

## FACILE, ONE POT SYNTHESIS OF BUMETANIDE, A LOOP DIURETIC OF SULFAMOYL CATEGORY TO TREAT HEART FAILURE

Mark Manidhar.Darla\*, Md Ashraf, Adishesu Devarapalli and TirupathiNaidu Toram

R.V. Labs, Guntur, Andra Pradesh, India.

\*Corresponding Author: [phani.r.s.ch@gmail.com](mailto:phani.r.s.ch@gmail.com)

### ABSTRACT

Initially in preparing Bumetanide, we have adopted to different methods of synthesis. We had taken (chloro nitro sulfonamide acids) and carried out etherification with phenol, subsequent reduction with Palladium carbon and alkylating with butyraldehyde gave the final Bumetanide. In another method after etherification and reduction of nitro compound, free amine was treated with butyrylchloride to get mono acylated compound, which was reduced with Boron-DMS to get the final compound. We have synthesized the product in one pot. Taken the commercially well available nitro phenoxy sulfamyl benzoic acid and subjected to reduction in an autoclave with butyraldehyde at 100psi pressure. Here both reduction of nitro group followed by reductive amination is being completed. This reaction was monitored by TLC and LCMS. After reaching the maximum percentage of mono alkylation, reaction was stopped. Prolonging the reaction leads to di alkylation.

**Keywords:** Bumetanide, diuretic, reductive amination, dialkylation.

### INTRODUCTION

While studying the di alkylation of aromatic amines, it has been tried the di alkylation of 3-amino-4-phenoxy-5-sulfamyl benzoic acid, it was found that 3-butylamino-4-phenoxy-5-sulfamyl benzoic acid (**Bumetanide**) was formed initially and later 3-dibutylamino-4-phenoxy-5-sulfamyl benzoic acid. This reaction was monitored by both TLC and LC-MS.

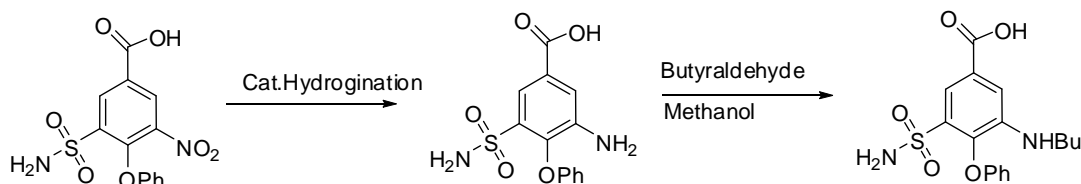
Good quality and yield of **Bumetanide** was observed by stopping the reaction immediately after absence of 3-amino-4-

phenoxy-5-sulfamyl benzoic acid by TLC/LC-MS.

The earlier methods for the synthesis of Bumetanide were as follows

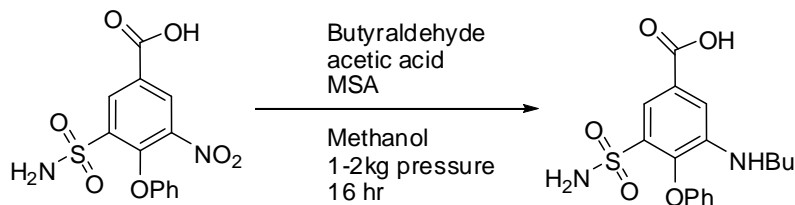
### SU631514

Patent describes 3-nitro-4-phenoxy-5-sulfamoylbenzoic acid and subsequent alkylation of the resulting 3-amino-4-phenoxy-5-sulfamoylbenzoic acid to the corresponding butylamine deriv. using butyraldehyde in a MeOH medium.

