Multicomponent Reactions: Microwave-assisted Efficient Synthesis of Dihydropyrimidinones (thiones) and Quinazolinones under Green Chemistry Protocol as Probes for Antimicrobial Activities

M. M. H. Bhuiyan*, Hamidunnessa, and M. M. Mahmud

Department of Chemistry, University of Chittagong, Chittagong 4331, Bangladesh

Received 3 October 2011, accepted in final revised form 5 December 2011

Abstract

Microwave promoted diammonium hydrogen phosphate, (NH₄)₂HPO₄, catalyzed three-component Biginelli reaction between an aldehyde, a 1,3-dicarbonyl compound and urea or thiourea under solvent-free conditions afforded the corresponding dihydropyrimidinones and quinazolinones in high yields. The synthesized compounds have been screened for their antimicrobial activity against Pseudomonas aeruginosa, Staphylococcus aureus, Vibrio choloriae, Shigella dysenteriae, Salmonella typhi bacteria and Aspargillus flavus, Saccharomyces cerevisiae and Candida albicans fungi respectively. Some of the synthesized compounds exhibited pronounced antimicrobial activities.

Keywords: Multicomponent reactions; Dihydropyrimidinone; Microwave irradiation; Antimicrobial activity.

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doi: 10.3329/jsr.v4i1.8688

1. Introduction

The multicomponent reactions (MCRs) are one of the most important protocols in organic synthesis and medicinal chemistry [1,2]. The diversity, efficiency and rapid access to small and highly functionalized organic molecules makes this approach of central current interest in the construction of combinatorial libraries and optimization in drug discovery process [3-5]. In addition, MCRs are more environmentally benign and atom economic, as they avoid time-consuming and costly purification processes as well as protection–deprotection steps. They provide a powerful tool for the one-pot synthesis of diverse and complex compounds as well as small and druglike heterocycles [6]. The 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) have recently emerged as important target molecules due to their therapeutic and pharmacological properties [7] such as antiviral [8], antimitotic [9], anticarcinogenic [10], antihypertensive [11,12] and noteworthy, as calcium channel modulators [13]. DHPMs were also screened as neuropeptide antagonists [14],

*Corresponding author: mosharef65@yahoo.com
agents in treating anxiety [15], optic nerve dysfunction [16] and recently as antioxidant agents [17]. The dihydropyrimidine core unit is also found in nature and in potent HIV-gp-120-CD4 inhibitors [18]. Therefore, the synthesis of this heterocyclic core unit is of much current importance, and quite a number of synthetic procedures based on the modifications of the century-old Biginelli’s reaction [19] involving acid-catalyzed three-component condensation of 1,3-dicarbonyl compound, aldehyde, and urea, have been developed during past few years [20-34]. Basically, these methods are all similar, using different Lewis acid catalysts such as BF$_3$ [20], FeCl$_3$ [21], InCl$_3$ [22], BiCl$_3$ [23], LaCl$_3$ [24], LiClO$_4$ [25], Mn-(OAc)$_3$ [26], CAN [27] in a solvent such as CH$_3$CN, CH$_2$Cl$_2$, or tetrahydrofuran (THF). Recently, a number of procedures under solvent-free conditions using Yb(OTf)$_3$ [28], montmorillonite [29], ionic liquid [30], MgBr$_2$ [31], NbCl$_5$ [32], silica sulfuric acid [33] and 12-molybdophosphoric acid H$_3$PMo$_{12}$O$_{40}$[34] as catalysts have also been reported. However, despite their potential utility, many of these methods involve expensive reagents, stoichiometric amounts of catalysts, strongly acidic conditions, long reaction time, unsatisfactory yields, incompatibility with other functional groups, cumbersome product isolation, difficulties in handling (especially on a large scale), and the solvents used are not at all acceptable in the context of green synthesis. Thus, a practical and more efficient alternative using an inexpensive and environmentally friendly reagent is still of interest for one-pot synthesis of dihydropyrimidinones and thiones under mild conditions.

