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Synthesis and Biological Activities of 1-Keto-3-Carboxy-6,7-Methylenedioxy-1,2,3,4-Tetrahydronaphthalene Derivatives

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1-Keto-3-carboxy - 6,7-methylenedioxy - 1,2,3,4-tetrahydronaphthalene **(I)** was converted to its ester, 1-keto-3-carbmethoxy-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene **(II)** which was treated with hydrazine hydrate to give 1-keto-3-hydrazocarbonyl-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene **(III).** Compound **(III)** was condensed with various aromatic aldehydes to give corresponding 3-arylidene hydrazocarbonyl-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene **(IVa–h).** On condensation with various substituted benzoxazones, compound **(III)** gave quinazoline-4-(3H)-one derivatives **(Vi–k).** Above condensation reactions were also carried out in a microwave oven at 10% energy. Compound **(I)** was treated with various benzhydrazides in presence of excess of $POCl_3$ to yield substituted oxadiazoles **(VIa–b).**

Key Words: Synthesis, Biological activity, 1-keto-3-carboxy-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene derivatives.

INTRODUCTION

A large number of substituted hydrazides and their condensation products including heterocyclic compounds having five or six membered rings are known for biological activities[1]. The present paper reports the synthesis of 1-keto-3-hydrazocarbonyl-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene **(III)** from 1-keto-3-carbmethoxy-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene **(II)** and its condensation with various substituted aromatic aldehydes **(a–h)** to yield corresponding 3-arylidene-hydrazocarbonyl-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalenes **(IVa–h).** Some of the Schiff bases were synthesized using a microwave oven in better yields and in less time. 1-Keto-3-hydrazocarbonyl-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene **(III)** was treated with various substituted benzoxazones[2] to give the corresponding quinazoline-4 (3H)-ones **(Vi–k).** The same products were synthesized using a microwave oven where the better yields were obtained in less time.

1-Keto-3-carboxy-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene **(I)** was refluxed with various benzhydrides in presence of excess of $POCl_3$ to give oxadiazole derivatives **(V a–b).**

EXPERIMENTAL

All melting points of the compounds synthesized are uncorrected. Micro-analysis of the compounds was carried out on a Colemn instrument. IR spectra

(KBr) were recorded on a Perkin-Elmer Paragon-2000 instrument. UV spectra were recorded on Spectronic-Genesys-8. NMR spectra were recorded on Varian NMR instrument at 300 MHz and AMX-500 Bruker instrument (500 MHz) using TMS as the internal standard. All the compounds gave satisfactory C, H and N analyses.

1-Keto-3-carboxy-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (I) was prepared by the method given by Campbell *et al.*[3]

Synthesis of 1-keto-3-carbmethoxy-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (II): 1-keto-3-carboxy-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene **(II)** (5 g) was dissolved in methanol (50 mL) by warming on a water bath. Conc. H_2SO_4 (1 mL) was added slowly with cooling and the reaction mixture was refluxed for 3–4 h on a water bath. After cooling it was poured into water when a brown solid was obtained. It was then crystallized from ethyl acetate.

Synthesis of 1-keto-3-hydrazocarbonyl-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (III): A mixture of **(II)** (4.96 g, 0.02 mol) and hydrazine hydrate (98%, 1.5 mL, 0.03 mol) was refluxed in absolute ethanol (50 mL) on a water bath for 3–4 h when the reaction mixture was cooled a white solid obtained was crystallized from ethanol.

Synthesis of 3-[N-methylidene-2-aryl]-hydrazocarbonyl-1-keto-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (IVa–h): A mixture of **(I)** (1.24 g, 0.005 mole) and each of aromatic aldehydes **(a–h)** (0.005 mol) were dissolved in ethanol and refluxed on a steam bath for 4–5 h. The reaction mixture on cooling gave a solid which was crystallised from 1,4-dioxane : water (1 : 1).

Synthesis of 2-substituted-3-(3-carboxamidyl-1-keto-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene)quinazoline-4-(3H)-one (Vi–k): A mixture of **(III)** (0.248 g, 0.001 mol) and substituted benzoxazone derivatives **(i–k)** (0.001 mol) in pyridine (5 mL) were refluxed for about 4–5 h. After the completion of the reaction the reaction mixture was cooled when a solid was separated. It was crystallized from ethyl acetate-pet ether mixture.

Compounds **(IVa–c)** and **(Vi–k)** were also prepared in a microwave oven at 10% energy level. The yield of the compounds was found to be more than the conventional methods. Also the time required to complete the reactions was less.

General procedure for the reactions carried out in the microwave oven

The microwave oven used was Domestic BPL BMO-700T, modified for the use of water condenser. To synthesize **(IVa–c)**, in a two-necked round-bottom flask equipped with a water condenser were taken 1-keto-3-hydrazocarbonyl-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene **(III)** and substituted aryl aldehydes **(a–c)** in DMF (15 mL) as solvents in an equimolar ratio. The reaction mixture was irradiated in a microwave oven for 15–20 min. After completion of reaction the solvent was distilled off. The residue obtained was crystallized from 1,4-dioxane : water (1 : 1). Compounds **(Vi–k)** were synthesized in the same manner using pyridine as a solvent.

