

Studies on the Synthesis of 3-Nitrobenzaldehyde

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Synthesis of 3-nitrobenzaldehyde, an intermediate for the drugs belonging to the second generation dihydropyridine family of calcium channel blockers, like nitrendipine, nicardipine, nimodipine and nilvadipine, has been attempted by four different routes. A single step nitration reaction resulted in the highest yield.

THE study of cardiovascular drugs have gained considerable importance due to the higher incidence of diseases such as hypertension, myocardial infarction and congestive heart failure. Calcium channel blockers are promising adjuncts in the treatment of hypertrophic cardiomyopathy and dilated congestive cardiomyopathy^{1,2}. They are preferred for obstructive and non-obstructive cardiomyopathy^{1,2}. Nitrendipine, nicardipine, nimodipine and nilvadipine are some of the drugs belonging to the second generation dihydropyridine family of calcium channel blockers. These drugs are structurally related to nifedipine, but have been developed to provide greater vascular selectivity, less direct myocardial depression, more flexible dosage regimens and an improved side effect profile.

3-Nitrobenzaldehyde is an important intermediate in the synthesis of these drugs. Indigenous production of 3-nitrobenzaldehyde is at the elementary stage and is insufficient to meet its growing demand. The demand for this intermediate is being met extensively by imports. Hence, sincere attempts to synthesise 3-nitrobenzaldehyde indigenously, are essential.

The synthesis of aldehydes is more diverse and extensive than the synthesis of any other class with possible exception of amines and ketones³. The general methods for the synthesis of aldehydes are few. The aldehydes, in

the middle of the different oxidation levels of organic compounds, may be prepared both by oxidation and reduction.

EXPERIMENTAL

Purity of the synthesised compounds and the progress of the reactions were monitored by TLC, using silica gel GF coated plates. The spots were detected by placing the developed plates in an UV cabinet. The purity of the synthesised products was confirmed by determining their melting points (MP) and by recording IR spectra of the same. All melting points were determined in open glass capillaries. IR absorption spectra were recorded on a JASCO FT/IR-5300 spectrophotometer using KBr pellet method. The characteristic IR absorption bands and melting points are shown in Table 1.

3-Nitrobenzaldehyde was synthesised by four different routes as shown in Fig. 1.

Scheme I was a single step procedure involving nitration of benzaldehyde (1) using nitrating mixture. Benzaldehyde was nitrated at 3-position using a mixture of concentrated sulphuric acid [25 ml] and fuming nitric acid [2.15 ml]. The nitrating mixture was placed in a bath containing salt and ice mixture. Benzaldehyde, [6.25 g, 0.06 M] was added dropwise to the flask at such a rate that temperature did not exceed 5°. After the addition, the reaction mixture was warmed to 40° for half an hour, cooled

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Table 1 : Characteristic data obtained for 3-Nitrobenzaldehyde

Scheme No.	Step No.	Compound No.	M.P. o	Overall % yield	% yield	IR bands (cm ⁻¹)
I	1	4	56-57	65.20	65.20	1535, 1352 (C-N str), 1707 (C=O str), 2879 (C-H str)
II	1	5	67-69		47.27	1533 (C-N str), 1761 (C=O str), 1240 (C-O str)
	2	4	56-57	46.96	46.96	Same as in Scheme I
III	1	6	78		71.50	1529, 1352 (C-N str), 1718 (C=O str), 1292, 1269 (C-O str)
	2	7	30		58.78	1530 (C-N str), 3352 (O-H str)
	3	4	57-58	17.30	1.20	Same as in Scheme I
IV	1	8	60-61		32.98	1527, 1352 (C-N str), 560 (C-Br str)
	2	9	189-190		95.57	1531 (C-N str), 2949, 1464 (C-H str, CH ₂), 1041 (C-N-C str) C 1413 (N-CH ₂ str)
	3	4	57	14.20	44.80	Same as in Scheme I.

to room temperature and was poured in thin stream over finely crushed ice with vigorous stirring. The yellow solid that precipitated was first washed with water, then with sodium carbonate solution and finally again with water. The crude product thus obtained was recrystallised from petroleum ether (60°-80° fraction). Pure 3-nitrobenzaldehyde (4) was obtained in 24.7 % yield. Few modifications were carried out to increase the yield of (4). When the amount of fuming nitric acid was increased from 2.1 ml (0.05 M) to 6 ml (0.15 M) and when the reaction mixture was stirred at 40° for two hours after complete addition of benzaldehyde to the nitrating mixture, it was possible to increase the yield of (4) upto 65.2 %. The IR spectrum of (4) was compared with that of 3-nitrobenzaldehyde, obtained from Koch-Light Laboratories, England. The two spectra matched with each other.

