# Synthesis of highly functionalized, pyrimido[4,5-*b*]quinoline, dihydropyrido[2,3-*d*]pyrimidine and benzo[*h*]pyrimido[4,5-*b*]quinoline derivatives *via* a three-component reaction in aqueous medium

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**Abstract-** Some novel pyrimido[4,5-*b*]quinolines, dihydropyrido[2,3-*d*]pyrimidines and benzo[*h*]pyrimido[4,5-*b*]quinoline derivatives **6/8/10** were synthesized from a three component reaction of 6-aminouracils **1**, aryl aldehydes **2** and cyclic β-diketones/cyclic β-diamides **5/7/9** catalyzed by PTSA in aqueous medium.

***Key words**: N,N-Dimethyl-6-amino uracil, 2-Hydroxynaphthalene-1,4-dione, Barbituric acid, PTSA, Quinoline, dihydropyrido[2,3-d]pyrimidine, Multicomponent reaction.*

## Introduction

The importance of quinoline and its annelated derivatives is well recognised by synthetic and biological chemists.[1] Pyrimido[4,5-*b*]quinolines (also known as 5-deazaflavins, dF) are an important classes of annelated quinolines of biological importance.[2] It is structurally similar to the pyrimido[4,5-*b*]quinoxaline ring system of the naturally occurring flavins.

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,[3] antitumor,[4] cardiotonic,[5] hepatoprotective,[5a] antihypertensive,[5a] and bronchodilator[6] properties. Additionally, some compounds of this class exhibit antialergic,[7] antimalarial,[8] analgesic[9] and antifungal activity.[10] Consequently, efforts have been directed towards the synthetic manipulation of uracil for the preparation of these complex molecules.[11]

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.[12] In the human body DHPs go through a cytochrome P450 (CYP) catalysed biochemical process and oxidized into their corresponding pyridine derivatives.[13] It is worth mentioning that the 1,4-DHP motif present in coenzymes NADH and NADPH mediates hydrogen-transfer reactions in living systems.[14] Thus, there is a continuous quest to comprehend these biological processes and synthesis of novel functionalized dihydropyridine derivatives.[15]

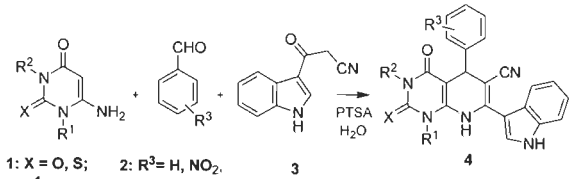
Multicomponent reactions (MCRs) have emerged as efficient and powerful tools in modern synthetic organic chemistry because the synthesis of complex organic molecules from simple and readily available substrates can be achieved in a very fast and efficient manner without the isolation of any intermediate.[16] MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production. Therefore, developing new MCRs and improving known MCRs are popular areas of research in current organic chemistry.

An important aspect of green chemistry pertains to the elimination of volatile organic solvents or their replacement by non-

flammable, non-volatile, non-toxic and inexpensive "green solvents".[17] Water complies all these stringent requirements and often exhibits important rate enhancements,[18] unique selectivity and reactivity.[19] Consequently, the development of synthetically useful reactions in water is of considerable interest.[20] In this context, the design of synthetic routes to privileged heterocyclic scaffolds of medicinal relevance that combine the synthetic efficiency of multi component protocols with the environmental benefits of using water as the reaction medium constitutes a very important challenge for green chemistry.[21]

p-Toluenesulfonic acid (PTSA) is environmentally benign, inexpensive, and economically feasible catalyst that offers several advantages.[22] Therefore, organic reactions that exploit PTSA catalyst in water could prove ideal for industrial synthetic organic chemistry applications provided that the catalyst shows high catalytic activity in water.

