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Authors: Anggi Eka Putra, Yohei Oe, and Tetsuo Ohta

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FULL PAPER

Selective *N-mono*-alkylation of 6-aminouracils with alcohols: An environmentally benign protocol for synthesis of 6-alkylaminouracils

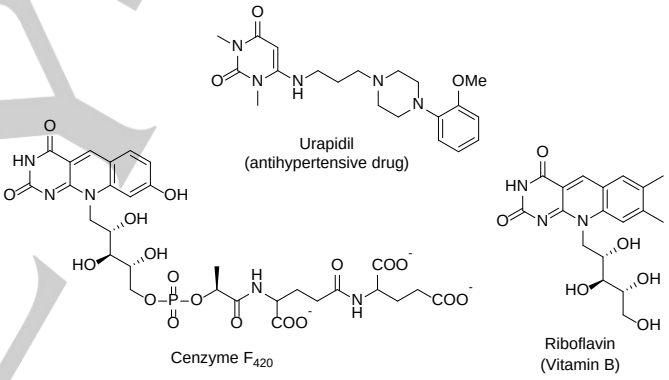
Anggi Eka Putra,[a] Yohei Oe, * [a],[b] and Tetsuo Ohta[a],[b]

Abstract: A highly selective *N*-alkylation of 6-aminouracils with alcohols achieved by using iridium catalysis on the basis of borrowing hydrogen methodology is presented. Reactions of 6-aminouracils and alcohols in the presence of $[Cp^*IrI_2]_2$ were found to afford 6-monoalkyluracils selectively in high yield (up to 99%), mostly in a short reaction time (2 h). These results provide a new, green, and efficient protocol to access 6-alkylaminouracils, which are very important intermediates for synthesis of biologically active molecules.

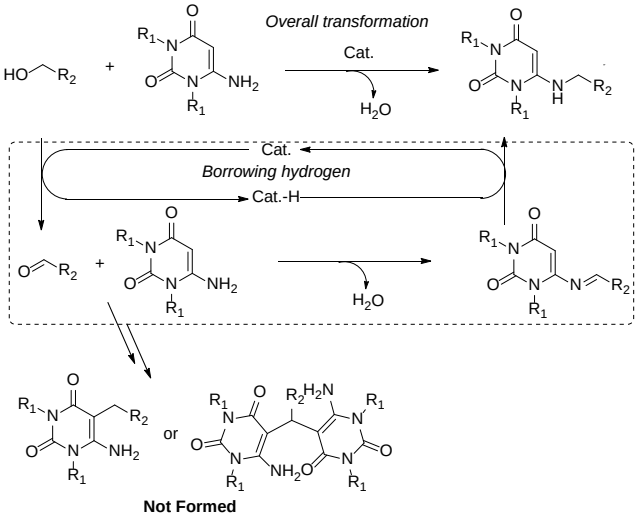
Introduction

As the main principle of green chemistry, minimizing the use and generation of hazardous substances has become an important consideration in modern chemical research.[1] Particularly in organic chemistry, one general example is the development of an alternative alkylating reagent to replace haloalkanes. Alcohol is considered as an ideal replacement for the haloalkanes because it has less toxicity and generates water as a byproduct instead of inorganic salts.[2] Although alcohol is a relatively inert electrophile, it has been proved to be a useful alkylating reagent under a catalytic system called the "borrowing hydrogen" or "hydrogen autotransfer" strategy.[2-5]

Uracils that have an aminoalkyl group at 6-position (6-aminoalkyluracilas) are known as key intermediates for synthesis of various molecules that play important roles in biological processes such as flavins, dezaflavins, purines, pteridines and xanthines derivatives (Scheme 1).[6] Generally, 6-alkylaminouracils are prepared by treating 6-halouracils[7] or 6-cyanouracil[8] with the corresponding amines. As general alkylation of nucleophilic substances with haloalkanes, quantitative amounts of toxic inorganic salts are formed (e.g., HCl, HBr, HCN). One of the most direct routes to 6-alkylamino uracil is direct *N*-alkylation of parent 6-aminouracils. However, this route may face a chemoselectivity problem because 6-aminouracils also react with electrophiles at *C*5 position.[9] We and several other research groups have successfully achieved selective alkylation of heterocyclic compounds including indoles, oxindoles, coumarines, quinolones, and barbituric acids with alcohol via borrowing hydrogen methodology.[10] Unlike the alkylation of indoles in which the alkylation takes place at an unsaturated carbon nucleophilic site rather than *N*-position,[10c,e,i] in the current study, we found that highly selective *N-mono*-alkylation of 6-aminouracils could be achieved with iridium catalysis under a borrowing hydrogen condition without detecting any alkylation on C=C bond position. This finding provides a new, green, and efficient protocol to access 6-alkylaminouracil derivatives.



