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Palladium-Catalyzed Direct Arylation of 5-Halouracils and 5-Halouracil Nucleosides with Arenes and Heteroarenes Promoted by TBAF

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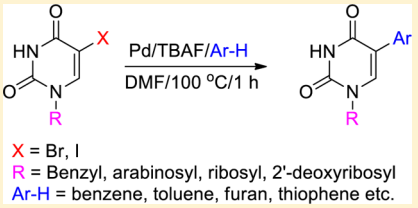
Supporting Information

ABSTRACT: The 1-*N*-benzyl-5-iodo(or bromo)uracil undergoes Pd-catalyzed [$Pd_2(dba)_3$] direct arylation with benzene and other simple arenes in the presence of TBAF in DMF without the necessity of adding any ligands or additives to give 5-arylated uracil analogues. The TBAF-promoted coupling also occurs efficiently with electron rich heteroarenes at 100 °C (1 h) even with only small excess of heteroarenes. The protocol avoids usage of the arylboronic acid or stannane precursors for the synthesis of 5-(2-furyl, or 2-thienyl, or 2-pyrrolyl)uracil nucleosides, which are used as important RNA and DNA fluorescent probes. The fact that 1-*N*-benzyl-3-*N*-methyl-5-iodouracil did not undergo the TBAF-promoted couplings with arenes or heteroarenes suggests that the C4-alkoxide (enol form of uracil) facilitates coupling by participation in the intramolecular processes of hydrogen abstraction from arenes. TBAF-promoted arylation was extended into the other enolizable heterocyclic systems such as 3-bromo-2-pyridone. The π-excessive heteroarenes also coupled with 5-halouracils in the presence of $Pd(OAc)_2/Cs_2CO_3$/PivOH combination in DMF (100 °C, 2 h) to yield 5-arylated uracils.



INTRODUCTION

The 5-substituted pyrimidine nucleosides are important synthetic intermediates, which also show a broad spectrum of biological activity.[1] Highly potent and selective antiviral drugs of this class include (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU)[2] and bicyclic furanopyrimidine-2-one nucleoside analogues, which display remarkable antiviral potency against the Varicella-Zoster virus.[3] Uracil and uracil nucleosides substituted with aryl groups at positions 5 and/or 6 also display a wide range of biological activities.[4]

Syntheses of the 5-(alkenyl or alkynyl) modified pyrimidines have been achieved by organometallic and/or Pd-assisted cross-couplings with 5-halopyrimidine nucleosides[1,5] and by dehydrogenative alkenylation of uracils with alkenes.[6] The arylation and heteroarylation of the uracil ring at the 5 position have been accomplished efficiently using Suzuki,[7] Stille,[8] and other coupling reactions.[1] The 5-(2-furyl)uridine and 5-(2-thienyl)-2′-deoxyuridine analogues, which were prepared in these ways, have been incorporated into RNA and DNA fragments using solid support and used as fluorescent probes.[9] Hocek and co-workers showed that 5-aryl and 5-(2-thienyl) modified dU(or C)TPs are substrates for DNA polymerases and can be used for DNA staining and electrochemical labels.[10] The Stille procedure was also successful on a polyuridine RNA strand bearing 5-iodouridine base, although 60 equiv of 2-(tributylstannyl)furan reagent and 15 equiv of $Pd_2(dba)_3$ catalyst along with 30 equiv of $P(furyl)_3$ ligand were required.[11]

Direct arylation of aromatic rings with Pd-activated aryl halides has been recently established as an excellent set of protocols for the synthesis of biaryls.[12] These protocols, which eliminate the use of organometallics substrates, have begun to compete with traditional Pd-catalyzed cross-couplings[13] as a tool for the synthesis of biaryls. Direct arylations, in which arene-derived organometallic components are replaced by simple arenes, can proceed efficiently intra-[14] or intermolecularly[14b,15] and are especially efficient with electron-rich heteroaromatics.[12d] The Pd-catalyzed direct arylation reactions of aryl halides are postulated to occur via electrophilic aromatic substitution (electrophilic palladation with nucleophilic arenes) or concerted palladation-deprotonation involving proton abstraction by halide or carboxylate ligands.[12,14c,16]

