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Regioselective arylation of uracil and 4-pyridone derivatives via copper(I) bromide mediated C–H bond activation☆

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ABSTRACT

A facile and effective synthesis of 6-aryluracil derivatives was accomplished by the direct C–H bond activation for arylation. A series of 6-aryl-1,3-dimethyluracils were synthesized from the reaction of 1,3-dimethyluracil with various phenyl iodides in DMF, in the presence of copper(I) bromide as the catalyst and lithium *tert*-butoxide as the base. This methodology is applicable to a variety of 5-substituted uracils as well as 4-pyridone to provide direct accesses to versatile uracil and 4-pyridone derivatives.

1. Introduction

C-Aryl-substituted uracils are an important class of pyrimidine derivatives that have received substantial attention for decades. 5-Aryluracils and, in particular, their nucleoside derivatives, owing to their structural resemblance to thymine, have been shown to possess a wide variety of biological activities and have been extensively utilized as biosensors[1–8] or dimensional analogs[9–15] for various biological targets. There has also been a growing interest in the 6-aryluracil derivatives for their potential biological applications.[16–28] Except limited structures could be obtained by the de novo synthesis from acyclic precursors,[17,19,20,22,25,29–36] the synthesis of 5- or 6-aryluracils has mostly been achieved by the palladium-catalyzed cross-coupling reactions from the corresponding halouracils, in which both Suzuki–Miyaura[26–28,37] and Stille[18,38–43] reactions were applicable. However, the synthesis of 6-aryluracils has been restricted by the preparation of 6-halouracil derivatives from uracil[27,44] or barbituric acid derivatives,[45,46] which suffered from lower yields, limited scales and harsh conditions. Thus, there is a need to develop a more effective process for the synthesis of 6-aryluracils.

Direct activation of C–H bond for arylation has become a promising method for the synthesis of *C*-arylated heterocycles in recent years.[47–57] Nevertheless, a thorough survey of the literature revealed that only few examples utilizing the direct activation of the uracil C–H bond for functionalization have been documented.[58–65] In 1986, Itahara first reported that both sugar-protected uridine derivatives and 1,3-dimethyluracil (1,3-DMU, **1a**) underwent the C–C bond formation reaction at the 5-position with maleimides in the presence of a stoichiometric amount of palladium acetate in acetic acid.[65] In 2009, a $Pd(OAc)_2$ catalyzed direct arylation of *N*-substituted uracils with aryl iodides was reported by Hocek et al., in which the regiochemistry was switchable by the addition of copper(I) iodide.[62,64] In the absence of CuI, the reaction led preferentially to the 5-aryluracils, while the reaction gave 6-aryluracils as the major products with a large excess of CuI. Later on, an improved protocol for $Pd(OAc)_2$ catalyzed 5-arylation of 1,3-DMU (**1a**) was reported by Kim et al. in 2011.[60] Only very recently in 2012, Kim et al. also reported that the 6-aryluracils could be obtained as the major products by the palladium(II) trifluoroacetate-catalyzed double C–H activation between 1,3-DMU (**1a**) and the arene solvents, such as benzene and xylenes, in the presence of an excess of silver acetate and pivalic acid.[59]

The formation of 6-aryluracils from 1,3-DMU (**1a**) and aryl iodides reported by Hocek et al. has received our attention.[64] When 1,3-DMU (**1a**) was reacted with aryl iodides in the presence of 3 equiv of CuI and cesium carbonate as a base in DMF, without any Pd catalyst and ligand, the reaction proceeded over two days with

☆ This paper is dedicated to Professor Ji-Wang Chern on the occasion of his 60th birthday

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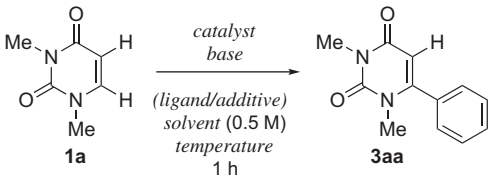
moderate yields but afforded exclusively the 6-aryluracils. In addition, Daugulis and Do reported a general approach that heterocycles possessing C–H bonds with p*K*a lower than 35 could be activated for arylation by CuI and 1,10-phenanthroline (1,10-Phen) in combination with various bases and solvents.[55] They also demonstrated a single example that the 6-aryluracil could be obtained in 61% yield from the copper-catalyzed cross-coupling reaction between 1,3-DMU (**1a**) and 3-methylanisole.[61] The reaction used 10 mol % of CuI/1,10-Phen as the catalyst, potassium phosphate as the base, iodine as the oxidant, and pyridine as an additive in 1,2-dichlorobenzene, but required two days for the completion. All reports suggested that copper is amenable for the C–H bond activation at the 6-position of uracil. In our effort to explore the chemical synthesis and biological significance of 6-substituted uracil derivatives, we have also embarked on the investigation of the direct activation of uracil C–H bond for functionalization. Herein, we report our synthesis of 6-aryluracil and 2-aryl-4-pyridone derivatives via a copper(I) bromide catalyzed regioselective activation of C–H bond for arylation.

2. Results and discussion

1,3-Dimethyluracil (1,3-DMU, **1a**) was chosen as a model substrate to investigate the direct arylation via the activation of the C–H bond at the 6-position of uracil derivatives. The screening of the reaction conditions started with 20 mol % of copper(I) halides[55,57] as the catalyst with various solvents, bases, arylating reagents, temperature, and ligands/additives (part of the results is summarized in Table 1). The maximal yield was obtained when the reaction was carried out in DMF with phenyl iodide (**2a**) as the arylating reagent, copper(I) bromide as the catalyst, and lithium *tert*-butoxide as the base (entry 3 in Table 1). The survey of the conditions also concluded that both the copper catalyst and the alkoxide base were required for the reaction, and the reaction yields were presumably the same in open air and under an argon atmosphere. The use of an inexpensive copper catalyst allowed the catalyst loading to be increased to 40 mol % to further improve the yield. Hence, this optimized condition (entry 19 in Table 1) was used as the standard condition for the subsequent studies. It is noteworthy that this reaction protocol is highly regioselective at the 6-position of 1,3-DMU (**1a**). Only 6-Ph–1,3-DMU (**3aa**) was isolated from the reaction while 5-Ph–1,3-DMU (**1g**) was almost negligible (0–0.5% among all the conditions) and 5,6-diPh–1,3-DMU (**3ga**) was not observed from the ^{1}H NMR of the reaction mixture.

The reactions of 1,3-DMU (**1a**) with a variety of phenyl iodides (**2a**–**i**) possessing *o*-, *m*- or *p*-substituents, as shown in Table 2, were examined to establish the scope of the aryl iodide

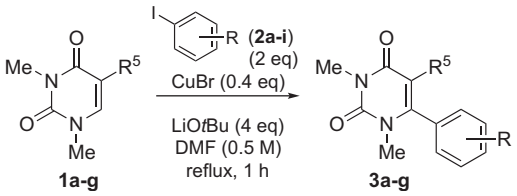
Table 1
Examination and optimization of the reaction conditions[a]



Entry	Catalyst (equiv)	Base (equiv)	Ligand/additive (equiv)	Arylating reagent (2 equiv)	Solvent[b]	Yield[c] (%)
1	CuBr (0.2)	Cs_2CO_3 (2)		Ph–I	DMF	N.R.[d]
2	CuBr (0.2)	LiOH (2)		Ph–I	DMF	N.R.[d]
3	CuBr (0.2)	LiO^tBu (2)		Ph–I	DMF	76
4	CuBr (0.2)	NaO^tBu (2)		Ph–I	DMF	21
5	CuBr (0.2)	LiO^tBu (2)		Ph–I	THF	5
6	CuBr (0.2)	LiO^tBu (2)		Ph–I	DME	20
7	CuBr (0.2)	LiO^tBu (2)		Ph–I	Dioxane	41
8	CuBr (0.2)	LiO^tBu (2)		Ph–I	Toluene	30
9	CuBr (0.2)	LiO^tBu (2)		Ph–I	*tert*-Amyl-OH	10
10[e]	CuBr (0.2)	LiO^tBu (2)		Ph–I	DMSO	N.D.[f]
11	CuBr (0.2)	LiO^tBu (2)	PPh_3 (0.2)	Ph–I	DMF	67
12	CuBr (0.2)	LiO^tBu (2)	1,10-Phen[g] (0.1)	Ph–I	DMF	62
13	CuBr (0.2)	LiO^tBu (2)	L-Proline (0.1)	Ph–I	DMF	57
14	CuBr (0.2)	LiO^tBu (2)	TMEDA[h] (0.1)	Ph–I	DMF	60
15	CuBr (0.2)	LiO^tBu (2)		Ph–$B(OH)_2$	DMF	N.R.[d]
16	CuBr (0.2)	LiO^tBu (2)		Ph–Br	DMF	6
17	CuBr (0.1)	LiO^tBu (2)		Ph–I	DMF	63
18[i]	CuBr (0.2)	LiO^tBu (2)		Ph–I	DMF	15
19	CuBr (0.4)	LiO^tBu (4)		Ph–I	DMF	87 (82)[j]
20	CuCl (0.4)	LiO^tBu (4)		Ph–I	DMF	79
21	CuI (0.4)	LiO^tBu (4)		Ph–I	DMF	79
22	CuCN (0.4)	LiO^tBu (4)		Ph–I	DMF	70
23	$Cu(OAc)_2$ (0.4)	LiO^tBu (4)		Ph–I	DMF	78
24	$CuSO_4$ (0.4)	LiO^tBu (4)		Ph–I	DMF	34
25	CuBr (0.4)	—		Ph–I	DMF	N.R.[d]
26	—	LiO^tBu (4)		Ph–I	DMF	N.D.[f]

