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MICROWAVE-ASSISTED SINGLE-STEP SYNTHESIS OF ACID HYDRAZIDES FROM CORRESPONDING ACIDS UTILIZING NEWLY DESIGNED APPARATUS

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ABSTRACT
Many Acid hydrazides are essential intermediates in organic synthesis. Their conventional synthesis require a two-step pathway; esterification and hydrazine hydrate treatment; in order to obtain the hydrazide. The microwave-assisted synthetic methodology was utilized as a greener and straightforward single-step approach for their synthesis in highly encouraging yields. Thus, the aim of the present work was to synthesize acid hydrazides of Diclofenac, Indomethacin, Ibuprofen, and Mefenamic acid using microwave radiation with the aid of a newly designed fit-in ice condenser. The acid hydrazides of the selected compounds were synthesized utilizing both the conventional and the proposed microwave-assisted single-step methods. The developed technique was successfully yielded 86.7%, 40.9% and 65.5% acid hydrazides of Diclofenac, Indomethacin and Mefenamic acid in just 3 min., 10 min. and 3 min., respectively. In comparison to the conventional method, the developed method was simpler with a very short reaction time and quantified yields. The structures of the synthesized acid hydrazides were also confirmed using FT-IR and ^{1}H-NMR. The proposed method with the modified fit-in ice condenser proved to be efficient, cost-effective and time-saving in the synthesis of acid hydrazides under study in a single step.

INTRODUCTION

Chemistry plays a significant role in our daily lives; in the form of medicines, food colors, soaps, detergents, sunscreen lotions, toothpaste, pharmaceuticals, and other products. However, as a result of the different techniques used in chemical synthesis, several hazardous compounds were also produced which in turn polluting the environment. Therefore, to counteract these issues, scientists from diverse fields are attempting to develop new green techniques. Microwave-assisted organic synthesis is an excellent solution to many restraints in organic synthesis as the

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microwave radiations increase the friction between molecules and so collisions resulting in an increase in the reaction rates with high selectivity [1-3]. Hence, it reduces the time of reactions dramatically, prevents side reactions, and increases yields %. Special microwave devices (microwave reactors) was found to control time, pressure, and temperature. On the other hand, these advances are expensive and required skills.

Acid hydrazides have long been recognized as significant intermediates in the organic synthesis of a variety of chemicals, such as hydrazone, heterocyclic synthesis, and target molecules. They are crucial critical intermediates in the synthesis of many physiologically active heterocycles, and their synthesis has received a lot of attention due to their value as building blocks [4-7] and as versatile precursors for the synthesis of a range of substituted heterocycles [8-11]. Different acid hydrazide derivatives were also synthesized fom many drugs containing a carboxylic acid group in order to enhance their gastric tolerance, reduce their gastric irritation, and get a new pharmacological activity [12-14].

Thus, the aim of the present work was to synthesize the acid hydrazides of Diclofenac, Indomethacin, Ibuprofen, and Mefenamic acid (Fig. 1) directly from the acids using microwave radiation, skipping the esterification step, with the specially designed fit-in ice condenser (Fig. 2).

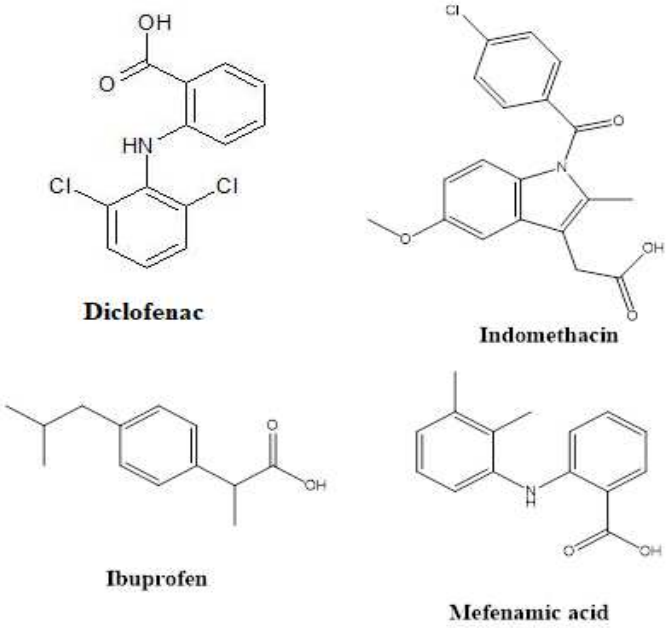


Figure 1: Chemical structure of parent compounds

EXPERIMENTAL

Materials:

Diclofenac, Indomethacin, Ibuprofen, and Mefenamic acid working standards were obtained from Amipharma laboratories –Sudan. Ethanol absolute SDF- South Korea, Methanol absolute SDF- South Korea, and Hydrazine hydrate 99%- SDF- South Korea.