## Materials and Methods

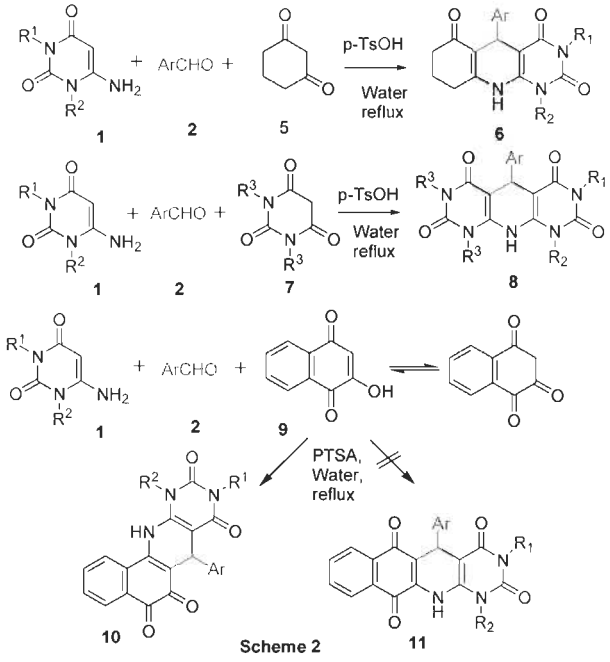



Scheme 1

As part of our continued interest in the synthesis of diverse heterocyclic compounds of biological importance, [23] recently we reported the synthesis of some novel dihydropyrido[2,3-*d*]pyrimidines *via* a three-component reaction of 6-amino uracil, aryl aldehyde and 3-cyanoacetyl indoles using $InCl_3$ as catalyst and ethanol as solvent.[24] However, now we have observed that if the ethanol is replaced by water (more protic) and $InCl_3$ by much cheaper paratoluenesulphonic acid (PTSA), products are obtained much easily and in shorter reaction time. Thus, in a simple experimental procedure[25] when equimolar amounts of *N,N*-dimethyl-6-amino uracil **1a**, aryl aldehyde **2a** and 3-cyanoacetyl indole **3** were refluxed in water using PTSA as catalyst for 2 h, afforded after work-up dihydropyrido[2,3-*d*]-pyrimidine **4a** in excellent yield. The product was isolated simply by filtration and purified by recrystallization from ethanol. The structure of the compound was ascertained from the spectroscopic data, elemental analysis and by comparing with the authentic sample. Similarly, compounds **4b-f** were synthesised and characterised (Table 1).

As discussed in the earlier paper[28] the formation of this type of compound is in contrast to some of our previous observations in which cyanide group was involved in the cyclization process. However, the new observation leads us to the idea that if we study the reaction by utilizing some selective cyclic β-dicarbonyl or cyclic β-diamides in place of 3-cyanoacetyl indoles, we may get some novel and very interesting classes of complex annelated heterocyclic compounds. As a result of this effort, we are reporting here the synthesis of some novel funtionalized pyrimido[4,5-*b*]quinolines,dihydro-pyrido[2,3-*d*]pyrimidines and benzo[*h*]pyrimido-[4,5-*b*]quinoline derivatives **6/8/10** from a three component reaction of 6-amino uracils **1**, aryl aldehydes **2** and cyclic β-dicarbonyl/cyclic β-diamides **5/7/9** using PTSA as catalyst in aqueous medium (Scheme 2).

Initially we studied the one-pot three-component reaction by utilising equimolar amount of *N,N*-dimethyl-6-amino uracil **1a**, benzaldehyde **2a**, and cyclohexane-1,3-dione **5** in refluxing water in the presence of PTSA as catalyst (Scheme 2). To our delight, we observed the formation of pyrido- quinoline **6a** in excellent yield. The best result was obtained by carrying out the reaction using 10 mol % PTSA at reflux temperature for 2 hours. The generality of the reaction was established by synthesizing a series of compounds **6a-d** and characterizing them (Table 2).