Synthesis of 2-aryl-5-(4-chloro-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene)-1,3,4-oxadiazoles (VIa–b): A mixture of **(I)** (0.234 g, 0.001

mol), aryl hydrazides **(a, b)** (0.001 mol) and $POCl_3$ (10 mL) were heated for 4–5 h on a water bath. The reaction mixture was cooled and then poured into ice-cold water. It was then basified with 10% NaOH. The solid obtained was crystallized from ethanol-water mixture.

RESULTS AND DISCUSSION

The IR spectra of 1-keto-3-carbmethoxy-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene **(II)** showed an absorption band at 1731 cm^{-1} due to ester carbonyl group while the peak at 1670 cm^{-1} was due to cyclic carbonyl group. The IR spectra of 1-keto-3-hydrazocarbonyl-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene **(III)** showed an absorption band at 3305 cm^{-1} due to —NH stretching. The characteristic feature of the spectrum is the shifting of the peak at 1731 to 1642 cm^{-1} due to hydrazide group attached to the carbonyl group. The IR spectra of **(VIa)** and **(VIb)** showed the absence of —NH peak, which proved that cyclization had taken place.

NMR spectrum for the compound **(IVa)** can be explained as follows: Signals occurring at δ 3, 3.6 and 3.8 ppm were due to five methylene protons of the tetralone ring. A signal occurring at δ 3.9 ppm was due to three methoxy protons. A sharp singlet at δ 6 ppm was due to two methylenedioxy protons. Multiplet at 6.9–7.2 ppm and 7.6–8.2 ppm could be due to seven aromatic protons. A singlet at δ 8.45 ppm was due to —NH proton.

NMR spectrum for compound **(IVb)** can be explained as follows: Signals occurring from δ 2.6–3 ppm and δ 3.4–3.8 ppm were due to five methylene protons of the tetralone ring. A sharp singlet at δ 6 ppm was due to two methylenedioxy protons. The multiplet in the region of δ 7.4–8.4 ppm and δ 8.4–9 ppm was due to seven aromatic protons of the tetralone ring as well as pyridyl ring. A singlet at δ 7 ppm was due to the proton of —NH group.

NMR spectrum of the compound **(Vj)** showed the signals as follows: Signals occurring from δ 2–3 ppm may be due to five methylene protons of the tetralone ring. A sharp singlet at δ 6 ppm may be due to two methylenedioxy protons. Multiplet in the region of δ 7 to 7.5 ppm could be due to eleven aromatic protons of the tetralone ring as well as benzoxazone ring. A singlet at 8.4 may be due to the proton attached to the amido carbonyl group.

NMR spectrum of the compound **(VIa)** showed the signals as follows: Signals occurring from δ 2–2.6 ppm were due to three methylene protons of the naphthalene ring. A sharp singlet at δ 6 ppm was due to two methylenedioxy protons. The singlet at δ 6.8 ppm was due to the proton at the third position of the naphthalene ring (=CH—). The multiplet in the region of δ 7 to 7.5 ppm was due to seven aromatic protons of the naphthalene ring and phenyl ring.

Comparison of conventional methods and microwave method

The compounds synthesized by using a microwave oven were found to be identical in all respects with the compounds, which had been synthesized employing conventional methods. It was found that the reactions were very rapid with good yields and better quality; less time was required for completion of the reaction.

Synthetic strategy has been outlined below:

