Microwave-assisted urea catalyzed Knoevenagel condensation of aldehydes with active methylene compounds

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Abstract

Rapid and efficient method for the synthesis of substituted olefins such as 2-(4-chlorophenylmethylene) malononitrile, 2-(4-hydroxyphenylmethylene) malononitrile and 2-cyano-3-(4-hydroxyphenyl) acrylamide etc under the influence of microwave irradiation are described. Urea has been utilized as an efficient catalyst for the Knoevenagel condensation of aldehydes with acidic active methylene compounds such as malononitrile, ethylcyanoacetate and cyanoacetamide to afford substituted olefins under the influence of microwave irradiation. The reaction proceeds smoothly under mild and solvent free conditions and the products are obtained in good yield. The method is applicable for a wide range of aldehydes including aromatic and heterocyclic substrates.

Keywords: Microwave; Active methylene; Green procedure; Urea catalyst; Substituted cyanoacetamide; Knoevenagel condensation

Introduction

The Knoevenagel condensation has numerous application in the synthesis of fine chemicals (Freeman, 1981), hetero Diels-Alder reactions (Borah et al., 2005) as well as heterocyclic compounds of biological significance (Tietze, 1996). The condensation of aldehydes with active methylene compounds is an important and widely employed method for carbon-carbon double bond formation in organic synthesis. The reaction is usually carried out by bases (Yang et al., 2006), such as sodium hydroxide or sodium ethoxide in organic solvents. Organic weak bases such as aliphatic amines, ethylenediamine and piperidine or corresponding ammonium salt are also used for Knoevenagel reaction (Acker et al., 1962). The Knoevenagel condensations between aldehydes and malononitrile in dry media catalyzed by ZnCl₂, (Rao, 1991), silica gel (Cruz et al., 1996) have been reported.

Bhuian et al. (2012) reported the synthesis of arylidene malononitriles by the reaction of malononitriles and aldehydes.

Microwave-assisted solvent-free reactions (Wang, 2001) represent very powerful green chemical technology procedures from both the economical and synthetic point of view. In literature report the synthesis of substituted olefins have been described by Sun Qi et al. (2005) using conventional thermal methods involved long reaction time.

The ability of microwave irradiation to reduce reaction time led to an idea for this synthesis to be carried out under the influence of microwave irradiation. In our previous report we have reported microwave assisted synthesis of arylidene derivatives using NH₄OAc as a catalyst (Ahmed et al., 2018). In continuation of our interest to study the organic reaction or transformation under microwave irradiation we herein, report synthesis of known and new arylidene malononitriles, acrylamide using microwave irradiation.

Materials and methods

All chemicals were purchased from (Sigma-Aldrich, Merck, and Alfa Aesar) and were used without further

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purification. The Chemicals 4-fluorobenzaldehyde (98%), 4-hydroxybenzaldehyde (98%), 4-nitrobenzaldehyde (98%), 2-nitrobenzaldehyde (98%), 3-nitrobenzaldehyde (98%), 4-chlorobenzaldehyde (97%) and cyanoacetamide (98%) from Sigma-Aldrich. Cinnamaldehyde (98%), and ethylcyanoacetate from Merck, 2-furaldehyde (98%), 4-methylbenzaldehyde (98%), 4-methoxybenzaldehyde (99%) and malononitrile (99%) were purchased from Alfa Aser. GALLEN KAMP melting point apparatus was used to record the melting point of the solid compound, the heating was done carefully to ensure a steady rise of temperature. 1H NMR spectra were recorded on a JEOL JNM ECS FT NMR at 400 MHz spectrometer using tetramethylsilane as an internal standard. Coupling constants $J$ are given in Hz. Infrared spectra were observed on a Shimadzu FTIR- spectrometer (IR prestige 21). Analytical TLC was performed on pre-coated aluminium sheet and the product was visualized by UV light. All reactions were carried out in a domestic microwave oven (Samsung, MW76ND).

