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Novel Method for Synthesis of Sulphaguanidine

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ABSTRACT

The microwave-enhanced synthesis of sulphaguanidine is achieved rapidly and in good yield via the step-wise reaction of cyanamide with sulphonamide in the presence of acidic alumina or montmorillonite clays (KSF and K10).

Key words: Sulphaguanidine, Microwave enhanced synthesis, montmorillonite clays.

INTRODUCTION

The sulpha drugs are drugs containing sulfonamide group (-SO_2NH-) and they are synthetic antimicrobial agents with a wide spectrum encompassing most gram-positive and many gram-negative organisms.[1-5] These drugs were the first efficient treatment to be employed systematically for the prevention and cure of bacterial infections.[6,7] Their use introduced and substantiated the concept of metabolic antagonism. Sulfonamides, as antimetabolites, compete with *p*-aminobenzoic acid for incorporation into folic acid. The action of sulfonamides illustrates the principle of selective toxicity where some difference between mammal cells and bacterial cells is exploited. All cells require folic acid for growth. Folic acid (as a vitamin is in food) diffuses or is transported into human cells. However, folic acid cannot cross bacterial cell walls by diffusion or active transport. For this reason bacteria must synthesize folic acid from *p*-aminobenzoic acid. Till now more than 15,000 sulfonamide derivatives, analogues, and related compounds have been synthesized, which are effective for diuretics, antimalerial, leprosy and antithyroid agents and employed for other diseases.[8,9] The basic structure of sulfonamide cannot be modified if it is to be an effective competitive “mimic” for *p*-aminobenzoic acid. Essential structural features are the benzene ring with two substituents *para* to each other; an amino group in the fourth position; and the singly substituted 1-sulfonamido groups. Sulphaguanidine, being important sulpha drugs, needs efficient and productive methods for its synthesis. Herein, we report for the first time the microwave assisted synthesis of sulphaguanidine in conjunction with solid acids.

MATERIAL AND METHODS

The starting materials and the reagents were thoroughly dried and purified before use by the standard known methods.[10] Reagents of analytical reagent (AR) grade were used for the experimental work and they were purchased from reputed chemical companies such as Rankem, s.d. Fine Chemicals, Acros, Fluka etc.

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR 435 spectrometer and the ν_{max} is expressed in cm^{-1}. The electronic spectra were recorded on a Shimadzu UV-260 spectrophotometer and the λ_{max} are expressed in nanometers. The ^1H NMR spectra were recorded on Bruker Avance 300 spectrometer using TMS as internal standard (chemical shifts in ppm). The abbreviation s, d, t, q, m and bs stand for singlet, doublet, triplet, quartret, multiplet and broad singlet respectively.

General Procedure for the synthesis of Sulphaguanidine

Method – I: Solution Phase Reaction

A mixture of Cyanamide (**1**) (1.0 mmol) and hydrochloric acid (0.5 mL, 2M) was taken (Scheme 1). The reaction mixture was refluxed for two hours at 140-160 °C. The reaction mixture was allowed to cool to room temperature and without separating the product, was further subjected to next step of the reaction. Sulphonamide (**3**) (0.5 mmol) was added to the reaction mixture and was further stirred at 100-110 °C for 12 hours. The reaction mixture was cooled to room temperature and put in refrigerator overnight leading to the separation of the light yellow solid, sulphaguanidine (**4**). The product was recrystallized with water.

Method – II: Reaction under Microwave (solution phase)

Cyanamide (**1**) (0.5 mmol), and hydrochloric acid was thoroughly grounded and subjected to microwave irradiation in a borasil sealed tube for 4 minutes. The temperature inside the beaker was found to be 110-120 °C. The temperature was recorded immediately after removing the tube from the microwave oven. To the reaction mixture, sulphonamide (**3**) was added and subjected to microwave irradiation for 4 minutes. The reaction mixture was allowed to cool to room temperature. The crude product was dissolved in hot water and filtered through celite. The filtrate was concentrated to dryness and the crude product was recrystallized from water affording **4** as light yellow solid.