[a] Temperature=reflux (unless specified otherwise); time=1 h; under air atmosphere.
[b] Reaction concentration=0.5 M.
[c] The yields were determined by ^{1}H NMR analysis of the crude products using caffeine as an internal standard.
[d] N.R.=no reaction.
[e] Temperature=180 °C.
[f] N.D.=no desired product (complicated result).
[g] 1,10-Phen=1,10-phenanthroline.
[h] TMEDA=*N*,*N*,*N*′,*N*′-tetramethylethylenediamine.
[i] Temperature=120 °C.
[j] Isolated yield.

Table 2
The reactions of 1,3-dimethyluracil derivatives (**1a**–**g**) with various phenyl iodides (**2a**–**i**)



Entry	Reactant	R^5	Ar–I	R	Product, yield[a] (**1a**–**g** recovered)[b]
1	**1a**	H	**2a**	H	**3aa**, 82%
2	**1a**	H	**2b**	4-Me	**3ab**, 58% (15%)
3	**1a**	H	**2c**	4-MeO	**3ac**, 54% (19%)
4	**1a**	H	**2d**	4-Cl	**3ad**, 55% (21%)
5	**1a**	H	**2e**	4-Br	**3ae**, 28% (24%)
6	**1a**	H	**2f**	4-NO_2	**3af**, 20%[c]
7	**1a**	H	**2g**	2-Me	**3ag**, 85%
8	**1a**	H	**2h**	3-MeO	**3ah**, 72%
9	**1a**	H	**2i**	2-MeO	**3ai**, 66%
10	**1b**	Me	**2a**	H	**3ba**, 21% (45%)
11	**1b**	Me	**2b**	4-Me	**3bb**, 46% (29%)
12	**1b**	Me	**2c**	4-MeO	**3bc**, 31% (40%)
13	**1b**	Me	**2d**	4-Cl	**3bd**, 29% (60%)
14	**1c**	F	**2a**	H	**3ca**, 47%
15	**1c**	F	**2b**	4-Me	**3cb**, 41% (6%)
16	**1c**	F	**2d**	4-Cl	**3cd**, 42% (8%)
17	**1d**	Cl	**2a**	H	**3da**, 68%
18	**1d**	Cl	**2b**	4-Me	**3db**, 44% (9%)
19	**1d**	Cl	**2c**	4-MeO	**3dc**, 45% (6%)
20	**1d**	Cl	**2d**	4-Cl	**3dd**, 35% (10%)
21	**1e**	Br	**2a**	H	**3ea**, 39%+**3aa**, 23%
22	**1e**	Br	**2b**	4-Me	**3eb**, 32%+**3ab**, 9%
23	**1e**	Br	**2d**	4-Cl	**3ed**, 24%+**3ad**, 12%
24	**1f**	NO_2	**2a**	H	N.D.[d]
25	**1g**	Ph	**2a**	H	**3ga**, 47%

[a] Isolated yields.
[b] Numbers in parentheses represent the recovered reactants **1a**–**g**, if denoted.
[c] 4-Nitrophenyl iodide (**2f**, 5 equiv), reaction time=5 h (only 6.3% of **3af** was obtained and 58% of **1a** was recovered under the standard condition).
[d] N.D.=no desired product.

components for the reaction. Under the standard condition (entry 19 in Table 1), 1,3-DMU (**1a**) reacted with most of the phenyl iodides to form the 6-aryluracil derivatives **3aa**–**ai** in 28–85% yields, except the strong electron-withdrawing *p*-nitrophenyl iodide (**2f**) gave a very low yield. The yield was improved by extending the reaction time and increasing the amount of *p*-nitrophenyl iodide (**2f**) (entry 6 and note c in Table 2).

The reaction was then applied to a series of 5-substituted uracil derivatives, including 5-methyl-, 5-fluoro-, 5-chloro-, 5-bromo-, 5-nitro-, and 5-phenyl-1,3-dimethyluracil derivatives (**1b**–**g**, respectively), in order to explore the generality of the uracil substrates. Most of their 6-arylated products were obtained in moderate to good yields (entries 11–23 and 25 in Table 2), except the reaction of 5-NO_2–1,3-DMU (**1f**) gave no desired product but a complicated result (entry 24 in Table 2). The slight decrease in yields for the 5-substituted 1,3-DMU derivatives (**1b**–**e** and **1g**) was possibly attributed to both the steric and electronic effects of the substituents at the 5-position of 1,3-DMU.

When 5-Br–1,3-DMU (**1e**) was used as the reactant, the formation of the debrominated 6-aryluracil by-products (**3aa**, **3ab**, and **3ad**) has received our attention (entries 21–23 in Table 2). We rationalized that the debromination possibly involved an elimination–addition mechanism in which a 'hetaryne (**4**)' could be formed by the deprotonation followed by the elimination of HBr from 5-Br–1,3-DMU (**1e**) in prior to the arylation[55,57,66,67] (Fig. 1). However, the dehalogenated 6-aryluracils were not observed in the

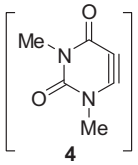


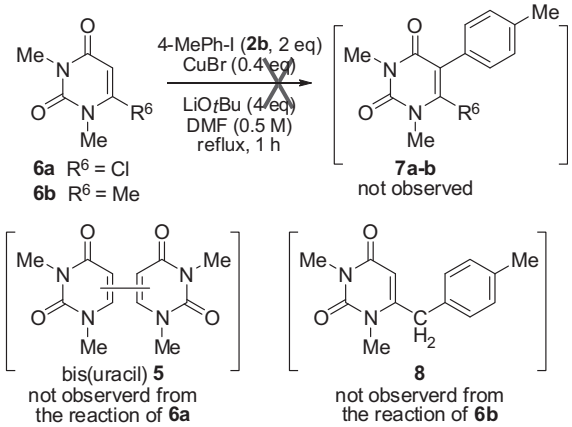
Fig. 1. The benzynoid (or 'hetaryne') **4** formed from 5-Br–1,3-DMU (**1e**).

reaction of 5-F–1,3-DMU (**1c**) and 5-Cl–1,3-DMU (**1d**) under the same condition. Moreover, the 5-halo-1,3-DMUs (R^5=F, Cl, Br, **1c**–**e**, respectively) did not undergo the classic Ullmann-type reaction[68] under the standard condition as neither the 5-arylated 1,3-DMU nor the bis-uracil adducts (**5**) were observed.

The synthesis of 5,6-diphenyl-1,3-dimethyluracil (**3ga**) has also been demonstrated. 5-Ph–1,3-DMU (**1g**) could be prepared by well-established palladium-catalyzed cross-coupling reactions from 5-Br–1,3-DMU (**1e**),[27] or by a more recently developed palladium-catalyzed direct C–H bond activation reactions from 1,3-DMU (**1a**).[60,64] The 6-phenyl substituent was then installed by our methodology to afford the 5,6-diphenyl adduct (**3ga**) in 47% yield (entry 25 in Table 2).

