RAPID SOLVENT-FREE MICROWAVE ASSISTED SYNTHESIS OF SOME N'-BENZYLIDENE SALICYLIC ACID HYDRAZIDES

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ABSTRACT

Condensation reaction has been carried out for the synthesis of some N'-benzylidene-2-hydroxybenzohydrazides using microwave assisted solvent-free method. The structures of all the products obtained in the present work are supported by spectral and analytical data (UV, IR, and ^{1}H-NMR spectroscopy). The desired hydrazides are in 62-80% yields under microwave irradiation. The reaction was completed in 8-10 min.

Keywords: *N'-benzylidene-2-hydroxybenzohydrazides; solvent-free; microwave irradiation*

ABSTRAK

Sintesis beberapa turunan N'-benziliden-2-hidroksibenzohidrazida telah dilakukan melalui reaksi kondensasi menggunakan metode iradiasi gelombang mikro dalam kondisi bebas pelarut. Struktur senyawa hasil sintesis ditentukan berdasarkan analisis data spektra (UV, IR, dan ^{1}H-NMR spektroskopi). Diperoleh hasil 62-80% dari senyawa hidrazida yang disintesis dengan iradiasi gelombang mikro. Reaksi berlangsung selama 8-10 menit.

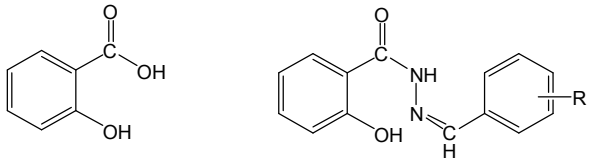
Kata Kunci: *N'benziliden-2-hidroksibenzohidrazida; bebas pelarut; iradiasi gelombang mikro*

INTRODUCTION

Over the years various innovative methods have been devised to speed up the chemical reactions. In these environmentally conscious days the development of technology is directed toward environmentally sound and eco-friendly methods. The usage of microwave energy to accelerate the organic reactions is of increasing interest and offers several advantages over conventional heating techniques [1]. Synthesis of the molecules which normally requires a long time can be achieved conveniently and rapidly in microwave oven. Less reaction time, easy work up and cleaner products are the major advantages of microwave heating. Further more the reaction can be carried out under solvent free conditions which hold a strategic position as the solvents are very toxic, expensive, and problematic to use. Solvent free condition is especially suitable for microwave activation. Thus the use of microwave energy for the synthesis of organic compounds forms a part of green chemistry [2]. The feasibility of microwave-assisted synthesis has been demonstrated in various transformations like condensation [3], cycloaddition [4], synthesis of various heterocyclic compounds [5-6], and in many other chemical reaction.

Acyl derivatives of hydrazines are called acid hydrazides or hydrazides. These constitute an important class of biologically active organic compounds. The therapeutic uses of hydrazides are well-documented in the literature. Hydrazide and the condensation products are also reported to possess a wide range of biological activities such as antibacterial activity and tuberculostatic properties [7[. Some hydrazides also showed analgesic activity. The replacement of the acidic moiety of mefenamic acid, a known NSAID drug, with N-arylidene hydrazides moiety can increase the analgesic activity [8].

Salicylic acid is another analgesic agent, also with acidic moiety. The synthesis of 2-hydroxybenzohydra zide has been successfully done in high yield [7]. Various long chain aliphatic acid hydrazides react with



Salicylic acid

N'-benzylidenesalicylic acid
(= Nbenzylidene-2-hydroxybenzohydrazide)

Fig 1. Structure of N'-benzylidenesalicylic acid hydrazide

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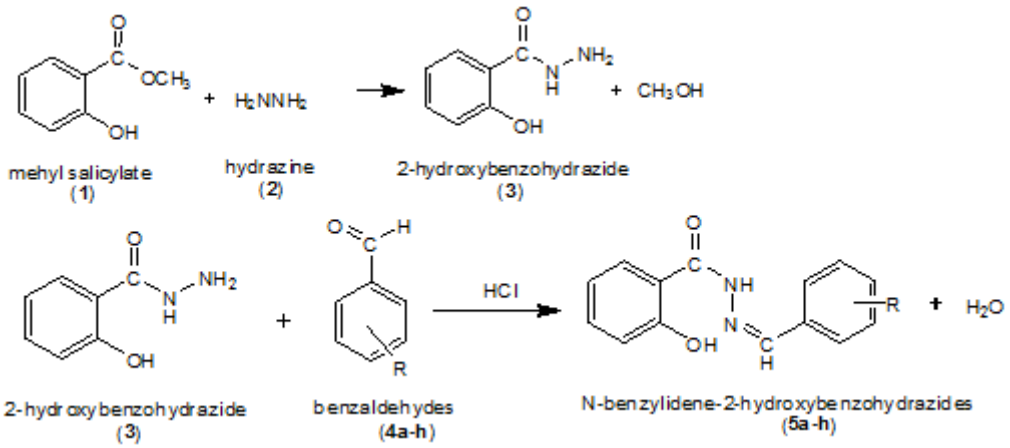


