International Journal of Sciences: Basic and Applied Research (IJSBAR)

ISSN 2307-4531
(Print & Online)

http://gssrr.org/index.php?journal=JournalOfBasicAndApplied

Synthesis of 5-chloro-thiosulfadiazine Compounds Using Two-Phase Systems of Organic Solvents

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Abstract

We report a direct and simple protocol for the synthesis of 5-chloro-thiosulfadiazine compounds. This reaction has been achieved using two-phase systems of organic solvents (NaOAc/ H_2O and Na_2CO_3/ H_2O. The use of NaOAc or Na_2CO_3 for the preparation of chloro compounds provided all the advantages of cost, safety, and environmental concerns; thus, this method will give broad utility to the organic/medicinal chemist that is pursuing the synthesis of sulfonamides derivatives.

Keywords: Sulfadiazine; Thiophene ; Na_2CO_3; NaOAc; H_2O.

1. Introduction

Since the discovery of sulfonamides in 1935, extensive studies have been made, and a huge number of structurally sulfonamide derivatives have been reported [1]. Sulfonamides are still one of the most attractive drugs in medicinal chemistry because of their wide availability [2]. The importance of these drugs in medicinal chemistry, such as sulfadiazine, is well known as antibacterial, antifungal, anti-inflammatory, and anticancer agents [3-8]. Recently, thiophene has been considered as one of the most interesting rings in synthetic chemistry. It is a class of heterocyclic compounds that is readily available, stable, and easily functionalized [9]. Moreover, it is found to play a vital role in drug design and exhibits a broad spectrum of biological activities such as antibacterial, antifungal, anti-inflammatory and anticancer [10-13].

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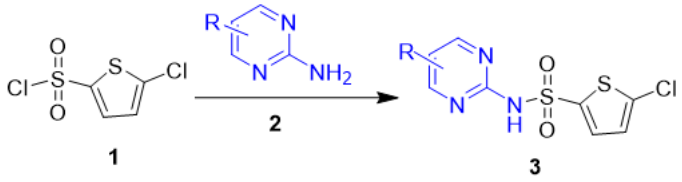
Although several replacements of sulfonamides have been made utilizing five and six-membered rings, no such modification has been done with thiophenes. Thus, in this work, we report a simple and efficient method for the synthesis of 5-chloro-thiosulfadiazine compounds (scheme1).



scheme1: This work to synthesize the primary chloro of thiosulfadiazine compounds

2. Experimental

All compounds and other reagents were purchased from Sigma Aldrich and Oakwood Chemicals and were used without further purification. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bucker Avance 400 MHz NMR spectrometer. The mass spectra were obtained using the atmospheric solid analysis probe method as an ionization source.

2.1. Synthesis of 5-chloro-thio sulfadiazine compounds using NaOAc

To a round bottom flask, sodium acetate (7.3 mmol, 0.6 g) was dissolved in water (4 ml). Then, substituted 2-amino pyrimidine (3.7 mmol) and 5-chloro-thiophene-2-sulfonylchloride (3.7 mmol) were added. The reaction mixture was heated and stirred at 85 $^{\circ}$C . After completion of reaction, the mixture was filtered and washed with 5% HCl. The crude was recrystallized with ethanol.

2.1.1. 5-chloro-N-(pyrimidin-2-yl)thiophene-2-sulfonamide (3a)

It was obtained as an orange solid in 87 % yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.10 (1H, t, *J* = 4.9 Hz), 7.21 (1H, d, *J* = 4.0 Hz), 7.65 (1H, d, *J* = 4.1 Hz), 8.63 (2H, s). ^{13}C NMR (400 MHz, DMSO)δ 110.43, 125.54, 126.58, 128.56, 150.36, 158.01, 158.87. HRMS (ASAP-MS) m/z: calcd for $C_8H_6ClN_3O_2S_2$ $[M+H]^+$, 275.9662; found, 275.9617.