Direct arylation of the electron-poor pyrimidines[17] and pyridine oxides[15a,18] with aryl halides as well as intramolecular arylation at C6 or C5 of the 5-(or 6)-[*N*-(2-bromobenzyl)-*N*-methylamino]-1,3-dimethyluracil derivatives[19] have been reported. Hocek and co-workers developed regioselective Pd-catalyzed direct C−H arylation of 1,3-diprotected uracil derivatives at the 5 or 6 position controlled by the presence or absence of CuI.[20] Kim and co-workers recently reported Pd-catalyzed 5-arylation of 1,3-dimethyluracil with aryl bromides as well as oxidative homocoupling of the 1,3-dimethyluracil derivatives.[21] The 6-aryluracil derivatives were also prepared by CuBr-mediated arylation of the 1,3-dimethyluracil with aryl iodides.[22]

Direct arylation of the 3-*N* unprotected uracil analogues, which allows for enolization between 4-oxo group and the hydrogen at 3-*N* position is underdeveloped. This tautomerization is critical in the biology and chemistry of RNA/DNA and in the nucleoside-derived drug metabolism. The currently

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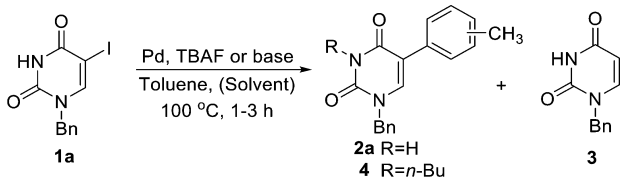
Table 1. Optimization of the Arylation of 1-*N*-Benzyl-5-iodouracil 1a with Toluene[a]



entry	reagent/solvent	Pd	TBAF (equiv)	base (2 equiv)	time (h)	**2a**[b] yield (%)[c,d]	**3** yield (%)[d]
1	toluene	$Pd_2(dba)_3$	7	–	6	45[e]	3
2	toluene	$Pd_2(dba)_3$	7	–	0.75	75 (71)[f]	5
3	toluene	$Pd_2(dba)_3$	6	–	1	60	15
4	toluene	$Pd_2(dba)_3$	5	–	1	48[g]	17
5	toluene	$Pd_2(dba)_3$	3	–	1	30	8
6	toluene	$Pd(OAc)_2$	7	–	1	70 (68)[h]	7
7	toluene/DMF[i]	$Pd_2(dba)_3$	7	–	1	82 (65)	7
8	toluene/DMF[j]	$Pd_2(dba)_3$	7[k]	–	1	65 (50)[l]	19
9	toluene/DMA[i]	$Pd_2(dba)_3$	7	–	1	20	10
10	toluene/dioxane[i]	$Pd_2(dba)_3$	7	–	1	40	46
11	toluene/DMF[j]	$Pd_2(dba)_3$	–	KF[m]	2	–	11
12	toluene/DMF[j]	$Pd_2(dba)_3$	–	Cs_2CO_3[n]	2	–	25
13	toluene/DMF[j]	$Pd(OAc)_2$	–	$KOSiMe_3$	2	–	80 (65)
14	toluene/DMF[j]	$Pd(OAc)_2$	–	Ag_2CO_3[o]	2	–	17
15	toluene/DMF/H_2O	$Pd(OAc)_2$	–	K_2CO_3	2	–	23
16	toluene/DMF[j]	$Pd_2(dba)_3$	TBAI[p]	–	2	–	33
17	toluene/DMF[j]	$Pd_2(dba)_3$	TBAI	CsF[q]	2	–	14
18	toluene/DMF[j]	$Pd(OAc)_2$	2	Cs_2CO_3[r]	2	10	8

