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Synthesis of Pyrimidine-Annelated Heterocycles: Regioselective Heterocyclization of 5-(Cyclohex-2-enyl)-1,3-dimethyl-6-hydroxyuracil [1]

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Summary. 5-(Cyclohex-2-enyl)-1,3-dimethyl-6-hydroxyuracil undergoes regioselective heterocyclization to afford fused tricyclic heterocycles upon treatment with bromine and *m-CPBA*. However, the same substrate furnished bridged tricyclic heterocycles when treated with N-iodosuccinimide and conc. H_2SO_4 and a mixture of bridged tricyclic heterocycles and fused tricyclic heterocycles when treated with hexamine hydrotribromide or pyridine hydrotribromide.

Keywords. Pyridine hydrotribromide; N-Iodosuccinimide; *m*-Chloroperoxybenzoic acid; Heterocycles; Cyclization.

Introduction

5-Substituted uracils and their nucleosides are of biological significance because of their use in the chemotherapy of cancer [2]. We have reported on the synthesis of a number of pyrimidine-annelated heterocycles fused at positions 5 and 6 of uracil. In continuation of this work, we tackled the problem of the regioselective synthesis of a number of hitherto unreported pyrimidine-annelated heterocycles starting from 5-(cyclohex-2-enyl)-1,3-dimethyl-6-hydroxyuracil (**3**).

Results and Discussion

Aiming at the synthesis of heterocycles derived from the substrate used in the present study to explore the synthesis of pyrimidine-annelated heterocycles, 5-(cyclohex-2-enyl)-1,3-dimethyl-6-hydroxy uracil (**3**) was synthesized by C-alkylation of 1,3-dimethyl-6-hydroxy uracil (**1**) with 3-bromocyclohex-2-ene (**2**) in refluxing acetone in the presence of anhydrous potassium carbonate (Scheme 1). We considered five different routes for this purpose. Recently, we have reported [3] the heterocyclization of 6-(cyclohex-2-enyl)-1,3-dimethyl-5-hydroxy uracil by

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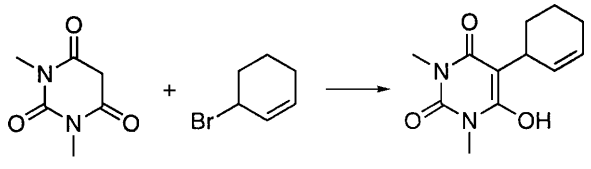
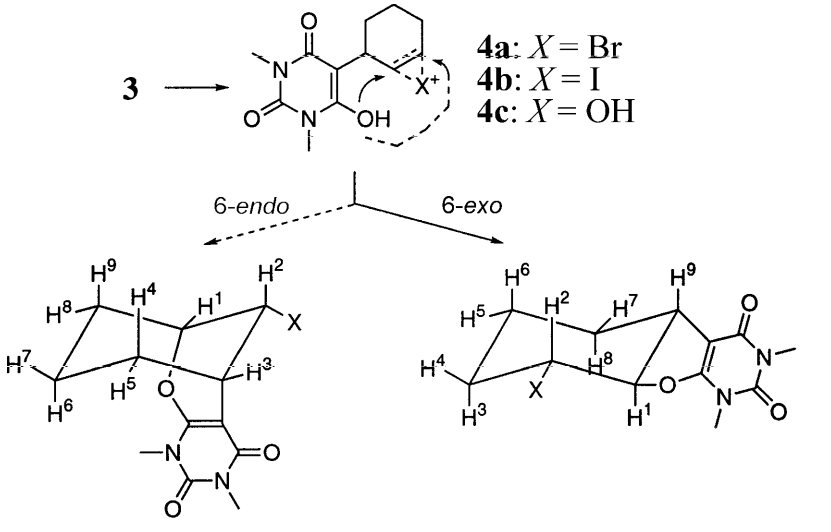


