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Synthesis of 5-(2-Hydroxybenzoyl)-1,3-Disubstituted Uracils

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Abstract: A new synthesis of novel nucleoside analogues is reported. These 5-(2-hydroxybenzoyl)-1,3-disubstituted uracils have been prepared by the coupling of chromone-3-carboxylic acid with carbodiimides, leading to 3-chromone-*N*-acylureas, which underwent organocatalyzed N-cyclization and chromone ring opening. In the case of ditolylcarbodiimide, the corresponding uracil was obtained by a one-pot, uncatalyzed reaction with chromone-3-carboxylic acid.

Key words: chromone derivatives, nucleoside analogues, uracil analogues, organic synthesis, 2D NMR

One of the four nucleobases in ribonucleic acid is uracil (U), a naturally occurring pyrimidine derivative that is part of several pharmacologically important molecules (Figure 1). A large and growing body of literature has documented investigations on diverse multistage protocols to prepare 1,3-disubstituted uracils emphasizing their potent anti-HIV activity.[1] The uracil heteronucleus has found further biological applications, and compounds containing this moiety display antiviral,[2] anticancer,[3] and antimicrobial[4] activities, cytotoxicity to cancer cells,[5] and various enzyme inhibitory activities, namely for human deoxyuridine triphosphatase, thymidine phosphorylase and poly(ADP-ribose)polymerase-1.[6] Moreover, uracil derivatives are increasingly used in cancer treatment, for instance 5-fluorouracil (5-FLU) is an approved drug and one of the most potent thymidylate synthase inhibitors (GI_{50} = 17.1 μM)[7] (Figure 1).

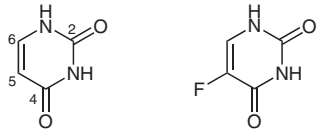

Figure 1 Structure of uracil (U) and 5-fluorouracil (5-FLU)

Although extensive research has been carried out on the synthesis of uracil derivatives, this has led to only a few simple and convenient synthetic routes. Recent literature reports reveal several multistage and/or chemical consuming methods to build the uracil nucleus and its polysubstituted derivatives.[8] A solid-phase condensation of resin-bound unsymmetrically substituted ureas with diketene in acetic acid gives 6-methyl-1,3-disubstituted uracils in good to excellent yields.[8a] The Baylis–Hillman reaction has been applied in the synthesis of substituted uracils through a multistep procedure.[8c] Interesting results were achieved by the microwave activation of metal carbene complexes, in particular, in the synthesis of uracil derivatives, through the reaction of alkynyl alkoxy carbene complexes with ureas.[8b] The synthesis of 1,3-disubstituted uracils was also accomplished in good yields by the amino-selenenylation of α,β-unsaturated esters and cyclization with isocyanates, followed by oxidation–elimination of the phenylseleno group.[8d]

Because uracil derivatives exhibit a wide range of biological potential in drug discovery and development, developing reliable synthetic routes for their synthesis remains of interest. In the present investigation, we describe a simple synthetic access to 5-(hydroxybenzoyl)-1,3-disubstituted uracil compounds **4a**–**c** through ring transformation of chromone-3-carboxylic acid (**1**) upon reaction with carbodiimides **2a**–**c**. This greener approach avoids multistep procedures and obviates laborious purification steps resulting from multicomponent approaches.

Uncatalyzed nucleophilic addition of **1** to the C=N double bond of carbodiimide **2a** and **2b** followed by an O→N acyl shift, led to the isolation of 3-chromone-*N*-acylureas **3a** and **3b** (Scheme 1). The reaction proceeds upon heating to reflux in chloroform for 30 min, to give compounds **3a** and **3b** in 74 and 80% yields, respectively, after recrystallization from the appropriate solvent.[9] This first rapid step is then followed by N-cyclization and concomitant chromone ring opening, under organobase-catalysis using 4-pyrrolidinopyridine (4-PPy), leading to the uracil-based products **4a** and **4b** (Scheme 1 and Scheme 2). To simplify the synthetic route, this second step was realized in situ by adding 4-PPy directly to the first reaction mixture to transform **3a** and **3b** into uracil derivatives **4a** (64%) and **4b** (51%), respectively, without their isolation as intermediates.[10] Thus, the whole in situ two-step synthetic approach consists of a ring transformation of chromone-3-carboxylic acid **1** into uracil **4a** and **4b** (Scheme 1). This procedure could be shortened to a one-pot, uncatalyzed reaction only when reacting the tolyl-substituted carbodiimide **2c** with acid **1**, leading to direct production of the desired uracil derivative **4c** under environmentally friendly conditions, without the formation of any 3-chromone-*N*-acylurea or other intermediates. In this case, the reaction was accomplished by heating to reflux in chloroform for 30 min, affording compound **4c** in 77% yield after recrystallization from ethanol (Scheme 1).[11]

