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$NaNO_2$/HCl/TBAB Catalyst: A Controlled Aerobic Oxidation of Sulfide Substrate in the Preparation of Polmacoxib Intermediate Under Mild Conditions

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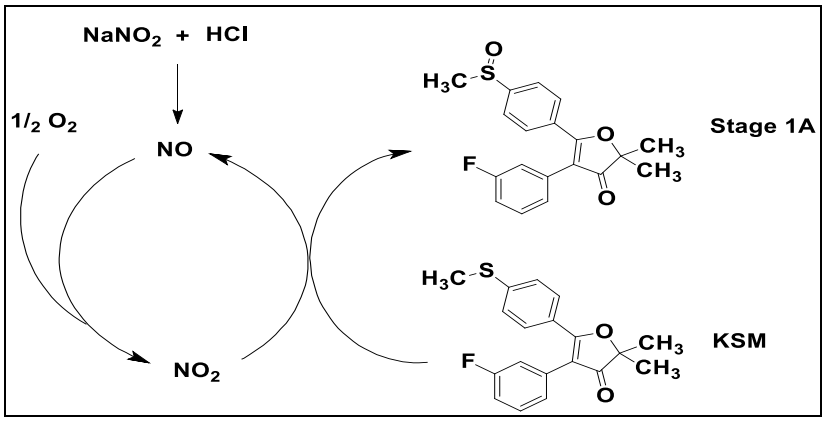
The oxidation of sulfide substrate in one of the synthetic stages of Polmacoxib drug substance has been efficiently performed employing cost efficient $NaNO_2$-HCl reagents in phase transfer catalyst TBAB containing biphasic MDC-Water reaction media at 0-5 °C temperature to afford sulfoxide intermediate (1A) as an only product. The formed products were characterized by techniques such as NMR, MS and IR spectroscopy. To the best of our knowledge, the present work is the first report on utilization of $NaNO_2$/TBAB/HCl catalytic system for the preparation of Polmacoxib stage 1A intermediate. Cost and energy efficiency, use of commercially available catalysts, high yields and purity are merits of the present work.

Graphical abstract



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1. Introduction

A nonsteroidal anti-inflammatory drug (NSAID's) is a class of medicine that reduce inflammation with relieving pain and fever. Since the last century, nonsteroidal anti-inflammatory drugs (NSAIDs) have extensively used in the treatment of arthritis and arthritis-associated disorders, migraine, pain associated with surgery, etc. Conventional NSAIDs, namely naproxen, aspirin, diclofenac, piroxicam, ibuprofen, etc. [1], inhibit both the inflammation causative enzymes namely cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), which is responsible for their anti-inflammatory effects. However, COX-1 inhibition leads to some serious side effects of gastrointestinal toxicity and thinning of blood. Hence, new drugs, which could selectively inhibit COX-2 enzyme, were under development in the decade of 2020 [2].