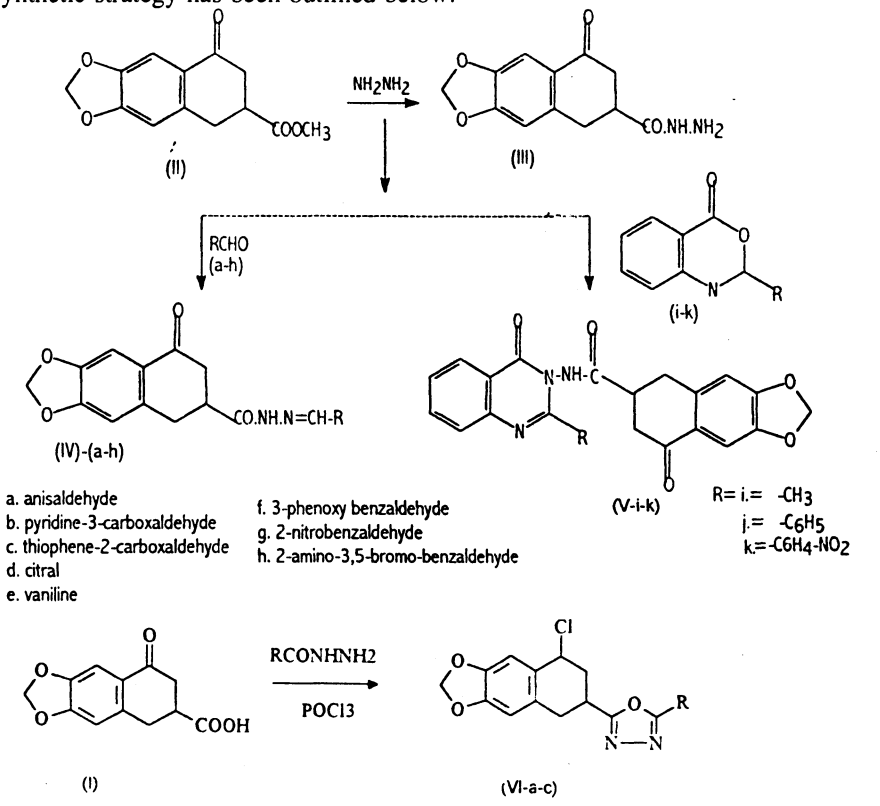

TABLE-1
COMPARISON OF CONVENTIONAL METHOD AND THE METHOD USING MICROWAVE OVEN

Compd. No.	Microwave irradiation			Conventional methods		
	Solvent used	Reaction time (min)	Yield (%)	Solvent used	Reaction time (h)	Yield (%)
Schiff Bases:						
IVa	DMF	20	80	Ethanol	4	69
IVb	DMF	23	83	Ethanol	4	78
IVc	DMF	20	78	Ethanol	4	72
Quinazolinones:						
Vi	Pyridine	15	78	Pyridine	4	73
Vj	Pyridine	15	82	Pyridine	4	72
Vk	Pyridine	15	76	Pyridine	4	66

TABLE-2
ANALYTICAL AND SPECTRAL DATA OF COMPOUNDS
(IVa–h), (Vi–k) AND **(VIa–c)**

Compd. No.	R	m.f.	m.p. (°C)	Yield (%)	IR (cm^{-1})	UV (nm)
IVa	4-Methoxy phenyl	$C_{20}H_{18}N_2O_5$	230	78.19	3204, 1657	281, 332
IVb	3-Pyridyl	$C_{18}H_{15}N_3O_4$	230	68.96	3246, 1658, 1614	288, 312
IVc	2-Thiophenyl	$C_{17}H_{14}N_2O_4S$	250	72.30	3249, 1668	312
IVd	3,7-Dimethyl-2,6-octadienal	$C_{22}H_{26}N_2O_4$	210	68.13	3203, 1663	274, 316
IVe	3-Hydroxy-4-methoxy phenyl	$C_{20}H_{18}N_2O_6$	165	58.23	3219, 1660	328
IVf	3-Phenoxy phenyl	$C_{25}H_{20}N_2O_5$	180	76.32	3188, 1652	283, 330
IVg	2-Nitro phenyl	$C_{19}H_{15}N_3O_6$	254	79.51	3207, 1665, 1618	292, 343
IVh	2-Amino-3,5-bromo phenyl	$C_{19}H_{15}N_3O_4Br_2$	280	77.22	3292, 1657, 1610	268, 306
Vi	$-CH_3$	$C_{21}H_{17}N_3O_5$	185	73.32	3429, 1662	273, 316
Vj	$-C_6H_5$	$C_{26}H_{19}N_3O_5$	190	72.06	3412, 1709, 1672	272, 314
Vk	$C_6H_4NO_2$	$C_{26}H_{18}N_4O_7$	280	69.00	3255, 1662	261, 317
VIa	$-C_6H_5$	$C_{19}H_{13}N_2O_3Cl$	272	62.00	absence of —NH peak	—
VIb	$-C_6H_5{\cdot}CH_2$	$C_{20}H_{15}N_2O_3Cl$	282	69.00	Absence of —NH peak	—

TABLE-3
ANTIBACTERIAL ACTIVITY OF COMPOUNDS

Compd. No.	Name of the culture used	Minimum inhibition concentration (MIC) in micro gm						
		1000	800	500	200	100	50	25
IVb	*Klb. pneumonia*	+	+++	+++	+++	+++	+++	+++
IVc	*Corynebacterium diphtheriae*	–	++	++	++	++	++	++
IVe	*Sarcina*	+	+++	+++	+++	+++	+++	+++
IVf	*S. Aureus*	+	++	++	++	++	++	++

– complete inhibition (no growth), + least growth, ++ less growth,
+++ no inhibition (maximum growth)

TABLE-4
ANTIFUNGAL ACTIVITY OF COMPOUNDS

Compd. No.	Name of the culture used
IVd	*Penicillium*
IVf	*Candida albicans*
IVh	*Penicillium*

All the above compounds showed inhibition for 72 h for the fungal cultures (Table-4). Afterwards the growth was shown.

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