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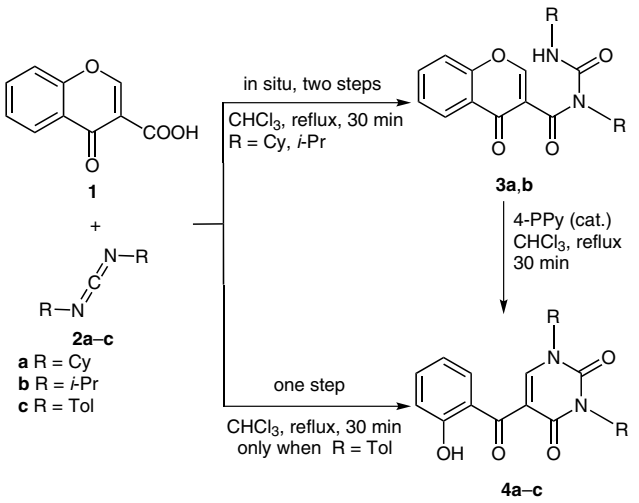

Scheme 1 Synthesis of 5-(2-hydroxybenzoyl)-1,3-disubstituted uracils **4a–c**

All compounds were characterized by extensive NMR spectroscopic analysis (^{1}H, ^{13}C, HSQC and HMBC spectra). These data allowed a distinction between the chromone (**3a** and **3b**) and the uracil (**4a** and **4b**) rings. The vinylic protons (H-2)/carbons (C-2) of chromones **3a** and **3b** appear at δ = 8.07–8.08/154.2 ppm, whereas those of H-6/C-6 of uracils **4a**, **4b** and **4c** appear at δ = 7.69–7.94/142.5–147.4 ppm, due to the influence of the neighboring electronegative oxygen or nitrogen. Other important features that may help to differentiate between these two types of compounds are the resonances of the NH protons of compounds **3a** and **3b**, assigned as a broad signal or doublet (due to the coupling with the cyclohexyl tertiary proton) at δ = 6.49–6.74 ppm; and the OH protons of compounds **4a–c**, appearing as a singlet at δ = 11.71–11.79 ppm, due to strong deshielding resulting from an intramolecular hydrogen bond established with the carbonyl group.

In summary, we have developed a novel and facile synthetic route to 5-(2-hydroxybenzoyl)-1,3-disubstituted uracil derivatives. The protocol involves, in the first step, coupling of commercially available chromone-3-carboxylic acid and carbodiimide derivatives to produce 3-chromone-*N*-acylureas.[12] The second step involves ring transformation of chromone into uracil under organobase-catalyzed reaction conditions. The whole two-step reaction could be performed in a one-pot procedure without isolation of 3-chromone-*N*-acylureas as intermediates. The reaction of chromone-3-carboxylic acid with ditolylcarbodiimide affords the desired uracil derivative in a green, non-catalyzed synthetic route.

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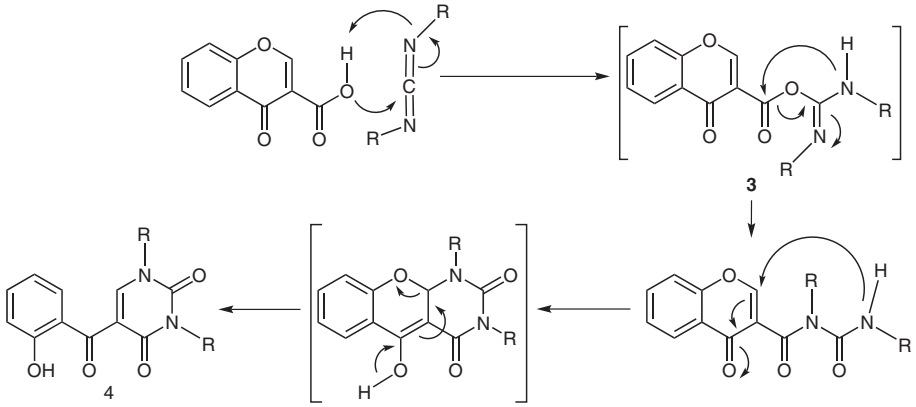

Scheme 2 Proposed mechanism for the formation of 5-(2-hydroxybenzoyl)-1,3-disubstituted uracils **4a–c**

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(9) **Synthesis of *N*,*N*-Disubstituted (Carbamoyl)-4-oxo-4*H*-chromene-3-carboxamide 3a and 3b:** Chromone-3-carboxylic acid **1** (1 g, 5.26 mmol) was added to the appropriate carbodiimide **2** (5.26 mmol, 1 equiv) in $CHCl_3$ (20 mL) and the reaction mixture was heated to reflux for 30 min. The solvent was evaporated to dryness and the resulting resinous solid was recrystallized from EtOH to afford compound **3a**. In the case of **3b**, the recrystallization solvent was a mixture of light petroleum and EtOAc (5:1).