2.1.2. 5-chloro-N-(4,6-dimethylpyrimidin-2-yl) thiophene-2-sulfonamide (3b)

It was obtained as a yellow solid in 79 % yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 2.16 (6H, s), 6.33(1H, s), 6.93 (1H, d, *J* = 3.8 Hz), 6.96 (1H, d, *J* = 3.8 Hz). ^{13}C NMR (400 MHz, DMSO) δ 23.78, 109.15, 125.46, 126.56, 128.49, 150.53, 163.79, 167.23. HRMS (ASAP-MS) m/z: calcd for $C_{10}H_{10}ClN_3O_2S_2$ $[M+H]^+$, 303.9975; found, 303.9974.

2.1.3. 5-chloro-N-(4,6-dimethoxypyrimidin-2-yl) thiophene-2-sulfonamide (3c)

It was obtained as a white solid in 77% yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 3.85 (6H, s), 5.64 (1H, s), 6.93 (1H, d, *J* = 3.8 Hz), 6.96 (1H, d, *J* = 3.8 Hz). ^{13}C NMR (400 MHz, DMSO) δ 54.21, 49.73, 125.45, 126.55, 128.51, 150.51, 160.08, 163.22, 171.40. HRMS (ASAP-MS) m/z: calcd for $C_{10}H_{10}ClN_3O_4S_2$ $[M+H]^+$, 335.9874; found, 335.9882.

2.1.4. 5-chloro-N-(4-methylpyrimidin-2-yl)thiophene-2-sulfonamide (3d)

It was obtained as a brown solid in 80% yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 2.20 (3H, s), 6.44 (1H, d, *J* = 5.0 Hz), 6.93 (1H, d, *J* = 3.9 Hz), 6.96 (1H, d, *J* = 3.9 Hz), 8.07 (1H, d, *J* = 5.0 Hz). ^{13}C NMR (400 MHz, DMSO) δ 23.95,109.94, 125.48, 126.56, 128.50 ,150.48, 158.16, 163.88, 167.58. HRMS (ASAP-MS) m/z: calcd for $C_9H_8ClN_3O_2S_2$ $[M+H]^+$, 289.9818; found, 289.9869.

2.1.5. 5-chloro-N-(5-chloropyrimidin-2-yl)thiophene-2-sulfonamide (3e)

It was obtained as a white solid in 61 % yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 6.93 (1H, d, *J* = 3.7 Hz), 6.97 (1H, d, *J* = 3.7 Hz) 8.26 (2H, s). ^{13}C NMR (400 MHz, DMSO) δ 112.30, 117.70, 126.48,128.50,150.58, 156.57,162.40. HRMS (ASAP-MS) m/z: calcd for $C_8H_5Cl_2N_3O_2S_2$ $[M+H]^+$, 309.93; found, 309.93.

2.1.6. 5-chloro-N-(4-hydroxy-6-methylpyrimidin-2-yl) thiophene-2-sulfonamide (3f)

The product was obtained as a white solid in 83% yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 2.13 (3H, s), 5.70 (1H,s), 6.94 (1H, d, J = 3.7 Hz), 6.96 (1H, d, J = 3.7 Hz). ^{13}C NMR (400 MHz, DMSO) δ 21.01, 102.42, 125.60, 126.61, 128.66 ,150.23, 153.89, 156.10, 162,16. HRMS (ASAP-MS) m/z: calcd for $C_9H_8ClN_3O_3S_2$ $[M+H]^+$, 305.9768; found, 305.9715.

2.1.7. 5-chloro-N-(4-chloropyrimidin-2-yl)thiophene-2-sulfonamide (3g)

It was obtained as a pale-yellow solid in 79 %. ^{1}H NMR (400 MHz, DMSO-d6) δ 6.80 (1H, d, *J* = 5.56), 6.93 (1H, d, *J* = 3.8 Hz), 6.96 (1H, d, *J* = 3.8 Hz), 8.26 (1H, d, *J* = 5.56 Hz). ^{13}C NMR (400 MHz, DMSO) δ 117.70,125.44, 126.55, 128.47 ,150.56, 156.55, 162.50. HRMS (ASAP-MS) m/z: calcd for $C_8H_5Cl_2N_3O_2S_2$ $[M+H]^+$, 309.9292; found, 309.9290.

