Synthesis of novel sulfonamide derivatives containing phthalimide moiety

Rayenne Redjemia, Meriem Boussaker, Rania Bahadi & Malika Berredjem*

Laboratory of Applied Organic Chemistry, Synthesis of Biomolecules and Molecular Modeling Group, Badji Mokhtar University, P.O. Box 12, Annaba 23000, Algeria.

Article Info

Article history:

Received: 29/07/2022
Revised: 2/08/2022
Accepted: 4/08/2022

Keywords:

Sulfonamides, phthalimide, sulfanilamide, ultrasound irradiations.

ABSTRACT

An efficient and eco-friendly green methodology is developed for the synthesis of novel sulfonamide derivatives from sulfanilamide and phthalic anhydride in ethanol as a solvent, using ultrasound irradiations. Higher yield, shorter reaction time, green conditions and optimization with the design of experiment are the major advantages of this method. The structures of the synthesized compounds were carefully characterized by ^{1}H, ^{13}C NMR as well as IR.

Corresponding Author:
Malika Berredjem,
Departement of Chemistry, Badji Mokhtar University, P.O. Box 12, Annaba 23000, Algeria.
Email: mberredjem@yahoo.fr ; malika.berredjem@univ-annaba.org

1. INTRODUCTION

The discovery of antibiotics was a real revolution in the field of infectious pathologies. Antibiotic therapy has saved a very large number of lives and it was believed that infectious diseases would be brought under control, sometimes described as miraculous treatments. Antibiotic resistance is a growing problem that threatens human health globally [1,2], it is not the human body that becomes resistant to the antibiotic but the bacteria themselves by becoming less sensitive to the drugs or not at all. This has prompted researchers to develop new antibiotics from different families such as penicillins, fluoroquinolones, glycopeptides and sulfonamides [3,4]. In recent years, the fight against several diseases requires the use of some sulfonamide derivatives that represent a class of compound having interesting pharmacological activities. Over 30 drugs containing this functionality used in clinical, including carbonic anhydrase inhibitors [5,6], antitumor [7], glycogen phosphorylase inhibitory [8], VIH protease [9, 10], antifungal [11], antiinflammatory [12], nonpeptidic vasopressin receptor antagonists [13], translation initiation inhibitors [14] and in Alzheimer's disease [15].

Sulfanilamide is the simplest representative in the group of sulfonamide drugs [16]. It is a low priced drug having chemotherapeutic properties popular in developing countries with serious bacterial resistance problem [17,18]. It functions by competing with para aminobenzoic acid (PABA) in folic acid biosynthesis, hence suppressing the key growth metabolic factor essential for bacterial growth [19]. On the other hand, phthalimide analogues are also of great interest in organic synthesis and medicinal chemistry due to their bioavailability [20].

De Castro Barbosa *et al.* [21] performed the synthesis and pharmacological evaluation of a new series of phenylsulfonamide derivatives based on a structural modification of the anti-inflammatory prototype 2–(4–(thiomorpholinosulfonyl)phenyl)isoindoline–1,3–dione. The obtained results show that the compound tetrafluorophthalimide **1** is distinguished by an in vitro anti-TNF-alpha effect similar to the analogous compound thalidomide. Machado *et al.* [22] synthesized a new phthalimide derivative containing the sulfonamide group **2**, **3** with a structure related to thalidomide. These compounds are able to inhibit the production of TNF-alpha.

Figure 1**:** Structures of bioactive compounds containing phthalimide and sulfonamide moieties.

In this particular context and in our continued research to develop novel, rapid and green approaches in the design of efficient synthetic methods using ultrasound irradiation as source of energy, here we describe the synthesis of two novel sulfonamides derivatives.

2. EXPERIMENTAL

2.1. Materials

The chemicals used in this work were obtained from Fluka and Merck Chemical Company and were used without purification. Ultrasound assisted reactions were carried out using a FUNGILAB ultrasonic bath with a frequency of 40 kHz and a nominal power of 250 W. The reactions were carried out in an open glass tube (diameter: 25 mm; thickness: 1 mm; volume: 20 cm^3) at room temperature. All reactions were monitored by thin layer chromatography (TLC) on silica Merck 60 F254 percolated aluminum plates and were developed by spraying with ninhydrin solution (1% in EtOH). Column chromatography was performed with Merck silica gel (230–400 mesh). Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. IR spectra were recorded as KBr pellets on a Perkin Elmer 781 spectrophotometer.

