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AN EFFICIENT SYNTHESIS OF 5-UNSUBSTITUTED-3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONE USING GRINDING METHOD

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ABSTRACT
Herein we reported green method for the synthesis of 5-Unsubstituted-3,4-Dihydropyrimidin-2(1*H*)-One using grinding method. This method having several advantages such as excellent yield, shorter reaction time and economic availability.

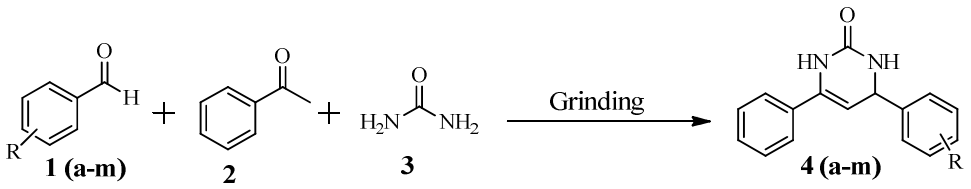
KEYWORDS : Aromatic aldehydes, grinding technique, dihydropyrimidin-2(1*H*)-One

1. Introduction

3,4-Dihydropyrimidine-2(1*H*)-one (DHPM) and their derivatives exhibit a wide range of biological activities, pharmaceutical and therapeutic properties such as antiviral, antitumor, antibacterial and anti-inflammatory activities.[1-5]

Synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2(1*H*)ones are achieved by cyclocondensation of aromatic aldehydes, aromatic ketone and urea. There are only few methods reported for the synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2 (1*H*) one derivatives such as using atomized Na metal [6], PPh_3 [7], $H_3PMo_{12}O_{40}$ [8] H_2NSO_3H, TMSCl [9] and Polymer-Supported 4-Aminoformoyldiphenylammonium Triflate (PSAFDPAT).[10] Pasha *et al*, reported method for the construction of the 4,6- diarylpyrimidin-2(1*H*)-ones derivatives using atomized Na using THF as solvent under ultrasonic irradiation [11].

In recent years, grinding method gaining much more importance because of its performance under solvent free as well as environment-friendly conditions [12-14]. The utility of grinding method has been reported for various organic transformations such as Reformatsky reactions [15], Knoevenagel's reaction [16], Michael's additions [17], aldol condensation [18], coupling reactions [19] and Dieckmann condensations [20]. Most of these organic transformations are carried out at room temperature in absence of solvent using only a mortar and pestle. In owing to importance of grinding method, we developed a new methodology for the synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2(1*H*)ones *via* cyclocondensation of aromatic aldehyde, acetophenone and urea using grinding technique (**Scheme 1**)



Scheme 1 synthesis of 5-Unsubstituted-3,4-Dihydropyrimidin-2(1*H*)-One derivatives (**4a-m**)

2. Experimental

2.1 General

All chemical were purchased from Aldrich chemical company and used without further purification. ^{1}H-NMR spectra were recorded on Bruker Advance 400 MHz, in DMSO in presence TMS as an internal standard.^{13}C-NMR spectra recorded on Bruker DRX-300 MHz, in DMSO as solvent. Mass spectra were recorded on water UPLC TQD Mass spectrometer, showing $M^{+\cdot}$ peak. Melting points were recorded in open capillary method and are uncorrected.

2.2 General procedure for synthesis of 5-Unsubstituted-3,4-Dihydropyrimidin-2(1*H*)-One derivatives.

A mixture of aromatic aldehyde (1 mmol), acetophenone (1 mmol) and urea (1.2 mmol) was thoroughly grind with a pestle in an open mortar at r.t. for appropriate time (**Table 3**). The reaction was monitored by thin layer chromatography (TLC), after completion of reaction the solid product was pour on crushed ice and filtered. The product was crystallized using ethanol as solvent. A series of 5-unsubstituted-3,4-Dihydropyrimidin-2(1*H*)-One derivatives (**4a-m**) was synthesized using above procedure. The products were confirmed by melting point and compared with reported melting point.

