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Synthesis and Nuclear Magnetic Resonance Studies of 2-Thiophenecarboxaldehyde Nicotinic Hydrazone and 2-Thiophenecarboxaldehyde Benzhydrazone

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Synthesis and NMR spectral studies of bidentate N and S heterocycles of 2-thiophenecarboxaldehyde nicotinic hydrazone and 2-thiophenecarboxaldehyde benzhydrazone have been carried out. The compounds, 2-thiophenecarboxaldehyde nicotinic hydrazone and 2-thiophenecarboxaldehyde benzhydrazone were synthesized by reacting stoichiometric quantities of nicotinic hydrazide and benzhydrazide with 2-thiophene carboxaldehyde in methanol in the presence of glacial acetic acid at refluxing temperature. Upon cooling the reaction mixture, the products were obtained as colorless solids. ^{1}H, ^{13}C, ^{1}H-^{1}H COSY, and ^{1}H-^{13}C HSQC experiments have been conducted to characterize the compounds.

Key words: 2-thiophenecarboxaldehyde nicotinic hydrazone; 2-thiophenecarboxaldehyde benzhydrazone; 2D NMR

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During the last two decades, much interest has been focused on compounds containing hydrazide and hydrazone moieties and their complexes with first row transition metal ions. This is in view of the fact that they are involved in biological systems and analytical chemistry [1-4]. The chemistry of acid hydrazone is an active area of study, and numerous transition metal complexes containing hydrazones as ligands have been investigated.

There have been a number of reports on the synthesis of new acyl hydrazones, like 1, 3-phenylene bis (methanylylidene) di (benzohydrazide) and 1,3-phenylene bis (methanylylidene) di (nicotinohydrazide), where the carbonyl oxygen of a hydrazone promotes the formation of a chelate binding center [5]. Some hydrazones, like macrocyclic terephthalic acid hydrazone prepared from the reaction between 2, 6 diformyl-4-methyl phenol and 1, 4-dicarbonyl phenyl dihydrazide, were used as reagents in quantitative analysis (especially in colorimetric and flurometric determination) of metal ions [6, 7].

There are also reports about hydrazones acting as effective drugs in the treatment of iron overload diseases or genetic diseases such as beta-thalassemia [8]. Hydrazones have found wide applications in synthetic chemistry [9] and they are also used as indicators. Hydrazones are now being used extensively in the detection and quantitative determination of several metal ions, for the preparation of compounds having diverse structures in analytical chemistry, and for the identification and isolation of carbonyl compounds where the proton exchange takes place from the peroxy to the ferryl intermediate of oxidase cytochrome [10-14].

The acyl hydrazones show various coordination modes with metal ions depending on the reaction conditions and the stability of the metal complexes formed. The number and types of the substituents in hydrazones also influence the coordination mode. Schiff bases containing R-C=N- group form an interesting class and serve as chelating agents capable of coordinating to one or more metal ions, producing mononuclear or polynuclear complexes. Such complexes serve as models for metallo-proteins. The hydrazones have been used as herbicides, insecticides, nematocides, rodenticides, and plant growth regulators [15-19].

EXPERIMENTAL

1. General Remarks

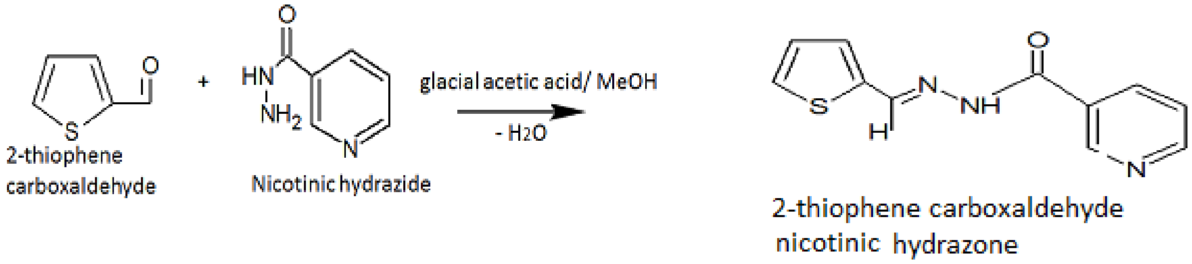
2-thiophene carboxaldehyde, nicotinic hydrazide, benzhydrazide, methanol, glacial acetic acid, and vanadyl acetylacetonate were procured from Sigma Aldrich and used without further purification.

Two hydrazones were synthesized using nicotinic hydrazide, benzhydrazide, and 2-thiophene carboxaldehyde as starting materials. They were characterized by various physico-chemical techniques. The hydrazones were chosen as ligands for the preparation of metal complexes.

