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Original Article

A Modified Method for the Synthesiss of Nitrofurazone

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Abstract

Nitrofurazone is one of the antibacterial nitrofuran agents used topically for skin infections. The drug is effective on the majority of infectious microorganisms. Because of the importance of this drug in clinic, in this study various methods of synthesis of nitrofurazone were examined and the most appropriate method, applicable to pharmaceutical industry was chosen and optimized from the points of quality and yield.

Keywords: Nitrofurazone; Synthesis; Quality control.

Introduction

Nitroheterocyclic drugs are used for the treatment of a wide range of bacterial and protozoal diseases. The Nitrofuran group of drugs is very large and displays a wide spectrum of clinical and nonclinical applications. Nitrofurans are known to produce DNA strand breaks as a consequence of reduction of their nitro group. One of the nitrofuran drugs is nitrofurazone. This drug is used primarily against gram-negative infections of skin injuries typified by *Escherichia coli, Pseudomonas and Proteus* (1). For the synthesis of nitrofurazone various methods have been used (2-10). The starting material used in the synthesis may be 5-nitrofurfural diacetate (2-6), 5-nitro-2-furaldehyde (7), 2-furaldehyde (8-9) or nitrofurfuraloxime (10). Since 2-furaldehyde is a cheap substance and could be used in an industrial scale production of nitrofurazone, in this study those methods in which 2-furaldehyde is used as a starting material were chosen and applied with varying conditions of time, temperature, pH and changing catalysts to obtain a product with an appropriate quality and good enough yield, to be scaled up in industry.

Experimental

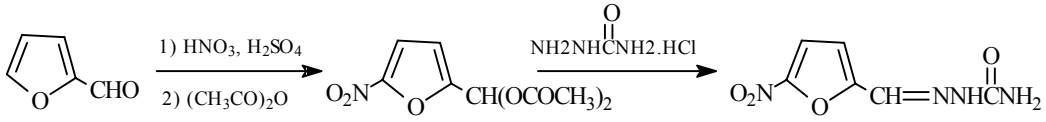
Methods

All chemical compounds were from Merck Co. and of analytical grades. IR spectra were recorded on Perkin-Elmer model 840. ^{1}H-NMR spectra were recorded on varian-400 spectrometer. Quality controls of the products were carried out according to United States Pharmacopeia (11).

Materials

Synthesis of 5-nitrofurfural diacetate

A mixture of concentrated nitric acid (4.3 ml) and sulfuric acid (0.3 ml) was added dropwise to acetic anhydride (45 ml) at -5°C to 5°C. To this solution a double-distilled furfural



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(5.2 ml) was added, under the same condition. The mixture was stirred in ice bath for 1 h. Then water (40 ml) was added to the mixture at room temp. After 30 min and adjusting pH at 2.5-2.7, the mixture was warmed (55°C, 1 h) and then left overnight at room temperature. The precipitate thus formed was collected and recrystallized from ethanol. [m.p.: 90°C, yield: 52%. ^{1}H-NMR ($CDCl_3$, δ): 7.71 (s, 1H, C-H), 7.30 (d, 2H, H-C_4 furan), 6.74 (d, 2H, H-C_3 furan), 2.18 (s, 6H, CH_3)].

Synthesis of Nitrofurazone

Method 1: 5-niotrofurfural diacetate (4.86 g, 20 mmol) and semicarbazide Hydrochloride (2.56 g, 23 mmol) were dissolved in ethanol-water solvent (1:1, 20 ml) and refluxed (2 h). The precipitate thus formed was collected, washed with ethanol and water and then dried (1 h, 105°C) [m.p.: 240°C, yield: 82%. IR (KBr ν): 3430 (N-H), 1710 (C=O), 1580 (C=N), 1520, 1350 (NO_2)].

Method 2: 5-nitro furfural diacetate (20 mmol) in 50% sulfuric acid (50 ml) was boiled (1-2 min). The mixture was added dropwise to a solution of semicarbazide HCl (2.56 g, 23 mmol) in water (250 ml). After 20 min stirring the precipitate was collected, washed and dried. m.p.: [238ºC, yield: 80%].

Method 3: 5-nitrofurfural diacetate (20 mmol) and semicarbazide HCl (23 mmol) were dissolved in ethanol-water-sulfuric acid (4, 34, 1.1 ml) and refluxed (1 h). The precipitate was then collected, [m.p.: 233°C, yield: 79%].

Method 4: The above procedure was carried out using hydrochloric acid (1.61 ml) instead of sulfuric acid [m.p.: 235ºC, yield: 80%].

Method 5: 5-nitro-furfural diacetate (4.86 g) and $SnCl_2$ (0.2 g) were mixed in water-HCl (20 ml, 1.61 ml) and refluxed for 30 min. Semicarbazide HCl (2.56 g) was then added to the mixture. After filtering and cooling, the product was collected and dried. [m.p.: 231°C, yield: 82%].

Method 6: 5-nitrofurfural diacetate (20 ml) in a mixture of ethanol-water-HCl (4, 34 and 1.61 ml respectively) warmed at 70°C for 20 min. Then semicarbazide HCl (2.56 g) was added and the reaction was continued for another 40 min. The precipitate was then collected and dried [m.p.: 236°C, yield: 85%].

Method 7: The above method was repeated but water was divided into two parts. One part (17 ml) was used for the furfural and the other part for the semicarbazide HCl solution [m.p.: 236°C, yield: 89%].

Method 8: The reaction was performed as method 7 but the amount of water used in either part was 10 ml [m.p.: 238, yield: 92%].

Table 1: Physico-chemical characteristics of nitrofurazone samples

Method	Yield (%)	Purity (%)	Loss on drying	Ashes	pH (1% solution)
1	82	83.5	+	+	+
2	80	90.7	+	+	+
3	79	94.1	+	+	+
4	80	96.3	+	+	+
5	82	91.1	+	+	+
6	85	101.5	+	+	+
7	89	101.2	+	+	+
8	92	102	+	+	+

+ : in accordance to U.S.P.

Results and discussion

For the synthesis of nitrofurazone, methods 1-5 gave the product with a relatively low purity and yield (Table 1). This may infer that the long heating time of the reaction and also the presence of strong acid could damage the final product.This is confirmed by the fact that nitrofrazone molecule degrades in the presence of harmful conditions and gives 5-nitro-furfuryliden aside, the structure of which is (12):

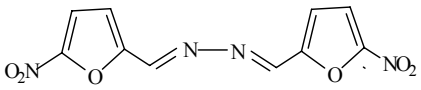

Figure 1. Nitro-furfuryliden azide

By shortening the time of reaction and replacing concentrated HCl instead of concentrated H_2SO_4, product with better quality was obtained. However, methods 6-8 showed that reducing the reaction solvent volume may still improve the product from the points of quality and quantity. As a result method 8 (Table 1) could be considered as an optimized procedure, to be scaled up for a pilot preparation in industry.

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