Scheme 1. Representative examples of 6-alkylaminouracil moiety in bioactive compounds



Scheme 2. This work

[a] A. E. Putra, Y. Oe, T. Ohta
Graduate School of Life and Medical Sciences
Doshisha University
1-3 Tatara Miyakodani, Kyotanabe-shi, Kyoto 610-0394, Japan
E-mail: yoe@mail.doshisha.ac.jp
[b] Y. Oe, T. Ohta
Department of Biomedical Information, Faculty of Life and Medical Sciences
Doshisha University
1-3 Tatara Miyakodani, Kyotanabe-shi, Kyoto 610-0394, Japan

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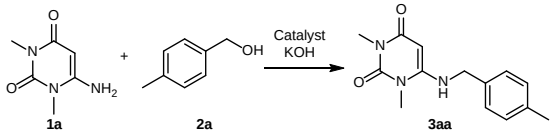
Results and Discussion

Table 1. Optimization of reaction condition[a]



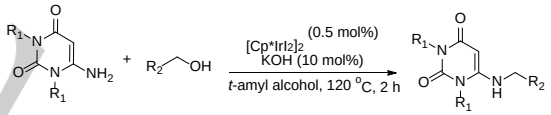
Entry	Catalyst (mol%)	Solvent	*t* (h)	Yield (%)[b]
1	$[Cp^*IrCl_2]_2$ (1)	H_2O	16	32
2	$[Cp^*IrI_2]_2$ (1)	H_2O	16	38
3	$[Cp^*Ir(NH_3)_3][Cl]_2$ (2)	H_2O	16	32
4	$[Cp^*Ir(NH_3)_3][I]_2$ (2)	H_2O	16	28
5	$IrCl_3.nH_2O$ (2)	H_2O	16	n.r.
6[c]	$[Cp^*IrI_2]_2$ (1)	-	16	95
7[c]	$[Cp^*IrI_2]_2$ (0.5)	-	16	93
8[c]	$[Cp^*IrI_2]_2$ (0.2)	-	16	86
9[c,d]	$[Cp^*IrI_2]_2$ (0.5)	-	16	93
10[c,d]	$[Cp^*IrI_2]_2$ (0.5)	-	6	94
11[d]	$[Cp^*IrI_2]_2$ (0.5)	-	6	92
12[d]	$[Cp^*IrI_2]_2$ (0.5)	-	3	91
13[d]	$[Cp^*IrI_2]_2$ (0.5)	-	1	75

[a] Unless stated otherwise, reaction conditions: mixture of **1a** (1 mmol), **2a** (1.2 mmol), catalyst, KOH (30 mol%) in water (1mL) was heated at 120 °C for 16 h. [b] Determined by ^{1}H NMR. [c] 2 mmol of **2a** was used. [d] KOH was 10 mol%.

Because most 6-aminouracils are highly soluble in hot water but not in organic solvents,[11] we decided to begin our investigation by conducting the reaction of 1,3-dimethyl-6-aminouracils (**1a**) and 4-methylbenzylalcohol (**2a**) in water. Although the presence of water might be problematic due to reversible reaction on the formation of imine intermediate, several iridium complexes have been reported to successfully catalyze the amination of alcohol in water.[12] Thus, we screened iridium catalysts, and the results are outlined in Table 1 (entries 1-5). We observed the formation of the corresponding product **3aa** in 32% yield without detecting other byproducts by using $[Cp^*IrCl_2]_2$ (2 mol% of Ir) in the presence of KOH (30 mol%) at 120 °C in water (entry 1). This result contradicts a previous report that aminouracil **1a** reacted with aldehydes selectively at C5 position followed by a second nucleophilic attack to produce bis(6-aminouracil-5-yl)methanes in water.[9a] Selective *N*-alkylation was also observed when water soluble $[Cp^*Ir(NH_3)_3][X]_2$ (X= Cl or I) was used as a catalyst (entries 3-4). Slightly better yield was obtained by using $[Cp^*IrI_2]_2$ to give the corresponding *N*-alkylated product **3aa** in 38% yield (entry 2). On the other hand, no reactions were detected when simple iridium salts $IrCl_3.nH_2O$ as well as several ruthenium complexes known as active catalysts for borrowing hydrogen reactions such as $RuCl_2(PPh_3)_3$,[3,10d-e] $RuHCl(CO)(PPh_3)_3$,[13] and $\{RuCl_2(p\text{-cyemene})]_2$/ 2 dppf$\}$[14] were used. On the basis of this screening, $[Cp^*IrI_2]_2$ was selected for this work. After further optimization, yield of **3aa** was drastically improved in the absence of any solvents but with an excess amount of **2a** (entry 6), where the aminouracil **1a** was slightly solved in **2a**. With some optimization, the reaction yielded the desired product **3aa** in 91% only in 3 h and 0.5 mol% of $[Cp^*IrI_2]_2$ (entry 12). We noticed that the corresponding *N-mono*-alkylated **3a** was obtained selectively without other by-products such as *C5*-alkylaminouracils or dialkylation products being detected.