They were

(1) 2-thiophenecarboxaldehyde nicotinic hydrazone

(2) 2-thiophenecarboxaldehyde benzhydrazone



Scheme 1. Synthesis of 2-thiophene carboxaldehyde nicotinic hydrazine

The melting points were determined. The melting points of 2-thiophenecarboxaldehyde nicotinic hydrazone and 2-thiophenecarboxaldehyde benzhydrazone were found to be 238˚C and 204˚C, respectively. Microanalysis was carried out on an elemental model vario EL III CHNS analyzer. IR spectra were recorded on Thermo Nicolet AVATAR 370 DTGS model FT-IR spectrophotometer as KBr pellets and the data were collected in the transmission mode. ^{1}H and ^{13}C spectra were recorded on Bruker AMX 400 FT-NMR spectrometer with DMSO- d_6 as the solvent and TMS as the internal standard.

2. Preparation of 2-thiophenecarboxaldehyde Nicotinic Hydrazone

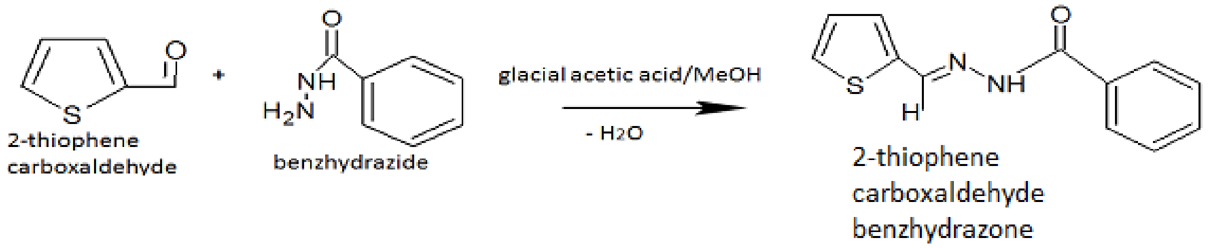
Nicotinic hydrazide (0.14 g, 1 mmol) was dissolved in methanol (30 ml) and to this was added 2-thiophene carbaldehyde (0.11 ml, 1 mmol), followed by two drops of glacial acetic acid. The mixture was refluxed for 6 hours and kept aside for cooling, during which colorless 2-thiophenecarboxaldehyde nicotinic hydrazone crystals (Scheme 1) separated out. The mixture was filtered and the crystals were washed with methanol. The crystals were dried over P_4O_{10} *in vacuo*.

2-thiophene carboxaldehyde nicotinic hydrazone. colorless crystal, m.p.:238˚C yield; 70%; IR (KBr, νmax, cm^{-1}): 3236 ῦ (NH), 1645 ʋ (C=O), 1558 ʋ (C=N), 846 ʋ (C-S-C). ^{1}H-NMR (500 MHz, CDCl3): 12.0 (NH), 9.1 (C-H, azomethine), 7.0-8.8 (Ar-H)); ^{13}C-NMR (125 MHz, $CDCl_3$): C(1) 148.5, C(3) 129.2, C(4) 128.6, C(5) 135.3, C(6) 138.8, C(9) 161.5 , C(11) 131.2, C(12) 151.3, C(14) 152.2, C(15) 127.8, C(16) 143.5. UV-visible (acetonitrile, 10^{-4} M, cm^{-1}): 442 nm (22624 cm^{-1}) (n-π*), 284 nm (35211 cm^{-1}) (π -π*)

3. Preparation of 2-thiophenecarboxaldehyde Benzhydrazone

Benzhydrazide (0.14 g, 1 mmol) was dissolved in methanol (30 ml) and to this was added 2-thiophene carbaldehyde (0.11 ml, 1 mmol), followed by two drops of glacial acetic acid. The mixture was refluxed for 6 hours and kept aside for cooling, during which colorless 2-thiophenecarboxaldehyde benzhydrazone crystals separated out (Scheme 2). The mixture was filtered and the crystals were washed with methanol. The crystals were dried over P_4O_{10} *in vacuo*.

2-thiophene carboxaldehyde benzhydrazone. colorless crystal, m.p.:204˚C yield; 73%; IR (KBr, νmax, cm^{-1}): 3253 ʋ (N-H), 1642 ʋ (C=O), 1549 ʋ (C=N), 852 ʋ (C-S-C). ^{1}H-NMR (500 MHz, $CDCl_3$): 11.8 (NH), 9.1 (C-H, azomethine), 7.0-8.8 (Ar-H).); ^{13}C-NMR (125 MHz, $CDCl_3$): C(0) 131.644, C(1) 142.881, C(3) 128.868, C(4) 127.488, C(5) 130.805, C(6) 133.368, C(9) 162.937, C(11) 139.090, C(12) 130.805, C(13) 128.402, C(14) 127.784, C(15) 128.402 ppm. UV-visible (acetonitrile, 10^{-4} M, cm^{-1}): 396 nm (252525 cm^{-1}) (n-π*), 286 nm (34965 cm^{-1})



Scheme 2. Synthesis of 2-thiophene carboxaldehyde benzhydrazone

RESULTS AND DISCUSSION

The microanalysis of the heterocycles was in good agreements with the molecular formulae. The electronic spectra of substituted hydrazones were recorded in acetonitrile solution (10^{-4} M). UV-Vis spectra of the ligands displayed bands around 400 and 290 nm, which were assigned to n-π* and π -π* transitions (Fig. (1) and (2)).