***N*-Cyclohexyl-*N*-(cyclohexylcarbamoyl)-4-oxo-4*H*-chromene-3-carboxamide (3a):** Yield: 1.550 g (74%); white solid; mp 185 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87–2.01 (m, 20 H, CH_2-cyclohexyl), 3.40–3.53 (m, 1 H, H-1‴), 4.19 (tt, *J* = 11.7, 3.8 Hz, 1 H, H-1″), 6.49 (d, *J* = 7.2 Hz, 1 H, 4′-NH), 7.42–7.53 (m, 2 H, H-6, H-8), 7.73 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1 H, H-7), 8.07 (s, 1 H, H-2), 8.22 (dd, *J* = 8.0, 1.7 Hz, 1 H, H-5). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.4, 25.19, 25.26, 26.0, 30.7 and 32.1 (CH_2-cyclohexyl), 49.7 (C-1‴), 55.7 (C-1″), 118.3 (C-8), 123.9 (C-3), 124.1 (C-10), 125.9 (C-6, C-5), 134.5 (C-7), 153.2 (C-3′), 154.2 (C-2), 156.1 (C-9), 162.3 (C-1′), 175.4 (C-4). MS (ESI$^+$): *m*/*z* = 419 [$C_{23}H_{28}N_2O_4$ + Na]$^+$. Anal. Calcd for C, 69.67; H, 7.12; N, 7.07. Found: C, 69.69; H, 7.14; N, 7.07.

***N*-Isopropyl-*N*-(isopropylcarbamoyl)-4-oxo-4*H*-chromene-3-carboxamide (3b):** Yield: 1.324 g (80%); white solid; mp 137–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.6 Hz, 6 H, 2‴-CH_3), 1.42 (d, *J* = 6.8 Hz, 6 H, 2″-CH_3), 3.72–3.89 (m, 1 H, H-1‴), 4.50 (sept, *J* = 6.8 Hz, 1 H, H-1″), 6.74 (br s, 1 H, 4′-NH), 7.42–7.54 (m, 2 H, H-6, H-8), 7.74 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1 H, H-7), 8.08 (s, 1 H, H-2), 8.23 (dd, *J* = 8.0, 1.7 Hz, 1 H, H-5). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7 (2″-CH_3), 21.9 (2‴-CH_3), 42.8 (C-1‴), 48.8 (C-1″), 118.3 (C-8), 124.1 (C-3), 124.2 (C-10), 126.0 (C-6, C-5), 134.5 (C-7), 153.2 (C-3′), 154.2 (C-2), 156.1 (C-9), 163.4 (C-1′), 175.1 (C-4). MS (ESI$^+$): *m*/*z* = 339 [$C_{17}H_{20}N_2O_4$ + Na]$^+$. Anal. Calcd for C, 64.54; H, 6.37; N, 8.86. Found: C, 64.51; H, 6.34; N, 8.84.

(10) **Synthesis of 1,3-Disubstituted-5-(2-hydroxybenzoyl)-pyrimidine-2,4(1*H*,3*H*)-dione 4a and 4b:** Chromone-3-carboxylic acid **1** (1 g, 5.26 mmol) was added to the appropriate carbodiimide **2a**–**b** (5.26 mmol, 1 equiv) in $CHCl_3$ (20 mL). The reaction mixture was heated to reflux for 30 min. After complete consumption of **1**, and formation of **3a** or **3b** (TLC), 4-PPy (0.04 g, 0.05 equiv) was added to the reaction mixture, which was then heated to reflux for a further 30 min. The solvent was then evaporated to dryness and the resulting resinous solid was recrystallized from EtOH to afford compound **4a** or **4b**.