1 **2** **3**

Scheme 1

treatment with elemental bromine [4]. The heterocyclization of 6-(cyclohex-2-enyl)-1,3-dimethyl-5-N-methylamino uracil was also achieved with elemental bromine. **3** was therefore treated with bromine in chloroform solution, and structure **5a** was assigned to the obtained product from its elemental analysis and spectroscopic data. The IR spectrum of **5a** showed a band at 1640 cm^{-1} due to the carbonyl group. The ^1H NMR spectrum of **5a** revealed a broad singlet at 3.21 ppm due to H-9, a broad singlet at 3.91 ppm due to H-1, and a broad singlet at 4.74 ppm due to H-2. The mass spectrum of **5a** had its molecular ion peak at $m/z = 314$, 316. This product was unstable when heated with Pd/C in diphenyl ether, and no tractable product was obtained (Scheme 2).

We have recently reported the use of pyridine hydrobromide perbromide [5–9] and hexamine hydrobromide perbromide [10] for this type of heterocyclization. Thus, **3** was also treated with one equivalent of pyridine hydrobromide perbromide and hexamine hydrobromide perbromide to give a mixture of **5a** (20%) and another new product (60%) melting at 122°C. This new compound was characterized as the bridged tricyclic bromo compound **7a** from its elemental analysis and spectroscopic data. The IR spectrum of **7a** showed a band at 1660 cm^{-1} due to the



3 → **4a**: X = Br; **4b**: X = I; **4c**: X = OH

6-*endo* 6-*exo*

7a: X = Br
7b: X = I
7d: X = OH

5a: X = Br
6: X = 3-$ClC_6H_3CO_2$

Scheme 2

carbonyl group. The ^{1}H NMR spectrum of **7a** revealed a quartet at 3.60 ppm ($J = 6$ Hz) due to H-3, a doublet of a double doublet at 4.23 ppm ($J = 4.6$, 6, 10 Hz) due to H-1, and a triplet at 5.02 ppm ($J = 6$ Hz) due to H-2. The mass spectrum of **7a** exhibited a molecular ion peak at $m/z = 314$, 316. Compound **7a** remained unaffected when treated with alcoholic KOH at 40°C for 2 h or heated with Pd/C in diphenyl ether, thus indicating its bridged tricyclic structure.

We have also recently studied the N-iodosuccinimide mediated cyclization of *ortho*-(cyclohex-2-enyl) phenols [11]. Accordingly, we treated **3** with N-iodosuccinimide in acetonitrile to give a white crystalline solid (85%) melting at 147°C. This compound was characterized as the bridged tricyclic product **7b** from its elemental analysis and spectroscopic data. The IR spectrum of **7b** showed a band at 1650 cm^{-1} due to the carbonyl group. The ^{1}H NMR spectrum of **7b** featured a quartet at 3.54 ppm ($J = 6$ Hz) due to H-3, a doublet of a double doublet at 4.36 ppm ($J = 4.6$, 6, 10 Hz) due to H-1, and a triplet at 5.13 ppm ($J = 6$ Hz) due to H-2. Its molecular ion peak was found at $m/z = 362$. **7b** remained unchanged when treated with alcoholic KOH at 25°C for 2 h. The formation of products **5a**, **7a**, and **7b** from **3** may be explained *via* the formation of the halonium ion **4a**,**b** which then undergoes 5-*exo*-trig to give **5a** and 6-*endo*-cyclization to give **7a** and **7b** (Scheme 2).

We next turned our attention to epoxidative cyclization which has been used for the synthesis of pyrans [12–14]. The substrate **3** was treated with one equivalent of *m*-chloroperoxybenzoic acid in dry (thiophene-free) benzene at reflux to give a white crystalline solid (85%) melting at 198°C. This was characterized as the benzoate **6** from its elemental analysis and spectroscopic data, including its mass spectrum which conclusively established the incorporation of the *m*-chlorobenzoate function. This was also corroborated by 2D-NMR, ^{13}C, and DEPT experiments (Scheme 2).