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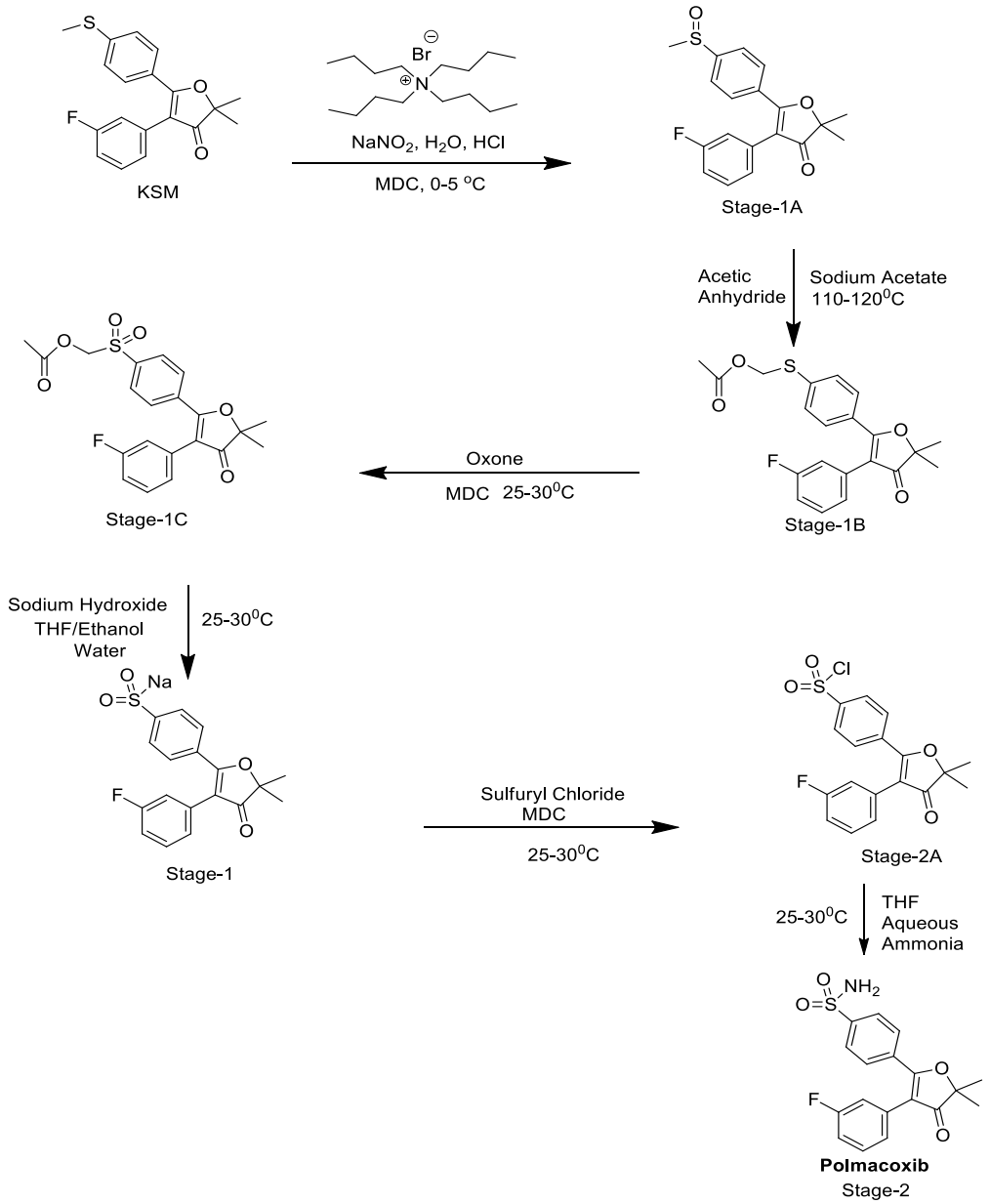
In 2015, Crystal Genomics, a south Korian company developed a selective COX-2 enzyme inhibitor molecule, 4-(3-(3-Fluorophenyl)-5,5-dimethyl-4-oxo-4,5-dihydrofuran-2-yl)-benzene sulphonamide under the trade name Acelex® which is now known as Polmacoxib in pharmaceuticals field. Later on, Polmacoxib was licenced to Dong-A ST Pharma Company and TR-Pharma Company for commercialization in South Korea and Turkey - Middle East-North Africa region, respectively. Polmacoxib is now available as orally administrated capsules and its recommended daily dose is 2 mg once in a day [3-10].

As the Drug Polmacoxib is a commercialized product, till date diverse synthetic strategies have been employed by various companies for its higher scale production [11-15]. However, due to competitive market requirements, still there is a huge scope to improve and develop new cost and environment friendly synthetic strategies even for the sub stages of this drug molecule.

In this context, we have reported the first ever method for the oxidation of sulfide substrate in the first synthetic stage of Polmacoxib drug molecule employing cost efficient $NaNO_2$-HCl reagents system in biphasic MDC-Water reaction media catalyzed by TBAB at 0-5 °C temperature to afford sulfoxide intermediate (1A) as a sole product in high yield. The route of synthesis of Polmacoxib drug molecule is depicted below in Scheme1.