2.1.8. 5-chloro-N-(4-hydroxypyrimidin-2-yl)thiophene-2-sulfonamide (3h)

It was obtained as a white solid in 77 % yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 6.80 (1H, d, *J* = 5.0 Hz), 6.93 (1H, d, *J* = 3.8 Hz), 6.96 (1H, d, *J* = 3.8 Hz), 8.07 (1H, d, *J* = 5.0 Hz). ^{13}C NMR (400 MHz, DMSO) δ 23.95,109.94, 125.48, 126.56, 128.50 ,150.48, 158.16, 163.88, 167.58. HRMS (ASAP-MS) m/z: calcd for $C_8H_6ClN_3O_3S_2$ $[M+H]^+$, 291.9611; found, 291.9610.

2.1.9. 5-chloro-N-(4-chloro-6-methylypyrimidin-2-yl)thiophene-2-sulfonamide (3i)

The product was obtained in 80 % yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 2.13 (3H, s), 5.71 (1H,s), 6.93 (1H, d, *J* = 3.9 Hz), 6.96 (1H, d, *J* = 3.9 Hz). ^{13}C NMR (400 MHz, DMSO) δ 20.01, 108.69, 111.88, 126.40, 129.98, 153.18, 161.00, 162.99, 169.53. HRMS (ASAP-MS) m/z: calcd for $C_9H_7Cl_2N_3O_2S_2$ $[M+H]^+$, 323.94; found, 323.95.

2.1.10. 5-chloro-N-(4-chloro-6-methoxypyrimidin-2-yl)thiophene-2-sulfonamide (3j)

The product was obtained as a solid in 83% yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 3.82 (3H, s), 6.11 (1H,s), 6.93 (1H, d, J = 3.9 Hz), 6.96 (1H, d, J = 3.9 Hz). ^{13}C NMR (400 MHz, DMSO) δ 54.21,94.73, 125.45, 126.55, 128.51 ,150.51, 160.08, 163.22, 171,40. HRMS (ASAP-MS) m/z: calcd for $C_9H_7Cl_2N_3O_3S_2$ $[M+H]^+$, 339.93; found, 339.94.

2.2. Synthesis of 5-chloro-thiosulfadiazine compounds using Na_2CO_3

5- chloro thiophene-2-sulfonyl chloride (6 mmol) was added slowly to the mixture of amino pyrimidine and Na_2CO_3 (8 mmol) in water (9 ml). The reaction mixture was heated and stirred at 80 °C for 30 min. After completion of reaction, the solid was filtered and washed with 10% HCl. The crude was pure without further purification.

2.2.1. 5-chloro-N-(pyrimidin-2-yl)thiophene-2-sulfonamide (3a)

It was obtained as a solid in 90 % yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.10 (1H, t, *J* = 4.9 Hz), 7.21 (1H, d, *J* = 4.0 Hz), 7.65 (1H, d, *J* = 4.1 Hz), 8.63 (2H, s). ^{13}C NMR (400 MHz, DMSO)δ 110.43, 125.54, 126.58, 128.56, 150.36, 158.01, 158.87. HRMS (ASAP-MS) m/z: calcd for $C_8H_6ClN_3O_2S_2$ $[M+H]^+$, 275.9662; found, 275.9617.

2.2.2. 5-chloro-N-(4,6-dimethylpyrimidin-2-yl) thiophene-2-sulfonamide (3b)

It was obtained as an orange solid in 81 % yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 2.16 (6H, s), 6.33(1H, s), 6.93 (1H, d, *J* = 3.8 Hz), 6.96 (1H, d, *J* = 3.8 Hz). ^{13}C NMR (400 MHz, DMSO) δ 23.78, 109.15, 125.46, 126.56, 128.49, 150.53, 163.79, 167.23. HRMS (ASAP-MS) m/z: calcd for $C_{10}H_{10}ClN_3O_2S_2$ $[M+H]^+$, 303.9975; found, 303.9974.

