Asian Journal of Chemistry Vol. 19, No. 6 (2007), 4188-4192

Synthesis and Antioxidant Activity of Substituted Phenylalkene Hydroxamic Acids

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A series of phenylalkene hydroxamic acids ahve been synthesized by acylation of hydroxylamine with substituted acyl chlorides of the substituted cinnamic acids. The substituted cinnamic acids were prepared from substituted benzaldehydes by emphasizing knoevengel reaction. The title compounds were screened for antioxidant activity, *in vitro*. Compounds A_7, A_{10}, A_{11} exhibited most significant activity activities amongst all the evaluated compounds. Compound A_{10} showed lowest IC_{50} value (8.668 mM) ad A_5 showed highest IC_{50} value (954.734 mM).

Key Words: Hydraxamic acids, Antioxidant.

INTRODUCTION

The hydroxamic acid functionality have been reported to have biological activities[1-4]. It is to be expected that, hydroxamic acids might affect the formation and scavenging of reactive oxygen species and influence processes involving free radical-mediated injury. The hydroxamic acid functionality can be incorporated in a variety of simple molecules of produce potent antioxidants and inhibitors of lipoxygenase[5-7]. These compounds showed interesting interaction with the free radical 1,1-diphenyl-2-picryl-hydrazyl (DPPH), scavenging activity on $^{\bullet}OH$, inhibition of soybean lipoxygenase and a significant inhibition of carrageenan induced paw edema in rats.

EXPERIMENTAL

Novel synthesis of substituted cinnamic acids targeted compounds were achieved by route as in **Scheme-I**. The phenylalkene hydroxamic acids were prepared by synthetic route as shown in **Scheme-II** involving acylation of hydroxylamine with substituted acyl chlorides of the substituted cinnamic acids.

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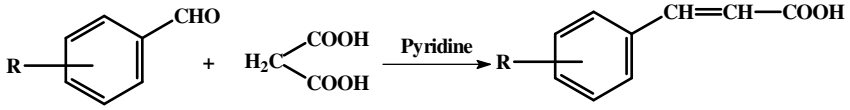
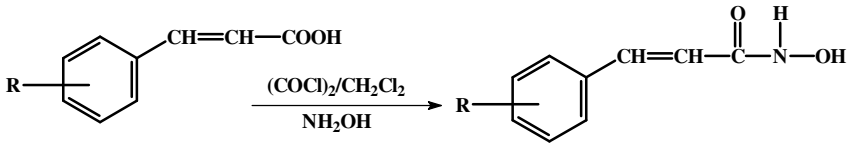


Scheme-I



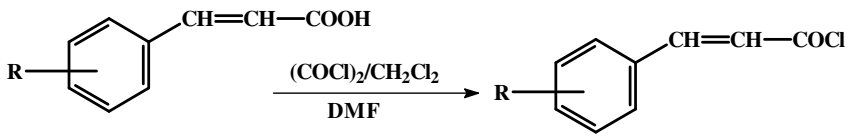
Scheme-II

All the chemicals used in the synthesis were of synthetic grade. Various substituted benzaldehydes were obtained from E. Merck (I) Ltd. and Loba Chemie Pvt. Ltd. and other necessary chemicals used were of synthetic grade. Precoated TLC plates of Merck India were used to follow the course of reactions.

All the chemicals used in the synthesis were of laboratory grade. Melting points were determined by open capillary tubes and is uncorrected. The purity of the synthesized compounds was checked by TLC using silica gel-G glass plate method using ethyl acetate:methanol:glacial acetic acid (6:4:0.5) and methanol: dichloromethane (1:1) as eluents and visualized by using iodine chamber. IR spectra were recorded (in KBr) on FTIR 8300 (Shimadzu) spectrometer. All the compounds showed satisfactory microanalytical results for C, H and N. All the chemicals used were of analytical grade.

Synthesis of substituted cinnamic acids (1): A mixture containing malonic acid (0.2 mol) and appropriate benzaldehyde (0.1 mol) was dissolved in pyridine (42 mL) and was refluxed for 2 h. After cooling to room temperature, the reaction mixture was poured into 2 N hydrochloric acid. The product was precipitated immediately. It was collected by filtration and recrystallized from ethanol (**Scheme-I**).

Synthesis of corresponding acid chlorides (2): Corresponding substituted acid (**1**) (14.5 mmol) and dimethyl formamide (14.5 mmol) were dissolved in methylene chloride (100 mL) and cooled to 0ºC. Oxalyl chloride (32.6 mmol) was added slowly. Vigorous gas evolution was noted. Stirred for 40 min.



Synthesis of hydroxamic acids (3): The acid chlorides (**2**) formed in the first step were quite unstable. Therefore, the solution of acid chloride was immediately added to a solution of hydroxylamine hydrochloride (58 mmol) and triethylamine (87 mmol) in tetrahydrofuron (50 mL)/H_2O (10 mL). After being stirred for an additional 0.5 h the mixture was poured into 2 N hydrochloric acid and extracted with methylene chloride. The organic phase was dried over magnesium sulfate and evaporated in vacuum. The residue was recrystallized from ethanol (**Scheme-II**).

Details of the physical and spectral data of all the synthesized phenylalkene hydroxamic acids are briefed in Table-1.

Antioxidant acitivity

DPPH assay method is based on the reduction of methanolic solution of DPPH by free radical scavenger[8,9]. The ability of the test compounds to scavenge the free radicals was determined by an *in vitro* assay method using a stable free radical DPPH (1,1-diphenyl,2-picrylhydrazyl)[10]. Compounds and DPPH solutions were prepared in methanol. For estimating antioxidant activity, 1.5 mL of different concentration of compound solution *i.e.*, 1, 10, 100 and 1000 µgm were added to 1.5 mL of 0.2 mM DPPH solution, mixed thoroughly. After 15 min the decrease in absorbance of test mixture due to quenching of DPPH free radical was read at 517 mm[11]. Antioxidant activity was measured in terms of per cent inhibition of absorbance of DPPH. The per cent inhibition activity was calculated according to the formula

$$\text{Inhibition } (\%) = \frac{(A - A')}{A} \times 100$$

where, A = Absorbance of control; A′ = Absorbance of test.