Scheme 1. Multistage route for the synthesis of Polmacoxib.

2. Results and Discussion

Initially, the pilot experiment was performed with Polmacoxib KSM (10 mmol) taking $NaNO_2$ (30 mmol), dichloromethane (MDC) 30 V w.r.t. KSM Wt., Conc. HCl (12 V w.r.t. KSM Wt.) and water (5.0 V w.r.t. KSM Wt.) at 0-5°C temperature without any phase transfer catalyst. The reaction did not go to completion even after longer reaction time of 48 hours and yielded only 40% of oxidation product after workup (Entry 1, Table 1). Then the reaction was carried out with 60 mmol of $NaNO_2$ keeping other conditions intact, however;

outcome was only 51 % yield with co-formation of undesired over oxidation impurities (Entry 2, Table 1). When initial pilot experiment performed adding 100 mol% TBAB as a phase transfer catalyst, the reaction completed in 6 hours providing 81 % of desired product (Entry 3, Table 1) highlighting necessity of TBAB phase transfer catalyst for the reaction.

In order to optimize TBAB quantity, experiments were conducted employing 80, 60, 50, 40 and 30 mol% of TBAB (Entries 4-8, Table 1). Gratifyingly, 50 mol % TBAB was found to be sufficient to catalyze the reaction well with negligible impact on the reaction yield. Furthermore, low isolated yield of the product was recorded for 40 and 30 mol% of TBAB (Entries 7 and 8, Table 1). Interestingly, when reaction carried out at 10-15°C temperature, sulfide reactant consumed in shorter reaction time but isolated yield was only 77 % because of the formation of competitive over oxidation byproducts (Entry 9, Table 1).

Freezing the TBAB quantity to 50 mol %, attention was then focused on the optimization of $NaNO_2$ quantity. Experiments were performed with different equivalents of $NaNO_2$ with unaltered other conditions. Notably, lower product yields were observed for 15, 10 and 5 mmol of $NaNO_2$ (Entries 10-12, Table 1) whereas formation of higher concentrations of over oxidation impurities was noted for 50 mmol and 40 mmol amount of $NaNO_2$ reagent (Entries 13 and 14, Table 1). The optimum quantity of $NaNO_2$ was found to be 20 mmol furnishing 80 % of desired product with negligible formation of over oxidation impurities (Entry 15, Table 1).

The effect of Conc. HCl quantity on the reaction was examined by carrying out reactions with 12, 10 and 20 V Conc. HCl w.r.t. KSM weight. Notably, 10 V Conc. HCl was found to be significant providing 81 % desired product in 8 hours (Entry 16, Table 1) whereas higher volumes of Conc. HCl triggered generation of over oxidation impurities and consequently lowered yield of the product (Entry 17, Table 1).

Table 1. Optimization of reaction conditions for oxidation of sulfide KSM

Entry	$NaNO_2$ (mmol)	Conc. HCl (V/W)	TBAB (mol %)	Temp. (°C)	Time (h)	Yield (%)
1	30	12	0	0-5	48	40[b]
2	60	12	0	0-5	48	51[ab]
3	30	12	100	0-5	8	81
4	30	12	80	0-5	8	81
5	30	12	60	0-5	8	80
6	30	12	50	0-5	8	80
7	30	12	40	0-5	10	74
8	30	12	30	0-5	10	68
9	30	12	50	10-15	4	77[a]
10	15	12	50	0-5	10	73
11	10	12	50	0-5	16	75[b]
12	5	12	50	0-5	32	50[b]
13	50	12	50	0-5	4	74[a]
14	40	12	50	0-5	5	76[a]
15	20	12	50	0-5	8	80
16	20	10	50	0-5	8	81
17	20	20	50	0-5	8	75[a]

Reaction conditions: KSM- 10 mmol, MDC: Water - 30:5 Vol. w.r.t. KSM Wt., [a] Over oxidation impurities formed, [b] reaction not completed.

Having optimized conditions in hand, efforts were then directed towards screening of different percentage of MDC: Water ratios for the oxidation reaction as depicted in table 2.