2.2.3. 5-chloro-N-(4,6-dimethoxypyrimidin-2-yl) thiophene-2-sulfonamide (3c)

It was obtained as a white solid in 88% yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 3.85 (6H, s), 5.64 (1H, s), 6.93 (1H, d, *J* = 3.8 Hz), 6.96 (1H, d, *J* = 3.8 Hz). ^{13}C NMR (400 MHz, DMSO) δ 54.21, 49.73, 125.45, 126.55, 128.51, 150.51, 160.08, 163.22, 171.40. HRMS (ASAP-MS) m/z: calcd for $C_{10}H_{10}ClN_3O_4S_2$ $[M+H]^+$, 335.9874; found, 335.9882.

2.2.4. 5-chloro-N-(4-methylpyrimidin-2-yl)thiophene-2-sulfonamide (3d)

It was obtained as a dark brown solid in 71% yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 2.20 (3H, s), 6.44 (1H, d, *J* = 5.0 Hz), 6.93 (1H, d, *J* = 3.9 Hz), 6.96 (1H, d, *J* = 3.9 Hz), 8.07 (1H, d, *J* = 5.0 Hz). ^{13}C NMR (400 MHz, DMSO) δ 23.95,109.94, 125.48, 126.56, 128.50 ,150.48, 158.16, 163.88, 167.58. HRMS (ASAP-MS) m/z: calcd for $C_9H_8ClN_3O_2S_2$ $[M+H]^+$, 289.9818; found, 289.9869.

2.2.5. 5-chloro-N-(5-chloropyrimidin-2-yl)thiophene-2-sulfonamide (3e)

It was obtained as a yellow solid in 74 % yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 6.93 (1H, d, *J* = 3.7 Hz), 6.97 (1H, d, *J* = 3.7 Hz) 8.26 (2H, s). ^{13}C NMR (400 MHz, DMSO) δ 112.30, 117.70, 126.48,128.50,150.58, 156.57,162.40. HRMS (ASAP-MS) m/z: calcd for $C_8H_5Cl_2N_3O_2S_2$ $[M+H]^+$, 309.93; found, 309.93.

2.2.6. 5-chloro-N-(4-hydroxy-6-methylpyrimidin-2-yl) thiophene-2-sulfonamide (3f)

The product was obtained as a white solid in 85 % yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 2.13 (3H, s), 5.70 (1H,s), 6.94 (1H, d, J = 3.7 Hz), 6.96 (1H, d, J = 3.7 Hz). ^{13}C NMR (400 MHz, DMSO) δ 21.01, 102.42, 125.60, 126.61, 128.66 ,150.23, 153.89, 156.10, 162,16. HRMS (ASAP-MS) m/z: calcd for $C_9H_8ClN_3O_3S_2$ $[M+H]^+$, 305.9768; found, 305.9715.

2.2.7. 5-chloro-N-(4-chloropyrimidin-2-yl)thiophene-2-sulfonamide (3g)

It was obtained as a dark-yellow solid in 70 %. ^{1}H NMR (400 MHz, DMSO-d6) δ 6.80 (1H, d, *J* = 5.56), 6.93 (1H, d, *J* = 3.8 Hz), 6.96 (1H, d, *J* = 3.8 Hz), 8.26 (1H, d, *J* = 5.56 Hz). ^{13}C NMR (400 MHz, DMSO) δ 117.70,125.44, 126.55, 128.47 ,150.56, 156.55, 162.50. HRMS (ASAP-MS) m/z: calcd for $C_8H_5Cl_2N_3O_2S_2$ $[M+H]^+$, 309.9292; found, 309.9290.

2.2.8. 5-chloro-N-(4-hydroxypyrimidin-2-yl)thiophene-2-sulfonamide (3h)

It was obtained as a solid in 81 % yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 6.80 (1H, d, *J* = 5.0 Hz), 6.93 (1H, d, *J* = 3.8 Hz), 6.96 (1H, d, *J* = 3.8 Hz), 8.07 (1H, d, *J* = 5.0 Hz). ^{13}C NMR (400 MHz, DMSO) δ 23.95,109.94, 125.48, 126.56, 128.50 ,150.48, 158.16, 163.88, 167.58. HRMS (ASAP-MS) m/z: calcd for $C_8H_6ClN_3O_3S_2$ $[M+H]^+$, 291.9611; found, 291.9610.