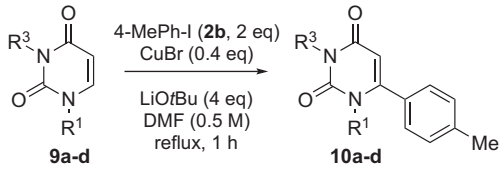
Meanwhile, the reactivity of the 6-substituted 1,3-DMU (**6a**,**b**) toward the arylation condition was also examined. The reaction of 6-Cl–1,3-DMU (**6a**) with *p*-iodotoluene (**2b**) under the standard condition gave no arylated product at either the 5- or 6-position (**7a** or **3ab**). 6-Me–1,3-DMU (**6b**) was subjected to the standard condition with *p*-iodotoluene (**2b**) but the arylation did not occur at either the 5-position (**7b**) or the 6-methyl group (**8**) (Scheme 1). The investigation further confirmed that the arylation under our optimized condition did not occur at the 5-position of uracil. Furthermore, the standard condition did not activate the 5- and 6-chlorouracils (**1d** and **6a**) for homo- or cross-coupling reactions.[59]

In an effort to evaluate the substituent effects on the uracil nitrogens, fully and partially *N*-unsubstituted uracil (**9a**,**b**), as well as uracil derivatives bearing removable protecting groups at the N^1- and N^3-positions[62] (**9c**,**d**), including uracil (**9a**), 1-methyluracil (**9b**), 1,3-di-(*p*-methoxybenzyl)uracil (**9c**), and 1,3-di-(benzyloxymethyl)uracil (**9d**), were subjected to the standard condition with *p*-iodotoluene (**2b**). It was found that only the reaction of 1,3-di-(*p*-methoxybenzyl) uracil (**9c**) could proceed to afford the desired 6-(4-tolyl)uracil product (**10c**). The results indicated that the protection or substitution at both nitrogens of uracil is required for the reaction (Table 3). Since the removal of the PMB (*p*-methoxybenzyl) group has been demonstrated,[62] this approach would provide a facile access to the *N*-unsubstituted 6-aryluracil derivatives.



Scheme 1.

Table 3
The reactions of various *N*-substituted uracil derivatives **9a**–**d** with *p*-iodotoluene (**2b**)

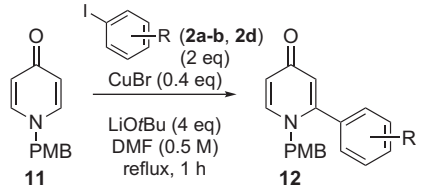


Entry	Reactant	R^1	R^3	Product (yield)[a]
1	**9a**	H	H	N.R.[b]
2	**9b**	Me	H	N.D.[c]
3	**9c**	PMB	PMB	**10c** (43%)
4	**9d**	BOM	BOM	N.D.[c]

[a] Isolated yields.
[b] N.R.=no reaction.
[c] N.D.=no desired product.

The success in uracil derivatives prompted us to further expand the scope of this methodology to the 4-pyridone derivatives. 1-(*p*-Methoxybenzyl)-4-pyridone (**11**) was employed in the reaction with various phenyl iodides (**2a**,**b** and **2d**) under the standard condition. The arylation regioselectively took place at the 2-position to give the corresponding 2-aryl-1-(*p*-methoxybenzyl)-4-pyridones (**12a**,**b** and **d**) in 28–33% yields without any modification of the reaction condition (Table 4). The structure of **12d** was confirmed by intensive NMR studies including ^{1}H, ^{13}C, DEPT-135, COSY, HMQC, HMBC, and NOESY experiments to identify the location of the arylation.

Table 4
The reactions of 1-(*p*-methoxybenzyl)-4-pyridone (**11**) with various phenyl iodides (**2a**,**b** and **d**)

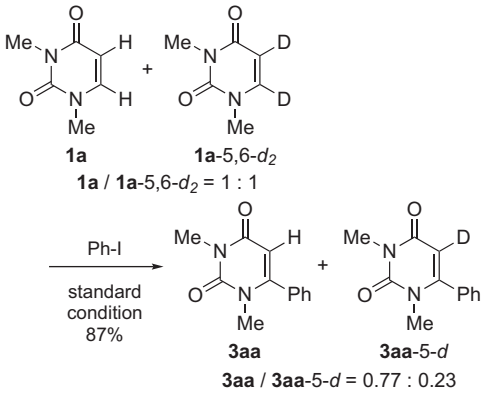


Entry	Ar–I	R	Product (yield)[a]
1	**2a**	H	**12a** (28%)
2	**2b**	4-Me	**12b** (33%)
3	**2d**	4-Cl	**12d** (31%)

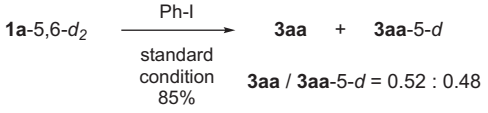
[a] Isolated yields.

Preliminary deuterium isotope studies were carried out in order to gain insight into the reaction details. An intermolecular competition reaction using an equimolar mixture of 1,3-DMU (**1a**) and 5,6-di-deuterated 1,3-DMU[69–71] (**1a**-5,6-d_2) with PhI (**2a**) under the standard condition afforded the product in 87% yield with the ratio of **3aa**/**3aa**-5-*d*=3.35 (Scheme 2). When the 5,6-di-deuterated 1,3-DMU (**1a**-5,6-d_2) alone was subjected to the same condition, the desired 6-phenyl-substituted product was obtained in 85% yield. Unexpectedly, analysis of the proton NMR spectrum of the product indicated that only 48% of deuterium retained at the 5-position (**3aa**-5-*d*) (Scheme 3). Since the partial proton-deuterium exchange at the 5-position occurred during the reaction, the kinetic isotope effect appears to be greater than 3.35 and suggests that the C–H bond cleavage at the 6-position was involved in the rate-limiting step.

The loss of deuterium at the 5-position of **3aa**-5-*d* was due to deprotonation followed by reprotonation from which was originally thought to be the water residue in the solvent. To



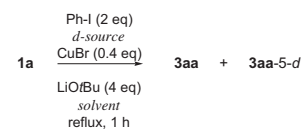
Scheme 2.



Scheme 3.

distinguish the proton source, a reaction of 1,3-DMU (**1a**) with PhI (**2a**) was carried out in the presence of one drop of D_2O under the standard condition and the product was obtained in 74% yield with 17% of deuterium incorporation at the 5-position. Similarly, when one drop of acetic acid-d_4 was used instead of D_2O in the reaction, the product was obtained in 81% yield with 18% of deuterium incorporation (Table 5). The addition of D_2O or acetic acid-d_4 only slightly decreased the yields but did not affect the proceeding of the reaction. However, the deuterium incorporation level was much lower than the proton exchange observed in the reaction of **1a**-5,6-d_2. The observation has prompted us to speculate that the proton was abstracted from DMF during the reaction in Scheme 3. Hence, the reaction of 1,3-DMU (**1a**) with PhI (**2a**) in DMF-d_7 under the standard condition was carried out to give the arylated product in 82% yield with 41% of deuterium incorporation, which was comparable to the loss of deuterium in the reaction of **1a**-5,6-d_2. The investigation confirmed the proton source and the participation of DMF in the reaction, which was, to our knowledge, unprecedented in the literature although the *tert*-butoxide base in DMF has been widely used.[55,57]

