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Der Pharma Chemica, 2011, 3 (5):69-72
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Bioactive halogenosubstituted cinnamic acids: Synthesis by Knoevenagel condensation using conventional as well as microwave irradiation

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ABSTRACT

Halogenosubstituted vanillins were prepared by halogenations. Halogenosubstituted vanillins on Knoevenagel condensation with malonic acid to form halogenosubstituted cinnamic acids by using conventional method as well as microwave irradiation technique. All halogenosubstituted cinnamic acids were screened for antibacterial activity. All newly synthesized halogenosubstituted cinnamic acids showed antibacterial activity to a remarkable extent.

Keywords: Halogenosubstituted cinnamic acids, malonic acid, microwave, Knoevenagel reaction, antibacterial activity.

INTRODUCTION

As the principle biological role for the complement cascade is the neutralization and removal of invading pathogens. It is clear that it is an important part in the immune system. The complement system has been implicated as a factor in the extraction and propagation of tissue injury in numerous diseases including neurodegenerative disorders [1]. The involvement of complement in the early recognition phases of inflammatory response as well as the as the wide array of pro-inflammatory consequences of complement activation makes the complement system as attractive target for therapeutic intervention and has led to the isolation, design and synthesis of variety of complement inhibitors [2,3] as well as the identification of small molecule compounds from the compound library [4]. The greater understanding of the role of the complement system in the pathogenesis of several diseases has increased the need for more specific and more potent complement inhibitors. It is reported that low molecular weight compounds such as substituted cinnamic acids [5], tetrazoles [6], etc are noncytotoxic in vitro and inhibitory against human pathogen cell and work as versatile synthon in medicinal chemistry [7-11].

The work has been aimed to synthesize some new halogenosubstituted cinnamic acids by Knoevenagel condensation with malonic acid using conventional method as well as under microwave irradiation.

MATERIALS AND METHODS

Experimental

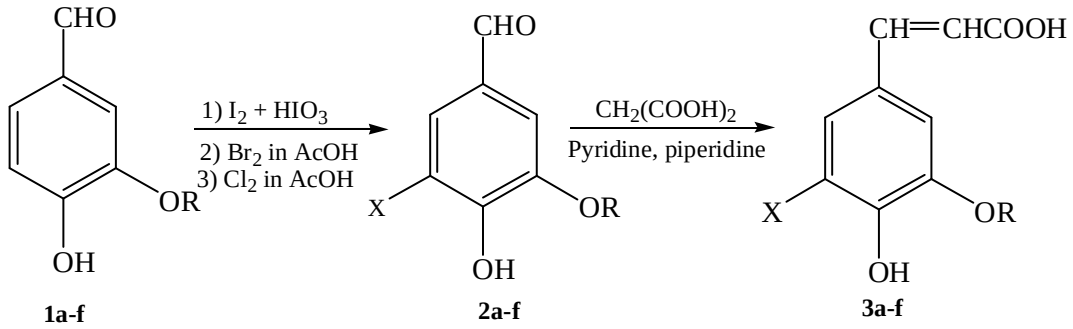
Melting points were determined in an open capillary tube and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer spectrometer. ^{1}H NMR spectra were recorded on a Gemini 300-MH$_Z$ instrument in DMSO as solvent and TMS as an internal standard.

General procedure for synthesis of halogenosubstituted cinnamic acids by conventional method

Halogenosubstituted vanillin (0.01 mol) was dissolved in pyridine (7 ml) added to it malonic acid (0.01 mol) and two drops of piperidine. Reaction mixture was refluxed for 3 hr. On cooling or on pouring in cold water, solid separated out. Separated solid was filtered, washed with water and crystallized from ethanol. Melting point yield and analytical data is given in Table-I.

Microwave assisted synthesis

Equimolar mixture of halogenosubstituted vaniline, malonic acid dissolved in pyridine and two drops of piperidine were irradiated in microwave oven for 2 min. with giving short interval of time. The progress of reaction was monitored on TLC. On cooling reaction mixture, solid was separated. Solid obtained was filtered and crystallized from ethanol. M.P. and mixed M.P. with samples prepared by conventional method was undepressed.



X=Cl/Br/I, R=CH_3/CH_2CH_3

Scheme-I: Synthesis of Halogenosubstituted Cinnamic acid

Spectral Data

Compound 3b:

IR: ν max (cm^{-1}): 3310, 3005, 1682, 1595, 1570, 1491, 1259.