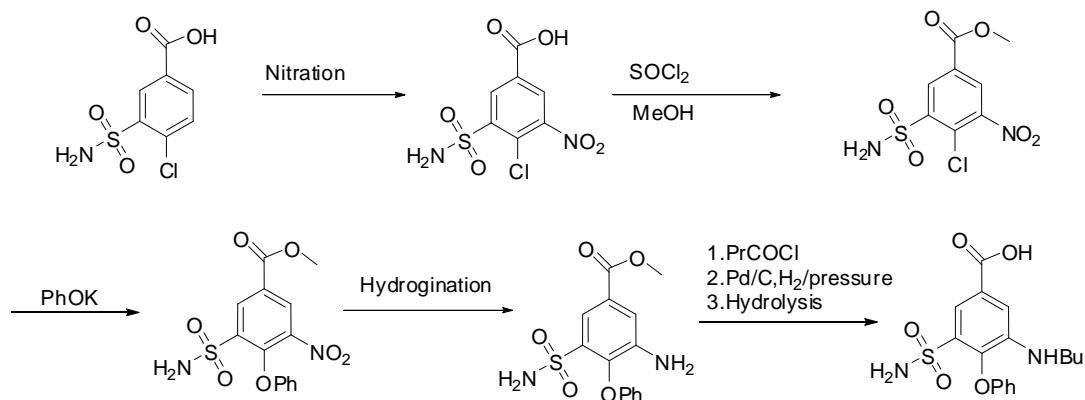


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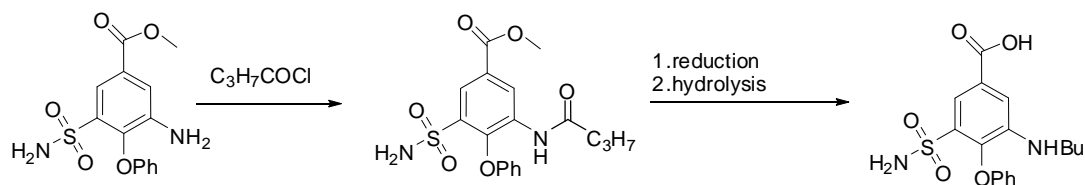
Patent describes reductive amination of 3-nitro-4-phenoxy-5-sulfamoylbenzoic acid with butyraldehyde in an autoclave presence of 10% palladium carbon, acetic acid-methane sulfonic acid in methanol medium at 1-2 atm pressure for longer hours.

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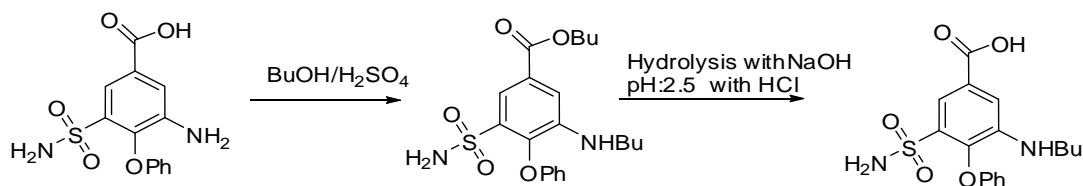
4-chloro-5-sulfamoylbenzoic acid was successively condensed with DMF, nitrated, esterified with MeOH via the acid chloride, reacted with PhOK, hydrogenated to the amino deriv., N-butylated, reduced, and hydrolyzed to give **Bumetanide**

**US 3991097**

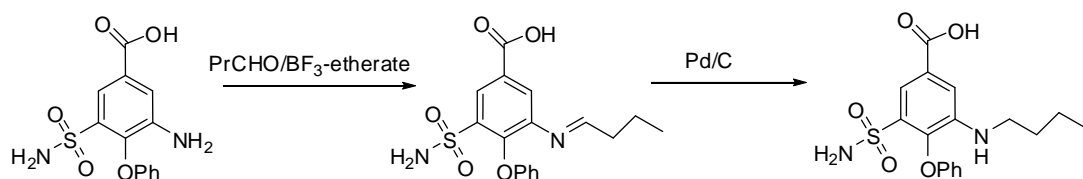
This patent involves the acylation of 3-amino-4-phenoxy-5-sulfamoylbenzoic acid methyl ester followed by reduction with BF<sub>3</sub>-etherate and Sodium Borohydrate then hydrolyzed.