Proton nuclear magnetic resonance (1H NMR) spectra were recorded on a Bruker spectrometer at 250, 400 MHz. Chemical shifts is reported in δ units (ppm) with TMS as reference (0.00 ppm). All coupling constants (J) are reported in Hertz. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Carbon nuclear magnetic resonance (13C NMR) spectra were recorded on a Bruker at 62, 100 MHz. Chemical shifts are reported in δ units (ppm) relative to $CDCl_3$ (77.0 ppm).

2.2. Typical procedure for the preparation of sulfonamide

In a glass tube (diameter: 25 mm; thickness: 1 mm; volume: 20 mL) a mixture of sulfanilamide (1 mmol) and phthalic anhydride (1 mmol) was taken at room temperature in the presence of 2 ml of ethanol. The reaction mixture was then sonicated by an ultrasonic bath at a frequency of 40 kHz during a time between 30 and 60 min. After completion of the reaction, as monitored by TLC the mixture was purified by column chromatography over silica gel using a dichloromethane as an eluent.

3. RESULTS AND DISCUSSION

3.1. Synthesis

The development of new clean and efficient processes for the preparation of new compounds is currently an important research area in organic chemistry. Thus in recent year, the application of ultrasound has gained a very important boost in organic synthesis [23-27]. Sonochemistry offers a more flexible and easier route for a wide variety of synthesis compared to conventional methods; it can also improve yields and reduce the time of reactions.

In this work, we synthesised tow derivatives of sulfonamide by condensation of sulfanilamide with phthalic anhydride under green and soft conditions by using ultrasonic irradiations as source of activation. Compound 3 is obtained with a yield of 55%, on the other hand compound 4 is formed with 35% (Schemes 1 and 2).

Scheme 1**:** Synthesis of new sulfonamide derivatives from sulfanilamide and phthalic anhydride.

Scheme 2**.** Mechanistic proposal for synthesis of new sulfonamide derivatives from sulfanilamide and phthalic anhydride

Table 1. Characteristics of sulfamides **3** and **4**

Entry	**Product**	**Yield (%)**	**m.p. (°C)**	**Time (min)**	**Rf CH_2Cl_2/MeOH: 9/1**
3		55	238-240	30	0.10
4		35	252-254	30	0.30

3.2. Structural Study

The obtained product **3** is characterized by the appearance of a singlet at 3.25 ppm corresponding to the 2 protons of nitrogen group. All the protons of the two aromatic rings resonate in the form of a multiplet between 7.5 and 8 ppm. The singlet at 10.6 ppm corresponds to the proton of OH group. In ^{13}C NMR, the structure is confirmed by the appearance of 8 carbons between 120 and 145 ppm of the two aromatic rings, the two carbonyl groups appeared at165 and 168 ppm. On the other hand, the IR analysis shows a characteristic band at 3375 cm^{-1} corresponding to the OH group of the acid function. Two bands characteristic of the two carbonyl groups at 1637 and 1714 cm^{-1}. The SO_2 group is confirmed by two bands respectively at 1148 and 1311 cm^{-1}.

For compound **4**, in ^{1}H NMR, the structure is confirmed by the appearance of a singlet at 2 ppm corresponding to the two protons of the nitrogen group. The protons of the aromatic cycles resonate in the form of a multiplet between 7.7 and 8.3 ppm. In ^{13}C NMR, the structure is confirmed by a peak at 167 ppm of the two carbonyls. All the carbons of the two aromatic rings appeared between 120 and 140 ppm.
In infrared (IR), the formation of N-sulfonylphthalimide **4** is characterized by the disappearance of the band of the OH group. We notice 3 characteristic bands at 3262, 1721, 1705 cm^{-1} corresponding respectively to the NH_2 and two carbonyls.

CONCLUSION

This research study reports the synthesis and characterization of new sulfonamide derivatives **3** and **4**. These derivatives are efficiently synthesized in one-step from sulfanilamide and phthalic anhydride using an immersion ultrasonic assisted method.

Acknowledgements

This work was conducted at the Applied Organic Chemistry Laboratory (UBM Annaba) and was financially supported by The General Directorate for Scientific Research and Technological Development (DG-RSDT) of Algerian Ministry of Scientific Research (MESRS) through the FNR 2000 Program.