2.2.9. 5-chloro-N-(4-chloro-6-methylypyrimidin-2-yl)thiophene-2-sulfonamide (3i)

The product was obtained as a white solid in 89 % yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 2.13 (3H, s), 5.71 (1H,s), 6.93 (1H, d, *J* = 3.9 Hz), 6.96 (1H, d, *J* = 3.9 Hz). ^{13}C NMR (400 MHz, DMSO) δ 20.01, 108.69, 111.88, 126.40, 129.98, 153.18, 161.00, 162.99, 169.53. HRMS (ASAP-MS) m/z: calcd for $C_9H_7Cl_2N_3O_2S_2$ $[M+H]^+$, 323.94; found, 323.95.

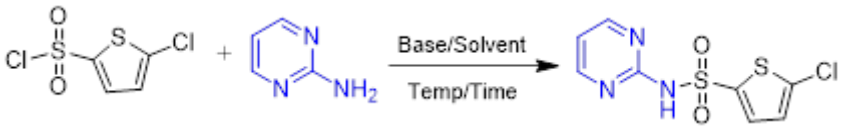
2.2.10. 5-chloro-N-(4-chloro-6-methoxypyrimidin-2-yl)thiophene-2-sulfonamide (3j)

The product was obtained as a white solid in 84 % yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 3.82 (3H, s), 6.11 (1H,s), 6.93 (1H, d, J = 3.9 Hz), 6.96 (1H, d, J = 3.9 Hz). ^{13}C NMR (400 MHz, DMSO) δ 54.21,94.73, 125.45, 126.55, 128.51 ,150.51, 160.08, 163.22, 171,40. HRMS (ASAP-MS) m/z: calcd for $C_9H_7Cl_2N_3O_3S_2$ $[M+H]^+$, 339.93; found, 339.94.

3. Results and Discussions

To optimize the reaction conditions, compound **2** was chosen as the model substrate. As it is widely known, several derivatives of sulfonamides have been prepared using a one-phase system of organic bases like pyridine [14]. Thus, we started our work by examining the literature method to determine if thiophene bearing sulfonamides could be similarly prepared as benzene sulfonamides. Cooling a mixture of 1 and 2 in pyridine (entries 1 and 2) resulted in a 50 and 45 % yield of product. NMR analysis of the crude reaction mixtures showed did not complete conversion of the starting material to product. It was noted that 2-amino pyrimidine was slightly soluble in cold pyridine. Even though we increased the reaction time for 24 hrs, no increase in yield was noted (entry 3).

Table 1: Optimization of Reaction Conditions.

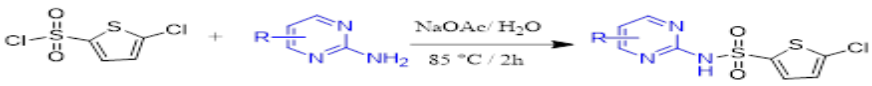


1	2			3	
Entry	**Base**	**Solvent**	**°C**	**Time**	**yield**
1	pyridine	-	0	1 h	50 %
2	pyridine	-	0	3 h	45 %
3	pyridine	-	0	24 h	40 %
4	pyridine	-	rt	24 h	28 %
5	pyridine	acetone	0	4 h	53 %
6	pyridine	acetone	rt	24 h	33 %
7	NaOAc	water	0	3 h	0
8	NaOAc	water	85	2 h	87 %
9	Na_2CO_3	water	0	6 h	0
10	Na_2CO_3	water	80	30 min	90 %

This poor yield was due to insolubility of 2-amino pyrimidine in cold pyridine. When we ran the reaction at room temperature, we observed that the product was formed with low yield and some pyridine byproducts (entry 4). We tried to remove the pyridine form the reaction mixture by extraction method. We used mild acidic solution (5-10 % Aq. HCl) during work-up. Unfortunately, we could not isolate and analyze the byproducts due to difficulty removing the pyridine solvent. To circumvent this problem, we tried to use a mixture of pyridine and anhydrous acetone to decrease the amount of pyridine and improve the yield, but no significant advantage was observed (entries 5 and 6). Although the use of pyridine as a base has led to remarkable progress in the formation of sulfonamides, unsuccessful results for the synthesis of thiophene compounds have been noted.

