An Expeditious Synthesis of Bioactive 4-Aryl-3, 4-Dihydropyrimidines Using Insitu Generated HCl

Sunita B. Shindea, Ambadas B. Rodea, Satish A. Dakea, Dattaye S. Bhosalea, Vinayak S. Sonekarb, Narsing M. Andurkara, Rajendra P. Pawara

aOrganic Chemistry Synthesis Laboratory, Dnyanopasak College, Parbhani-431401, MS, India
bDepartment of Chemistry, Deogiri College, Aurangabad-431 005, MS, India
*Email: rppawar@yahoo.com

Received: 3 October 2010; Accepted: 29 October 2010

Abstract

An efficient protocol has been reported by insitu generation of HCl from cyanuric chloride and used for the synthesis of 4-aryl-3,4-dihydropyrimidines.

Keywords: 4-Aryl-3,4-dihydropyrimidines; Cyanuric Chloride; Hydrochloric Acid; Multicomponent Reactions

1. Introduction

One step multicomponent reactions (MCRs) became more popular during the last decade [1-4]. Multistep synthesis produces a considerable amount of waste due to the complex isolation procedure involving expensive, toxic, and hazardous solvents in each step. Thus, MCRs are found to be economically and environmentally beneficial. Due to several advantages, these reactions becomes the millstone of small molecules combinatorial synthesis libraries [5-6]. One of the MCR attracted considerable attention recently is the Biginelli reaction. Biginelli reactions involve the cyclocondensation of β-keto ester with aryl aldehydes and urea resulting in the formation of 4-aryl-3,4-dihydro pyrimidines [7].

Dihydropyrimidinones and their derivatives are known for a wide range of biological and therapeutic properties such as antibacterial, antiviral, antitumor and anti-inflammatory activities [7-9]. DHPM analogs have been used as backbones for calcium channel blockers, anti-hypertensive agents and β-la-adrenergic receptor antagonists [10-11]. Batzelladine alkaloids with dihydropyrimidine core unit have been found to be potent HIV gp-120-CD4 inhibitors [12-13].

Three-component one-pot synthesis of DHPMs was reported firstly by the Italian chemist Pietro Biginelli 100 years back. It involves a condensation of benzaldehyde, ethyl acetocetate and urea in acidic media [14]. Recently, different methods have been
developed for the synthesis of DHPMs to improve and modify this reaction. These methods involve microwave irradiation [15], ultrasound irradiation [16], ionic liquids [17], Lewis and protic acid promoters [18-24]. However, most of the reported methods suffer from certain drawbacks such as the use of expensive reagents, strong acidic conditions, long reaction times and low yield of products. To avoid these limitations, the development of more efficient methods accompanied with higher yield of products is needed. This we achieved by the cyclocondensation of ethyl acetoacetate with different substituted benzaldehydes and urea using 2,4,6-trichloro[1,3,5] triazine (TCT) catalyst in presence of water.

2,4,6-Trichloro [1,3,5] triazine (cyanuric chloride or TCT) is stable, non-volatile, inexpensive and safe reagent used synthetically for the preparation of various types of compounds such as alkyl chloride [25] Beckmann rearrangement products [26], isonitriles [27], bis(indolyl)methane [28], thiiranes [29], and dihydropyridines [30].

In present investigation 4-aryl-3,4-dihydropyrimidines were synthesized by the cyclocondensation of ethyl acetoacetate with different benzaldehydes and urea using 2,4,6-trichloro [1,3,5] triazine (TCT) catalyst in presence of water as shown in Scheme 1.

2. Experimental

   Synthesis of Ethyl 1,2,3,4-tetrahydro-4 – (4 ‒methoxyphenyl) ‒6 ‒methyl ‒2-oxopyrimidine ‒ 5 ‒carboxylate (4b):

   A mixture of anisaldehyde (0.136g, 1mmol), ethyl acetoacetate (0.130g, 1mmol), urea (0.09g, 1.5mmol), 2,4,6-Trichloro [1,3,5] triazine (TCT) (0.055g, 0.03mmol) and H₂O (5-7 drops) was heated at 100°C for 20-25 minutes. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with water (20mL) and further stirred for 15 minutes at room temperature. The resulting solid was separated, dried and recrystallized in ethanol.

2.1. Spectral Data

   ¹HNMR and ¹³CNMR spectra were recorded at room temperature on a varian Inova Spectrometer in CDCl₃ using TMS as internal standard.

   Ethyl 4-butyl-1,2,3,4-tetrahydro-6-methyl -2-oxopyrimidine-5-carboxylate (4g): M.P. 157-158°C; ¹HNMR (DMSO-d₆, 250 MHz) δ: 6.15 (s, 1H, -NH), 6.20 (s, 1H, -NH), 0.97 (t, 3H, -CH₃), 1.35 (m, 2H, -CH₂), 1.27 (p, 2H, -CH₂), 1.57 (t, 2H, -CH₂), 4.15 (q, 2H, -CH₂), 1.35 (t, 3H, -CH₃), 1.72 (s, 3H, -CH₃), 4.25 (s, 1H, Ar-H). ¹³C (DMSO-d₆, 63 MHz) δ: 167.5, 150.4, 147.1, 104.5, 61.5, 55.7, 32.7, 25.9, 23.1, 15.1, 14.5 and 14.0.