Lastly, cold conc. H_2SO_4 has been widely used for the cyclization of *ortho*-allyl phenols [15–17]. **3** was treated with conc. H_2SO_4 at 0–5°C to give a white solid (60%) of m.p. 92°C. This was characterized as the bridged tricyclic product **7d** from its elemental analysis and spectroscopic data. The IR spectrum of **7d** showed a band at 1640 cm^{-1} due to the carbonyl group. The ^{1}H NMR spectrum of **7d** revealed a broad singlet at 3.17 ppm due to H-4 and a broad singlet at 4.85 due to H-1. The mass spectrum of **7d** had its molecular ion peak at $m/z = 236$ (Scheme 2).

In conclusion, the heterocyclization of **3** was found to be regioselective with elemental bromine, N-iodosuccinimide, *m*-chloroperoxybenzoic acid, and cold conc. H_2SO_4 to give the heterocycles **5a**, **7b**, **6**, and **7d**, whereas the reaction of **3** with pyridine hydrobromide perbromide or hexamine hydrobromide perbromide is not regioselective, giving a mixture of both fused tricyclic heterocycle **5a** and bridged tricyclic heterocycle **7a**.

Experimental

Melting points were measured on a sulfuric acid bath and are uncorrected. UV absorption spectra were recorded in EtOH on a Hitachi 200-20 spectrophotometer. IR spectra were run on KBr disks on a Perkin-Elmer 1330 apparatus. ^{1}H NMR spectra were determined for solutions in $CDCl_3$ with *TMS* as internal standard on a 300 MHz Bruker NMR spectrometer. Elemental analyses were found to agree with the calculated values. Mass spectra were determined at RSIC (CDRI) Lucknow on a JEOL D-300

(El) instrument. 2D-NMR and ^{13}C (CPD, DEPT) experiments were carried out in $CDCl_3$ on a Bruker 400 MHz spectrometer. Silica gel (60–120 mesh) from Spectrochem, India, was used for chromatographic separations. Petroleum ether refers to the fraction boiling between 60°C and 80°C.

5-(Cyclohex-2-enyl)-1,3-dimethyl-6-hydroxyuracil (**3**; $C_{12}H_{16}N_2O_3$)

A mixture of 1.56 g 1,3-dimethylbarbituric acid (10 mmol), 1.6 g 3-bromocyclohexene (10 mmol), and 3 g anhydrous potassium carbonate in 100 cm^3 dry acetone was refluxed for 6 h. The reaction mixture was cooled, filtered, and the solvent was removed. The residue was extracted with 3×25 cm^3 $CHCl_3$, the organic layer was separated and washed with 2×25 cm^3 H_2O, dried (Na_2SO_4), and the solvent was evaporated. Purification of the crude product by column chromatography (benzene:petroleum ether = 1:1) on silica gel gave **3**.

Yield: 60% (1.41 g); white solid; m.p.: 90°C; ^1H NMR ($CDCl_3$, δ, 300 MHz): 1.47–1.98 (m, 6H), 3.29 (s, 3H, N–Me), 3.30 (s, 3H, N–Me), 3.46–3.47 (m, 1H), 5.52–5.56 (m, 1H), 5.79–5.86 (m, 1H) ppm; IR (KBr): $\nu = 1120$, 1480, 1650, 2970 cm^{-1}; UV/Vis (EtOH): $\lambda_{max} = 225$, 270 nm; MS: $m/z = 236$ (M^+).

8-Bromo-1,3-dimethyl hexahydrobenzofuro[2,3-d]pyrimidine-2,4-dione (**5a**; $C_{12}H_{15}BrN_2O_3$)

Elemental bromine (0.25 g, 1.5 mmol) in 20 cm^3 $CHCl_3$ was added slowly to a well-stirred solution of 0.35 g **3** (1.5 mmol) in 5 cm^3 $CHCl_3$ at 0–5°C. Stirring was continued for additional 6 h. The mixture was then extracted with $CHCl_3$, and the $CHCl_3$ solution was washed with 2×10 cm^3 5% Na_2CO_3 solution, 2×30 cm^3 H_2O, and dried (Na_2SO_4). Evaporation of $CHCl_3$ left a gummy residue which was purified by column chromatography on silica gel. Compound **5a** was obtained when the column was eluted with benzene:ethylacetate = 1:1 and recrystallized from $CHCl_3$/petroleum ether.