[a]Couplings were performed on 0.14 mmol scale of **1a** [0.05 M (entries 1−10) or 0.07 M (entries 11−18)] with 0.05 equiv of Pd catalyst. [b]Mixture of *o*/*m*/*p* isomers (3:2:1, GC−MS). [c]Overall yield for *o*/*m*/*p* isomers. [d]Determined by GC−MS. Isolated yield in parentheses. [e]Also **4** (35%) was formed. After 18 h the yield of **4** was 85%. [f]70% yield at 90 °C for 1.5 h. 40% yield at 80 °C for 4 h. [g]35% with 4 equiv of TBAF. [h]69% yield at 90 °C for 1.5 h. [i]1:1 (v/v). [j]1:9 (v/v). [k]When neat TBAF·3H_2O (7 equiv) was used **2a** (67%) and **3** (20%) were produced. [l]25% yield in toluene/DMF (1:20, v/v). [m]Reaction with CsF or Ag_2CO_3 or K_2CO_3 also did not yield **2a**. [n]Attempts with different equivalents of base (0.5−4.0) or prolonged reaction time (4 h) were also unsuccessful. [o]Couplings also did not proceed in the presence of Cs_2CO_3 or AgOAc and their combination with pivalic acid. [p]Couplings in the presence of tetrabutylammonium chloride, bromide, or hydroxide also failed. [q]With 65% HF·pyridine coupling also failed. [r]Also couplings in the presence of CsF did not improve yield of **2a**.

available methods for direct 5-arylation of the uracil analogues were noted to be either not suitable for the natural (3-*N*-unsubstituted) uracils[20b] or caused cleavage of the nucleoside glycosidic bond.[21a] Moreover, there have been no reports of direct arylation of 5-halopyrimidine nucleosides with arenes, which would supplement the well-established Suzuki and Stille approaches. Herein, we report Pd-catalyzed direct arylation of 5-halouracils with arenes and electron-excessive heterocycles promoted by TBAF or bases that provide access to 5-arylated uracils and uracil nucleosides. The protocol avoids usage of arylboronic acid or stannane precursors and is applicable to the natural nucleosides.

RESULTS AND DISCUSSION

Heating of 1-*N*-benzyl-5-iodouracil **1a** in toluene (6 h, 100 °C) in the presence of $Pd_2(dba)_3$ and TBAF (1 M/THF containing 5% of water) afforded a mixture of 5-(*o*,*m*,*p*-methylphenyl) uracil products **2a** [45% overall yield for *o*/*m*/*p* (3:2:1) isomers]. In addition to the isomeric mixture of **2a**, the reduced substrate **3** (3%) and 3-*N*-butylated byproducts **4** were also detected in the crude reaction mixture (35%; Table 1, entry 1). The ratio for the *o*/*m*/*p* isomers of **2a** was established by comparison with authentic samples prepared by Suzuki coupling[7c] between **1a** and the corresponding tolylboronic acids (see Experimental Section). Careful investigation of reaction time and temperature revealed that arylation of **1a** was completed in less than 1 h (45 min) at 100 °C (entry 2). Reactions at 90 °C for 1.5 h and at 80 °C for 4 h produced **2a** in 70 and 40% yields, respectively. Remarkably, no alkylation (butylation) at the *N*-3 position was observed (GC−MS) on heating for up to 1.5 h at 100 °C or 3 h at 90 °C. At least 7 equiv of TBAF (1 M/THF) were required to produce **2a** in highest yields with the best **2a** to **3** ratios (entries 2−5). Among the other Pd catalysts tested, $Pd(OAc)_2$ also produced **2a** in similar yields (entry 6).

In an effort to lower the ratio of arene (toluene) to **1a**, we sought for the inert solvents suitable for this arylation reaction. Thus, couplings proceeded efficiently in 1:1 and 1:9 (v/v) mixture of toluene/DMF (entries 7 and 8). Arylation in toluene/DMA and toluene/dioxane (1:1, v/v) also gave **2a** but in lower yields (entries 9 and 10), while no product was formed in toluene/THF (1:1; v/v) at reflux.

