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Simple one-pot green method for large-scale production of mesalamine, an anti-inflammatory agent

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Abstract: We report a rapid and efficient synthesis protocol for mesalamine via a green approach with 2-chloro-5-nitrobenzoic acid as the starting material, for its large-scale production. This one-pot method involves the conversion of a chloro group into a hydroxyl group using aqueous KOH solution, followed by the reduction of a nitro group to amine using Pd/C. The product was characterised and confirmed by ^{1}H-nuclear magnetic resonance (NMR), ^{13}C NMR, IR and mass spectrometry techniques. The salient features of the method include excellent conversion (99.3%), high yield (93%), cost effectiveness and validated results for benign, large-scale production.

Keywords: anti-inflammatory; green approach; mesalamine; one pot synthesis; Pd/C.

1 Introduction

Inflammation is a protecting mechanism utilised by tissues against endogenous and exogenous antigens, induced by microbial infection or tissue injury and is characterised by redness, enema, fever, pain, and loss of performance. Inflammation associated with various chronic diseases including arterial sclerosis, obesity, diabetes, neurodegenerative diseases and even cancer, is a serious health concern [1, 2]. Non-steroidal medication (NSAIDs) is widely used for the treatment of inflammatory and painful conditions, as well as autoimmune disease, soft tissue lesions, fever and urinary tract infections [3, 4]. The activity of NSAIDs results from protein inhibition of cyclooxygenase (COX) mediated production of pro-inflammatory prostaglandins and thromboxanes [5]. COX enzymes exist in three isoforms: COX-1, COX-2 and COX-3 [6, 7]. COX-1 is the constitutional enzyme in most cells and plays an important role in the protection of the stomach tissue layer, protoplasm aggregation and nephritic blood flow. The COX (COX-1 and COX–2) is associated with nursing inducible isozyme system, and is considerably expressed throughout inflammation, pain, and oncogenesis [7], whereas COX-3, a splice variant of COX-1, is taken into account as another target for drugs [6–8]. Conventional NSAIDs inhibit COX-1 and COX-2 and therefore their administration usually causes epithelial duct [9, 10], renal [11, 12], and hepatic effects [13].

Mesalamine belongs to the class of salicylates, which are known to exhibit anti-inflammatory activity. It is also a key intermediate for sulphasalazine, olsalazine and balsalazide [14]. It is slightly soluble in dehydrated alcohol and methyl alcohol and insoluble in chloroform, ether, *n*-hexane and ester. It is prescribed for the treatment and management of colitis. It primarily provides relief from pain to some extent in patients affected by this disease [15–21]. 5-Aminosalicylic acid is an active medicine for colitis due to its multiple actions on numerous functions of the immune system [22, 23].

Mesalamine is a simple compound, but is difficult to prepare in high purity and in good yields, especially on a large scale. Few synthetic routes for mesalamine are reported in the literature, such as the coupling of diazonium salt derived from sulfanilic acid with salicylic acid [24]. In this method, the product undergoes hydrogenation, resulting in low purity and yield. Another method based on the condensation of phenyl diazonium salt with salicylic acid, followed by hydrogenation to give the desired mesalamine, is also reported [25]. A protocol involving the nitration of salicylic acid followed by reduction to form the target compound is also described, but with low purity and yield [26]. A two-step procedure involving carboxylation of *p*-acetaminophenol or

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p-aminophenol in the presence of a solid base catalyst is reported to give a 63% yield [27]. Generally, upscaling the laboratory experiments and their large-scale production is challenging [28, 29].

Motivated by the application of mesalamine in inflammation control, we attempted the one-pot synthesis of mesalamine from 2-chloro-5-nitrobenzoic acid, to broaden its scope for industrial scale production. In this communication, we describe an efficient one-pot method in which 2-chloro-5-nitrobenzoic acid is converted to 2-hydroxy-5-nitrobenzoic acid using excess aqueous KOH (4.0 equivalents) to ensure completion of hydrolysis; this is further converted to the desired product, mesalamine, under hydrogen atmosphere using 10% Pd/C as the catalyst. By this strategy, the target compound, mesalamine, was obtained in an excellent yield (93%). Tables 1 and 2 summarise the results of the optimisation of the reaction conditions.

2 Materials and methods

2.1 General methods

AR grade reagents and solvents were used without further purification. All the reactions were carried out in oven-dried flasks. IR spectra were recorded on a Perkin-Elmer 1000 instrument (Sigma-Aldrich, Delhi, India) in the KBr phase and absorptions are reported in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded on 400 MHz (Varian) spectrometers in appropriate solvents using

Table 1: Optimisation of reaction conditions for the preparation of 2-hydroxy-5-nitrobenzoic acid (2).

Sample no.	Base	Equivalents	Time (h)	Temperature (°C)	Conversion (%)
1	Aq. Na_2CO_3	4.0	24	110	No conversion
2	Aq. Na_2CO_3	4.0	24	130	No conversion
3	Aq. NaOH	4.0	6	110	57.6
4	Aq. NaOH	4.0	8	110	71.0
5	Aq. NaOH	4.0	24	110	71.9
6	Aq. NaOH	4.0	6	130	59.8
7	Aq. NaOH	4.0	8	130	63.5
8	Aq. NaOH	4.0	12	130	74.5
9	Aq. NaOH	4.0	24	130	79.6
10	Aq. KOH	4.0	6	110	72.5
11	Aq. KOH	4.0	8	110	77.0
12	Aq. KOH	4.0	12	110	82.5
13	Aq. KOH	4.0	24	110	88.0
14	Aq. KOH	4.0	6	130	92.9
15	**Aq. KOH**	4.0	**8**	**130**	**98.9**

Bold face values are best optimization conditions.

