Classical and Microwave-Assisted Synthesis of Substituted-Dihydroxy-imidazolidine-2-thiones Compounds

Sübstütiye Dihidroksi-imidazolidin-2-tiyon Bileşiklerinin Klasik ve Mikrodalga Destekli Sentezi

Research Article

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ABSTRACT

In this study, N-N'-disubstitued thiourea and N-N'-disubstituted-4,5-dihydroxy-2-imidazolidine-2-thione were prepared through the reaction of suitable primary aromatic amines with phenylisothiocyanate and 4-methoxyphenylisothiocyanate. The synthesis of N-N'-disubstitued thiourea were carried out by classic methods. Later, the acid-catalyzed cyclocondensation in refluxing acetonitrile of aqueous glyoxal and led to the formation of the corresponding N,N'-disubstitued-4,5-dihydroxyimidazolidin-2-thiones. Thiourea derivatives were prepared both classical method and microwave assisted synthesis. Microwave-assisted reaction was performed in temperature and pressure control devices with the atmospheric pressure environment. The structures of synthesized organic compounds were characterized by FT-IR and ^{1}HNMR spectroscopy.

Key words

Cyclic thiourea, aromatic amine, microwave-assisted synthesis, imidazolideine-2-thione.

ÖZ

Bu çalışmada, aromatik aminlerin, fenilizotiyosiyanat ve 4-metoksi-fenilizotiyosiyanat ile tepkimesi ile, N-sübstütiye-N'-feniltiyoüre ve türevleri sentezlendi. Daha sonra sentezlenen bu bileşikler, asidik ortamda sulu glioksal çözeltisi ile reflaks edildi ve N,N'-disübstütiye-4,5dihidroksi-imidazolidin-2-tiyon bileşikleri sentezlendi. N-sübstütiye-N'-feniltiyoürenin sentezi, geleneksel ısıtma yöntemi kullanılarak gerçekleştirildi. Tiyoüre türevlerinin sentezi hem klasik yöntem hem de mikrodalga destekli sentez yöntemiyle yapıldı. Mikrodalga destekli tepkimeler, sıcaklık ve basınç kontrollü cihazla atmosfer basınçlı ortamda gerçekleştirildi. Tüm ürünler, FT-IR ve ^{1}H-NMR spektroskopik analiz yöntemleri ile karakterize edildi.

Anahtar kelimeler

Halkalı tiyoüre, aromatik amin, mikrodalga destekli sentez, imidazolidin–2-tiyon.

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INTRODUCTION

Cyclic thioureas are important compounds because of their wide range of applications [1]. Thiourea, because of their electronegativity of the sulphur atom in the structure is a particularly versatile reagents used in organic synthesis [2]. These compounds are used as ligands for metal complexes synthesis [3-6]. Thiourea and its derivatives are coordinated to a metal ion either by the Sulphur (S) or Nitrojen (N) atoms [3]. Besides, Due to the hydrogen atom on the molecule and the active S and N show the capability to bond H and are therefore able to function as catalysts in many organic reactions [2,3].

Thiourea derivatives has attracted interest due to their potential use as reagents for the separation of metal ions [7-9] and in biological applications for example; antibacterial [3,8,10,11], antiviral [7] antifungal agents [7,8,12-14]. And thioureas have recently taken attention as protease inhibitors of human immunodeficiency virus (HIV) [3,15,16]. Some thiourea derivatives has in vivo and in vitro activity and parasitic worms [14,17]. Thioureas and derivatives have wide variety of applications [18] For example; these compound widely used in the mining industry [14,19], and agriculture, use in photography as fixing agents, to remove stains from negatives and rubber industry as promoter [20,21].

The imidazolidine-2-thione ring derivatives have powerful bioactivities property. N,N'-disubstituted 4,5-dihydroxyimidazolidine-2-thione have a ectoparasiticidal action [22,23]. They have anti diabetic properties [22,24] and anti-HIV activity [22,25]. These compounds have role in medicinal chemistry. Such as; they have an antimicrobial, antirheumatic, antidepressant, immunomodulator, anti-inflammatory, analgesic properties [26-29].

Microwave (MW) have been observed for a wide range of organic reactions [30]. Microwave irradiation has opened a new view in organic chemistry [31]. Because, microwave synthesis increases the chemical yields and the reaction time is lower than other methods. So that is economic, without pollution, solvent-free reaction with microwave [32,33].

MATERIAL and METHODS

Chemicals and Instrument

All of the chemicals were purchased from Aldrich and Merck. Melting points of the compounds were determined using an Electro-thermal IA 9100 digital melting points apparatus. Microwave synthesis was made with Cem Discover Labmate tec mode (2450 MHz). The ^{1}H-NMR spectra was obtained Bruker 300 MHz in DMSO-d_6 and $CHCl_3$-d_6, IR dates were recorded by Perkin Elmer FT-IR.

General Method for N-N'-Disubstitued Thiourea From Reaction of Phenyl Isothiocyanate and Aromatic Amines (1a-e)

A mixture of phenyl isothiocyanate **(1)** (5 mmol) and different amines **(a-e)** (Aniline, 4-chloro aniline, p-Toluidine, 2-aminothiazole, 2-Aminopyridine) (5 mmol) were added to a solution of ethanol (20 ml, 95%). The reaction mixture was refluxed for 4 hours at 78°C. At the end of reaction, solvents were evaporated. The residue was filtered and recrystallized from ethanol [34]. All of products **1a-e** were synthesis under the same reaction conditions.