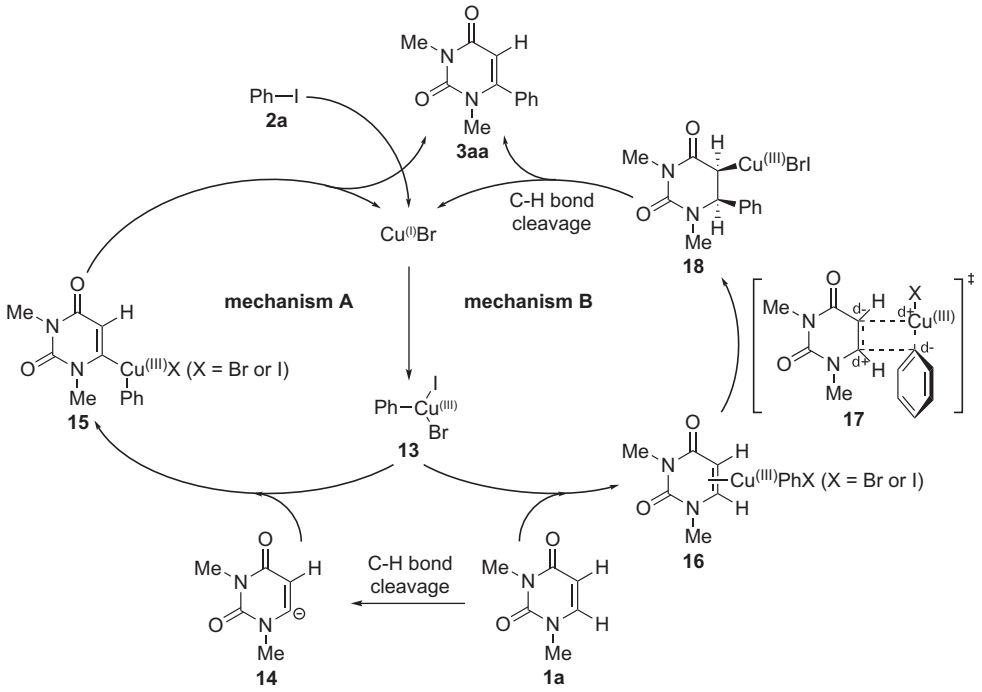
Table 5
Identification of the proton source in the reaction



Entry	*d*-Source/solvent[a]	Yield[b]	Deuterium content[c] (**3aa**/**3aa**-5-*d*)
1	A	74%	0.83:0.17
2	B	81%	0.82:0.18
3	C	82%	0.59:0.41

[a] Deuterium source/solvent: A=1 drop of D_2O in DMF; B=1 drop of acetic acid-d_4 in DMF; C=DMF-d_7.
[b] Isolated yields.
[c] Determined by ^{1}H NMR.

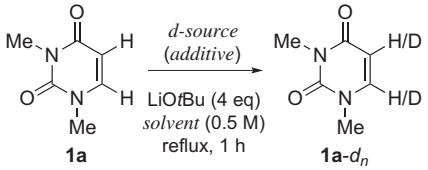
Based upon the preliminary isotope effect data, a Ullmann-type reaction[68] mechanism involving the formation of the uracil 6-carbanion as an intermediate was sketched.[57] (mechanism A in Scheme 4) In this proposed mechanism, the catalytic cycle started with an oxidative addition of CuBr to PhI (**2a**) to form the phenyl copper(III) complex **13**. Meanwhile, regioselective deprotonation by LiO^{t}Bu at the 6-position of 1,3-DMU (**1a**) formed the uracil 6-carbanion intermediate **14**. We rationalize that the regioselectivity of the reaction was attributed to the p*K*a difference between the 5-CH and the 6-CH of 1,3-DMU (**1a**). Subsequently, the uracil 6-carbanion (**14**) replaced the halide from the copper(III) complex **13** by transmetallation to afford the diaryl copper(III) complex **15**, which then underwent a reductive elimination to give the coupled product **3aa** and regenerated the active copper(I) species.[57] Although the p*K*a for the 6-CH of 1,3-DMU (**1a**) has been estimated to be approximately 30–34,[72–75] it still remained to be further elucidated whether the uracil 6-carbanion was formed in the reaction.



Scheme 4.

Thus, two sets of experiments using the deuterium source (D_2O, acetic acid-d_4, and DMF-d_7) to trace the existence of the uracil 6-carbanion **14** in the reaction were conducted. In one set of the experiments, 1,3-DMU (**1a**) was subjected to the standard condition except in the absence of PhI (**2a**), while in the other set, PhI (**2a**) and CuBr were omitted from the standard condition. Both sets were added one drop of either D_2O or acetic acid-d_4 in DMF or carried out in DMF-d_7 as the deuterium source. The levels of the deuterium incorporation were anticipated to reflect the formation of the carbanion in the reaction (Table 6). Nevertheless, all the experimental results showed no significant differences in deuterium incorporation between the 5- and 6-positions in the recovered 1,3-DMU (**1a**-d_n). In particular, when the experiments were carried out in DMF-d_7 in the absence of PhI (**2a**), the levels of the deuterium incorporation at the 5- and 6-positions were all above 70% and indicated that the deprotonation at the 5- and 6-positions took place at the same probability under the reaction conditions (entries 1–3 and 6–8 in Table 6). Accordingly, these investigations suggested that the formation of the uracil carbanion at either 5- or 6-position was irrelevant to the regioselectivity of the reaction and did not support the proposed mechanism A (Table 6).

Table 6
Identification of the formation of uracil carbanions



Entry	*d*-Source/solvent[a]	Additive (equiv)	Recovered yield[b]	5-H/D[c]	6-H/D[c]
1	A	CuBr (0.4)	67%	0.86:0.14	0.88:0.12
2	B	CuBr (0.4)	96%	0.80:0.20	0.85:0.15
3	C	CuBr (0.4)	65%	0.30:0.70	0.22:0.78
4	C[d]	CuBr (0.4)	75%	0.80:0.20	0.74:0.26
5	D	CuBr (0.4)	75%	0.67:0.33	0.56:0.44
6	A	—	35%	0.76:0.24	0.78:0.22
7	B	—	57%	0.88:0.12	0.90:0.10
8	C	—	41%	0.12:0.88	0.18:0.82
9	C[d]	—	81%	0.81:0.19	0.76:0.24
10	D	—	42%	0.30:0.70	0.30:0.70

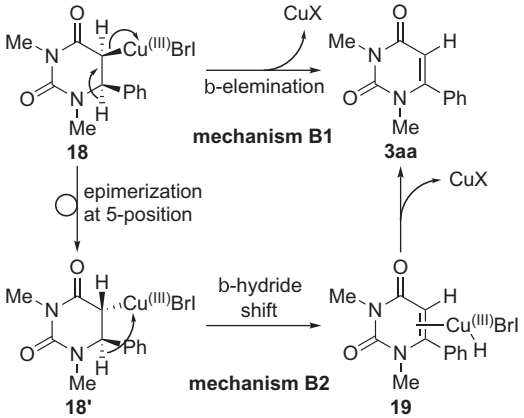
[a] Deuterium source/solvent: A=1 drop of D_2O in DMF; B=1 drop of acetic acid-d_4 in DMF; C=DMF-d_7 [DCON$(CD_3)_2$]; D=DMF-*d* [DCON$(CH_3)_2$].
[b] Isolated yields.
[c] Determined by ^{1}H NMR.
[d] Reaction temperature=120 °C.

The investigations also raised a question on which deuterium from DMF-d_7 was transferred to the substrate. We presumed that DMF decomposes at reflux temperature to form $(CD_3)_2$N-D/H, which acts as the deuterium/proton source in the reaction. To test this hypothesis, the same set of reactions was carried out in DMF-d_7

at 120 °C and the deuterium incorporation was found to be much lower than at reflux temperature (entries 4 and 9 in Table 6). In order to further illuminate the deuterium/proton source, the same set of reactions were carried out in DMF-*d* at reflux temperature and the results clarified that the deuterium was mainly abstracted from the formyl proton due to the decomposition of DMF-d_7 (entries 5 and 10 in Table 6).

Therefore, an alternative mechanism was proposed (mechanism B in Scheme 4), in which the 5,6-double bond of the 1,3-DMU (**1a**) first coordinated to the copper center of the phenyl copper(III) complex (**13**) followed by a migratory insertion in a *syn* fashion to form the *cis*-5,6-dihydro-6-phenyluracil copper(III) complex (**18**). The addition of the phenyl copper(III) complex (**13**) across the 5,6-double bond of the 1,3-DMU (**1a**) was the determinative step for the regioselectivity. We rationalized that the selectivity was attributed to the intrinsic bond polarity matching between the C5–C6 double bond of 1,3-DMU (**1a**) and the phenyl–copper bond of **13** (transition state **17** in Scheme 4). As a result, the electrophilic copper center of the phenyl–copper(III) complex (**13**) attached to the more nucleophilic C5-position in 1,3-DMU (**1a**), and then the phenyl group migrated to the C6-position to provide the *cis*-5,6-dihydro-6-phenyluracil copper(III) complex (**18**).