Many substituted quinazolinones have been found to be physiologically active compounds [35-37] such as antibiotics [38,39], and potent non-nucleoside reverse transcriptase inhibitors of the human immunodeficiency virus (HIV-1) [40]. A number of synthetic methods for the preparation of substituted (3H)-quinazolin-4-ones have been described [41-45]. Recently, the synthesis of the monosubstituted quinazolinones in solution and also dry media has been reported [46,47]. Disubstituted 4-(3H)-quinazolinones are also synthesized through a multi-step reaction in solution under microwave irradiation [48-51].

Recently, Microwave heating has emerged as a powerful technique to promote a variety of chemical reactions [52]. Microwave reactions under solvent-free conditions are attractive in offering reduced pollution, low cost and offer high yields together with simplicity in processing and handling [53]. The Biginelli reaction is important for the preparation of dihydropyrimidine derivatives and excellent results are found for reactions carried out with microwave enhancement [54].

Therefore, a great need still exists for versatile, simple and environmentally friendly processes whereby DHPMs may be formed under milder, more practical and microwave conditions. Diammonium hydrogen phosphate, (NH$_4$)$_2$HPO$_4$ is a very inexpensive, non-toxic and commercially available compound that can be used in the laboratory without special precautions. To the best of our knowledge, there is only one report regarding the application of diammonium hydrogen phosphate in the preparation of organic compounds under thermal condition [55]. Here we report, for the first time, the use of diammonium
hydrogen phosphate as catalyst in the synthesis of dihydropyrimidinones and quinazolinones under microwave condition.

2. Experimental

2.1. Physical measurements

Melting points were recorded with electro thermal melting point apparatus and are uncorrected. Thin layer chromatography was performed on Kieselgel GF$^2_{254}$ and visualization was accomplished by iodine vapour or UV Flame. The infrared (IR) spectra were recorded by FTIR spectrophotometer (Model-8900, Shimadzu, Japan) using KBr matrix in the range 4000-200 cm$^{-1}$. $^1$H-NMR (400 MHz and 500 MHz) and $^{13}$C-NMR (100 MHz and 125 MHz) spectra were recorded on JEOL GS$^{\times}$400, GEOL JNM-AL 400 (400 MHz) and JEOL GS$^{\times}$400, GEOL JNM-AL 400 (100 MHz) spectrometer (internal standard tetramethyl silane) in CDCl$_3$, CD$_3$OD and DMSO-$d_6$ as solvent. Chemical shifts were reported in $\delta$ unit (ppm) with reference to TMS as an internal standard and $J$ values are given in Hz. The carbon, hydrogen and nitrogen percentages in synthesized products were analyzed according to the approved method ASTM D-5291 by employing Leco-CHNS-932 analyzer. All reactions were carried out in a commercially available LG microwave oven (MB – 3947C) having a maximum power output of 800 W operating at 2450 MHz.

2.2 General procedure for the synthesis of dihydropyrimidinones (thiones) and quinazolinones

A mixture of aromatic aldehyde (1 mmol), 1,3-dicarbonyl compounds (ethyl acetoacetate, acetylacetone, dimedone) (1 mmol), urea/thiourea (1.5 mmol) and diammonium hydrogen phosphate (0.3 mmol) was irradiated under microwave condition at 160-320 watt for 60-180 sec. After complete conversion of the reaction (TLC; ethyl acetate: n-hexane; 1:5, v/v), the mixture was washed with water to remove excess of urea/thiourea and catalyst diammonium hydrogen phosphate and filtered. The solid mass was recrystallized from ethyl acetate and n-hexane solvent mixture.