1,3-Diphenyl thiourea (1a), white microcrystals from EtOH (86%); mp: 151–152°C , ^{1}H NMR (DMSO-d_6): δ = 9.79 (s, 2H, NH), 7.5–7.10 (d, 4H), (t, 4H), (t, 2H), Ar-H), *3.36 ppm; rest of DMSO H_2O, 2.50 ppm; rest of DMSO proton residue.*

1- (4-Chlorophenyl)-3-phenyl-thiourea (1b), white microcrystals from EtOH (87%); mp: 152-153°C, ^{1}H NMR (CDCl-d)*:* δ= 8.14 (t, 2H, NH), 7.44–7.28, (m, 9H, Ar-H), 7.25; rest of $CDCl_3$.

1-(4-methylphenyl)-3-phenyl thiourea (1c), white microcrystals from EtOH (99%); mp: 148–150°C ^{1}H NMR ($CDCl_3$-d): δ= 8.02 (s, 2H, NH), 7.40–7.25 (m,9H, Ar-H), 2.35 (s, 3H, aliphatic CH).

1-Phenyl-3-(1,3-thiazol-2-yl) thiourea (1d), Off-white microcrystals from EtOH (72%); mp: 169-170°C, ^{1}H NMR ($CDCl_3$-d): δ= 12.70 (s, 1H, NH) 10.79 (s, 1H, NH), 7.54–6.89 (m, 7H, Ar-H).

1-Phenyl-3-pyridin-2-yl-thiourea (1e), off-white microcrystals from EtOH (72%); mp: 169-170°C, ^{1}H NMR ($CDCl_3$-d): δ= 13.75 (s, 1H, NH), 9.50 (s, 1H, NH), 8.24–6.99 (m, 9H, Ar-H).

General Method for N-N'-Disubstitued Thioureas from Reaction of 4-Methoxy Phenyl Isothiocyanate and Aromatic Amines (2a-f)

The synthesis of the thiourea compounds **2a-f** were made same method with general method for N-N'-disubstitued thioureas from reaction of phenyl isothiocyanate with aromatic amines [34]. 4-Methoxy phenyl isothiocyanate **(2)** (5 mmol) and different aromatic amines **(a-f)** (aniline, 4-chloroaniline, p-toluidine, 2-aminothiazole, 2-aminopyridine, 4-methoxy aniline) (5 mmol) were added to a solution of ethanol (20 ml, 95%). The reaction mixture was refluxed at 78°C. At the end of reaction solvents were evaporated. The residue was filtered and recrystallized from ethanol.

1-(4-Methoxyphenyl)-3-phenyl thiourea (2a), off-white microcrystals from EtOH (75%); mp: 141-143°C, ^{1}H NMR (DMSO-d_6): δ= 9.58 (s, 2H, NH), 7.45 (d, 2H, Ar-H), 7.30 (m, 4H, Ar-H), 7.12 (t, 1H, Ar-H), 6.91 (m, 2H, Ar-H), 3.70 (s, 3H, O-CH_3), 3.61 ppm; rest of DMSO/H_2O, 2.50 ppm; rest of DMSO proton.

1-(4-Chlorophenyl)-3-(4-methoxyphenyl) thiourea (2b), white microcrystals from EtOH (94%); mp: 180–181°C, ^{1}H NMR (DMSO-d_6): δ= 9.70 (s, 1H, NH), 9.43(s, 1H, NH), 7.51 (d, 2H, Ar-H), 7.38–6.87 (m, 6H, Ar-H), 3.71 (s, 3H, O-CH_3).

1-(4-Methoxyphenyl)-3-(4-methylphenyl) thiourea (2c), white microcrystals from EtOH (75%); mp: 148-150°C, ^{1}H NMR (DMSO-d_6): δ= 9.50 (s, 2H, NH), 7.31 (m, 4H, Ar-H), 7.14 (d, 2H, Ar-H), 6.91 (d 2H, Ar-H), 3.74 (s, 3H, O-CH_3), 2.28 (s, 3H, -CH_3).

1-(4-Methoxyphenyl) -3- (1,3-thiazol-2-yl) thiourea (2d), off-white microcrystals from EtOH (61%); mp: 188–189°C,^{1}H NMR (DMSO-d_6): δ=12.19 (s, 1H, NH), 10.49 (s, 1H, NH), 7.50–6.92 (d, 5H, Ar-H), 6.97 (m, 1H, Ar-H), 3.75 (s, 3H, O-CH_3).

1-(4-Methoxyphenyl)-3-pyridin-2-yl-thiourea (2e), off-white microcrystals from EtOH (61%); mp: 188–189°C, ^{1}H NMR (DMSO-d_6): δ= 13.59 (s, 1H, NH), 11.00 (s, 1H, NH), 8.32 -6.95 (m, 8H, Ar-H), 3.77 (s, 3H, O-CH_3).

1,3-bis-(4-methoxyphenyl) thiourea (2f), white microcrystals from CH_2Cl_2 (70%); mp: 189–190°C,^{1}H NMR (DMSO-d_6): δ= 9.44 (s, 2H, NH), 7.32–6.98 (d, 8H, Ar-H), 3.75 (s, 6H, O-CH_3).

Synthesis of N-N'-Disubstituted-4,5-Dihydroxy-2-Imidazolidine-2-Thione from N-N'-Disubstituted Thioureas (3a-e, 4a-c)

In this section, 3a-e, 4a-c compounds were synthesis via classical method and microwave assisted synthesis.

