

Research Article



Montmorillonite K-10 Supported Solvent-Free Synthesis of Novel 2-thioxoimidazole-4-one N-nucleosides

Shalini Jaiswal*, I. R. Siddiqui

Department of Chemistry, university of Allahabad, UP, India.

*Corresponding author's E-mail: shalinijaiswal@gmail.com

Accepted on: 29-01-2014; Finalized on: 30-04-2014.

ABSTRACT

Imidazole drugs have broad applications in many areas of clinical medicine. The literature reveals that anticancer and antimicrobial properties of imidazole were associated with substitutions at 1 position. Due to the growing awareness about environmental pollution and environmental legislation, recent years have witnessed a phenomenal increase in the application of microwave irradiation (MW) in organic synthesis. Use of mineral supported reagent assisted by microwave irradiation under solvent-free condition provides environmentally benign protocol with additional advantages such as enhanced reaction rate, higher yields of pure product, easier workup, better selectivity, improved ease of manipulation, rapid optimization of reactions in parallel which fulfil basic principles of green chemistry. Encouraged by above reports and as part of our research programme for development of eco-friendly synthetic protocol for biologically active compounds as well as in pursuing of our work on new solvent-free cyclisation process we developed a novel K-10 clay catalysed, MW activated synthesis of 2-thioxoimidazole-4-one N-nucleosides. Interestingly it is the first example of microwave induced synthesis of 2-Thioxoimidazole-4-one N-nucleosides. The key element in our approach is the utilization of α -halo acid as a bifunctional building block whose application to the construction of various heterocycles of chemical and biological interest is well documented. An expeditious mineral (montmorillonite K-10) catalysed cyclocondensation of α -halo carboxylic acid and aryl amine on ribosyl/deoxyribosyl thiourea under solvent-free microwave irradiation to yield 2-thioxoimidazole-4-one N-nucleosides. Transformation of ribosyl/deoxyribosyl thiourea under reaction conditions into isothiocyanate followed by nucleophilic addition of aryl amine on isothiocyanate generated aryl substituted ribosyl/deoxyribosyl thiourea which in turn underwent cyclocondensation with bifunctional α -halo acid through a dipolar complex to yield 2-thioxoimidazole-4-one N-nucleosides.

Keywords: 2-Thioxoimidazole-4-one N-nucleosides, K-10 supported, solvent-free microwave irradiation, cyclocondensation.

INTRODUCTION

Medicinal chemistry concerns with the discovery, development, interpretation and the identification of mechanism of action of biologically active compounds at the molecular level. Various biologically active synthetic compounds have five-membered nitrogen-containing heterocyclic ring in their structures and Imidazole is a heterocyclic compound with five membered unsaturated ring structure composed of 3 carbons and 2 nitrogen atoms at non-adjacent positions.

Imidazole drugs have broad applications in many areas of clinical medicine.^{1, 2} Imidazole were reported as analgesics, anti-inflammatory, antiparasitic, anthelmintic, platelet aggregation inhibitors and antiepileptic agents³⁻⁸. The literature reveals that anticancer and antimicrobial properties of imidazole were associated with substitutions at 1 position.

Due to the growing awareness about environmental pollution and environmental legislation, recent years have witnessed a phenomenal increase in the application of microwave irradiation (MW) in organic synthesis⁹⁻¹².

Most important of these are 2-Thioxoimidazole which exhibit antiviral particularly anti-HIV activity¹². Most available drugs approved by FDA to treat AIDS patients are nucleosides analogous but no attempt so far to synthesize nucleosides analogous incorporating 2-

thioxoimidazolidinone as nucleobase although they appear to be attractive scaffolds for exploiting chemical diversity and generating a drug like library to screen for last candidates. The fight against HIV by developing more efficacious multi-target drugs has been the prime driving force for glycosidation of 2-thioxoimidazolidinone.

One pot multi-component reactions have emerged as an improved synthetic strategy for tailor-made structural scaffolds in drug discovery process¹³⁻¹⁶. MCRs have gained significantly and steady increasing academic, economical and ecological interest because they address fundamental principle of synthetic efficiency and reaction design.

Use of mineral supported reagent assisted by microwave irradiation under solvent-free condition provides environmentally benign protocol with additional advantages such as enhanced reaction rate, higher yields of pure product, easier workup, better selectivity, improved ease of manipulation, rapid optimization of reactions in parallel which fulfil basic principles of green chemistry¹⁶⁻¹⁸.

