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# An Improved Process for the Preparation of 4-(N,N-Disubstituted amino)butaraldehyde Acetals

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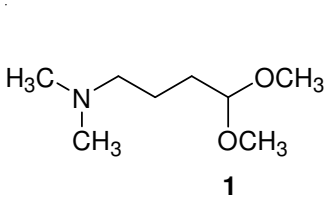
An improved manufacturing process has been developed by performing the reaction of 4-chloro butaraldehyde (**3**) generated *in situ* from commercially available starting material sodium salt of 4-chloro-1-hydroxy butane sulphonic acid (**4**) with methanol or ethanol and further on displacement of alkyl chloride with aqueous dimethyl amine furnished title compounds **1** and **5**. The improved process allows to manufacture the intermediates **1** and **5** at considerably low cost and in higher yield.

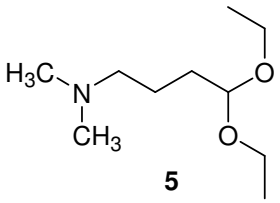
**Key Words: Synthesis, 4-(N,N-disubstituted amino)-butyraldehyde acetals.**

## INTRODUCTION

The substituted butaraldehyde derivatives are important building blocks for the synthesis of various tryptamine derivatives. In particular, 4-(N,N-dimethylamino)butyraldehyde dimethyl or diethylacetals are crucial intermediates for the synthesis of commercially available antimigraine drugs, like sumatriptan[1], zolmitriptan[2] and rizatriptan[3]. An efficient, cost effective synthetic process of 4-(N,N-dimethylamino)butyraldehyde dimethyl acetal (**1**) and 4-(N,N-dimethylamino)butyraldehyde diethyl acetal (**5**) were described




**1**




**5**

Structural framework of 4-(N,N-disubstitutedamino)butaraldehyde acetals

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in good overall yields using commercially available raw materials. In one general synthesis[4] for compounds **1** and **5**, reported in two steps starting from propynal diethyl acetal. Propynal diethyl acetal was subjected to Mannich reaction with a disubstituted diamine and formaldehyde and further on complete reduction gave corresponding 4-(N,N-dimethylamino)butyraldehyde acetal derivatives (**1** or **5**). The main draw-back of the above-described route (a) Preparation of starting acetal compound was extremely difficult on commercial scale (b) chromium oxidation was involved which was not stable under normal conditions, and (c) high pressure hydrogenation. Apart from the above route there were three synthetic routes reported. The synthetic route as reported by Keglevic[5] prepared the compound **5** in 45 % yield starting from 4-amino butaraldehyde diethyl acetal. The main disadvantages in this reported synthesis are (a) starting material used in this process is not commercially available, (b) basic raw material, acrolein is also not widely available and requires special handling techniques due to its lachrymatory nature and polymerization property and (c) use of poisonous chemicals like sodium cyanide and potassium cyanide. Chen *et al.*[6] synthesized **1** in 66 % yield in three steps from 4-chlorobutyryl chloride. This route also got its disadvantages like (a) 4-chlorobutyryl chloride is not commercially available, (b) preparation of this raw material involves corrosive chemistry (c) Rosenmund reduction was involved in the first step, which requires special technique and the yields can vary and (d) large excess of dimethyl amine used in the final stage. Keeping in view of the difficulties in implementing the above routes for synthesis compounds **1** and **5**, it is worthwhile to develop a simple, convenient and an economical process.

## EXPERIMENTAL

The $^1$H NMR spectra were recorded in $CDCl_3$ at 200 MHz on a Varian Gemini 200 MHz FT NMR spectrometer. The chemical shifts are reported in ppm relative to tetramethylsilane (TMS) as the internal standard. The FT-IR spectra were recorded in the solid state as KBr dispersion using a Perkin-Elmer 1650 FT-IR spectrophotometer. The mass spectrum (70 eV) was recorded on HP-5989A LC/MS spectrometer. The solvents and reagents were used without further purification.

### 4-(N,N-dimethylamino)butanal dimethyl acetal (1)

**Stage-1: 4-Chorobutanal dimethyl acetal (2):** To a solution of sodium carbonate (100 g, 0.950 mol) in water (500 mL), sodium salt of 4-chloro-1-hydroxy butane sulphonic acid (**4**) (100 g, 0.475 mol) was added at 5 ºC and stirred for 0.5 h. Methylene dichloride (500 mL) was added into reaction mixture and stirred for 0.5 h at 5 ºC.

