Pyrido[2,3-$d$]pyrimidines: A novel tandem Michael cyclization of 6-aminouracils with arylidene cyanocacetate using BiCl$_3$

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Uracil unit is abundantly available in living organisms; apart from this, Uracil scaffolds have prime importance to chemists and biologists due to its wide range of pharmacological activities such as antitumor, anti-diarrhea, anti-convulsants, antibacterial, antimicrobial, tyrosine kinase inhibitor, calcium channel antagonists, antileishmanial, diuretic, anti-inflammatory and analgesic, cardiotonic, nepotoprotective, anti-hypertensive, anti-bronchitic, anti-fungal, anti-herpes, anti-diabetic etc.

Consequently of these potent activities, systematic molecular manipulations have been done on its basic skeleton and a variety of clinically used drugs like 5-flourouracil (anti-cancer drug), AZT, DDC, DDI, BVDU etc. (nucleoside based anti-AIDS agents) have been synthesized. Though, derivatives of uracils are very difficult to prepare, it has been a challenge to chemists for chemical manipulations on this molecule. The C$_3$C$_6$ enaminc double bond of uracils have lead to the production of a variety of differently decorated pyrido[2,3-$d$]pyrimidine derivatives which indeed are associated with further several attractive biological properties as well as synthetic targets of current interest. Uracil is a bifunctional nucleophilic substrate that readily reacts with electron deficient systems and yields pyrido[2,3-$d$]pyrimidines. Several groups including ours have been systematically exploring reactions of this bifunctional substrate with electron deficient alkenes. Our group first ever successfully build novel heterocycles via intramolecular 1,3-dipolar cycloadditions.

In continuation to our interest in uracil chemistry, herein we report the first ever use of BiCl$_3$ for the Michael condensation of 6-aminouracils and arylidene ethylcyanocacetate (Scheme I). Bismuth-(III)chloride is non-toxic in nature and environment benign protocols extensively explored its catalytic activity in many important reaction such as Aldol, Knoevenagel, Doebner modification, Michael, Hantzsch, BIGINELLI, Strecker, Pechmann and several others. Encouraged by both importance of uracils and excellent applications of BiCl$_3$, we investigated tandem-Michael-cyclization of 6-aminouracils with Knoevenagel products for the synthesis of a variety of pyrimidine annulated pyrimidine. It is worth mentioning here that the use of BiCl$_3$ as a catalyst is very new in pyridopyrimidine chemistry.

Results and Discussion

Investigation was initiated with pilot experiments, a mixture of 1,3-Dimethyl-6-aminouracil 1a (10 mmol) with arylidene ethylcyanocacetate 2a (10 mmol) and BiCl$_3$ (5 mol%) in dry DMF (40 mL) was refluxed for 4 hr to obtain ethyle-7-amino-1,3-dimethyl-2,4-dioxo-5-phenyle-1,2,3,4,7,8-hexa-hydropyrido-[2,3-$d$]pyrimidine-6-carbonitrile 4 in excellent yield but astonishingly obtained product was 1,3-dimethyl-2,4,7-trioxo-5-phenyl-1,2,3,4,7,8-hexa-hydro-pyrido[2,3-$d$]pyrimidine-6-carboxylate 4 in excellent yield but astonishingly obtained product was 1,3-dimethyl-2,4,7-trioxo-5-phenyl-1,2,3,4,7,8-hexa-hydro-pyrido[2,3-$d$]pyrimidine-6-carbonitrile 2 (Scheme II). Poor yield of product (Table I, entry 3) lead to optimize both selection of catalyst and their quantity. In this direction a number of reactions were carried out involving various Lewis acid catalysts (Table I).
Table I — Optimization of catalyst in tandem-Michael cyclization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalysts (5 mol %)</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1.</td>
<td>NaCl</td>
<td>0</td>
</tr>
<tr>
<td>2.</td>
<td>LiBr</td>
<td>15</td>
</tr>
<tr>
<td>3.</td>
<td>BiCl₃</td>
<td>78</td>
</tr>
<tr>
<td>4.</td>
<td>AlCl₃·H₂O</td>
<td>25</td>
</tr>
<tr>
<td>5.</td>
<td>Alum</td>
<td>20</td>
</tr>
</tbody>
</table>

Reaction Condition: 1,3-Dimethyl-6-amino uracil 1a (10 mmol) with arylidene ethylcyanoacetate 2a (10 mmol) and catalysts (5 mol %) in dry DMF (40 mL) refluxed for 4 hr. Isolated yields after recrystallization.

In continuance a range of catalyst amount (2 to 50 mol %) was used to obtain best yield (Table II). It was concluded that 10 mol % BiCl₃ is enough to obtain excellent yields of 1,3-dimethyl-2,4,7-trioxo-5-aryl-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidine-6-carbonitrile 3a.