Classical Methods: N-N'-disubstitue thiourea compounds (2 mmol) and aqueous glyoxal (2 mmol of 40%) were added in acetonitrile (30 ml). After 3-4 drops of formic acid put into the mixture and was refluxed 5 hours [35]. Then ending of the reaction, solvents were evaporated and product was crystallized using a suitable solvent or mixture of solvents.

Microwave Assisted Synthesis at Atmosphere Pressure : After classical method was optimized, pass to under microwave irradiation. N-N'disubstituted thiourea compounds (2 mmol) and aqueous glyoxal (2 mmol of 40%) were added in acetonitrile (30 ml). Later, 3-4 drops of formic acid added and flask was placed in a microwave synthesized under reflux. Then reaction, products were crystallized using a suitable solvent.

4,5-Dihydroxy-1,3-diphenyl-imidazolidine-2-thione (3a), white microcrystals from $CHCl_3$ (52%); mp: 177–178°C, ^{1}H NMR (DMSO-d_6): δ= 7.54–7.52 (d, 2H, OH), 7.54–7.16 (m, 12 H, Ar-H ve OH), 5.23 (d, 2H, imidazolidine CH).

1-(4-Chlorophenyl)-4,5-dihydroxy-3-phenyl-imidazolidine-2-thione (3b), white microcrystals from $CHCl_3$ (40%); mp: 175–176°C, ^{1}H NMR (DMSO-d_6): δ= 7.59–7.15 (m, 11H, Ar-H ve OH), 5.24 (d, 2H, imidazolidine CH).

1-(4-methylphenyl)-4,5-dihydroxy-3-phenyl-imidazolidine-2-thione (3c), white microcrystals from $CHCl_3$ (48%); mp: 167–168°C, ^{1}H NMR (DMSO-d_6): δ= 5,66 (d, 2H, imidazolidine CH), 7.54-7.32 (m, 10 H, Ar-H and 1 OH), 3.66 (s, 1H, OH), 1.59 (s, 3H, -CH_3).

1-Phenyl-3-pyridin-2-yl-4,5-dihydroxy-imidazolidin-2-thione (3d), white microcrystals from toluene, THF-Hexzane (1:1) (42%); mp: 155–156°C, ^{1}H NMR (DMSO-d_6): δ= 8,41 (d, 2H, OH), 8.50–7.15 (m, 9H, Ar-H), 5.96 (d, 1H, imidazolidine CH), 5.21 (d, 1H, imidazolidine CH).

4,5-Dihydroxy-1-phenyl-3-(1,3-thiazol-2-yl)-imidazolidine-2-thione (3e), off-white microcrystals from Acetonitrile (55%); mp: 167–169°C, ^{1}H NMR (DMSO-d_6): δ= 5.95 (s, 1H, imidazolidine CH), 5.21 (1H, s, imidazolidine CH), 7.62–7.28 (m, 9H, Ar-H ve OH).

4,5-Dihydroxy-1,3-bis (4-methoxyphenyl) imidazolidine-2-thione [36] (4a), off-white microcrystals from Acetonitrile (58%); mp: 178-179°C, ^{1}H NMR (DMSO-d_6): δ= 5.10 (d, 2H, imidazolidine CH), 7.45–6.96 (m, 10H, Ar-H ve OH), 3.78 ppm (s, 6H, O-CH_3).

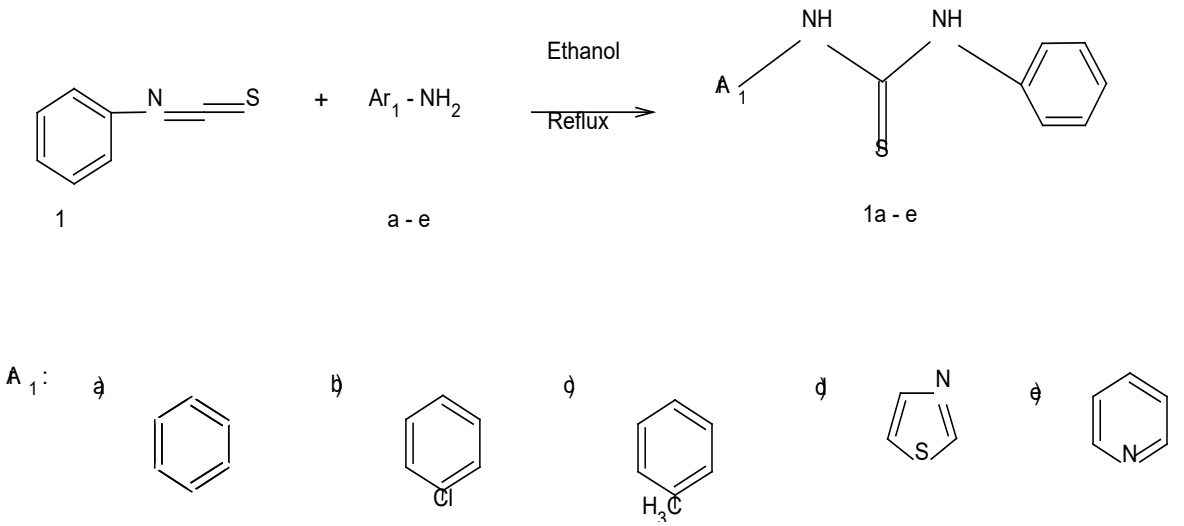
4,5-Dihydroxy-1-(4-methoxyphenyl)-3-(1,3-thiazol-2-yl) imidazolidine-2-thione (4b), off-white microcrystals from Acetonitrile (60%); mp: 184–185°C, ^{1}H NMR (DMSO-d_6): δ = 5.94 (d, 1H, imidazolidine CH), 5.14 (d, 1H, imidazolidine CH), 7.60–7.08 (m, 8H, Ar-H ve OH), 3.80 (s, 3H, -CH_3).