Method – III: Reaction under Microwave (solid phase)

Cyanamide (**1**) (0.5 mmol), and solid acid such as montmorillonite clay, acidic alumina, silica gel G (1.5 g) was thoroughly grounded and subjected to microwave irradiation in a borasil beaker (25 mL) for 4 minutes with an interval after every 1 min. The temperature inside the beaker was found to be 110-120 °C. The temperature was recorded immediately after removing the beaker from the microwave oven. To the reaction mixture, sulphonamide (**3**) was added and subjected to microwave irradiation for 4 minutes with one minute interval. The reaction mixture was allowed to cool to room temperature. The crude product was dissolved in hot water and filtered through celite. The filtrate was concentrated to dryness and the crude product was recrystallized from water affording **4** as light yellow solid.

Mp.: 193-195 °C (Very light yellow solid) (lit.[11] mp. 190-193 °C)

Solubility: soluble in hot water and dil. mineral acids, sparingly soluble in ethanol or acetone; insoluble in NaOH at room temperature.

^1H NMR (DMSO-d_6): 2.3 (2H, b, NH´2/NH_2), 4.2 (2H, b, ArNH_2), 6.74-6.76 (2H, m, Ar-H), 7.68-7.70 (2H, m, Ar-H).

^{13}C NMR (DMSO-d_6): 163, 150, 129, 126, 126, 115, 115.

Elemental Analysis for $C_7H_{10}N_4O_2S$ (%) [mol. wt. 214.24]: Calcd. C (39.24); H (4.70); N (26.15); S (14.96); Found C (39.33); H (4.79); N (26.25); S (14.90)

RESULT AND DISCUSSION

Cyanamide (**1**) on acid catalyzed condensation gives dicyandiamide (**2**), which on further reaction with sulphonamide gave the desired sulphaguanidine (**4**) (Scheme 1). This reaction was performed by three methods:

(i) Solution-phase conventional method and

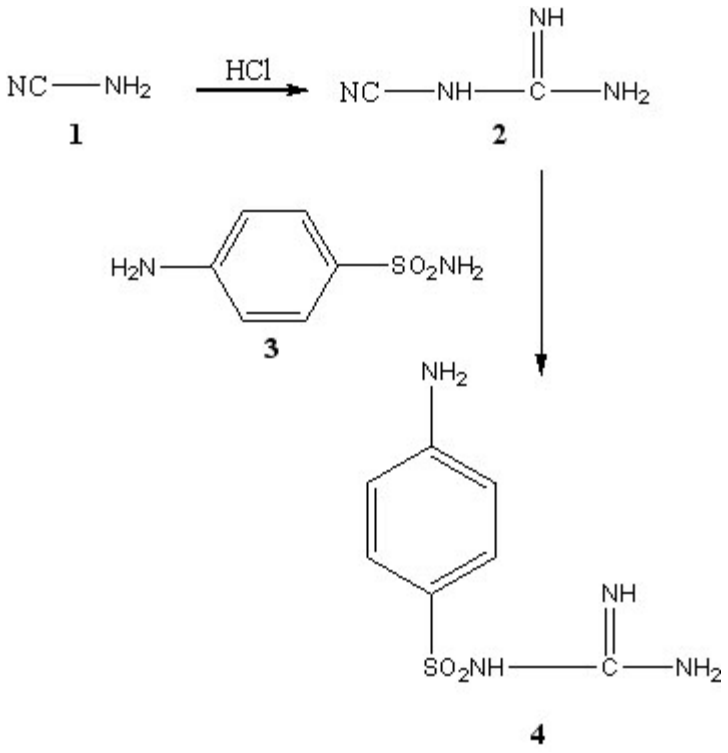
Table 1: Isolated yield of sulphaguanidine under different reaction conditions

S. No.	Reaction Conditions			Yield (Isolated)
1.	Conventional Solution Phase			32
2.	Microwave Irradiation	Solution Phase		48
3.		Solid Phase	Montmorillonite Clay KSF	79
4.			Montmorillonite Clay K10	83
5.			Acidic Alumina	75

(ii) Environmental friendly microwave irradiation solution phase

(iii) Environmental friendly microwave irradiation in conjunction with solid acid such as montmorillonite clays and related solid acids.

