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Short communication

Rapid synthesis of sulfone derivatives as potential anti-infectious agents

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Dedicated to the memory of our late Benoît Célariès

Abstract

An original one-pot microwave reaction was developed for the synthesis of sulfone derivatives as new potent antimicrobial agents. This eco-friendly methodology conducted in 30 min led to desired products with good yields. The sulfones (**4a** and **4b**) were obtained via the reaction of **3a** with the corresponding halo-derivatives in the presence of sodium hydride.

All compounds were tested for their antibacterial and antifungal activities against four bacterial strains (two gram positive, and two gram negative ones) and two yeasts. The disk diffusion method has shown an interesting antibacterial activity for seven compounds (**3b–g** and **4b**) against *Staphylococcus aureus*. Among these seven compounds, five derivatives (**3b–e** and **3g**) showed activity against *Candida tropicalis*.

Keywords: Microwave; Sulfones; Anti-infectious

1. Introduction

Synthesized in 1908 by Fromm and Wittmann [1], dapsone, bis(4-aminophenyl)sulfone, is still the only representative member of its pharmacological class (except for acedapsone, an acetylated prodrug). Dapsone is a well-known anti-infectious agent with antimicrobial [2] and antiparasitic [3,4] activities and, as sulfonamides, inhibits the synthesis of folic acid due to structural similarity with *p*-aminobenzoic acid. It is also recognized as being effective against several of non-infectious and inflammatory diseases [5]. There are some pieces of evidence that anti-inflammatory action is not linked to the antibacterial action. In our knowledge, its pharmacomodulation has never been investigated.

The synthesis of sulfones from sulfonyl chlorides has found an extensive use in organic synthesis [6]. Mixed salts, such as sodium sulfite and sodium bicarbonate [7], or sodium sulfite and disodium hydrogen phosphate [8,9] are often used in the synthesis of sodium sulfinate derivatives. These sulfinates could then be easily *S*-alkylated. Heavy metals in various solvents: Sm/$HgCl_2$ in THF [10], Zn in water [11], In in water [12], activated Ni [13] were used to catalyze this alkylation reaction.

Thus, we report herein the synthesis of new sulfones and the evaluation of their antibacterial and antifungal activities.

2. Chemistry

Following the extensive development of the use of microwave irradiation in organic synthesis [14–22], a one-pot microwave assisted synthesis of new aryl-phenacyl sulfones (**3a–h**) is hereby presented. Among the different anti-infectious pharmacophores, nitroimidazoles' and nitrofuranes' activity is clearly dependent on the presence of the nitro group. In addition, it has been reported that replacement of the amino group in *p*-aminobenzoic acid analogues by a nitro

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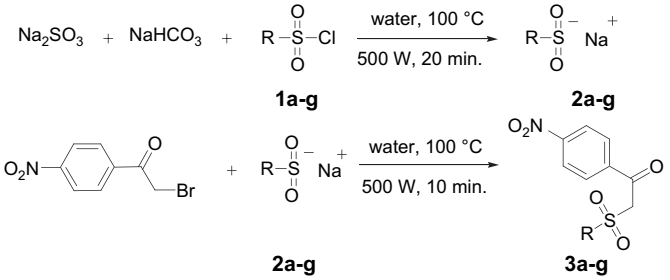
group does not affect bacteriostatic effect [23] contrary to most of other substitutions of the amino group. So, we designed to incorporate a nitro group in the sulfone structure, hoping to improve their biological activity.

Thus, a water solution of sodium sulfite, sodium bicarbonate and sulfonyl chlorides (**1a–g**) was irradiated in a microwave oven at 500 W for 20 min to give the corresponding sodium sulfinates (**2a–g**). An ethanolic solution of 2-bromo-4′-nitroacetophenone was then added and the resulting reaction mixture was stirred under irradiation for 10 min to give the corresponding sulfones (**3a–g**). Both reaction times and yields are depicted in Table 1. Also, for comparison purposes, we have done a parallel synthetic study of sulfones (**3a–g**) using a reported method by classical heating conditions (Table 1). Thus, an aqueous solution of sodium sulfite, sodium bicarbonate and sulfonyl chloride was heated with stirring at 70–80 °C for 2 h [7]. Then, an ethanolic solution of 2-bromo-4′-nitroacetophenone was added and stirred under reflux was continued for further 5–6 h to give **3a–g** (Scheme 1).