Afterward, the base abstracted the 6-proton to promote an *anti* elimination to afford the desired product **3aa** and regenerated the active copper(I) species (mechanism B1 in Scheme 5). Alternatively, a β-hydride elimination mechanism similar to the Heck reaction was also possible, although this mechanism may require the *trans*-5,6-dihydro-6-phenyluracil copper(III) complex (**18′**). Subsequently, the formation of the 6-Ph–1,3-DMU–copper complex (**19**) followed by the dissociation of the product **3aa** and the reductive elimination of the copper(I) catalyst accomplished the catalytic cycle (mechanism B2 in Scheme 5). The postulated β-elimination of the copper(III) complex **18** (mechanism B1) and the β-hydride elimination of the copper(III) complex **18′** (mechanism B2) both involved the C–H bond breaking at the 6-position which were consistent with the deuterium isotope effect observed in the experiment (Scheme 5).



Scheme 5.

3. Conclusion

In summary, our investigation has provided a facile and practical synthesis of 6-aryluracil and 2-aryl-4-pyridone derivatives, which utilized inexpensive copper(I) bromide as a catalyst to regioselectively activate the C–H bond for arylation at the 6-position of uracil and 2-position of 4-pyridone. The reaction protocol is convenient to carry out under ambient atmosphere without the exclusion of moisture and air. Further application of this methodology will be amenable to the synthesis of a variety of uracil and 4-pyridone derivatives.

4. Experimental section

4.1. General chemical procedures

Nuclear magnetic resonance (NMR) spectra were obtained with Bruker Avance-400 or Avance-500 instruments. The chemical shift values are reported in δ values (parts per million, ppm) relative to the standard chemical shift for the deuterated solvent, $CDCl_3$, or DMSO-d_6.[76] The coupling constant (*J*) values are expressed in hertz (Hz). Mass spectrometry was acquired by the Advanced Instrument Center, Department of Chemistry, National Taiwan University, Taipei, Taiwan. Thin-layer chromatography (TLC) was performed on silica gel GHLF-254 plates (Merck Reagents). Compounds on thin-layer chromatography were visualized by illumination under UV light (254 nm). Solvent systems are expressed as a percentage of the more polar component with respect to total volume (v/v%). Merck Silica gel (230–400 mesh) was used for flash column chromatography and this technique has been described by Still et al.[77] Evaporations were carried out under reduced pressure (water aspirator) with the bath temperature below 50 °C unless specified otherwise. Materials obtained from commercial suppliers were used without further purification.

4.2. General procedure for the CuBr catalyzed C–H bond activation for arylation

To a mixture of 1,3-dimethyluracil (0.140 g, 1 mmol), CuBr (0.057 g, 0.4 mmol, 0.4 equiv), and the aryl iodide (2 mmol, 2 equiv) in DMF (2 mL) was added LiO^tBu (0.320 g, 4 mmol, 4 equiv). The reaction mixture was heated at reflux temperature for 1 h. After cooling to the room temperature, the reaction was quenched by adding saturated aqueous NH_4Cl solution. The solvent was removed under reduced pressure. The residue was partitioned between EtOAc and H_2O. The organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure to dryness. The residue was purified by flash column chromatography to give the product.

4.2.1. 1,3-Dimethyl-6-phenyluracil[27,59,60,64,78] *(**3aa**).* Compound **3aa** was prepared by the general procedure and purified by flash column chromatography (82%, Hex/EtOAc=7:3, R_f=0.28 (Hex/EtOAc=5:5)). An analytical sample was recrystallized from Hex/EtOAc. Mp 104–106 °C (Hex/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43–7.41 (m, 3H, Ph), 7.28–7.26 (m, 2H, Ph), 5.62 (s, 1H, 5-H), 3.32 (s, 3H, CH_3), 3.15 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.4, 154.6, 152.6, 133.4, 130.2 (CH), 129.0 (CH), 127.8 (CH), 102.4 (CH), 34.6 (CH_3), 28.0 (CH_3). MS (EI, 20 eV) *m*/*z* 84 (37), 118 (35), 215 (65), 216 (100) (M^+). HRMS calcd for $C_{12}H_{12}N_2O_2$ (M^+): 216.0899. Found: 216.0895.

4.2.2. 1,3-Dimethyl-6-(p-tolyl)uracil[60,62,64,79] *(**3ab**).* Compound **3ab** was prepared by the general procedure and purified by flash column chromatography (58%, Hex/EtOAc=7:3, R_f=0.33 (Hex/EtOAc=5:5)). Mp 110–112 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22 (d, 2H, *J*=8.0 Hz, Ph), 7.16 (d, 2H, *J*=8.0 Hz, Ph), 5.60 (s, 1H, 5-H), 3.32 (s, 3H, CH_3), 3.16 (s, 3H, CH_3), 2.35 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.5, 154.8, 152.7, 140.4, 130.5, 129.6 (CH), 127.7 (CH), 102.3 (CH), 34.6 (CH_3), 28.0 (CH_3), 21.3 (CH_3). MS (EI, 20 eV) *m*/*z* 72 (84), 132 (36), 229 (75), 230 (100) (M^+). HRMS calcd for $C_{13}H_{14}N_2O_2$ (M^+): 230.1055. Found: 230.1050.

4.2.3. 1,3-Dimethyl-6-(p-methoxyphenyl)uracil[60,64,79] *(**3ac**).* Compound **3ac** was prepared by the general procedure and purified by flash column chromatography (54%, Hex/EtOAc=7:3, R_f=0.23 (Hex/

EtOAc=5:5)). Mp 98–100 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22 (dd, 2H, J=6.9, 1.8 Hz, Ph), 6.93 (dd, 2H, J=7.0, 1.8 Hz, Ph), 5.61 (s, 1H, 5-H), 3.81 (s, 3H, CH_3), 3.33 (s, 3H, CH_3), 3.19 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.5, 161.0, 154.7, 152.8, 129.4 (CH), 125.6, 114.4 (CH), 102.3 (CH), 55.5 (CH_3), 34.7 (CH_3), 28.0 (CH_3). MS (EI, 20 eV) m/z 72 (46), 148 (28), 245 (72), 246 (100) (M^+). HRMS calcd for $C_{13}H_{14}N_2O_3$ (M^+): 246.1004. Found: 246.0995.

*4.2.4. 1,3-Dimethyl-6-(p-chlorophenyl)uracil (**3ad**).* Compound **3ad** was prepared by the general procedure and purified by flash column chromatography (55%, Hex/EtOAc=7:3, R_f=0.25 (Hex/EtOAc=5:5)). Mp 126–130 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, 2H, J=8.3 Hz, Ph), 7.24 (d, 2H, J=8.4 Hz, Ph), 5.6 (s, 1H, 5-H), 3.31 (s, 3H, CH_3), 3.15 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.2, 153.5, 152.5, 136.5, 131.8, 129.4 (CH), 129.2 (CH), 102.6 (CH), 34.6 (CH_3), 28.0 (CH_3). MS (EI, 20 eV) m/z 72 (52), 152 (50), 249 (94), 250 (100) (M^+), 251 (19), 252 (10) (M+2). HRMS calcd for $C_{12}H_{11}N_2O_2Cl$ (M^+): 250.0509. Found: 250.0503.

*4.2.5. 1,3-Dimethyl-6-(p-bromophenyl)uracil (**3ae**).* Compound **3ae** was prepared by the general procedure and purified by flash column chromatography (28%, Hex/EtOAc=7:3, R_f=0.28 (Hex/EtOAc=5:5)). Mp 116–120 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (d, 2H, J=8.4 Hz, Ph), 7.17 (d, 2H, J=8.4 Hz, Ph), 5.60 (s, 1H, 5-H), 3.30 (s, 3H, CH_3), 3.14 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.1, 153.4, 152.5, 132.3 (CH), 132.2, 129.4 (CH), 124.7, 102.6 (CH), 34.5 (CH_3), 28.0 (CH_3). MS (EI, 20 eV) m/z 72 (93), 196 (73), 198 (70), 293 (95), 294 (100) (M^+), 295 (97), 296 (98) (M+2). HRMS calcd for $C_{12}H_{11}N_2O_2Br$ (M^+): 294.0004. Found: 293.9993.

*4.2.6. 1,3-Dimethyl-6-(p-nitrophenyl)uracil[27] (**3af**).* Compound **3af** was prepared by the general procedure and purified by flash column chromatography (20%, Hex/EtOAc=7:3, R_f=0.28 (Hex/EtOAc=5:5)). Mp 136–140 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (d, 2H, J=8.7 Hz, Ph), 7.56 (d, 2H, J=8.8 Hz, Ph), 5.71 (s, 1H, 5-H), 3.40 (s, 3H, CH_3), 3.21 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.1, 152.5, 152.3, 149.1, 139.5, 129.3 (CH), 124.5 (CH), 103.3 (CH), 34.8 (CH_3), 28.4 (CH_3). MS (EI, 20 eV) m/z 163 (48), 260 (95), 261 (100) (M^+). HRMS calcd for $C_{12}H_{11}N_3O_4$ (M^+): 261.0750. Found: 261.0742.