Next, due to the unsuccessful results of using pyridine, we tried to mix two phase systems of organic solvent like NaOAc or Na_2CO_3 with water. To our knowledge, water was reported as one of the greenest solvents for chemical reactions because of cost, safety, and environmental concerns [15]. The reaction was carried out in the presence of a mixture of NaOAc and water. We ran the reaction at 0 ˚C for 3 h. Unfortunately, no product was observed (entry 7). Attempts to perform the product at lower temperatures in this reaction provided only starting materials, so a higher temperature was necessary to prepare the compounds. Under thermal condition, the product was formed with a good yield (entry 8). Mixed solvents of Na_2CO_3 and water were also tested. We found that using of Na_2CO_3 in water at 80°C led to a significant diminished yield (entry 10) while no significant observed in cold condition (entry 9). At this point it was noted that extremely poor solubility of **2** at cold condition. We were pleased to observe that the solubility of the reactants in the presence of NaOAc and Na_2CO_3 increased significantly compared to pyridine. From the above results it was clear that a mixture of NaOAc/water and Na_2CO_3/ water at thermal condition were found to be efficient, leading to good yield. As NaOAc and Na_2CO_3 solvents provided the best yield, we examined the scope of this methodology.

Synthesis of 5-chloro-thiopsulfadiaizine compounds using NaOAc



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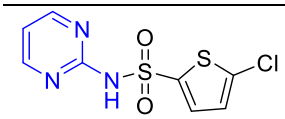	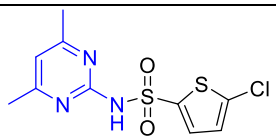	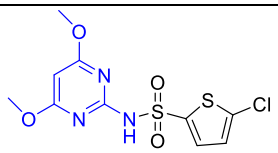
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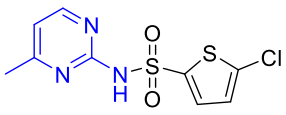	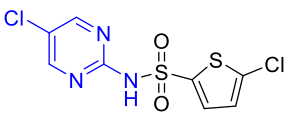	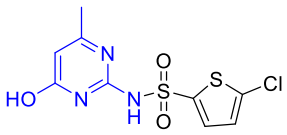
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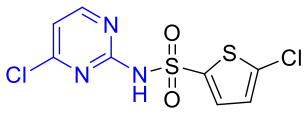
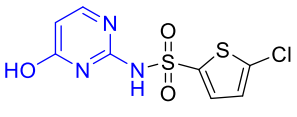
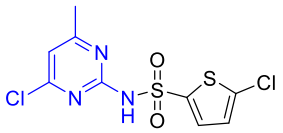
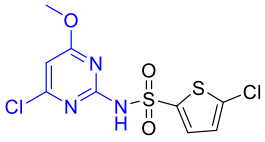
		
3g, 79%	3h, 77%	3i, 80%
		
3j, 83%		

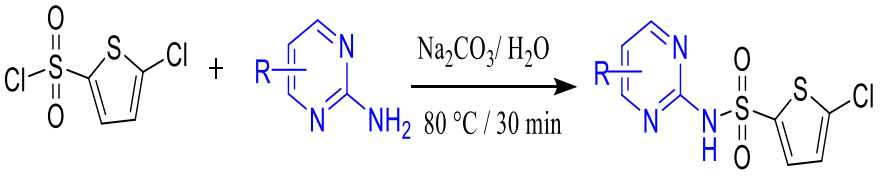
Scheme 2: Synthesis of 5-chloro-thiosulfadiazine compounds using NaOAc

