Aqueous phase synthesis of polysubstituted pyrimidines/pyrrolidines catalyzed by β-cyclodextrin

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ABSTRACT

Highly substituted pyrimidine/pyrrolidine derivatives were synthesized for the first time in water under neutral conditions by the reaction of aromatic amines, dimethyl/diethyl acetylene dicarboxylates, formaldehyde mediated by β-cyclodextrin (β-CD) in good to excellent yields. β-Cyclodextrin can be recovered and reused without any loss of catalytic activity. The β-Cyclodextrins employed were inexpensive and readily available when compared to other types of cyclodextrins (α, γ).

1. Introduction

Pyrimidine derivatives are versatile building blocks in synthetic organic chemistry and many bioactive molecules [1-4] with pyrimidine skeleton served as M1 muscarinic receptor agonists for the treatment of Alzheimer’s disease [5,6] and human immune deficiency virus (HIV) protease inhibitors [7]. Pyrimidine moiety is an important class of N-containing heterocyclic system [8,9], which exhibits wide spectrum of biological activities such as bactericidal [10], fungicidal [11], analgesic [12], anti-hypertensive [13], antimicrobial [14] and anti-infective properties [15]. Research in potential poly-substituted pyrimidines prompted for the development of a variety of synthetic strategies. Vishwakarma et al. reported the synthesis of poly-substituted 1,2,3,4-tetrahydropyrimidines [16]. Das et. al. reported the synthesis of poly substituted pyrrolidines and tetra-hydropyrimidines involving indium as a catalyst in aqueous medium [17]. Zhu et. al. described a one-pot synthesis of poly-substituted tetrahydropyrimidines via the proton-promoted MCRs [18].

In view of different biological activities associated with pyrimidine/pyrrolidine derivatives and in continuation of our interest in the use of cyclodextrins as mild and efficient biomimetic catalysts in promoting various organic transformations [19-27], we here report the synthesis of poly-substituted tetra-hydropyrimidine/pyrrolidine derivatives by the reaction of substituted anilines with but-2-yne-dioates and formaldehyde under neutral conditions involving β-cyclodextrin in water medium.

2. Experimental

2.1. Instrumentation

All chemicals were purchased from Fluka and S. D. Fine Chemicals and directly used for the synthesis. All reactions were carried out without any special precautions in an atmosphere of air. Analytical Thin Layer Chromatography (TLC) was carried out by using silica gel 60F254 pre-coated plates. Visualization was accomplished with UV lamp or I2 staining. Melting point was obtained by Fischer-Johns melting-point apparatus and uncorrected. All products were characterized by their NMR and Mass spectra. 1H NMR were recorded on 200 MHz, in CDCl3 as the internal standard and chemical shifts were reported in parts per million (ppm, δ) downfield from the tetramethylsilane. NMR Spectra: Varian 200 spectrometer; in CDCl3; δ in ppm, J in Hz. Mass spectra: VG Autospec; in m/z. IR were recorded on a Thermo Nicolet Nexus 670 FT-IR spectrometer.
2.2. Synthesis

2.2.1. General procedure for the synthesis of poly-substituted pyrrolidines

β-Cyclodextrin (1.135 g, 1 mmol) was dissolved in water (15 mL) by warming up to 60 °C until a clear solution was formed. To this clear solution, aniline (1.0 mmol) was added and stirred for 10 min, and then dimethylacetylene dicarbonyl (1.0 mmol) was added. After stirring for half an hour 4 equivalents of formaldehyde (4.0 mmol) was added. The reaction mixture was stirred until completion of the reaction as indicated by TLC. The reaction mixture was cooled and β-Cyclodextrin was filtered. The aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the organic layers were washed with water, saturated brine solution, and dried over anhydrous Na2SO4. The combined organic layers were evaporated under reduced pressure and the resulting crude product was purified by column chromatography by using ethyl acetate: hexane (2:8; v: v) as eluent to give the corresponding ethyl 3-(ethoxymethyl)-4,5-dioxo-1-phenylpyrrolidine-3-carboxylate as pure product in good yield (Scheme 1).

**Table 1. β-CD catalyzed synthesis of polysubstituted pyrrolidines.***

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-CF3-C6H5</td>
<td>CH3</td>
<td>4.5</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>3-CH3-C6H4</td>
<td>CH3</td>
<td>4.5</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>4-CF3-C6H5</td>
<td>CH3</td>
<td>4.5</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>4-CH3-C6H4</td>
<td>CH3</td>
<td>4.5</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>3-CH3-C6H4</td>
<td>CH3</td>
<td>4.5</td>
<td>68</td>
</tr>
</tbody>
</table>

*Reaction conditions: Amine (1.0 mmol), DMAD/DEAD (1.0 mmol), Formaldehyde (4.0 mmol), β-Cyclodextrin (10 mol%), 60 °C.

*Isolated yield.

Scheme 1

![Scheme 1](image)

<table>
<thead>
<tr>
<th>R1</th>
<th>Product</th>
<th>Molar ratio of the reactants: 1:1:4</th>
<th>β-CD/H2O 60 °C</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R'</td>
<td>R2OOC</td>
<td></td>
<td></td>
<td>68-75%</td>
</tr>
<tr>
<td>-CH3</td>
<td>-C6H5</td>
<td></td>
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</tr>
</tbody>
</table>

2.2.2. General procedure for the synthesis of 1,2,3,6-tetrahydro pyrimidines

β-Cyclodextrin (1.135 g, 1 mmol) was dissolved in water (15 mL) by warming up to 60 °C until a clear solution was formed. To this clear solution, aniline (1.0 mmol) was added and stirred for 10 min, and then dimethylacetylene dicarbonyl (1.0 mmol) was added. After stirring for half an hour another 1 equivalent of aniline (1.0 mmol) was added followed by the addition of 4 equivalents of formaldehyde (4.0 mmol). The reaction mixture was stirred until completion of the reaction as indicated by TLC. The reaction mixture was cooled and β-CD was filtered. The aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the organic layers were washed with water, saturated brine solution, and dried over anhydrous Na2SO4. The combined organic layers were evaporated under reduced pressure and the resulting crude product was purified by column chromatography by using ethyl acetate: hexane (2:8; v: v) as eluent to give the corresponding dimethyl 1,3-diphenyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate as pure product in good yield (Scheme 2).

**Scheme 2.** Dimethyl 1,3-diphenyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (Table 2, Entry 1): Yield: 65%. Color: Yellow oil.
4. Conclusion

In conclusion, a novel aqueous phase synthesis of poly-substituted tetrahydro pyrimidine/pyrrolidine derivatives was developed by the reaction of the corresponding aniline with but-2-ynedioate and formaldehyde promoted by β-cyclodextrin. These cyclodextrin-mediated aqueous phase reactions as environmentally benign methodology may find widespread application in organic and medicinal chemistry.

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