Equipment:

Fit-in ice condenser (borosilicate glass, thickness 3mm) composed of three parts; outer wall, inner wall, and drainage joint; connected with Quickfit joints (Fig. 2). Flat bottom flask 50 mL, and Pre-coated TLC silica gel 60 F_{254} from Merck

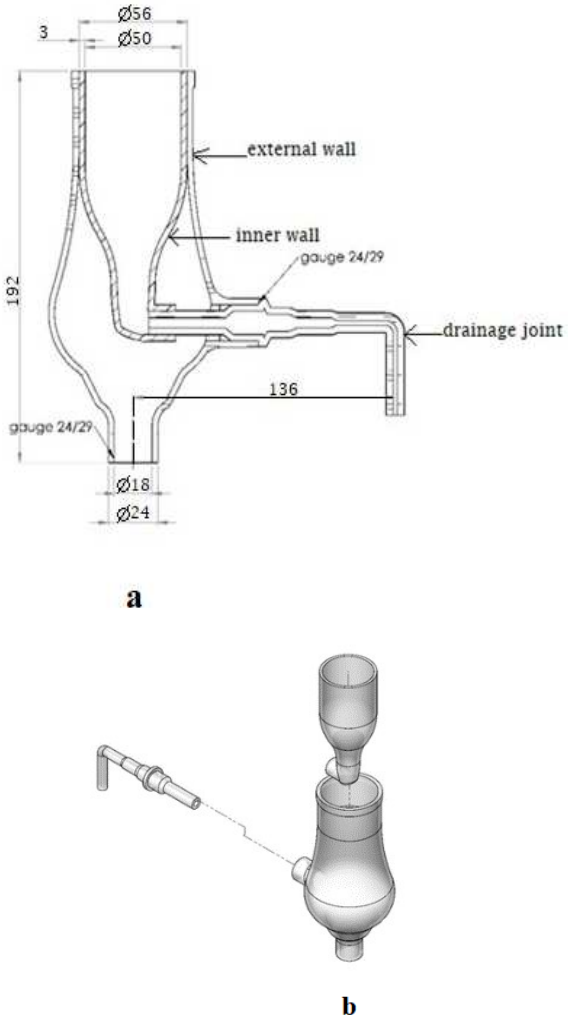


Figure 2: a. 2D section of the modified fit-in ice condenser. b. 3D view to show the assembly of condenser parts

Apparatus setting:

Firstly, the inner part was installed and secured with quick fit joint to the outer part, and then the drainage joint was inserted

and secured with double joints to both the inner and the outer wall. The flat bottom flask (50ml in size) was fitted with fit-in ice condenser through glass joint, ice was then placed inside the upper cavity of the condenser, and the whole apparatus was inserted inside the cavity of the microwave.

A receiving beaker was placed to contain the dripping water out of the drainage joint. After ensuring the steadiness of the apparatus, the microwave was initiated to work. After the completion of the reaction time, the apparatus was removed from the microwave cavity, and allowed to cool before removing the condenser from the flat bottom flask.

Procedures:

Developed technique (direct synthesis, single step):

In a 50 mL flat bottom flask, diclofenac acid (0.5010 g, 0.00169 mole) was transferred. 2 mL hydrazine hydrate was added to the mixture. The flask was fitted with the condenser and microwave heated for 10 seconds (power: 700 W). After that, 10 mL of ethanol was added, and the mixture was microwave-refrigerated for 3 minutes (power: 140 W). The reaction was quenched by adding ice chips, and crystals were then separated, filtered and dried at room temperature (compound 1H).

Indomethacin (0.998 g, 0.0027 mole) was transferred into a 50 mL flat bottom flask. 2 mL of hydrazine hydrate was added. The flask was fitted with the condenser and refluxed under microwave heating (power: 700 W) for 10 seconds. 10 mL of ethanol was then added, and the mixture was refluxed for 10 min under the microwave radiation (power: 140 W). The reaction was quenched by adding ice chips, and crystals were then separated, filtered and dried at room temperature (compound 2H).