*4.2.7. 1,3-Dimethyl-6-(o-tolyl)uracil[60,64,79] (**3ag**).* Compound **3ag** was prepared by the general procedure and purified by flash column chromatography (85%, Hex/EtOAc=7:3, R_f=0.33 (Hex/EtOAc=5:5)). Mp 128–130 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32–7.28 (m, 1H, Ph), 7.22–7.19 (m, 2H, Ph), 7.08 (d, 1H, J=8.0 Hz, Ph), 5.55 (s, 1H, 5-H), 3.31 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 2.16 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.4, 154.0, 152.4, 135.1, 132.9, 130.6 (CH), 130.0 (CH), 127.9 (CH), 126.4 (CH), 101.9 (CH), 33.1 (CH_3), 27.9 (CH_3), 19.2 (CH_3). MS (EI, 20 eV) m/z 144 (40), 215 (50), 230 (100). HRMS (EI) calcd for $C_{13}H_{14}N_2O_2$: 230.1055. Found: 230.1049.

*4.2.8. 1,3-Dimethyl-6-(m-methoxyphenyl)uracil[60,79] (**3ah**).* Compound **3ah** was prepared by the general procedure and purified by flash column chromatography (72%, Hex/EtOAc=7:3, R_f=0.38 (Hex/EtOAc=5:5)). Mp 100–108 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (t, 1H, J=8.0 Hz, Ph), 6.95 (dd, 1H, J=8.3, 2.3 Hz, Ph), 6.83 (d, 1H, J=7.6 Hz, Ph), 6.78 (d, 1H, J=2.0 Hz, Ph), 5.62 (s, 1H, 5-H), 3.77 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 3.15 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.4, 159.8, 154.5, 152.6, 134.5, 130.2 (CH), 119.9 (CH), 115.5 (CH), 113.6 (CH), 102.2 (CH), 55.4 (CH_3), 34.5 (CH_3), 28.0 (CH_3). MS (EI, 20 eV) m/z 72 (92), 245 (60), 246 (100) (M^+). HRMS calcd for $C_{13}H_{14}N_2O_3$ (M^+): 246.1004. Found: 246.0994.

*4.2.9. 1,3-Dimethyl-6-(o-methoxyphenyl)uracil[79] (**3ai**).* Compound **3ai** was prepared by the general procedure and purified by flash column chromatography (66%, Hex/EtOAc=7:3, R_f=0.33 (Hex/EtOAc=5:5)). Mp 116–118 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.34 (m, 1H, Ph), 7.08 (dd, 1H, J=7.2, 1.6 Hz, Ph), 6.93 (t, 1H, J=7.4 Hz, Ph), 6.89 (d, 1H, J=8.4 Hz, Ph), 5.53 (s, 1H, 5-H), 3.74 (s, 3H, CH_3), 3.27 (s, 3H, CH_3), 3.03 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.5, 155.9, 152.7, 152.3, 131.8 (CH), 129.5 (CH), 122.3, 121.0 (CH), 110.9 (CH), 102.3 (CH), 55.4 (CH_3), 33.0 (CH_3), 27.8 (CH_3). MS (EI, 20 eV) m/z 158 (25), 246 (100) (M^+). HRMS (EI) calcd for $C_{13}H_{14}N_2O_3$ (M^+): 246.1004. Found: 246.1002.

*4.2.10. 1,3,5-Trimethyl-6-phenyluracil (**3ba**).* Compound **3ba** was prepared by the general procedure and purified by flash column chromatography (21%, Hex/EtOAc=7:3, R_f=0.38 (Hex/EtOAc=5:5)). Mp 104–106 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49–7.47 (m, 3H, Ph), 7.18 (d, 2H, J=7.4 Hz, Ph), 3.40 (s, 3H, CH_3), 3.04 (s, 3H, CH_3), 1.66 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.9, 152.2, 149.8, 133.2, 129.7 (CH), 129.4 (CH), 128.0 (CH), 108.6, 34.6 (CH_3), 28.4 (CH_3), 12.9 (CH_3). MS (EI, 20 eV) m/z 229 (100), 230 (60) (M^+). HRMS (ESI) calcd for $C_{13}H_{14}N_2O_2$ (M+H): 231.1134. Found: 231.1134.

*4.2.11. 1,3,5-Trimethyl-6-(p-tolyl)uracil (**3bb**).* Compound **3bb** was prepared by the general procedure and purified by flash column chromatography (46%, Hex/EtOAc=7:3, R_f=0.40 (Hex/EtOAc=5:5)). Mp 156–160 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (d, 2H, J=7.8 Hz, Ph), 7.07 (d, 2H, J=8.0 Hz, Ph), 3.42 (s, 3H, CH_3), 3.06 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 1.68 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.0, 152.4, 150.1, 139.8, 130.4, 130.1 (CH), 128.0 (CH), 108.7, 34.6 (CH_3), 28.5 (CH_3), 21.5 (CH_3), 12.9 (CH_3). MS (EI, 20 eV) m/z 243 (100), 244 (83) (M^+). HRMS (ESI) calcd for $C_{14}H_{16}N_2O_2$ (M+H): 245.1290. Found: 245.1309.

*4.2.12. 1,3,5-Trimethyl-6-(p-methoxyphenyl)uracil (**3bc**).* Compound **3bc** was prepared by the general procedure and purified by flash column chromatography (31%, Hex/EtOAc=7:3, R_f=0.25 (Hex/EtOAc=5:5)). Mp 144–148 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.09 (d, 2H, J=8.8 Hz, Ph), 6.98 (d, 2H, J=8.7 Hz, Ph), 3.84 (s, 3H, CH_3), 3.39 (s, 3H, CH_3), 3.05 (s, 3H, CH_3), 1.67 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.9, 160.4, 152.3, 149.8, 129.5 (CH), 125.4, 114.8 (CH), 108.9, 55.5 (CH_3), 34.6 (CH_3), 28.4 (CH_3), 12.9 (CH_3). MS (EI, 20 eV) m/z 259 (100), 260 (78) (M^+). HRMS (ESI) calcd for $C_{14}H_{16}N_2O_3$ (M+H): 261.1239. Found: 261.1255.

*4.2.13. 1,3,5-Trimethyl-6-(p-chlorophenyl)uracil (**3bd**).* Compound **3bd** was prepared by the general procedure and purified by flash column chromatography (29%, Hex/EtOAc=7:3, R_f=0.43 (Hex/EtOAc=5:5)). Mp 168–178 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (d, 2H, J=8.1 Hz, Ph), 7.15 (d, 2H, J=8.3 Hz, Ph), 3.42 (s, 3H, CH_3), 3.06 (s, 3H, CH_3), 1.68 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.7, 152.2, 148.6, 136.0, 131.6, 130.0 (CH), 129.6 (CH), 109.0, 34.7 (CH_3), 28.5 (CH_3), 12.9 (CH_3). MS (EI, 20 eV) m/z 263 (100), 264 (68) (M^+), 265 (20), 266 (25) (M+2). HRMS (ESI) calcd for $C_{13}H_{13}N_2O_2Cl$ (M+H): 265.0744. Found: 265.0720.

*4.2.14. 1,3-Dimethyl-5-fluoro-6-phenyluracil (**3ca**).* Compound **3ca** was prepared by the general procedure and purified by flash column chromatography (47%, Hex/EtOAc=7:3, R_f=0.45 (Hex/EtOAc=5:5)). Mp 104–108 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55–7.53 (m, 3H, Ph), 7.35–7.33 (m, 2H, Ph), 3.45 (s, 3H, CH_3), 3.15 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.3 (d, J=27 Hz), 151.0, 139.2 (d, J=25 Hz), 137.6 (d, J=230 Hz), 130.9 (CH), 129.5 (CH), 128.9 (d, J=2 Hz, CH), 127.5, 34.4 (CH_3), 28.8 (CH_3). MS (EI, 20 eV) m/z 234 (100) (M^+). HRMS (ESI) calcd for $C_{12}H_{11}N_2O_2F$ (M+H): 235.0883. Found: 235.0891.