4,5-Dihydroxy-1-(4-methoxyphenyl)-3-pyridin-2-yl-imidazolidine-2-thione (4c), white microcrystals from THF (44%); mp: 165–167°C, ^{1}H NMR (DMSO-d_6): δ = 5.93 (d, 1H, imidazolidine CH), 5.11 (d, 1H, imidazolidine CH), 8.36 (d, 1H, OH), 7.07 (d, 1H, OH), 8.48–7.02 (m, 8H, Ar-H), 3.79 (s, 3H, O-CH_3).

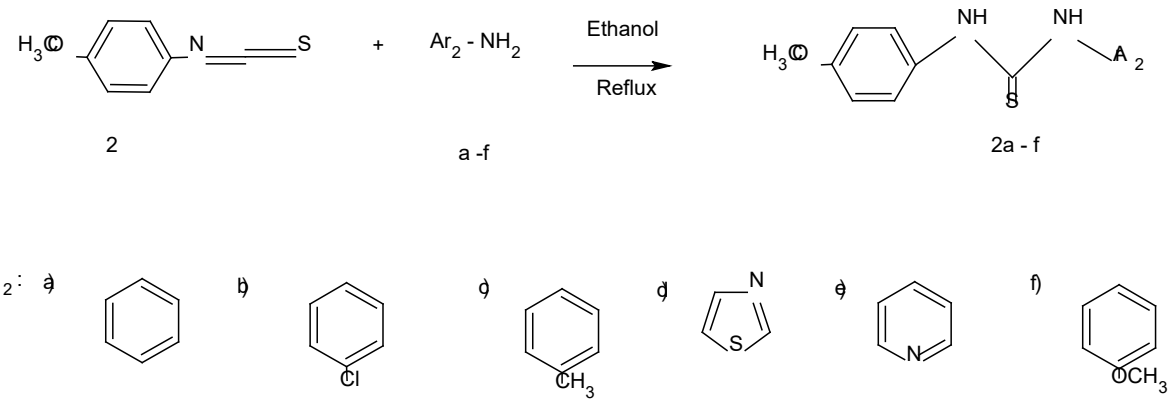
RESULTS and DISCUSSION

In this study, phenyl isothiocyanate and 4-methoxy-phenyl isothiocyanate used as reagents. Starting materials have been activated with the respective substituted aromatic amines. The reaction of N-N'-disubstituted thioure and glyoxal is led to the formation N-N'-disubstituted-4,5-dihydroxy-imidazolidin-2-thione compound. The synthesis of N-N'-disubstituted thiourea are easily. The synthesis of these compounds can take place for a short time, so, there is no need for microwave synthesis. Because the aim is to save time in the microwave. Synthesis of N, N'-disubstituted thiourea **(1a-e)** reactions are shown in Scheme 1.

First step is reaction of compounds **1a-e**. In Table 1, it is shown to us; preparation of N- N'-disubstituted phenylthiourea from aromatic amines and phenyl isothiocyanate; its chemical forms, yield and melting points. In reactions of **1a-e** was get high yield. Yields of compounds **1a-e** are between 70-99% . And melting points of **1a-e** are between 151-170°C. Reaction time ranges of 2a-f from 3 to 4,5 hours. Table 2 is showns to us reaction time of compounds. We can see in Table 3 chemical forms, yield and meltig points of **2a-f** and Scheme 2 is showns chemical reaction of **2a-f**. Impurities were in all compounds. So, **1a-e** and **2a-d** compounds are crystallized by ethyl alcohol,



Scheme 1. Synthesis of N-N'-disubstitued thioureas from reaction of phenyl isothiocyanate and aromatic amines.



Scheme 2. Synthesis of N-N'-disubstitued thioureas from reaction of 4-methoxy-phenyl isothiocyanate and aromatic amines.

Table1. Preparation of disubstituted thioureas from aromatic amines and phenyl isothiocyanate.

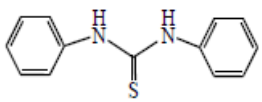
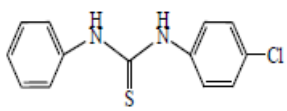
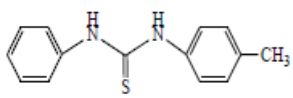
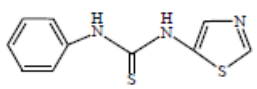
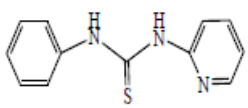
Compound	Ar_1	Product	Yield (%)	Mp (°C)
1a	Aniline		86	151-152
1b	4-Chloro aniline		87	152-153
1c	p-Toluidin		99	148-150
1d	2-Aminothiazole		72	169-170
1e	2-Aminopyridine		87	168-170