1,3-Dicyclohexyl-5-(2-hydroxybenzoyl)pyrimidine-2,4(1*H*,3*H*)-dione 4a: Yield: 1.342 g (64%); white solid; mp 80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07–2.04 and 2.35–2.48 (m, 20 H, CH_2-cyclohexyl), 4.46–4.58 (m, 1 H, H-1′), 4.84 (tt, *J* = 12.2, 3.7 Hz, 1 H, H-1″), 6.85–6.91 (m, 1 H, H-5‴′), 6.97–7.02 (m, 1 H, H-3‴′), 7.44–7.53 (m, 2 H, H-4‴′, H-6‴′), 7.71 (s, 1 H, H-6), 11.77 (s, 1 H, 2‴′-OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 25.1, 25.5, 26.1, 28.2 and 32.0 (CH_2-cyclohexyl), 54.7 (C-1″), 56.3 (C-1′), 113.0 (C-5), 118.0 (C-3‴′), 118.5 (C-5‴′), 119.3 (C-1‴′), 132.5 (C-6‴′), 136.5 (C-4‴′), 143.0 (C-6), 150.3 and 159.8 (C-2, C-4), 162.4 (C-2‴′), 195.4 (C-1‴′). MS (ESI$^+$): *m*/*z* = 397 [$C_{23}H_{28}N_2O_4$ + H]$^+$. Anal. Calcd for C, 69.67; H, 7.12; N, 7.07. Found: C, 69.65; H, 7.11; N, 7.05.

1,3-Diisopropyl-5-(2-hydroxybenzoyl)pyrimidine-2,4(1*H*,3*H*)-dione 4b: Yield: 0.846 g (51%); white solid; mp 128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.8 Hz, 6 H, 2′-CH_3), 1.51 (d, *J* = 6.9 Hz, 6 H, 2″-CH_3), 4.95 (sept, *J* = 6.8 Hz, 1 H, H-1′), 5.24 (sept, *J* = 6.9 Hz, 1 H, H-1″), 6.89 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1 H, H-5‴′), 7.00–7.04 (m, 1 H, H-3‴′), 7.47–7.54 (m, 2 H, H-4‴′, H-6‴′), 7.69 (s, 1 H, H-6), 11.79 (s, 1 H, 2‴′-OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1 (2″-CH_3), 21.5 (2′-CH_3), 46.6 (C-1″), 48.8 (C-1′), 113.5 (C-5), 118.3 (C-3‴′), 118.6 (C-5‴′), 119.4 (C-1‴′), 132.6 (C-6‴′), 136.8 (C-4‴′), 142.5 (C-6), 150.2 and 159.9 (C-2, C-4), 162.7 (C-2‴′), 195.5 (C-1‴′). MS (ESI$^+$): *m*/*z* = 339 [$C_{17}H_{20}N_2O_4$ + Na]$^+$. Anal. Calcd for C, 64.54; H, 6.37; N, 8.86. Found: C, 64.56; H, 6.40; N, 8.90.

(11) **Synthetic Procedure for 1,3-Ditolyl-5-(2-hydroxybenzoyl)pyrimidine-2,4(1*H*,3*H*)-dione (4c):** Chromone-3-carboxylic acid **1** (1 g, 5.26 mmol) was added to ditolylcarbodiimide **2c** (1.17 g, 5.26 mmol, 1 equiv) in chloroform (20 mL) and the reaction mixture was heated to reflux for 30 min. The solvent was then evaporated to dryness and the resulting resinous solid was recrystallized from ethanol to afford **4c**. Yield: 1.682 g (77%); yellowish white solid; mp 224 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 and 2.40 (s, 6 H, 4′/4″-CH_3, tolyl), 6.88 (ddd, *J* = 8.1, 7.2, 1.0 Hz, 1 H, H-5‴′), 7.00 (dd, *J* = 8.4, 1.0 Hz, 1 H, H-3‴′), 7.17–7.20 (m, 8 H, H-2′/2″,6′/6″ and H-3′/3″,5′/5″), 7.48 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 1 H, 4‴′), 7.66 (dd, *J* = 8.1, 1.6 Hz, 1 H, H-6‴′), 7.94 (s, 1 H, H-6), 11.71 (s, 1 H, 2‴′-OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1 and 21.2 (4′/4″-CH_3,), 114.3 (C-5), 118.1 (C-3‴′), 118.8 (C-5‴′), 119.3 (C-1‴′), 126.0 and 127.8 (C-2′/2″,6′/6″), 130.0 and 130.2 (C-3′/3″,5′/5″), 131.6 (C-1″), 132.8 (C-6‴′), 135.8 (C-1′), 136.9 (C-4‴′), 139.0 and 139.6 (C-4′/4″), 147.4 (C-6), 150.3 and 160.0 (C-2, C-4), 162.7 (C-2‴′), 194.6 (C-1‴′). MS (ESI$^+$): *m*/*z* = 435 [$C_{25}H_{20}N_2O_4$ + Na]$^+$. Anal. Calcd for C, 72.80; H, 4.89; N, 6.79. Found: C, 72.85; H, 4.91; N, 6.79.

(12) The described method allowed the synthesis of only 1,3-disubstituted uracil derivatives, and depends upon the range of carbodiimide derivatives and chromone-3-carboxylic acids available.