Scheme 1.

This study revealed that 30 min were needed for the completion of the reaction under microwave conditions, while the classical heating conditions required a reaction time between 5 and 6 h. However, comparable yields were reported with both operating conditions (Table 1).

Due to the presence of an active methylene group in the structure of the sulfones (**3a–g**), these derivatives may be used as useful intermediates for the synthesis of more complex structures. For example, when **3a** was treated with NaH followed by reaction with alkyl halides, such as chloromethylbenzene and 2-chloromethylimidazo[1,2-*a*]pyrazine, the products obtained were, respectively, **4a** and **4b** (Scheme 2). Other reactions leading to different heterocyclic compounds are in progress.

Two different alkyl halides were used. This simple and effective reaction proves the interest of sulfone derivatives as reagents for multi-step synthesis.

3. Antimicrobial activity

All the synthesized sulfones were evaluated for their antimicrobial activity against various strains of bacteria and fungi using disk diffusion method (Table 2) and microplate assay method (Table 3).

Except compound **4a**, all the other sulfones showed good activity against *Staphylococcus aureus* (Table 2). The best activity was obtained with compound **3c**. Five sulfones (**3b–e** and **3g**) were active against *Candida tropicalis*, **3b** being the most effective.

The results of the antimicrobial activity by the disk diffusion method showed an antibacterial activity for several products. Obviously, the antibacterial activity of the sulfones tested is more pronounced on gram positive than on gram negative bacteria. The most susceptible strain of bacteria was *S. aureus*, and the most susceptible yeast was *C. tropicalis*. No significant activity was noted against gram negative bacteria.

The diameters of growth inhibition area for the studied compounds were in the range 10–28 mm for *S. aureus* and 12–22 mm for *C. tropicalis.* Compound **2** showed no activity against any of the tested strains.

According to the results obtained by the disk diffusion method, the minimal inhibitory concentration (MIC) values of the active compounds were determined for the most sensitive organisms. The MIC values obtained confirm the existence of a significant activity against *S. aureus* and *C. tropicalis*. Among tested compounds, the most potent sulfones are the dinitro derivative (**3c**) and the chloronitro derivative (**3e**). They showed higher potency than dapsone.

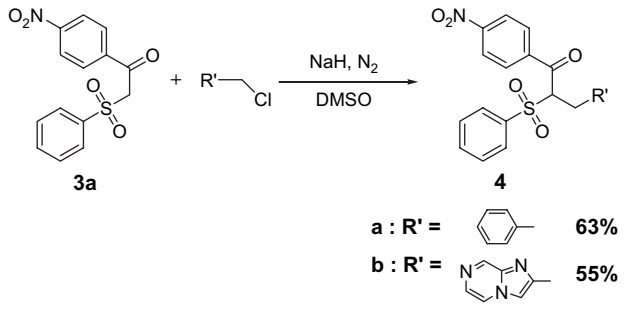
Microplate assay is limited by the water solubility of the compounds. Thus, it became difficult to determine the absorbance of solutions with concentration higher than 0.1 mg/mL. However, at 0.1 mg/mL concentration in disk diffusion method, growth inhibition was noted for six derivatives out of the seven sulfones tested.

4. Conclusion

In conclusion, microwave irradiation protocol allowed us to synthesize sulfones in aqueous solutions with good yields and in short time. These sulfones (**3a–g**) were tested for their

Table 1
Classical heating method versus one-pot microwave assisted synthesis of new aryl-phenacyl sulfones

Compound	R	Time (classical heating) hours	Yield (classical heating) %	Time (microwave) min	Yield (microwave) %
3a	C_6H_5–	5	92	30	90
3b	*p*-CH_3–C_6H_4–	5	73	30	69
3c	*p*-NO_2–C_6H_4–	5.5	63	30	55
3d	*p*-F–C_6H_4–	6	45	30	42
3e	*p*-Cl–C_6H_4–	5.5	53	30	51
3f	*p*-I–C_6H_4–	6	64	30	60
3g	1-Naphthyl-	6	50	30	44



Scheme 2.

antimicrobial activity and the results showed that two derivatives (**3c** and **3e**) possess a quantifiable activity.

