SHORT PAPER

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Microwave-assisted condensation reactions exploiting hexamethylenetetramine as a catalyst under solvent-free conditions[†]

Nilay Karchgaudhuri, Aparna De and Alok Kumar Mitra*

Department of Chemistry, University of Calcutta, 92, Acharya Prafulla Chandra Road, Calcutta – 700 009, India

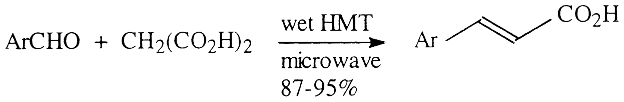
Hexamethylenetetramine has been exploited for the first time successfully as a catalyst for the Doebner reaction and Knoevenagel condensation along with the rate enhancement by microwave irradiation under solvent-free conditions.

Keywords: hexamethylenetetramine, Doebner reaction, Knoevenagel condensation

The most fundamental reactions of organic syntheses involve carbon–carbon bond formation. The Doebner reaction[1] and Knoevenagel condensation[2] are reactions of synthetic utility for the generation of new carbon–carbon bonds. Doebner reaction has been utilised to produce cinnamic acids[3] and their derivatives which have signigficant biological[4] importance and synthetic utility. The Knoevanagel condensation has wide application in the synthesis of fine chemicals.[5] Knoevenagel condensations using a variety of catalysts have been studied, *viz*: $AlPO_4$–Al_2O_3,[6] $BiCl_3$,[7] $ZnCl_2$[8] *etc*. Other methods involve P_2O_5 – poperidine / chlorobenzene (microwave),[9] modified hydrotalcite / toluene[10] and also solid phase reactions.[11]

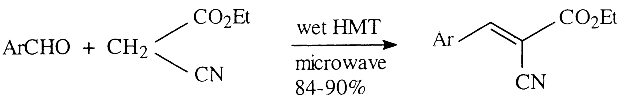
Our goal was to carry out these reactions under solvent-free eco-friendly condition with rate enhancement exploiting a new reagent. The wide applicability of microwave irradiation[12] in organic reaction enhancement encouraged us to carry out the reactions under microwave irradiation. In continuation of our ongoing programme to develop synthetic protocols uitilising microwave irradiation under solvent-free condition,[13] we have exploited hexamethylenetetramine (HMT) instead of the hazardous pyridine for the synthesis of cinnamic acids by the Doebner reaction as well as the condensation products of ethyl cyanoacetate and aromatic aldehydes by the Knoevengal condensation. Moreover, the reactions have been carried out in a solvent-free condition. The advantage of using HMT is that the reagent is inexpensive and easily available and the work-up procedure is also very simple. We report here for the first time the application of HMT for Doebner reaction and Knoevenagel condensation, in solvent-free condition under microwave irradiation, avoiding the stepwise control of temperature during the reaction by conventional method.

We exploited malonic acid and various aromatic aldehydes containing electron donating groups such as hydroxy, methoxy and electron withdrawing group such as nitro to achieve various cinnamic acids in the presence of wet HMT by solvent-free Doebner reaction (Scheme 1a). The reactions proceed efficiently in very high yields at ambient pressure within a few minutes (Table 1a). Some of these cinnamic acids are naturally occurring compounds viz. *p*-coumaric acid[14] (**3**), couramic acid methyl ether[14] (**4**), ferulic acid[14] (**6**), and 3,4-dimethoxycinnamic acid[14] (**7**). They have been used as synthons of several lignans[15] and cyclobutane derivatives[16] The coupling constant of the olefinic protons ($J = 16$ Hz) in ^1H NMR spectra indicated the formation of *trans* acids excusively.



Scheme 1a

We have exploited ethyl cyanoacetate and several aromatic aldehydes in the presence of HMT under solvent-free condition to demonstate the rate enhancement of Knoevangel reactpon (Scheme 1b). These reaction products have been utilised for the synthesis of cyanocoumarins,[17] mercaptopyrimidine as an intermediate for an antimetabolite,[18] as substrates for the Guareshit reaction,[19] and in the preparation of the synthesis of diterpene alkaloid.[20] The reactions were successfully carried out within few minutes (Table 1b) with high yields of a single geometric isomers. However unambiguous stereochemical assignment could not readily be made.



Scheme 1b

In conclusion, we have found a solvent-free, eco-friendly microwave-assisted method for new carbon–carbon bond formation exploiting hexamethylenetetramine as catalyst in Doebner reaction and Knoevenagel condensation.

Experimental

The IR spectra were run on Perkin-Elmer 782 spectrometer. ^1H NMR spectra were recorded in d-choloform solution on Bruker AM300L instrument operating at 300 MHz using tetramethylsilane as the internal standard. The reactions were carried out in a domestic microwave oven (BPL-SANYO, BMO-700T, 2450 MHz).