REFERENCES

[1] Costa V.M.D, King C.E., Kalan L., Morar M., Sung W.W., Schwarz C., Froese D., Zazula G., Calmels F., Debruyne R., Golding G.B., Poinar H.N., Wright G.D., 2011. Antibiotic resistance is ancient, *Nature*, Vol. 7365, 457- 61.

[2] Andersson D., Hughes D., 2011. Persistence of antibiotic resistance in bacterial populations, *FEMS Microbiology Reviews*, Vol. 35, 901-11.

[3] Perlovich G.L., Strakhova N.N., Kazachenko V.P., Volkova T.V., Tkachev V.V., Schaper K.J., Raevsky O.A., 2008. Sulfonamides as a subject to study molecular interactions in crystals and solutions: Sublimation, solubility, solvation, distribution and crystal structure, *Int. J. Pharm*., Vol. 349, 300–13.

[4] Garnero C., Aiassa V., Longhi M., 2012. Sulfamethoxazole: hydroxypropyl-β-cyclodextrin complex: preparation and characterization, *J. Pharm. Biomed.*, Vol. 63, 74–79.

[5] Gavernet L., Gonzalez Funes J.L., Palestro P.H., Bruno Blanch L.E., Estiu G.L., Maresca A., Barrios I., Supuran C.T., 2013. Inhibition pattern of sulfamide-related compounds in binding to carbonic anhydrase isoforms I, II, VII, XII and XIV, *Bioorg. Med. Chem*., Vol. 21, 1410-18.

[6] Winum J-Y., Innocenti A., Nasr J., Montéro J-L., Scozzafava A., Vullo D., Supuran C-T., 2005. Carbonic anhydrase inhibitors: synthesis and inhibition of cytosolic/tumor-associated carbonic anhydrase isozymes I, II, IX, and XII with N-hydroxysulfamides – A new Zn-binding function in the design of inhibitors, *Bioorg. Med. Chem. Lett.*, Vol. 15, 2353-58.

[7] Crespo R., De Bravo M.G., Colinas P.A., Bravo R.D., 2010. In vitro antitumor activity of N-glycosyl sulfonamides, *Bioorg. Med. Chem., Lett.*, Vol. 20, 6469-74.

[8] Tite T., Tomas L., Docsa T., Gergely P., Kovensky J., Gueyrand D., Wadouachi A., 2012. *Synthesis of N-aryl spiro-sulfamides as potential glycogen phosphorylase inhibitors, Tetrahedron. Lett.*, Vol. 53, 959-61.

[9] Markgrem P-O., Schaal W., Hamalainem M., Karlen A., Hallberg A., Samuelsson B., Danielson U-H., 2002. Relationships between structure and interaction kinetics for HIV-1 protease inhibitors, *J. Med. Chem*., Vol. 2, 5430-39.

[10] Stranix B.R., Sauvé G., Bouzide A., Coté A., Sévigny J.Y., Perron V., 2004. Lysine sulfonamides as novel HIV-protease inhibitors: Nε-disubstituted ureas, *Bioorg. Med. Chem. Lett.*, Vol. 14, 3971-3974.

[11] Stokes S.S., Albert R., Buurman Ed.T., Andrews B., Shapiro A.B., Green O.M., Mckenzie A.R., Otterbein L.R., 2012. Inhibitors of the acetyltransferase domain of N-acetylglucosamine-1-phosphate-uridylyltransferase/glucosamine-1-phosphate-acetyltransferase (GlmU). Part 2: Optimization of physical properties leading to antibacterial aryl sulfonamides, *Bioorg. Med. Chem. Lett*., Vol. 22, 7019-23.

[12] Rahavi Ezabadi I., Camoutsis C., Zoumpoulakis P., Geronikaki A., Soković M., Glamočilija J., Čirič A., 2008. Sulfonamide-1,2,4-triazole derivatives as antifungal and antibacterial agents: Synthesis, biological evaluation, *lipophilicity, and conformational studies, Bioorg. & Med. Chem.*, Vol. 16, 1150-61.

[13] Serradeil-Le Gal C., 2001. An overview of SR121463, *a selective non-peptide vasopressin V2 receptor antagonist. Cardiovascular Drug Rev*., Vol. 19, 201–14.