The water and MDC percentage was calculated considering water content from 36 % concentrated HCl (contains 64 % water by volume) and water taken for dissolution of $NaNO_2$ using the formulae (Fig. 1).

$$\text{\% of water in reaction mass} = \frac{\text{Quantity of water from conc. HCl + Quantity of water taken for dissolution of } NaNO_2}{\text{Quantity of MDC + Quantity of water from conc. HCl + Quantity of water taken for dissolution of } NaNO_2}$$

And,

$$\text{\% of MDC in reaction mass} = 100 - \text{\% of water in the reaction mass}$$

Fig. 1. Formulae to calculate water and MDC percentage.

It was observed that, higher percentage of water in the reaction led to the formation of sticky reaction mass and lower isolated yields (Entries 1-3, Table 2). The best result was obtained for the MDC: Water ratio of 75:25 % affording desired product in 81% yield (Entry 4, Table 2). Interestingly, despite of reaction goes to completion, reducing the solvent volume with same percentage of 75:25 % to the total 30.4 volume (23.0 vol. MDC, 6.4 vol. water from Conc. HCl and 1.0 vol. $NaNO_2$ dissolution water) led to the generation of undesired over-oxidation impurities in the reaction (Entry 6, Table 2). In addition, water less than 25 % generated over oxidation byproducts along with desired sulfoxide product (Entry 5, Table 2).

The sulfoxide intermediate was prepared through present method, confirmed by NMR, IR and Mass spectrometry, and then used as a reactant for synthesis of subsequent stages of the Polmacoxib drug referring the previously reported processes [11-12]. Each subsequent intermediate was well characterized by NMR, IR and Mass spectrometry.

The plausible mechanism for $NaNO_2$ – HCl induced oxidation is depicted in Fig. 2. The reaction of $NaNO_2$ and HCl releases NO [11-13]. Which gets easily oxidized to NO_2 by

molecular dioxygen in the air. The formed NO_2 acts as an oxidizer that oxidizes sulphide KSM to sulfoxide product stage 1A) and NO as a by-product, which can be again re-oxidized to NO_2 by molecular dioxygen. Being a phase transfer catalyst, TBAB facilitates the effective interaction between organic and aqueous phase that is necessary for the reaction to take place.

Table 2. Optimization of solvent percentage and volume.

Entry	Solvent quantities (Volumes w.r.t. wt. of KSM)			Approx. Solvent ratio (%)		Yield (%)
	MDC	Water*	Water#	MDC	Water	
1	30.0	6.4	10.0	65	35	40[a]
2	30.0	6.4	8.0	68	32	56[a]
3	30.0	6.4	6.0	71	29	77
4	30.0	6.4	4.0	75	25	81
5	30.0	6.4	2.0	78	22	77[b]
6	23.0	6.4	1.0	75	25	75[b]

Reaction conditions: Sulfide KSM- 10 mmol, $NaNO_2$ – 20 mmol, Conc. HCl – 10 V w.r.t. KSM Wt., TBAB – 50 mol%, Temperature – 0-5°C, [a] Sticky reaction mass observed, [b] Over oxidation impurities formed. * Water form HCl, # Water for dissolution of $NaNO_2$.

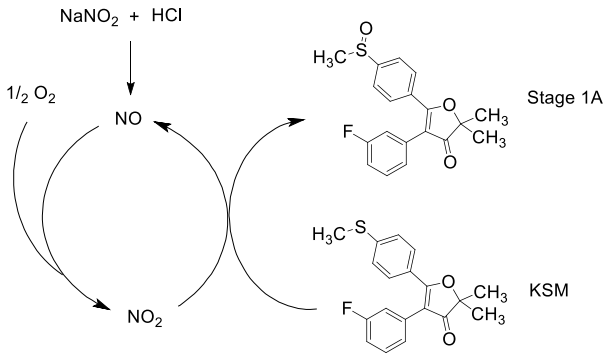


Fig. 2. Plausible mechanism for the oxidation of sulfide reactant to sulfoxide product.