**US3971819/ US3806534**

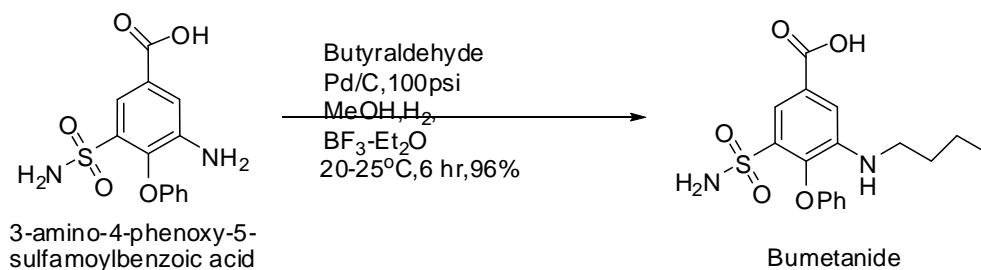
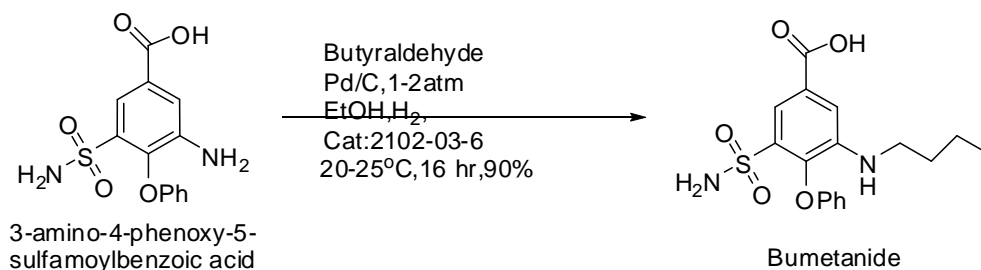
3-amino-4-phenoxy-5-sulfamoylbenzoic acid was simultaneously esterified and alkylated to butanol to get 3-butylamino-4-phenoxy-5-sulfamoylbenzoic acid butyl ester, which was hydrolyzed with sodium hydroxide and acidified to pH 2.5 with dilute hydrochloric acid to get title compound.

**WO2009/10115427**

3-amino-4-phenoxy-5-sulfamoylbenzoic acid was converted to oxime with butyraldehyde in presence of  $\text{BF}_3$ -etherate followed reduction with palladium carbon. This was alkylated with Butanol in presence of Sulfuric acid to get title compound.

**Faming Zhuanli Shenqing Gongkai Shuomingshu, 101591276, 02 Dec 2009.**

In this journal, in an autoclave, 3-amino-4-phenoxy-5-sulfamoylbenzoic acid is subjected to reductive amination with butyraldehyde under hydrogen pressure, palladium carbon and  $\text{BF}_3$ -Ethearate were used as catalyst.



In our one pot method, it has been observed that formation of Bimetanide was in minimum time (6.0 hr), in which reaction was monitored by TLC and LC-MS. As soon as the starting material was absent, hydrogen gas passing was stopped and the catalyst has been filtered.

The filtrate was concentrated to minimum volume and sufficient amount of n-hexane was added, stirred and filtered. The yield and quality of the product was very much satisfactory.

**EXPERIMENTAL**

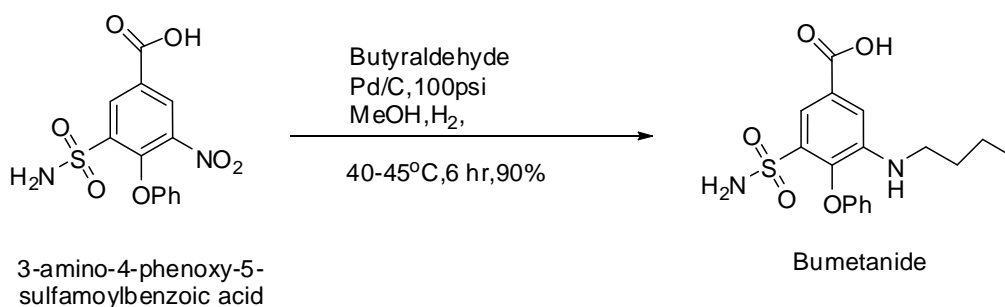
Melting points were determined on Buchi-540 melting point apparatus and are un-corrected. FT-IR spectra were recorded as KBr pellet on Nicolet-380 FT-IR instrument (Model Thermo Electron corporation-Spectrum one),  $^1\text{H}$  and  $^{13}\text{C}$  NMR (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using  $\text{DMSO-d}_6$  and  $\text{CDCl}_3$  as solvent. Mass spectra were recorded on Agilent triple

quadrupole mass spectrometer equipped with turbo ion spray interface at  $360^\circ\text{C}$ .

The dry reactions were carried out under nitrogen atmosphere with magnetic/mechanical stirring. Unless and otherwise mentioned all the chemicals, reagents, solvents used were of LR grade. TLC were run on pre-coated silica-gel plates, which were visualized using UV light.

**One pot synthesis of Bumetanide:**

We started the reaction with commercially well available 3-nitro-4-phenoxy-5-sulfamoylbenzoic acid.