^{1}H NMR: δ 2.1 (s, 3H, CH_3), 6.96 (d, 1H, CH_α), 7.44 (d, 1H, CH_β), 7.10 (s, 1H, ArH), 7.95 (s, 1H, ArH), 10.82 (s, 1H, COOH).

Compound 3e:

IR: ν max (cm^{-1}): 3300, 3005, 1680, 1585, 1572, 1491, 1259.

^{1}H NMR: δ (1.5 (t, 3H, CH_3), 4.4 (q, 1H, CH_2), 6.92 (d, H, CH_α), 7.42 (d, 1H, CH_β) 7.75 (s, 1H, ArH), 10.71 (s, 1H, COOH).

RESULTS AND DISCUSSION

In the present study, we have synthesized iodo / bromo / chloro and alkoxy substituted cinnamic acid (scheme-**I**) and studied for antibacterial activity. Iodo substituted vanillin / iodo ethyl vanillin was synthesized by modified method of iodination using iodine and iodic acid as iodinating agent [12]. Bromo vanillin / bromo ethyl vanillin was synthesized by bromination [13] using bromine in acetic acid in presence of sodium acetate in cold condition at 10-15°C. Chloro vanillin / ethyl chlorovanillin was prepared by chlorination [13] using molecular chlorine in acetic acid, prepared by the action of conc. HCl on $KMnO_4$. All these prepared halogenosubstituted vanillins were used for the synthesis of halogenosubstituted cinnamic acid.
Halogenosubstituted vanillin/ethyl vanillin and malonic acid was dissolved in pyridine, 2-3 drops of piperidine was added and reaction mixture was refluxed on water bath for 3 hr. On cooling or on pouring in water solid separated. Obtained solid was filtered, washed with water and crystallized from ethanol.

Table-I Analytical, physical and bioactivity data of compounds

Entry	R	X	M.P. (^{0}C)	Yield (%)	Appearance	Molecular formula	Halogen Analysis Reported (Found)	Antibacterial Activity (zone of inhibition in mm)		
								Xc	*E. coli*	*Bs*
3a	CH_3	Br	196	70	Brown	$C_{10}H_9O_4Br$	29.30 (29.00)	20	14	18
3b	CH_3	I	165	73	Faint brown	$C_{10}H_9O_4I$	39.66 (39.32)	26	21	22
3c	CH_3	Cl	180	65	Faint brown	$C_{10}H_9O_4Cl$	15.35 (15.25)	**29**	22	26
3d	C_2H_5	Br	98	73	White	$C_{11}H_9O_4Cl$	27.67 (27.35)	18	11	13
3e	C_2H_5	I	124	62	Dark brown	$C_{11}H_{11}O_4I$	38.02 (37.78)	26	18	25
3f	C_2H_5	Cl	135	55	Dark brown	$C_{11}H_{11}O_4Cl$	14.46 (14.20)	24	20	26
Ampicillin								**27**	**23**	**28**

Same substituted cinnamic acids were synthesized by heating reaction solution, prepared as above, in microwave oven for 2 min. (scheme-**I**). The structure of newly synthesized compound was confirmed by halogen analysis and spectral data.

Antibacterial Screening

The antibacterial activity of newly synthesized compounds (3a-f) was determined by cup plate agar diffusion method [14]. The compounds were evaluated for antibacterial activity against *Xanthomonas citric* (Xc), *Escherichia coli* (E. coli) and *Bacillus subtilis* (Bs). The antibiotic ampicillin (25 mg/ml) was used as standard antibiotic for comparison. The culture strains of bacteria were maintained on nutrient agar plate seeded with 0.1 ml of respective bacterial culture stain suspension prepared in sterile saline (0.85 %) of 10^5 CUF/MS dilution. The wells of 6 mm diameter were filled with 0.1 ml of solution at fixed concentration 25 µg/ml separately for each bacterial strain. All the plates were incubated at 37 ± 0.5°C for 24 hr. The zone of inhibition of compounds was measured using mm scale (Table-**I**).

CONCLUSION

In summary, we have prepared some halogenosubstituted cinnamic acids by conventional method and microwave irradiation technique. The antibacterial activity study shows that all the halogenosubstituted cinnamic acids showed potent activity.

Acknowledgements
The authors express their thanks to the Principal, Yeshwant Mahavidyalaya, Nanded for providing all laboratory facilities and also thankful to Dr. Yeshwant B. Vibhute for their guidance.

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