Ibuprofen (2.5361 g, 0.0115 mole) was placed in a 50 mL flask with a flat bottom. 2 mL hydrazine hydrate was added to the mixture. The flask was equipped with a condenser and microwave heated (power: 700 W) for 10 seconds to reflux the contents. After that, 10 mL of ethanol was added, and the mixture was microwaved for 3 minutes on high (power: 140 W). The reaction was stopped using ice chips, and the chemicals were separated in a TLC plate.

Mefenamic acid (7.9997 g, 0.0331 mole) was transferred into a 50 mL flat bottom flask. 2 mL of hydrazine hydrate was added. The flask was fitted with a condenser and refluxed under microwave heating (power: 700 W) for 10 seconds, then 10 mL of ethanol was added, and the mixture was refluxed for 3 min under the microwave (power: 140 W). The reaction was quenched by adding ice chips, and crystals were then separated, filtered and dried at room temperature (compound 4H).

Conventional mode (two-steps method):

Synthesis of Esters:

Diclofenac acid (10.016 g, 0.0338 mole) was transferred into a flat bottom flask, dissolved in 20 ml of methanol, 1 ml of conc. sulfuric acid was added drop wise with continuous shaking. The flask was fitted with the fit-in ice condenser and the mixture was heated under microwave radiation for 6 min (full power mode, 700 W). Crystals of the formed ester (1E) was separated upon cooling, collected and then purified by recrystallization from 30% methanol.

Indomethacin (3.0150 g, 0.0084 mole) was transferred into a flat bottom flask, dissolved in 20 ml of absolute ethanol, 1 ml of conc. sulfuric acid was then added drop wise with continuous shaking. The flask was fitted with the fit-in ice condenser and the mixture was heated under microwave radiation for 8 min (full power mode, 700 W). A yellow oily layer (2E) was formed upon cooling and then collected. After recrystallization of 30% methanol, yellow crystals of the ester 2E were obtained.

Ibuprofen (3.017 g, 0.0146 mole) was transferred into a flat bottom flask, dissolved in 20 ml of specially dried methanol, 1 ml of conc. sulfuric acid was added drop wise with continuous stirring. The flask was fitted with the fit-in ice condenser and the mixture was heated under microwave radiation for 7 min and 30 sec (full power mode, 700 W). A clear colorless liquid (3E) was separated upon cooling.

In order to synthesize the ester 4E, Mefenamic acid (3.005 g, 0.0124 mole) was transferred into a flat bottom flask, dissolved in 20 ml of specially dried methanol, 1 ml of conc. sulfuric acid was added drop wise with continuous stirring. The flask was equipped with an ice condenser, and the solution was microwave heated for 8 minutes and 30 seconds (full power mode, 700 W). In 150 mL of carefully dried methanol, mefenamic acid (5.002 g, 0.0207 mole) was likewise dissolved, and 4.5 mL of conc. sulfuric acid was added dropwise with constant shaking. The mixture was heated under reflux for 26 hr. TLC was used for reaction follow-up.

Synthesis of Acid Hydrazides:

Diclofenac methyl ester 1E (3.016 g, 0.0097 mole) was transferred into a 100 ml round bottom flask, 10 ml of 99% hydrazine hydrate was added. The mixture was heated at 50 °C under condensation for 15 min, and then a sufficient amount of ethanol was added through the condenser to ensure complete dissolution. The mixture was then refluxed at 67 °C for 3 hrs. The reaction was quenched by adding iced water, and precipitate was formed. It was then collected by filtration and dried at room temperature (Compound 1H).

The synthesized Indomethacin ethyl ester 2E (3.0150 g, 0.0084 mole) was transferred into a 100 ml round bottom flask, 10 mL of 99% hydrazine hydrate was then added. The mixture was heated at 50 °C under reflux for 15 min, and then a sufficient amount of ethanol was added through the condenser to ensure complete dissolution. The mixture was refluxed at 67 °C for 3 hrs. A precipitate was separated upon the addition of iced water, which was then collected by filtration and dried at room temperature (Compound 2H).

In a 50 mL round bottom flask, 2 mL of ibuprofen methyl ester 3E (0.0022 mole) was transferred, followed by 20 mL of 99 percent hydrazine hydrate. Crystals were separated, filtered, and dried at room temperature after the mixture was agitated overnight (Compound 3H).