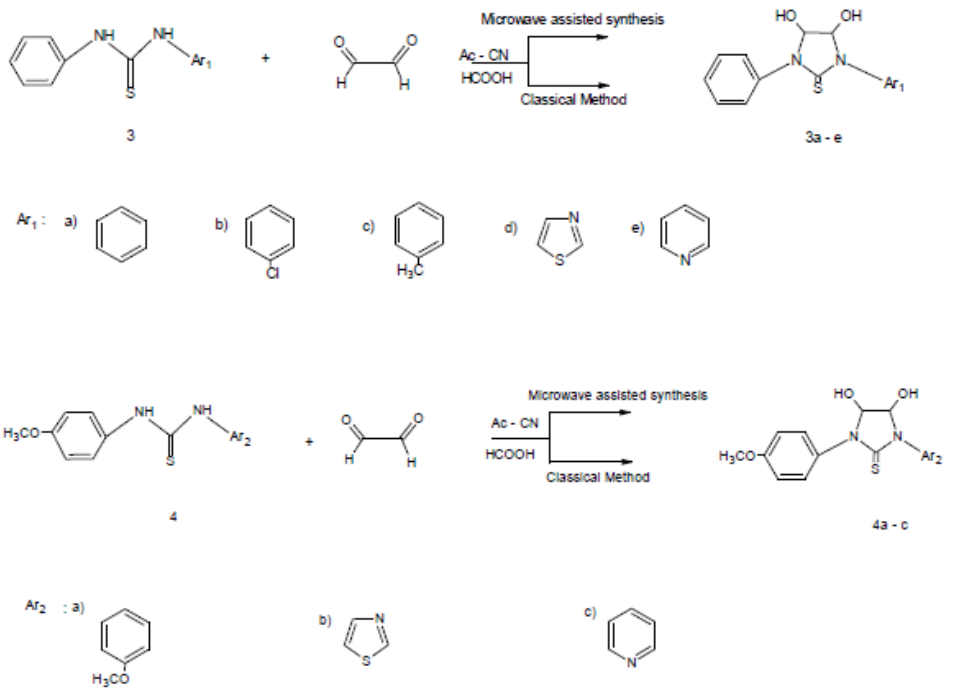
Table 2. Reaction time of 2a-f compounds.

Compound	Reaction time (hour)
2a	3
2b	4
2c	3
2d	4.5
2e	3
2f	3.5

except **2f**. This compound was crystallized by dichloromethane high yield comparative to in ethyl alcohol.

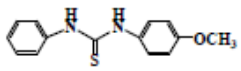
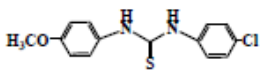
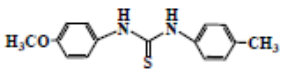
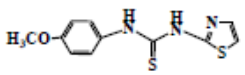
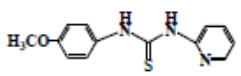
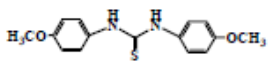
N-N'-Disubstituted-4,5-dihydroxy-2-imidazolidine-2-thione compounds (**3a-e, 4a-c)** were prepared both microwave assisted synthesis and classical methods. These two methods have same results. But microwave assisted synthesis has an advantage according to classical method. Because reaction time of microwave assisted synthesis is lower than classical method. Scheme 3 is shown to us reactions for **3a-e** and **4a-c** . We can see chemical formula about **3a-e, 4a-c** products for microwave assisted synthesis at atmosphere pressure in Table 4. The synthesis was made at atmospheric pressure, so pressure was 0 Bar. Microwave synthesis of the N-N'-disubstituted-4,5-dihydroxy-imidazolidine-2-thione compounds after trying several parameters and obtained the best results in the 200 W, 15 minutes 125°C reaction conditions. Once these parameters are optimized, microwave synthesis was performed in the same conditions in other derivatives. Power, temperature, time and pressure graph of 1-(4-methylphenyl)-4,5-dihydroxy-3-phenyl-imidazolidine-2-thione compound were shown at Scheme 4. At graph "A curve is shown temperature; B curve is shown change in power. Table 5 is shown to us parameters for microwave assisted synthesis. The reaction time is shorter in microwave-assisted synthesis. This is an advantageous situation for a chemist and chemical reaction. Melting points were found to be the same value in both methods.

FT-IR analysis is a dynamic technique for chemical compounds. This technique gives knowledge about the strength of the bonds of the compound. In general, we examined to IR spectrum of **1a-e, 2a-f,** observed strong peak of the isothiocyanate (N= C= S frame) at 2000 cm^{-1} which starting compound was



Scheme 3. Synthesis of N-N'-Disubstituted-4,5-dihydroxy-2-imidazolidine-2-thione compound.

Table 3. Preparation of disubstituted thioureas from aromatic amines and 4-Methoxy-phenyl isothiocyanate.

Compound	Ar_2	Pruduct	Yield (%)	Mp (°C)
2a	Aniline		75	141-143
2b	4-Chloro aniline		94	189-190
2c	p-Toluidine		75	148-150
2d	2-Aminothiazole		67	199-200
2e	2-Aminopyridine		61	188-189
2f	4-Methoxy aniline		70	189-190