2.2.1 Spectral data

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (1): White crystals. IR (KBr) $\nu_{\text{max}}$ (cm$^{-1}$): 3244.0, 3116.8, 2979.8, 1726.2 (C=O, ester), 1703.0 (C=O, ketonic), 1651.0, 1598.9, 1465.8, 1388, 1290.3, 1091.6, 783.0. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 7.53 (s, 1H, NH), 7.26-7.33 (m, 5H, Ph), 5.50 (s, 1H, NH), 5.40 (s, 1H, CH, H-4), 4.07 (q, 2H, OCH$_2$, $J$=6.85 Hz), 2.36 (s, 3H, CH$_3$), 1.17 (t, 3H, CH$_3$, $J$=6.85 Hz). $^{13}$C-NMR (125MHz, CDCl$_3$) $\delta$ 165.92, 153.42, 146.59, 143.68, 128.51, 127.75, 126.47, 101.05, 60.01, 55.27,
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5-Ethoxycarbonyl-6-methyl-4-(4-methoxy-phenyl)-3,4-dihydropyrimidin-2(1H)-thione (2): Yellow crystals. IR (KBr) ν_{max} (cm^{-1}): 3381.0, 3274.9, 3176.5, 1608.6 (C=O), 1512.1 (C=C), 1471.6, 1413.7, 1174.6, 1085.9, 729.0. 1H-NMR (500 MHz, CDCl₃): δ 7.21 (d, 2H, Ar-H, J = 8.60 Hz), 6.85 (d, 2H, Ar-H, J = 8.60 Hz), 5.35 (s, 1H, CH, H-4), 4.10 (q, 2H, OCH₂), 3.81 (s, 3H, OCH₃), 2.36 (s, 3H, CH₃), 1.56 (bs, 2H, 2×NH), 1.18 (t, 3H, CH₃, J = 6.85 Hz). Analysis calculated for C₁₅H₁₈N₂O₃S (306.39): C, 58.80; H, 5.92; N, 9.14; S 10.47; Found: C, 59.24; H, 5.32; N, 8.62; S 9.90.

5-Acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione (3): Orange crystals. IR (KBr) ν_{max} (cm^{-1}): 3280.7, 3180.4, 3116.8, 2997.2, 1614.3 (C=O), 1571.9 (C=C), 1465.8, 1326.9, 1197.7, 1116.7, 759.9. 1H-NMR (400 MHz, CD₃OD): δ 7.38-7.32 (m, 5H, Ph), 5.45 (s, 1H, CH, H-4), 2.37 (s, 3H, CH₃), 2.16 (s, 3H, CH₃), 1.57 (brs, 2H, 2×NH). 13C-NMR (100MHz, CDCl₃): δ 196.11, 173.93, 143.00, 141.60, 128.83, 126.54, 110.86, 55.50, 29.94, 18.63. DEPT – 135 (100 MHz, CDCl₃): δ 129.51, 128.82, 126.77, 126.53, 110.86, 55.50, 29.94, 18.63. Analysis calculated for C₁₃H₁₄N₂OS (246.33): C, 63.96; H, 5.73; N, 11.37; S 13.02; Found: C, 64.40; H, 5.23; N, 11.62, S 13.43.

7,7-Dimethyl-4-phenyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (6): Orange crystal. IR (KBr) ν_{max} (cm^{-1}): 3082.0, 3056.7, 3024.2, 2962.5, 1593.1 (C=O), 1490.9 (C=C), 1448.4, 1375.2. 1H-NMR (500 MHz, CDCl₃): δ 7.27 (m, 2H, H-3’, H-5’, Ar-H), 7.18 (m, 1H, H-4’, Ar-H), 7.10 (d, 2H, H-2’, H-6’, Ar-H, J = 8.00 Hz), 5.54 (s, 1H, CH,
H-4), 2.39 (m, 6H, 2×CH₂, 2×NH), 1.24 (s, 3H, CH₃), 1.10 (s, 3H, CH₃). ¹³C-NMR (125 MHz, CDCl₃): δ 190.40, 189.32, 137.97, 128.13, 126.68, 125.75, 115.48, 46.95, 46.33, 32.64, 31.32, 29.60, 27.31. DEPT – 90 (125 MHz, CDCl₃): δ 128.13, 126.68, 127.75, 32.64. DEPT – 135 (125 MHz, CDCl₃): δ 128.13, 126.68, 127.75, 46.95 (CH₂), 46.33 (CH₃), 32.64, 29.60 (CH₃), 27.31(CH₃). Analysis calculated for C₁₆H₁₈N₂OS (286.40): C, 67.10; H, 6.34; N, 9.78; S 11.02; Found: C, 68.20; H, 5.93; N, 9.36, S 11.45.

