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Synthesis of some novel functionalized dihydropyrido[2,3-*d*]pyrimidines via an one-pot three-component reaction catalysed by $InCl_3$

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ABSTRACT

Some novel functionalized dihydropyrido[2,3-*d*]pyrimidine derivatives **4** were synthesized using a one-pot three-component reaction of 6-aminouracils **1**, aryl aldehydes **2** and 3-cyanoacetyl indole **3** using $InCl_3$ as catalyst.

Hantzsch 1,4-dihydropyridines (1,4-DHP) are an important class of compounds with vital medicinal value which are used for the treatment of cardiovascular disease such as hypertension and angina pectoris (I, Fig. 1).[1] In human body, the DHP's go through a cytochrome P450 (CYP) catalysed biochemical process and oxidized into the corresponding pyridine (II, Fig. 1).[2] It is worth mentioning that the 1,4-DHP motif present in coenzymes NADH and NADPH mediates hydrogen-transfer reactions in living system.[3] Thus, there is a continuous quest to comprehend these biological process and to develop suitable methods for the synthesis of functionalized dihydropyridines and their annelated analogues.[4]

The importance of uracil (pyrimidine-2,4-dione) and its annelated derivatives is well recognized by the synthetic as well as biological chemists.[5] Pyrido[2,3-*d*]pyrimidines represent a broad class of annelated uracils which have received considerable attention over the past years due to their wide range of biological activities such as antibacterial,[6] antitumour,[7] cardiotonic,[8] hepatoprotective,[8a] antihypertensive,[8a] and bronchodilator[9] properties. Additionally, some compounds of this class exhibit antialergic,[10] antimalarial,[11] analgesic[12] and antifungal activities.[13] Consequently, efforts have been directed towards the synthetic manipulation of uracil for the preparation of these complex molecules.[14]

Indole nucleus is a prominent structural subunit present in many naturally occurring compounds that possess significant pharmacological and biological properties.[15] A number of indole derivatives having heterocycles at the 3-position have been obtained from nature with potential biological activity.[16] For example, five novel indole alkaloids, meridians A–E (III, Fig. 1) have been isolated from tunicate *Splidium meridium*, which show cytotoxicity towards tumour cell lines and have potent inhibition against several protein kinases.[17] Tryotophandehydrobutyrine diketo-piperazine (TDD, IV, Fig. 1) is an inhibitor of glutathione-*S*-transferase (GST) enzymes[18] due to which many tumour cells become resistant to chemotherapeutic agents.

In recent years, indium chloride catalysed reactions have attracted tremendous interest throughout scientific communities imparting high regio- and chemo-selectivities in various chemical transformations,[19] due to its low toxicity, air and water compatibility, operational simplicity and remarkable ability to suppress side reactions in acid sensitive substrates.

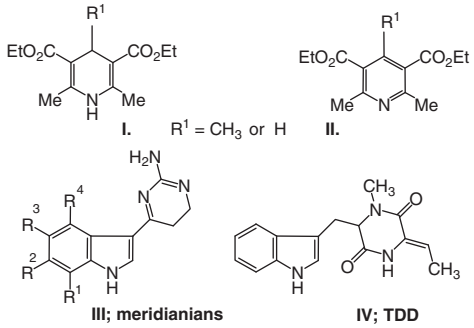

Figure 1. Biologically active dihydropyridines, pyridines and indoles.