Encouraged by above reports and as part of our research programme for development of eco-friendly synthetic protocol for biologically active compounds¹⁹⁻²⁴ as well as in pursuing of our work on new solvent-free cyclisation process we developed a novel K-10 clay catalysed, MW activated synthesis of hitherto unknown 2-



thioxoimidazole-4-one N-nucleosides (**Scheme 1**). Interestingly it is the first example of microwave induced synthesis of 2-Thioxoimidazole-4-one N-nucleosides. The key element in our approach is the utilization of α -haloacid as a bifunctional building block whose application to the construction of various heterocycles of chemical and biological interest is well documented.²⁴

MATERIALS AND METHODS

Melting points were determined by open glass capillary method and are uncorrected. All chemicals used were reagent grade and were used as received without purification. A Laboratory Microwave Oven (Model BP 310/50) operating at 2450 MHz and power output of 600 W was used for all the experiments. The progress of reactions was monitored by TLC (silica gel). IR spectra were recorded on a Shimadzu FTIR-420 spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded at 400°C on a Bruker AVANCE DPX (400 MHz) FT spectrometer in CDCl₃ using TMS as an internal reference (chemical shift in δ , ppm). Mass spectra were recorded on JEOL SX-303 (FAB) mass spectrophotometer at 70ev. Elemental analyses were carried out using a Coleman automatic C, H, N analyser.

Microwave assisted synthesis of 2-thioxoimidazole-4-one N-nucleosides (4a-l)

To a solution of ribosyl/deoxyribosyl thiourea **1** (5.0 mmol), α -halo carboxylic acid **2** (5.0 mmol) and aryl amine **3** (5.0 mmol) in DCM (10 ml) was added montmorillonite K-10 clay (0.50 g) with thorough mixing and the solvent was evaporated under reduced pressure. The contents were taken in 20 ml vial and subjected to microwave irradiation at 600 W for 2 min. The reaction mixture was then thoroughly mixed outside the microwave oven for 3 min and again irradiated for another 2 min. This irradiation-mixing cycle was repeated for the total irradiation time **Table I**. After completion of the reaction as indicated by TLC (Hexane: AcOEt, 8:2 V/V) the product was extracted with dichloromethane (3x50 ml). The extract was filtered and filtrate was evaporated under reduced pressure to obtain the product. The final product was recrystallised from ethanol to obtain analytically pure compounds (**4a-l**).

Thermal synthesis of 2-thioxoimidazole-4-one N-nucleosides (4a-l)

Montmorillonite K-10 clay (0.50g) was added to a solution of ribosyl/deoxyribosyl thiourea **1** (5.0 mmol), α -halo carboxylic acid **2** (5.0 mmol) and aryl amine **3** (5.0 mmol) in DCM (50 ml) with constant stirring and the reaction mixture was refluxed on thermostat oil-bath at 88 °C for the time specified in **Table I**. After completion of the reaction as indicated by TLC (Hexane: AcOEt, 8:2 V/V). The product was extracted with dichloromethane (3x50 ml). The extract was filtered and filtrate was evaporated under reduced pressure to obtain the product. The final product was recrystallised from ethanol to obtain analytically pure compounds (**4a-l**).