In scheme II⁵, (4) was prepared in two steps via 3-nitrobenzaldiacetate (5) intermediate. In the first step, chromium trioxide [6 g, 0.04 M] in acetic anhydride [30 g, 0.30 M] was added to a cooled and stirred mixture of 3-nitrotoluene (2) [3 g, 0.22 M], acetic anhydride [24 g, 0.24 M] and concentrated H₂SO₄ [4.8 ml] at such a rate that temperature did not exceed 10°. Stirring was continued for three more hours after addition of chromium trioxide. This mixture was then poured on crushed ice. Oily product, 3-nitrobenzaldiacetate (5), was separated which solidified on continuous stirring for 15-20 min. Neutralisation of the reaction mixture with 2 % sodium carbonate resulted in 47.3 % of (5). The success of the reaction depends on the skill of converting oily product into a solid mass. It is essential that oily layer be stirred vigorously until it solidifies completely, otherwise varying yields are obtained. In the

second step, (5) [2.6 g, 0.01 M] was refluxed with a mixture of 95 % ethanol [10 ml] and concentrated H_2SO_4 [25 ml] for 40 min. The mixture was then cooled to 0° . The precipitated product was filtered and recrystallised from petroleum ether ($60-80^\circ$) to obtain pure (4) in 46.96 % yield.

In Scheme III, 3-nitrobenzoic acid (3) was converted to 3-nitromethylbenzoate (6) which was reduced to 3-nitrobenzylalcohol (7). The compound (7) was then oxidised to (4) using $\text{K}_2\text{Cr}_2\text{O}_7$ in acidic medium. In the first step⁶, a mixture of (3) [10 g, 0.16 M], absolute methanol [30 ml] and concentrated H_2SO_4 [1 ml] was refluxed for 3 hours. On cooling, yellow solid separated out which was recrystallised from hot methanol to obtain 71.5 % yield of (6). In second step⁷, (6) [6 g, 0.033 M] and sodium borohydride [3.12 g, 0.083 M] were added to t-butanol [50 ml]. Absolute methanol [24 ml] was added dropwise over a period of 2 h. to the above refluxing mixture. The mixture was refluxed for further 6 h. It was then quenched with water. The organic solvents were distilled off. The aqueous solution was extracted with 30 ml of chloroform. Yellowish brown crystals of (7) could be obtained in 58.78 % yield from the organic layer. When water was used in place of a mixture of methanol and t-butanol, negligible amount of (7) was obtained. By increasing the molar ratio of NaBH_4 : (6) from 2.5 to 4, it was found that the reaction time could be decreased by 6 h. without any change in the percent yield of (7). In the third step⁸, potassium dichromate [5.6 g, 0.01 M] in water [20 ml] and concentrated H_2SO_4 [5 ml] were added to (7) [3 g, 0.019 M]. The reaction mixture was steam distilled and the distillate was collected. White, crystalline solid obtained was filtered and dried to get 1.2 % of (4). Attempts to oxidise (7) to (4) in neutral aqueous sodium dichromate solution at high temperature⁹ and by aqueous ceric ammonium nitrate¹⁰ solution were unsuccessful.