Yield: 50% (0.17 g); white solid; m.p.: 176°C; ^1H NMR ($CDCl_3$, δ, 300 MHz): 1.14–2.17 (m, H-3,4,5,6,7,8), 3.21 (br s, H-9), 3.31 (s, 3H, N–CH_3), 3.38 (s, 3H, N–CH_3), 3.91 (br s, H-1), 4.74 (br s, H-2) ppm; IR (KBr): $\nu = 1200$, 1490, 1640, 2970 cm^{-1}; UV/Vis (EtOH): $\lambda_{max} = 217$, 285 nm; MS: $m/z = 314$, 316 (M^+).

8-Bromo-1,3-dimethyl-hexahydro-bicyclo[3.3.1]benzopyrano [2,3-d]pyrimidine-2,4-dione (**7a**; $C_{12}H_{15}BrN_2O_3$)

A solution of 0.35 g **3** (1.5 mmol) in 100 cm^3 $CHCl_3$ was stirred with 0.45 g hydrobromide perbromide (1.5 mmol) or 0.58 g hexamethylene tetramine hydrotribromide (1.5 mmol) at 0–5°C for 1 h. The $CHCl_3$ solution was washed with 2×25 cm^3 5% Na_2CO_3 solution, 2×25 cm^3 H_2O, and dried (Na_2SO_4). Evaporation of $CHCl_3$ left a gummy residue which was purified by column chromatography on silica gel. Compound **7a** was obtained when the column was eluted with benzene, and **5a** (20%) was obtained when the column was eluted with benzene:ethylacetate = 1:1. **7a** was recrystallized from $CHCl_3$/petroleum ether.

Yield: 60% (0.28 g); white solid; m.p.: 122°C; ^1H NMR ($CDCl_3$, δ, 300 MHz): 1.58–2.17 (m, H-4,5,6,7,8,9), 3.30 (s, 3H, N–CH_3), 3.37 (s, 3H, N–CH_3), 3.60 (q, H-3, $J = 6$ Hz), 4.23 (ddd, H-1, $J = 4.6$, 6, 10 Hz), 5.02 (t, H-2, $J = 6$ Hz) ppm; IR (KBr): $\nu = 1110$, 1460, 1660, 2980 cm^{-1}; UV/Vis (EtOH): $\lambda_{max} = 217$, 265 nm; MS: $m/z = 314$, 316 (M^+).

8-Iodo-1,3-dimethyl-hexahydro-bicyclo[3.3.1]benzopyrano[2,3-d] pyrimidine-2,4-dione (**7b**; $C_{12}H_{15}IN_2O_3$)

A solution of 0.2 g **3** (1 mmol) in 50 cm^3 dry CH_3CN was stirred at 0–5°C with 0.23 g N-iodosuccinimide (1 mmol) for 1 h. The solvent was distilled off, and the residue was dissolved in 50 cm^3 $CHCl_3$.

The $CHCl_3$ solution was washed with 20 cm^3 saturated Na_2SO_3 solution, 2×25 cm^3 H_2O, and dried (Na_2SO_4). Removal of $CHCl_3$ gave a gummy residue which was purified by column chromatography on silica gel. Elution of the column with benzene:ethylacetate = 9:1 gave **7b** which was recrystallized from $CHCl_3$/petroleum ether.