**General procedure**

To a mixture of aromatic aldehyde 1 (2 mmol) and active methylene compound 2 (2 mmol) was added catalytic amount of urea (10 mol %, 0.2 mmol) in a Pyrex glass 50 mL beaker and mixed thoroughly using a glass rod. The mixture was then subjected to microwave irradiation at 180W-800W for 1 to 5 min. The progress of the reaction was followed by TLC ($n$-hexane: ethyl acetate). After complete conversion and cooling of the reaction, the solid reaction mixture was washed with water to remove urea. Recrystallization of the mixture was done using ethyl acetate and $n$-hexane solvent mixture to give the pure product 3 under the scheme 1.

**Scheme 1**

$$R^1\text{CHO} + C\equiv N \rightarrow R^1-C\equiv N+H_2O$$

$R^1=$ aromatic and heterocyclic

$R^2= -CN, -CO_2C_2H_5, -CONH_2$

2-(4-nitrophenyl)methylene)malononitrile (3a): yield 90%, yellowish white solid, m.p. 158-159°C, (lit.160°C (Sun Qi et al 2005)); IR (KBr): $\nu_{max}$: 3039(sp2 C-H), 2927(sp3 C-H), 2231(C≡N), 1504(C=C) and 1521 and 1344(N-O) cm$^{-1}$; $^1H$ NMR (400 MHz, CDCl$_3$) $\delta$(ppm): 8.41 (2H, d, $J=8.8$Hz, =CH), 8.09 (2H, d, $J=8.8$Hz, Ar), 7.89 (1H, s, -CH).

2-(4-methylbenzyldiene)malononitrile (3b): yield 96%, white solid, m.p. 131-132°C, (lit.134°C (Ren et al 2002)); IR (KBr): $\nu_{max}$(cm$^{-1}$): 3035(sp2 C-H), 2927(sp3 C-H), 2223(C≡N) and 1589(C=C) cm$^{-1}$; $^1H$ NMR (400 MHz, CDCl$_3$) $\delta$(ppm): 7.80 (2H, d, $J=8.2$Hz, Ar), 7.71 (1H, s, =CH), 7.32 (2H, d, $J=8.2$Hz, Ar), 2.44 (3H, s, -CH$_2$).

2-(4-fluorobenzaldehyde)malononitrile (3c): yield 94%, light brown solid m.p. 119°C, (lit.124-125°C (Fan et al 2004)); IR (KBr): $\nu_{max}$(cm$^{-1}$): 3043(sp2 C-H), 2231 (C≡N) and 1658 (C=C) cm$^{-1}$; $^1H$ NMR (400 MHz, DMSO) $\delta$(ppm): 8.53 (1H, s, =CH), 8.02-8.06 (2H, t, $J=8$Hz, Ar), 7.48-7.52 (2H, m, Ar).

2-(4-Chlorophenyl)methylene)malononitrile (3d): yield 95%, white solid, m.p. 158-160°C, (lit. 165°C (Sun Qi et al 2005)); IR (KBr): $\nu_{max}$(cm$^{-1}$): 3034(sp2 C-H), 2223 (C≡N) and 1585 (C=C) cm$^{-1}$; $^1H$ NMR (400 MHz, CDCl$_3$) $\delta$(ppm): 7.72(1H, s, =CH), 7.83 (2H, d, $J=8$Hz, Ar), 7.53 (2H, d, $J=8$Hz, Ar).

2-(3-nitrophenyl)methylene)malononitrile (3e): yield 89%, creamy white solid, m.p. 102-103°C, (lit. 104-105°C (Sun Qi et al 2005)); IR (KBr): $\nu_{max}$(cm$^{-1}$): 3086(sp2 C-H), 2225 (C≡N), 1597 (C=C) and 1529&1355(N-O) cm$^{-1}$; $^1H$ NMR (400 MHz, CDCl$_3$) $\delta$(ppm): 8.67 (1H, t, $J=1.8$Hz, Ar), 8.49 (1H, dd, $J=1.5$, 8.1 Hz, Ar), 8.34 (1H, d, $J=7.8$Hz, Ar), 7.90 (s, 1H, =CH), 7.80 (1H, t, $J=8.1$Hz, Ar).
2-(4-Hydroxyphenylmethylene)malononitrile (3f): yield 96%, yellow solid, m.p. 171-172°C, (lit. 189-190°C)(Sun Qi et al. 2005); IR (KBr): $\nu_{\text{max}}$(cm$^{-1}$): 3354(OH), 3030(sp$^2$ C-H), 2227(C=N=C), and 1670(C=C) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$(ppm): 7.89 (2H, d, $J$=9.0 Hz, Ar), 7.65 (1H, s, =CH), 6.97 (2H, d, $J$=9.0 Hz, Ar), 5.75 (1H, s, OH).

