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An efficient, high yield protocol for the one-pot synthesis of dihydropyrimidin-2(1*H*)-ones catalyzed by iodine

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Abstract—The use of iodine, as a catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones is reported.

The one-pot, three-component synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones has gained great importance in organic and medicinal chemistry as the dihydropyrimidine scaffold displays a facinating array of pharmacological properties. The first report was by the Italian chemist Pietro Biginelli in 1893.[1] Ethyl acetoacetate, an aldehyde and urea are the three components used for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones. The reaction reported by Biginelli was carried out in the presence of a catalytic amount of hydrochloric acid at reflux for 18 h. The yields of dihydropyrimidinones (DHPMs) were moderate (20–50%). Dihydropyrimidinone derivatives are the core unit in several biologically active marine alkaloids.[2–4] Among them, and most potent are the crambine[2] and batzelladine alkaloids.[3] Along with potent HIV gp-120 CD_4 inhibitor activity,[2,5] these compounds exhibit antiviral, antitumour, antibacterial and anti-inflammatory activities.[6] Organic compounds containing a DHPM as a core unit show excellent calcium channel modulation.[6,7] Due to their therapeutic applications different strategies have been employed for the synthesis of DHPMs and several protocols have been reported.[8,9] However, some of the methods employed for DHPM synthesis have drawbacks, for example, the use of strongly acidic conditions,[10] the use of protic acids[11] and prolonged reaction times.

To avoid these limitations we have searched for a new catalyst, with high catalytic activity, easy availability, short reaction time and simple work-up. Iodine attracted our attention, since it has been used as a mild Lewis acid in the dehydration of tertiary alcohols to alkenes, in the formation of ethers, as well as β-keto enol ethers,[12] for esterification,[13] transesterification,[13,14] acetylation[15] and benzothiophene[16] formation.

In the present work, we report the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones by iodine-catalyzed cyclocondensation of aldehyde **1**, ethyl acetoacetate **2** and urea **3**.[17] This reaction was carried out in toluene at reflux temperature for 3–5 h. This one-pot protocol has a simple work-up with excellent yields for substituted aromatic aldehydes (Table 1). The cyclocondensation with aliphatic aldehydes such as *n*-butanal and *n*-hexanal (entries 10 and 13) were sluggish under the present reaction conditions and afforded the corresponding dihydropyrimidin-2(1*H*)-ones in 76% and 69% yields, respectively. However, no by-products or side reactions were observed in either of the cases and unreacted starting materials accounted for the remaining mass after 4 h of reaction time. The yield of **4n** obtained from *n*-hexanal was improved to 80% by increasing the proportion of catalyst to 15% and prolonging the reaction time to 6 h. Aldehyde **1a** synthesized by a known method,[18] was subjected to cyclocondensation with ethyl acetoacetate and urea (Scheme 1). The reaction proceeded very cleanly to afford **4a** containing both guanosine and dihydropyrimidine moieties in 90% yield. A comparative study of this cyclocondensation with reported

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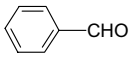
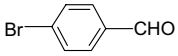
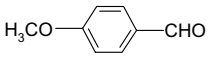
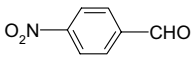
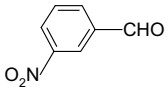
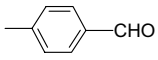
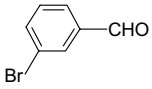
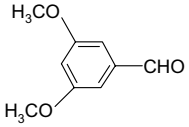
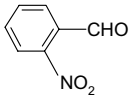
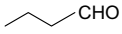
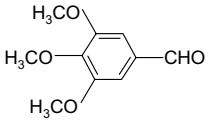
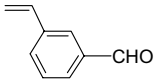
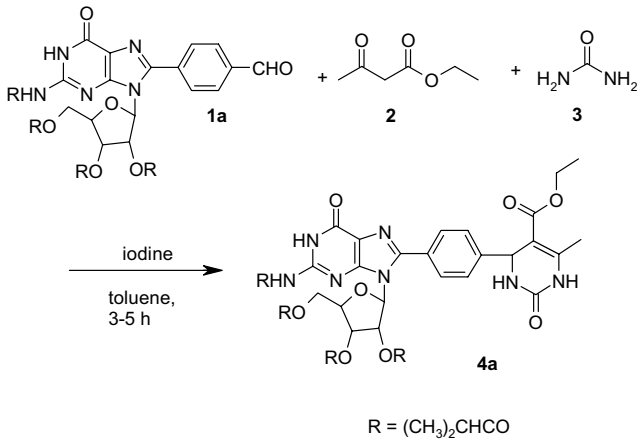
Table 1. Iodine-catalyzed synthesis of dihydropyrimidinones **4**[a]