Fig 2. Synthesis pathway of N'-benzylidene-2-hydroxybenzohydrazides

aromatic aldehydes to give corresponding 2-hydroxybenzyidenehydrazides by microwave irradiation technique [9]. We now wish to report here in synthesis of several derivatives of N'-benzylidene salicylic acid hydrazides (= N'-benzylidene-2-hydroxybenzohydrazides) by incorporating different substituted benzaldehydes at 2-hydroxybenzohydrazide under solvent-free condition using microwave irradiation (Fig. 1). The analgesic activity of these hydrazides will be published somewhere else.

Two steps of reaction were held: (1) formation of 2-hydroxybenzohydrazide from methyl salicylate and hydrazine; (2) condensation reaction of N'-benzylidene salicylic acid hydrazides and substituted benzaldehydes (Fig. 2).

EXPERIMENTAL SECTION

Materials

All reagents were obtained from commercial sources and used without further purification. The purity of products and progress of the reaction were monitored by TLC using pre-coated plates (Merck). Melting points were measured in open glass capillaries on an Electro-thermal Melting-point Apparatus and were uncorrected.

Instrumentation

A Kirin KMW820DN domestic microwave oven (output 800 W) was used at 160 W and 320 W power levels for synthesis of 2-hydroxybenzohydrazide and N'-benzylidene-2-hydroxybenzohydrazides respectively.

The UV spectra were recorded on UV-Vis Shimadzu-160 spectrophotometer using ethanol as solvent (λ nm). The IR spectra were recorded on FT-IR Buick Scientific 1500 spectrophotometer using KBr (υ cm^{-1}). ^{1}H-NMR spectra were recorded at room temperature on a 500 MHz FT-NMR JEOL JNM 500 spectrometer in DMSO-D_6 using TMS as internal standard (chemical shift δ ppm).

Procedure

Synthesis of 2-hydroxybenzohydrazide (3)

A mixture of methyl salicylate (1.3 mL, 10 mmol) and hydrazine hydrate 80% (1.2 mL, 20 mmol) were thoroughly mixed to form a thick paste. The paste was air-dried and the residual mass was subjected to microwave irradiation for 8 min while stirring every 2 min (160 W). The progress of the reaction was monitored by TLC. The solid that formed was washed with water, and purified by recrystallization from ethanol.

Synthesis of N'-benzylidene-2-hydroxybenzo hydrazides (5a-h)

To a mixed of 2-hydroxybenzohydrazide (1.5 g, 10 mmol) and substituted benzaldehydes (20 mmol) in ethanol (3 mL) in a conica flash were stirred until a thick mass was formed. The thick mass was air-dried and the residual mass was subjected to microwave irradiation for 2 min (320 W). The reaction was monitored by TLC. After completion of the reaction, the solid product was washed with water, and after that was purified by recrystallization from ethanol.

RESULT AND DISCUSSION

Methyl salicylate (**1**) was treated with hydazine (**2**) at room temperature; the reaction was carried out by microwave irradiation technique. The product obtained was 2-hydroxybenzohydrazide (**3**) in 78% yield as previously reported [7]. The corresponding N'-benzylidene-2-hydroxybenzohydrazides (**5a-h**) obtained by condensation reaction of 2-

hydroxybenzohydrazide (**3**) and substituted benzaldehydes (**4a-h**).

UV spectrum of 2-hydroxybenzohydrazide (**3**) in ethanol showed absorption at 205 and 300 nm, similar pattern for absorption of methyl salicylate (237 and 305 nm). The UV spectra of the corresponding N'-benzylidene-2-hydroxybenzohydrazides (**5a-h**) showed an absorption at 315-324 nm due to the addition of benzylidene group which was conjugated to the hydrazides moiety.

IR spectrum of 2-hydroxybenzohydrazide (**3**) showed absorption at 1647 and 1531 cm^{-1} corresponding to C=O and C-N stretching vibration of the amide group. Two bands at 3269 and 3320 cm^{-1} appeared due to the presence of OH and NH_2 groups respectively.

The corresponding N'-benzylidene-2-hydroxybenzohydrazides (**5a-h**) showed similar spectra except absence of that bands due to the NH_2 group, Each compound showed absorption at 1627-1638 and 1512-1567 cm^{-1} corresponding to C=O and C-N amide. Three new bands at 1594-1610; 1266-1312; and 2836-2887 cm^{-1} due to the C=N; C-N; and N=C-H stretching vibrations of N'-benzidenes group.