Scheme-1

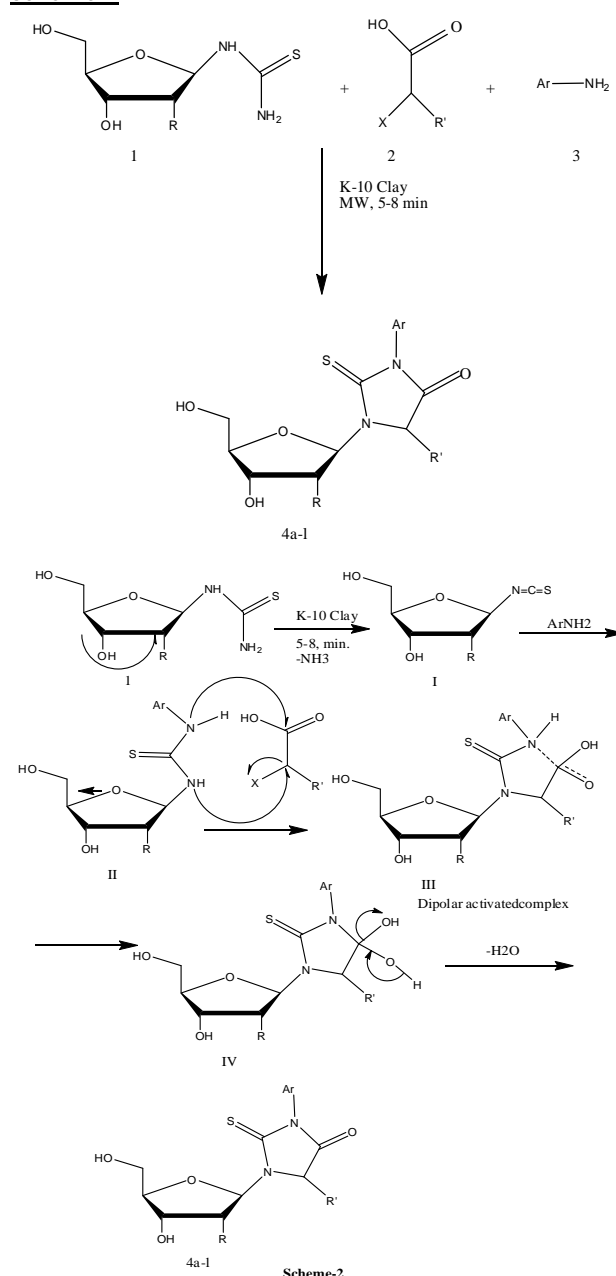


Table-1

Compound	R	R'	Ar
4a	OH	H	C ₆ H ₅
4b	OH	H	4-NO ₂ - C ₆ H ₄
4c	OH	H	4-Br- C ₆ H ₄
4d	OH	Me	C ₆ H ₅
4e	OH	Me	4-NO ₂ - C ₆ H ₄
4f	OH	Me	4-Br- C ₆ H ₄
4g	OH	Et	C ₆ H ₅
4h	OH	Et	4-NO ₂ - C ₆ H ₄
4i	OH	Et	4-Br- C ₆ H ₄
4j	OH	4-Cl- C ₆ H ₄	C ₆ H ₅
4k	OH	4-Cl- C ₆ H ₄	4-NO ₂ - C ₆ H ₄
4l	OH	4-Cl- C ₆ H ₄	24-Br- C ₆ H ₄

Table-2

Compound	Time		Yield (%)	
	MWI (min)	Thermal (hour)	MWI	Thermal
4	5	2	81	35
5	7	4	76	32
6	6	3	78	33
7	6	3	83	34
8	7	4	77	33
9	6	4	79	35
10	5	3	85	36
11	6	4	78	34
12	7	4	80	35
13	6	3	82	34
14	7	5	79	32
15	8	5	80	33

1-(β-D-Ribofuranosyl) 3-phenyl-2-thioxoimidazolidin-4-one (4a)

Yield 81 % (MWI), 35% (Thermal); m.p. 115-116 °C; ¹H NMR (400 MHz, DMSO-d₆), δ 4.30 (s, 2H, 2Xh-5), 3.65-3.92 (m, 4H, H-2', H-3', 2XH-5'), 3.90-4.00 (m, 1H, H-4'), 4.99 (d, 1H, J_{12'}, 4.2Hz, H-1'), 2.00-2.40 (br s, 3H, 3Xoh, exchangeable with D₂O), 7.10-7.71 (m, 5H, H-2'', H-3'', H-4'', H-5'', H-6''); ¹³C NMR (100MHz, DMSO-d₆) δ 178 (C-2), 168 (C-4), 54.0 (C-5), 141.0 (C-1''), 120.5 (C-2'', C-6''), 128.6 (C-3'', C-5''), 124.4 (C-4''), 87.2 (C-1''), 75.7 (C-2''), 70.8 (C-3'), 76.4 (C-4'), 62.0 (C-5'); EIMS m/z, 324 (M⁺). Anal. Calcd. For C₁₄H₁₆N₂O₅S: C, 51.84; H, 4.97; N, 8.64; S, 9.89. Found: C, 51.89; H, 5.00; N, 8.60; S, 9.87.

1-(β-D-Ribofuranosyl)-3-(4-nitrophenyl)-2-thioxoimidazolidin-4-one (4b)

Yield 76 % (MWI), 31% (Thermal); m.p. 120-122 °C; ¹H NMR (400 MHz, DMSO-d₆), δ 4.37 (s, 2H, 2xH-5), 3.66-3.92 (m, 4H, H-2', H-3', 2XH-5'), 3.91-4.00 (m, 1H, H-4'), 4.96 (d, 1H, J_{12'}, 4.2Hz, H-1'), 2.10-2.42 (br s, 3H, 3Xoh, exchangeable with D₂O), 7.92 (dd, 2H, J_{2'',6''}, 5.6Hz, H-2'', H-6'') 8.31 (dd, 2H, J_{3'',5''}, 5.6 Hz, H-3'', H-5''); ¹³C NMR (100 MHz, DMSO-d₆) δ 177 (C-2), 170 (C-4), 53.0 (C-5), 147.0 (C-1''), 122.5 (C-2'', C-6''), 123.6 (C-3'', C-5''), 145.0 (C-4''), 87.4 (C-1'), 75.6 (C-2'), 72.0 (C-3'), 76.4 (C-4'), 63.1 (C-5'); EIMS m/z, 369 (M⁺). Anal. Calcd. For C₁₄H₁₆N₃O₇S: C, 45.53; H, 4.09; N, 11.38; S, 8.69. Found: C, 45.39; H, 4.19; N, 11.40; S, 8.67.