The structural and spectroscopic assignments were made through the combined use of 1D and 2D NMR experiments such as ^{1}H, ^{13}C, ^{1}H-^{1}H COSY, and ^{1}H-^{13}C HSQC experiments. The proton NMR spectrum of 2-thiophenecarboxaldehyde nicotinic hydrazone recorded in DMSO-d_6 displayed a singlet at δ 12.0 and this was assigned to NH proton at position 8. A signal at δ 9.1 was attributed to the proton on the azomethine carbon at position 6. The peaks due to protons on the thiophene and pyridine rings were in the range of 7 to 8.8 ppm.

The ^{13}C-NMR spectrum of 2-thiophenecarboxaldehyde nicotinic hydrazone was recorded in DMSO-d_6. The spectrum provided information about the carbon skeleton of the molecule. Among all the carbons, the carbonyl carbon at position 9 was the most deshielded and it resonated at δ 161.5. The carbons adjacent to the ring nitrogen at positions 12 and 14 were also deshielded and these resonated at δ 151.3 and 152.2, respectively. The proton NMR spectrum of 2-thiophenecarba benzhydrazone recorded in DMSO-d_6 exhibited a singlet at δ11.8 and this was ascribed to NH proton at position 8. A signal at δ 8.8 was attributed to the proton on the azomethine carbon at position 6. The resonances due to protons on the thiophene and benzene rings were in the range of 7.1 to 8.0 ppm. The *ortho* protons of the benzene ring at 11, 15 showed a doublet at 7.9 ppm. The *meta* and *para* protons exhibited triplets at δ 7.6 and 7.7, respectively, owing to vicinal coupling.

The ^{13}C-NMR spectrum of 2-thiophenecarboxaldehyde benzhydrazone was recorded in DMSO-d_6 (Fig. 4). The carbonyl carbon at position 9 was the most deshielded because of the π bond and the electronegative oxygen associated with it. It resonated at δ 62.9. Carbon 1 in the thiophene ring displayed a signal at δ142.9, implying its deshielded environment.

The electronic spectra of the prepared hydrazones were taken in acetonitrile. UV-Vis spectra of the ligands displayed bands which corresponded to n-π* and π -π*.