A QSAR study, which may help us to find the most efficient structure, in order to improve activity or solubility is currently in progress.

5. Experimental protocols

5.1. Chemistry

Microwave assisted reactions were done in a multimode microwave oven ETHOS Synth Lab Station (Ethos start, Milestone Inc.). Melting points were determined with a B-540 Büchi melting point apparatus. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Brüker ARX 200 spectrometer in $CDCl_3$ at the service interuniversitaire de RMN de la Faculté de Pharmacie de Marseille. ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in parts per million with respect to $CDCl_3$ 7.26 ppm (^{1}H) and 77 ppm (^{13}C). Elemental analysis was carried out at the Centre de Microanalyses de la Faculté des Sciences et Techniques de Saint-Jérôme. The following adsorbent was used for flash column chromatography: silica gel 60 (Merck, particle size 0.063–0.200 mm, 70–230 mesh ASTM). TLC was performed on 5 cm × 10 cm aluminium plates coated with silica gel $60F_{254}$ (Merck) in appropriate solvent. Analysis indicated by the symbols of the elements was within ±0.4% of the theoretical values.

Table 3
Minimal inhibitory concentrations using the microdilution method

Compound	MIC (mg/mL)	
	Staphylococcus aureus	*Candida tropicalis*
3b	>0.1	>0.1
3c	*0.1*	*0.1*
3d	>0.1	>0.1
3e	*0.1*	*0.1*
3f	>0.1	>0.1
3g	>0.1	>0.1
4b	>0.1	>0.1
Dapsone	>0.1	>0.1
Streptomycin	0.025	–
Amphotericin	–	0.012

5.1.1. General procedure for the microwave assisted synthesis of sulfone derivatives *3a–g*

To a solution of sulfonyl chloride (6 mmol) in water (15 mL), sodium sulfite (1.26 g, 10 mmol) and sodium bicarbonate (0.840 g, 10 mmol) were added. The reaction mixture was heated under reflux in a microwave oven under irradiation at 500 W during 20 min. Then, an ethanolic solution of 2-bromo-4′-nitroacetophenone (0.500 g, 2.05 mmol) was added. Heating of the reaction mixture was continued for 10 min under the same conditions. After cooling, the reaction mixture was neutralized by adding diluted chlorhydric acid and the solid product obtained was filtered and crystallized from the appropriate solvent.

*5.1.1.1. 2-Benzenesulfonyl-1-(4-nitrophenyl)-ethanone **3a**.* Colorless crystals, m.p. 138 °C (ethanol) (Lit.: 136–138 °C [24]), ^{1}H NMR ($CDCl_3$), δ: 8.34 (d, $J = 8.9$ Hz, 2H), 8.15 (d, $J = 8.9$ Hz, 2H), 7.88 (d, $J = 7.2$ Hz, 2H), 7.64 (m, 3H), 4.77 (s, 2H). ^{13}C NMR ($CDCl_3$), δ: 64.0 (CH_2), 124.0 (2CH), 128.5 (2CH), 129.4 (2CH), 130.5 (2CH), 134.6 (CH), 138.4 (C), 140.0 (C), 186.8 (C=O), C–NO_2 not observed in these conditions. Anal. Calcd for $C_{14}H_{11}NO_5S$ (305.31): C, 55.08; H, 3.63; N, 4.59. Found: C, 55.25; H, 3.52; N, 4.22.

Table 2
Antibacterial activity by the disc diffusion method, mean of inhibition diameters (mm)

Compound	*E. coli*	*P. aeruginosa*	*S. aureus*	*E. hirae*	*C. albicans*	*C. tropicalis*
DMSO	–	–	–	–	–	–
3b	12	–	11	–	–	22
3c	–	–	28	–	–	12
3d	–	–	25	–	–	19
3e	–	–	24	–	–	19
3f	–	–	11	–	–	–
3g	–	–	10	–	–	12
4a	–	–	–	–	–	–
4b	–	–	16	–	–	–
Streptomycin	–	–	27	–	–	–
Penicillin	–	24	–	14	–	–
Chloramphenicol	34	–	–	–	–	–
Fluconazole	–	–	–	–	18	21

– = No growth inhibition.

