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Design and synthesis of two sulfathiazole derivatives using a three-component system

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Two sulfonamide derivatives were synthetized using a three-component system; in the first stage the compound 4-{[(2-hydroxy-naphtalen-1-yl)-phenyl-methyl]-amino}-*N*-thiazol-2-yl-benzenesulfonamide (**4**) was obtained by the reaction of β-naphtol, benzaldehyde and sulfathiazole (**3**) in ethanol. The second stage was achieved by the reaction of **3** with 1-hexyne and benzaldehyde using cupric chloride as a catalyst to form 4(hex-1-ynyl-phenyl-amino)-*N*-thiazol-2-yl-benzenesulfonamide (**6**). The structure of the compounds obtained was confirmed by elemental analysis, spectroscopy and spectrometry data. The proposed method offers some advantages such as good yields, simple procedure, low cost, and ease of workup.

INTRODUCTION

Since many years sulfonamide derivatives have been synthetized; for example, a sulfonamide derivative was prepared by the reaction of sulfonic acid salts with amines and alcohols using the reagent triphenylphosphine ditriflate [1]. There are other reports on the synthesis of 1-[4-(N-pyrimidin-2-yl-sulfamoyl)phenyl]-1,11-dihydro-11-oxo-4-methylpyrimido[4',5':4,5]selenolo[2,3-b]quinolone by the reaction of an iminoether with 4-amino-*N*-pyrimidin-2-ylbenzenesulfonamide under reflux in glacial acetic acid [2]. Other studies described the obtaining of 4-(1,2,3,4-tetrahydro-4,4,6-trimethyl-2-thioxo-1-pyrimidinyl)-N-(2-thiazolyl)-bezene sulfonamide using sulfathiazole and 4-methyl-4-isothiocyanato-2-pentanone [3]. The synthesis of *N*-(2-anilinopyridin-3-yl)-4-methylbenzenesulfonamide by the reaction of N^2-phenylpyridine-2,3-diamine with 4-methylbenzenesulfonyl chloride [4] is also reported.

The sulfamethoxazolato anion is obtained by the reaction of sulfamethoxazole with Ph_3PAuCl and AgCl in methanol/triethylamine [5]. 4-(1,2,3,4-Tetrahydro-4,4,6-trimethyl-2-thioxo-1-pyrimidinyl)-N-(2-thiazolyl)-bezenesulfonamide is synthetized by the reaction of sulfathiazole with 4-isothiocyanato-2-pentanone under reflux [6]. The procedures for synthesis of sulfonamide derivatives described in the literature require, however, expensive reagents and special conditions. Therefore, in this study two new sulfonamide derivatives were synthetized using a three-component system.

MATERIAL AND METHODS

General methods

The compounds used in this study were purchased from Sigma-Aldrich Co., Ltd. The melting points of the different compounds were determined on an Electrothermal (900 model) apparatus. Infrared (IR) spectra were recorded on a Perkin Elmer Lambda 40 spectrometer using KBr pellets. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300/5 FT NMR spectrometer at 300 and 75.4 MHz in $CDCl_3$ using TMS as internal standard. EIMS spectra were obtained on a Finnigan Trace GCPolaris Q spectrometer. Elemental analysis data were acquired from a Perkin Elmer Ser. II CHNS/0 2400 elemental analyzer.

Synthesis of 4-{[(2-hydroxy-naphtalen-1-yl)-phenyl-methyl]-amino}-N-thiazol-2-yl-

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benzenesulfonamide (4)

A solution of β-naphtol (100 mg, 0.69 mmol), sulfathiazole (192 mg, 0.69 mmol) and benzaldehyde (70 µl, 71 mmol) in 10 mL of ethanol was stirred for 72 h at room temperature. The reaction mixture was evaporated to a smaller volume. Then, the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (3:1) yielding 60 % of product, m.p. 118-120 ºC; IR (V_{max}, cm^{-1}): 3530 (OH), 3450 (C-NH-Ar) and 1325 (S=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 5.45 (s, IH), 6.50 (d, 2H, *J* = 9.0 Hz), 7.06 (broad, 3H), 7.08-7.12 (m, 2H), 7.16 (d, 1H, *J* = 9.0 Hz), 7.19(m, 1H), 7.21-7.23 (m, 2H), 7.46-7.52 (m, 2H), 7.57 (d, 1H, J = 3.5 Hz), 7.59 (m, 1H), 7.73 (m, 1H), 7.75 (d, 2H, J = 9.0Hz), 7.80 (m, 1H) ppm. ^{13} C NMR (75.4 Hz, $CDCl_3$) δ_C: 56.68 (**C**-17), 114.11 (**C**-20), 116.04(**C**-14, **C**-12), 116.50 (**C**-5), 119.70 (**C**-18), 120.89 (**C**-24), 123.80 (**C**-26), 127.02 (**C**-25) 127.10 (**C**-11, **C**-15), 127.36 (**C**-22), 127.80 (**C**-31), 128.50 (**C**-21), 129.68 (**C**-27), 129.90 (**C**-30, **C**-32), 130.66 (**C**-29, **C**-33), 132.90 (**C**-28), 135.42 (**C**-4), 137.65 (**C**-10), 137.70 (**C**-23), 153.70 (**C**-19), 154.22 (**C**-13), 168.02 (**C**-2) ppm. EI-MS *m/z:* 487.75 (M^+, 12), 334.27, 169.21. Anal. Calcd for $C_{26}H_{21}N_3O_3S_2$: C, 64.04; H, 4.34; N, 8.62; O, 9.84; S, 13.15. Found: C, 64.02; H, 4.33.