1-(β-D-Ribofuranosyl)-3-(4-bromophenyl)-2-thioxoimidazolidin-4-one (4c)

Yield 78 % (MWI), 33% (Thermal); m.p. 132-133 °C; ¹H NMR (400 MHz, DMSO-d₆), δ 4.36 (s, 2H, 2Xh-5), 3.66-3.92 (m, 4H, H-2', H-3', 2XH-5'), 3.91-4.10 (m, 1H, H-4'), 4.96 (d, 1H, J_{12'}, 4.2Hz, H-1'), 2.00-2.42 (br s, 3H, 3Xoh, exchangeable with D₂O) 7.52 (dd, 2H, J_{2'',6''}, 5.6Hz, H-2'', H-6'') 7.42 (dd, 2H, J_{3'',5''}, 5.6 Hz, H-3'', H-5''); ¹³C NMR (100MHz, DMSO-d₆) δ 176.5 (C-2), 167.9 (C-4), 53.3 (C-5), 139.0 (C-1''), 123.5 (C-2'', C-6''), 133.0 (C-3'', C-5''), 120.0 (C-4''), 87.4 (C-1''), 75.6 (C-2'), 72.2 (C-3'), 76.4 (C-4'), 63.0

(C-5'); EIMS m/z, 401 (M⁺). Anal. Calcd. For C₁₄H₁₅N₂O₅S: C, 41.72; H, 3.72; N, 6.92; Br, 19.80; S, 7.94. Found: C, 41.89; H, 3.74; N, 6.94; Br, 19.86; S, 7.96.

1-(β-D-Ribofuranosyl)-5-methyl-3-phenyl-2-thioxoimidazolidin-4-one (4d)

Yield 83 % (MWI), 34% (Thermal); m.p. 123-124 °C; ¹H NMR (400 MHz, DMSO-d₆), δ 4.00 (q, 1H, H-5), 0.93 (d, 3H, Js CH₃, 2.5 Hz, -CH₃) 3.66-3.92 (m, 4H, H-2', H-3', 2XH-5'), 4.10 (m, 1H, H-4'), 4.96 (d, 1H, J_{12'}, 4.2 Hz, H-1') 2.10-2.42 (br s, 3H, 3Xoh exchangeable with D₂O), 7.92 (dd, 2H, J_{2'',6''}, 5.6Hz, H-2'', H-6'') 8.31 (dd, 2H, J_{3'',5''}, 5.6 Hz, H-3'', H-5''); ¹³C NMR (100MHz, DMSO-d₆) δ 177.0 (C-2), 170.2 (C-4), 62.0 (C-5), 15.0 (CH₃), 147.0 (C-1''), 122.0 (C-2'', C-6''), 127.9 (C-3'', C-5''), 145.0 (C-4''), 87.2 (C-1'), 75.6 (C-2'), 72.0 (C-3'), 76.4 (C-4'), 63.0 (C-5'); EIMS m/z, 383 (M⁺). Anal. Calcd. For C₁₅H₁₇N₃O₇S: C, 46.99; H, 4.37; N, 10.94; S, 8.39. Found: C, 46.89; H, 4.44; N, 10.94; S, 8.36.

1-(β-D-Ribofuranosyl)-5-methyl-3-(4-nitrophenyl)-2-thioxoimidazolidin-4-one (4e)

Yield 83 % (MWI), 34% (Thermal); m.p. 123-124 °C; ¹H NMR (400 MHz, DMSO-d₆), δ 4.00 (q, 1H, H-5), 0.93 (d, 3H, Js CH₃, 2.5 Hz, -CH₃) 3.66-3.92 (m, 4H, H-2', H-3', 2XH-5'), 4.10 (m, 1H, H-4'), 4.96 (d, 1H, J_{12'}, 4.2 Hz, H-1') 2.10-2.42 (br s, 3H, 3Xoh exchangeable with D₂O), 7.92 (dd, 2H, J_{2'',6''}, 5.6Hz, H-2'', H-6'') 8.31 (dd, 2H, J_{3'',5''}, 5.6 Hz, H-3'', H-5''); ¹³C NMR (100MHz, DMSO-d₆) δ 177.0 (C-2), 170.2 (C-4), 62.0 (C-5), 15.0 (CH₃), 147.0 (C-1''), 122.0 (C-2'', C-6''), 127.9 (C-3'', C-5''), 145.0 (C-4''), 87.2 (C-1'), 75.6 (C-2'), 72.0 (C-3'), 76.4 (C-4'), 63.0 (C-5'); EIMS m/z, 383 (M⁺). Anal. Calcd. For C₁₅H₁₇N₃O₇S: C, 46.99; H, 4.37; N, 10.94; S, 8.39. Found: C, 46.89; H, 4.44; N, 10.94; S, 8.36.

1-(β-D-Ribofuranosyl)-5-methyl-3-(4-bromophenyl)-2-thioxoimidazolidin-4-one (4f)

Yield 79 % (MWI), 34% (Thermal); m.p. 133-134 °C; ¹H NMR (400 MHz, DMSO-d₆), δ 4.00 (q, 1H, H-5), 0.93 (d, 3H, Js CH₃, 2.5 Hz, -CH₃) 3.66-3.92 (m, 4H, H-2', H-3', 2XH-5'), 3.91-4.10 (m, 1H, H-4'), 4.96 (d, 1H, J_{12'}, 4.2 Hz, H-1') 2.10-2.42 (br s, 3H, 3Xoh exchangeable with D₂O), 7.55 (dd, 2H, J_{2'',6''}, 5.6Hz, H-2'', H-6''), 7.31 (dd, 2H, J_{3'',5''}, 5.6 Hz, H-3'', H-5''); ¹³C NMR (100MHz, DMSO-d₆) δ 177.0 (C-2), 170.2 (C-4), 62.0 (C-5), 15.0 (CH₃), 139.8 (C-1''), 123.0 (C-2'', C-6''), 133.0 (C-3'', C-5''), 125.0 (C-4''), 85.2 (C-1'), 76.0 (C-2'), 72.0 (C-3'), 76.4 (C-4'), 63.1 (C-5'); EIMS m/z, 417 (M⁺). Anal. Calcd. For C₁₅H₁₇BrN₃O₅S: C, 43.19; H, 4.17; N, 6.94; S, 7.39. Found: C, 43.89; H, 4.04; N, 6.94; S, 7.66.