Separated organic layer and aqueous layer extracted with methylene dichloride (250 mL). Combined the total organic phase and dried over sodium sulfate. Methanol (96 mL, 2.375 mol) was directly added to the filtrate and the reaction mixture was stirred for 15 min. Conc. sulphuric acid was added dropwise over 0.5 h at 25-30 ºC with vigorous stirring. This solution was stirred for 3 h and the solid was filtered. The filtrate was washed with 5 % aqueous sodium bicarbonate solution (300 mL) followed by 10 % salt solution (500 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude product was distilled to afford 63 g (87 %) 4-chloro butanal dimethyl acetal (**2**) as a colourless liquid with 98.5 % purity by GC: b.p. 50 ºC/8.5 mm Hg.

$^1$H NMR ($CDCl_3$, 200 MHz): δ 1.67-1.90 (m, 4H), 3.30 (s, 6H), 3.60 (t, $J$ = 7.0 Hz, 2H), 4.38 (t $J$ = 6.0 Hz, 1H). IR ($cm^{-1}$): 2989 (-$CH_2$-), 2831 (-CH-), 1070 (-C-O-), 651 (C-Cl). Mass: m/z 121 (M-31), 75 (M-77).

**Stage-2: 4-(N,N-Dimethylamino)butanal dimethyl acetal (1):** 4-Chlorobutanal dimethyl acetal (**2**) (100 g, 0.655 mol) was dissolved in aqueous dimethyl amine solution (200 mL) and the solution is stirred for 15 min at ambient temperature. The reaction mixture was then warmed to 50 ºC and stirred for 3 h. After the reaction mixture was cooled to room temperature, the product was extracted with methylene chloride (2 × 250 mL). The combined organic layers were washed with 5 % $NaHCO_3$ solution (2 × 100 mL) and brine solution (2 × 100 mL). The organic layer was evaporated and the residue was distilled to afford 88 g (84 %) of 4-(N,N-dimethylamino)butanal dimethyl acetal (**1**) as a colourless liquid with 99.6 % purity by GC: b.p. 40 ºC/1 mm Hg.

$^1$H NMR ($CDCl_3$, 200 MHz): δ 1.47-1.63 (m, 4H), 2.21 (s, 6H), 2.24 (t, $J$ = 7.0 Hz, 2H), 3.31 (s, 6H), 4.37 (t, $J$ = 5.4 Hz, 2H). IR ($cm^{-1}$): 2945 (-$CH_2$-), 2816 (-CH-), 1464 (C-N), 1074 (-C-O-). Mass: m/z 162.5 (M+1).

**4-(N,N-Dimethylamino)butanal diethyl acetal (5)**

**Stage-1: 4-Chorobutanal diethyl acetal (6):** To a solution of sodium carbonate (100 g, 0.950 mol) in water (500 mL), sodium salt of 4-chloro-1-hydroxybutane sulphonic acid (**4**) (100 g, 0.475 mol) was added at 5 ºC and stirred for 0.5 h. Methylene dichloride (500 mL) was charged into reaction mixture and stirred for 0.5 h at 5 ºC.

Separated organic layer and aqueous layer extracted with methylene dichloride (250 mL). Combined the total organic phase and dried over sodium sulfate. Ethanol (138 mL, 2.375 mol) was directly added to the filtrate and the reaction mixture was stirred again for 15 min. Conc. sulphuric acid was added dropwise over 0.5 h at 25-30 ºC with vigorous stirring. This solution was stirred for 3 h and the solid was filtered. The filtrate was washed with 5 % aqueous sodium bicarbonate solution (300 mL) followed by 10 % salt solution (500 mL). The organic layer was dried over sodium

sulfate and concentrated *in vacuo*. The crude product was distilled to afford 73 g (85 %) 4-chlorobutanal diethyl acetal (**6**) as a colourless liquid: b.p. 90 ºC/15 mm Hg.

$^1$H NMR ($CDCl_3$, 200 MHz): δ 1.2 (t, *J* = 6.83, 6H), 1.72-1.79 (m, 2H), 1.81-1.90 (m, 2H), 3.42-3.46 (m 2H), 3.56 (t, *J* = 6.83, 2H), 3.62-3.68 (m 2H), 4.5 (t, *J* = 5.37, 1H). IR ($cm^{-1}$): 2975 (-$CH_2$), 2871 (-CH), 1063 (-C-O-), 649 (C-Cl). Mass: m/z 144.1 [M-35.5].