Synthesis of 4(hex-1-ynyl-phenyl-amino)-N-*thiazol-2-yl-benzenesulfonamide (6)*

A solution of 1-hexyne (80 µl, 0.70 mmol), sulfathiazole (192 mg, 0.69 mmol) benzaldehyde (75 µl, 0.70 mmol) and cupric chloride anhydrous (140 mg, 1.04 mmol) in 10 ml of ethanol was stirred for 72 h at room temperature. The reaction mixture was evaporated to a smaller volume. Then, the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (3:1) yielding 45 % of product, m.p. 178-180 ºC; IR (V_{max}, cm^{-1}): 3310 (C≡C), 1320 (S=O) and 1170 (C-N); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.91 (t, J = 6.3 Hz, 3H), 1.47 (m, 4H), 2.21 (t, J= 6.8 Hz, 2H), 6.67 (m, 2H), 6.78 (m, 1H), 7.17 (d, J = 3.4 Hz, 1H), 7.20 (m, 2H), 7.33 (m, 2H), 7.50 (d, J = 3.4 Hz, 1H), 7.88 (m, 2H), 8.98 (broad, 1H) ^{13} C NMR (75.4 Hz, $CDCl_3$) δ_C: 13.60 (**C**-28), 16.95 (**C**-25), 21.98 (**C**-27), 32.03 (**C**-26), 61.08 (**C**-24), 75.02 (**C**-23), 113.10 (**C**-18, **C**-22), 116.26 (**C**-12, **C**-14), 116.57 (**C**-5, 119.60 (**C**-20), 128.37 (**C**-15), 128.50 (**C**-21), 135.32 (**C**-4), 138.80 (**C**-10), 147.02(**C**-17), 152.34 (**C**-13), 166.98 (**C**-2). EI-MS *m/z* (M^+ 12)*:* 411.15 (M^+, 12), 218.08(100), 174.24(60), 103.07 (65), 76.15 (78). Anal. Calcd for $C_{21}H_{21}N_3O_2S_2$: C, 61.29; H, 5.14; N, 10.21; O, 7.78, S, 15.58. Found: C, 61.03; H, 5.11.

RESULTS AND DISCUSSION

In many procedures a three-component system is used for the synthesis of several compounds. The most widely practiced method employs boric acid [7], silica sulfuric acid [8], poly(4-vinylpyridine-co-divinylbenzene)-Cu(II) complex [9], H_2SO_4[10], silica triflate [11] and phosphorus pentoxide [12]. Nevertheless, despite their wide scope, the former protocols suffer from several drawbacks, *e.g.*, limited stability or dangerous preparation of some reagents. In this study we report a straightforward route for the synthesis of **4** using a modification of a method reported by Dabiri and coworkers [13]. According to this procedure, **4** is obtained by reaction of β-naphtol, benzaldehyde and sulfathiazole in ethanol (Figure 1). The ^{1}H NMR spectrum of **4** shows

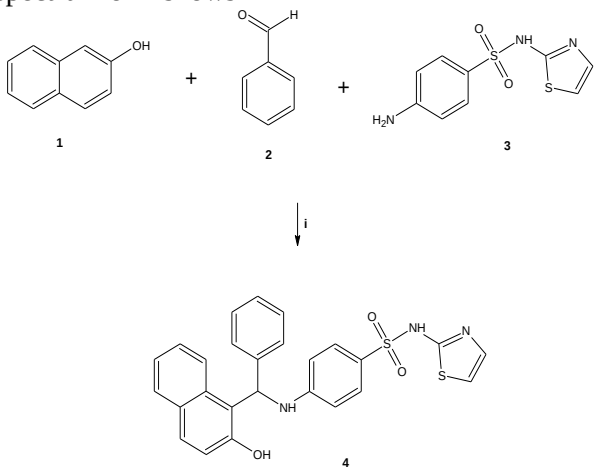

Fig. 1. Synthesis of 4-{[(2-hydroxy-naphtalen-1-yl)-phenyl-methyl]-amino}-*N*-thiazol-2-yl-benzenesulfonamide (**4**). Reaction between β-naphtol (**1**), benzaldehyde (**2**) and sulfathiazole (**3**) to form **4** using boric acid as catalyst. i = ethanol/rt.