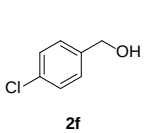
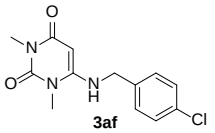
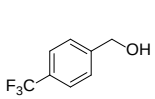
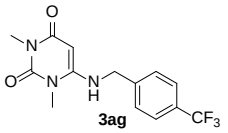
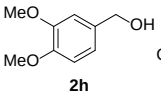
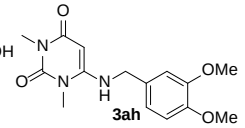
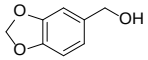
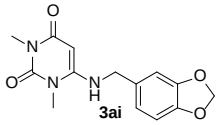
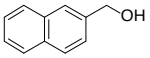
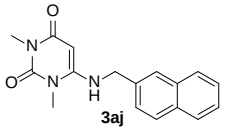
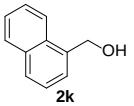
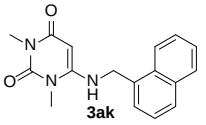
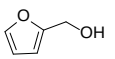
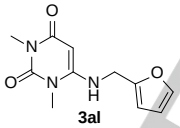
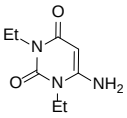
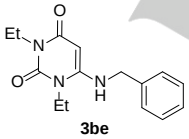
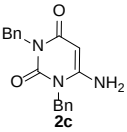
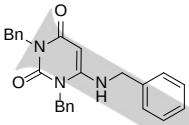
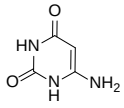
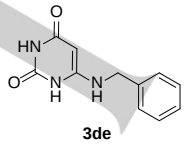
With the optimized reaction condition in hand, we moved our attention to check the scope and limitation of this reaction (Table 2). Initially, *meta*- and *ortho*-methylbenzyl alcohol (**2b** and **2c**) were tested. However, the reactions needed to be stopped earlier because the reaction mixture was solidified after 1 h. A similar result was also obtained when 4-chlorobenzyl (**2f**) alcohol was subjected to the reaction. ^{1}H NMR spectra of the solid mixture revealed the formation of the corresponding products in 60-80% yields. Most likely, the high melting point of the corresponding product (>120°C) prevented vigorous stirring of reaction mixture and adversely affected the conversion of reaction. Therefore, a solvent-free system was clearly inefficient for this transformation. To overcome this problem, *t*-amyl alcohol was introduced to the reaction system, and we were glad to find that the reaction smoothly yielded the corresponding products in excellent yields in only 2 hours (Table 2). To the best of our knowledge, this is one of the shortest reaction times for C-N bond formation through borrowing hydrogen methodology, which generally requires 16 h or more.[2b, d- f]

Table 2. Alkylation of 6-aminouracils with various aromatic alcohols[a]



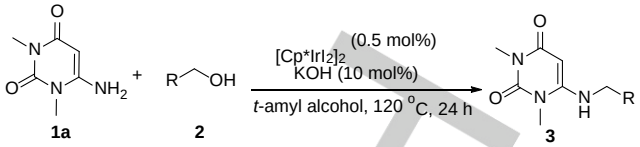
Entry	6-aminouracil	Alcohol	Product	Yield (%)
1	**1a**	**2a**	**3aa**	96 (89)
2	**1a**	**2b**	**3ab**	95 (89)
3	**1a**	**2c**	**3ac**	95 (94)
4	**1a**	**2d**	**3ad**	96 (86)
5	**1a**	**2e**	**3ae**	92(90)