1-(β-D-Ribofuranosyl)-5-ethyl-3-phenyl-2-thioxoimidazolidin-4-one (4g)

Yield 89 % (MWI), 36% (Thermal); m.p. 123-124 °C; ¹H NMR (400 MHz, DMSO-d₆), δ 3.56 (t, 1H, H-5), 1.79 (m, 2H, -CH₂-), 0.96 (t, 3H, -CH₃) 3.66-3.92 (m, 4H, H-2', H-3', 2XH-5'), 3.91-4.10 (m, 1H, H-4'), 4.96 (d, 1H, J_{12'}, 4.2 Hz, H-1') 2.10-2.42 (br s, 3H, 3xOH exchangeable with D₂O), 7.00-7.64 (m, 5H, H-2'', H-3'', H-4'', H-5'', H-6''); ¹³C NMR (100MHz, DMSO-d₆) δ 177.0 (C-2), 168.2 (C-4), 62.0 (C-5), 22.7 (-CH₂-), 8.2 (-CH₃), 85.2 (C-1'), 76.0 (C-2'), 72.0 (C-



3'), 76.4 (C-4'), 63.1 (C-5'), 141 (C-1''), 121.0 (C-2'', C-6''), 128.0 (C-3'', C-5''), 125.0 (C-4''),; EIMS m/z, 352 (M⁺). Anal. Calcd. For C₁₆H₂₀N₂O₅S: C, 54.19; H, 5.17; N, 7.94; S, 9.10. Found: C, 53.49; H, 5.84; N, 7.94; S, 9.86.

1-(β-D-Ribofuranosyl)-5-ethyl 3-(4-nitrophenyl)-2-thioxoimidazolidin-4-one (4h)

Yield 78 % (MWI), 34% (Thermal); m.p. 130-132 °C; ¹H NMR (400 MHz, DMSO-d₆), δ 3.56(t, 1H, H-5), 1.79 (m, 2H, -CH₂-), 0.96(t, 3H, -CH₃), 3.66-3.92 (m, 4H, H-2', H-3', 2xH-5'), 3.91-4.10 (m, 1H, H-4'), 4.96 (d, 1H, J_{1,2}, 4.2 Hz, H-1), 2.10-2.42 (br s, 3H, 3xOH exchangeable with D₂O), 7.92 (dd, 2H, J_{2'',6''}, 5.6 Hz, H-2'', H_{6''}) 8.31 (dd, 2H, J_{3'',5''}, 5.6 Hz, H-3'', H-5''); ¹³C NMR (100MHz, DMSO-d₆) δ 177.0 (C-2), 168.2 (C-4), 62.0 (C-5), 22.7 (-CH₂-), 8.2 (-CH₃), 85.2 (C-1'), 76.0 (C-2'), 72.0 (C-3'), 76.4 (C-4'), 63.1 (C-5'), 147 (C-1''), 122.0 (C-2'', C-6''), 123.8 (C-3'', C-5''), 128.0 (C-4''),; EIMS m/z, 397 (M⁺). Anal. Calcd. For C₁₆H₁₉N₃O₇S: C, 48.39; H, 4.87; N, 10.54; S, 8.10. Found: C, 48.49; H, 4.84; N, 10.54; S, 8.06.

1-(β-D-Ribofuranosyl)-5-ethyl 3-(4-bromophenyl)-2-thioxoimidazolidin-4-one (4i)

Yield 80 % (MWI), 35% (Thermal); m.p. 140-142 °C; ¹H NMR (400 MHz, DMSO-d₆), δ 3.56(t, 1H, H-5), 1.79 (m, 2H, -CH₂-), 0.96(t, 3H, -CH₃), 3.66-3.92 (m, 4H, H-2', H-3', 2xH-5'), 3.91-4.10 (m, 1H, H-4'), 4.96 (d, 1H, J_{1,2}, 4.2 Hz, H-1), 2.10-2.42 (br s, 3H, 3xOH exchangeable with D₂O), 7.53 (dd, 2H, J_{2'',6''}, 5.6 Hz, H-2'', H_{6''}), 7.41 (dd, 2H, J_{3'',5''}, 5.6 Hz, H-3'', H-5''); ¹³C NMR (100MHz, DMSO-d₆) δ 177.0 (C-2), 168.2 (C-4), 62.0 (C-5), 22.7 (-CH₂-), 8.2 (-CH₃), 85.2 (C-1'), 76.0 (C-2'), 72.0 (C-3'), 76.4 (C-4'), 63.1 (C-5'), 139 (C-1''), 123.0 (C-2'', C-6''), 133.8 (C-3'', C-5''), 120.0 (C-4''),; EIMS m/z, 397 (M⁺). Anal. Calcd. For C₁₆H₁₉N₂O₅S: C, 48.39; H, 4.87; N, 10.54; S, 8.10. Found: C, 48.49; H, 4.84; N, 10.54; S, 8.06.