signals at 5.40 ppm for methylene bound to both phenyl and amine groups; at 6.50 and 7.75 ppm for phenyl group bound to amine group; at 7.08–7.12 and 7.21-7.23 ppm for protons involved in the phenyl group which is bound to the methylene group; at 7.16 ppm for hydrogen of thiazole ring; at 7.19, 7.46-7.73 and 7.80 ppm for naphtol fragment. Finally, another signal at 7.06 ppm for both amino and hydroxyl groups was found. The ^{13}C NMR spectrum contains peaks at chemical shifts of 56.68 ppm for the carbon of the methylene bound to both

phenyl and amine groups. Other signals at 116.50, 135.42 and 168.02 ppm for carbons involved in the thiazole ring; at 127.80 and 129.90–132.90 ppm for phenyl group bound to methylene group; at 114.10, 119.70-127.02, 127.36, 128.50-129.68 and 137.70–153.70 ppm for naphtol fragment; 116.04, 127.10, 137.65 and 154.22 ppm for phenyl group bound to amine group were found. Finally, the presence of **4** was confirmed by the mass spectrum which showed a molecular ion at m/z 487.75.

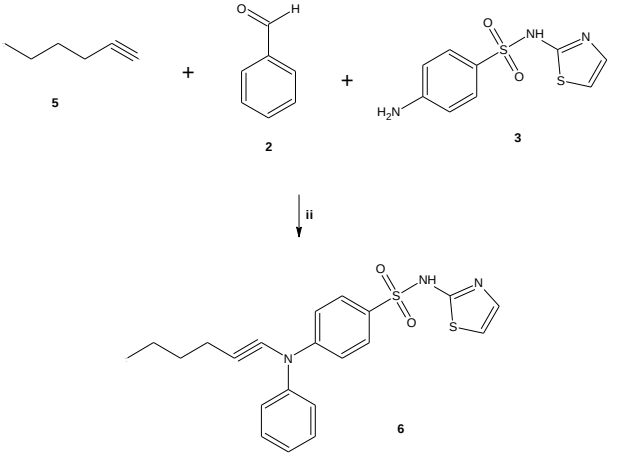

Fig. 2. Synthesis of 4(hex-1-ynyl-phenyl-amino)-*N*-thiazol-2-yl-benzenesulfonamide (**6**). Reaction between 1-hexyne (**5**), benzaldehyde (**2**) and sulfathiazole (**3**) to form **6** using cupric chloride as catalyst. i = ethanol/rt.

In a second stage the synthesis of 4(hex-1-ynyl-phenyl-amino)-*N*-thiazol-2-yl-benzenesulfonamide was achieved which has as chemical characteristic an alkyne group bound to amine group (Figure 2). It is important to mention that there are some reports which indicate the synthesis of several alkyne derivatives involving the use of a copper(I) reagent which has been found to be an efficient catalyst for an enantioselective one-pot three-component synthesis between aldehydes, amines and alkynes [14] . Other studies indicate that cupric chloride is a good catalyst for the synthesis of alkyne derivatives [15]. For this reason, in this study the compound **6** was obtained by the reaction of 1-hexyne, sulfathiazole and benzaldehyde using cupric chloride as a catalyst. The ^{1}H NMR spectrum of **6** shows signals at 0.91 ppm for methyl group; at 1.47–2.21 ppm for methylenes involved in alkyne fragment; at 6.60-7.20, 7.33 and 7.88 ppm for protons of phenyl groups; at 7.17 and 7.50 ppm for methylenes involved in thiazole ring; at 8.98 ppm for amine group. The ^{13}C NMR spectrum of **6** contains chemical shifts at 13.60 ppm for methyl group; 16.95-32.03 ppm for methylenes involved in the arm of alkyne fragment; at 61.08–75.02 ppm for alkyne group; at 113.10–116.26, 119.60–128.50, 138.80–147.02 and 156.34 ppm for phenyl groups; at 116.57, 135.32 and 166.98 ppm for thiazole ring. The presence of **6** was further confirmed by the mass spectrum which showed a molecular ion at m/z 411.15.

In conclusion, the synthesis of sulfonamide derivatives using a three-component system offers some advantages such as good yields, simple procedure, low cost, and ease of workup.

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КОНСТРУИРАНЕ И СИНТЕЗА НА ДВЕ ПРОИЗВОДНИ НА СУЛФОТИАЗОЛА В ТРИ-КОМПОНЕНТНА СИСТЕМА

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(Резюме)

Синтезирани са две сулфонамидни производни на сулфотиазола при използването на три-компонентна система. В първия етап е получено съединението 4-{[(2-хидрокси-нафтален-1-ил)-фенил-метил]-амино}-*N*-тиазол-2-ил-бензенсулфонамид (**4**) чрез реакция с β-нафтол, бензалдехид и сулфатиазол (**3**) в етанол. Вторият етап се постига чрез реакция на **3** с 1-хексин и бензалдехид, използвайки меден хлорид като катализаторза образуването на 4(хекс-1-инил-фенил-амино)-*N*-ъиазол-2-ил-бензенсулфонамид (**6**). Структурата на получените съединения е потвърдена от елементен анализ, ИЧ- и ЯМР-спектроскомия и спектрометрия. Предложеният метод предлага някои предимства, като добри добиви, проста процедура, ниски разходи и лесна обработка.