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SYNTHESIS OF CINNAMIC ACID DERIVATIVES USING ETHANOL AS SOLVENT OR MICROWAVE ASSISTED METHOD.

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Abstract: A comparison study about some parameters which influence the condensation of veratraldehyde with malonic acid in the presence of piperidine using ethanol as solvent and microwave irradiation was done, the obtainment of several substituted cinnamic acids are reported.

Substituted cinnamic acids posses a wide range of activities such as antiallergic agents[1], corrosion inhibitors[2], in veterinary preparations[3], in topical formulation[4] and in the synthesis of substituted styrenes[5,6].

In connection with our interest in the preparation of substituted cinnamic acids we needed to develop a convenient procedure for the preparation of 3,4-dimethoxycinnamic acid. This acid (fig 1) has been synthesized by three main methods (i) using Perkin[7] reaction condensing 3,4-dimethoxibenzaldehyde (veratraldehyde) with acetic anhydride in the presence of sodium acetate, (ii) condensing veratraldehyde with malonic acid using pyridine as solvent in the

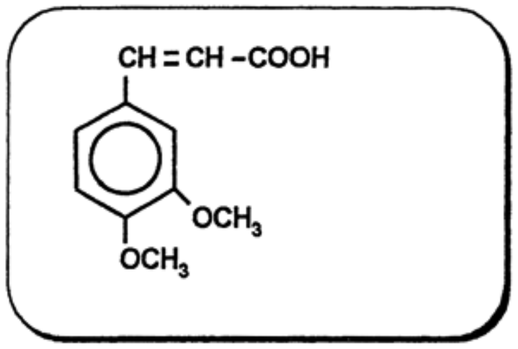


Fig.1

presence of piperidine in catalytic quantities (Doebner[8,9] reaction) or (iii) using alcohol as solvent in the presence of ammonia or pyridine (Knoevenagel[10,11] condensation).

Recently, Knoevenagel condensation has been reported to proceed efficiently under microwave irradiation without solvent and with piperidine as a base in the condensation of carbonyl derivatives with active methylene compounds leading to various methylene derivatives in good to excellent yield in minutes of microwaves irradiation[12]. Here we present the comparison procedure for the synthesis of cinnamic acids using alcohol as solvent or microwave irradiation in presence of piperidine in the reaction media.

RESULTS AND DISCUSSION

Veratraldehyde and malonic acid react in ammoniacal ethanolic solution to give 3,4-dimethoxicinnamic acid in 50% yield. Using ethanol as solvent and pyridine as catalyst in 14 hr. reaction time, Walling[11] obtained 77% yield. In order to improve the synthetic procedure, we explore primarily the possibility to reduce the reaction time using ethanol as solvent in the condensation of veratraldehyde with malonic acid described by Walling. Reducing the reaction time to 10 hr., we only obtained a 64% yield, the use of larger or smaller quantities of each reactant to those reported for Walling (1 mol of veratraldehyde, 1,1 mol of malonic acid and 25 mL of pyridine using 200 mL of ethanol) does not improve the reaction yield.

The effect of piperidine using pyridine or ethanol as solvent in Knoevenagel condensation has been reported[13], some authors refer the use of equimolecular amounts of piperidine and the condensing aldehyde, in this work we performed some experiments changing the piperidine concentration using boiling ethanol (200 mL) , veratraldehyde (1 mol), malonic acid (1 mol) in 14 hr. reaction time.

Table 1 Effect of the amount of piperidine on the yield.

Piperidine (mol)	0.1	0.5	1	1.5	2	2.5
Yield(%)	45	65	78	88	88	86
Stand. Dev.(%)	1.7	1.5	2.0	1.8	1.3	2.1

All experiments performed in this work were repeated five times, the yields reported represent a media of the obtained values for each reaction.

Knoevenagel condensation is catalyzed by bases[10,11], an increase in the medium basicity must increase the reaction yield. Experimental results shown in table 1 demonstrate that using 1.5 mol of piperidine per mol of veratraldehyde was enough for satisfactory results. It is noteworthy that when we used more than 1.5 mol of piperidine the yield of the acid remained constant.