By following the above reaction procedure a variety of substituted 6-aminouracils, 1a-b were reacted with substituted arylidene ethylcyanoacetate, 2a-d to obtain an array of biologically active pyrido[2,3-d]pyrimidines, 3a-h in very good to excellent yields (Table III).

Synthesized compounds were well characterized and confirmed by spectral techniques e.g. IR, NMR and mass. The compound 3a showed sharp absorption in IR spectra at 2220 cm⁻¹ due to the presence of –CN group while the C=O groups showed strong absorption 1755 and 1655 cm⁻¹ and absence of absorption bands related to ester (–COOC₂H₅) further confirmed the structure of compound 3a. In proton NMR spectra, two singlet appears at δ 3.31 and 3.72.
Experimental Section

Melting points were determined in open capillaries and are uncorrected. Reagent grade chemicals were purchased from commercial source and used as received. IR spectra were recorded in KBr discs on a Perkin-Elmer 240C analyser. ¹H NMR spectra were recorded on a Bruker Avance II 400-MHz spectrometer using trimethylsilane (TMS) as internal standard. The progress of the reaction was monitored by thin-layer chromatography (TLC) using silica gel G (Merck). Knoevenagel products used in this protocol were prepared by using literature method.

General procedure for synthesis of pyrido[2,3-d]pyrimidines, 3a-h

A mixture of arylidene ethylcyanoacetate 2a-d (10 mmol), 6-aminouracils 1a-b (10 mmol) and BiCl₃ (10 mol %) in 40 mL dry DMF was refluxed for 4-5 hr (see Table III). After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature and excess solvent was removed under vacuum. The solid thus obtained was recrystallized from DMF:ethanol (2:8) to afford pyrido[2,3-d]pyrimidines 3a-h in very good to excellent yields (Table III).

Physical and Spectral data

1,3-Dimethyl-2,4,7-trioxo-5-phenyl-1, 2, 3, 4, 7, 8-hexahydropyrido[2,3-d]pyrimidine-6-carbonitrile, 3a: Yield 90%. m.p. 298-99°C, IR (KBr): 3111, 2234, 1720, 1678, 1448, 1430 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.31 (S, 3H, N-CH₃), 3.72 (S, 3H, N-CH₃), 7.24-7.53 (d, J = 7.96, 2H, Ar-H); MS: m/z 341, 343.

1, 3-Dimethyl-5-(4-methylphenyl)-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidine-6-carbonitrile, 3b: Yield 88%. m.p. 321-24°C, IR (KBr): 3231, 2229, 1699, 1679, 1448, 1432 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 3.14 (S, 3H, N-CH₃), 3.58 (S, 3H), 2.51 (S, 3H, Ar-CH₃), 7.11-7.13 (d, J = 8.04 2H, Ar-H), 7.23-7.25 (d, J = 7.96, 2H, Ar-H); MS: m/z 322. Anal. Calcd for C₁₆H₁₅N₃O₂: C, 63.35; H, 3.80; N, 18.09%

5-(4-Chlorophenyl)-1,3-dimethyl-2, 4, 7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidine-6-carbonitrile, 3c: Yield 90%. m.p. >300°C, IR (KBr): 3147, 2227, 1723, 1694, 1655, 1428 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 3.58 (S, 3H, N-CH₃), 3.18 (S, 3H, N-CH₃), 7.26-7.53 (d, J = 8.4, 2H, Ar-H), 7.49-7.51 (d, J = 8.4, 2H, Ar-H); MS: m/z 341, 343.
Anal. Calcd for C_{16}H_{11}N_2O_3: C, 56.07; H, 3.23; N, 16.35. Found: C, 55.94; H, 3.11; N, 16.23%.

5-(4-Methoxyphenyl)-1, 3-dimethyl-2, 4, 7-trioxo-1, 2, 3, 4, 7, 8-hexahydropyrido[2, 3-d]pyrimidine-6-carbonitrile, 3d: Yield 84%. m.p. >300°C, IR (KBr): 3147 2205, 1728, 1697 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 3.8 (S, 3H, N-CH₃), 7.19-7.45 (m, 5H, Ar-H); MS: m/z 338. Anal. Calcd for C_{16}H_{11}N_2O_3: C, 60.35; H, 4.17; N, 18.36%.

Conclusion
In conclusion, BiCl₃ catalysed efficient, novel, one pot procedure for the synthesis of pyrido [2,3-d]pyrimidines with very good to excellent yields in 4-5 hr reaction time has been developed. Used catalyst BiCl₃ is nontoxic, mild and inexpensive. Lewis acid, that catalysed the reaction very efficiently and yields unexpected pharmacologically important pyrido[2,3-d]pyrimidines.

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References