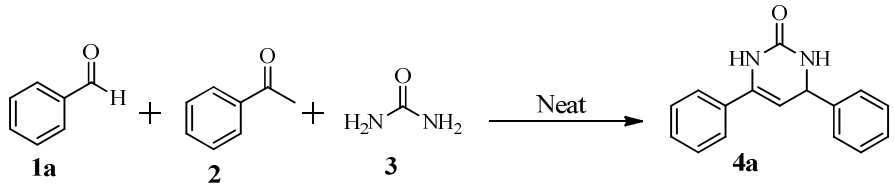
2.3 Spectroscopic data for representative compound

(4-(4-chlorophenyl)-6-phenylpyrimidin-2(1*H*)-one) (4c)

Colour:White crystals, Yield: 95 %, m.p.: 258-260 °C, **^{1}H NMR (400 MHz, DMSO-*d*6)** δ ppm: 6.23(s, 1H, -CH), 6.38-6.44 (m, 5H, Ar- H), 7.07-7.14- (m, 4H, Ar-H), 7.37 (s, 1H, -NH). **^{13}C NMR (100 MHz, DMSO-d_6)** δ ppm 98.70, 125.1, 125.3, 126.2, 127.2, 127.4, 127.5, 127.6, 127.8, 127.9, 128.0, 128.4, 128.5, 134.1, 135.5, 145.2, 153.5. **Mass (ES-MS)** EI-MS *m*/*z* cal. 284.07, *m*/*z* obs. $[M^{+\cdot}+H] = 285.09$.

3. Result and Discussion:

On preliminary basis, one-pot three-component condensation reaction of benzaldehyde **1a**, acetophenone **2** and urea **3** under neat conditions at 90 ºC temperature was considered as a standard model reaction (**Scheme 2)**



Scheme 2 Standard model reaction

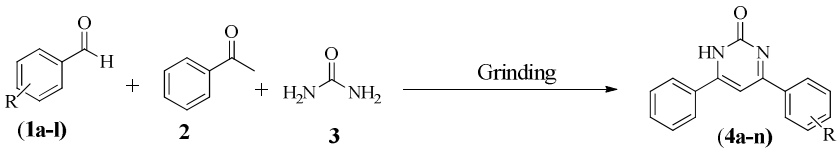
First the model reaction was carried out under neat condition using conventional heating and grinding respectively with changing various catalysts (summarized in **Table 1**). After screening of different catalysts such as triethyl amine, piperidine, morpholine for model reaction. We found that by without catalyst under grinding condition for model reaction, we observed that the desire product **4a** was formed within 40 min. with 92 % yield (**Table 1, entry 4**).

Table 1 Optimization of catalysts for model reaction.

Entry	Catalyst 10 (mol %)	Conditions	Time (min.)	Yield[b] (%)
1	Triethyl amine	Neat at 90 °C	120	45
		grinding	60	55
2	Piperidine	Neat at 90 °C	120	43
		grinding	60	46
3	Morpholine	Neat at 90 °C	120	43
		grinding	60	54
4	**Without catalyst**	**Neat at 90 °C**	**120**	**80**
		grinding	**40**	**92**

Then we carried out derivatives of 4,6-diphenyl-3,4-dihydropyrimidine-2(1*H*) one by changing the aromatic aldehydes we found that electron withdrawing or donating group on aromatic aldehyde did not effect on yield and time of product formation summarized in (**Table 2)**

Table 2



Entry	Product	R	Time (Min)	Yield[b]	Melting point (°C) Found	Reported
1	**4a**	H	40	92	234-236	233-240[9]
2	**4b**	4-Me	45	90	288-290	287-290[9]
3	**4c**	4-Cl	56	89	256-258	258-260[9]
4	**4d**	4-HO	57	87	258-260	260-263[9]
5	**4e**	4-MeO	46	91	259-261	258-260[9]
6	**4f**	4-N,N-$(CH_3)_2$	45	85	288-290	290-293[9]
7	**4g**	4-F	40	84	157-159	159-161[28]
8	**4h**	4-Br	42	90	256-258	255-256[28]
9	**4i**	3-Cl	41	91	208-210	210-2128[28]
10	**4j**	2-Cl	38	90	218-220	220-223[28]
11	**4k**	2,4-$(Cl)_2$	40	89	220-224	223-225[28]
13	**4m**	3,4-$(Cl)_2$	32	85	>290	>290[28]
14	**4n**	4$(CH_3)_2$CH-	45	78	286-288	287-288[12]

Conclusion:

We have demonstrated new eco-friendly methodology for the synthesis of 5-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-one derivatives using grinding method at room temperature. Merit of this methodology over other existing one is excellent yield within short reaction and simple reaction procedure. This protocol provides wide range of access to compounds that are useful in medicinal and heterocyclic chemistry.

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