7,7-Dimethyl-4-(4-nitrophenyl)-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (7): Yellow crystals. IR (KBr) ν max (cm⁻¹): 3076.3, 2958.6, 1589.2 (C=O), 1512.1 (C=C), 1411.8, 1373.7, 1344.3, 1299.9, 848.6. ¹H-NMR (400 MHz, CDCl₃): δ 8.15 (d, 2H, H-3', H-5', Ar-H, J = 6.40 Hz), 7.25 (d, 2H, H-2', H-6', Ar-H, J = 7.80 Hz), 5.55 (s, 1H, CH, H-4), 2.48-2.36 (m, 6H, 2×CH₂, 2×NH), 1.24 (s, 3H, CH₃), 1.12 (s, 3H, CH₃). ¹³C-NMR (100 MHz, CDCl₃): δ 190.89, 189.51, 146.48, 145.97, 127.57, 123.43, 114.79, 46.86, 46.28, 33.15, 29.45, 27.35. DEPT – 90 (100 MHz, CDCl₃): δ 127.57, 123.43, 46.86 (CH₂), 46.28 (CH₂), 33.15, 29.45 (CH₃), 27.35 (CH₃). Analysis calculated for C₁₆H₁₇N₃O₃S (331.40): C, 57.99; H, 5.17; N, 12.68; S 9.68; Found: C, 58.65; H, 4.80; N, 12.05; S 9.20.

7,7-Dimethyl-4-(3-methoxyphenyl)-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (8): White crystals. IR (KBr) ν max (cm⁻¹): 3056.9, 2933.5, 1595.0 (C=O), 1490.9, 1423.4 (C=C), 1375.2, 1163.0, 1037.6, 788.8. ¹H-NMR (400 MHz, CDCl₃): δ 7.18 (t, 1H, H-5', Ar-H, J = 8.24 Hz), 6.69 (dd, 3H, H-2', H-4', H-6', Ar-H, J = 8.24 Hz, 9.6 Hz), 5.52 (s, 1H, CH, H-4), 3.74 (s, 3H, OCH₃), 2.39 (m, 6H, 2×CH₂, 2×NH), 1.24 (s, 3H, CH₃), 1.10 (s, 3H, CH₃). ¹³C-NMR (100 MHz, CDCl₃): δ 190.28 (C=O), 189.28 (C=S), 159.43, 139.74, 128.97, 119.10, 115.44, 112.84, 110.10, 54.92, 46.93, 46.28, 32.65, 31.25, 29.59, 27.21. DEPT – 90 (100 MHz, CDCl₃): δ 129.08, 119.20, 112.93, 111.07, 32.74. DEPT – 135 (100 MHz, CDCl₃): δ 128.97, 119.10, 112.84, 110.97, 54.92 (OCH₃), 46.93 (CH₂), 46.27 (CH₃), 32.65, 29.59 (CH₃), 27.21 (CH₃). Analysis calculated for C₁₇H₂₀N₂O₂S (316.43): C, 64.53; H, 6.37; N, 8.85; S 10.13; Found: C, 65.20; H, 5.92; N, 9.00, S 10.78.

2.3. Antimicrobial screening

The synthesized compounds (1-8) were screened for antibacterial activity against five pathogenic organisms: Pseudomonas aeruginosa, Staphylococcus aureus (ATCC 6538), Vibrio cholerae, Shigella dysenteriae (AE 14396) and Salmonella typhi (AE 14612 (Table-1) and antifungal activity against three organisms: Aspergillus flavus, Saccharomyces cerevisiae and Candida albicans (Table-2). The disc diffusion method [56] and poisoned-food technique [57] were used for antibacterial and antifungal activities respectively.

The tested compounds were dissolved in N,N-dimethylformamide (DMF) to get a solution of 1 mg mL⁻¹. The inhibition zones were measured in millimeters at the end of an incubation period of 48 hrs at (35±2)°C. DMF alone showed no inhibition. Nutrient agar
(NA) and potato dextrose agar (PDA) were used as basal media to test the bacteria and fungi, respectively. Commercial antibacterial Ampicillin and antifungal Nystatin were also tested under similar conditions for comparison.