The ^{1}H NMR spectrum of 2-hydroxybenzo hydrazide (**3**) displayed a broad singlet at 4.23 (2H) corresponding to NH_2 protons. A singlet appeared at δ 7.9 ppm due to the NHCO proton.

Similar pattern for the proton resonance was also observed in the ^{1}H NMR spectrum of substituted hydrazides. The corresponding substituted hydrazides displayed singlet due to N=CH proton at δ 11.7-11.9 ppm while the benzenoid protons appeared as multiplet at 6.3-8.1 ppm.

The spectral data of new synthesized compounds are as follows:

Compound 3: *2-hydrxyibenzohydrazide*

White needle crystal with specific odor; mp. 139-140 °C. UV (10 ppm, EtOH); λ (nm) : 205 (A = 0.52), and 300 (A = 0.40). IR (KBr, υ, cm^{-1}); 3269 (O-H); 3320 (NH_2); 3056 (Csp^2-H); 1647 (C=O amide), 1531(C-N amide); 1300 (C-N); 1485 (C=C-Ar). ^{1}H-NMR (DMSO-D_6, δ ppm); 4.23 ((s, broad) (2H, NH_2); 6.94-7.78 (m) (4H, Ar-H); 7.9 (s) (1H, CONH).

Compound 5a: *N'-benzylidene-2-hydroxybenzohydrazide*

UV (10 ppm, EtOH); λ (nm) : 206 A = 1.2), 300 (A = 1.09) and 313 (A = 0.98). IR (KBr, υ, cm^{-1}); 3239 (O-H); 3027 (Csp^2-H); 2855 (N=C-H); 1630 (C=O amide), 1564 (C-N amide); 1612 (C=N); 1457 (C=C-Ar); 1312 (C-N benzylidene); ^{1}H-NMR (DMSO-D_6, δ ppm); 12.20 (s) (1H, O-H); 6.85-8.07 (m) (9H, Ar-H); 8.47 (s) (1H, CONH); 11.81 (s) (1H, N=C-H).

Compound 5b: *N'-(2-chlorobenzylidene)-2-hydroxy benzohydrazide*

UV (10 ppm, EtOH); λ (nm) : 202 A = 0.78), 304 (A = 0.47) and 318 (A = 0.49). IR (KBr, υ, cm^{-1}); 3468 (O-H); 3066 (Csp^2-H); 2837 (N=C-H); 1637 (C=O amide), 1548 (C-N amide); 1605 (C=N); 1453 (C=C-Ar); 1307 (C-N benzylidene); ^{1}H-NMR (DMSO-D_6, δ ppm); 6.97-8.05 (m) (8H, Ar-H); 8.87 (s) (1H, CONH); 11.79 (s) (1H, N=C-H); 12.09 (s) (1H, O-H).

Compound 5c: *N'-(2,4-dichlorobenzylidene)-2-hydroxy benzohydrazide*

UV (10 ppm, EtOH); λ (nm) : 229 (A = 0.89) and 322 (A = 0.98). IR (KBr, υ, cm^{-1}); 3452 (O-H); 3033 (Csp^2-H); 2829 (N=C-H); 1631 (C=O amide), 1545 (C-N amide); 1606 (C=N); 1447 (C=C-Ar); 1308 (C-N benzylidene); ^{1}H-NMR (DMSO-D_6, δ ppm); 6.95-8.04 (m) (8H, Ar-H); 8.81 (s) (1H, CONH); 11.73 (s) (1H, N=C-H); 12.11 (s) (1H, O-H).

Compound 5d: *N'-(4-hydroxy-3-methoxybenzylidene)-2-hydroxybenzohydrazide*

UV (10 ppm, EtOH); λ (nm) : 208 (A = 1.02) and 333 (A = 01.09). IR (KBr, υ, cm^{-1}); 3419 (O-H); 3080 (Csp^2-H); 2941 (Csp^3-H); 2878 (N=C-H); 1638 (C=O amide), 1562 (C-N amide); 1594 (C=N); 1447 (C=C-Ar); 1289 (C-N benzylidene); ^{1}H-NMR (DMSO-D_6, δ ppm); 3.90 (s) (3H, -OCH_3); 6.78-8.21 (m) (7H, Ar-H); 8.50 (s) (1H, CONH); 11.85 (s) (1H, N=C-H); 12.24 (s) (1H, O-H).