Scheme IV was a three step reaction. Side chain bromination of 3-nitrotoluene (2) resulted in the formation of 3-nitrobenzyl bromide (8) which was first converted to hexaminium salt (9) and then hydrolysed to 3-nitrobenzaldehyde (4). In the first step, the modification of the original procedure¹¹ led to the increase in the yield of (8) from 6.7% to 32.98%. In the modified procedure, the reaction time was increased by 30 min, the reaction temperature was increased by 10° and the molar ratio of (2) : bromine was increased from 1:1 to 1:3. The compound (2) [30 g, 0.22 M] was placed in three necked flask and was heated to $155-160^\circ$. Liquid bromine [52.7 g, 0.33 M] was

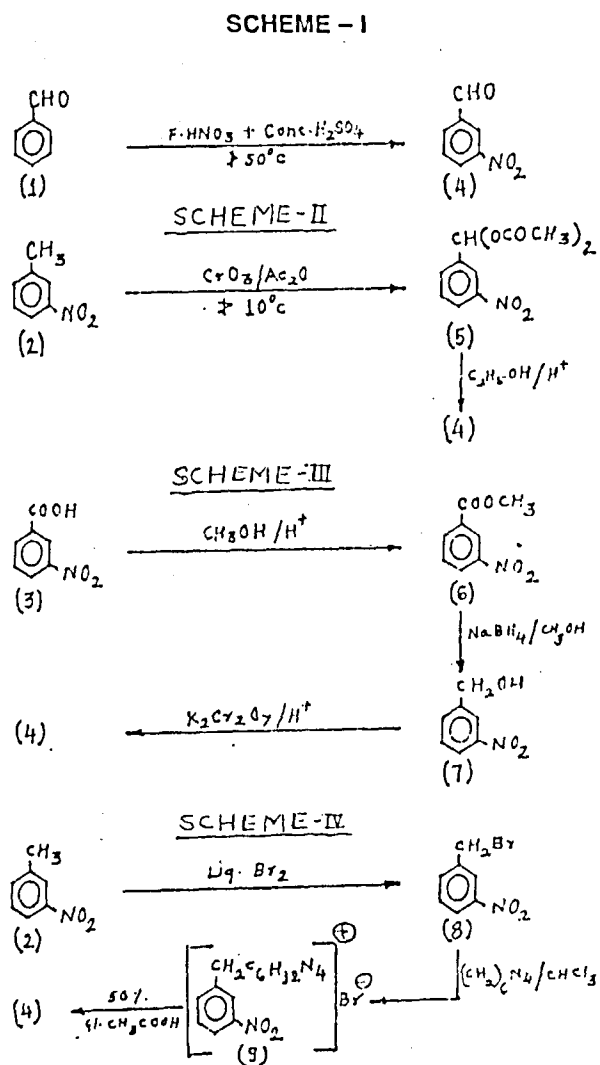


Fig. 1 : Various Routes for the Synthesis of 3-nitrobenzaldehyde

added dropwise with stirring to maintain the temperature in the range of $155-160^\circ$. The reaction mixture was further heated for 40 min and then poured into a flask containing 400 ml of petroleum ether ($60-80^\circ$) and boiled for 15 min with 10 g of activated charcoal. The solution was then filtered and cooled to get pale yellow coloured crystals of (8) in 32.98 % yield. In the second step¹² hexamine [18.2 g, 0.15 M] was dissolved in chloroform [70 ml]. The compound (8) [14.4 g, 0.07 M] was added to it and the mixture was refluxed for 4 hours. Chloroform [30 ml] was removed, acetone [35 ml] was added. The reaction mixture was cooled in ice. The crystalline, white precipitate that separated was

filtered and washed with chloroform to obtain 95.6 % of hexaminiun salt (9). In the third step¹², (9) [22.68 g, 0.064 M] was refluxed with 50 % glacial acetic acid [100 ml] for one hour. Addition of water [100 ml] and concentrated HCl [25 ml] and cooling of the reaction mixture, resulted in the precipitate of (4). It was filtered, washed with water and recrystallised from petroleum ether (60-80°) to get 44.8 % yield.

RESULTS AND DISCUSSION

The comparative overall percent yield of 3-nitrobenzaldehyde was calculated based on the very first starting material and is given in Table 1.

Scheme I was a single step reaction giving the highest yield (65.2 %) and utilising all cheaper raw materials. It was, therefore, the most economical of all the four schemes. Schemes III and IV, involving three step synthesis, resulted in low yield (17.4 and 14.2 % respectively) of (4) and require further improvisation. Scheme IV was uneconomical from the point of industrial applicability since it involved three steps, used expensive reducing agent, NaBH₄, and gave product in low yield. Scheme II involved a two step synthesis and resulted in 46.96 % yield. Thus, scheme I could be suitable for economic synthesis of 3-nitrobenzaldehyde.

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