***SHORT PAPER***

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# Microwave-assisted efficient synthesis of dihydro pyrimidines: improved high yielding protocol for the Biginelli reaction

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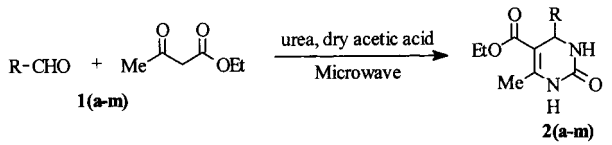
Dihydropyrimidines were synthesised in high yields by one-pot cyclocondensation reaction of aldehydes, aceto-acetates and urea using various acid catalysts like Amberlyst-15, Nafion-H, KSF clay and dry acetic acid under microwave irradiation.

Dihydropyrimidines are important class of compounds which are becoming increasingly significant due to their therapeutic and pharmacological properties.[1] Several functionalised derivatives are used as calcium channel modulators and anti-hypertensive $\alpha_{1a}$-antagonists.[2] Synthetic strategies for the dihydropyrimidine nucleus would involve one-pot to multi-step approaches. The simple and direct method originally reported by Biginelli involving three component condensation reactions (*i.e.* aldehydes, β-keto ester and urea) often suffer from low yields practically in case of substituted aromatic aldehydes.[3] Several modifications and improvements have been sought. Although high yields could be achieved by following complex multi-step procedures, these methods lack the simplicity of original one-pot Biginelli protocol.[4] Recent reports on $BF_3OEt_2$ or polyphosphate esters mediated Biginelli reaction[5] requires 15 to 18 h of reaction time to achieve moderate to high yields of the products. More recently, KSF[6] has also been employed for this transformation which involves longer reaction time (10 to 48 h) to obtain good yields. However, in spite of their potential utility, some of the reported methods suffer from drawbacks like longer reaction times, unsatisfactory yields and cumbersome product isolation procedures.

In continuation of our interest on microwave-assisted organic transformations,[7] herein we describe a novel, efficient and high yielding protocol for the preparation of dihydropyrimidines. Among various acid catalysts, dry acetic acid is found to be more effective for this transformation because of its high polarity which couples effectively with microwaves and generates heat energy required to promote the reaction. The rate enhancement under microwave irradiation may be attributed to the effective absorption of microwaves by the polar media. Thus, microwaves have been applied to accelerate reaction rates and to improve the yields of the products. The classical synthesis of dihydropyrimidines requires long reaction time at reflux temperature to obtain moderate yields. In general, microwave-assisted reactions are clean, rapid and afford higher yields than those obtained by conventional methods. An equimolar quantity of aldehyde, β-keto ester and urea were mixed with dry acetic acid and subjected to microwave irradiation at 650 W using BPL, BMO-700T microwave oven for an appropriate time. The temperature regime 90–95 °C was observed during microwave irradiation. After cooling to room temperature, the reaction mass was diluted with water and filtered to afford pure product as crystalline solid. Similarly, the reactants were admixed with KSF clay (montmorillonite KSF, Aldrich) and subjected to microwave irradiation at 650 W for 6–8 min to obtain 75–85% yields of the products.




**Scheme 1**

Further, we have studied the reaction time and yields of the products by using ion exchange-resins such as Amberlyst-15 and Nafion-H for Biginelli reactions. The reaction was carried out by refluxing the reactants in toluene in the presence of either Amberlyst-15 or Nafion-H for 6 to 15 h to achieve good yields of the products. There was not much difference in yields and reaction times either by Amberlyst-15 or Nafion-H as catalysts. Although, solid acids like Amberlyst-15, Nafion-H and KSF clay affording good yields of products in high purity but the adopted isolation procedures were cumbersome due to the insolubility of the products in most of the organic solvents except in DMSO or hot methanol. The solid acid catalyst KSF could be recovered by filtration and reused twice in the reaction after activation at 110 °C for 6 h. Similarly, ion-exchange resins were also recovered by filtration and reused in the reaction for three times after activation under reduced pressure at 60 °C for 4–5 h. The results, summarised in Table 1, indicate the generality of the reaction for various substituted aldehydes.

In summary, a rapid and high yielding protocol for the synthesis of dihydropyrimidines from aldehydes, β-ketoesters and urea using various acid catalysts in solvent-free conditions under microwave irradiation has been described for the first time. The adopted procedure is simple, rapid and eco-friendly due to the easy experimental and product isolation procedures, hence it is useful addition to the existing methods.

## Experimental

Melting points were recorded on Buchi capillary melting point apparatus. The $^1$H NMR spectra were recorded on Varian Gemini 2000 MHz spectrometer using TMS as an internal standard in DMSO-$d_6$. IR spectra were recorded on Nicolet FT IR-740.