**Stage-2: 4-(N,N-Dimethyl amino)butanal diethyl acetal (5):** 4-Chloro butanal diethyl acetal (**6**) (100 g, 0.533 mol) was dissolved in aqueous dimethyl amine solution (200 mL) and the solution is stirred for 15 min at ambient temperature. The reaction mixture was then warmed to 50 ºC and stirred again for 3 h. After the reaction mixture was cooled to room temperature, the product was extracted with methylene chloride (2 × 250 mL). The combined organic layers were washed with 5 % $NaHCO_3$ solution (2 × 100 mL) and brine solution (2 × 100 mL). The organic layer was evaporated and the residue was distilled to afford 88.5 g (84.4 %) of 4-(N,N-dimethyl amino)butanal diethyl acetal (**5**) as a colourless liquid: b.p. 85 ºC/15 mm Hg.

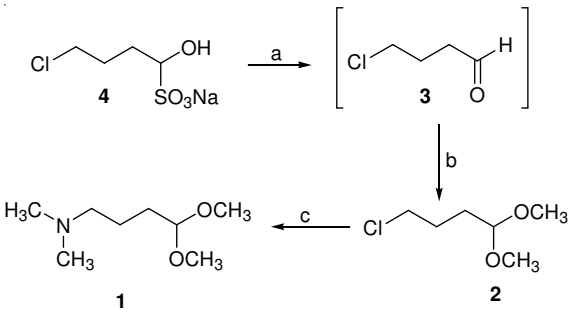
$^1$H NMR ($CDCl_3$, 200 MHz): δ 1.17-1.22 (m, 6H), 1.48-1.56 (m, 2H), 1.58-1.62 (m, 2H), 2.21 (s, 6H), 2.26 (t, *J* = 7.32, 1H), 3.42-3.48 (m, 2H), 3.62-3.72 (m, 2H), 4.51 (t, *J* = 5.37, 1H). IR ($cm^{-1}$): 2973 (-$CH_2$), 2816 (-CH), 1453 (C-N), 1062 (-C-O). Mass: m/z 190.5 (M+1).

## RESULTS AND DISCUSSION

The efforts to develop a robust and economic process for preparation of intermediates **1** and **5** are described below in greater detail.

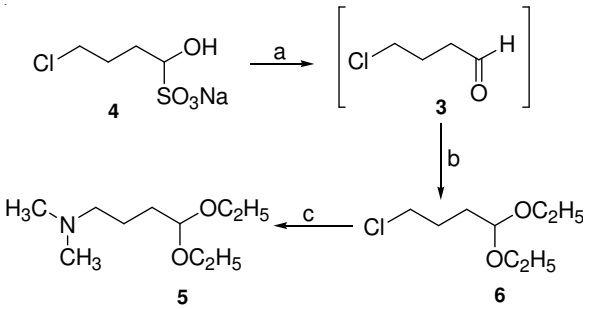
**Preparation of 4-(N,N-dimethylamino)butanal dimethyl acetal (1):** The sodium salt of 4-chloro-1-hydroxy butane sulphonic acid (**4**) is opted as a starting raw material due to its commercial availability. The requisite compound **1** was prepared *via* a two-stage process. (a) Generation of unisolated 4-chlorobutarldehyde (**3**) made from **4** under alkaline condition followed by reaction with methanol in presence catalytic amount of sulphuric acid produced **2**. (b) Displacement of alkyl chloride with dimethyl amine afforded 4-(N,N-dimethylamino)butanal dimethyl acetal (**1**) in good yield (**Scheme-I**).

**Preparation of 4-(N,N-dimethylamino)butanal diethyl acetal (5):** 4-(N,N-dimethylamino)butanal diethyl acetal (**5**) can be prepared in the same fashion. The requisite compound **1** was prepared *via* a two-stage process. (a) Generation of unisolated 4-chlorobutarldehyde (**3**) made from the starting material **4** under alkaline condition followed by reaction with ethanol in presence catalytic amount of sulphuric acid produced **6**. (b) Displacement of alkyl chloride with dimethyl amine afforded 4-(N,N-dimethylamino)-butanaldiethyl acetal (**5**) in good yield (**Scheme-II**).



**Conditions:** (a) (i) Sodium carbonate, dichloromethane, 5 ºC, 0.5 h (ii) Methanol, conc. $H_2SO_4$, room temperature, 3 h, 87 %. (b) Aqueous dimethyl amine solution (30 %), 50 ºC, 3 h, 76.0 %

**Scheme-I**



**Conditions:** (a) (i) Sodium carbonate, dichloromethane, 5 ºC, 0.5 h (ii) Ethanol, conc. $H_2SO_4$, room temperature, 3 h, 85 % (b) aqueous dimethyl amine solution (30 %), 50 ºC, 3 h, 84.4 %

**Scheme-II**

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