Table 2 shows the results of different experiences of condensation of veratraldehyde and malonic acid employing different quantities of the acid, in all cases we used 1 mol of veratraldehyde, 1.5 mol of piperidine and the reaction time

Table 2 Effect of the amount of malonic acid on the yield

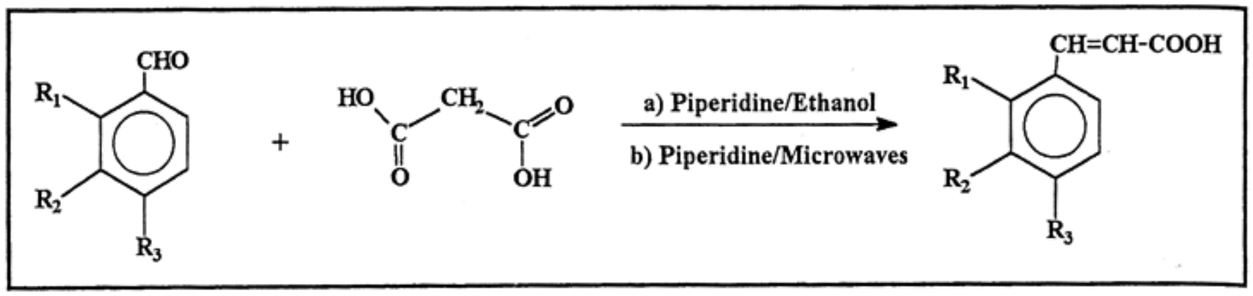
Malonic acid (mol)	1	1.3	1.5	2	2.5
Yield (%)	78	82	87	86	84
Stand. Dev.(%)	1.5	2	1.8	2.1	1.9

was 14 hr.. It was observed that the minimum quantity of malonic acid was 1.5 mol for the best yield of 87%. Using the same reaction conditions, the time was reduced to 7 hr. and the yield remained constant.

A reaction time less than 7 hr. decreases the yield, thus using 5 hr. reaction time the yield was 69% and is reduced to 30% in 3 hr.

In order to generalize the conditions established for this synthesis several substituted cinnamic acids were synthesized with good yield using 1 mol of aldehide 1.5 mol of malonic acid, 1.5 mol of piperidine and 200 mL ethanol, in all

Table 3: Synthesis of several cinnamic acids derivatives using ethanol as solvent or microwaves irradiation.



No	R_1	R_2	R_3	Yields (%) Conventional heating (EtOH 100°C 7 hr.)	Yields (%) Microwave (660 W, 15 sec.)	m.p. °C	m.p. (Lit..)
1	H	H	H	80	100	132-34	131-132 [14]
2	H	NO_2	H	79	99	197-99	196-97[15]
3	Cl	H	H	80	78	208-10	211-12[16]
4	H	OMe	OMe	88	81	181-83	180[17]
5	H	H	Me_2N	76	83	215-17	216[18]

cases the reaction was kept at reflux for seven hours.

We also evaluated the use of microwave irradiation and in this reaction several experiments were carried out. Irradiation of 3,4-dimethoxibenzaldehyde and malonic acid without piperidine was unsuccessful, the use of 1.5 mol of piperidine per mol of 3,4-dimethoxibenzaldehyde and 1.5 mol of malonic acid yield 3,4-dimethoxicinnamic acid almost quantitatively using 15 seconds reaction time at 660W in a domestic oven, a study about the influence in the relationship of reactants using microwave irradiation will be studied in a next communication.

Table 3 shows the yield obtained in substituted cinnamic acids synthesized using ethanol as solvent (7 hr.) or mw irradiation (15 seconds).

The cinnamic acids derivatives were characterized through melting points, as well as the comparison of IR spectra with authentic samples.

EXPERIMENTAL PART

General Procedure:

Synthesis of cinnamic acids derivatives using ethanol as solvent.

A mixture of benzaldehyde derivative (1 mol), malonic acid (1.5 mol), piperidine (1.5 mol), ethanol (200 mL) was refluxed for seven hours, the reaction mixture was poured into ice, acidificated with hydrochloric acid (pH 4) filter, washed with chilled water (500 mL) and recristalized in ethanol yielding a corresponding cinnamic acid derivative (see table 3).

Synthesis of cinnamic acids derivatives using microwave irradiation

Benzaldehyde derivative (1 mmol), malonic acid (1.5 mmol), piperidine (1.5 mmol) were mixed in an Erlenmeyer flask. The mixture was subject to microwave irradiation for 15 seconds and 660W. The mixture was poured into ice acidificated with hydrochloric acid (pH 4) filter washed with water and recristalized in ethanol yielding a corresponding cinnamic acid derivative (see table 3).

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