*5.1.1.2. 1-(4-Nitrophenyl)-2-(toluene-4-sulfonyl)-ethanone **3b***. Pale yellow crystals, m.p. 147 °C (CH_2Cl_2/hexane) (Lit.: 146–147 °C [24]), ^{1}H NMR ($CDCl_3$), δ: 8.34 (d, $J = 9.0$ Hz, 2H), 8.15 (d, $J = 9.0$ Hz, 2H), 7.75 (d, $J = 7.9$ Hz, 2H), 7.37 (d, $J = 7.9$ Hz, 2H), 4.74 (s, 2H), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$), δ: 21.7 (CH_3), 64.2 (CH_2), 124.0 (2CH), 128.5 (2CH), 130.0 (2CH), 130.5 (2CH), 135.4 (C), 140.0 (C), 145.9 (C), 187.0 (C=O), C–NO_2 not observed in these conditions. Anal. Calcd for $C_{15}H_{13}NO_5S$ (319.33): C, 56.42; H, 4.10; N, 4.39. Found: C, 56.23; H, 4.06; N, 4.17.

*5.1.1.3. 2-(4-Nitrobenzenesulfonyl)-1-(4-nitrophenyl)-ethanone **3c***. Yellow crystals, m.p. 188 °C (ethanol) (Lit.: 190–192 °C [24]), ^{1}H NMR ($CDCl_3$), δ: 8.45 (d, $J = 9.0$ Hz, 2H), 8.38 (d, $J = 9.0$ Hz, 2H), 8.14 (m, 4H), 4.84 (s, 2H). ^{13}C NMR ($CDCl_3$), δ: 63.4 (CH_2), 124.2 (2CH), 124.5 (2CH), 130.3 (2CH), 130.4 (2CH), 139.5 (C), 143.6 (C), 186.5 (C=O), C–NO_2 not observed in these conditions. Anal. Calcd for $C_{14}H_{10}N_2O_7S$ (350.30): C, 48.00; H, 2.88; N, 8.00. Found: C, 48.21; H, 3.05; N, 8.09.

*5.1.1.4. 2-(4-Fluorobenzenesulfonyl)-1-(4-nitrophenyl)-ethanone **3d***. Colorless crystals, m.p. 139–140 °C (CH_2Cl_2/hexane, 3:7), ^{1}H NMR ($CDCl_3$), δ: 8.36 (d, $J = 9.0$ Hz, 2H), 8.16 (d, $J = 9.0$ Hz, 2H), 7.90 (dd, $J = 1.4$, 4.9 Hz, 2H), 7.26 (d, 2H), 4.77 (s, 2H). ^{13}C NMR ($CDCl_3$), δ: 63.9 (CH_2), 116.8 (d, $J = 23.0$ Hz, 2CH), 124.0 (2CH), 130.4 (2CH), 131.6 (d, $J = 9.9$ Hz, 2CH), 134.3 (d, $J = 3.3$ Hz, C), 139.8 (C), 151.0 (C), 166.3 (d, $J = 258.3$ Hz, C), 186.9 (C=O), C–NO_2 not observed in these conditions. Anal. Calcd for $C_{14}H_{10}FNO_5S$ (355.37): C, 52.01; H, 3.12; N, 4.33. Found: C, 52.11; H, 3.19; N, 4.29.

*5.1.1.5. 2-(4-Chlorobenzenesulfonyl)-1-(4-nitrophenyl)-ethanone **3e***. Yellow crystals, m.p. 150 °C (CH_2Cl_2/hexane) (Lit.: 156–157 °C [24]), ^{1}H NMR spectrum ($CDCl_3$), δ: 8.36 (d, $J = 9.0$ Hz, 2H), 8.16 (d, $J = 9.0$ Hz, 2H), 7.82 (d, $J = 8.9$ Hz, 2H), 7.56 (d, $J = 8.9$ Hz, 2H), 4.77 (s, 2H). ^{13}C NMR spectrum ($CDCl_3$), δ: 63.8 (CH_2), 124.1 (2CH), 129.8 (2CH), 130.1 (2CH), 130.5 (2CH), 136.7 (C), 139.8 (C), 141.6 (C), 151.0 (C–NO_2), 186.8 (C=O). Anal. Calcd for $C_{14}H_{10}ClNO_5S$ (339.75): C, 49.49; H, 2.97; N, 4.12. Found: C, 49.80; H, 3.12; N, 3.93.