Table 2. *(Continued)*

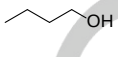
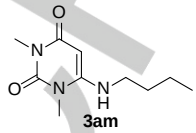
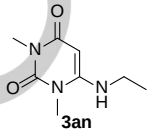
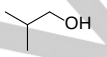
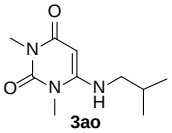
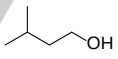
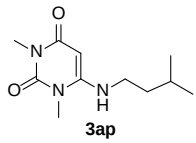
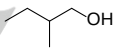
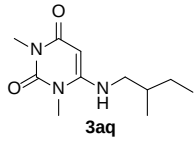
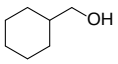
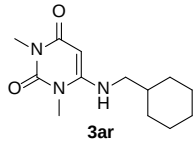
Entry	6-aminouracil	Alcohol	Product	Yield (%)
6	**1a**	 **2f**	 **3af**	96 (91)
7	**1a**	 **2g**	 **3ag**	62
8[b]	**1a**			75 (73)
9	**1a**	 **2h**	 **3ah**	96 (93)
10	**1a**	 **2i**	 **3ai**	98 (89)
11	**1a**	 **2j**	 **3aj**	89 (79)
12	**1a**	 **2k**	 **3ak**	99 (91)
13	**1a**	 **2l**	 **3al**	60 (50)
14	 **2b**	**2e**	 **3be**	94 (84)
15	 **2c**	**2e**	 **3ce**	93 (79)
16	 **1d**	**2e**	 **3de**	n. r.

[a] Reaction conditions: A mixtuire of aminouracils (1 mmol), alcohols (1.2 mmol), $[Cp^*IrI_2]_2$ (0.5 mol%), KOH (10 mol%), and *t*-amyl alcohol (1 mL) was heated at 120°C for 2 h. Yield was determined by ^{1}H NMR, and values in parentheses indicated isolated yield. [b] Reaction time was 6 h.

Table 3. Alkylation of 6-aminouracils **1a** with various aliphatic alcohols[a]



1a **2** **3**

Entry	Alcohol	Product	Yield (%)
1[b]	 **2m**	 **3am**	64 (52)
2[c]	 **2n**	 **3an**	38 (37)
3	 **2o**	 **3ao**	86 (75)
4	 **2p**	 **3ap**	74 (66)
5	 **2q**	 **3aq**	80 (78)
6	 **2r**	 **3ar**	88 (73)

[a] Reaction conditions: A mixtuire of aminouracils (1 mmol), alcohols (1.2 mmol), $[Cp^*IrI_2]_2$ (0.5 mol%), KOH (10 mol%), and *t*-amyl alcohol (1 mL) was heated at 120°C for 2 h. Yield was determined by ^{1}H NMR, and values in parentheses indicated isolated yield. [b] Reaction time was 30 h. [c] Ethanol (2 mL) was used as solvent at 110 °C.

By using the re-optimized conditions above, we tested various types of aromatic alcohols as well 6-aminouracils (Table 2). All primary benzylic alcohols having electron donating groups such as methyl- and methoxy- at any position yielded the corresponding 6-alkylaminouracils in excellent yield (entries 1-4, 9). Similar results were also obtained when an electron withdrawing group such as 4-chlorobenzyl alcohol was used. Although it gave a lower yield, a strong electron withdrawing group ($-CF_3$) was also tolerated. Excellent yields were observed when napththalenementhanols were subjected to the reaction system (entries 11-12). Lower yield was obtained when furfuryl alcohol were used (60% yield, entry 13). On the other hand, excellent results were obtained when 1,3-diethyl- and 1,3-dibenzyluracil were used as substrates (entries 14-15). Unfortunately, no reaction was detected when unalkylated 6-aminouracil **1d** was subjected to the reaction, apparently due to its poor solubility (entry 16). The desired *N*-alkylated product was

not also obtained by the reaction of **1a** with 1-phenylethanol under the similar reaction conditions for 18 h.

After obtaining good results for the alkylation of 6-aminouracils with aromatic alcohols, we then tested the aliphatic alcohols in the reaction (Table 3). To our delight, all tested aliphatic alcohols including linear (**2m, n**), branched (**2o-q**) and alicyclic (**2r**) alcohols are generally tolerated to give the *N*-*mono*-alkylated products in moderate to excellent yields, though longer reaction time was required.

Finally, we investigated the catalytic activity of $[Cp^*IrCl_2]_2$ under the re-optimized reaction conditions again, since the chloride complex is commercially avairable unlike the iodide one. However, the reaction of **1a** with **2a** by using $[Cp^*IrCl_2]_2$ instead of $[Cp^*IrCl_2]_2$ afforded **3aa** in slightly lower 88% NMR yield (vs 96% in entry 1, Table 2). Similarly, only 13% NMR yield of **3am** was obtained by the reaction of **1a** with 1-butanol (**2m**) in the presence of $[Cp^*IrCl_2]_2$ catalyst (vs 64% in entry 1, Table 3). These results indicatated that $[Cp^*IrI_2]_2$ is better catalyst for the presnt *N*-alkylation of 6-aminouracils with primary alcohols than the comercially available chloride complex.