[14] Kennedy J.F., Thorley M., *Pharmaceutical Substances, 3rd ed*., Kleeman A., Engel J., Kutscher B., Reichert D., (Eds.), Thieme: Stuttgart; 1999.

[15] Vullo D., De Luca V., Scozzafava A., Carginale V., Rossi M., Supuran C.T., Capasso C., 2013. The extremo-α-carbonic anhydrase from the thermophilic bacterium Sulfurihydrogenibium azorense is highly inhibited by sulfonamides, *Bioorg. Med. Chem.*, Vol. 21, 4521-25.

[16] Remko M., von der Lieth C.W., 2004. Theoretical study of gas-phase acidity, pKa, lipophilicity, and solubility of some biologically active sulfonamides, Bioorg. *Med. Chem*., Vol. 12, 5395–403

[17] Maskell J.P., M.Sefton A., Hall L.M., 1997. Mechanism of sulfonamide resistance in clinical isolates of Streptococcus pneumonia, *Antimicrob Agents Chemother*., Vol. 41, 2121-26.

[18] Topacli C., Topacli A., 2003. Facile synthesis, single crystal analysis, and computational studies of sulfanilamide derivatives, *J. Mol. Struct*., Vol. 644, 145-158.

[19] Kremer E.K., Facchin G., Estevez E., Albores P., Baran E.J., Ellena J., Torre M.H., 2006. Copper complexes with heterocyclic sulfonamides: Synthesis, *spectroscopic characterization, microbiological and SOD-like activities: Crystal structure of [Cu(sulfisoxazole)2(*$H_2O)_4$*] · 2*H_2O*, J. Inorg. Biochem*, Vol. 100, 1167-75.

[20] Kok S.H.L., Gambari R., Chui C.H., Yuen M.C.W., Lin E., Wong R.S.M., 2008. Synthesis and anti-cancer activity of benzothiazole containing phthalimide on human carcinoma cell lines, *Bioorg Med Chem*., Vol. 16, 3626-31.

[21] De Castro Barbosa M.L., Ramos T.J.F., De Arantes A.C.S., Martins M.A., Silva P.M.R. Barreiro E.J., Lima L.M., 2012. Synthesis and pharmacological evaluation of novel phenyl sulfonamide derivatives designed as modulators of pulmonary inflammatory response, *Molecules.*, Vol. 17, 14651-72.

[22]. Machado A.L., Lima L.M., Araújo-Jr J.X., Fraga C.A.M., Koatz V.L.G., Barreiro E.J., 2005. Design, synthesis and antiinflammatory activity of novel phthalimide derivatives, *structurally related to thalidomide, Bioorg. Med*. Chem. Lett., Vol. 15, 1169–72.

[23] Bouasla R., Bechlem K., Belhani B., Grib Ismahene., Aouf N.E., Berredjem M., 2017. A Novel and Green Method for N-acylation of Amines and Sulfonamides under Ultrasound Irradiation, *Oriental Journal of Chemistry*, Vol. 33, 1454–60.

[24] Grib I., Belhani B., Bechlem K., Bouasla R., Aouf N.E., Berredjem M., 2017. Ultrasonic assisted green protocol for the synthesis of sulfamides, Phosphorus, Sulfur, *and Silicon and the Related Elements*, Vol. 192, 827-30.

[25] Bouchareb F., Berredjem M., Bouzina A., Guerfi M., 2020. Ultrasound-promoted, rapid and green synthesis of phosphonamide derivatives under catalyst and solvent-free conditions, *Phosphorus Sulfur Silicon Relat. Elem*., Vol. 196, 422-30.

[26] Guerfi M., Berredjem M., Bouzina A., Ben Hadda T., Marminon C., Otmane Rachedi K., 2020. Novel - sulfamidophosphonate analogues of fotemustine: efficient synthesis using ultrasound under solvent-free conditions, *Monatsh. Chem*., Vol. 15, 1859-65.

[27] Bahadi R., Boughoula R., Berredjem M., Bachari K., Bouzina A., Bouacida S., Sbartai H., Benalliouche F., Redjemia R., 2022. A convenient synthesis, biological activity and X-ray crystallography of novel α-aminophosphonate derivatives, *Phosphorus Sulfur Silicon Relat. Elem*., Vol. 197 In Press, Available online 20 May 2022.
DOI: 10.1080/10426507.2022. 2064859.