The preparation of sulphaguanidine was performed using both conventional method as well as microwave irradiation. For the conventional method, cyanamide (**1**) (1.0 mmol) and hydrochloric acid (0.5 mL, 2M) was mixed. The reaction mixture was put on refluxing for two hours at 140-160 °C. The reaction was monitored with TLC at regular interval of time. When, TLC showed the completion of the reaction, the reaction mixture was allowed to cool to room temperature and without separating the product, was further subjected to next step of the reaction. Sulphonamide (**3**) (0.5 mmol) was added to the reaction mixture and was further stirred at 100-110 °C for 12 hours. Again, the progress of the reaction was monitored with TLC at regular interval of time. When, TLC showed the completion of the reaction, the reaction mixture was cooled to room temperature and put in refrigerator overnight



Scheme 1:

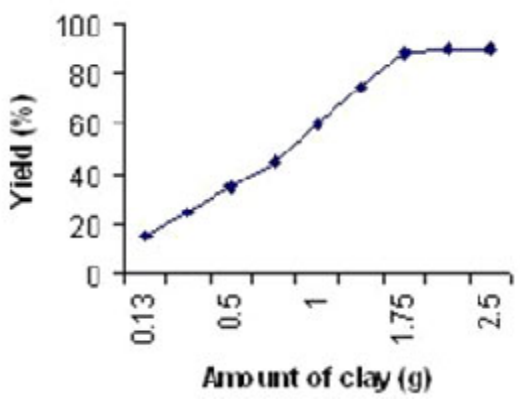


Fig. 1: Optimization of yield with amount of clay

leading to the separation of the light yellow solid, sulphaguanidine (**4**). The product was recrystallized with water and confirmed preliminary with melting point. The maximum yield obtained with this method was 32%. Since, the yield was very low, so other methods were also tried (Table 1).

Cyanamide (**1**) (0.5 mmol), and montmorillonite clay KSF was thoroughly grounded, so that both the reagents got mixed homogeneously. Further, the reaction mixture was subjected to microwave irradiation in a borasil beaker (25 mL) for 4 minutes with an interval after every 1 min. The temperature inside the beaker was found to be 110-120 ^{o}C. The temperature was recorded immediately after removing the beaker from the microwave oven. To the reaction mixture, sulphonamide (**3**) was added and subjected to microwave irradiation for 4 minutes with one minute interval. The reaction mixture was allowed to cool to room temperature. The crude product was dissolved in hot water and filtered through celite 545. The filtrate was concentrated to dryness and the crude product was recrystallized from water affording **4** as light yellow solid. This reaction was performed various times with different amount of montmorillonite clay. This was done to optimize the yield of the product using minimum amount of clays (Figure 1). It was found that the yield became constant after addition of 1.5 g of the clay. Keeping this amount of the clay as standard amount, the reaction was performed with different solid acids such as montmorillonite clay K10, acidic alumina and silica gel G. The yield with silica gel G was not appreciable. Out of these solid acids, montmorillonite clay K10 gave the maximum yield of 83% (Table 1).

The formation of sulphaguanidine was confirmed by various spectroscopic data including UV-visible, IR, NMR and elemental analysis. In ^{1}H NMR spectroscopy, a broad singlet for two protons was assigned to aniline protons. Two multiplets for two protons each in the region 6.74-6.76 and 7.68-7.70 were assigned to the aromatic protons. The presence of seven carbons was confirmed with ^{13}C NMR.

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