Conclusions

We successfully developed a highly selective *N*-mono-alkylation of 6-aminouracils with alcohols by using iridium catalysis on the basis of borrowing hydrogen methodology. This result provides an efficient and green approach to synthesize 6-alkylaminouracils, which are useful intermediates for various biological active compounds. A wide range of substrates was tolerated to afford the corresponding 6-alkylaminouracils in high yields and selectively in a short reaction time.

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Experimental Section

General Information: Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker Ascend 400 spectrometer (400 MHz) with tetramethylsilane at 0 ppm as the internal standard for the ^{1}H NMR (400 MHz) and $CDCl_3$ at 77 ppm and DMSO-d_6 at 44 ppm for the ^{13}C NMR (100 MHz). High resolution mass spectrometry (HRMS) spectra were recorded with a JEOL JMS-700. Reagents obtained from commercial sources were used without further purification.

Procedure for *N*-monoalkylation of 6-aminouracils: 6-aminouracils (2 mmol), alcohol (2.4 mmol), $[Cp^*IrI_2]_2$ (0.005 mmol), KOH (0.01 mmol) and *t*-amyl alcohol (1 mL) were added to an Ar-purged 20 mL reaction tube equipped with a J-Young stop valve. The mixture was degassed using three or more freeze-pump-thaw cycles, purged with Ar gas and stirred at 120 °C for 2 hours. After the reaction finished, the solvent was evaporated under reduced pressure, and pure corresponding products were isolated by column chromatography or re-crystallization.

6-(4-Methylbenzylamino)-1,3-dimethyluracil (3aa): Isolated as colorless needles. ^{1}H NMR (400 Hz, $CDCl_3$) δ: 2.35 (s, 3H), 3.29 (s, 3H), 3.40 (s, 3H), 4.19 (d, J = 5.2 Hz), 4.86 (br, 1H), 4. 88 (s, 1H), 7.26 (s, 4H). ^{13}C NMR (100 Hz, $CDCl_3$) δ: 21.04, 27.71, 28.57, 47.11, 76.23, 127.59, 129.68, 132.78, 138.13, 151.81, 152.64, 162.89. HRMS: Calcd. For $C_{14}H_{17}N_3O_2$ 259.1321; Found 260.1396 $[M + H]^+$

6-(3-Methylbenzylamino)-1,3-dimethyluracil (3ab): Isolated as white solid. ^{1}H NMR (400 Hz, $CDCl_3$) δ: 2.33 (s, 3H), 3.28 (s, 3H), 3.39 (s, 3H), 4.19 (d, J = 4.8Hz), 4.78 (br, 1H), 4.86 (s, 1H), 7.19-7.25 (m, 4H). ^{13}C NMR (100 Hz, $CDCl_3$) δ: 18.92, 27.78, 28.71, 45.57, 76.18, 126.53, 128.36, 128.54, 130.92, 133.59, 136.41, 151.86, 152.74, 162.97. HRMS: Calcd. For $C_{14}H_{17}N_3O_2$ 259.1321; Found 260.1396 $[M + H]^+$

6-(2-Methylbenzylamino)-1,3-dimethyluracil (3ac): Isolated as white solid. ^{1}H NMR (400 Hz, $CDCl_3$) δ: 2.34 (s, 3H), 3.28 (s, 3H), 3.41 (s, 3H), 4.19 (d, J = 4.8Hz), 4.85 (s, 1H), 5.10 (br, 1H), 7.07-7.13 (m, 3H), 7.25 (t, J = 7.6Hz, 3H). ^{13}C NMR (100 Hz, $CDCl_3$) δ: 21.34, 27.72, 28.68, 47.27, 76.16, 124.53, 128.23, 128.90, 128.95, 135.86, 138.81, 151.83, 152.80, 162.96. HRMS: Calcd. For $C_{14}H_{17}N_3O_2$ 259.1321; Found 260.1396 $[M + H]^+$

6-(4-Methoxybenzylamino)-1,3-dimethyluracil (3ad): Isolated as colorless needles. ^{1}H NMR (400 Hz, $CDCl_3$) δ: 3.29 (s, 3H), 3.39 (s, 3H), 4.16 (d, J = 4.8 Hz, 2H), 4.88 (s, 1H), 6.89 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 Hz, $CDCl_3$) δ: 27.74, 28.62, 46.88, 55.31, 76.19, 114.41, 127.81, 129.05, 151.84, 152.65, 159.57, 162.93. HRMS: Calcd. For $C_{14}H_{17}N_3O_3$ 275.1270; Found 276.1356 $[M + H]^+$

