CHAPTER-III

Microwave Assisted Synthesis of 2,3,4-Trisubstituted 1,2-Dihydropyrimido [1,2-a] Benzimidazole

This work has been revised communicated

Introduction

Various benzimidazole derivatives are of special interest because of their diverse pharmaceutical activities like antihistaminic, anesthetic, antipyretic, and anti-tumor. Hence, the problem on the synthesis of new benzimidazole derivatives has been undertaken.

Past work

Master and coworkers has been reported the synthesis of 2,4-Dimethylpyrimido[1,2-a]benzimidazole-7-yl-phenylmethenone [1] from the mixture of 2-amino-5-benzoylbenzimidazole and acetyl acetone. They also reported the synthesis of compound [2] from benzoyl isothiocyanate.

Wanda Nawrocka et.al, have carried out the synthesis of 2-substituted aminobenzimidazole [3] from 2-aminobenzimidazoles and substituted aromatic aldehydes in the presence of n-BuOH and NaBH₄. These compounds evaluated for their antiproliferative and cytotoxic activity against the human cancer cell namely SW707 (rectal), HCV29T (bladder), A549 (lung) and T47D (breast cancer).
2-Aminobenzimidazole reacted with ethyl cyanoacetate to give access to an efficient synthesis of 4-amino-1, 4-benzo [4, 5] imidazo-[1, 2-a] pyrimidine-2-one.  

Balkis Al-Saleh have reported the synthesis of 1,2,4-triazolo[4,3-a] pyrimidines, benzimidazole [3,2-a] pyrimidine and pyrazolo[1,5-a]pyrimidine from 2-amino triazole, 2-aminobenzimidazole and 3-aminopyrazole followed by the reaction with enamines, enaminonitriles and α-β-unsaturated esters.
Ammar\textsuperscript{8} has reported the synthesis of new 3-cyano-2-(3-tolylamino) pyrazolo [1, 5-a] pyrimidine [8] from the reaction of 3-amino pyrazole with cinnamonitriles in ethanol in presence of piperidine to give good yield of the product.

Settimo \textit{et.al.}\textsuperscript{9} carried out the synthesis of pyrimido [1, 2-a] benzimidazole-4-one derivatives [9] starting with 2-aminobenzimidazole and diethyl ethoxymethylene malonate, which exhibited anti-proliferative activity.
Hataba and co-workers\textsuperscript{10} have reported the synthesis of condensed benzthiazole derivatives \textsuperscript{[10]} from 2-amino benzthiazole condensed with ethyl cyanoacetate.

A.Yahay-Zadesh\textsuperscript{11} has carried out the synthesis of 9-aryl-6-aminopurines \textsuperscript{[11]} from 5-amino-1-aryl -1H-imidazole-4-carbonitriles. \textsuperscript{[12]}
The preparation of the 7-amino-5-aryl-4,5-dihydro-1,2,4-triazolo[1,5-a]pyrimidine-6-carbonitriles was carried out by the reaction of malonodinitrile with amino-triazole in 30% dimethylamine to give 20-30% yield.\textsuperscript{12}

The preparation of the 4-amino-1, 2-dihydro-2-phenylpyrimido [1, 2-a] benzimidazole-3-carbonitriles \textsuperscript{[13]} has been reported by the reaction of malonodinitrile with 2-aminobenzimidazole in 30% dimethylamine with 20-30% yield.

Sergey A. Komykhov and co-workers\textsuperscript{12} have reported the synthesis involving the reaction of α-β-unsaturated nitriles as a bielectrophiles with aminoazoles to give different products. \textsuperscript{[14, 15, 16]}
Present work

A new methodology for the synthesis of 2,3,4-trisubstituted 1,2-dihydropyrimido [1,2-a] benzimidazole has been described using domestic microwave, which resulted in the dramatic increase in yield of chemical transformations, cleaner products compared with conventional heating. 

