COMMUNICATION

A C G publications

Org. Commun. 17:2 (2024) 128-132

organic communications

Eco-friendly synthesis of new thiophene-based Schiff bases containing piperidine rings

Sertan Aytaç [1,2*] and Özlem Gündoğdu Aytaç [1,2]

[1]*Department of Food Processing, Kaman Vocational School, Kırşehir Ahi Evran University, Kırşehir, Türkiye*
[2]*Department of Chemistry, Faculty of Science, Atatürk University, 25050, Erzurum, Türkiye*

(Received June 07, 2024; Revised June 26, 2024; Accepted June 27, 2024)

Abstract: It is known that compounds containing sulfur in their structure have a wide range of biological activities, such as antibacterial, antiallergic, antimicrobial, anticancer, and anticonvulsant. In addition, nitrogen-containing heterocyclic compounds are also found in nature and the structure of drugs. Various compounds, such as piperidine and its derivatives, are also widely used in the synthesis of many drugs. Various Schiff bases have been synthesized in drug development studies, and they have been used in clinical applications as drugs and drug candidates. In this context, the synthesis of new thiophene-based Schiff bases containing piperidine rings is aimed. Green chemistry objectives were adhered to in the syntheses. Thiophene-2-carbaldehyde and piperidine derivatives were used as starting compounds, and new compounds containing thiophene-based piperidine were synthesized without adding any catalyst or solvent to the reaction medium. The desired Schiff base compounds were successfully synthesized in high yield and in a short time.

Keywords: Schiff base; thiophene; piperidine; biological activity; microwave; green chemistry.

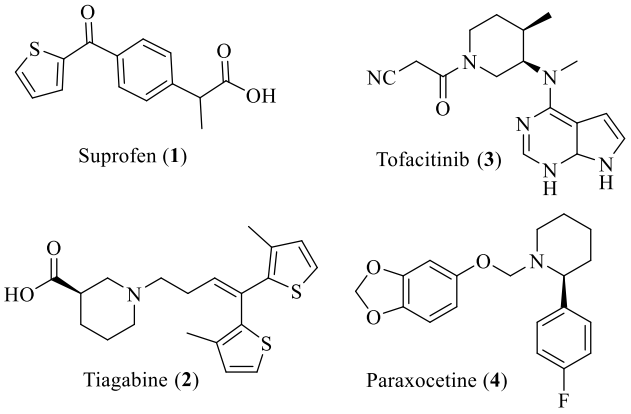
1. Introduction

Since sulfur-containing compounds are known to have antibacterial, antiallergic and chemotherapeutic effects, studies on the synthesis of such compounds and their complexes are quite common.[1] Various thiophene compounds have been designed as drugs and drug candidates.[2] Compounds containing the thiophene group as a pharmacophore in their structure have many biological properties such as antiasthmatic, diuretic, anticancer, antibacterial, anti-HIV and anticonvulsant.[3,4] Examples of such compounds used as drugs are suprofen (**1**), which has an anti-inflammatory effect, and tiagabine (**2**), which has an anticonvulsant effect.[5] (Scheme 1). Heterocyclic compounds containing nitrogen in their structure are found in nature and in medicines.[6] Most of them have biological properties such as anticancer, antimicrobial, analgesic and anti-inflammatory in the human body.[7]

Piperidine and its derivatives, one of the nitrogen-containing heterocyclic compounds, are widely used in the synthesis of many vital drugs.[8] The piperidine ring is a significant pharmacophore group that is commonly employed in drug research. Many compounds with this ring system in their structure have been shown to have depressive, anxiolytic, anticonvulsant, and antinociceptive effects.[9] Tofacitinib (**3**), used in autoimmune system diseases, and paroxetine (**4**), used in psychological diseases, are examples of drugs that contain piperidine in their structure and are used in clinics.[9,10] (Scheme 1).