Scheme 2

**Table 2:** Synthesis of pyrimido[4,5-*b*]quinolines **6** and dihydropyrido[2,3-*d*]pyrimidines **8**

| Compound 1 | Aldehydes 2 | Cyclic diketone/ cyclic diamide | Products | Yield |
|---|---|---|---|---|
| 1 | Ph (2a) | 5 | 6a-d | 84 |
| | p-$CH_3C_6H_5$ (2b) | | | 80 |
| | p-$ClC_6H_5$ (2c) | | | 89 |
| | p-$NO_2C_6H_5$ (2d) | | | 92 |
| 1 | Ph (2a) | 7a | 8a-d | 82 |
| | p-$CH_3C_6H_5$ (2b) | | | 78 |
| | p-$ClC_6H_5$ (2c) | | | 85 |
| | p-$NO_2C_6H_5$ (2d) | | | 90 |
| 1 | Ph (2a) | 7h | 8e-h | 76 |
| | p-$CH_3C_6H_5$ (2b) | | | 72 |
| | p-$ClC_6H_5$ (2c) | | | 86 |
| | p-$NO_2C_6H_5$ (2d) | | | 88 |

**Table 1:** PTSA catalyzed one-pot synthesis of dihydropyrido[2,3-*d*]pyrimidines **4** in water.

| Entry | $R^1$ | $R^2$ | X | $R^3$ | Prod. | Reac. Time (hour) | Yd. (%) |
|---|---|---|---|---|---|---|---|
| 1. | $CH_3$ | $CH_3$ | O | Ph | **4a** | 2.5 | 82 |
| 2. | $CH_3$ | $CH_3$ | O | p-$NO_2$Ph | **4b** | 2 | 80 |
| 3. | $CH_3$ | $CH_3$ | O | p-$CH_3$Ph | **4c** | 3 | 78 |
| 4. | H | $CH_3$ | O | Ph | **4d** | 2.5 | 83 |
| 5. | H | $CH_3$ | O | p-$NO_2$Ph | **4e** | 2 | 78 |
| 6. | H | $CH_3$ | O | p-$CH_3$Ph | **4f** | 3 | 81 |
| 7. | H | H | S | Ph | **4g** | 3 | 74 |
| 8. | H | H | S | p-$NO_2$Ph | **4h** | 2.5 | 79 |
| 9. | H | H | S | p-$CH_3$Ph | **4i** | 3 | 76 |

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

In order to expand the scope of the method, some cyclic β-diamides *viz* barbituric acids **7** were reacted with 6-amino uracils **1** and variety of aldehydes **2** under identical reaction conditions which afforded the expected pyridopyrimidines **8** in high yield (Table 2).

However, when we reacted 2-hydroxy naptha-quinone **9** with *N*,*N*-dimethyl 6-amino-uracil **1a** and benzaldehyde **2a** in similar reaction conditions the angularly annelated benzo[*h*]pyrimido[4,5-*b*]-quinoline derivative **10a** was obtained in excellent yield. The structure of the compound was ascertained from the spectroscopic data and elemental analysis. Formation of the compound **10** and nonformation of compound **11** can be well explained by the mechanism (Scheme 3). The generality of the reaction was established by synthesising a series of compounds **10a-n** and characterizing them (Table 3).

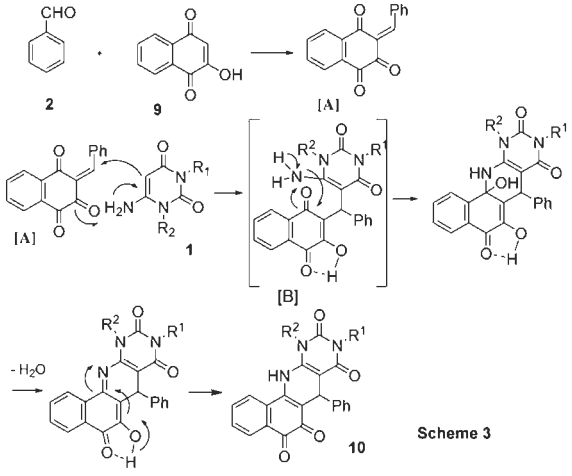
Initially, the three-component coupling reaction of *N*,*N*-dimethyl 6-amino-uracil **1**, benzaldehyde **2a**, and 2-hydroxynaphthalene-1,4-dione **9** was examined in water without any catalyst. It was found that only trace amount of the desired product **10a** was formed even after 3-4 h of reflux, while undesired Knoevenagel condensation product was formed as a major one. Subsequently, various acidic catalysts such as L-proline, acetic acid, $InCl_3$, $Yb(OTf)_3$, and PTSA were tested in water. L-proline and acetic acid could trigger the reaction providing only trace amount of the product after 4 h of heating while $InCl_3$ and $Yb(OTf)_3$ gave the desired product in low yield along with Knoevenagel condensation. PTSA loading was subsequently examined and found that 10 mol % of PTSA provided the maximum yield in minimum time. Thus, the best yield, cleanest reaction, and most facile