Scheme-III
Mechanistic pathway for compound 3a-e
Scheme-IV

Mechanistic pathway for compound 4a-e
Results and discussion

The reaction of 2-aminobenzimidazole 1 with β-aryl-α-cyanoacrylonitrile derivatives a in presence of catalytic amount of TEA in an open glass container and the reaction mixture irradiated in a microwave oven for 30-40 sec. with intermittent irradiation to afford 70-90% yield of (3a-e). In the classical approach, this cyclocondensation reaction requires longer reaction time. In addition, this method suffers from tedious and time-consuming work-ups. In contrast, under microwave irradiation, the reactions are completed within only 30-40 sec and afforded good yields of the products.13-20 The products were characterized on the basis of their IR, 1H NMR, 13C NMR and Mass spectral data.

In the same way, equimolar amount of 2-aminobenzimidazole 1 and ethyl β-(substituted phenyl)-α-cyanoacrylates b was mixed in an open glass container and irradiated under microwave oven for 30 sec with intermittent irradiation afforded about 90% yields of (4a-e). In the IR spectrum 4a-e showed the absence of the ester carbonyl absorption band and the presence of amide band in the region 1697 cm⁻¹. The yield and reaction time used for the microwave assisted synthesis have been incorporated in Table 2. Microwave irradiations were conducted in a domestic microwave oven [SAMSUNG M197DN (2450 MHz, 1500W)].

Experimental

Synthesis of 2-aminobenzimidazole :

The starting material 2-amino benzimidazole are commonly synthesized by reacting o-phenylenediamine with guanidine²¹ by reported method and characterized.
General procedure for synthesis of compound (3a-e):

2-Aminobenzimidazole (0.266 gm, 2 mmol) 1, with β-aryl-α-cyanoacrylonitrile derivatives a (2 mmol) and catalytic amount of triethyl amine (TEA) in ethanol was taken into a open glass container and irradiated with microwave for 30-60sec. The progress of reaction was monitored on TLC using benzene: ethyl acetate (90:10) as the eluent. The mixture was cooled and recrystallized in ethanol to get the desired product.

4-Amino-2-phenyl-1,2-dihydropyrimido[1,2-a]benzimidazole-3-carbonitrile (3a):

Yield: 0.400 gm.

M.P. 207°C (Ref13: 205-207°C);

IR (KBr): $\nu_{\text{max}}$ 1650 (C=N), 3319 (NH), 2227 (CN) cm$^{-1}$;  
---Fig-1

$^1$H NMR (DMSO-$_d$6): $\delta$, 7.3-7.9 (11H, m, Ar-H), 9.9 (2H, br, s, NH$_2$) ppm.  
---Fig-2

MASS (m/z, amu): 289  
---Fig-3

$^{13}$CNMR (DMSO-$_d$6): $\delta$, 120, 126, 127,128, 129, 131, 134, 136, 137, 138, 139, 144, 149, 157, 170, 198.  
---Fig-4

Elemental analysis:

Found: C, 71.19; H, 4.60; N, 24.35%; C$_{17}$H$_{13}$N$_5$

Calculated: C, 71.06; H, 4.56; N, 24.37%

4-Amino-2-(4-methoxyphenyl)1,2-dihydropyrimido [1, 2-a] benzimidazole-3-carbonitrile (3b):

Yield: 0.285 gm.

M.P. 215°C (Ref13: 212-213°C)  

IR (KBr): $\nu_{\text{max}}$1637 (C=N), 3325(N-H), 2222 (CN) cm$^{-1}$;  
---Fig-5
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$^1$H NMR (DMSO-$d_6$): $\delta$, 6.9-7.9 (10H, m, ArH), 9.8 (2H, br, s, NH$_2$), 2.5 (3H, s, OCH$_3$) ppm.  
---Fig-6

$^1$C NMR (DMSO-$d_6$): $\delta$, 25, 117, 120, 123, 125, 129, 131, 134, 137, 142, 170.  
---Fig-7

Elemental analysis:

Found: C, 68.11; H, 4.70; N, 22.35%; C$_{18}$H$_{15}$N$_5$O

Calculated: C, 68.13; H, 4.76; N, 22.07%.

4-Amino-2-(4-chlorophenyl) 1,2-dihydropyrimido [1,2-a] benzimidazole-3-carbonitrile (3c):

Yield: 0.386 gm.