3. Material and Methods

3.1 General information

All solvents and chemicals were obtained commercially and were used as received without further purification. Infrared (IR) spectra were recorded on a Tensor 27 spectrometer on ATR probe. ^{1}H NMR & ^{13}C NMR spectra were obtained in dimethyl sulfoxide (DMSO)-d_6 solution with Me_4Si as internal standard using a Bruker 300 spectrometer. Electrospray ionization (ESI) mass spectra were performed on Thermo Finnigan LCQ Classic Mass Spectrometer. HPLC measurements were run on Hypersil BDS C8 (250 mm × 4.6 mm, 5um; make: Shimadzu Prominence Liquid Chromatograph) with flow rate 1.2 mL/min having column oven temperature of 25 °C. UV detection occurred at wavelength 235 nm.

3.2 General experimental procedure for the preparation of compounds and characterization data

Stage-1A: To a well stirred cold solution of sulfide KSM (10.0 gm) in dichloromethane (300.0 mL) slowly added conc. HCl (100.0 mL) at 0-5 °C u/ N_2 atm. Added solution of $NaNO_2$ (4.2 gm 2.0 eq.) in water (42.0 mL) to the reaction mixture followed by Tetrabutylammonium bromide (TBAB) phase transfer catalyst (PTC) (5.0 gm) at 0-5 °C. Stirred reaction mass at 0-5 °C for 1.0 hr u/N_2 atmosphere & then stirred U/ air for 7-8 hour. After completion of reaction (monitored by TLC) slowly adjusted reaction mass pH 8-9 by using 10% aqueous sodium hydroxide solution (38 gm sodium hydroxide dissolved in 380.0 mL of purified water) at 0-10°C. Stirred well, settled and separated layers at 0-10 °C. Taken aqueous layer and extracted with MDC (50.0 mL) at 25-30°C. Washed combined organic layer containing product solution with 2×100.0 mL DM water at 25-30 °C. Added organic layer on sodium sulphate and distilled out u/vacuum below 40 °C. Charged ethyl acetate (30.0 mL) to the residue obtained and heated RM at 75-80 °C to get clear solution. Gradually cooled RM to 25-30 °C and stirred for 2.0 hrs. Further cooled RM to 0-5 °C and stirred for 30.0 minutes. Filtered product of stage 1A and washed with ethyl acetate (5.0 mL) at 0-5 °C. Dried wet material at 45-50 °C for 10-12 hrs. Dry wt. = 8.5 gm (Yield = 81%). Off-white solid powder, IR (ATR): 2931. 80, 1687.71, 1620.21, 1496.76, 1454.33, 1193.94, 1103.28, 1051.20 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz,): δ 7.80-7.72 (m, 4H), 7.47-7.40 (m, 1H), 7.23-7.05 (m, 3H), 2.80 (S, 3H), 1.50 (S, 6H) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz): δ 203.85, 176.88, 163.70, 160.47, 150.58, 132.03, 131.16, 130.62, 128.73, 125.46, 124.05, 116.12, 114.67, 112.73, 42.88 and 22.84 ppm. MS m/z 345 [M+H].

Stage-1B: The compound was prepared referring literature process with minor changes [11, 12]. In a clean and dry RBF charged acetic anhydride (85.0 mL) and stage-1A (8.5 gm) at 25-30 °C. Charged sodium acetate (8.1 gm, 4.0 eq.) and heated reaction mass to 110-120 °C for 12.0 hours. After completion of reaction (monitored by TLC) gradually cooled RM to 25-30 °C. Filtered inorganic salts through Buchner funnel. Distilled out filtrate u/ vacuum below 90°C to from residue of stage 1B. Residue wt.9.7 gm (Yield=96.43%). Light reddish colored residue, IR (ATR): 3082.25, 3001.24, 1784.15, 1749.44, 1550.77, 1498.69, 1454.33, 1151.50, 1078.21 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.56-7.50 (m, 4H), 7.49-7.39 (m, 1H), 7.21-7.17 (m, 1H), 7.16-7.01 (m, 2H), 5.58 (S, 2H), 2.05 (S, 3H), 1.48 (S, 6H) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz): δ 203.65, 177.19, 169.82, 163.71, 160.48, 140.19, 132.40, 130.58, 128.63, 127.52, 125.52, 116.16, 114.54, 111.83, 64.88, 22.89 & 20.63 ppm. MS m/z 387 [M+H].