2-(2-Furylmethylene)malononitrile (3g): yield 90%, blackish brown solid, m.p. 62-63°C, (lit. 72°C(Sun Qi et al. 2005)); IR (KBr): $\nu_{\text{max}}$(cm$^{-1}$): 3124(sp$^2$ C-H), 2227 (C=C) 1589 (C=C) ; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$(ppm): 7.80 (1H, d, $J$= 1.6 Hz, Ar), 7.50 (1H, s, =CH); 6.70 (1H, dd, $J$= 3.6 & 1.6 Hz, Ar), 7.35 (1H, d, $J$=4.0Hz, Ar).

2-(3-Pyridylmethylene)malononitrile (3h): yield 95%, brownish solid, m.p. 80-82°C, (lit. 83-84°C(Sun Qi et al. 2005)); IR (KBr): $\nu_{\text{max}}$(cm$^{-1}$): 3032(sp$^2$ C-H), 1662 (C=C) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$(ppm): 8.89 (1H, d, $J$= 2.4 Hz, Ar), 8.83 (1H, dd, $J$ = 1.2 & 4.8 Hz, Ar), 8.50 (1H, dd, $J$ = 1.5 , 8.0 Hz, Ar).7.83 (1H, s, =CH), 7.53(1H, d, $J$= 4.8, 7.8 Hz, Ar).

Ethyl 2-cyano-3-styryl-2-propenoate (3i): yield 92%, yellowish solid m.p. 111-112°C, (lit.115°C(Sun Qi et al. 2005)); IR (KBr): $\nu_{\text{max}}$(cm$^{-1}$): 3030(sp$^2$ C-H), 2250 (C=C=N), 1743(C=O) and 1662 (C=C) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$(ppm): 8.00 (1H, d, $J$= 3.9 & 6.9 Hz, =CH) 7.57- 7.61 (2H, m, Ar), 7.41- 7.44(3H, m, Ar), 7.26 (2H, q, $J$=3.6 Hz, =CH$_2$). 4.35 (2H, q, $J$=7.2Hz, OCH$_2$). 1.38 (3H, t, $J$=7.2Hz, -CH$_3$).

2-cyano-3-(4-hydroxyphenyl)acrylamide (3j): yield 95%, white solid, m.p. 245-246°C, (lit. 245°C(Sun Qi et al. 2005)); IR (KBr): $\nu_{\text{max}}$(cm$^{-1}$): 3454 and 3366 (N-H str. For NH$_2$), 3186 (O-H str. ), 3079 (aromatic C-H str.), 3030 (sp2 C-H str.), 2229 (C≡N str.), 1658 (CO str.), 1624 (alkene C=C str.), 1600 and1514 (aromatic C=C str.), 1290 (C-N str), 1251 (C-O str). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$(ppm): 10.53(br, s, 1H), 8.05(s, 1H), 7.87(d, $J$=8.8, 2H), 7.74(s, 1H, NH), 7.61(s, 1H, NH). 6.93(d, $J$=8.8, 2H).