Replacement of the 1 M TBAF/THF solution with neat TBAF·3 H_2O also yielded **2a** (entry 8, footnote *k*) with similar yield. It is noteworthy that each of these fluoride reagents introduced approximately the same amount of water to the reaction mixture. Water is known to play multiple roles in enhancing the efficiency of the couplings including the formation of the reactive hydroxypalladium intermediates.[23]

Heating of **1a** in a mixture of toluene/DMF (1:9, v/v) in the presence of either other fluoride sources such as CsF or KF (2 equiv) or bases such as Cs_2CO_3, Ag_2CO_3, K_2CO_3, or $KOSiMe_3$, instead of TBAF, failed to produce **2a** leading mainly to **3** (entries 11−15). The outcome was not improved by varying

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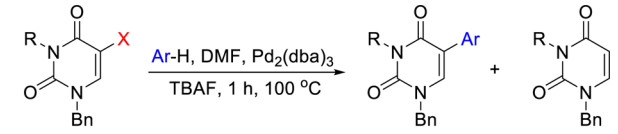
the bases, Pd catalysts, and reaction times (entry 12) or by addition of the pivalic acid (entry 14). Likewise carrying out couplings using a mixture of DMF/H_2O (5:1, v/v), to improve the solubility of salts, was unsuccessful (entry 15).

Arylations were also unsuccessful either in the presence of tetrabutylammonium hydroxide or chloride, bromide, or iodide (entry 16) or in the combination of the latter with other fluoride sources (CsF or HF; entry 17). Coupling with 2 equiv of TBAF with other bases or fluoride sources produced **2a** in low yields (e.g., entry 18).

Direct arylation of the 5 position of the uracil ring promoted by TBAF has general applicability; hence, reaction of 5-halouracils **1a** or **1b** with various arenes and heterocyclic arenes are presented in Table 2. Thus, heating of 5-iodouracil **1a** in benzene/DMF (1:9, v/v) in the presence of TBAF (7 equiv) at

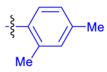
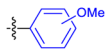
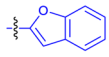
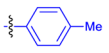
Table 2. Arylation of 5-Halouracils 1 with Arenes and Electron-Rich Heteroaromatics Promoted by TBAF[a]



1a, R = H, X = I
1b, R = H, X = Br
1c, R = Me, X = I

2, R = H
5, R = Me

3, R = H
6, R = Me

Entry	Substrate	Product	Ar-	**2** or **5** Yield[b,c] (%)	**3** or **6** Yield[b] (%)
1	**1a**	**2b**		71 (59)	13
2	**1a**	**2c**		88[d] (55)[e]	5
3	**1a**	**2d**		76[f] (68)	21
4	**1b**	**2b**		78[g] (71)	20
5	**1a**	**2e**		95[h,i] (81)	--
6	**1a**	**2f**		72[h,j] (66)	22
7	**1a**	**2g**		97[h] (91)	--
8	**1a**	**2h**		80[h] (70)	2
9	**1a**	**2i**		61[h] (54)	28
10	**1b**	**2e**		91 (85)	--
11	**1c**	**5a**		-	75 (73)
12	**1c**	**5g**		-	59[k]

[a]Couplings were performed on 0.14 mmol scale of substrates **1** (0.07 M) in the presence of 7 equiv of TBAF and 0.05 equiv of Pd catalyst with Ar−H to DMF ratio of 1:9 (v/v) unless otherwise noted. [b]Determined by GC−MS. [c]Isolated yield in parentheses. [d]Overall yield for three possible isomers (ratio, 14:5:1). [e]Yield for 2,4-dimethylphenyl isomer of **2c**. [f]Overall yield for mixture of *o*/*m*/*p* (ratio, 4:1:1) isomers. [g]With 14 equiv of TBAF. [h]With 3.5 equiv of TBAF. [i]77% at 90 °C. [j]47% with benzofuran:**1a** ratio (1.5:1). [k]Coupling with furan instead of thiophene also produced **6** (60%).