1-(β-D-Ribofuranosyl)-5-(4-chlorophenyl)-3-phenyl-2-thioxoimidazolidin-4-one (4j)

Yield 82 % (MWI), 34% (Thermal); m.p. 140-142 °C; ¹H NMR (400 MHz, DMSO-d₆), δ 4.85 (s, 1H, H-5), 7.00 (dd, 2H, J_{2'',6''}, 5.3 Hz, H-2'', H_{6''}), 7.15 (dd, 2H, J_{3'',5''}, 5.3 Hz, H-3'', H-5'') 3.65-3.92 (m, 4H, H-2', H-3', 2xH-5'), 3.90-4.10 (m, 1H, H-4'), 4.96 (d, 1H, J_{1,2}, 4.2 Hz, H-1), 2.00-2.32 (br s, 3H, 3xOH, exchangeable with D₂O), 7.10-7.64 (dd, m, 5H, H-2'', H-3'', H-4'', H-5'', H-6''); ¹³C NMR (100MHz, DMSO-d₆) δ 177 (C-2), 168.2 (C-4), 65.0 (C-5), 84.5 (C-1'), 76.0 (C-2'), 70.6 (C-3'), 76.3 (C-4'), 61.9 (C-5'), 140.8 (C-1''), 120.5 (C-2'', C-6''), 128.6 (C-3'', C-5''), 124.4 (C-4''), 134.0 (C-1'''), 129.4 (C-3''', C-4'''), 132.7 (C-4'''); EIMS m/z, 434 (M⁺). Anal. Calcd. For C₂₀H₁₉ClN₂O₅S: C, 55.84; H, 4.40; Cl, 8.17; N, 6.64; S, 7.39. Found: C, 55.89; H, 4.30; Cl, 8.23; N, 6.60; S, 7.87.

1-(β-D-Ribofuranosyl)-5-(4-chlorophenyl)-3-(4-nitrophenyl)-2-thioxoimidazolidin-4-one (4k)

Yield 79 % (MWI), 32% (Thermal); m.p. 145-146 °C; ¹H NMR (400 MHz, DMSO-d₆), δ 4.80 (s, 1H, H-5), 7.00 (dd, 2H, J_{2'',6''}, 5.3 Hz, H-2'', H_{6''}), 7.15 (dd, 2H, J_{3'',5''}, 5.3

Hz, H-3'', H-5''), 3.68-3.92 (m, 4H, H-2', H-3', 2xH-5'), 3.90-4.10 (m, 1H, H-4'), 4.96 (d, 1H, J_{1,2}, 4.2 Hz, H-1), 2.00-2.32 (br s, 3H, 3xOH, exchangeable with D₂O), 7.22 (dd, 2H, J_{2'',6''}, 5.6 Hz, H-2'', H_{6''}), 8.31 (dd, 2H, J_{3'',5''}, 5.6 Hz, H-3'', H-5'') ¹³C NMR (100MHz, DMSO-d₆) δ 177 (C-2), 168.2 (C-4), 65.8 (C-5), 84.5 (C-1'), 76.0 (C-2'), 70.6 (C-3'), 76.3 (C-4'), 61.9 (C-5'), 147.8 (C-1''), 122.5 (C-2'', C-6''), 123.6 (C-3'', C-5''), 145.4 (C-4''), 134.0 (C-1'''), 131.2 (C-2''', C-6'''), 129.4 (C-3''', C-5'''), 132.7 (C-4'''); EIMS m/z, 479 (M⁺). Anal. Calcd. For C₂₀H₁₈BrN₃O₇S: C, 50.84; H, 3.40; Cl, 8.17; N, 8.74; S, 6.69. Found: C, 50.89; H, 3.70; Cl, 8.23; N, 8.60; S, 6.87.