General procedure: (a) Doebner reaction: A mixture of the aromatic aldehyde (3 mmol), malonic acid (6 mmol) and hexamethylenetetramine (6 mmol) moistened with water (0.5 ml) was placed in a 25 ml Erlenmeyer flask. The flask was then placed in an alumina bath (heat sink) inside a domestic microwave oven and irradiated for the specified time (Table 1a) at medium power level (600 W). The mixture was then cooled and neutralised with cold 1:1 hydrochloric acid. The precipitated acid was filtered off and washed with cold water and recrystallised from ethanol. The products were characterised by comparing melting points, IR and ^1H NMR spectral data of the reported compounds.[21]

(b) Knoevenagel condensation: A mixture of aldehyde (1 mmol), ethyl cyanoacetate (1 mmol) and hexamethylenetetramine (1 mmol) moistened with water (0.5 ml) was taken in a 25 ml Erlenmeyer flask placed over alumina bath (heat sink). It was irradiated in a microwave oven for few minutes (Table 1b), at medium power level (600 W). The reaction was monitored by TLC. The product was extracted with ethyl

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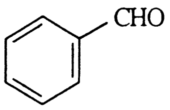
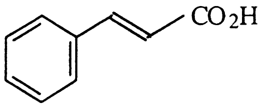
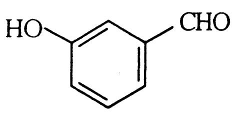
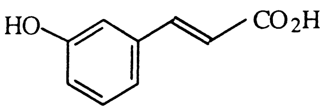
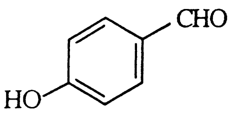
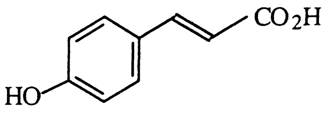
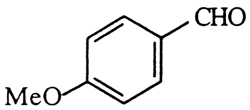
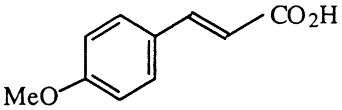
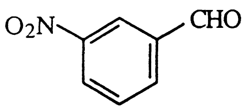
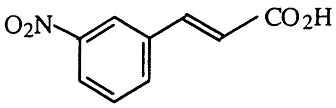
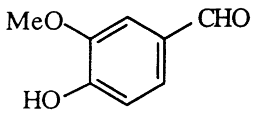
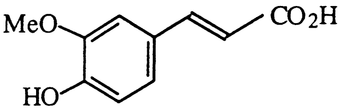
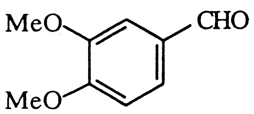
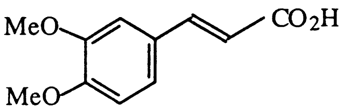
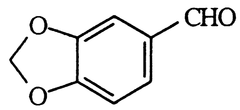
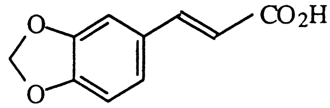
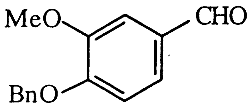
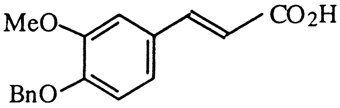
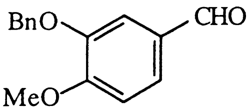
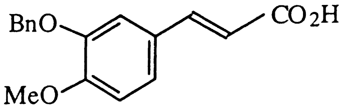
* To receive any correspondence. E-mail: akmitra@cucc.ernet.in

[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

Table 1a Microwave-assisted Doebner reaction exploiting HMT as catalyst under solvent-free conditions

Entry	Aldehyde	Product	t/min	Yield[a]/%
1			5	91
2			5	87
3			6	88
4			5	93
5			2	95
6			6	89
7			5	92
8			5	93
9			6	89
10			5	88

[a]Yields refer to pure products.

acetate (3 × 5 ml) and washed with brine (2 × 5 ml) and dried over anhydrous sodium suphate. The products were obtained by evaporation of solvent followed by the filtation on a short silica gel column. The products were characterised by comparing their melting points, IR and ^{1}H NMR spectral data with literature data.[22]

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Table 1b Microwave-assisted Knoevenagel condensation of ethyl cyanoacetate and aromatic aldehyde under solvent-free conditions using HMT as catalyst