*4.2.15. 1,3-Dimethyl-5-fluoro-6-(p-tolyl)uracil (**3cb**).* Compound **3cb** was prepared by the general procedure and purified by flash column

chromatography (41%, Hex/EtOAc=7:3, R_f=0.48 (Hex/EtOAc=5:5)). Mp 128–132 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (d, 2H, J=8.2 Hz, Ph), 7.21 (d, 2H, J=8.0 Hz, Ph), 3.43 (s, 3H, CH_3), 3.14 (s, 3H, CH_3), 2.42 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.3 (d, J=26 Hz), 151.0, 141.2, 139.4 (d, J=25 Hz), 137.6 (d, J=228 Hz), 130.1 (CH), 128.7 (d, J=2 Hz, CH), 124.4, 34.3 (CH_3), 28.7 (CH_3), 21.6 (CH_3). MS (EI, 20 eV) m/z 248 (100) (M^+). HRMS (ESI) calcd for $C_{13}H_{13}N_2O_2F$ (M+H): 249.1039. Found: 249.1044.

*4.2.16. 1,3-Dimethyl-5-fluoro-6-(p-chlorophenyl)uracil (**3cd**).* Compound **3cd** was prepared by the general procedure and purified by flash column chromatography (42%, Hex/EtOAc=7:3, R_f=0.48 (Hex/EtOAc=5:5)). Mp 178–182 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (d, 2H, J=8.4 Hz, Ph), 7.29 (d, 2H, J=8.4 Hz, Ph), 3.44 (s, 3H, CH_3), 3.16 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.1 (d, J=26 Hz), 150.9, 138.1 (d, J=25 Hz), 137.7 (d, J=230 Hz), 137.4, 130.4 (d, J=1 Hz, CH), 129.9 (CH), 125.8, 34.4 (CH_3), 28.8 (CH_3). MS (EI, 20 eV) m/z 267 (78), 268 (100) (M^+), 269 (27), 270 (41) (M+2). HRMS (ESI) calcd for $C_{12}H_{10}N_2O_2FCl$ (M+H): 269.0493. Found: 269.0512.

*4.2.17. 5-Chloro-1,3-dimethyl-6-phenyluracil[80] (**3da**).* Compound **3da** was prepared by the general procedure and purified by flash column chromatography (68%, Hex/EtOAc=8:2, R_f=0.45 (Hex/EtOAc=5:5)). Mp 122–126 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53–7.51 (m, 3H, Ph), 7.27–7.25 (m, 2H, Ph), 3.45 (s, 3H, CH_3), 3.11 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.4, 151.3, 150.7, 131.8, 130.4 (CH), 129.5 (CH), 127.9 (CH), 108.4, 35.4 (CH_3), 29.4 (CH_3). MS (EI, 20 eV) m/z 118 (82), 250 (100) (M^+), 252 (38) (M+2). HRMS (ESI) calcd for $C_{12}H_{11}N_2O_2Cl$ (M+H): 251.0587. Found: 251.0566.

*4.2.18. 5-Chloro-1,3-dimethyl-6-(p-tolyl)uracil (**3db**).* Compound **3db** was prepared by the general procedure and purified by flash column chromatography (45%, Hex/EtOAc=8:2, R_f=0.40 (Hex/EtOAc=5:5)). Mp 182–186 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (d, 2H, J=7.9 Hz, Ph), 7.16 (d, 2H, J=8.1 Hz, Ph), 3.47 (s, 3H, CH_3), 3.13 (s, 3H, CH_3), 2.43 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.5, 151.5, 151.0, 140.8, 130.2 (CH), 128.9, 127.9 (CH), 108.6, 35.5 (CH_3), 29.5 (CH_3), 21.7 (CH_3). MS (EI, 20 eV) m/z 132 (58), 264 (100) (M^+), 266 (38) (M+2). HRMS (ESI) calcd for $C_{13}H_{13}N_2O_2Cl$ (M+H): 265.0744. Found: 265.0759.

*4.2.19. 5-Chloro-1,3-dimethyl-6-(p-methoxyphenyl)uracil (**3dc**).* Compound **3dc** was prepared by the general procedure and purified by flash column chromatography (44%, Hex/EtOAc=8:2, R_f=0.28 (Hex/EtOAc=5:5)). Mp 126–132 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20 (d, 2H, J=8.7 Hz, Ph), 7.04 (d, 2H, J=8.7 Hz, Ph), 3.87 (s, 3H, CH_3), 3.47 (s, 3H, CH_3), 3.15 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.1, 159.5, 151.5, 150.8, 129.6 (CH), 123.9, 114.9 (CH), 108.9, 55.6 (CH_3), 35.6 (CH_3), 29.5 (CH_3). MS (EI, 20 eV) m/z 148 (38), 279 (50), 280 (100) (M^+), 282 (36) (M+2). HRMS (ESI) calcd for $C_{13}H_{13}N_2O_3Cl$ (M+H): 281.0693. Found: 281.0691.

*4.2.20. 5-Chloro-1,3-dimethyl-6-(p-chlorophenyl)uracil (**3dd**).* Compound **3dd** was prepared by the general procedure and purified by flash column chromatography (35%, Hex/EtOAc=8:2, R_f=0.48 (Hex/EtOAc=5:5)). Mp 156–160 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (d, 2H, J=8.5 Hz, Ph), 7.24 (d, 2H, J=8.4 Hz, Ph), 3.47 (s, 3H, CH_3), 3.14 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.3, 151.3, 149.6, 136.9, 130.1, 130.03 (CH), 129.55 (CH), 108.8, 35.5 (CH_3), 29.5 (CH_3). MS (EI, 20 eV) m/z 152 (78), 283 (81), 284 (100) (M^+), 285 (45), 286 (41) (M+2), 287 (2), 288 (0.5) (M+4). HRMS (EI) calcd for $C_{12}H_{10}N_2O_2Cl_2$: 284.0119. Found: 284.0109.

*4.2.21. 5-Bromo-1,3-dimethyl-6-phenyluracil[20] (**3ea**).* Compounds **3aa** and **3ea** were obtained from the reaction of 5-bromo-1,3-dimethyluracil (**3e**) with the general procedure and purified by flash column chromatography (Hex/EtOAc=8:2, then $CHCl_3$; compound **3aa**: 23%, R_f=0.28 (Hex/EtOAc=5:5); **3ea**: 39%, R_f=0.45 (Hex/EtOAc=5:5)). Compound **3ea**: mp 124–128 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54–7.52 (m, 3H, Ph), 7.27–7.24 (m, 2H, Ph), 3.48 (s, 3H, CH_3), 3.14 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.5, 152.5, 151.7, 133.8, 130.4 (CH), 129.6 (CH), 127.8 (CH), 98.6, 35.9 (CH_3), 29.7 (CH_3). MS (EI, 20 eV) m/z 118 (92), 294 (100) (M^+), 296 (78) (M+2). HRMS (EI) calcd for $C_{12}H_{11}N_2O_2Br$: 294.0004. Found: 293.9998.

*4.2.22. 5-Bromo-1,3-dimethyl-6-(p-tolyl)uracil (**3eb**).* Compounds **3ab** and **3eb** were obtained from the reaction of 5-bromo-1,3-dimethyluracil (**3e**) with the general procedure and purified by flash column chromatography (Hex/EtOAc=8:2, then $CHCl_3$; compound **3ab**: 9%, R_f=0.28 (Hex/EtOAc=5:5); compound **3eb**: 32%, R_f=0.48 (Hex/EtOAc=5:5)). Compound **3eb**: mp 222–224 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 (d, 2H, J=7.8 Hz, Ph), 7.13 (d, 2H, J=8.0 Hz, Ph), 3.47 (s, 3H, CH_3), 3.13 (s, 3H, CH_3), 2.43 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.5, 152.7, 151.7, 140.6, 130.9, 130.2 (CH), 127.6 (CH), 98.6, 35.9 (CH_3), 29.7 (CH_3), 21.6 (CH_3). MS (EI, 20 eV) m/z 132 (58), 308 (60) (M^+), 310 (100) (M+2). HRMS (ESI) calcd for $C_{13}H_{13}N_2O_2Br$ (M+H): 309.0239. Found: 309.0577.