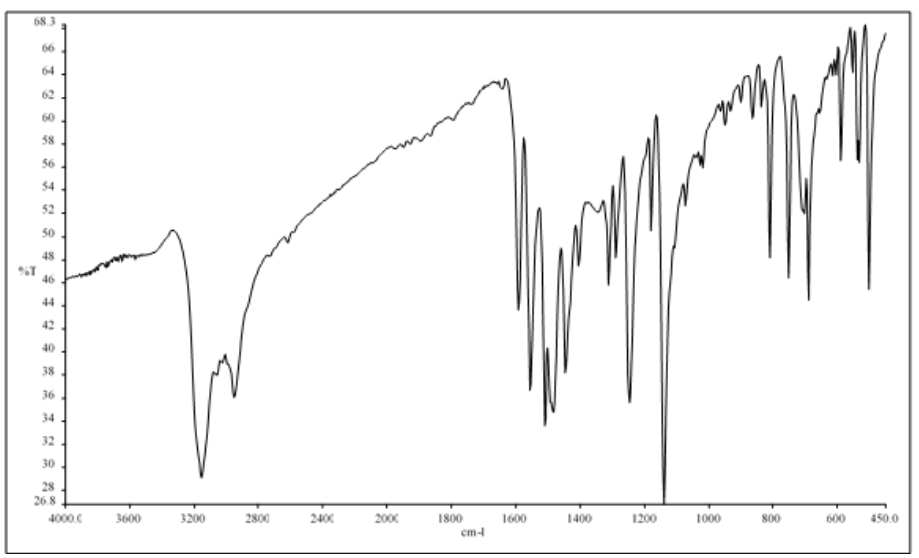


Figure 1. FT-IR spectrum of (1c) 1- (4-methylphenyl) -3-phenyl thiourea.

Table 4. Formula, yield and melting point of 3a – e, 4a – c compounds in Mw synthesis.

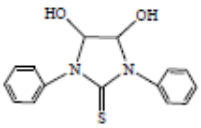
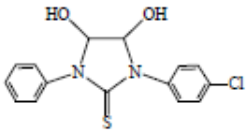
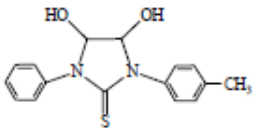
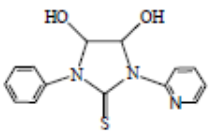
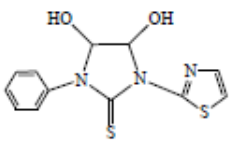
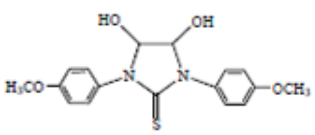
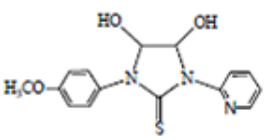
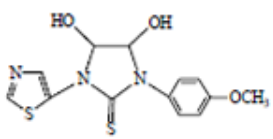
Compound	Pruduct	Yield (%)	Mp (°C)
3a		52	177-178
3b		40	175-176
3c		48	167-168
3d		42	155-156
3e		55	167-169
4a		58	178-179
4b		34	165-167
4c		60	180-185

Table 5. Power, temperature, time and pressure parameters for microwave assisted synthesis of N-N'-Disubstituted-4,5-dihydroxy-2-imidazolidine-2-thione.

Power (W)	Solvent	Temperature (°C)	Reaction time (min)	Pressure (Bar)
200	Acetonitrile	125	15	0

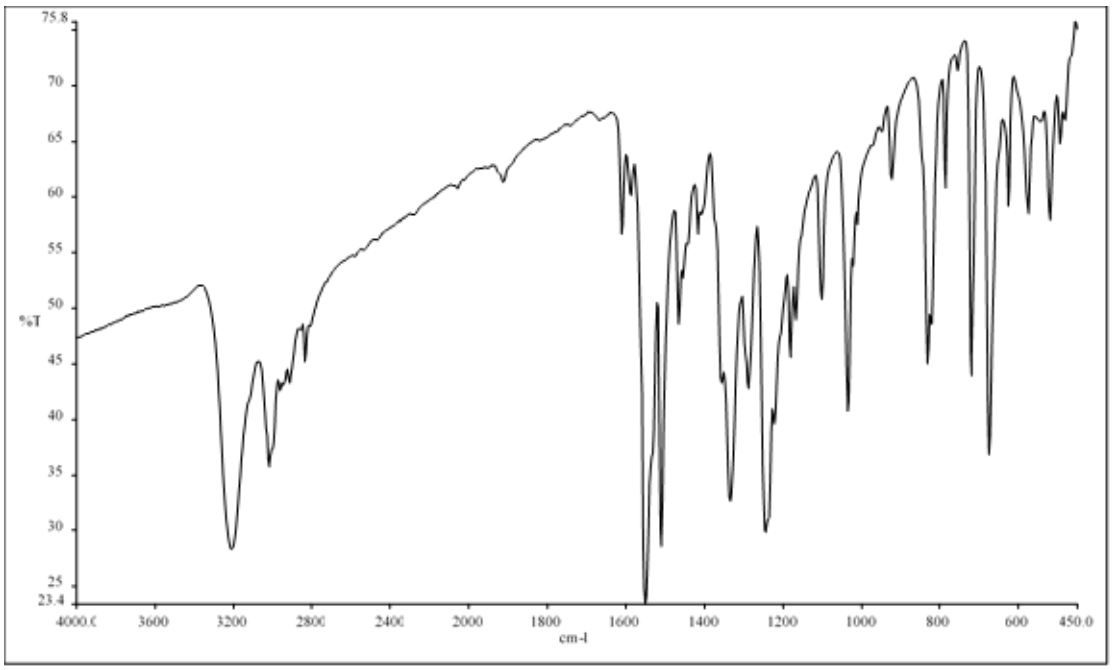


Figure 2. FT-IR spectrum of (2c) 1- (4-Methoxyphenyl) -3- (4-methylphenyl) thiourea.