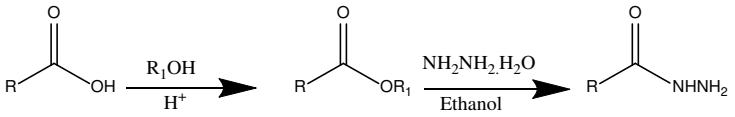
Identification tests:

The structure identification was carried using IR and NMR analysis. The NMR was carried on Bruker 400 MHz NMR spectrometer, the chemical shift values are expressed in δ (ppm) units using (TMS) as an internal standard, and the coupling constants (*J*) are expressed in Hertz (Hz). IR was carried on Shimadzu FT-IR spectrometer. Melting point testing was carried without correction on Stuart SMP10. The thin layer chromatography was carried with pre-coated TLC silica gel 60 F_{254} from Merck. In solubility testing, commercially available solvents were used.

RESULTS AND DISCUSSION

In recent years, because of raising environmental awareness, there has been a surge and interest in the synthesis of organic molecules utilizing green chemistry methods like microwave irradiation. Different pathways and methods were utilized in the synthesis of organic compounds with essential therapeutic activities. Since acid hydrazides group are essential intermediates in various synthetical pathways, it is vital to synthesize them utilizing simple, cost effective and time saving methods. Thus, in the present study, those compounds were selected due to their importance in the inflammatory pathway of the pathogenesis of diseases starting at pain and infections to oncogenesis. They relieve pain and inflammation by blocking the effects of the enzymes cyclooxygenase (COX-1 and COX-2). This prevents prostaglandin synthesis (prostaglandins elevate body temperature and make nerve endings more sensitive to pain transmission).

Generally, there are two methods applied for their synthesis, conventional [15], and microwave-assisted single-step method. Although the former method resulted in good yields, it was found to be time consuming and required two-steps pathway (Scheme I). The feasibility of microwave assisted synthesis has been demonstrated in a variety of transformations, due to its main characteristics of increased reaction rates, greater selectivity, and experimental ease of manipulation resulting in efficient, environmentally friendly, and cost effective synthetic pathways for a variety of compounds [16-18]. Moreover, herein the proposed method for acid hydrazides' synthesis has utilized simpler equipment and a newly designed condenser that outweigh the expensive and sophisticated microwave redactors, resulting in a significant reduction in synthesis cost with acceptable yield.



R: Diclofenac/Indomethacin/ Ibuprofen/Mefenamic acid
R_1: CH_3/C_2H_5

Scheme I: general representation of the conventional synthesis of acid hydrazides shows the two-step reaction

In the present study, acid hydrazides of Diclofenac, Indomethacin, Ibuprofen, and Mefenamic acid were synthesized using a microwave-assisted single-step method and the conventional method to carry out a comparison between them.

At first, esters of the four compounds were synthesized using the microwave radiation and obtained results were summarized in Table 1. Following that, the acid hydrazides of the compounds were synthesized either directly from the corresponding acid using the proposed method, or conventionally from the previously synthesized esters. A simple comparison was then

made between the obtained results from the proposed method and conventional synthesis of acid hydrazides (Table 2). Although the latter resulted in high yields, the developed technique was found to reduce the reaction time from the hour scale to minutes accompanied by a reasonable increase in %yield

Table 1: Results of the synthesized Esters

Compound	Time	Yield%
1E	6 min	97.65%
2E	8 min	72.1%
3E	7 min and 30 sec	95.6%
4E	8 min and 30 sec	F

*F: Failed to be synthesized

Table 2: Results of Acid hydrazides synthesis (mode, time, yield %)

Compound	Mode	Time*	Yield%
1H	Conventional	3hrs	84.9%
	Proposed technique	3:10 min	86.7%
2H	Conventional	3hrs	71.4%
	Proposed technique	10:10 min	40.9%
3H	Conventional	12hrs	95.4%
	Proposed technique	3:10 min	F
4H	Conventional	NA	F
	Proposed technique	3:10 min	65.5%

***Time in conventional mode does not include that for the esterification step. F= failure. NA= not available due to esterification failure**

Various reports revealed the synthesis of Diclofenac acid hydrazide in 5hrs and 12hrs with a yield of 81% and 95%, respectively [5, 10]. It is clear that those reports are supporting the priority and advantages of the present method which outweigh them in the time scale (Table 2). Moreover, the proposed technique yielded 86.7% of 1H in less than 4 min compared to 84.9% following the two-steps conventional method (Scheme I), Additionally, ester synthesis utilizing the developed method gave 97.65% in just 6 min, which in turn made the two-steps synthetic pathway of acid hydrazide even faster. 72.1% of compound 2E (Figure 3) was obtained in 8 min which was then used in 2H synthesis yielding 71.4% in 3hr reflux. Another reported method suggested mixing ethanol and hydrazine hydrate from the beginning and refluxing for 30 hrs will yield 52% [19]. Interestingly, compound 2H (Fig. 3) was obtained directly from Indomethacin with a good yield of 40.9% in 10 min utilizing the proposed single-step method.