*Typical procedure A*: A mixture of *p*-nitrobenzaldehyde (1.51 g, 10 mmol), ethyl acetoacetate (1.30 g, 10 mmol) and dry acetic acid (0.18 g, 3 mmol) was admixed in a pyrex test tube and subjected to microwave irradiation at 650 W (BPL, BMO-7OOT, operating at 240 MHz) for 4 min. After cooling to room temperature, the solid mass was washed with water, filtered and dried *in vacuo* to afford pure product **2b** (88% yield) 2.80 g as a white crystalline solid. m.p. 207–208 °C, $^1$H NMR (DMSO-$d_6$) δ : 9.3 (s, NH), 8.20 (d, 2H, *J* = 8.7 Hz), 7.9 (d, 1H, *J* = 2.46 Hz), 7.50 (d, 2H, *J* = 8.7 Hz), 5.27 (d, 1H, *J* = 1.6 Hz), 3.98 (q, 2H, *J* = 7.1 Hz), 2.25 (s, 3H), 1.1 (t, 3H, *J* = 7.1 Hz). IR (Neat) : 3230, 3109, 1701, 1641, 1591, 1520 cm$^{-1}$.

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

**Table 1** Microwave-assisted efficient synthesis of dihydropyrimidines

| Entry | R[a] | Microwave irradiation[b] Time (min) | Microwave irradiation[b] Yield (%) | Conventional heating[c] Time (hrs) | Conventional heating[c] Yield (%) | m.p. (°C) Found | m.p. (°C) Reported |
|---|---|---|---|---|---|---|---|
| a | Phenyl | 2 | 86 | 12 | 80 | 201–202 | 202 |
| b | 4-$NO_2C_6H_4$ | 4 | 88 | 15 | 79 | 207–208 | 208 |
| c | 4-$C1C_6H_4$ | 3 | 84 | 13 | 70 | 212–213 | 213 |
| d | 2,3-$(Cl)_2C_6H3$ | 3 | 82 | 10 | 78 | 213–214 | 215 |
| e | 4-$MeC_6H_4$ | 2 | 85 | 8 | 73 | 170–171 | – |
| f | 4-$MeOC_6H_4$ | 2 | 88 | 12 | 71 | 202–203 | 202 |
| g | 3-$NO_2C_6H_4$ | 4 | 90 | 14 | 84 | 227–228 | 226 |
| h | β-Naphthyl | 3 | 88 | 11 | 77 | 248–250 | – |
| i | 2-Thienyl | 2 | 97 | 6 | 83 | 207–208 | – |
| j | Piperonyl | 2 | 87 | 10 | 72 | 189–190 | 187 |
| k | 3,4-$(MeO)_2C_6H3$ | 3 | 85 | 13 | 78 | 176–178 | 177 |
| l | 2,6-$(Cl)_2C_6H3$ | 4 | 82 | 15 | 71 | 302–304 | 304 |
| m | 4-HO-$C_6H_4$ | 5 | 86 | 12 | 76 | 225–226 | 227 |

[a]All products were characterized by IR, $^1$H NMR, Mass spectra and by comparison of physical characteristics with authentic samples.
[b]Pulsed irradiation (1 min with 20 sec interval) at output of 650 W.
[c]Refluxed in toluene in the presence of either Amberlyst-15 or Nafion-15 as catalyst.

*Typical procedure B*: A mixture of *p*-nitrobenzaldehyde (1.51 g, 10 mmol), ethyl acetoacetate (1.30 g, 10 mmol), urea (0.6 g, 10 mmol) and Amberlyst-15 or Nafion-H (2 g) was refluxed in toluene (10 ml) for specified time (Table 1). After complete conversion, as indicated by TLC, the reaction mass was filtered off with hot methanol and the filtrate was concentrated *in vacuo* to afford pure product **2b** (79% yield) 2.52 g as a crystalline solid: m.p. 207–208 °C.

*Representative data for compound* **2e**: $^1$H NMR (DMSO-$d_6$) δ : 8.85 (brs, NH), 7.15–7.25 (m, 4H), 6.8 (brs, NH), 5.35 (d, 1H, *J* = 1.7 Hz), 4.05 (q, 2H, *J* = 7.0 Hz), 2.3 (s, 6H), 1.20 (t, 3H, *J* = 7.0 Hz). IR (Neat): 3300, 3250, 3125, 1715, 1650, 1590, 1505 $cm^{-1}$.

*Compound* **2h**: $^1$H NMR (DMSO-$d_6$) δ : 9.05 (brs, NH), 6.95–7.35 (m, 8H), 5.55 (d, 1H *J* = 1.8 Hz), 4.15 (q, 2H, *J* = 6.9 Hz), 2.35 (s, 3H), 1.25 (t, 3H, *J* = 6.9 Hz). IR (Neat): 3250, 3125, 1705, 1635, 1570, 1465 $cm^{-1}$.

*Compound* **2i**: $^1$H NMR (DMSO-$d_6$) δ : 9.05 (brs, NH), 6.95–7.25 (m, 4H), 5.65 (d, 1H, *J* = 1.7 Hz), 4.20 (t, 2H, *J* = 6.8 Hz), 2.40 (s, 3H), 1.30 (t, 3H, *J* = 6.8 Hz). IR (Neat): 3200, 3105, 1695, 1650, 1585, 1485 $cm^{-1}$.

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