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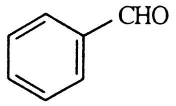
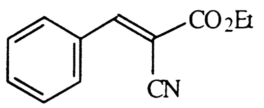
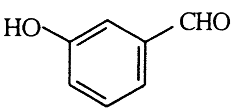
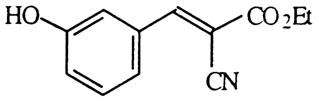
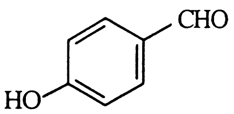
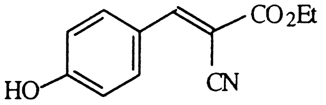
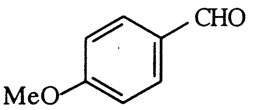
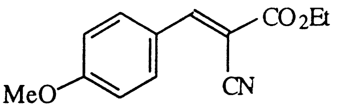
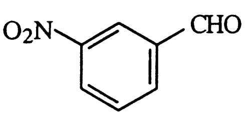
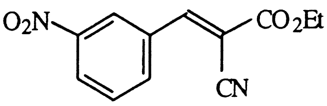
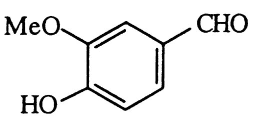
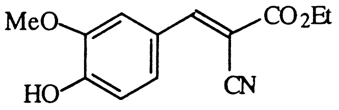
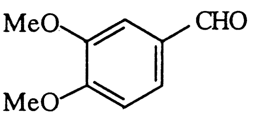
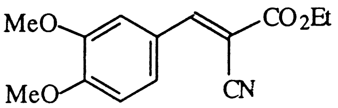
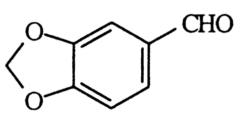
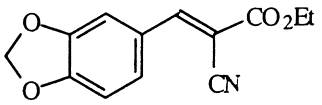
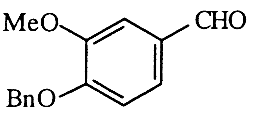
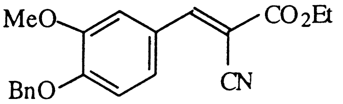
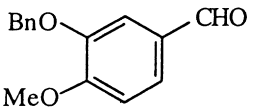
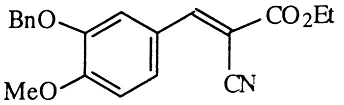
1			5	89
2			5	84
3			7	85
4			7	86
5			3	90
6			6	88
7			6	87
8			6	87
9			5	88
10			6	86

[a]Yields refer to pure products.

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Melting points and ^{1}H NMR spectral data of Doebner condensation products

Entry	M.p./°C	Lit./°C m.p.	^{1}H NMR (δ)
1	132	133[23]	–
2	198	–	7.57 (1H, d, J = 16Hz, 3-H), 7.15-6.71 (4H, m, Ar-H), 6.34 (1H, d, J = 16 Hz, 2-H), 5.82 (1H, br.s, OH)
3	207	206[23]	7.43 (1H, d, J = 15.9 Hz, 3-H), 7.41 (2H, d, J = 8.4 Hz, Ar-H), 6.74 (2H, d, J = 8.4 Hz, Ar-H), 6.22 (1H, d, J = 16 Hz, 2-H), 3.56 br.s, OH)
4	172	172[23]	7.66 (1H, d, J = 15.9 Hz, 3-H), 7.43 (2H, d, J = 8.6 Hz, Ar-H), 6.87 (2H, d, J = 8.6 Hz, Ar-H), 6.25 (1H, d, J = 15.9 Hz, 2-H), 6.25 (1H, d, J = 15.9 Hz, 2-H), 3.80 (3H, 5, OCH_3)
5	195	197[24]	8.36 (1H, s, Ar-H), 8.21–7.80 (2H, m, Ar-H), 7.75 (1H, d, J = 16 Hz, 3-H), 7.52 (1H, m, Ar-H), 6.53 (1H, d, J = 16 Hz, 2-H)
6	167	168[25]	7.65 (1H, d, J = 16 Hz), 3-H), 7.35– 6.85 (3H, m, Ar-H), 6.22 (1H, d, J = 16 Hz, 2-H), 4.71 (1H, br.s, OH). 3/87 (3H, s, OCH_3)
7	177	180[25]	7.74 (1H, d, J = 16 Hz, 3-H), 7.16–6.88 (3H, m, Ar-H), 6.33 (1H, d, J = 16 Hz, 2-H), 3.90 (6H, s, 2 × OCH_3)
8	238	238[24]	7.60 (1H, d, J = 15.9 Hz, 3-H), 6.96–6.77 (3H, m, Ar-H), 6.20 (1H, d, J = 15.9 Hz, 2-H), 5.94 (2H, s, OCH_2O)
9	189–190	190–191[21]	7.71 (1H, d, J = 16 Hz, 3-H), 7.75–6.86 (8H, m, Ar-H), 6.30 (1H, d, J = 16 Hz, 2-H), 5.21 (2H, s, OCH_2), 3.91 (3H, s, OCH_3)
10	206–207	206–208[21]	7.64 (1H, d, J = 15.9 Hz, 3-H), 7.40–6.82 (8H, m, Ar-H), 6.16 (1H, d, J = 15.9 Hz, 2-H), 5.11 (2H, 5, OCH2), 3.85 (3H, 5, OCH_3)

