Synthesis of *trans*-cinnamic acids from aryl aldehydes and aryl aldehyde bisulfite adducts with malonic acid using piperazine

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Piperazine as a new reagent for the condensation of aryl aldehydes and their bisulfite adducts with malonic acid are described which afford the corresponding cinnamic acids in excellent yields and short reaction times in the absence of solvents under microwave irradiation.

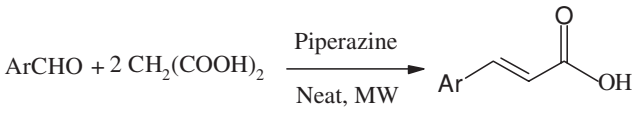
Keywords: bisulfites, cinnamic acids, piperazine, malonic acid

The generation of carbon–carbon single or double bonds is important in organic synthesis. The Knoevenagel condensation[1] and Doebner reaction[2] are among general methods available for the formation of carbon–carbon bonds. In the last few years, there has been a continuing interest in Doebner products due to their possessing biological activity[3] and synthetic utility.[4] Cinnamic acids are the products of this condensation reaction which are obtained from aromatic aldehydes and malonic acid.

Microwave irradiation is a useful technique in organic synthesis and is an efficient method for the synthesis of cinnamic acids.[5] We have exploited odourless and easy to work piperazine, instead of the hazardous pyridine, as an efficient reagent for the synthesis of cinnamic acids from aryl aldehydes and malonic acid in the absence of solvents under microwave irradiation (Scheme 1).

The reactions of various aryl aldehydes containing electron releasing and electron withdrawing groups with malonic acid were studied and the results summarised in Table 1. Cinnamic acid derivatives were obtained in excellent yields within a few minutes.

Aldehyde bisulfite adducts are a protected form of aldehydes and can be used for purification and isolation of aldehydes.[6] These crystalline compounds are stable and a good alternative to aldehydes especially those which are not stable. Thus, the possibility of the bisulfite addition product of *p*-methylbenzaldehyde reacting with malonic acid was examined, and it was found that the reaction under solvent-free conditions with the promotion of microwave irradiation afforded only 55% yield after 5 min. As indicated in Table 2, this reaction is strongly solvent dependent with microwave assistance under homogenous conditions and the solvent of choice is ethylene glycol.



Scheme 1

Obviously, the reaction times for bisulfite adducts are longer than the reaction times for the corresponding aldehydes (Table 1, Scheme 2).

In conclusion, the simple procedure, the high yields of the products, the short reaction times and the lack of problems in the removal of piperazine are among the advantages of this method.

General procedure for the condensation of aryl aldehyde with malonic acid

In a round bottomed flask, piperazine (1 mmol) was added to a mixture of aldehyde (1 mmol) and malonic acid (2 mmol). The mixture was irradiated with microwaves under solvent free conditions for the appropriate time according to Table 1.

Table 1 Synthesis of cinnamic acids from aryl aldehydes and aryl aldehyde bisulfite adducts with malonic acid under microwave irradiation[a]

Entry	Aryl	Aryl aldehyde[b]		Aryl aldehyde bisulfite[c]		M.p./°C	
		Time/min	Yield[d]/%	Time/min	Yield[d]/%	Found	Reported[7]
1	C_6H_5	3.5	91	5	88	118–120	133
2	4-$CH_3C_6H_4$	4	92	5	90	179–181	198–199
3	2-$CH_3OC_6H_4$	4	95	5	90	184–185	186
4	4-$CH_3OC_6H_4$	4	95	4.5	93	171–176	188–189.5
5	2,4-$(CH_3O)_2C_6H_3$	4.5	88	4	86	187–189	188–190
6	2,5-$(CH_3O)_2C_6H_3$	4.5	86	4.5	85	144–146	147
7	4-FC_6H_4	4.5	93	8	91	202–203	203
8	2-ClC_6H_4	4	93	6	90	210–211	212
9	3-ClC_6H_4	4	92	5.5	88	153–155	162.5–163
10	4-ClC_6H_4	4	92	6.5	90	236–240	249–250
11	2,4-$Cl_2C_6H_3$	4.5	90	7	82	238–240	239–240.5
12	2-BrC_6H_4	4	90	6	89	214–215	215–216
13	3-BrC_6H_4	4	92	6.5	88	176–178	178–179
14	4-BrC_6H_4	4	95	7	92	252–254	215–216
15	3-$O_2NC_6H_4$	4	95	7.5	92	199–201	200–201
16	4-$O_2NC_6H_4$	5	89	8	89	236–240	286
17	1-Naphthyl	5	91	6	87	154–155	156

[a]Products are known compounds and were characterised by comparison of their spectral data (^{1}H NMR, IR) and melting points with those reported in the literature. [b]Microwave power, 900 W. [c]Microwave power, 180 W. [d]All yields refer to isolated products.

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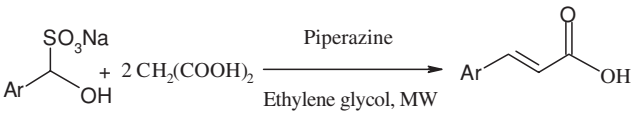

Scheme 2

Table 2 The effect of solvent on the reaction of *p*-methoxybenzaldehyde bisulfite with malonic acid under microwave irradiation

Entry	Solvent	Time/min	Yield/%
1	Neat[a]	5	–
2	Neat[b]	5	55
3	Acetic acid	5	45
4	water	5	–
5	Ethylene glycol	5	90
6	Methanol	5	–
7	Acetonitrile	5	–
8	Nitromethane	5	–
9	Dimethyl sulfoxide	5	75

[a]Microwave power, 180 W. [b]Microwave power, 900 W.

After completion of the reaction, as indicated by TLC, the dilute HCl was added to the reaction mixture and then the solution filtered. The crude product was washed with water and purified by recrystallisation using ethanol. The products were obtained in 86–95 % yields.

General procedure for the condensation of aryl aldehyde bisulfite adducts with malonic acid

In a round bottomed flask, to a mixture of aldehyde bisulfite adduct (1 mmol) and malonic acid (2 mmol) in 1.5 ml ethylene glycol, piperazine (1.2 mmol) was added and the reaction mixture was irradiated using the microwave oven for the appropriate time according to Table 1. After completion of the reaction (followed by TLC), the reaction mixture was cooled to room temperature. The solid product was filtered, washed with H_2O and dried. Recrystallisation from ethanol afforded the product with high purity in 82–93 % yields.

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