulphuric acid at < pH 2 that resulted the precipitate which was filtered and washed with water affording racemic naproxen **3** in >90% overall yield. The simultaneous racemization outcome is detailed in [Table 1]. In three different experiments, the complete racemization was observed.

**Table 1:** Simultaneous racemization of (*R*)-enantiomer along with nitrile hydrolysis

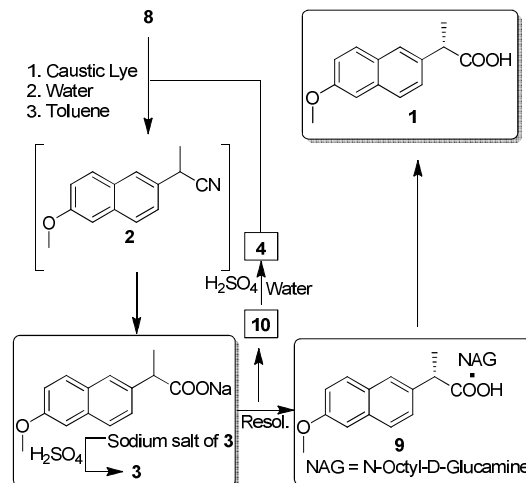
| Expt . No. | SOR   | %Purity | %Chiral purity | %Yield |
|------------|-------|---------|----------------|--------|
| 1          | +0.02 | 99.25   | 49:50.4        | 93.5   |
| 2          | -0.03 | 99.32   | 50:49.5        | 92.1   |
| 3          | +0.01 | 99.12   | 49.2:50.5      | 94.0   |

Improvements in overall yield, cost, E factor and time cycle reduction are found to be significant for this particular product. The quantitative comparative values are featured in the [Table 2].

**Table 2:** Comparison of current and improved process

| Process  | %Yield | UC*(\$) | E factor (kg) | TC <sup>#</sup> (h) |
|----------|--------|---------|---------------|---------------------|
| Current  | 85     | 6.3     | 66            | 719                 |
| Improved | 90     | 4.9     | 52            | 336                 |

\*UC: Utility Cost/kg of **1**; <sup>#</sup>TC: Time Cycle



**Scheme 2:** Improved process for **1**

## Conclusion

An elegant, scalable, Green and cost effective, novel recycling process that features simultaneous racemization of (*R*)-naproxen and hydrolysis of nitrile intermediate has been developed.

## Experimental Section

The <sup>1</sup>H NMR and <sup>13</sup>CNMR spectra were recorded in CDCl<sub>3</sub> on Varian 400 MHz; the chemical shifts were reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state KBr dispersion using Shimadzu IR Prestige-21 spectrophotometer. The mass spectra were recorded on Shimadzu LCMS (model no.: LCMS 2010 ev). The melting points were determined by using Polmon (Model No.: MP96) melting point apparatus. The specific optical rotation was recorded on Jasco P-2000 polarimeter and at 580 nm. The chiral HPLC was recorded on SHIMADZU HPLC Model: LC-20AD Prominence liquid chromatograph by using Pirkle Covalent Regis (*S,S*) wheelk-O1 250X4.6 mm ID (5μ).

**Dehydration of aldoxime **8**, hydrolysis of nitrile **2** & racemization of **4** to obtain **3****

A solution of aldaoxime 100 g, (0.43 mol) in toluene (700 mL) added to caustic lye (2.8 mol; 150 mL) and raised the temperature of the reaction mass to 110 °C. Subsequently, water (11 mL) was added and the reaction mixture was further heated to 125 °C. Thereafter, undesired enantiomer containing solution in toluene [1600 mL; equivalent to 55 g, (0.239 mol) containing ~15% (*S*)-enantiomer and 85% *R*-enantiomer] to reaction mass with simultaneous distillation and heated under reflux for 10-12 h. Thereafter, temperature of the reaction mass was reduced to 90 °C and water (468 mL) was added to the reaction mass and the impurities were removed by washing with toluene (3 X 175 mL) at pH 12 and 8. Eventually, the aq. layer was cooled to 60 to 70 °C and acidified with conc. sulphuric acid. The solid obtained was filtered and washed with water to obtain racemic crude naproxen.

The above crude was recrystallized in toluene (450 mL) and dried at 60 to 65 °C under vacuum to afford 145 g white crystalline powder of (*RS*)-2-(6-methoxy naphthalene-2-yl)propanoic acid **3** in 93% yield. Purity by HPLC: 99.3%. MP: 155 to 158°C. <sup>1</sup>H NMR δ 1.56-1.58 (d, 3H), 3.84-3.86 (d, 1H), 3.89 (s, 3H) 7.08 (d, 2H) 7.09 (d, 1H), 7.11-7.13 (d, 1H), 7.41 (s, 1H), 7.69 (s, 1H), <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 180.91, 157.63, 134.80, 133.67, 129.26, 128.83, 127.19, 126.15, 126.11, 119.07, 105.51, 55.25, 45.23, 18.07 MS: calcd for C<sub>14</sub>H<sub>14</sub>O<sub>3</sub> 230 (M<sup>+</sup>), found 231(MH<sup>+</sup>).

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