6-Benzylamino-1,3-dimethyluracil (3ae): Isolated as white solid. ^{1}H NMR (400 Hz, $CDCl_3$) δ: 3.23 (s, 3H), 3.40 (s, 3H), 4.19 (d, J = 5.2 Hz, 2H), 4.74 (s, 1H), 5.9 (br, 1H), 7.22-7.33 (m, 5H). ^{13}C NMR (100 Hz, $CDCl_3$) δ: 27.62, 28.84, 46.91, 75.80, 127.13, 127.89, 128.80, 136.12, 151.73, 153.12, 163.03. HRMS: Calcd. For $C_{13}H_{15}N_3O_2$ 245.1164; Found 246.1246 $[M + H]^+$

6-(4-Chlorobenzylamino)-1,3-dimethyluracil (3af): Isolated as white solid. ^{1}H NMR (400 Hz, $CDCl_3$) δ: 3.62 (s, 3H), 3.42 (s, 3H), 4.20 (d, J = 5.2 Hz, 2H), 4.74 (s, 1H), 5.46 (br, 1H), 7.20 (d, J = 8.4 Hz), 7.31 (d, J = 6.8 Hz). ^{13}C NMR (100 Hz, $CDCl_3$) δ: 27.74, 28.82, 76.18, 128.67, 129.11, 133.96, 134.50, 151.72, 152.85, 162.92. HRMS: Calcd. For $C_{13}H_{14}ClN_3O_2$ 279.0775; Found 280.0852 $[M + H]^+$

6-(4-Trifluoromethylbenzylamino)-1,3-dimethyluracil (3ag): Isolated as white solid. ^{1}H NMR (400 Hz, $CDCl_3$) δ: 3.27 (s, 3H), 3.45 (s, 3H), 3.32 (d, J = 5.2 Hz, 2H), 4.75 (s, 1H), 5.32 (br, 1H), 7.40 (d, J = 8.0Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 Hz, $CDCl_3$) δ: 27.82, 28.82, 46.69, 76.54, 125.99, 126.02, 127.57, 130.36, 140.07, 151.79, 152.81, 162.89. HRMS: Calcd. For $C_{14}H_{14}F_3N_3O_2$ 313.1038; Found 314.1109 $[M + H]^+$

6-(3,4-Dimethoxybenzylamino)-1,3-dimethyluracil (3ah): Isolated as white solid. ^{1}H NMR (400 Hz, $CDCl_3$) δ: 3.31 (s, 3H), 3.40 (s, 3H), 3.88 (d, J = 2.4 Hz, 6H), 4.17 (d, J = 4.8Hz, 2H), 4.63 (br, 1H), 4.93 (s, 1H), 6.82 (s, 1H), 8.86-6.87 (m, 2H). ^{13}C NMR (100 Hz, $CDCl_3$) δ: 27.78, 28.59, 47.41, 55.97, 76.31, 111.09, 111.50, 120.28, 128.17, 149.16, 149.47, 151.85, 152.54, 162.89. HRMS: Calcd. For $C_{15}H_{19}N_3O_4$ 305.1376; Found 306.1454 $[M + H]^+$

6-Piperonylamino-1,3-dimethyluracil (3ai): Isolated as white solid. ^{1}H NMR (400 Hz, DMSO-d_6) δ: 3.06 (s, 3H), 3.35 (s, 3H), 4.22 (s, 2H), 4.54 (s, 1H), 5.99 (s, 2H), 6.82-6.88 (m, 2H), 6.94 (s, 1H), 7.42 (s, 1H). ^{13}C NMR (100 Hz, $CDCl_3$) δ: 27.52, 29.77, 45.58, 74.87, 101.36, 107.89, 108.57, 120.52, 132.24, 146.70, 147.91, 151.92, 153.54, 161.91. HRMS: Calcd. For $C_{14}H_{15}N_3O_4$ 289.1063; Found 290.1145 $[M + H]^+$