3. Results and Discussion

   To find out the utility of catalyst, mixtures of equimolar amount of 4-methoxybenzaldehyde, ethyl acetoacetate and 1.5 molar of urea in water were refluxed for 10 h with different catalysts [24]. Various catalysts such as HCl, CuCl, CuCl₂, and TCT were used to explore the reaction. After 10 h, the crude products were poured onto crushed ice. After stirring for further 15 minutes, the product was purified by recrystallization in ethanol. The results are presented in Table 1 which shows that TCT was the best among tested catalysts.
Table 1. Effects of the Catalysts on the formation of Pyrimidin-2(1H)-ones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Amount of catalyst</th>
<th>Yield (%) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Free</td>
<td>----</td>
<td>39(^2)</td>
</tr>
<tr>
<td>2</td>
<td>HCl</td>
<td>1mL</td>
<td>44(^2)</td>
</tr>
<tr>
<td>3</td>
<td>CuCl</td>
<td>10mol%</td>
<td>63(^2)</td>
</tr>
<tr>
<td>4</td>
<td>CuCl₂</td>
<td>10mol%</td>
<td>71(^2)</td>
</tr>
<tr>
<td>5</td>
<td>TCT</td>
<td>3mol%</td>
<td>96(^2)</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: 4-methoxybenzaldehyde (1mmol), ethyl acetoacetate (1mmol), urea (1.5mmol), TCT (0.03mmol) and 1mL H₂O. \(^b\)Isolated yield.

Table 2. Effects of Temperature on the formation of Pyrimidin-2(1H)-ones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Time (min.)</th>
<th>Yield (%) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RT</td>
<td>60</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>60</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>45</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>100 and above</td>
<td>45</td>
<td>96</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: 4-methoxybenzaldehyde (1mmol), ethyl acetoacetate (1mmol), urea (1.5mmol), TCT (0.03mmol) and 1mL H₂O. \(^b\)Isolated yield.

To check the temperature effect on the formation of product, these reactions has been carried out at different temperatures (Table 2). The maximum yield of product was obtained at 100° C temperature \(24\).

Herein, the TCT was used as a source of HCl to catalyze these reactions. This catalyst was found to be excellent for the preparation of 4 - aryl - 3 , 4 - dihydropyrimidines. Hydrochloric acid is generated insitu from TCT and utilized efficiently to catalyze these reactions.

In this process, TCT reacts with ‘incipient’ moisture and releases 3 moles of hydrochloric acid and cyanuric acid by-product (removed by washing with water). In situ generated HCl acts as protic acid; activates the carbonyl oxygen and promotes the cyclocondensation process. However, Hantzsch reaction under these conditions donot proceed. It indicates that the ‘incipient’ moisture play an important role for the generation of HCl insitu from TCT. A plausible mechanism is shown in Scheme 2.

![Scheme 2](image)

Our attempts were failure to carry out these reactions using excess of water as an solvent. Whereas, 1:3 (TCT:H₂O) gave satisfactory results. However, in this cyclocondensation reaction 2moles of water are also formed as by-product. Interestingly, in this step of reaction the cyanuric chloride is hydrolysed to generate hydrochloric acid (HCl). Insitu generated HCl is consumed as a catalyst to enhance the rate of reactions.

The advantages of the process is, in this protocol direct addition of any acid has been avoided to make the process greener. Moreover, the reactions were carried out in aqueous media and the by-product cyanuric acid is separated simply by filtration. Thus, in this reaction the use of hazardous organic solvent has been also avoided. In summary, we developed an efficient and high yielding protocol for the synthesis of 4-aryl-3,4-dihydropyrimidines Table 3.

4. Cyanuric Chloride Catalysis

Cyanuric chloride or Triazine is the six-member heterocyclic compound with three nitrogen replacing carbon-hydrogen units in the benzene ring structure. Symmetrical 1,3,5-triazine is common in all isomers. They are prepared by thermal rearrangement from 2-azidocyclopropane, by condensation reaction from 1,2-dicarbonyl compound and amidrazone and by trimerization from cyanic acid amide. Triazines are the weak bases having much weaker resonance energy than the benzene. Hence they preferred nucleophilic substitution rather than electrophilic substitution.
Table 3. Conversion of aldehydes into dihydropyrimidines using in situ generated HCl from cyanuric chloride

<table>
<thead>
<tr>
<th>Entries</th>
<th>Reactants</th>
<th>Products(4)</th>
<th>Reaction time (min)</th>
<th>Yield (%)</th>
<th>Melting point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>-C₆H₅</td>
<td></td>
<td>25</td>
<td>92</td>
<td>202-204³¹</td>
</tr>
<tr>
<td>b</td>
<td>4-(CH₃O)-C₆H₄</td>
<td></td>
<td>45</td>
<td>96</td>
<td>199-201³¹</td>
</tr>
<tr>
<td>c</td>
<td>4-(NO₂)-C₆H₄</td>
<td></td>
<td>25</td>
<td>94</td>
<td>207-210³²</td>
</tr>
<tr>
<td>d</td>
<td>4-(Cl)-C₆H₅</td>
<td></td>
<td>25</td>
<td>92</td>
<td>210-212³¹</td>
</tr>
<tr>
<td>e</td>
<td>4-(F)-C₆H₅</td>
<td></td>
<td>25</td>
<td>94</td>
<td>173-175³²</td>
</tr>
<tr>
<td>f</td>
<td>2,4-(Cl)₂-C₆H₃</td>
<td></td>
<td>25</td>
<td>89</td>
<td>238-240³¹</td>
</tr>
</tbody>
</table>
5. Conclusions
A simple and efficient protocol has been investigated for the synthesis of biologically active 4-aryl-3,4-dihydropyrimidines using in situ generated hydrochloric acid from cyanuric chloride.

Acknowledgements
The authors are thankful to the Principal Dr. P. L. More, Dnyanopasak College, Parbhani, for his continuous encouragement during this work.

References