To Methanol (250.0 ml) in an Autoclave apparatus, 3-nitro-4-phenoxy-5-sulfamoylbenzoic acid (25g, 0.0811 moles), Butyraldehyde (29.2g, 0.4052 moles), 5.0 g of 10% palladium on carbon (50% moisture) was added. The autoclave was flushed with Nitrogen twice and then with Hydrogen gas. 100 psi hydrogen pressure and  $40-45^\circ\text{C}$  temperature were maintained during the reaction. The reaction was monitored by TLC and LC-MS. After six hours starting material was absent, immediately stopped the hydrogen gas and cooled the reaction mass to Room temperature. Filtered the catalyst under nitrogen blanket. The filtrate was concentrated to minimum volume and the semi solid mass diluted with n-Hexane. Cooled to below  $10^\circ\text{C}$  and filtered after 1.0 hr. A white crystalline solid of Bumetanide (26 g) with 90% of theoretical yield,  $\text{MP} 230-232^\circ\text{C}$ .

**$^1\text{H}$  NMR ( $\text{dmsO-d}_6$ ):**  $\delta$  0.79 (t, 3H, - $\text{CH}_3$ ), 1.1 (m, 2H, - $\text{CH}_2$ ), 1.25 (m, 2H, - $\text{CH}_2$ ), 3.05 (q, 2H, - $\text{CH}_2$ ), 5.05 (t, 1H, -NH), 6.82 (m, 2H, benzene), 7.05 (m, 1H, benzene), 7.25 (m, 2H, benzene), 7.35 (m, 1H, benzene), 7.4 (m, 2H, - $\text{NH}_2$ ), 7.65 (t, 1H, benzene), 13.2 (s, H, -OH,  $\text{D}_2\text{O}$  exchangeable)

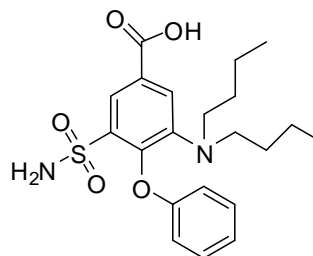
**$^{13}\text{C}$  NMR ( $\text{dmsO-d}_6$ ):**  $\delta$  166.6, 156.38, 142.49, 139.64, 137.73, 129.16, 128.22, 122.31, 115.62, 115.30, 42.09, 40.33, 39.50, 38.94, 30.23, 19.35, 13.62.

IR (KBr,  $\nu_{\text{max}}$ ): 3405 (-OH), 3284 (-NH), 1698 ( $\text{C}=\text{O}$ ), 1202 ( $\text{S}=\text{O}$ )  $\text{cm}^{-1}$ .

**MS:**  $m/z$  ( $\text{M}^+ + 1$ ) 365.0

Anal. Calcd for  $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_5\text{S}$ : C, 56.03; H, 5.53; N, 7.69; O, 21.95; S, 8.80, Found: C, 56.13; H, 5.55; N, 7.65; O, 22.0; S, 8.78.

It was found that in the filtrate after isolation of Bumetanide, a di butylated product was also formed in traces, which was confirmed by Mass and  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR

**Characterisation of di butylated Bumetanide**

**$^1\text{H}$  NMR ( $\text{dmsO-d}_6$ ):**  $\delta$  0.69-0.74 (t, 6H, - $2\text{CH}_3$ ), 0.9-1.03 (m, 4H, - $2\text{CH}_2$ ), 1.09-1.19 (m, 4H, - $2\text{CH}_2$ ),

2.69-3.01(t,4H,- 2CH<sub>2</sub>), 6.73-6.76(d,2H, benzene),6.95-7.02(t,2H,benzene), 7.19-7.24 (t,2H,benzene),7.32(s,2H,-NH<sub>2</sub>, D<sub>2</sub>O exchangeable),7.76(s,H,benzene),8.02(s,H,benzene),12.04(s,H,-COOH,)

<sup>13</sup>C NMR(dmsO-d<sub>6</sub>): δ 166.32,156.38,146.76, 144.48,138.89,128.81,127.12,125.17,122.09, 120.53,115.63,40.65,40.33,40.05,39.77,39.50, 39.22,38.94,38.66,28.15,19.53,19.

IR (KBr, ν<sub>max</sub>): 3403.6(-OH),3285(-NH),1698(-C=O),1202(-S=O) cm<sup>-1</sup>.

MS: m/z(M<sup>+</sup>+1): 421.52

Anal. Calcd for C<sub>21</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub>S: C, 59.98; H, 6.71; N, 6.66; O, 19.02; S, 7.63, Found: C, 70.01;H, 6.69; N, 6.59; O,19.12;S,7.65

### CONCLUSION

Bumetanide was synthesized with good yield and quality, which was found very convenient and time saving.

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