work-up was achieved employing 10 mol % of PTSA in water at 100 °C. Similar results were obtained when **5/7** were utilized with **1** and **2** under identical reaction conditions. In addition, we also noticed that when the reaction was carried out in DMF, $CH_3CN$, $C_2H_5OH$ and toluene, the yield of the product was very poor.

Table 3: Synthesis benzo[*h*]pyrimido[4,5-*b*]-quinoline derivative **10** in water using PTSA as a catalyst.

| Ent. | Aldehyde | $R^1$ | $R^2$ | Prod. | Yd. (%) |
|---|---|---|---|---|---|
| 1. | $C_6H_5$ | $CH_3$ | $CH_3$ | **10a** | 75 |
| 2. | p-$CH_3C_6H_4$ | $CH_3$ | $CH_3$ | **10b** | 78 |
| 3. | p-$ClC_6H_4$ | $CH_3$ | $CH_3$ | **10c** | 74 |
| 4. | p-$NO_2C_6H_4$ | $CH_3$ | $CH_3$ | **10d** | 77 |
| 5. | p-$OCH_3C_6H_4$ | $CH_3$ | $CH_3$ | **10e** | 80 |
| 6. | p-$OH(OCH_3)C_6H_3$ | $CH_3$ | $CH_3$ | **10f** | 84 |
| 7. | O-$OHC_6H_4$ | $CH_3$ | $CH_3$ | **10g** | 82 |
| 8. | p-{$N(CH_3)_2$}$C_6H_4$ | $CH_3$ | $CH_3$ | **10h** | 78 |
| 9. | O-$ClC_6H_4$ | $CH_3$ | $CH_3$ | **10i** | 78 |
| 10. | O-$BrC_6H_4$ | $CH_3$ | $CH_3$ | **10j** | 76 |
| 11. | 2-formyl furan | $CH_3$ | $CH_3$ | **10k** | 73 |
| 12. | Ph | $CH_3$ | H | **10l** | 77 |
| 13. | p-$ClC_6H_4$ | $CH_3$ | H | **10m** | 78 |
| 14. | p-$CH_3C_6H_4$ | $CH_3$ | H | **10n** | 76 |

A probable mechanism for the formation of product is outlined in the scheme 3. The reaction occurs *via* an initial Knoevenagel condensation between the aldehyde **2** and 2-hydroxynaphthalene-1,4-dione **9** to give the intermediate **[A]**. The intermediate **[A]** then undergoes Michael addition to *N*,*N*-dimethyl-6-amino uracil **1** followed by intermolecular cyclization and dehydration to give the compound **10**. The intramolecular hydrogen bonding between *ortho*-hydroxyl and carbonyl group as shown in structure **[B]** favours the formation angularly annelated product **10** and not the **11**.




Scheme 3

## Conclusion

In conclusion, we have reported the synthesis of some novel funtionalized pyrimido[4,5-*b*]-quino-lines, dihydropyrido[2,3-*d*]pyrimidines and benzo[*h*]pyrimido[4,5-*b*]quinoline derivatives from a three component reaction of 6-amino uracils, aryl aldehydes and cyclic β-dicarbonyl/cyclic β-diamides using PTSA as catalyst in aqueous medium. It is interesting to note that, the reactions were carried out in water, products were separated by simple filtration and purification was done by recrystallization from ethanol avoiding toxic organic solvents at any point of the experimental procedure. This method which can be further explored towards the synthesis of many other heterocyclic compounds of biological importance is a valuable addition to synthetic organic chemistry.