M.P: 238°C (Ref$^3$: 232°C)

IR (KBr): $\nu_{\text{max}}$ 1598 (C=N), 3436 (N-H), 2222 (CN) cm$^{-1}$;  
---Fig-8

$^1$H NMR (DMSO-$d_6$): $\delta$, 7.10-7.80 (9H, m, Ar-H), 8.3 (2H, br, s, NH$_2$), 10.0 (1H, s, NH) ppm.  
---Fig-9

Elemental analysis:

Found: C, 63.42; H, 3.75; N, 21.76%; C$_{17}$H$_{12}$ClN$_5$

Calculated: C, 63.46; H, 3.76; N, 21.77%.

4-Amino-2-(3-nitrophenyl) 1,2-dihydropyrimido [1,2-a] benzimidazole-3-carbonitrile (3d):

Yield: 0.298 gm.

M.P: 215°C (Ref$^3$: 216-217°C)

IR (KBr): $\nu_{\text{max}}$ 1610 (C=N), 3121 (N-H), 2223 (CN) cm$^{-1}$;  
---Fig-10

$^1$H NMR (DMSO-$d_6$): $\delta$, 7.2-7.7 (10H, m, ArH), 11.5 (2H, br, s, NH$_2$) ppm.  
---Fig-11

MASS (m/z, amu): 333  
---Fig-12
Elemental analysis:

**Found:** C, 71.19; H, 3.60; N, 25.28%; C\textsubscript{17}H\textsubscript{12}N\textsubscript{6}O\textsubscript{2}

**Calculated:** C, 61.44; H, 3.64; N, 25.29%.

4-Amino-2-(2-hydroxyphenyl)-1,2-dihydropyrimido-[1,2-a] benzimidazole-3-carbonitrile (3e):

**Yield:** 0.303 gm.

**M.P:** 240°C

**IR (KBr):** $\nu_{\text{max}}$ 1621 (C=N), 3423 (-OH), 3413 (N-H), 2260 (CN) cm\textsuperscript{-1}; ---Fig-13

**$^1H$ NMR (DMSO-d\textsubscript{6}):** $\delta$, 6.67-7.46 (9H, m, Ar-H), 11.7 (2H, br, s, NH\textsubscript{2}), 8.03 (1H, s, NH), 4.60(1H, s, -OH) ppm. ---Fig-14

Elemental analysis:

**Found:** C, 67.30; H, 4.30; N, 23.10%; C\textsubscript{17}H\textsubscript{13}N\textsubscript{5}O

**Calculated:** C, 67.32; H, 4.32; N, 23.09%.

**General procedure for synthesis of compound (4a-e):**

2-Aminobenzimidazole 1 (0.266gm, 2 mmol), with ethyl $\beta$- (substituted phenyl)-$\alpha$-cyanoacrylates b (2 mmol) and the catalytic amount of triethyl amine (TEA) in ethanol was taken into a open glass container and irradiated with microwave over the period of 30-60 sec. The progress of reaction was monitored on TLC using benzene: ethyl acetate (90:10) as the eluent. The compound was cooled and recrystallized in ethanol to get the desired product.

2-Oxo-4-phenyl-1,2-dihydropyrimido [1, 2-a] benzimidazole-3-carbonitrile (4a):

**Yield:** 0.457 gm.

**M.P:** 295°C;

**IR (KBr):** $\nu_{\text{max}}$ 1697 (C=O), 3303 (N-H), 2205 (CN) cm\textsuperscript{-1}; ---Fig-15

**$^1H$ NMR (DMSO-d\textsubscript{6}):** $\delta$, 6.9-8.2 (9H, m, Ar-H), 10.6 (1H, s, NH) ppm. ---Fig-16

**$^{13}CNMR (DMSO-d\textsubscript{6}):** 125, 126, 127, 129, 132, 133, 134, 170. ---Fig-17
Elemental analysis:

**Found:** C, 71.31; H, 3.50; N, 19.56%; C_{17}H_{10}N_{4}O

**Calculated:** C, 71.32; H, 3.52; N, 19.57%.

4-(4-Methoxyphenyl)-2-oxo-1,2-dihydropyrimido [1,2-a] benzimidazole-3-carbonitrile (4b):

Yield: 0.492 gm.