1-(β-D-Ribofuranosyl) 5-(4-chlorophenyl)-3-(4-bromophenyl)-2-thioxoimidazolidin-4-one (4l)

Yield 80 % (MWI), 33% (Thermal); m.p. 151-152 °C; ¹H NMR (400 MHz, DMSO-d₆), δ 4.85 (s, 1H, H-5), 7.00 (dd, 2H, J_{2'',6''}, 5.3 Hz, H-2'', H_{6''}), 7.15 (dd, 2H, J_{3'',5''}, 5.3 Hz, H-3'', H-5'') 3.67-3.92 (m, 4H, H-2', H-3', 2xH-5'), 3.93-4.10 (m, 1H, H-4'), 4.96 (d, 1H, J_{1,2}, 4.2 Hz, H-1), 2.10-2.32 (br s, 3H, 3xOH, exchangeable with D₂O), 7.53 (dd, 2H, J_{2'',6''}, 5.6 Hz, H-2'', H_{6''}), 7.41 (dd, 2H, J_{3'',5''}, 5.6 Hz, H-3'', H-5''); ¹³C NMR (100MHz, DMSO-d₆) δ 177 (C-2), 168.2 (C-4), 65.8 (C-5), 84.5 (C-1'), 76.0 (C-2'), 70.6 (C-3'), 76.3 (C-4'), 61.9 (C-5'), 139.8 (C-1''), 123.5 (C-2'', C-6''), 133.6 (C-3'', C-5''), 120.4 (C-4''), 134.0 (C-1'''), 131.4 (C-2''', C-6'''), 129.0 (C-3''', C-5'''), 132.7 (C-4'''); EIMS m/z, 513 (M⁺). Anal. Calcd. For C₂₀H₁₈ClBrN₂O₅S: C, 46.84; H, 3.40; Cl, 8.17; N, 5.64; S, 6.39. Found: C, 45.89; H, 3.70; Cl, 8.23; N, 5.60; S, 6.87.

RESULTS AND DISCUSSION

After preliminary experimentation, it was found that the three component synthesis (Scheme 1) was successful with montmorillonite K-10 clay supported intimate mixture of ribosyl/deoxyribosyl thioureas, α-halo acid and aryl amine under solvent-free microwave irradiation (MW) at 600 W for times specified in Table 1. Isolation and purification by recrystallised from ethanol afforded 2-thioxoimidazole-4-one N-nucleosides (4a-l) in excellent yields (Table 1).

Other mineral supports viz. silica gel, neutral or basic alumina were far less effective resulting in either no reaction (in case of basic alumina) or relatively very low yields (15-30%) of 4 (in case of silica gel and neutral alumina). That the first step in the involves the conversion of ribosyl/deoxyribosyl thiourea 1 under reaction conditions into corresponding isothiocyanate intermediate I (Scheme 1) was supported by trapping by p-tolyl thiourea derivatives.

In order to compare, the final temperature was measured by was measured by immersing a glass thermometer into the reaction mixture immediately after MW irradiation and was found to be <88°C. The reactions were also carried out using a thermostated oil-bath at the same temperature (88°C) as for the MW activated method but for a longer period of time (Table I). It was found that MW method has improved the yields significantly. This



observation can be rationalized on the basis of the formation of dipolar activated complex III from uncharged adduct in these reactions and greater stabilization of the more dipolar activated complex by dipole-dipole interaction with electric field of the microwaves as compared to the less polar adduct which may reduce the activation energy $[G^\ddagger]$ resulting in the rate enhancement.

CONCLUSION

In conclusion we have developed a novel mineral supported green, facile, high yielding synthetic protocol for the preparation of potentially pharmaceutically useful 2-thioxoimidazole-4-one N-nucleosides starting from readily available simple substrate under solvent-free microwave irradiation conditions. This expeditious chemical transformation led to synthetically readily maniplable product and may find application in library synthesis of such aglycon modified N-nucleosides.

Acknowledgement: Authors sincerely thank the UGC, New Delhi for financial support and SAIF, CDRI, Lucknow for providing microanalysis and spectra.