1. UV-visible Spectra of the Hydrazones

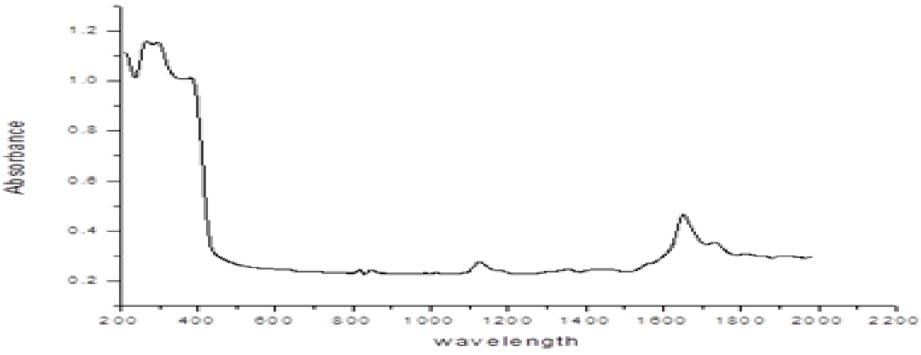


Figure 1. Electronic spectrum of 2-thiophene carboxaldehyde nicotinic hydrazone

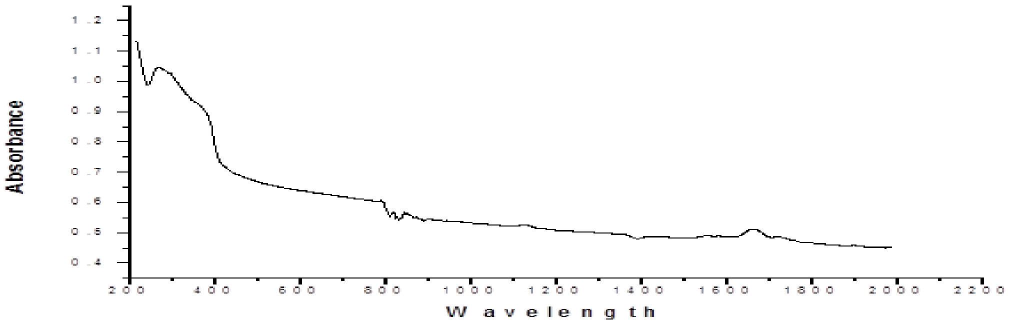


Figure 2. Electronic spectrum of 2-thiophene carboxaldehyde benzhydrazone

2. One Dimensional NMR Spectral Studies

^{1}H-NMR spectral studies

a) ^{1}H-NMR spectral studies of 2-thiophene carboxaldehyde nicotinichydrazone

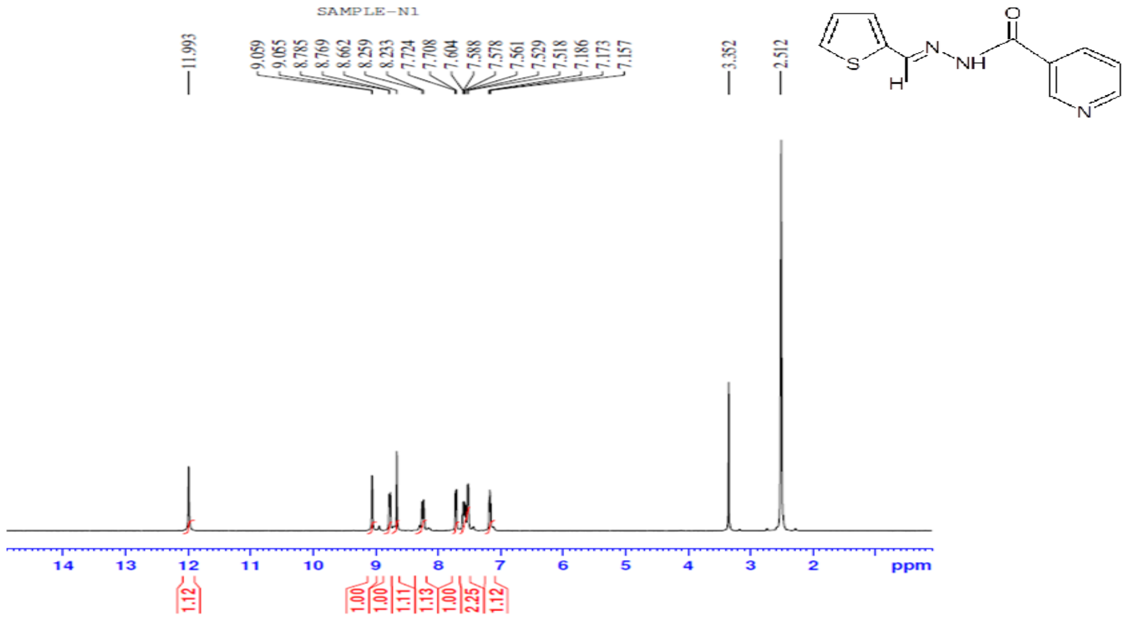


Figure 3. ^{1}H-NMR spectrum of 2-thiophene carboxaldehyde nicotinic hydrazone

b) ^{1}H-NMR spectral studies of 2-thiophene carboxaldehyde benzhydrazone

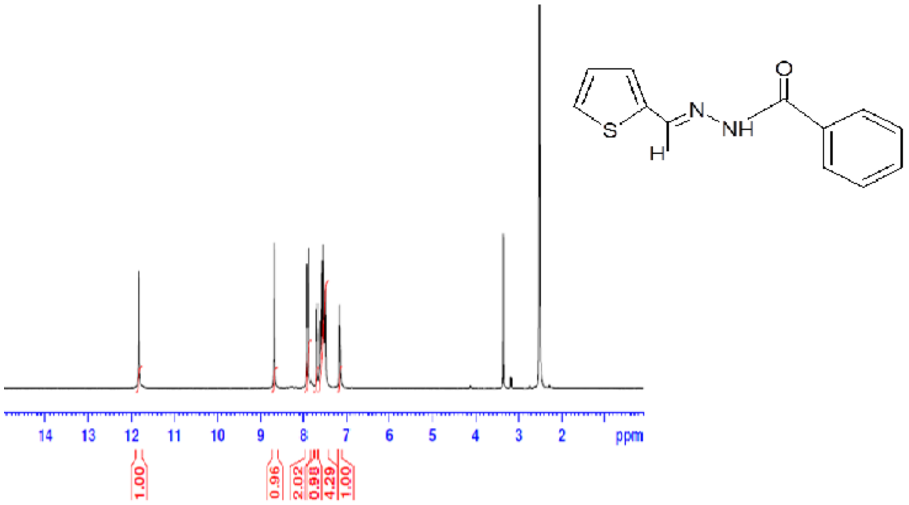


Figure 4. ^{1}H-NMR spectrum of 2-thiophene carboxaldehyde benzhydrazone

^{13}C-NMR spectral studies

a) ^{13}C-NMR spectral studies of 2-thiophene carboxaldehyde nicotinichydrazone

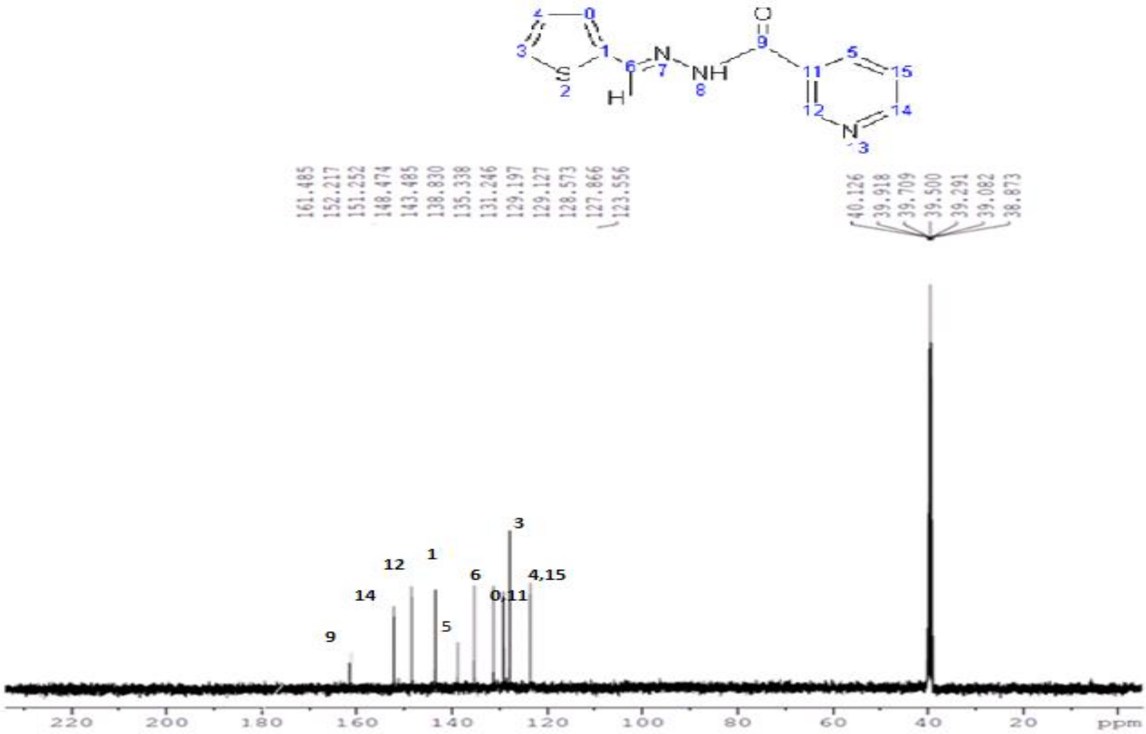


Figure 5. ^{13}C-NMR spectrum of 2-thiophene carboxaldehyde nicotinic hydrazone