Table 2: Optimisation of reaction conditions for the preparation of 2-hydroxy-5-amino benzoic acid (1).

Sample no.	Time (h)	Temperature (°C)	Catalyst (% Pd/C)	Conversion (%)
1	2	60	5	No
2	8	60	5	26
3	16	60	5	55
4	2	60	10	68.2
5	2	80	10	69.0
6	4	60	10	75.2
7	4	80	10	77
8	6	60	10	82.0
9	6	80	10	82.5
10	7	60	10	93.0
11	8	80	5	29.0
12	**8**	**60**	**10**	**99.3**

Bold face values are best optimization conditions.

tetramethylsilane as the internal standard, or the solvent signals as secondary standards, and the chemical shifts are shown in δ scales. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet for unresolved lines), etc. Mass spectra were recorded with a PE Scitex model API 3000 instrument. The compound was also analysed by high performance liquid chromatography (HPLC) for purity.

2.2 Large-scale preparation of mesalamine

Based on the success of the laboratory synthesis of the target compound in excellent yields and high purity, we successfully scaled up the quantities of reactants for large-scale production. 2-Chloro-5-nitrobenzoic acid (1 kg) was added to a stirred solution of KOH (1.4 kg) in water (6 l) over a period of 40 min at 30–35°C in an autoclave. The resulting mixture was stirred at 130°C for 7–8 h in a closed autoclave under 2.5–3 kg/cm^2 pressure. Then, the reaction mixture was cooled to 30°C and charged with 10% wet Pd/C (60 g) at 30–35°C under nitrogen atmosphere. After the removal of nitrogen gas, the resulting mixture in the autoclave was purged with hydrogen gas at 6–8 kg/cm^2 pressure and heated at 60–65°C for 8 h. After completion of reduction, the mixture was cooled to 30–35°C and the catalyst was filtered through celite and washed with water (500 ml). The aqueous layer was treated with sodium hydrosulphite (20 g), in ethyl acetate (1 l) at 30–35°C for 30 min. The pH of the solution was adjusted to 3.5–4.5 by adding concentrated hydrochloric acid and then stirred for 1 h. The solid was filtered and washed with water (1 l). The resulting solid was added to water (6 l) and the pH adjusted to 0.6–0.9 with 10% HCl solution and continuously stirred for about 30 min, until it resulted in a clear solution. The mixture was heated to 45–50°C and treated with sodium hydrosulphite (20 g) and active charcoal (30 g) at the same temperature for 30 min. The resultant solution was filtered through celite, washed with water (50 ml) and then mixed with ethyl acetate (50 ml) to obtain the filtrate. The pH of the solution was adjusted to 3.5–4.0 with aqueous sodium carbonate (10%) solution followed by stirring for 1 h at 30–35°C and then filtered. The resulting solid was washed with water (500 ml) followed by acetone (500 ml), dried at 65–70°C for 8–9 h to give the off-white solid (3). The yield was 93% with 99.95% purity. The filtered wet Pd/C catalyst material was transferred into a closed beaker under nitrogen atmosphere. For safety precautions, Pd/C was always kept submerged under water after recovery and ready for reuse.

IR: 3445, 2979, 1796, 1314 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ = 6.65 (d, 1H, *J* = 8.1 Hz), 6.84 (dd, 1H, *J* = 8.2, 2.3 Hz), 7.18 (d, 1H, *J* = 2.3 Hz), 8.64 (brs, 2H); LCMS: *m/z* 154 $(M+H)^+$; ^{13}C NMR (100 MHz, DMSO): δ = 114.7, 116.9, 117.1, 123.9, 134.7, 155.3, 177.7; HPLC: 99.95% pure.

3 Results and discussion

In the preliminary experiments, we investigated the conversion of 2-chloro-5-nitrobenzoicacid (1) to 2-hydroxy-5-nitrobenoicacid (2) in various alkaline conditions, using sodium carbonate, NaOH or KOH under various reaction parameters such as time and temperature. Progress of the reaction was monitored by analysing for formation of the intermediate employing HPLC and the results are tabulated in Table 1. Use of sodium carbonate resulted in incomplete conversion and NaOH gave 79.6% conversion, while KOH facilitated 98.9% conversion.

The conversion efficacy of 2-hydroxy-5-nitrobenzoic acid (2) to mesalamine (3) under varied conditions was examined. The use of 5% Pd/C as a catalyst under hydrogen atmosphere at 60°C reaction resulted in a 40% yield. The use of 10% Pd/C under similar conditions gave an excellent yield (93%) of mesalamine. Table 2 summarises the results, reflecting the effect of various controlling parameters, the catalyst loading, reaction time, and temperature on the yield of the desired product.

NMR, IR, HPLC and mass spectra of the synthesized compounds are reported in Supplementary Information available.

4 Conclusion

In summary, we developed a rapid and efficient one-pot method for the large-scale production of mesalamine via a green approach with 2-chloro-5-nitrobenzoic acid as the starting material. The proposed method, which gives an excellent yield of the desired product with minimal side reactions, proves superior to existing protocols for the production of the valuable drug, 2-hydroxy-5-amino benzoic acid, and offers an opportunity for safe industrial production.

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