* Corresponding author: E-Mail: saytac@ahievran.edu.tr

The article was published by ACG Publications
http://www.acgpubs.org/journal/organic-communications © April-June 2024 EISSN:1307-6175
DOI: http://doi.org/10.25135/acg.oc.170.24.06.3246
Available online: June 29, 2024



Scheme 1. Thiophene and piperidine containing some drugs

New drugs and new synthesis methods are needed to reduce or eliminate the effects on living metabolism of viruses and bacteria that have become resistant to various drug groups such as antibiotics and antivirals.[11] Recently, various Schiff bases containing N, O, S and P atoms in their structure have been synthesized and used in biological applications.[12] It is known in the pharmaceutical industry that Schiff bases have wide biological activity due to the imine group in their structure.[13-15] The synthesis of thiophene-based Schiff bases has become popular recently due to their biological importance.[16]

2. Background

There are various synthetic methods for Schiff bases preparation, the development of environmentally friendly (green chemistry) and high-yield approaches is still a desirable goal.[17] In Schiff base syntheses, the application of microwave irradiation in addition to classical methods eliminates the use of solvents and equipment such as the Dean-Stark apparatus and causes less harm to the environment than other synthesis approaches.[18,19]

It is seen from the literature that compounds containing sulfur and nitrogen atoms in their structure have important pharmacological effects.[20,21] In this context, the aim was to synthesize new thiophene-based Schiff base compounds containing piperidine derivatives in their structure, which are thought to have biological activity potential. While fast, highly efficient and environmentally friendly approaches in chemical syntheses have recently gained importance[19], the syntheses performed in this study adhered to the goals of green chemistry. The microwave method applied in the synthesis of Schiff bases is a more efficient method than the traditional synthesis method as it provides more effective and homogeneous heating.[22] Reactions that sometimes take days with traditional heating methods can occur in a much shorter time using microwave irradiation.[23] Based on this, another aim of the study is the synthesis of target molecules in a short time and with high efficiency.

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2. Experimental

2.1. Chemical Material and Apparatus

All chemicals used in the study were purchased from Sigma-Aldrich. Reactions were monitored by thin-layer chromatography (TLC). Reactions were carried out with a microwave oven (230 V-50 Hz, 900 W). ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz with a Varian brand NMR spectrometer using $CDCl_3$. Elemental analysis results were also recorded on the Leco CHNS932 device.

*2.2. General Synthesis of Schiff bases **9-11***

The compounds **9-11** synthesized within the scope of the study are given in Scheme 2. In the study. Thiophene-2-carbaldehyde (**5**) (1 mmol, 1 eq) and different piperidine compounds (**6-8**) (1 mmol, 1 eq) were directly exposed to microwave irradiation at 900 W under solvent- and catalyst-free

conditions in a 5 mL reaction vessel. The progress of the reaction was monitored by TLC. It was observed that the reactions were completed within 3-5 minutes.[18] After completion of the reaction, crude products were extracted with ethyl acetate (2x10 mL). The organic phase was dried with anhydrous Na_2SO_4. Solvent was evaporated under reduce pressure. Characterization of newly synthesized molecules were performed by spectroscopic methods and elemental analysis. Spectral data of the compounds showed that compounds (**9-11**) formed as single compounds.