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25. *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 water (10 mL). To this was added PTSA (20 mol%) and refluxed the reaction mixture for 2.5 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 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) $\nu_{max}$=3584, 3284, 2915, 2200, 1697, 1643.2, 1609.5 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 3.20 (s, 3H), 3.48 (s, 3H), 4.67 (s, 1H), 7.28 (m, 3H), 7.42 (m, 4H), 7.50 ( d, 1H), 7.98 (d, 1H), 9.72 (s, 1H), 11.88 (s, 1H) $^{13}C$ NMR (75MHz, DMSO-$d_6$) δ 28.20, 31.25, 85.10, 91.12, 110.43, 112.86, 112.98, 120.40, 121.78, 122.76, 127.00, 127.82, 128.45, 129.47, 129.66, 129.89, 129.98, 133.84, 136.68, 144.45, 144.87, 145.40, 152.20, 161.30. MS (EI) 410.12 $(M+H)^+$. Anal. Calcd for $C_{24}H_{19}N_5O_2$: C, 70.41; H, 4.64; N, 17.11%. Found: C, 70.56; H, 4.72; N, 17.29%.

Similarly compounds **4b-h**, **6a-d**, **8a-h**, **10a-n** were synthesized and characterized.

**1,3-Dimethyl-5-phenyl-5,8,9,10-tetrahydro-1H,7H-pyrimido[4,5-*b*]quinoline-2,4,6-trione (6a):** Yield: 84%; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 2.35-2.61(m, 6H), 3.29 (s, 3H), 3.50 (s, 3H), 5.59 (s, 1H), 7.13-7.36 (m, 5H), 12.81 (s,1H, NH); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 20.97, 27.29, 28.61, 29.65, 33.33, 44.47, 89.98, 114.34, 125.92, 126.32, 129.03, 130.33, 135.23, 135.78, 150.82, 154.42, 164.42, 177.68, 200.84. IR ($CHCl_3$) : 3400.1, 1692.8, 1657.2, 1594.7, 1356.4, 770.8 $cm^{-1}$ . ESI-MS (m/z) : 338.38 $(M+H)^+$ .

**1,3,6,8-Tetramethyl-10-phenyl-9,10-dihydro-1H,-8H-1,3,6,8,9-pentaaza-anthracene-2,4,5,7-tetraone (8a):** Yield: 82% ; $^1H$ NMR (DMSO-$d_6$, 300 MHz) δ 3.33 (s, 6H), 3.56 (s, 6H), 5.69 (s, 1H), 7.22-7.62 (m, 5H), 15.10 (s, 1H, NH) ; $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ 28.47, 28.77, 29.07, 89.65,127.00, 128.14, 128.47, 133.24, 150.92, 160.73, 166.39. IR (KBr) : 3323.0, 1703.0, 1664.7, 1597.6, 1358.4, 771.6 $cm^{-1}$ . ESI-MS ( m/z) : 382.39 $(M+H)^+$.

**1,3-Dimethyl-5-phenyl-5,12-dihydro-1H-1,3,12-tri-aza-napthapthacene-2,4,6,11-tetraone (10a):** Yield: 75% ; $^1H$ NMR (DMSO-$d_6$, 300 MHz) δ 3.35 (s, 3H), 3.66 (s, 3H), 5.49 (s, 1H), 7.14-7.29 (m, 5H), 7.70 (m, 2H), 8.12 (dd, 2H), 8.90 (s, 1H, NH) ; $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ 28.31, 28.97, 90.67, 121.20, 126.33, 126.74, 126.96, 127.15, 127.28, 128.27, 128.55, 128.60, 129.88, 132.41, 133.26, 135.28, 136.21, 142.31, 144.06, 150.85, 161.05, 179.52, 181. 72; IR (KBr) : 3392.2, 3012.4, 2923.4, 1701.7, 1656.0, 1616.9, 1500.5. $cm^{-1}$. ESI-MS ( m/z) : 400.12 $(M+H)^+$. Anal. Calcd for $C_{23}H_{17}N_3O_4$: C, 69.17; H, 4.26; N, 16.04%. Found: C, 69.25; H, 4.32; N, 15.98%.