Table 1. Antibacterial activity of the synthesized compounds.

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Pseudomonas aeruginosa</th>
<th>Staphylococcus aureus</th>
<th>Vibrio choloriae</th>
<th>Shigella dysenteriae</th>
<th>Salmonella typhi</th>
</tr>
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<tr>
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<td>--</td>
<td>10</td>
<td>10</td>
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<tr>
<td>Ampicillin</td>
<td>20</td>
<td>12</td>
<td>17</td>
<td>30</td>
<td>24</td>
</tr>
</tbody>
</table>

Table 2. Antifungal activity of the synthesized compounds.

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Aspargillus flavus</th>
<th>Saccharromyces cerevisiae</th>
<th>Candida albicans</th>
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<tr>
<td>1</td>
<td>70.90</td>
<td>62.67</td>
<td>19.46</td>
</tr>
<tr>
<td>2</td>
<td>86.42</td>
<td>85.33</td>
<td>68.68</td>
</tr>
<tr>
<td>3</td>
<td>63.14</td>
<td>85.33</td>
<td>61.97</td>
</tr>
<tr>
<td>4</td>
<td>61.20</td>
<td>93.33</td>
<td>23.94</td>
</tr>
<tr>
<td>5</td>
<td>76.72</td>
<td>84.00</td>
<td>83.80</td>
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<td>6</td>
<td>74.78</td>
<td>49.33</td>
<td>70.51</td>
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<td>7</td>
<td>53.54</td>
<td>81.33</td>
<td>9.10</td>
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<tr>
<td>8</td>
<td>61.20</td>
<td>66.67</td>
<td>14.00</td>
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<tr>
<td>Nystatin</td>
<td>90.00</td>
<td>85.00</td>
<td>85.00</td>
</tr>
</tbody>
</table>

3. Results and Discussions

Salehi and co-workers [55] have reported the synthesis of DHPMs under solvent-free conventional heating conditions at 80°C. Herein we have successfully carried out the same transformation under microwave irradiation in comparatively shortest duration. A variety of aldehydes were condensed with ethyl acetoacetate/acetylacetone/dimedone and urea (or thiourea) and the products were obtained in good to excellent yields (Scheme 1 and Table 3).
Table 3. Synthesis of DHPMs Using (NH₄)₂HPO₄ under microwave condition.

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>X</th>
<th>Watt/Time (sec)</th>
<th>Yield (%)</th>
<th>M.P. °C</th>
<th>Found / Reported</th>
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<tbody>
<tr>
<td>1</td>
<td>C₆H₅</td>
<td>Me</td>
<td>EtO</td>
<td>O</td>
<td>160/120</td>
<td>96</td>
<td>202-203</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4-MeO-C₆H₄</td>
<td>Me</td>
<td>EtO</td>
<td>S</td>
<td>160/90</td>
<td>85</td>
<td>150-152</td>
<td>150-151 [58]</td>
</tr>
<tr>
<td>3</td>
<td>C₆H₅</td>
<td>Me</td>
<td>EtO</td>
<td>S</td>
<td>160/90</td>
<td>95</td>
<td>150-151</td>
<td>208-210</td>
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<tr>
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<td>Me</td>
<td>S</td>
<td>160/90</td>
<td>90</td>
<td>185-186</td>
<td>186 (dec) [55]</td>
</tr>
<tr>
<td>5</td>
<td>4-NO₂-C₆H₄</td>
<td>Me</td>
<td>Me</td>
<td>S</td>
<td>160/120</td>
<td>84</td>
<td>213-214</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>C₆H₅</td>
<td>-CH₂C(CH₃)₂CH₂-</td>
<td>S</td>
<td>320/120</td>
<td>78</td>
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<td>251-253</td>
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<td>7</td>
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<td>S</td>
<td>320/180</td>
<td>85</td>
<td></td>
<td>217-219</td>
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<tr>
<td>8</td>
<td>3-MeO-C₆H₄</td>
<td>-CH₂C(CH₃)₂CH₂-</td>
<td>S</td>
<td>160/60</td>
<td>83</td>
<td></td>
<td>189-191</td>
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</table>