REFERENCES

1. Agh-Atabay, N.M.; Dulger, B.;Gucin, F. [μ -2-(2,4-difluorophenyl)-1,3-bis(1,2,4-triazol-1-yl) propan-2-olato]- μ_2 - N^2,O,O,N^2 -bis[(acetato- μ_2 - O,O)nickel(II)], *J. Med. Chem.* 38, 2003, 875-881.
2. Franchetti, P.; Marchetti, L.; Yalowitz, J.A.; Jayaram, H.N.; Goldstein, B.M.; Grifantini, M. Bioorg., Novel pyrrole C-nucleosides by nitrogen extrusion from pyridazine C-nucleosides, *Med. Chem. Lett.*, 11, 2001, 67-69.
3. Ucucu U, Karaburun N G, and Isikdag I, Synthesis and analgesic activity of some 1-benzyl-2-substituted-4,5-diphenyl-1H-imidazole derivatives, *Farmaco.*, 56, 2001, 285-290.
4. Yesilada A, Koyunoglu S, Saygili N, Kupeli E, Yesilada E, Bedir E. and Khan, I.,Synthesis, anti-inflammatory and analgesic activity screening of some new 4-(3H)-quinazolinone derivatives, *Arch. Pharm. Pharm. Med. Chem.*, 337, 2004, 96-104.
5. Sengupta A. K, and Bhattacharya T,Synthesis and antimicrobial activity of some substituted 2-phenyl-3-arylquinazol-4-ones, *J. Indian Chem.* 60, 1983*Soc.*, 373-376
6. Navidpour L, Shadnia H, Shafaroodi H, Amini M., Dehpour A. R., and Shafiee, A.,Design, synthesis and biological evaluation of substituted 2-alkylthio-1,5-diarylimidazoles as selective COX-2 inhibitors, *Bioorg. Med. Chem.*, 15, 2007, 1976-1982.
7. Quattara L, Debaert M, and Cavier R, Synthesis and antiparasitic activity of new nitro-5-imidazole derivatives, *Farmaco. (sci)*, 42(6), 1987, 449-456.
8. Dutta S, Mariappan G, Roy S, and Verma M, Anthelmintic activity of some 2-substituted 4, 5-diphenyl imidazole, *Indian Drugs.* 46(7), 2009, 50-53.
9. Yadav L D S, Singh S & Singh A, Novel clay-catalysed cyclisation of salicylaldehyde semicarbazones to 2H-benz[e]-1,3-oxazin-2-ones under microwave irradiation *Tetrahedron Lett*, 43, 2002,8551.
10. Mogilaiah K, Kavitha S and Babu H R, Microwave assisted s addition- elimination reaction of 3 -phenylimino-2-indolinone with 2-hydarzino-3-(p-cholrophenyl)-1,8-naphthyridine- A simple and facile synthesis of 3-(3- p-cholrophenyl-1,8-naphthyridine-2-yl-hydrzino_-2-indolinone, *Indian J Chem*, 42B, 2003, 1750.
11. Rosario, A.; Andres, J. I.; Lopez, M.T.; Heras, F.G.; Herranz, R.; Alacorn, B.; Carrasco, L. J. *Med. Chem.* 28, 1985, 834-838.
12. Mc Gee, D.P.C.; Martin, J.C.; Smee, D. F.; Verheyden, J.P.H.; Synthesis and Antiviral Activity of the 3-Deaza Analogue of 9-((1, 3-Dihydroxy-2-propoxy)Methyl)Guanine, *Nucleosides and Nucleotides.*, 9, 1999, 815-826.
13. Ugi, J.; Domling, A.; Multicomponent reactions in organic chemistry, *Endeavour*, 18, 1994, 115-122.
14. Krous, G. A.; Nagy, J. O.; Generation and cycloaddition of heteroatom-substituted 2-azaallyl anions with alkenes and alkynes. Synthesis of 1-pyrrolines and pyrroles, *Tetrahedron Lett*, 41, 1985, 3537-3545.
15. Heck, S.; Domling, A.; A Versatile Multi-Component One-Pot Thiazole Synthesis, *Synlett*, 2000, 424-426.
16. Posner, G. H.; Titanium-Promoted Stereoselective Synthesis of Hydroindolones from *p*-Quinamines by Domino Conjugate Additions, *Chem. Rev.*, 86, 1986, 831-834.
17. Verma, R. S., Three-component coupling strategy for the expeditious synthesis of novel 4-aminobenzoxazinone, N-nucleosides *Green Chem*, 1, 1999, 43-45.
18. Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J., The impact of microwave-assisted organic chemistry on drug discovery, *Tetrahedron*, 57, 2001, 9225-9283.
19. Siddiqui, I. R.; Singh, P. K.; Singh, J.; Singh, J.; Three-component solvent-free diastereoselective formation of oxo-thiazolidinylthiazoles under microwave irradiation, *Journal of Chemical Research*, 8, 2004, 554-555.
20. Chattree, A.; Siddiqui, I. R.; Waseem, M.A.; A Novel and Environmentally Benign synthesis of Imidazolidinone derivatives, *Journal of Applicable Chemistry*, 2, 2013, 171-174.
21. Siddiqui, I. R.; Singh, P. K.; Singh, J.; Singh, J.; Facile synthesis and fungicidal activity of novel 4,4'-bis[2''-(5'''-substituted rhodanin-3'''-yl)thiazol-4'' -yl]bibenzyls, *Indian J. Chem.*, 44B, 2005, 2102-2106.
22. Siddiqui, I. R.; Singh, P. K.; Srivastva, V.; Singh, Novel clay-catalysed expeditious cyclization to bis-benzothiazepine, *Indian J. Chem.* 44b, 2005, 2178-2182.
24. Siddiqui, I.R.; Siddique,S.A.; Srivastava, V.; Singh, P. K.; Singh, J.; A novel anthranilic acid based multi-component strategy for expeditious synthesis of 4(3H)-quinazolinone N-nucleosides, *ARKIVOC*, 12, 2008, 277-285.
23. Siddiqui, I. R.; Singh, P. K.; Srivastva, V.; Singh, Facile synthesis of acyclic analogues of carbocyclic nucleoside as potential anti-HIV pro-drug, *Indian J. Chem.*, 49B, 2010, 512-520.
25. Brown, F. C.; Bradsher, C. K.; Morgan, E.C.; Tetenbaum, M.; Wilder, Aqueous microwave-assisted one-pot synthesis of N-substituted rhodanines *P. J. Am. Chem Soc.*, 78, 1956, 384-388.

Source of Support: Nil, Conflict of Interest: None.