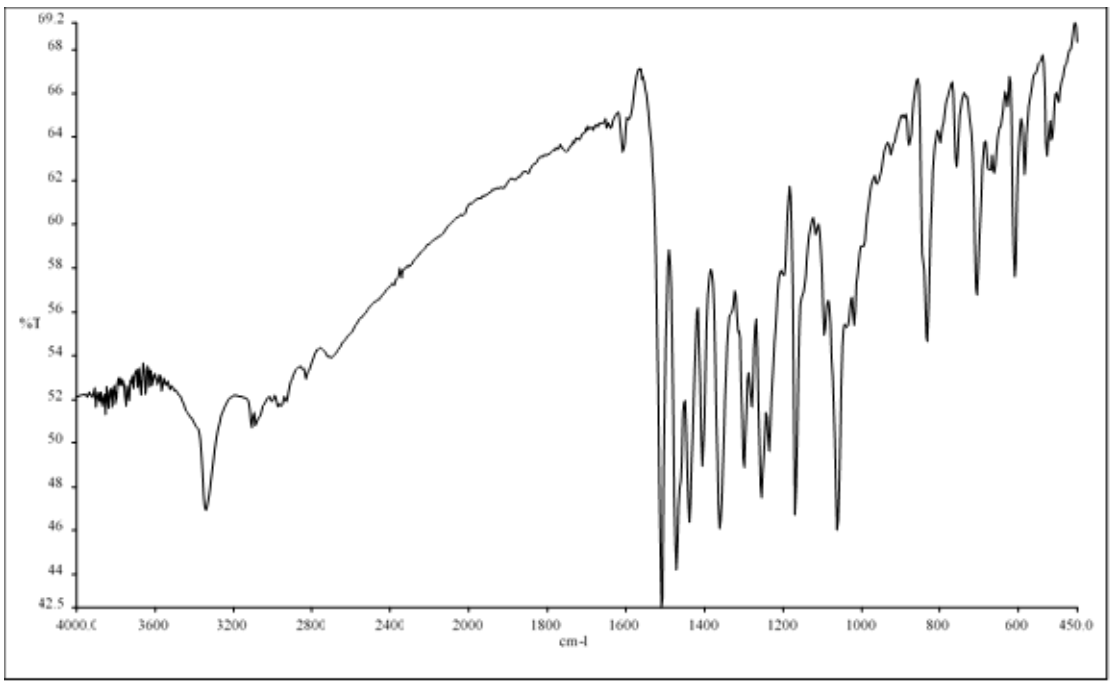


Figure 3. FT-IR spectrum of (4b) 4,5-Dihydroxy-1- (4-methoxyphenyl) -3- (1,3-thiazol-2-yl) imidazolidine-2-thione.

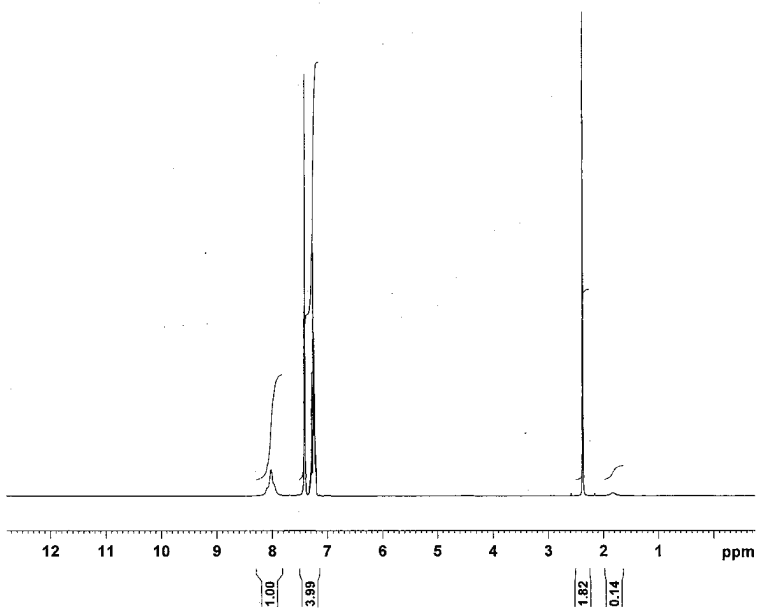


Figure 4. [1]H NMR spectrum of (1c) 1-(4-methylphenyl)-3-phenyl-thiourea (CHCl3-d).