Yield: 85% (0.26 g); white solid; m.p.: 147°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.56–2.20 (m, H-4,5,6,7,8,9), 3.30 (s, 3H, N–CH_3), 3.36 (s, 3H, N–CH_3), 3.54 (q, H-3, $J = 6$ Hz), 4.36 (ddd, H-1, $J = 4.6$, 6, 10 Hz), 5.13 (t, H-2, $J = 6$ Hz) ppm; IR (KBr): $\nu = 1180$, 1490, 1650, 2960 cm^{-1}; UV/Vis (EtOH): $\lambda_{max} = 218$, 264 nm; MS: $m/z = 362$ (M^+).

8-(3′-Chlorobenzoyloxy)-1,3-dimethyl-hexahydrobenzofuro[2,3-d] pyrimidine-2,4-dione (**6**; $C_{19}H_{19}ClN_2O_5$)

m-Chloroperbenzoic acid (50%; 0.51 g, 1.5 mmol) was added to 0.35 g **3** (1.5 mmol) in 30 cm^3 thiophene-free dry benzene, and the mixture was refluxed for 12 h. The reaction mixture was extracted with 2×25 cm^3 benzene, washed with 2×30 cm^3 $NaHCO_3$ solution and 2×25 cm^3 H_2O, and dried (Na_2SO_4). The solvent was removed, and the residue was subjected to column chromatography on silica gel. **6** was obtained when the column was eluted with ethylacetate:benzene = 1:3.

Yield: 85% (0.49 g); white solid; m.p.: 198°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.62–1.76 (m, 6H), 2.68 (m, H–C(4b)), 3.36 (s, 3H, N–CH_3), 3.38 (s, 3H, N–CH_3), 3.99 (br s, H–C(8)), 4.06 (br s, H–C(8a)), 7.43 (t, 1H, $J = 8$ Hz), 7.59–7.61 (m, 1H), 7.94 (d, 1H, $J = 8$ Hz), 8.01 (t, 1H, $J = 1.6$ Hz) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 29.54 (C-1), 168.48 (C-2), 29.60 (C-3), 165.25 (C-4), 19.76, 20.34, 27.22 (C-5, C-6, C-7), 70.0 (C-8a), 44.91 (C-4b), 80.79 (C-9a), 150.9 (C-4a), 167.6 (C-ester carbonyl), 129.87 (C-1′), 130.50 (C-2′), 135.26 (C-3′), 134.75 (C-4′), 130.41 (C-5′), 128.73 (C-6′) ppm; IR (KBr): $\nu = 1170$, 1450, 1660, 1730, 2960, 3020 cm^{-1}; UV/Vis (EtOH): $\lambda_{max} = 234$ nm; MS: $m/z = 390$, 392 (M^+).

1,3-Dimethyl hexahydro bicyclo[3.3.1]benzopyrano[2,3-d] pyrimidine-2,4-dione (**7d**; $C_{12}H_{16}N_2O_3$)

0.35 g of **3** (1.5 mmol) were added in portions to 2 cm^3 conc. H_2SO_4 at 0–5°C, and the mixture was stirred for 2 h at this temperature. The solution was then poured into crushed ice and extracted with 3×25 cm^3 $CHCl_3$. The organic layer was washed with 3×10 cm^3 5% Na_2CO_3 solution, 3×20 cm^3 H_2O, and dried (Na_2SO_4). Evaporation of $CHCl_3$ gave a gummy mass which was purified by column chromatography on silica gel. Elution of the column with benzene:ethylacetate = 3:1 gave **7d** which was recrystallized from $CHCl_3$/petroleum ether.

Yield: 60% (0.21 g); white solid; m.p.: 92°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.37–2.11 (m, H-2,3,5,6,7,8,9,10), 3.17 (br s, H-4), 3.33 (s, 3H, N–CH_3), 3.36 (s, 3H, N–CH_3), 4.85 (br s, H-1) ppm; IR (KBr): $\nu = 1190$, 1470, 1640, 2970 cm^{-1}; UV/Vis (EtOH): $\lambda_{max} = 217$, 264 nm; MS: $m/z =$ 236 (M^+).

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