Compound 5e: *N'-(3,4-dimethoxybenzylidene)-2-hydroxybenzohydrazide*

UV (10 ppm, EtOH); λ (nm) : 209 (A = 1.02) and 330 (A = 1.09). IR (KBr, υ, cm^{-1}); 3446 (O-H); 2958 (Csp^3-H); 2838 (N=C-H); 1632 (C=O amide), 1512 (C-N amide); 1605 (C=N); 1448 (C=C-Ar); 1269 (C-N benzylidene); ^{1}H-NMR (DMSO-D_6, δ ppm); 3.83 (s) (6H, -OCH_3); 6.94-7.95 (m) (7H, Ar-H); 8.40 (s) (1H, CONH); 11.87 (s) (1H, N=C-H); 12.21 (s) (1H, O-H).

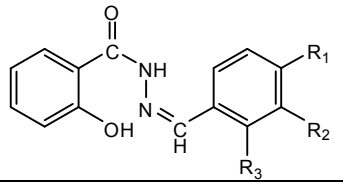
Compound 5f: *N'-(3,4-methylendioxybenzylidene)-2-hydroxybenzohydrazide*

UV (10 ppm, EtOH); λ (nm) : 210 (A.= 0.97) and 331 (A = 0.82). IR (KBr, υ, cm^{-1}); 3470 (O-H); 2924 (Csp^3-H); 2887 (N=C-H); 1632 (C=O amide), 1567 (C-N amide); 1605 (C=N); 1448 (C=C-Ar); 1263 (C-N benzylidene); ^{1}H-NMR (DMSO-D_6, δ ppm); 6.15 (s) (4H, -O-CH_2-O); 6.95-8.08 (m) (7H, Ar-H); 8.45 (s) (1H, CONH); 11.75 (s) (1H, N=C-H); 12.04 (s) (1H, O-H).

Compound 5g: *N'-(4-methybenzylidene)-2-hydroxy benzohydrazide*

UV (10 ppm, EtOH); λ (nm) : 202 (A = 0.78), 304 (A = 0.97) and 315 (A = 2.69). IR (KBr, υ, cm^{-1}); 3468 (O-H); 3037 (Csp^2-H); 2921 (Csp^3-H); 2854 (N=C-H); 1627 (C=O amide), 1555 (C-N amide); 1610 (C=N); 1457 (C=C-Ar); 1311 (C-N benzylidene); ^{1}H-NMR (DMSO-D_6, δ ppm); 2.35 (s) (3H, -CH_3); 6.29-7.69 (m)

Table 1. Physical Data of N'-benzylidene-2-hydroxybenzohydrazides



Entry	Substituent			Product	Melting point (°C)	Yield (%)
	R_1	R_2	R_3			
5a	H	H	H	White voluminous and odorless crystal	252-254	(77 ± 1.73)%
5b	H	H	Cl	Yellowish white and odorless crystal	220-222	(68 ± 1.53)%
5c	Cl	H	Cl	White voluminous and odorless crystal	236-238	(62 ± 2.12)%
5d	OH	OCH_3	H	Yeloowish powder with puncent odor	123-125	(77 ± 2.12)%
5e	OCH_3	OCH_3	H	White crystal with specific odor	191-193	(75 ± 1.70)%
5f	$O-CH_2-O$		H	Yellowish crystal with specific odor	276-278	(75 ± 1.15)%
5g	CH_3	H	H	Yellowish white and odorless crystal	220-222	(80 ± 1.06)%
5h	OCH_3	H	H	Yellowish voluminous and odorless crystal	222-224	(76 ± 1.03)%

(8H, Ar-H); 8.21 (s) (1H, CONH); 11.69 (s) (1H, N=C-H); 11.93 (s) (1H, O-H).

Compound 5h: *N'-(4-methoxybenzylidene)-2-hydroxy benzohydrazide*

UV (10 ppm, EtOH); λ (nm) : 202 (A = 0.78), 304 (A = 0.77) and 324 (A = 1.46). IR (KBr, υ, cm^{-1}); 3436 (O-H); 3070 (Csp^2-H); 2931 (Csp^3-H); 2836 (N=C-H); 1627 (C=O amide), 1556 (C-N amide); 1607 (C=N); 1456 (C=C-Ar); 1266 (C-N benzylidene); ^{1}H-NMR (DMSO-D_6, δ ppm); 3.82 (s) (3H, -OCH_3); 6.50-7.63 (m) (8H, Ar-H); 8.40 (s) (1H, CONH); 11.9 (s) (1H, N-H); 12.32 (s) (1H, O-H).

CONCLUSION

In summary, we have developed a simple and eco-friendly method for preparation of some N'-benzylidene salicylic acid hydrazide derivatives under solvent-free condition using microwave irradiation. The overall yield of the product using microwave irradiation technique was 62-80% and the reaction time was 8-10 min (Table 1). Easy experimental procedure and quantitative yield of the products make it useful synthetic method for the synthesis of hydrazides

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