2-cyano-3-(4-fluorophenyl)acrylamide (3k): yield 96%, white solid, m.p. 151°C; IR (KBr): $\nu_{\text{max}}$(cm$^{-1}$): 3488and 3381 (N-H str. For NH$_2$), 3169 (aromatic C-H str.), 3024 (sp2 C-H str.), 2216 (C≡N str.), 1701 (CO str.), 1687 (alkene C=C str.), 1600 and1504 (aromatic C=C str.), 1386 (C-N str), 1233 (C-O str). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$(ppm): 8.32(s, 1H), 8.01(d, $J$=8.4, 2H), 7.22(d, $J$=8.4, 2H), 6.38(s, 1H, N-H), 6.11(s, 1H, N-H).

2-cyano-3-(4-nitrophenyl)acrylamide (3l): yield 85%, light brown solid, m.p. 229-230°C; IR (KBr): $\nu_{\text{max}}$(cm$^{-1}$): 3442and 3346 (N-H str., NH$_2$), 3196 (aromatic C-H str.), 3024 (sp2 C-H str.), 2224 (C≡N str.), 1695 (CO str.), 1622 (alkene C=C str.), 1600 and1494 (aromatic C=C str.), 1510 and 1346 (nitro N=O str.), 1327 (C-N str), 1203 (C-O str.). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$(ppm): 8.39(d, $J$= 8.8 Hz, 2H), 8.30(s, 1H), 8.13(d, $J$=8.8, 2H), 8.05(s, 1H, N-H), 7.91(s, 1H, N-H).

2-cyano-3-(furan-2-yl)acrylamide (3m): yield 88%, light brown solid, m.p. 93-94°C; IR (KBr): $\nu_{\text{max}}$(cm$^{-1}$): 3488and 3381 (N-H str. For NH$_2$), 3169 (aromatic C-H str.), 3024 (sp2 C-H str.), 2216 (C≡N str.), 1701 (CO str.), 1687 (alkene C=C str.), 1600 and1504 (aromatic C=C str.), 1386 (C-N str), 1233 (C-O str.). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$(ppm): 10.83(s, 1H), 7.76(d, $J$=1.6, 1H), 7.25(d, $J$=3.6, 1H), 6.66(dd, $J$=3.6, $J$=1.6, 1H), 6.29(s, 1H, N-H), 5.76(s, 1H, N-H).

**Results and discussion**

In this report, we highlight our findings on the microwave assisted urea catalysed condensation of active methylene compounds, such as malononitrile, ethylcyanoacetate and cyanoacetamide with aromatic and heterocyclic aldehydes. Initially, the condensation reaction of p-hydroxybenzaldehyde with malononitrile and p-hydroxybenzaldehyde with cyanoacetamide was carried out at 300W for 1-3 min without urea. In both the cases the reactions were not proceeded. This is worth to mention that in every case we obtained the starting materials only. However, when the reaction was conducted using urea as catalyst, at 300W/1-3 min, the desired product is obtained. Accordingly, treatment of para-nitrobenzaldehyde with malononitrile in the presence 10 mol % of urea catalyst at 300W/1-3 min resulted in the formation of 3a 90 % yield under solvent free conditions. In a similar manner, a wide range of substrates such as 4-methyl, 4-fluoro, 4-chloro, 3-nitro, 4-hydroxy aldehydes etc with active methylene malononitrile including heterocyclic aldehydes 2-furaldehyde and pyridine-4-carboxaldehyde react efficiently under the same conditions (Table 1) to give the corresponding olefins 3b, 3c, 3d, 3e, and 3f respectively.
Table I. Products of urea catalyzed microwave-assisted Knoevenagel condensation of aldehydes with active methylene compounds