*4.2.23. 5-Bromo-1,3-dimethyl-6-(p-chlorophenyl)uracil (**3ed**).* Compounds **3ad** and **3ed** were obtained from the reaction of 5-bromo-1,3-dimethyluracil (**3e**) with the general procedure and purified by flash column chromatography (Hex/EtOAc=8:2 then $CHCl_3$; compound **3ad**: 12%, R_f=0.28 (Hex/EtOAc=5:5); compound **3ed**: 24%, R_f=0.45 (Hex/EtOAc=5:5)). Compound **3ed**: mp 188–190 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 (d, 2H, J=8.5 Hz, Ph), 7.21 (d, 2H, J=8.4 Hz, Ph), 3.45 (s, 3H, CH_3), 3.13 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.2, 151.5, 151.3, 136.7, 132.0, 130.0 (CH), 129.3 (CH), 98.8, 35.9 (CH_3), 29.7 (CH_3). MS (EI, 20 eV) m/z 152 (81), 327 (41), 328 (72) (M^+), 329 (79), 330 (100) (M+2), 331 (59), 332 (10) (M+4). HRMS (EI) calcd for $C_{12}H_{10}N_2O_2ClBr$: 329.9594. Found: 329.9589.

*4.2.24. 1,3-Dimethyl-5,6-diphenyluracil[78] (**3ga**).* Compound **3ga** was prepared by the general procedure and purified by flash column chromatography (47%, Hex/EtOAc=8:2 then $CHCl_3$, R_f=0.50 (Hex/EtOAc=5:5)). Mp 172–174 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27–7.26 (m, 3H, Ph), 7.10–7.09 (m, 5H, Ph), 6.99–6.97 (m, 2H, Ph), 3.47 (s, 3H, CH_3), 3.16 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.7, 152.3, 151.5, 133.3, 132.7, 131.2 (CH), 129.4 (CH), 128.9 (CH), 128.7 (CH), 127.8 (CH), 127.1 (CH), 114.9, 35.0 (CH_3), 28.6 (CH_3). MS (EI, 20 eV) m/z 118 (71), 291 (100), 292 (85) (M^+). HRMS (EI) calcd for $C_{18}H_{16}N_2O_2$: 292.1212. Found: 292.1203.

*4.2.25. 1,3-Di(4-methoxybenzyl)-6-(p-tolyl)uracil[62] (**10c**).* Compound **3ga** was prepared by the general procedure and purified by flash column chromatography (43%, Hex/EtOAc=8:2 then $CHCl_3$, R_f=0.63 (Hex/EtOAc=5:5)). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (d, 2H, J=8.6 Hz, Ph), 7.18 (d, 2H, J=7.9 Hz, Ph), 7.06 (d, 2H, J=8.0 Hz, Ph), 6.86 (d, 2H, J=8.7 Hz, Ph), 6.83 (d, 2H, J=8.8 Hz, Ph), 6.74 (d, 2H, J=8.7 Hz, Ph), 5.68 (s, 1H, 5-H), 5.15 (s, 2H, CH_2), 4.89 (s, 2H, CH_2), 3.78 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 2.38 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.2, 159.1, 159.0, 155.0, 152.6, 140.3, 130.8 (CH), 130.4, 129.4 (CH), 128.7, 128.4 (CH), 128.0 (CH), 113.9 (CH), 113.8 (CH), 103.5, 55.3 (2× CH_3), 48.9 (CH_2), 44.0 (CH_2), 21.4 (CH_3). MS (EI, 20 eV) m/z 121 (100), 442 (75) (M^+). HRMS (ESI) calcd for $C_{27}H_{26}N_2O_4$ (M+H): 443.1971. Found: 443.1964.

*4.2.26. 1-(4-Methoxybenzyl)-2-phenyl-4-pyridone (**12a**).* Compound **12a** was prepared by the general procedure and purified by flash column chromatography (28%, $CHCl_3$/MeOH=99:1, R_f=0.40

($CHCl_3$/MeOH=9:1)). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.30 (m, 4H, CH), 7.16 (d, 2H, J=7.0 Hz, CH), 6.73 (m, 4H, CH), 6.36 (d, 1H, J=5.8 Hz, CH), 6.27 (s, 1H, CH), 4.77 (s, 2H, CH_2), 3.69 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.0, 159.5, 152.2, 141.3 (CH), 134.1, 129.6 (CH), 128.7 (CH), 128.6 (CH), 128.2 (CH), 127.6, 120.2 (CH), 118.3 (CH), 114.4 (CH), 56.2 (CH_2), 55.3 (CH_3). MS (EI, 20 eV) m/z 121 (100), 291 (10) (M^+). HRMS (ESI) calcd for $C_{19}H_{17}NO_2$ (M+Na): 314.1157. Found: 314.1159.

*4.2.27. 1-(4-Methoxybenzyl)-2-(p-tolyl)-4-pyridone (**12b**).* Compound **12b** was prepared by the general procedure and purified by flash column chromatography (33%, $CHCl_3$/MeOH=99:1, R_f=0.35 ($CHCl_3$/MeOH=9:1)). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 (d, 1H, J=7.5 Hz, CH), 7.17 (d, 2H, J=7.6 Hz, CH), 7.10 (d, 2H, J=7.2 Hz, CH), 6.80–6.77 (m, 4H, CH), 6.37 (d, 1H, J=7.4 Hz, CH), 6.29 (s, 1H, CH), 4.79 (s, 2H, CH_2), 3.72 (s, 3H, CH_3), 2.33 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.1, 159.6, 152.5, 141.2 (CH), 139.8, 131.3, 129.4 (CH), 128.5 (CH), 128.2 (CH), 127.8, 120.3 (CH), 118.4 (CH), 114.4 (CH), 56.0 (CH_2), 55.4 (CH_3), 21.3 (CH_3). MS (EI, 20 eV) m/z 121 (100), 305 (20) (M^+). HRMS (ESI) calcd for $C_{20}H_{19}NO_2$ (M+H): 306.1494. Found: 306.1506.

*4.2.28. 1-(4-Methoxybenzyl)-2-(p-chlorophenyl)-4-pyridone (**12d**).* Compound **12d** was prepared by the general procedure and purified by flash column chromatography (31%, $CHCl_3$/MeOH=99:1, R_f=0.50 ($CHCl_3$/MeOH=9:1)). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, 1H, J=7.6 Hz, CH), 7.35 (d, 2H, J=8.1 Hz, CH), 7.15 (d, 2H, J=8.2 Hz, CH), 6.77 (m, 4H, CH), 6.41 (d, 1H, J=7.5 Hz, CH), 6.28 (s, 1H, CH), 4.78 (s, 2H, CH_2), 3.74 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.0, 159.8, 151.1, 141.6 (CH), 136.1, 132.6, 130.1 (CH), 129.1 (CH), 128.1 (CH), 127.5, 120.6 (CH), 118.6 (CH), 114.6 (CH), 56.4 (CH_2), 55.4 (CH_3). MS (EI, 20 eV) m/z 121 (100), 325 (10) (M^+), 327 (2) (M+2). HRMS (ESI) calcd for $C_{19}H_{16}NO_2Cl$ (M+H): 326.0948. Found: 326.0942.

4.3. 1-(4-Methoxybenzyl)-4-pyridone (11)

To a mixture of 4-hydroxypyridine (0.953 g, 10 mmol) and DBU (2.3 mL, 15 mmol, 1.5 equiv) in DMF (20 mL) was added *p*-methoxybenzyl chloride (2.0 mL, 15 mmol, 1.5 equiv). The reaction mixture was stirred at 66 °C for 4 h. After cooling to the room temperature, the solvent was removed under reduced pressure. The residue was partitioned between $CHCl_3$ and H_2O. The organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by flash column chromatography ($CHCl_3$/MeOH=9:1, R_f=0.30) to give the white solid (**11**, 1.89 g, 8.8 mmol, 88%). Mp 166–168 °C (from column); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, 2H, J=7.6 Hz, CH), 7.12 (d, 2H, J=8.8 Hz, CH), 6.88 (d, 2H, J=8.8 Hz, CH), 6.31 (d, 2H, J=7.6 Hz, CH), 4.87 (s, 2H, CH_2), 3.77 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.8, 159.9, 139.9 (CH), 129.1 (CH), 126.7, 118.5 (CH), 114.5 (CH), 59.5 (CH_2), 55.3 (CH_3).

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Supplementary data

^{1}H and ^{13}C NMR spectra for representative compounds. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.11.001.

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