b) ^{13}C-NMR spectral studies of 2-thiophene carboxaldehyde benzhydrazone

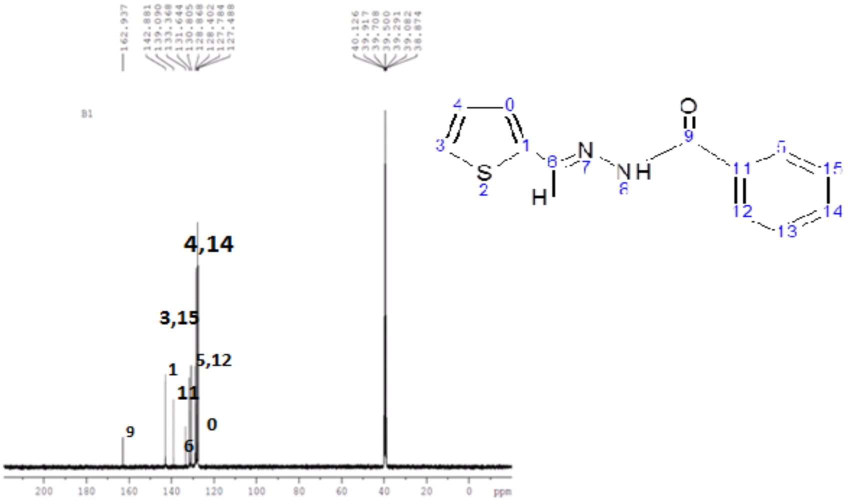


Figure 6. ^{13}C-NMR spectrum of 2-thiophene carboxaldehyde benzhydrazone

3. Two Dimensional NMR Spectral Studies

Homonuclear 2D NMR spectral studies of hydrazones

a) ^{1}H-^{1}H coupling (COSY) NMR spectral studies of 2-thiophenecarboxaldehyde nicotinic hydrazone

The COSY spectrum of the hydrazone (Fig. 7) indicated ^{1}H-^{1}H coupling. The diagonal contours at δ 11.9 and 9.1 due to NH and CH protons at positions 8 and 6, respectively, did not exhibit cross peaks, substantiating the assignments made in the spectrum. The contours for protons at positions 5, 9, 14, and 16, each exhibited a doublet in 1D NMR due to vicinal coupling. The protons at positions 4 and 15, each displayed a triplet owing to vicinal coupling with the neighboring protons on either side. In the 2D NMR, cross peaks were obtained for these protons.