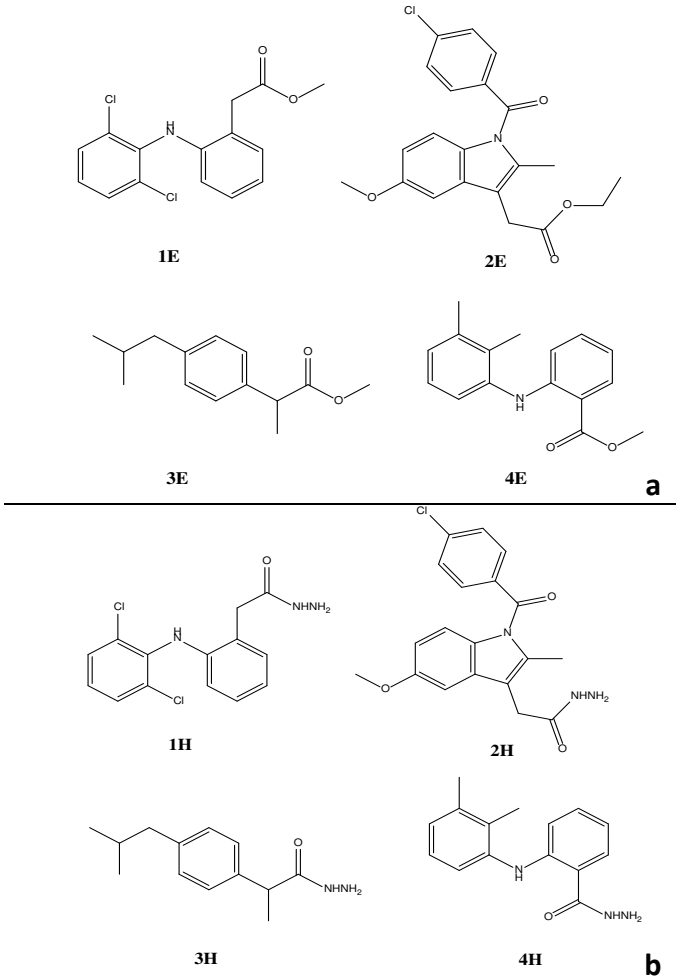


Figure 3: a. synthesized esters, b. Synthesized acid hydrazides

In regards to Ibuprofen, a reported method for the conventional synthesis of Ibuprofen methyl ester 3E required 12hrs refluxing [20]. However, using the fit-in ice condenser an excellent yield was obtained in a shorter time; 95% in less than 9 min. The acid hydrazide 3H was then synthesized from 3E after overnight stirring yielding 95.4%. Another method was also reported that 3H can be synthesized from the Ibuprofen directly in more than 21 hrs with a yield of 71% [21].

Unfortunately, the proposed method failed to separate a reasonable yield of 3H; this failure is believed to be due to the hydrolysis of 3H into Ibuprofen. This was confirmed by running

the solution on a TLC plate which showed the presence of Ibuprofen with traces (faint spot) of acid hydrazide.

Moreover, Mefenamic methyl ester 4E synthesis did not give promising results. TLC was used to follow up the reaction progress. It showed no ester formation after 26hrs of refluxing, while the same method was reported to give 80% in 18 hrs [22], and unpublished data suggested a two-week wait. As a result, 4H could not be synthesized as well, although reports mentioned 78-80% yield could be obtained [23]. 4H was then synthesized directly from Mefenamic acid using single-step synthesis to yield 65.5% in just 3 min and 10 sec. compared to 82% in 12 min with the microwave reactor [16]. Although the latter gave higher yield, the proposed method was proved to have superior performance in regards to reaction time.

Following the successful synthesis of the three acid hyrdrazides 1H; 2H; 4H with the proposed method, and 3H with the conventional method, different spectroscopic methods including FT-IR, ^{1}H-NMR and ^{13}C-NMR were used to identify the synthesized compounds. The obtained spectral data were found in consistent with the standards proving their identity and successful synthesis (Fig. 4 and 5).