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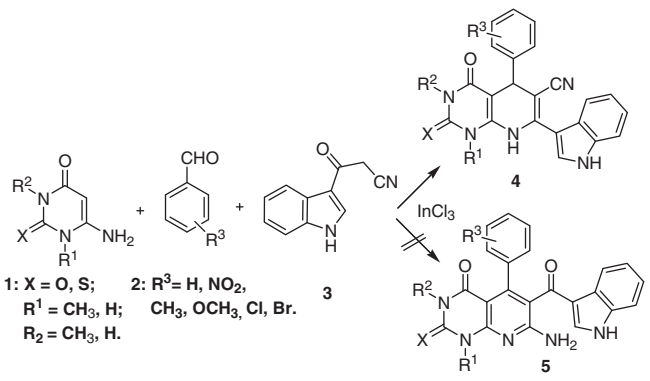
As part of our continued interest on the synthesis of diverse heterocyclic compounds of biological significance,[20] we reported the synthesis of various annelated uracils from the reaction of 6-amino uracils with cyano olefins.[21] In the present Letter, we report the synthesis of some novel dihydropyrido[2,3-*d*]pyrimidines **4** from an one-pot three-component reaction of 6-amino uracils **1**, aryl aldehyde **2** and 3-cyanoacetyl indole **3** using $InCl_3$ as catalyst (Scheme 1).

In a typical experimental procedure,[22] equimolar amounts of *N,N*-dimethyl-6-amino uracil **1a**, aryl aldehyde **2a** and 3-cyanoacetyl indole **3** were refluxed in ethanol using $InCl_3$ as catalyst for 6 h. After completion (monitored by TLC) of the reaction, the mixture was cooled, filtered and washed with water and ethanol. The solid product **4a** obtained was purified by recrystallization from ethanol. The structure of the compound was ascertained from the spectroscopic data and elemental analysis. The ^{1}H NMR spectra of the compound show the presence of two typical >NH protons at δ 9.69 and δ 11.88 respectively and the presence of one isolated proton at δ 4.70 as a singlet. The IR spectra show the presence of the nitrile group at 2200 cm^{-1}. The generality of the reaction was established by synthesizing a series of compounds **4b–q** and characterizing them (Table 1). In contrast to our earlier studies,[21] the nitrile group was not involved in the cyclization process to give the pyrido[2,3-*d*]pyrimidine **5** (Scheme 1). It might be due to the preferred activation of the carbonyl group by the catalyst, and steric hindrance of the two bulky groups (aryl and 3-subtituted indole) as shown in Scheme 2.

It was observed that aldehyde substrates bearing a variety of either electron donating or electron withdrawing functional groups were efficient for the three-component reaction, giving the corresponding dihydropyrido[2,3-*d*]pyrimidine derivatives **4** in high yields. The aromatic aldehydes with electron-withdrawing groups as substrates reacted very well at faster rate and the reaction time is shorter compared with aromatic aldehydes with electron-donating groups. However, the use of heterocyclic aldehyde, such as pyrole-2-carbaldehyde and thiophene-2-carbaldehyde afforded simply the Knoevenagel condensed compounds without any desired cyclized products.

The reaction was also studied simply in refluxing ethanol in the absence of the catalyst, and we observed the formation of only small amount of Knoevenagel condensed product of **2** and **3** without any cyclized compound **4**.

A reasonable mechanism of the reaction is given in the Scheme 2. First, the Knoevenagel condensed product **[A]** forms from the reaction of compounds **2** and **3,** which undergoes Michael addition to compound **1** to give the intermediate **[B]**. The amine group of the compound **[B]** then reacts with the intramolecular carbonyl group to give the dihydropyrido[2,3-*d*]pyrimidines **4**. The catalyst might have activated the condensation and cyclization steps by binding with the carbonyl group. Thus, in contrary to our earlier studies pyrido[2,3-*d*]pyrimidine derivatives **5** were not formed through an attack of the amine group at the nitrile group.

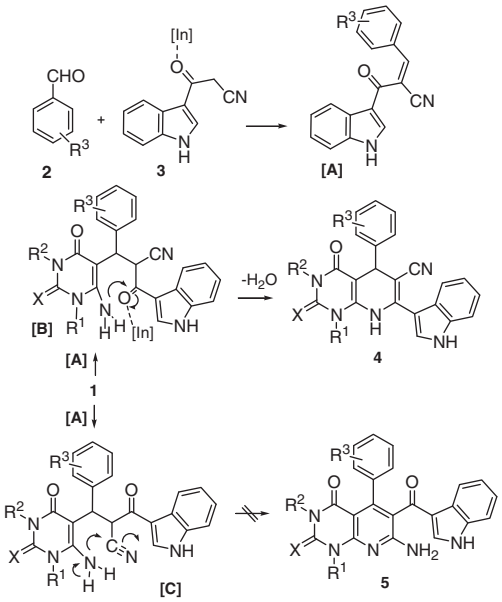


Scheme 1. Synthesis of dihydropyrido[2,3-*d*]pyrimidines **4**.