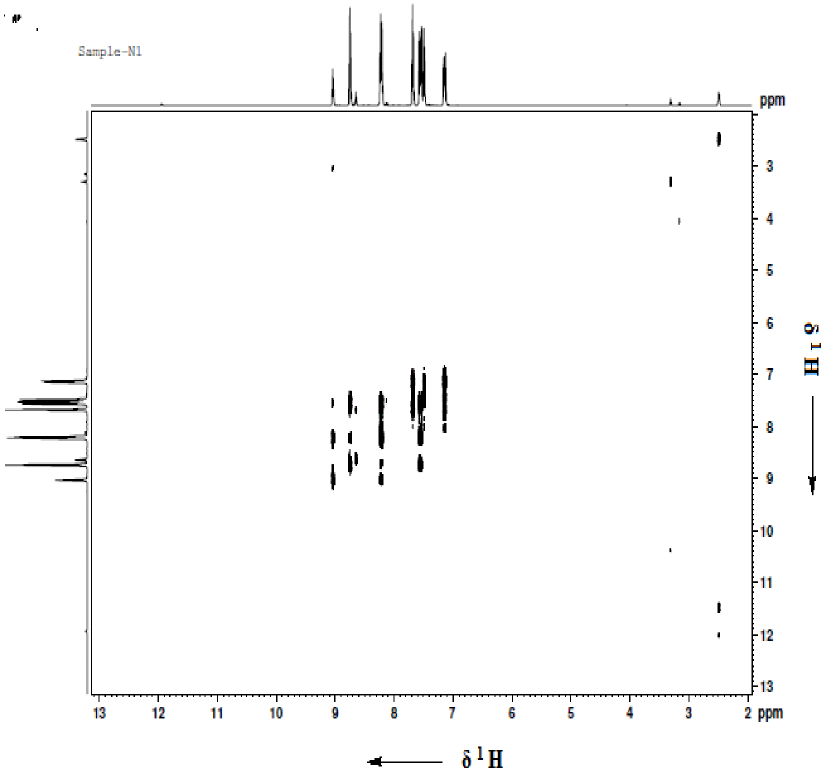


Figure 7. COSY spectrum of 2-thiophenecarboxaldehyde nicotinic hydrazone

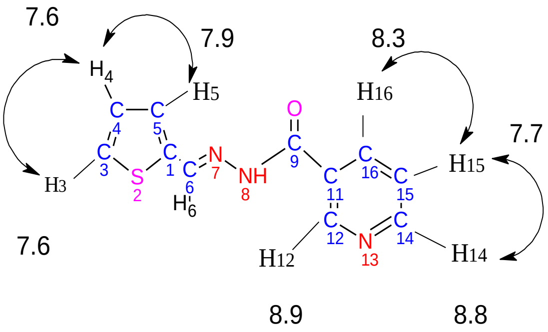


Figure 8. ^1H-^1H coupling of 2-thiophenecarboxaldehyde nicotinic hydrazone

b) ^1H-^1H coupling (COSY) NMR spectral studies of 2-thiophenecarboxaldehyde benzhydrazone

The COSY spectrum of 2-thiophenecarboxaldehyde benzhydrazone (Fig. 9) has revealed ^1H-^1H coupling. The contours at δ 11.9 and 8.8 due to NH and CH protons at positions 8 and 6, respectively, did not show off diagonal contours, supporting the assignments made in the 1D NMR spectrum. However, off-diagonal contours were observed for the contours arising from protons at positions 3, 4, 5, and 12 to 16, implying the existence of remaining protons owing to vicinal coupling. This corroborated the appearance of doublets for protons at positions 3, 5, 12, and 16, and triplets for protons at positions 4, 13, 14, and 15 in the 1D spectrum.