2-(2-((2, 6-dichlorophenyl) amino) phenyl) acetohydrazide (1H): is a white powder that is highly soluble in methanol and ethanol and poor water solubility. Melting point 160-162 °C. FT-IR characteristic bands of compound 1H were 3325, 3150 cm^{-1} (NH), 3060, 3025 cm^{-1} (CH Ar), 2950, 2925 cm^{-1} (CH_2), 1638 cm^{-1} (C=O). ^{1}H-NMR (400 MHz, None) δ 7.44 (d, 2H), 7.21 (dd, J = 7.5, 1.3 Hz, 1H), 7.11-7.07 (m, 1H, 7.09-7.04 (m, 1H), 6.89 (td, J = 7.4, 1.2 Hz, 1H), 6.41 (dd, J = 8.1, 1.1 Hz, 1H), 3.65 (s, 2H). ^{13}C NMR 100 MHz (Methanol-D) 143.24, 130.10, 129.66, 128.65 , 127.30, 124.10, 121.13, 117.03, 37.47.

2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetohydrazide (2H): is a white powder with a melting point: 163-165° C, soluble in water, highly soluble in methanol, ethanol, dimethyl sulfoxide, chloroform, and dichloromethane. FT-IR characteristic bands of compound 2H were 3320, 3250 cm^{-1} (NH), 3050 cm^{-1} (CH Ar), 2850 cm^{-1} (CH_3), 1625 cm^{-1} (O=C-N), 1600 cm-1 (C=N), 1100 cm^{-1} (C-O).

2-(4-isobutylphenyl) propanehydrazide (3H): is a white powder, has a melting point: 80-81° C, readily soluble in methanol, chloroform, dichloromethane and dimethyl sulfoxide, highly soluble in ethanol, with good water solubility.

FT-IR characteristic bands for compound 3H are 3300, 3200, 3160 cm^{-1} (NH), 3050 cm^{-1} (CH Ar), 2910 cm^{-1} (CH_3), 2860 cm^{-1} (CH_2), 1690 cm-1 (O=C-N). ^{1}H-NMR (400 MHz, DMSO-D_6) δ 9.13 (s, 1H, NH), 7.25-7.06 (m, 4H,Ar-H), 3.48 (q, J = 7.0 Hz, 1H), 2.40 (d, J = 7.2 Hz, 1H), 1.85-1.75 (m, 1H), 1.31 (d, J = 7.2 Hz, 3H), 0.85 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-D_6), 173.37 (C=O), 139.78, 139.78, 139.70, 129.16, 127.44, 44.71, 43.37, 30.11, 22.65, 18.83.

2-((2,3dimethylphenyl) amino) benzohydrazide (4H): is a white shiny crystals, it is melting point: 178-179° C, soluble in methanol, ethanol, chloroform, and dimethyl sulfoxide. Poor solubility in water and dichloromethane. Most characteristic IR Bands for compound 4H: 3340, 3300 cm^{-1} (NH_2), 3250 cm^{-1} (NH), 3050 cm^{-1} (CH aromatic), 2940, 2820 cm^{-1} (CH_3), 1650 cm^{-1} (O=C-N) (Figure S1). ^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.88 (dd, J = 7.8, 1.6 Hz, 1H), 7.13-7.09 (m, 2H), 7.02 (t, J = 7.8 Hz, 1H), 6.85-6.81 (m, 2H), 6.61-6.57 (m, 1H), 2.26 (s, 3H, CH_3), 2.12 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-D_6) 132.29, 125.0, 124.0, 119.0, 116.43, 112.0, 20.82.

CONCLUSION

Acid hydrazides are important intermediates in organic synthesis, and conventional synthesis requires a two-step route of esterification; then, acid hydrazide synthesis. The developed method with the modified fit-in condenser was found to proceed this reaction in a single step in minutes or at least help in the synthesis of esters in fast and high yields. Mefenamic acid hydrazide 4H was synthesized in less than 4 min, which was failed to be obtained conventionally due to esterification failure. Indomethacin acid hydrazide 2H was synthesized in almost 3 hrs using the ester while obtained in 10 minutes directly. Additionally the total time for Ibuprofen acid hydrazide 3H synthesis is 12 hrs from an ester using microwave radiation, conventionally will take a day or two. Those overall findings support the speed and yield of the proposed method making it an excellent alternatives for the synthesis of acid hydrazides.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