Stage-1C: The compound was prepared referring literature process with minor changes [11, 12]. In the RBF, containing stage 1B residue (9.5 gm) charged acetic acid (95.0 mL). Stirred the reaction mass for 15 min at below 30°C. Further cooled the reaction mass temperature to 5-10°C. Charged purified water (4.75 mL) into reaction mass at 5-10°C.Further cooled Rm to 10-15°C and slowly added Oxone (15.17 gm 2.0 eq) to RM and stirred at 10-15 °C for 1.0 hr. Raised RM temperature to 25-30 °C and stirred at same temperature for 12-15 hrs. After completion of reaction (monitored by TLC) charged dichloromethane (95.0 mL) to RM at 25-30 °C. Stirred for 15 minutes and filtered RM through Buchner funnel to remove inorganic salts. Collected filtrate-containing product. Charged water (47.5 mL) to the filtrate, stirred for 15 min, settled and separated layers. Organic layer dried over sodium sulphate. Distilled out organic layer below 40 °C to get residue of stage- 1C wt. 9.1 gm (Yield=91.36%). White solid powder, IR (ATR): 3020.53, 2962.33, 1759.08, 1683.86, 1627.92, 1610.56, 1367.53, 1350.02, 1085.92 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz,): δ 8.03-8.00 (d, J= 9, 2H), 7.84-7.81 (d, J=9, 2H), 7.47-7.39 (m, 1H), 7.23-7.16 (m, 1H), 7.13-7.12 (m, 1H), 7.10-7.03 (m, 1H), 5.46 (S, 2H), 2.51 (S, 3H), 1.51 (S, 6H) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz): δ 203.92, 176.09, 168.21, 163.70, 160.47,

139.38, 134.76, 131.56, 130.68, 129.14, 125.39, 116.05, 114.86, 113.71, 87.53, 75.25 & 22.80 ppm. MS m/z 419 [M+H].

Stage-1: The compound was prepared referring literature process with minor changes [11, 12]. To the RBF containing stage-1C residue (9.1 gm) charged THF (91.0 mL) and ethanol (91.0 mL) at 25-30 °C. Stirred for 15 minutes, slowly added sodium hydroxide solution (1.2 eq. NaOH, i.e. 1.184 gm NaOH dissolved in 91.0 ml water) to RM at 25-30 °C, stirred RM at 25-30 °C for 3.0 hours and progress was monitored by TLC. On Completion of reaction, distilled out solvent U / vacuum at 50 °C and stripped out residue with 3×9.1 mL 1:1 toluene ethanol mixture U/ vacuum. Charged toluene (91.0 mL) to the resulting residue and stirred for 15 min at 50 °C. Cooled RM to 25-30 °C. Filtered product of stage 1 and washed with toluene (8.5 mL). Suck dried well and dried stage-1 material at 40-45 °C for 10-12 hr. Dry wt. 7.5 gm (Yield = 93.63%). White solid powder, IR (ATR): 1649.14, 1614.42,1 454.33, 1303.88, 1294.24, 1105.21, 941.26 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz,): δ 7.523 (4H, S), 7.44 -7.37 (1H, m), 7.28-7.22 (1H, m), 7.10-7.09 (1H, m), 7.068-7.01 (1H, m), 1.48 (S, 6H) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz): δ 203.72, 178.52, 163.93, 60.44, 137.33, 132.52, 130.47, 128.89, 125.43, 124.58, 116.03, 114.38, 111.65, 86.93 & 22.94 ppm. MS m/z 369 [M+H].