*5.1.1.6. 2-(4-Iodobenzenesulfonyl)-1-(4-nitrophenyl)-ethanone **3f***. Yellow crystals, m.p. 209–210 °C (cyclohexane) (Lit.: 217 °C [24]), ^{1}H NMR (DMSO-d_6), δ: 8.31 (d, $J = 8.6$ Hz, 2H), 8.16 (d, $J = 8.6$ Hz, 2H), 8.02 (d, $J = 8.1$ Hz, 2H), 7.64 (d, $J = 8.1$ Hz, 2H), 5.50 (s, 2H). ^{13}C NMR (DMSO-d_6), δ: 62.7 (CH_2), 103.2 (C), 123.9 (2CH), 129.9 (2CH), 130.6 (2CH), 138.3 (2CH), 138.9 (C), 140.2 (C), 150.5 (C), 188.7 (C=O). Anal. Calcd for $C_{14}H_{10}INO_5S$ (431.20): C, 39.00; H, 2.34; N, 3.25. Found: C, 38.89; H, 2.10; N, 3.23.

*5.1.1.7. 2-(Naphthalene-1-sulfonyl)-1-(4-nitrophenyl)-ethanone **3g***. Buff crystals, m.p. 169–170 °C (CH_2Cl_2/hexane, 1:9), ^{1}H NMR ($CDCl_3$), δ: 8.76 (d, $J = 8.5$ Hz, 1H), 8.26 (d, $J = 8.9$ Hz, 2H), 8.19 (d, $J = 7.3$ Hz, 1H), 8.17 (d, $J = 8.2$ Hz, 1H), 8.05 (d, $J = 8.9$ Hz, 2H), 7.99 (m, 1H), 7.73 (m, 2H), 7.56 (t, $J = 7.7$ Hz, 1H), 4.94 (s, 2H). ^{13}C NMR ($CDCl_3$), δ: 63.4 (CH_2), 123.5 (CH), 123.9 (2CH), 124.3 (CH), 127.4 (CH), 128.7 (CH), 129.3 (C), 129.4 (CH), 130.3 (2CH), 131.4 (CH), 133.5 (C), 134.2 (C), 136.2 (CH), 140.1 (C), 186.8 (C=O). C–NO_2 not observed in these conditions. Anal. Calcd for $C_{18}H_{13}NO_5S$ (355.37): C, 60.84; H, 3.69; N, 3.94. Found: C, 60.46; H, 3.49; N, 4.10.

*5.1.2. General procedure for the preparation of **4a** and **b***

To a solution of 2-benzenesulfonyl-1-(4-nitrophenyl)-ethanone (0.500 g, 1.63 mmol) in DMSO (15 mL) under inert atmosphere, NaH (0.043 g, 1.8 mmol) was added. The reaction mixture was stirred for 1.5 h and then alkyl halide (1.8 mmol) in DMSO (2 mL) was added. After completion of the reaction (TLC), it was diluted with cold water and the solid precipitate was filtered and purified by flash column chromatography (eluent: toluene for **4a**, petroleum ether/acetone (6:4) for **4b**).

*5.1.2.1. 2-Benzenesulfonyl-1-(4-nitrophenyl)-3-phenyl-propan-1-one **4a***. Buff crystals, m.p. 171 °C (diethyl ether), ^{1}H NMR ($CDCl_3$), δ: 8.19 (d, $J = 9.0$ Hz, 2H), 7.84 (m, 4H), 7.73 (m, 1H), 7.60 (m, 3H), 7.14 (m, 3H), 7.05 (m, 1H), 5.28 (m, 1H), 3.39 (m, 2H). ^{13}C NMR ($CDCl_3$), δ: 34.2 (CH_2), 72.5 (CH), 123.8 (2CH), 127.4 (CH), 128.8 (2CH), 129.0 (2CH), 129.2 (2CH), 129.6 (2CH), 129.8 (2CH), 134.7 (CH), 135.3 (C), 136.1 (C), 141.6 (CH), 150.5 (C), 191.5 (C=O). Anal. Calcd for $C_{21}H_{17}NO_5S$ (395.43): C, 63.79; H, 4.33; N, 3.54. Found: C, 63.93; H, 4.38; N, 3.42.