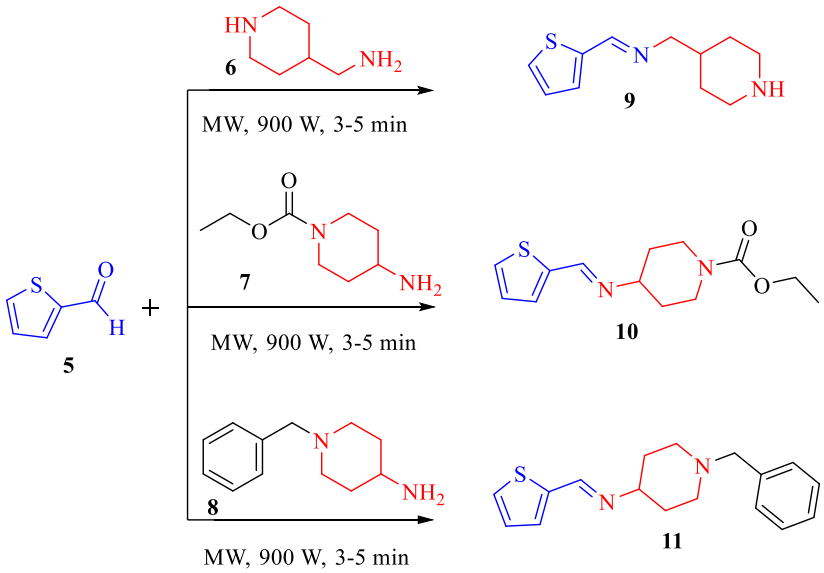

Figure 2. Synthesis of Schiff bases **9-11**

3. Present Study

In the classical heating method applied in the synthesis reactions provides the needed heat from the reaction vessel. However, it causes the temperature of the reaction environment to be relatively lower and sometimes insufficient too.[18] In the literature, new chemical syntheses resulting from the properties of microwave energy have also been carried out in line with the green chemistry goals, which is another aim of this study. In this study, which was carried out by considering past literature studies and synthesis plans, thiophene-2-carbaldehyde (**5**) and different piperidine (**6-8**) were used as starting compounds and new thiophene-based piperidine-containing compounds (**9-11**) were synthesized without adding any catalyst or solvent to the reaction medium. According to the analysis results, it was determined that there was a single compound in each reaction, and the corresponding Schiff base compounds were obtained without any purification process. The desired Schiff base compounds were successfully synthesized in high yield and in a short time.

N-(piperidin-4-ylmethyl)-1-(thiophen-2-yl)methanimine (***9***): 96% yields, brown oily, R_f : 0.77 (20% EtOAc: P. Ether) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.37-7.31 (m, 1H), 7.29-7.22 (m, 1H), 7.05-6.99 (m, 1H), 3.40 (d, *J* = 6.5 Hz, 2H), 3.04 (d, *J* = 11.1 Hz, 2H), 2.56 (t, *J* = 12.1 Hz, 2H), 2.42 (s, 1H), 1.84-1.73 (m, 1H), 1.67 (d, *J* = 13.0 Hz, 2H), 1.14 (dd, *J* = 22.5, 10.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.63, 142.66, 130.43, 128.85, 127.53, 68.08, 46.59, 37.64, 31.74. Elemental analysis Calcd. for $C_{11}H_{16}N_2S$; C, 63.42; H, 7.74; N, 13.45; S, 15.39 Found C, 63.48; H, 7.69; N, 13.48; S, 15.35.

Ethyl-4-((thiophen-2-ylmethylene)amino)piperidine-1-carboxylate (***10***): 98 % yields, ligth brown oily, R_f: 0.28 (20% EtOAc: P. Ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.36 (d, *J* = 5.0 Hz, 1H), 7.27 (t, *J* = 3.7 Hz, 1H), 7.03 (ddd, *J* = 5.1, 2.6, 1.2 Hz, 1H), 4.11 (dt, *J* = 8.5, 6.4 Hz, 4H), 3.42-3.25 (m, 1H), 2.99 (s, 2H), 1.70 (dd, *J* = 12.2, 8.1 Hz, 4H), 1.31-1.15 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.83, 153.03, 142.66, 130.74, 129.12, 127.56, 66.95, 61.47, 42.41, 33.27, 14.97. Elemental analysis

Calcd. for $C_{13}H_{18}N_2O_2S$; C, 58.62; H, 6.81; N, 10.52; S, 12.04 Found C, 58.66; H, 6.85; N, 10.47; S, 12.07.

N-(1-benzylpiperidin-4-yl)-1-(thiophene-2-yl)methanimine ***(11)***: 97 % yields, brown, oily, R_f : 0.12 (40% EtOAc: P.Ether) NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.42-7.24 (m, 7H), 7.06 (dd, *J* = 4.9, 3.7 Hz, 1H), 3.55 (s, 2H), 3.22 (ddd, *J* = 14.6, 10.1, 4.3 Hz, 1H), 3.01 – 2.89 (m, 2H), 2.14 (td, *J* = 11.5, 2.2 Hz, 2H), 1.98-1.83 (m, 2H), 1.74 (d, *J* = 11.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.56, 143.01, 138.92, 130.40, 129.30, 128.85, 128.43, 127.52, 127.17, 67.50, 63.34, 52.39, 33.63. Elemental analysis Calcd. for $C_{17}H_{20}N_2S$; C, 71.79; H, 7.09; N, 9.85; S, 11.27 Found C, 71.74; H, 7.13; N, 9.80; S, 11.24.

Conflicts Of Interest

No conflict of interest was declared by the authors.

Acknowledgements

We would like to thank Atatürk University Chemistry Department for providing us with laboratory and technical facilities for the studies; We would also like to thank Kırşehir Ahi Evran University for providing us the opportunity to work. We would like to thank Prof. Dr. Yunus KARA for his valuable support during the studies.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

ORCID
Sertan Aytaç: 0000-0002-3196-4545
Özlem Gündoğdu Aytaç: 0000-0002-6943-9674

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