The amount of compound required to produce 50 % inhibition of absorbance of DPPH was taken as IC_{50}. The IC_{50} values were computed from concentration of compound and per cent inhibition of DPPH peak.

RESULTS AND DISCUSSION

Oxidative stress has been implicated in the pathology of many diseases and conditions including cardiovascular diseases, diabetes, cancer, aging and inflammatory conditions[12]. Antioxidant may offter resistance against the oxidative stress by scavenging free radicals, inhibiting the liquid peroxidation and/or some other mechanisms[13].

DPPH is relatively stable free radical. In all the newly synthesized 14 compounds have been screened for antioxidant activity using the DPPH method. In the present study it was observed that with increase concentration of the synthesized compound DPPH absorbance at 517 nm were decreased which is stoichiometric with respect of number of electron. All

TABLE-1
PHYSICAL AND SPECTRA DATA OF PHENYLALKENE HYDROXAMIC ACIDS

Compd.	R	m.f.	m.p. (ºC)	λ_{max} (nm)	IR (KBr, cm^{-1})
A_0	H	$C_9H_9NO_2$	138-140	270	3407 ν(OH), 3107 ν(NH), 622 ν(NH), 1523 ν(CO)
A_1	4-NO_2	$C_9H_8N_2O_4$	268-270	282	3407 ν(OH), 3109 ν(NH), 1627 ν(NH), 1537 ν(CO)
A_2	4-Cl	$C_9H_8ClNO_2$	234-236	281	3407 ν(OH), 3026 ν(NH), 1677 ν(NH), 1591 ν(CO), 1083 ν(CCl)
A_3	4-CH_3	$C_{10}H_{11}NO_2$	138-140	279	3411 ν(OH), 3058 ν(NH), 1685 ν(NH), 1622 ν(CO), 2945 ν(CH), 1425 ν(CH)
A_4	4-CF_3	$C_{10}H_8FNO_2$	208-210	275	3409 ν(OH), 3170 ν(NH), 1691 ν(NH), 1631 ν(CO), 1284-1112 ν(CF)
A_5	3-Cl	$C_9H_8ClNO_2$	160-162	275	3411 ν(OH), 3081 ν(NH), 1677 ν(NH), 1566 ν(CO), 1090 ν(CCl)
A_6	3-OCH_3	$C_{10}H_{11}NO_3$	108-110	275	3411 ν(OH), 3051 ν(NH), 1677 ν(NH), 1577 ν(CO), 1244 ν(COC), 1049 ν(COC)
A_7	3-CH_3	$C_{10}H_{11}NO_2$	140-142	274	3433 ν(OH), 3072 ν(NH), 1662 ν(NH), 1631 ν(CO), 2923 ν(CH), 2852 ν(CH), 1431 ν(CH)
A_8	2-CH_3	$C_{10}H_{11}NO_2$	190-192	281	3411 ν(OH), 3026 ν(NH), 1676 ν(NH), 1623 ν(CO), 2920 ν(CH), 2852 ν(CH), 1421 ν(CH)
A_9	2-Br	$C_9H_8BrNO_2$	158-160	274	3464 ν(OH), 3047 ν(NH), 1649 ν(NH), 1610 ν(CO)
A_{10}	3,4,5-tri-OCH_3	$C_{12}H_{15}NO_5$	60-62	271	3455 ν(OH), 3095 ν(NH), 1689 ν(NH), 1585 ν(CO), 1242 ν(COC), 1135 ν(COC)
A_{11}	2-OCH_3	$C_{10}H_{11}NO_3$	108-110	274	3407 ν(OH), 3010 ν(NH), 1685 ν(NH), 1622 ν(CO), 1247 ν(COC), 1026 ν(COC)
A_{12}	2-Cl	$C_9H_8ClNO_2$	78-80	274	3367 ν(OH), 3053 ν(NH), 1689 ν(NH), 1083 ν(CCl)
A_{13}	4-OCH_3	$C_{10}H_{11}NO_3$	148-150	282	3407 ν(OH), 3064 ν(NH), 1685 ν(NH), 1623 ν(CO), 1255 ν(COC), 1027 ν(COC)

the synthesized compounds showed antioxidant activity. Table-2 indicate the compound A_7, A_{10}, A_{11} are more effective as antioxidant. Compound A_{10} showed lowest IC_{50} value (8.668 mM) ad A_5 showed highest IC_{50} value (954.734 mM).

TABLE-2
IC_{50} VALUES OF SUBSTITUTED PHENYLALKENE HYDROXAMIC ACIDS

Compound	R	IC_{50} (mmol)	Compound	R	IC_{50} (mmol)
A_0	H	92.880	A_7	3-CH_3	47.902
A_1	4-NO_2	413.254	A_8	2-CH_3	229.178
A_2	4-Cl	151.290	A_9	2-Br	416.477
A_3	4-CH_3	90.301	A_{10}	3,4,5-tri-OCH_3	8.668
A_4	4-CF_3	596.652	A_{11}	2-OCH_3	37.820
A_5	3-Cl	954.734	A_{12}	2-Cl	333.154
A_6	3-OCH_3	116.465	A_{13}	4-OCH_3	61.028

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(*Received*: 1 February 2006; *Accepted*: 28 March 2007) AJC-5540