Table 1
$InCl_3$ catalysed one-pot synthesis of dihydropyrido[2,3-*d*]pyrimidines **4**

Entry	R^1	R^2	X	R^3	Prod.	Reac. time	Yd. (%)
1	CH_3	CH_3	O	Ph	**4a**	6	82
2	CH_3	CH_3	O	*p*-NO_2Ph	**4b**	4	87
3	CH_3	CH_3	O	*p*-CH_3Ph	**4c**	8	78
4	CH_3	CH_3	O	*p*-OCH_3Ph	**4d**	7	75
5	CH_3	CH_3	O	*p*-ClPh	**4e**	5	83
6	CH_3	CH_3	O	*p*-BrPh	**4f**	5	85
7	H	CH_3	O	Ph	**4g**	7	80
8	H	CH_3	O	*p*-NO_2Ph	**4h**	4	85
9	H	CH_3	O	*p*-CH_3Ph	**4i**	8	71
10	H	CH_3	O	*p*-OCH_3Ph	**4j**	8	69
11	H	CH_3	O	*p*-ClPh	**4k**	5	83
12	H	H	S	Ph	**4l**	7	74
13	H	H	S	p-NO_2Ph	**4m**	6	79
14	H	H	S	*p*-CH_3Ph	**4n**	8	68
15	H	H	S	*p*-OCH_3Ph	**4o**	8	67
16	H	H	S	*p*-ClPh	**4p**	6	77
17	H	H	S	*p*-BrPh	**4q**	6	75

Prod. = product, Reac. = Reaction, Yd. = Yield.



Scheme 2. Reasonable mechanism of the reaction.

In summary, we have synthesized some novel dihydropyrido[2,3-*d*]pyrimidine derivatives via an one pot three component reaction catalysed by $InCl_3$. The work-up procedure of the reaction is simple and the products were isolated simply by filtration and purified by crystallization. Further study of the reaction is in progress.

Acknowledgments

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22. Representative procedure for the synthesis of dihydropyrido[2,3-*d*]pyrimidines **4**: *N*,*N*-Dimethyl-6-aminouracil **1a** (0.310 g, 2 mmol benzaldehyde **2a** (0.212 g, 2 mmol), 3-cyanoacetyl indole **3** (0.368 g, 2 mmol) were taken in a round bottom flask containing ethanol (10 mL). To this was added $InCl_3$ (5 mol %) and the reaction mixture was refluxed for 6 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled and filtered. The solid product obtained was washed with water and ethanol, and finally recrystallized from ethanol. The structure of the compound was ascertained as **4a** from the spectroscopic data and elemental analysis. Yield = 0.670 g (82%) *Compound **4a***: Off white solid: mp >300 °C. IR (KBr) ν_{max} = 3584, 3284, 2915, 2200, 1697, 1646, 1611 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.14 (s, 3H), 3.54 (s, 3H), 4.70 (s, 1H), 7.24 (m, 3H), 7.37 (m, 4H), 7.5 (d, 1H), 7.92 (d, 1H), 9.69 (s, 1H), 11.88 (s, 1H) ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.23, 30.45, 84.93, 89.03, 107.66, 112.79, 112.97, 120.19, 121.82, 122.69, 127.47, 127.64, 128.83, 129.06, 129.30, 129.59, 129.70, 132.89, 136.62, 144.05, 144.67, 145.47, 151.21, 161.19. MS (EI) 410.5 $(M+H)^+$. Anal. Calcd for $C_{24}H_{19}N_5O_2$: C, 70.41; H, 4.64; N, 17.11. Found: C, 70.62; H, 4.55; N, 17.19. Similarly compounds **4b**–**q** were synthesized and characterized.