6-(2-Naphthalenylmethylamino)-1,3-dimethyluracil (3aj): Isolated as white solid. ^{1}H NMR (400 Hz, $CDCl_3$) δ: 3.28 (s, 3H), 3.39 (s, 3H), 4.32 (d, J = 5.2 Hz, 1H), 4.88 (s, 1H), 5.1 (br, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.48-7.51 (m, 2H), 7.70 (s, 1H), 7.78-7.84 (m, 3H). ^{13}C NMR (100 Hz, $CDCl_3$) δ: 27.76, 28.69, 47.47, 76.30, 125.13, 126.40, 126.58, 126.64, 127.69, 127.73, 128.98, 132.97, 133.19, 133.24, 151.79, 152.76, 162.93. HRMS: Calcd. For $C_{17}H_{17}N_3O_2$ 295.1321; Found 296.1403 $[M + H]^+$

6-(1-Naphthalenylmethylamino)-1,3-dimethyluracil (3ak): Isolated as white solid. ^{1}H NMR (400 Hz, $CDCl_3$) *δ*: 3.29 (d, *J* = 4.0 Hz, 6H), 4.60 (d, *J* = 4.4 Hz, 2H), 4.79 (br, 1H), 5.00 (s, 1H), 7.44-7.46 (m, 2H), 7.52-7.58 (m, 2H), 7.84-7.91 (m, 3H). ^{13}C NMR (100 Hz, $CDCl_3$) *δ*: 27.77, 28.62, 45.67, 76.18, 122.71, 125.38, 126.28, 126.97, 127.02, 129.07, 129.40, 130.85, 131.16, 133.94, 151.79, 152.55, 162.94. HRMS: Calcd. For $C_{17}H_{17}N_3O_2$ 295.1321; Found 296.1403 $[M + H]^+$

6-(2-Furanylmethylamino)-1,3-dimethyluracil (3al): Isolated white solid. ^{1}H NMR (400 Hz, $CDCl_3$) *δ*: 3.34 (s, 3H), 3.44 (s, 3H), 3.79 (s, 2H), 4.73 (s, 2H), 6.15 (d, *J* = 3.6 Hz, 1H), 6.28 (d, J = 3.0 Hz, 1H), 7.284 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (100 Hz, $CDCl_3$) *δ*: 22.56, 28.31, 29.13, 86.09, 105.88, 110.59, 141.21, 150.80, 151.23, 153.36, 162.34. HRMS: Calcd. For $C_{11}H_{13}N_3O_3$ 235.0957; Found 236.1036 $[M + H]^+$

6-Butylamino-1,3-dimethyluracil (3am): Isolated as white solid. ^{1}H NMR (400 Hz, $CDCl_3$) *δ*: 0.96 (t, *J* = 7.2 Hz, 3H), 1.37-1.46 (m, 2H), 1.61-1.68 (m, 2H), 3.08-3.13 (m, 2H), 3.31 (s, 3H), 3.40 (s, 3H), 4.45 (br, 1H), 4.86 (s, 1H). ^{13}C NMR (100 Hz, $CDCl_3$) *δ*: 13.63, 20.06, 27.72, 28.40, 30.49, 42.96, 75.53, 151.91, 152.84, 162.95. HRMS: Calcd. For $C_{10}H_{17}N_3O_2$ 211.1321; Found 212.1400 $[M + H]^+$

6-Isobutylamino-1,3-dimethyluracil (3ao): Isolated as white solid. ^{1}H NMR (400 Hz, $CDCl_3$) *δ*: 0.99 (d, *J* = 6.8 Hz, 6H), 1.93-2.00 (m, 1H), 2.92 (t, *J* = 6.2 Hz), 3.30 (s, 3H), 3.42 (s, 3H), 4.76 (br, 1H), 4.83 (s, 1H). ^{13}C NMR (100 Hz, $CDCl_3$) *δ*: 20.16, 27,23, 27.68, 28.45, 50.68, 75.41, 151.89, 152.99, 162.93. HRMS: Calcd. For $C_{10}H_{17}N_3O_2$ 211.1321; Found 212.1400 $[M + H]^+$

6-(3-Methylbutylamino)-1,3-dimethyluracil (3ap): Isolated as white solid. ^{1}H NMR (400 Hz, $CDCl_3$) *δ*: 0.95 (d, *J* = 6.4 Hz), 1.53-1.58 (m, 2H), 1.65-1.71 (m, 1H), 3.09-3.14 (m, 2H), 3.31 (s, 3H), 3.40 (s, 3H), 4.67 (br, 1H), 4.84 (s, 1H). ^{13}C NMR (100 Hz, $CDCl_3$) *δ*: 22.32, 25.93, 27.68, 28.47, 37.25, 41.50,75.32, 151.88, 152.92, 162.96. HRMS: Calcd. For $C_{11}H_{19}N_3O_2$ 225.1427;Found 226.1551 $[M + H]^+$