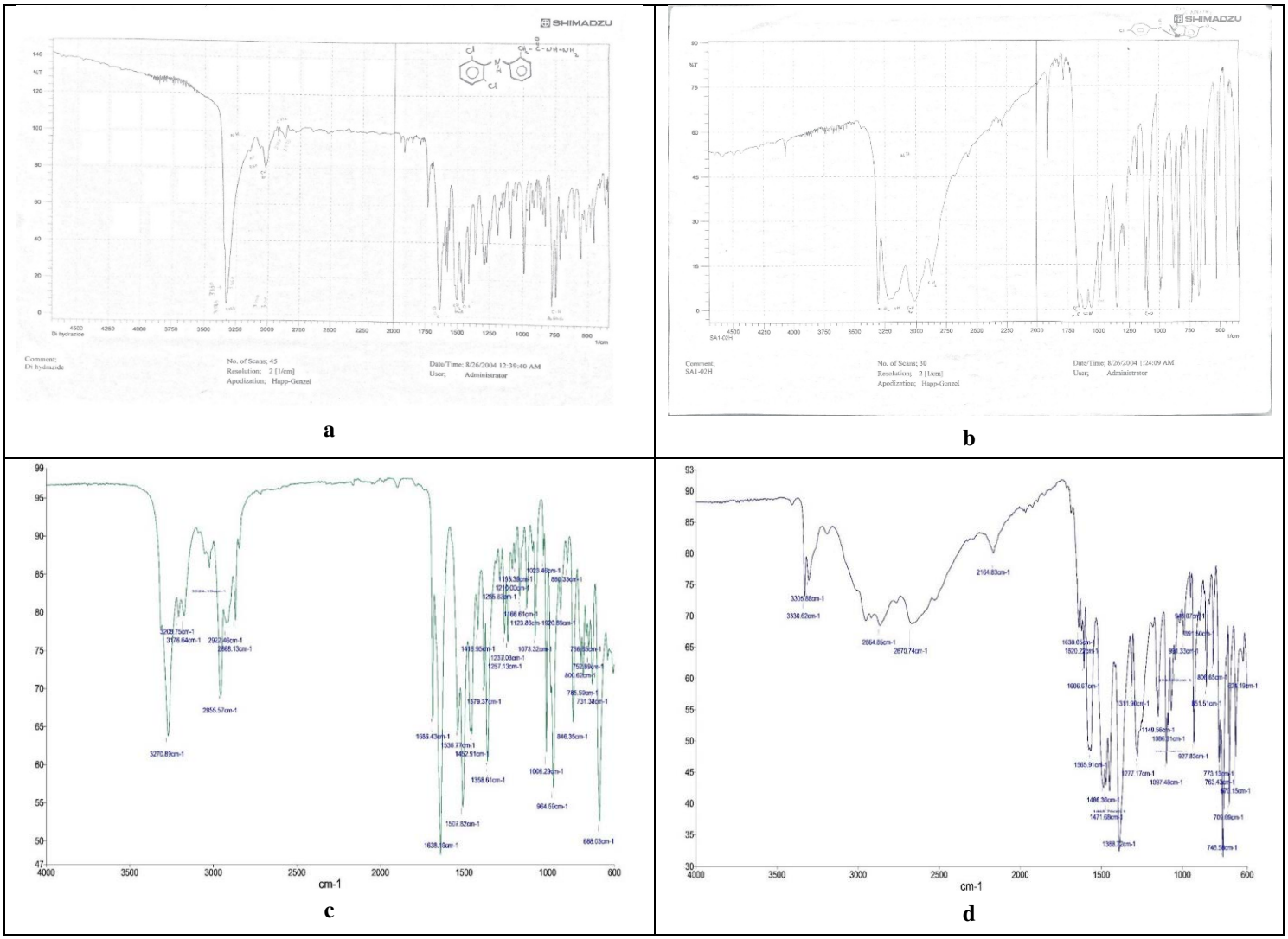


Figure 4: IR spectra. a. Diclofenac acid hydrazide, b. Indomethacin acid hydrazide, c. Ibuprofen acid hydrazide, d. Mefenamic acid hydrazide