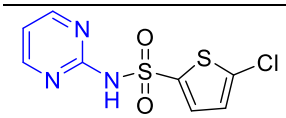
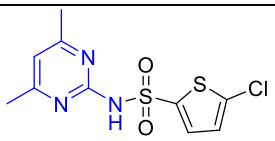
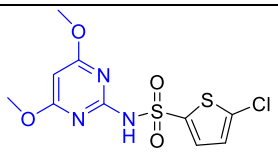
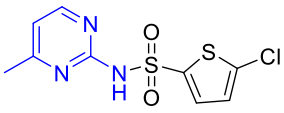
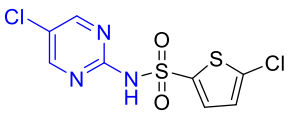
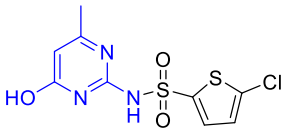
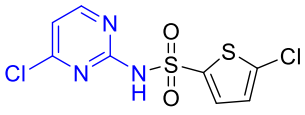
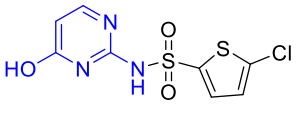
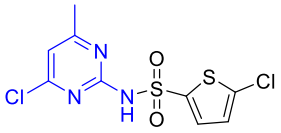
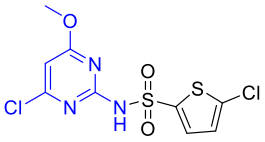
The reactivity of differentially substituted 2-amino pyrimidine with 5-chlorothiophene-2-sulfonyl chloride using NaOAc/water was investigated (scheme 2).

Moderate to good yields were achieved regardless of the electronic effects of substituents in the pyramidine ring (3a-j). While the presence 4-OH-, 4-Cl-, 4,6-OMe-, and 4,6-Me in pyrimidine gave the products in 77-87% yields when reacted with 5-Cl thiophene sulfonyl chloride (3b-d and 3f-j, respectively), 5-Cl- decreased the yield to 61% (3e).

Synthesis of 5-chloro-thiopsulfadiaizine compounds using Na_2CO_3

A series of 5-chloro-thiophene was examined using a mixture of sodium carbonate and water. As it was shown in Scheme 3, good to high yields were obtained (3a-3j). In comparison between the results in Scheme 2 with Scheme 3, the reactions of compounds in the presence of sodium carbonate were rapid, and the products were obtained in pure form after simply washing the products with small portions of 10% HCl than compounds in the presence of sodium acetate.



1	2a-j	3a-j
		
3a, 90%	3b, 81%	3c, 88%
		
3d, 71%	3e, 74%	3f, 85%
		
3g, 70%	3h, 81%	3i, 89%
		
3j, 84%		

Scheme 3: Synthesis of 5-chloro-thiosulfadiazine compounds using Na_2CO_3

The use of sodium carbonate as a base for the formation of S-N bond not only proved its efficiency but also allowed for the first time obtaining new compounds of 5-chloro-thiosulfadiazine compounds in excellent yields.

4. Conclusion

In conclusion, we have successfully developed an efficient and simple method for the synthesis of 5-cl thiosulfadiazine compounds by using a mixture of Na_2CO_3/H_2O and NaOAc/ H_2O.

The mix of two-phase systems of organic solvents for the synthesis of chloro compounds provides all the advantages of cost, safety, and environmental concerns; thus, we believe this method gives broad utility to the organic/medicinal chemist that is pursuing the synthesis of sulfonamides derivative.

5. Limitations

This strategy is not limited to synthesizing the chloro compounds but is also feasible for synthesizing different halogens with aliphatic and aromatic compounds.

6. Recommendation

According to the promising results above, this environmental method will allow scientists to synthesize a wide range of organic compounds.

Notes

The authors declare no competing financial interest.

Acknowledgments

The authors would like to thank Jazan University, Saudi Arabia for financial support.

The authors would also like to thank Abdulrahman Alharbi and Lama Abdullah for the support.

References

[1] Ajeet, A.; Mishra, A. K.; Kumar, A. Recent Advances in Development of Sulfonamide Derivatives and Their Pharmacological Effects- A Review. *Am. J. Pharmacol. Sci.* 2015, 3 (1), 18–24.

[2] Zhao, Y.; Shadrick, W. R.; Wallace, M. J.; Wu, Y.; Griffith, E. C.; Qi, J.; Yun, M.-K.; White, S. W.; Lee, R. E. Pterin-Sulfa Conjugates as Dihydropteroate Synthase Inhibitors and Antibacterial Agents. *Bioorg. Med. Chem. Lett.* 2016, 26 (16), 3950–3954.