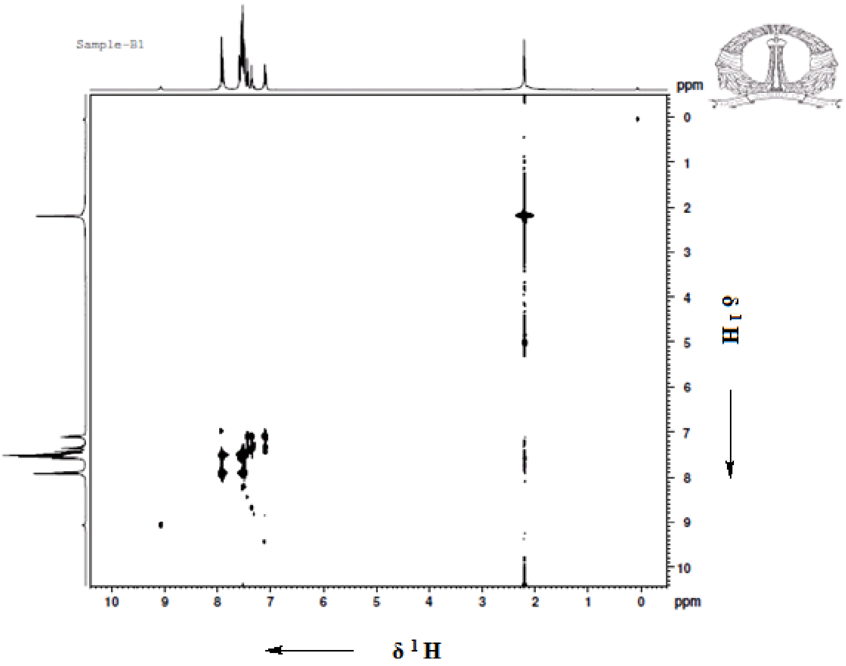


Figure 9. COSY spectrum of 2-thiophenecarboxaldehyde benzhydrazone

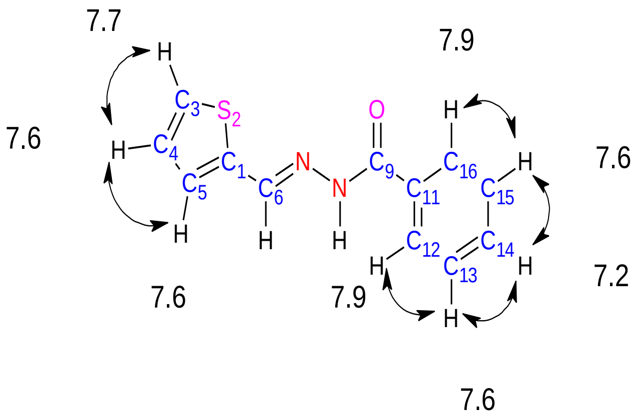


Figure 10. ^{1}H-^{1}H coupling of 2-thiophenecarboxaldehyde benzhydrazone

4. Heteronuclear 2D NMR Spectral Studies of Hydrazones

a) ^{1}H-^{13}C correlation (HSQC) NMR spectral studies of 2-thiophenecarboxaldehyde nicotinic hydrazone

Heteronuclear Single Quantum Coherence / Correlation (HSQC) experiment was used to find proton-connected carbons. This was a 2D experiment wherein X and Y axes represent the proton and carbon chemical shifts, respectively. The HSQC spectrum of 2-thiophenecarba nicotinic hydrazone is shown in Fig. 11. Accordingly, the contours corresponding to the carbons at positions 1 (148.5), 9 (δ 161.5), and 11 (δ 131.3) were absent, as these were not associated with hydrogens and thus supporting the assignments (Fig.12).

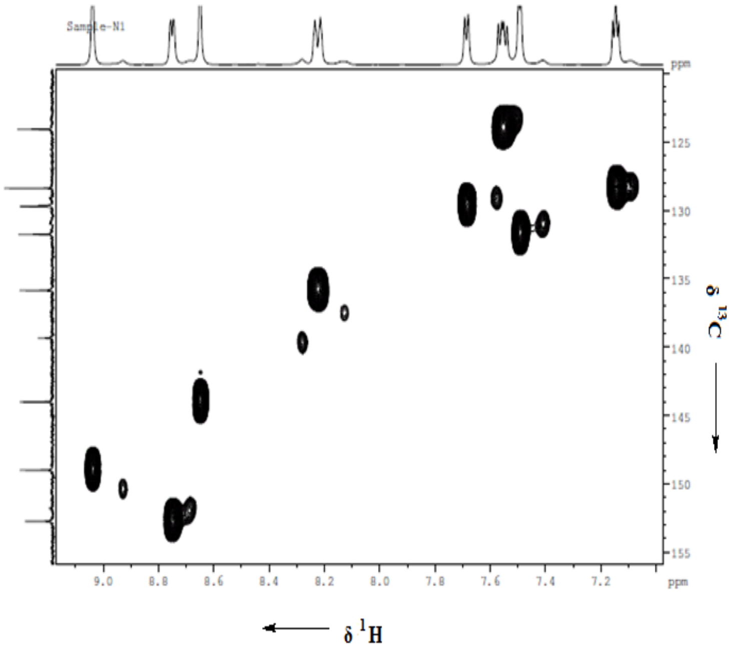
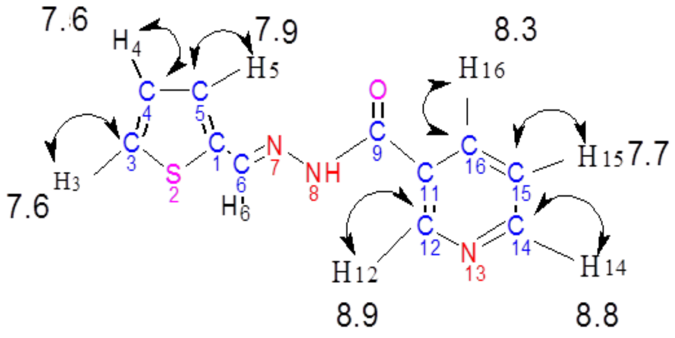