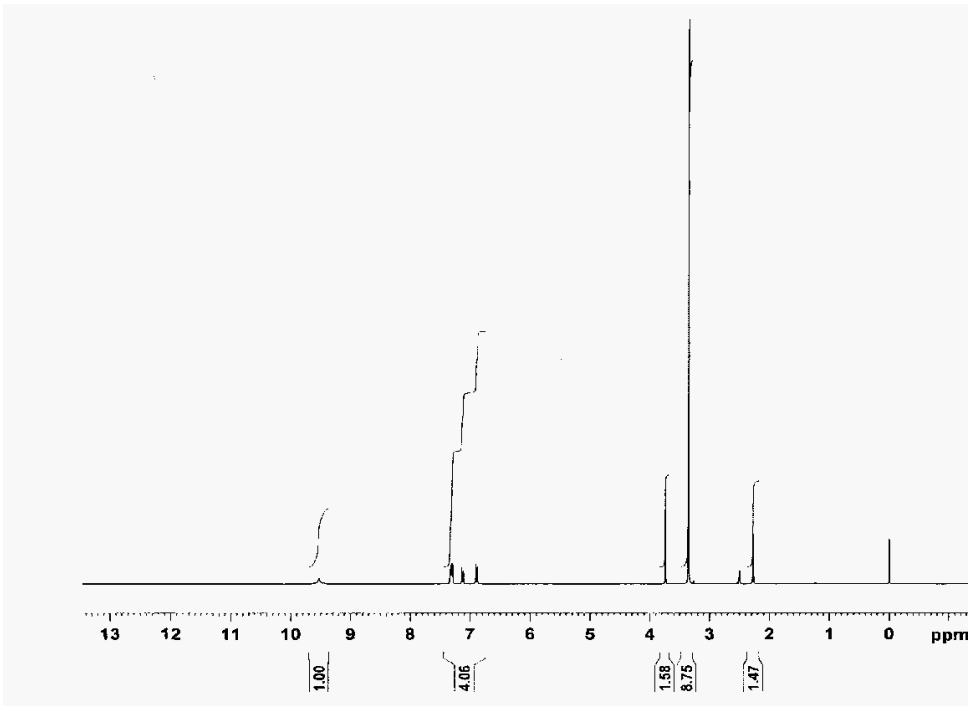


Figure 5. [1]H NMR spectrum of (2c) 1-(4-Methoxyphenyl) -3- (4-methylphenyl) thiourea (DMSO-d6).

disappeared. At spectrum; in the range of 3218-3150 cm^{-1}; N-H stretching vibration, 3105-3020 cm^{-1}; aromatic C-H stretching vibration, 1600-1595 cm^{-1}; C = C stresses and in the range of 1342–1100 cm^{-1} CS peaks are observed. The FT-IR spectrum of **1c** and **2c** are demonstrated in Figure 1 and Figure 2, respectively. Major peaks for **3a-e, 4a-c** compounds in the IR spectrum; band observed at 3460-3200 cm^{-1} is due to OH vibrations, 3030 cm^{-1}; aromatic stretching vibrations, 2890–2900 cm^{-1}; aliphatic CH peak, in peak near 2800 cm^{-1} to R-OCH_3 bands. The FT-IR spectrum of **4b** was demonstrated in Figure 3.

In [1]H NMR spectrum, the ratio of the protons integral height in the spectra of all the compounds supports the proposed structures. The [1]H NMR spectrum of **1c**, **2c** and **4b** are illustrated in Figure 4 and Figure 5, 6, respectively. We can see [1]H-NMR

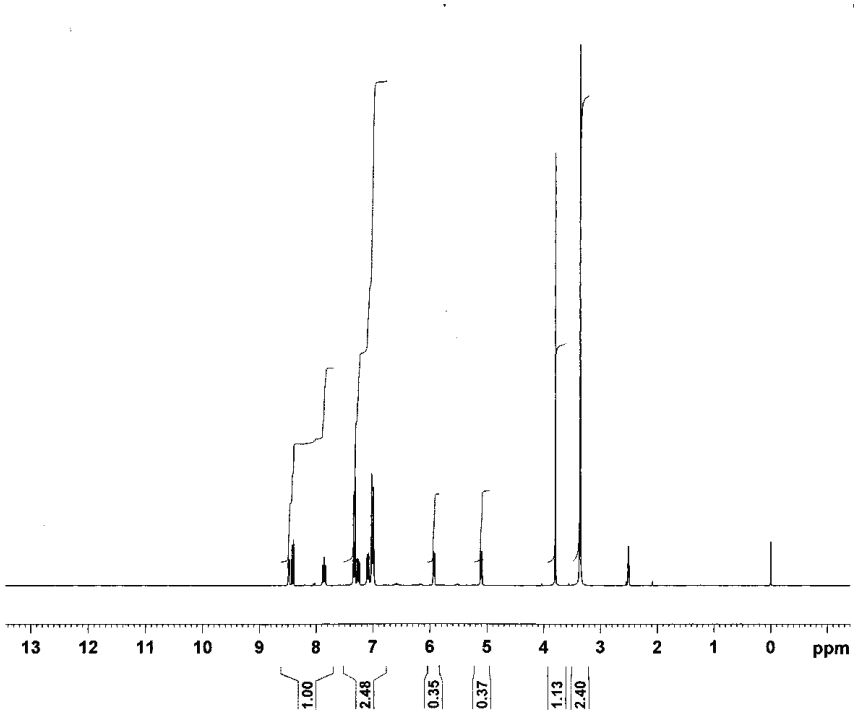


Figure 6. 1 H NMR spectrum of (4b) 4,5-Dihydroxy-1- (4-methoxyphenyl) -3-pyridin-2-yl-imidazolidin-2-thione.

spectrum of N-N'-substituted thiourea, NH peaks were observed around 8.00-13.75 ppm, mainly as broad singlet and sharp peak. These peaks are characteristic NH peak and indicate the presence of these structures. The containing pyrimidine and thiazole compounds, NH peak was shifted up to 13.75 ppm because of N and S atoms. The peaks in the 8.00 to 6.00 pm, supports the about the aromatic ring.

The ^{1}H NMR spectrum of N-N'-substituted-4,5-dihydroxy-imidazolidine-2-thione compounds showed peaks at 5.00-5.90 ppm reveal the imidazolidin CH peaks. OH and aromatic ring peaks are out of the in the immediate area. So, this peaks are entered intertwined.

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