Stage-2A: The compound was prepared referring literature process with minor changes [11, 12]. To the clean and dry RBF charged stage-1 (7.5 gm) and dichloromethane (75.0 mL) at RT .Slowly added sulfuryl chloride solution (2.0 eq. i.e 5.50 gm of sulfuryl chloride dissolved in 75.0 mL MDC) to it at 25-30°C. Stirred reaction mass for 3.0 hours at 25-30 °C. After completion of reaction (Monitored by TLC). Filtered reaction mass, distilled out filtrate U/vacuum below 40 °C to from stage-2A residue wt.6.2 gm (Yield = 80.00%). Yellow solid powder, IR (ATR): 3088.03, 3045.60, 2931.80, 1932.67, 1649.14,1 429.25, 1307.74, 1111.0 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz,): δ 8.06-8.03 (d, J=9, 2H), 7.91-7.88 (d, J=9, 2H), 7.41-7.34 (m, 1H), 7.12-7.03 (m, 3H), 1.48 (S, 6H) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz): δ 204.88, 175.01, 164.83, 161.56, 146.41, 136.27, 131.13, 130.84, 129.74, 127.31, 125.29, 116.74, 115.28, 88.12 & 23.48 ppm. MS m/z 381 [M+H].

Stage-2: The compound was prepared referring literature process with minor changes [11, 12]. To a dry RBF charged Tetrahydrofuran (112.5 mL) and aqueous ammonia (45.0 mL) at 25-30 °C. Slowly added solution of Stage-2A (6.2 gm in 15.0 mL THF) to RM at same temperature. Stirred RM for 3.0 hrs at 25-30 °C .After completion of reaction (Monitored by TLC) distilled out solvent U /vacuum below 50 °C. Cooled RM to 25-30 °C, Charged dichloromethane (187.5 mL) and purified water (75.0 mL) to it. Stirred well, settled and separated layer. Organic layer washed with 2×75.0 mL water and dried over sodium sulphate. Distilled out organic layer U / vacuum below 40 °C and charged ethanol (30.0 mL) to the residue. Heated the RM to 70-80 °C to get clear solution and filtered hot solution through hyflow bed. Cooled the filtrate to 25-30 °C and stirred for 2.0 hours. Further cooled RM to 5-10 °C, Filtered and washed with ethanol (3.75 mL) at 5-10 °C. Dried wet material at 45-50 °C for 12.0 hrs. The product (stage-2) was obtained with dry wt. 4.5 gm (Yield = 76.53%). White to yellow powder; IR (ATR): 2983.88, 2939.52, 1643.35, 1612.49, 1460.11, 1359.82, 1294.24, 1116.78, 948.98 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 7.91-7.88 (d, J=9, 2H), 7.86-7.83 (m, 2H), 7.72-7.69 (m, 2H), 7.43-7.35 (m, 1H), 7.17 -7.10 (m, 1H), 7.05 -7.00 (m, 2H), 1.51 (S, 6H) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz): δ 203.85, 176.82, 163.71, 160.48, 146.86, 132.24, 131.84, 130.63, 128.83, 126.03, 125.41, 116.08, 114.72, 87.38 & 22.86 ppm. MS m/z 362 [M+H]; HPLC Purity: 99.867%, Single any unknown max impurity: 0.048%.

4. Conclusions

In conclusion, the unique, cost effective, eco-friendly and scalable method has been developed for the controlled aerobic oxidation of sulfide to sulfoxide in one of the synthetic stages of COX-2 inhibitor NSAID Polmacoxib exploring the catalytic potential of $NaNO_2$ - HCl reagent under operationally simple reaction conditions. Nontoxic molecular dioxygen in the air as an oxygen source, feasible reaction temperature, water as a co-solvent and short reaction time makes the present procedure industrially viable and environmentally sustainable.

Supporting Information

Spectral data and characterization spectra of synthesized compounds.

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Author Contributions

Macchindra Kadam: Conceptualization, Methodology, Writing – Original Draft. Deepak Nale: Data Curation, Writing – Review & Editing. Datta Thorat: Analysis, Visualization. Venkateswara Rao Vallu: Project administration. Bollikonda Satyanarayana: Resources, Investigation. Padi Pratap Reddy: Funding acquisition. Sayujjata R. Vaidya: Supervision.

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