| Entry | R<sup>1</sup> | R<sup>2</sup> | Reaction time and Watt | Products<sup>a</sup> | Melting point<sup>c</sup> (°C) | Yield<sup>b</sup> (%) |
|-------|-------------|-------------|------------------------|-----------------|---------------------|------------------|
| i     | p-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub> & -CN | 1 min/300W | 3a                     | 158 – 159 (160 °C) | 90                  |
| ii    | p-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub> & -CN | 1.5 min/300W | 3b                     | 131 – 132 (134 °C) | 96                  |
| iii   | p-FC<sub>6</sub>H<sub>5</sub> & -CN | 3.5 min/300W | 3c                     | 119 (124-125 °C)  | 94                  |
| iv    | p-ClC<sub>6</sub>H<sub>4</sub> & -CN | 2.5 min/450W | 3d                     | 158 – 160 (165 °C) | 95                  |
| v     | p-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub> & -CN | 1.0 min/180W | 3e                     | 102 – 103 (104-105 °C) | 89                  |
| vi    | p-OHC<sub>2</sub>H<sub>5</sub> & -CN | 2 min/180W | 3f                     | 171 – 172 (189-190 °C) | 96                  |
| vii   | 2-furyl & -CN | 2.5 min/450W | 3g                     | 62– 63 (72 °C) | 90                  |
| viii  | 3-pyridyl & -CN | 1.0 min/180W | 3h                     | 80 – 83 (83-84 °C) | 95                  |
| ix    | PhCH=CH & -CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub> | 5 min/300W | 3i                     | 111 – 112 (115 °C) | 92                  |
| x     | p-OHC<sub>6</sub>H<sub>5</sub> & -CONH<sub>2</sub> | 2 min/300W | 3j                     | 245-246 (245 °C) | 95                  |
| xi    | p-FC<sub>6</sub>H<sub>5</sub> & -CONH<sub>2</sub> | 5 min/300W | 3k                     | 150 – 151 | 96                  |
| xii   | p-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub> & -CONH<sub>2</sub> | 1.5 min/300W | 3l                     | 229 – 230 | 85                  |
| xiii  | 2-furyl & -CONH<sub>2</sub> | 2 min/450W | 3m                     | 93 – 94 | 88                  |

<sup>a</sup> All products were characterized by m.p. and spectral techniques and melting was compared with literature value.<sup>b</sup>Isolated yield; <sup>c</sup>Values in parenthesis are lit M.P.
Furthermore, the treatment of aldehyde such as cinnamaldehyde with ethylecyanoacetate also give olefinic compounds 3i under similar conditions (Table 1, Scheme 1). Both electron-rich and electron-deficient aldehydes gave high yield of products. Heterocyclic aldehydes such as 2-furaldehyde and pyridine-4-carboxaldehyde gave the olefinic derivatives 2-furymethylene, 3g and 2-(3—pyridymethylene) olefinic 3h derivatives at 90% and 95% yield respectively. Similar reaction of 4-hydroxy, 4-fluoro, 4-nitro, and 2-furaldehyde with active methylene compounds 2-cyanoacetamide gave the corresponding olefins derivatives 2-cyano (3-(hydroxyphosphoryl)- propeneamid (3j), 2-cyano (3-(4-fluorophenyl)- propeneamid (3k), 2-cyano (3-(4-nitrophenyl)- propeneamid (3l), and 2-cyano (3-(furylethylyphenyl)- propeneamid (3n) respectively. Nitro, hydroxyl, heterocyclic group are well tolerable due to the short reaction time and relatively mild reaction conditions. The reaction does not proceed under similar condition in the absence of urea catalyst. The reaction does not take place at all, only starting materials obtained in reaction mixture.

All the products were characterized by IR and 1H NMR data analysis. The 1H NMR spectra of the products 3a – 3i showed the olefinic proton around 6 7 – 9 ppm in CDCl3 as singlet peak. In the IR spectrum, the absorption band observed at 1705 - 1730 cm−1 is due to carbonyl, and the band at 2214 -2225 cm−1 is due to the –CN groups and the band at 1650-1550 cm−1 is due to C=C groups. The spectroscopic data of all the products are given sequentially.

Conclusion
In conclusion, we have synthesized several substituted olefins using urea as catalyst under solvent free condition. The use of urea as a catalyst helps to avoid the use of environmentally unfavorable organic solvents as reaction medium since the reaction proceeds smoothly under solvent free conditions. This method could be applied to a wide range of aldehydes including aromatic and heterocyclic substrates. A microwave-assisted solvent-free reaction conditions with short time and inexpensive and easily available catalyst are the key features involved in the present protocol.

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