Melting points and 'H NMR spectral data of Knoevenage condensation products

Entry	M.p./°C	Lit. m.p./°C	^{1}H NMR (δ)
1	49	49	7.90 (IH, s, = CH), 7.62–7.08 (5H, m, Ar-H), 4.07 (2H, q, J = 7.2 Hz, OCH_2CH_3), 1.40 (3H, t, J = 7.2 Hz, OCH_2CH_3)
2	Semi-solid	Semi-solid	8.20 (IH, s, = CH), 7.62 (IH, m, 2′-H), 7.41–7.03 (3H, m, Ar-H), 4.26 (2H, q, J = 7.1 Hz, OCH_2CH_3), 1.39 (3H, t, J = 7.1 Hz, OCH_2CH_3)
3	171	172	8.10 (1H, s, = CH), 7.88 (2H, d, J = 8.6 Hz, Ar-H), 6.89 (2H, d, J = 8.6 Hz, Ar-H), 4.32 (2H, q, J = 7.2 Hz, OCH_2CH_3), 1.34 (3H, t, J = 7.2 Hz, OCH_2CH_3)
4	86	88	8.15 (1H, s, = CH), 7.99 (2H, d, J = 8.6 Hz, Ar-H), 6.97 (2H, d, J = 8.6 Hz, Ar-H), 4.33 (2H, q, J = 7.2 Hz, OCH_2CH_3), 3.90 (3H, s, OCH_3), 1.33 (3H, t, J = 7.2 Hz, OCH_2CH_3)
5	130	128–132	8.65 (1H, t, J = 1.7 Hz, 2′-H), 8.34 (1H, dd, J = 8.2, 1.7Hz, 4′-H), 8.25 (1H, s, = CH), 8.17 (1H, m, 6′-H), 7.67 (1H, m, 5′-H), 4.28 (2H, q, J = 7.1 Hz, OCH_2CH_3), 1.26 (3H, t, J = 7.1 Hz, OCH_2CH_3)
6	100	100	8.07 (1H, s, = CH), 7.77 (1H, s, 2′-H), 7.33 (1H, d,J = 8.3 Hz, Ar-H), 6.92 (1H, d, J = 8.3 Hz, Ar-H), 6.23 (1H, br.s, OH), 4.31 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.91 (3H, s, OCH_3), 1.34 (3H, t, J = 7.1 Hz, OCH_2CH_3)
7	157	158	8.09 (1H, s, = CH) 7.73 (1H, d, J = 2.1 Hz, 2′-H), 7.40 (1H, dd, J = 8.4, 2.1 Hz, 6′-H), 6.88 (1H, d, J 8.4 Hz, 5′-H), 4.30 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.88 (6H, s, 2 × OCH_3) 1.30 (3H, t, J = 7.1 Hz, OCH_2CH_3)
8	96	96	8.06 (1H, s, = CH) 7.63 (1H, d, J = 1.7 Hz, 2′-H), 7.34 (1H, dd, J = 8.2, 1.7 Hz, 6′-H), 6.84 (1H, d, J = 8.2 Hz, 5′-H), 6.01 (2H, s, OCH_2O), 4.30 (2H, q, J = 7.1 Hz, OCH_2CH_3), 1.33 (3H, t, J = 7.1 Hz, OCH_2CH_3)
9	131	132	8.12 (1H, s, = CH), 7.79 (1H, d, J = 2.1 Hz, 2′-H), 7.42 (1H, dd, J = 8.5, 2.1 Hz, 6′-H), 7.39–7.32 (5H, m, Ar-H), 6.94 (1H, d,J = 8.5 Hz, 5′-H), 5.22 (2H, s, OCH_2), 4.37 (2H, q,J = 7.1 Hz, OCH_2CH_3), 3.92 (3H, s, OCH_3), 1.34 (3H, t, 7.1 Hz, OCH_2CH_3)
10	123	122	8.05 (1H, s, = CH), 7.71 (1H, d, J = 2.1 Hz, 2′-H), 7.47–7.41 (5H, m, Ar-H), 7.33 (1H, dd, J = 8.2, 2.1 Hz, 6′-H), 6.89 (1H, d, J = 8.2 Hz, 5′-H), 5.13 (2H, s, OCH_2), 4.28 (2H, q, J = 7.1 Hz, OCH_2OCH_3), 3.89 (3H, s, OCH_3), 1.22 (3H, t, J = 7.1 Hz, OCH_2CH_3)

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