*5.1.2.2. 2-Benzenesulfonyl-3-imidazo[1,2-a]pyrazin-2-yl-1-(4-nitrophenyl)-propan-1-one **4b***. Colorless crystals, m.p. 156–157 °C (butan-2-ol), ^{1}H NMR ($CDCl_3$), δ: 8.81 (s, 1H), 8.26 (d, $J = 9.0$ Hz, 2H), 8.12 (d, $J = 9.0$ Hz, 2H), 7.94 (dd, $J = 1.3$, 4.5 Hz, 1H), 7.82 (m, 3H), 7.65 (d, $J = 7.3$ Hz, 1H), 7.53 (m, 3H), 5.99 (m, 1H), 3.68 (m, 2H). ^{13}C NMR ($CDCl_3$), δ: 26.9 (CH_2), 69.2 (CH), 111.4 (CH), 118.5 (CH), 123.7 (2CH), 129.3 (2CH), 129.5 (2CH), 129.9 (CH), 130.1 (2CH), 134.7 (CH), 136.5 (C), 141.5 (C), 142.8 (CH), 143.4 (C), 191.1 (C=O). C–NO_2 not observed in these conditions. Anal. Calcd for $C_{21}H_{16}N_4O_5S$ (436.44): C, 57.79; H, 3.70; N, 12.84. Found: C, 57.96; H, 3.73; N, 12.37.

5.2. Antimicrobial activity

5.2.1. Microorganisms and media

Six reference strains were used in our study.

Escherichia coli ATCC 10536.
Pseudomonas aeruginosa ATCC 15442.
Staphylococcus aureus ATCC 6538.
Enterococcus hirae ATCC 10541.
Candida albicans ATCC 90029.
Candida tropicalis IP 2031.

The bacterial strains were grown on Trypticase soy agar (Becton Dickinson) at 37 °C for 24 h and the yeast on Sabouraud agar for 48 h. Inocula were prepared in TCE (tryptone 0.1%, NaCl 8%, wt/vol) by adjusting the turbidity at 623 nm to obtain $1-3 \times 10^5$ CFU/mL. The antibacterial and antifungal effects were tested by the disk diffusion method [25] and the MIC of the more active products was determined by using a microplate assay.

5.2.2. Disk diffusion method [25]

This method allows assessing the susceptibility of the microorganisms to eight compounds selected.

Petri dishes were prepared with a base layer of Müeller–Hinton agar medium (MHA, Becton Dickinson) and a top layer (2 mL) of 0.2% MHA medium inoculated with each bacteria suspension ($1-3 \times 10^5$ CFU/mL). After drying, 6 mm diameter disks (biodisks Mérieux) soaked with 10 μL of different compounds were placed on the agar. Disks containing streptomycin (10 μg), penicillin G (10 U/IE), chloramphenicol (30 μg) and fluconazole (20 μg) were used as positive controls and DMSO (10 μL) as negative control. All tests were performed in duplicate, and the antibacterial activity was expressed as the mean of inhibition diameters (mm) produced.

5.2.3. Minimal inhibitory concentration

Antimicrobial activity was determined by using a microplate assay [26]. Broth microdilution method was used to determine the MIC and was performed in sterile 96-well microplates. Each compound (10 mg/mL in DMSO) was transferred to each microplate well, in order to obtain a two-fold serial dilution in 100 μL of Müeller–Hinton broth. The inocula (100 μL) containing 6×10^5 CFU of each bacteria and yeast were added to each well. The final volume was 200 μL of medium Müeller–Hinton broth. A number of wells were reserved for sterility control, inoculum viability and DMSO effect. After incubation for 24 h or 48 h, growth was assayed by absorbance measurement at 623 nm. MIC was defined as the lowest concentration of compound allowing no visible growth.

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