Entry	Aldehyde **1b–n**	Product	Time (h)	Yield[b] (%)
1		**4b**	4	95
2		**4c**	4	90
3		**4d**	3.8	91
4		**4e**	4.7	89
5		**4f**	3.4	92
6		**4g**	3	89
7		**4h**	3.6	91
8		**4i**	3.7	92
9		**4j**	3.5	80
10		**4k**	4.2	76
11		**4l**	3.8	94
12		**4m**	4	95
13	$CH_3(CH_2)_5CHO$	**4n**	4.1	69

[a] All reactions were performed with ethyl acetoacetate and urea.
[b] Isolated yield.



Scheme 1.

catalysts,[8g,9a] revealed that $CdCl_2$ is highly compatible with the functionalized aldehyde **1a** and afforded **4a** in 80% yield.

Based on literature reviews,[6] we speculate that the reaction proceeds via an acyl imine intermediate formed from condensation of the aldehyde and urea. Subsequent addition of the β-keto ester enolate, followed by cyclization and dehydration afforded the dihydropyrimidinone. Iodine may play a crucial role in accelerating the dehydrative steps and enolization of the β-keto ester.

In summary, we have shown that I_2 works as an excellent catalyst for the one-pot three-component synthesis of dihydropyrimidinones. This simple methodology represents a valid alternative to the existing procedures especially for compounds bearing acid sensitive groups.

Acknowledgements

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References and notes

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17. *General procedure for the preparation of 3,4-dihydropyrimidin-2(1H)-ones*: A mixture of aldehyde **1**(**a**–**n**) (10 mmol), ethyl acetoacetate **2** (10 mmol), urea **3** (15 mmol) and iodine (5 mol%) in toluene (10 mL) was stirred at reflux. After completion of the reaction a solid precipitated and was filtered off and washed with cold methanol to remove excess iodine. The crude product was recrystallized from methanol. The obtained products **4**(**a**–**n**) were identified by comparison with authentic samples and by ^{1}H and ^{13}C NMR and their melting points.
Spectral data for compound **4a**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 0.90–1.40 (m, 30H, CH_3, CH_3CH_2O, $(CH_3)_2CH$); 2.49–2.76 (m, 4H, $CH(CH_3)_2$); 4.09 (q, 2H, OCH_2CH_3, $J = 7.0$ Hz); 4.41 (q, 2H, H′5, $J = 3.30$ Hz); 4.63 (q, 1H, H′4, $J = 3.16$ Hz); 5.20 (s, 1H, *CH*); 5.79 (t, 1H, H′3, $J = 6.50$ Hz); 6.27 (d + t, 2H, H′1 and H′2, $J = 7.97$, 4.68 Hz); 7.45 (d, 2H, ArH, $J = 8.2$ Hz); 7.8 (s, 1H, NH, pyrimidinone); 8.02 (d, 2H, ArH, $J = 8.24$ Hz); 9.25 (s, 1H, amide NH, guanosine); 9.21 (s, 1H, NH, pyrimidinone); 12.11 (br, s, 1H, N′H, guanosine); ^{13}C NMR (DMSO-d_6, 125 MHz): 14.0, 17.6, 18.4, 18.5, 18.8, 18.9, 33.7, 33.9, 36.6, 53.7, 59.1, 62.2, 70.7, 72.6, 78.9, 87.6, 112.1, 115.1, 121.7, 129.9, 130.1, 134.0, 137.0, 146.2, 147.4, 148.5, 155.4, 159.1, 165.2, 175.5, 176.4, 177.4, 178.7; MS (FAB, pos): *m/z* $C_{40}H_{51}N_7O_{12}$; calculated: 821.4; found: 822.2 $(M+H)^+$, 844.2 $(M+Na)^+$.
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