Figure 11. HSQC spectrum of 2-thiophenecarboxaldehyde nicotinic hydrazone



Number	$\delta^{13}C$	δ^{1H}
3	129.9	7.6
4	128.6	7.6
5	135.3	7.9
12	151.2	8.9
14	152.2	8.8
15	127.8	7.7
16	143.5	8.3

Figure 12. ^1H-^{13}C coupling of 2-thiophenecarboxaldehyde nicotinic hydrazone

b) ^1H-^{13}C correlation (HSQC) NMR spectral studies of 2-thiophenecarboxaldehyde benzhydrazone

The HSQC spectrum of 2-thiophenecarboxaldehyde benzhydrazone is illustrated in Fig. 13 and the coupling is displayed in Fig. 14. In the spectrum, the contours corresponding to the non-protonated carbons at positions 1 (δ 142.9), 9 (δ 162.9), and 11 (δ 139.1) were absent, indicating the assignments as valid.

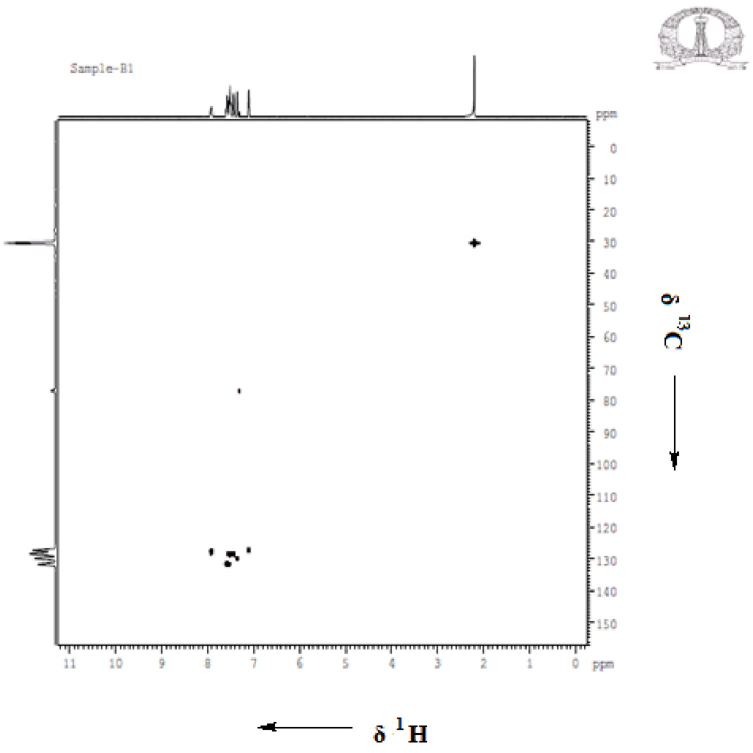
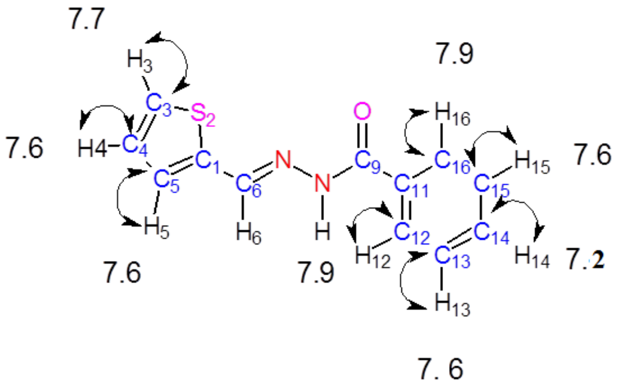


Figure 13. HSQC spectrum of 2-thiophenecarboxaldehyde benzhydrazone



Number	δ¹³C	δ¹H
3	128.9	7.7
4	127.5	7.6
5	131.6	7.6
12	130.8	7.9
13	128.4	7.6
14	127.8	7.2
15	128.4	7.6
16	130.8	7.9

Figure 14. ^{1}H-^{13}C coupling of 2-thiophenecarboxaldehyde benzhydrazone

CONCLUSIONS

In conclusion, we described the synthesis of 2-thiophenecarboxaldehyde nicotinic hydrazone and 2-thiophenecarboxaldehyde benzhydrazone as new bidentate ligands, and they were characterized by IR, UV-visible, CHNS, and NMR analyses. IR spectral data demonstrated the ligands to act via coordinating through azomethine nitrogen and oxygen atoms when going for complexation.

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