6-(2-Methylbutylamino)-1,3-dimethyluracil (3aq): Isolated as slightly yellowish solid. ^{1}H NMR (400 Hz, $CDCl_3$) *δ*: 0.92-0.98 (m, 6H), 1.17-1.28 (m, 1H), 1.41-1.49 (m, 1H), 1.71-1.77 (m, 1H), 2.86-2.92 (m, 1H), 3.00-3.06 (m, 1H), 3.31 (s, 3H), 3.41 (s, 3H), 4.46 (br, 1H), 4.85 (s, 1H). ^{13}C NMR (100 Hz, $CDCl_3$) *δ*: 11.11, 17.27, 27.11, 27.73, 28.37, 33.65, 49.05, 75.61, 151.91, 152.90, 162.92. HRMS: Calcd. For $C_{11}H_{19}N_3O_2$ 225.1427; Found 226.1551 $[M + H]^+$

6-(Cyclohexylmethylamino)-1,3-dimethyluracil (3ar): Isolated as light yellow solid. ^{1}H NMR (400 Hz, $CDCl_3$) *δ*: 0.92-1.01 (m, 2H), 1.15-1.30 (m, 3H), 1.61-1.77 (m, 6H), 2.94 (t, *J* = 6.2 Hz, 2H), 3.30 (s, 3H), 3.41 (s, 3H), 4.78 (br, 1H), 4.83 (s, 1H). ^{13}C NMR (100 Hz, $CDCl_3$) *δ*: 25.59, 26.17, 27.68, 28.47, 30.97, 36.48, 49.54, 75.36, 151.89, 153.01, 162.96. HRMS: Calcd. For $C_{13}H_{21}N_3O_2$ 251.1634; Found 252.1712 $[M + H]^+$

6-Benzylamino-1,3-ethyluracil (3be) Isolated as white solid. ^{1}H NMR (400 Hz, $CDCl_3$) *δ*: 1.16 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 3.90-3.99 (m, 4H), 4.22 (d, *J* = 5.2 Hz, 2H), 4.77 (s, 1H), 5.36 (br, 1H), 7.25-7.38 (m, 5H). ^{13}C NMR (100 Hz, $CDCl_3$) *δ*: 13.15, 13.43, 36.04, 37.10, 47.08, 76.45, 127.24, 128.07, 128.99, 136.23, 151.13, 152.23, 162.69. HRMS: Calcd. For $C_{15}H_{19}N_3O_2$ 273.1477; Found 274.1555 $[M + H]^+$

6-Benzylamino-1,3-dibenzyluracil (3ce): Isolated as white solid. ^{1}H NMR (400 Hz, $CDCl_3$) *δ*: 4.02 (d, *J* = 5.2 Hz), 4.79 (s, 1H), 4.96 (br, 1H), 5.12 (d, *J* = 10.0 Hz, 4H), 6.89-6.91 (m, 2H), 7.12-7.15 (m, 2H), 7.21-7.31 (m, 9H), 7.44 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR (100 Hz, $CDCl_3$) *δ*: 44.33, 45.84, 47.12, 126.29, 127.10, 127.32, 128.04, 128.31, 128.35, 128.65, 128.92, 129.39, 135.15, 135.83, 137.61, 152.18, 152.78, 162.64. HRMS: Calcd. For $C_{25}H_{23}N_3O_2$ 397.1790; Found 398.1863 $[M + H]^+$

Keywords: Aminouracils •Alcohols •Selective alkylation • Borrowing hydrogen • Iridium catalysis

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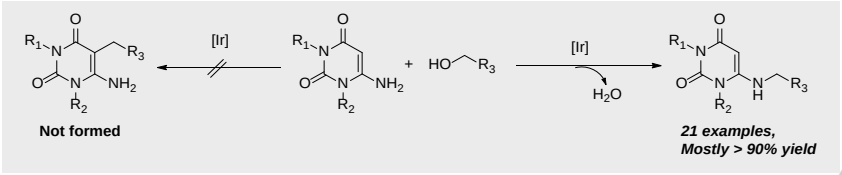

Highly selective *N*-mono-alkylation of 6-aminouracils with alcohols achieved by using iridium catalysis on the basis of borrowing hydrogen methodology is demonstrated. This reaction provides an efficient and green approach to synthesize 6-alkylaminouracils, which are useful intermediates in organic synthesis.

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Borrowing hydrogen*

Anggi Eka Putra, Yohei Oe, Tetsuo Ohta*

Page No. – Page No.

Selective *N-mono*-alkylation of 6-aminouracils with alcohols: An environmentally benign protocol for synthesis of 6-alkylaminouracils