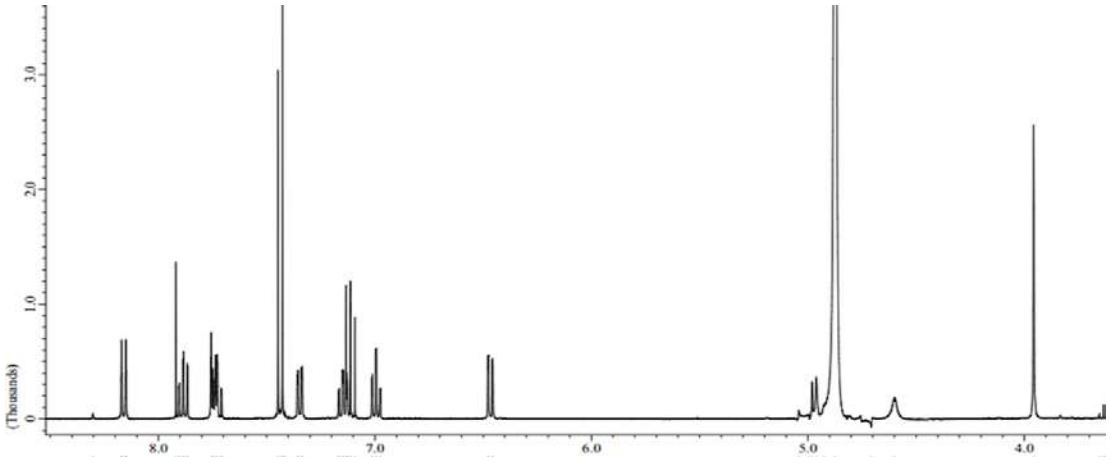


Figure 5a: ^{1}H-NMR spectrum of Diclofenac acid hydrazide (1H).

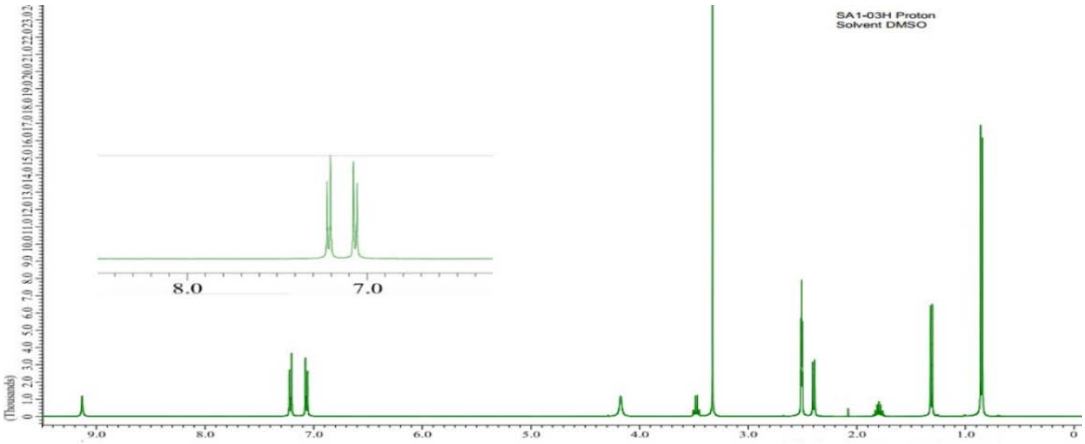


Figure 5b: [1]H-NMR spectrum of Ibuprofen acid hydrazide (3H).

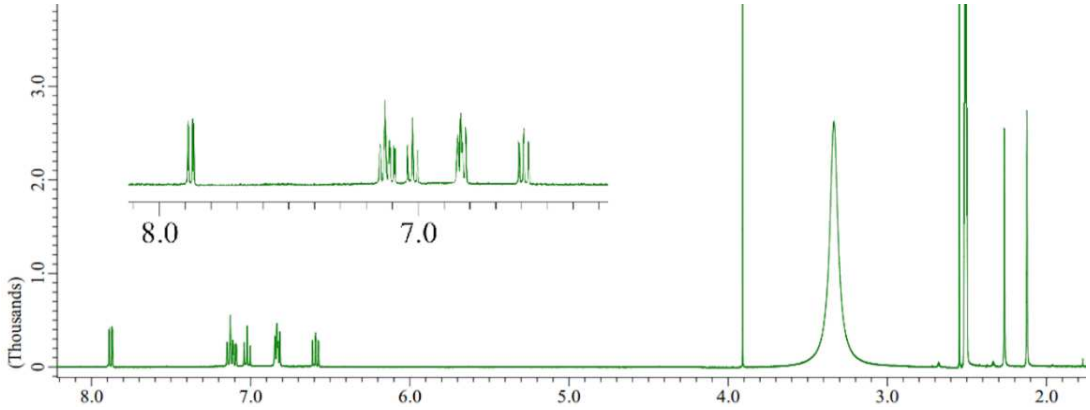


Figure 5c: [1]H-NMR spectrum of Mefenamic acid hydrazide (4H)

AUTHOR CONTRIBUTION

Sabah Mohammad conducted the practical work and wrote the manuscript draft; Shaza Shantier wrote the abstract revised and edited the draft; Elrashied Garelnabi supervised the work and approved the final draft.

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