An important feature of this procedure is the survival of variety of functional groups such as nitro and ether under the reaction conditions. Thiourea also reacts under similar reaction conditions to form the corresponding 3,4-dihydropyrimido-2(1H)-thiones in good to excellent yields. The structures of the products were deduced from their IR, ¹H NMR, ¹³C NMR and elemental analyses. For example the ¹H-NMR spectrum of the compound 7 displayed a deshielded doublet signal resonated at δ 8.15 (J = 6.40 Hz) corresponding to two aromatic protons, H-3’ and H-5’ ortho to the nitro group. Another doublet resonated at δ 7.25 (J = 7.80 Hz) corresponding to two aromatic protons were assigned to H-2’ and H-6’. One CH (H-4) proton of the quinazolinone ring resonated at δ 5.55 ppm was observed as singlet. A multiplet appeared at δ 2.48-2.36 integrated for six protons corresponding to 2×CH₂ and 2×NH. The spectrum showed two three-proton singlets at δ 1.24 and δ 1.12 due to two CH₃ protons located at C-7 position. The ¹³C NMR spectrum of compound 7 showed the presence of thirteen signals attributed to sixteen carbons of corresponding molecular formula C₁₆H₁₇N₃O₃S. The ¹³C NMR spectrum showed the existence of a carbonyl group (C=O) at δ 190.89, a thioxo group (C=S) at δ 189.51, besides five quaternary carbons resonated at δ 146.48 (C-8a), 145.97 (C-1’, C-4’), 114.79 (C-4a) and 31.37 (C-7). Two CH₃ carbons observed at δ 29.45 and 27.35. At the same
time two CH$_2$ groups and C-4 carbons appeared at δ 46.86, 46.28 and 33.15. On the other hand, signals resonated at δ 127.57 and 123.43 were ascribed for the four aromatic carbons. The DEPT–90 spectrum of the compound 7 showed the presence of three signals at δ 127.57, 123.43, 33.15 attributed to five CH groups in the molecule. The DEPT–135 spectrum of the compound 7 showed the presence of four signals at δ 127.57, 123.43 and 31.15 attributed to five CH groups and two signals resonated at δ 29.45 and 27.35 attributed to two CH$_3$ groups located at C-7 in the molecule. Two carbons of two CH$_2$ groups appeared at δ 46.86 and 46.28 as negative values. The microanalytical data of the compound 7 is also in good agreement with the assigned structure. Similarly the peaks in $^1$H-NMR and $^{13}$C-NMR spectra of the rest compounds were accordance with assigned structures.

Amongst the synthesized compounds screened for the antibacterial activity, compound 2 showed highest activity against S. aureus. Some of the compounds showed low antimicrobial activities and some were unable to show inhibition. For the antifungal activity all compounds, except 7, showed excellent results against all fungi. Compound 2, 3 and 5 revealed highest activity against S. cerevisiae, which was also approximately similar to that of the standard antibiotic, Nystatin. The other tested compounds also exhibited good to excellent results against all the fungi.

4. Conclusion

In this work, we have developed a new solvent-free strategy for the preparation of 3,4-dihydropyrimidin-2-(1H)-ones (and -thiones) as biologically interesting compounds via the condensation of aldehyde with 1,3-dicarbonyl compounds and urea or thiourea. The advantages of this method are high yields, relatively short reaction times, low cost, simple experimental and isolation procedures, and finally, it is in agreement with the green chemistry protocols. The activity data obtained during the study will be certainly useful to go for further research for drug designing and synthesizing new dihydropyrimidinone derivatives.

Acknowledgment

The authors wish to thank Dr. A. Rahman, Department of Biochemistry and Molecular Biology, University of Chittagong, Bangladesh, for his cooperation in determining the antimicrobial activity of the synthesized compounds. We also wish to thank Dr. M. Al-Amin, JSPS Postdoctoral Fellow, Department of Chemistry, Hokkaido University, Japan for recording the spectral data.

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