**M.P:** 240 °C

**IR (KBr):** $\nu_{\text{max}}$ 1697 (C=O), 3305 (N-H), 2205 (CN) cm$^{-1}$;  

**$^{1}$H NMR (DMSO-$d_6$):** $\delta$, 7.26-7.56 (9H, m, Ar-H), 9.52 (1H, s, NH), 3.55 (3H, s, OCH$_3$) ppm.

**$^{13}$C NMR (DMSO-$d_6$):** 25, 126, 128, 130, 132, 133, 135, 136, 137, 140, 168.

---Fig-18
---Fig-19
---Fig-20

Elemental analysis:

**Found:** C, 68.35; H, 3.81; N, 17.70%; C$_{18}$H$_{12}$N$_{4}$O$_{2}$

**Calculated:** C, 68.35; H, 3.82; N, 17.71%.

4-(4-Chlorophenyl)-2-oxo-1,2-dihydropyrimido [1,2-a] benzimidazole-3-carbonitrile (4c):

Yield: 0.576 gm.

**M.P:** 245°C;

**IR (KBr):** $\nu_{\text{max}}$ 1678 (C=O), 3325 (N-H), 2188 (CN) cm$^{-1}$;  

**$^{1}$H NMR (DMSO-$d_6$):** $\delta$, 7.46-7.67 (8H, m, Ar-H), 8.63 (1H, s, NH) ppm.

---Fig-21
---Fig-22

Elemental analysis:

**Found:** C, 63.65; H, 3.82; N, 17.46%; C$_{17}$H$_{9}$ClN$_{4}$O

**Calculated:** C, 63.66; H, 2.83; N, 17.47%.
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4-(3-Nitrophenyl)-2-oxo-1,2-dihydropyrimido [1,2-a] benzimidazole-3-carbonitrile (4d):

Yield: 0.529 gm.

M.P: 270°C;

IR (KBr): \(\nu_{\text{max}}\) 1698 (C=O), 3423 (N-H), 2228 (CN) cm\(^{-1}\); ---Fig-23

\(^1\)H NMR (DMSO-\(d_6\)): \(\delta\), 7.0-8.0 (8H, m, Ar-H), 10.0 (1H, s, NH) ppm.-Fig-24

Elemental analysis:

Found: C, 61.64; H, 2.25; N, 21.13%; \(\text{C}_{17}\text{H}_9\text{N}_5\text{O}_3\)

Calculated: C, 61.63; H, 2.74; N, 21.14%

4-(2-Hydroxyphenyl)-2-oxo-1,2-dihydropyrimido [1,2-a] benzimidazole-3-carbonitrile (4e):

Yield: 0.422 gm.

M.P: 290°C;

IR (KBr): \(\nu_{\text{max}}\) 1698 (C=O), 3410 (N-H), 3250 (O-H), 2248 (CN) cm\(^{-1}\).

Elemental analysis:

Found: C, 71.19; H, 3.30; N, 18.52%; \(\text{C}_{17}\text{H}_{10}\text{N}_4\text{O}_2\)

Calculated: C, 67.55; H, 3.33; N, 18.53%
Table 2: Yields and reaction time used for the microwave assisted synthesis.

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<th>Entry</th>
<th>R’</th>
<th>Microwave method</th>
<th>Conventional method</th>
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<td></td>
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<td>Reaction time (sec.)</td>
<td>Yield (%)</td>
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<td>o-OH</td>
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Fig. 16
Fig. 24
References

1. Wright J.B., *J. Am. Chem. Soc.*, 71, 2035, **1949**.
2. Cohn G., *Ber.*, 32, 2242, **1899**.
5. Wanda Nawrocha, Barbara Sztuba Maria W. Kowalska, Hanna Liszkiewicz, Joanna Wietrzyk, Anna Nasulexicz, Marzena Pelczynska and Adam opolski, *II Farmaco*, 59,83, **2004**.
6. Fikret Karci, Aykut Demircali, Izzel senser and Tatlie Tilki, *Dyes & Pigments*, 71, 90, **2006**.
15. Laurent R., Laporterio A. and Dubac, *J. Organometallic*, 13, 2493, **1994**.