[3] Alsughayer, A.; Elassar, A.-Z. A.; Mustafa, S.; Sagheer, F. Al. Synthesis, Structure Analysis and Antibacterial Activity of New Potent Sulfonamide Derivatives. *J. Biomater. Nanobiotechnol*. 2011, 02 (02), 143–148.

[4] Naaz, F.; Srivastava, R.; Singh, A.; Singh, N.; Verma, R.; Singh, V. K.; Singh, R. K. Molecular Modeling, Synthesis, Antibacterial and Cytotoxicity Evaluation of Sulfonamide Derivatives of Benzimidazole, Indazole, Benzothiazole and Thiazole. *Bioorg. Med. Chem*. 2018, 26 (12), 3414–3428. https://doi.org/10.1016/j.bmc.2018.05.015.

[5] Mansour, A. M.; Soliman, F. A.; Shehab, O. R.; Abdel-Ghani, N. T. Photodegradation of Sulfadiazine Catalyzed by P-Benzoquinones and Picric Acid: Application to Charge Transfer Complexes. *RSC Adv*. 2017, 7 (63), 39989–39996.

[6] Blanchard, C.; Brooks, L.; Ebsworth-Mojica, K.; Didione, L.; Wucher, B.; Dewhurst, S.; Krysan, D.; Dunman, P. M.; Wozniak, R. A. F. Zinc Pyrithione Improves the Antibacterial Activity of Silver Sulfadiazine Ointment. *mSphere*. 2016, 1 (5).

[7] Winters, K. J.; Janney, F. R. SULFADIAZINE: REVIEW OF ITS USE IN TREATMENT OF CHILDREN. *Am. J. Dis. Child*. 1943, 65 (5), 702–711.

[8] Woods, D. D. The Relation of P-Aminobenzoic Acid to the Mechanism of the Action of Sulphanilamide. Br *J Exp Pathol* 1940, 21 (2), 74–90.

[9] Mabkhot, Y. N.; Alatibi, F.; El-Sayed, N. N. E.; Kheder, N. A.; Al-Showiman, S. S. Synthesis and Structure-Activity Relationship of Some New Thiophene-Based Heterocycles as Potential Antimicrobial Agents. *Molecules* 2016, 21 (8). https://doi.org/10.3390/molecules21081036.

[10] Hu, Y.; Yang, S.; Shilliday, F. B.; Heyde, B. R.; Mandrell, K. M.; Robins, R. H.; Xie, J.; Reding, M. T.; Lai, Y.; Thompson, D. C. Novel Metabolic Bioactivation Mechanism for a Series of Anti-Inflammatory Agents (2,5-Diaminothiophene Derivatives) Mediated by Cytochrome P450 Enzymes. *Drug Metab. Dispos*. 2010, 38 (9), 1522–1531.

[11] Jha, K.; Kumar, S.; Tomer, I.; Mishra, R. Thiophene: The Molecule of Diverse Medicinal Importance. *J. Pharm. Res.* 2012, 5 (1), 560–566.

[12] Ryabova, V.; Ignatovich, L. Thiophene Substitution Chemistry. *In Thiophenes*; Joule, J. A., Ed.; Topics in Heterocyclic Chemistry; Springer International Publishing: Cham, 2015; pp 43–108.

[13] Kamboj, A. Pharmacological Action and Sar of Thiophene Derivatives: A Review. J. *Pharm. Res*. 2012, (5), 7.

[14] Żołnowska, B.; Sławiński, J.; Brzozowski, Z.; Kawiak, A.; Belka, M.; Zielińska, J.; Bączek, T.;

Chojnacki, J. Synthesis, Molecular Structure, Anticancer Activity, and QSAR Study of N-(Aryl/Heteroaryl)-4-(1H-Pyrrol-1-Yl)Benzenesulfonamide Derivatives. Int. *J. Mol. Sci*. 2018, 19 (5), 1482.

[15] Deng, X.; Mani, N. S. A Facile, Environmentally Benign Sulfonamide Synthesis in Water. *Green Chem*. 2006, 8 (9), 835.