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Scalable synthesis of 3,4-dihydropyrimidin-2(1H)-ones under solvent free condition

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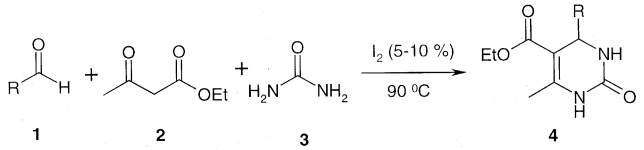
An improved solvent free, one pot procedure for the synthesis of 5-ethoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones catalyzed by iodine is developed. The process has been utilized successfully in large-scale synthesis of Biginelli products.

Keywords: Iodine, Aldehyde, Ethyl acetoacetate, Urea, Dihydropyrimidin-2(1H)-one, Solvent free condition
IPC Code: C07D239/00

Dihydropyrimidinones and their derivatives are very well known for their strong pharmacological properties[1]. They are finding wide applications as calcium channel blockers, antihypertensive agents, α-1a-antagonists and neuropeptide Y (NPY) antagonists[2]. Moreover, some bioactive alkaloids such as batzelladine B containing the dihydropyrimidinone unit have been isolated from marine sources which shows anti-HIV activity[3]. Therefore, this heterocyclic nucleus has gained a great importance and several modified procedures of the original Biginelli protocol[4] for obtaining dihydropyrimidinones have recently been reported[5]. However, many of these procedures are fraught with limitations such as the use of metal salts as catalyst, expensive reagents or catalyst, long reaction time and give unsatisfactory yields. In continuation of study on iodine catalysed reactions[6], a methodology for the synthesis of dihydropyrimidinones using iodine as catalyst (Scheme 1)[7] has been developed.



1 2 3 4

Scheme I

Incidentally, a similar method has been reported by Das *et al*[8]. recently using acetonitrile as solvent. But the method has several drawbacks, such as, long reaction time, use of excess of iodine (39.5 mole %), dry (inert) reaction condition etc. Besides these, the method uses solvent for reaction (acetonitrile) as well as for work-up (ethyl acetate). Since, dihydropyrimidinone are sparingly soluble in ethyl acetate, it is necessary to use excessive amount of solvent for extraction. Hence this method[8] cannot be extended for industrial preparation of dihydropyrimidinones.

In the present study, an efficient and environmentally benign protocol for the synthesis of 5-ethoxy carbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones has been developed in a one pot procedure under solvent free conditions. This method has been applied for the large-scale synthesis of Biginelli products without affecting the yield.

Experimental Procedure

Synthesis of 3,4-dihydropyrimidin-2(1H)-ones

Aldehyde (3 mmol), ethyl acetoacetate (3 mmol), urea (4.5 mmol) and iodine (0.3 mmol) were mixed in a 10 mL round bottom flask with a magnetic stirring bar and dipped in preheated oil bath at 90°C (bath temperature). The contents were stirred till the solution mixture converted to solid mass (15 min). The solid mass was heated for another 5 min and ice-cold saturated sodium thiosulphate solution (10 mL) was added. Thereafter, the crude solid product was filtered off, washed with ice-cold water (2 × 10 mL) and dried. The crude product was purified by recrystallization from ethanol.

In the large-scale synthesis, the reaction mixture consisted of aldehyde, ethyl acetoacetate, urea and iodine in a ratio 1:1:1.5:0.05 and heating was continued for 90 min at 90°C (bath temperature). Work-up procedure was same as in the small-scale synthesis.

Results and Discussion

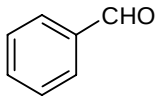
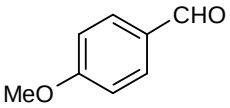
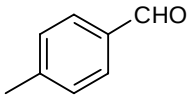
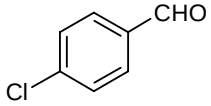
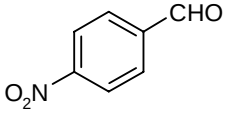
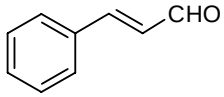
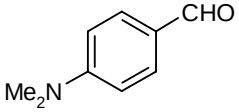
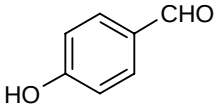
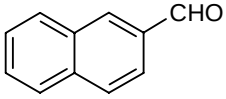
Initially the reaction was performed by carrying out in a similar way reported elswhere[8] using acetonitrile as solvent[7]. In the reported case, the best result was achieved by using 1.5 equivalent of urea. Further increment in the urea concentration did not improve

the process. Secondly, use of higher amount of catalyst did not enhance the rate significantly. A substantial improvement in the rate of reaction was observed when the reaction was carried out in solvent free condition. The reaction was carried out by heating a mixture of aldehyde (1 equiv.), ethylacetoacetate (1 equiv.), urea (1.5 equiv.) and iodine (0.1 equiv.) at 90°C (bath temperature). The results are summarized in Table 1. The reaction was complete in 15 min which otherwise take much longer time (5-7 h) when solvent was used. A simple work-up procedure was also employed to separate and purify the product from the reaction mixture.

On achieving the encouraging results, the methodology was extended for large-scale synthesis of dihydropyrimidin-2(1H)-ones. The methodology could successfully be applied for the synthesis of dihydropyrimidin-2(1H)-ones in 20 g scale. Initially, the reaction was done in 3 mmol scale. Later, the reaction was extended using benzaldehyde in different concentrations such as 9.4 mmol (1 g), 47 mmol (5 g), 94 mmol (10 g) and 188 mmol (20 g) without affecting the yield of the product (Table 2). While scaling up the reaction, it was found that 5 mole % of the catalyst is sufficient to promote the reaction effectively without affecting the rate of the reaction significantly. The procedure was extended for few aldehydes (Table 2).

In the reported study, a superior reaction condition was found for the synthesis of dihydropyrimidinones using iodine as catalyst under solvent free condition. The advantages of this method over earlier reports are: (i) solvent free condition (ii) easy work-up procedure (iii) use of lesser amount (5 mol %) of catalyst (iv) short reaction time (v) no stringent dry reaction condition required. Moreover, the process has been successfully utilized for the production of Biginelli products in 20 g scale.

Table 1—Solvent free synthesis of dihydropyrimidinones using iodine as catalyst[a]

Sl. No	Aldehyde	Yield[b]
a		86
b		90
c		75
d		91
e		92
f		73
g		86
h		78
i		88

a. Products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mp and matched with the literature data (ref. 5); b. Isolated yield.

Table 2— Large-scale synthesis of dihydropyrimidinones using iodine as catalyst[a]

Sl. No.	Aldehyde	Amt of aldehyde (g)	Amt of iodine (mole %)	Time (min)	Yield[b]
1	Benzaldehyde	1	10	20	86
2	Benzaldehyde	5	10	40	84
3	Benzaldehyde	10	10	60	87
	Benzaldehyde	10	5	90	89
	Benzaldehyde	20	5	90	91
4	Anisaldehyde	20	5	90	88
5	4-Tolaldehyde	20	5	90	87
6	4-Chlorobenzaldehyde	20	5	90	92
7	4-Hydroxybenzaldehyde	20	5	90	87

a. Reaction condition: urea: 1.5 equiv.; ethylacetoacetate: 1 equiv.; temp. 90°C; b. Isolated yield

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