100 °C for 1 h (ratio of benzene to **1a**, 16:1) produced 5-phenyluracil **2b** as a single product in addition to the reduced substrate **3** (Table 2, entry 1). Arylation of **1a** with xylene gave a mixture of the three regioisomers (88%) from which the 2,4-dimethylphenyl isomer **2c** was isolated in 55% yield (entry 2). Arene bearing the electron-donating methoxy group on the phenyl ring produced **2d** as a mixture of *o*/*m*/*p* regioisomers (entry 3). The ratio for the *o*/*m*/*p* isomers of **2d** was established by comparison with authentic samples prepared by Suzuki coupling[7c] between **1a** and the corresponding methoxyphenylboronic acids (see Experimental Section). However, arenes with EWG either failed (nitrobenzene) or gave the corresponding 5-arylated products in low yields (1,2,3,4,5-pentafluorobenzene, 15%, GC−MS). Arylation of 5-bromouracil **1b**, prepared by bromination of 1-*N*-benzyluracil with 1,3-dibromo-5,5-dimethylhydantoin in the presence of TMSOTf,[24] with benzene proceeded smoothly to afford **2b** in 78% yield but needed 14 equiv of TBAF (entry 4).

The arylation of 5-iodouracil **1a** with electron rich heteroaromatics requires only 3.5 equiv of TBAF and also occurs efficiently at 90 °C. Thus, **1a** coupled with furan to give 5-(2-furyl)uracil **2e** (95%) without any reduction product **3** (entry 5). Arylation of **1a** with benzo[*b*]furan proceeded in good yield even with only slight excess of benzo[*b*]furan to **1a** (1.5:1, mol/mol; benzo[*b*]furan/DMF, 1:100, v/v; entry 6). Reaction of **1a** with thiophene gave 5-(2-thienyl)uracil **2g** quantitatively (entry 7), while coupling with 2-substituted thiophenes provided single products **2h** or **2i** (entries 8 and 9). The 5-bromouracil **1b** also coupled efficiently with furan under similar conditions to give **2e** (entry 10). Interestingly, TBAF-promoted couplings between 3-*N*-methyl-5-iodouracil **1c** and toluene or thiophene (or furan) was unsuccessful yielding only the reduced product **6** (entries 11−12).

In contrast to the simple arenes (Table 1, entries 11−18), the π-excessive heteroarenes did couple successfully with 5-halouracils under TBAF-free conditions in the presence of bases (Table 3). For example on heating of **1a** with thiophene (15 equiv) in DMF (2 h, 100 °C) in the presence of $Pd(OAc)_2$ and K_2CO_3 (2 equiv) only reduced product **3** was formed (Table 3, entry 1). However, when the reaction was carried out in a mixture of DMF/H_2O (5:1, v/v) product **2g** was obtained in 75% yield (entry 2). Apparently the increased solubility of K_2CO_3 in the DMF/H_2O mixture changed the outcome of the reaction dramatically. The very low solubility of K_2CO_3 in organic solvents (e.g., less than 1% in DMA after 30 min heating at 120 °C) is known.[16b] Coupling yields were only slightly affected when 1 or 4 equiv of K_2CO_3 was used (entry 3). Direct arylation in the presence of NaOH or CsF or Ag_2CO_3 gave **2g** in lower yields (entries 4−6) but proceeded efficiently with Cs_2CO_3 (entry 7). Arylation at 80 °C (2 h) gave **2g** in lower yield (53%) but with an increased ratio relative to **3** (entry 8), while reaction at 60 °C (4 h) produced **2g** in only 15% (entry 9). As expected because of the solubility difference between K_2CO_3 and Cs_2CO_3, the heteroarylation in the presence of Cs_2CO_3 was also successful in neat DMF (entry 10). Addition of the pivalic acid[16b] to the reaction mixture not only increased the yields but also the ratio of **2g** to **3** (entry 11). In the presence of pivalic acid coupling proceeded at 80 °C (entry 12) but gave **2g** in low yield at 60 °C. It is worth mentioning that, in general, direct arylation of **1a** promoted by TBAF gave the best results with the $Pd_2(dba)_3$ catalyst, while base-promoted coupling proceeded more efficiently with $Pd(OAc)_2$.

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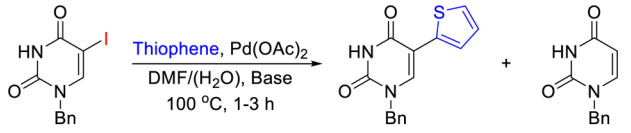
Table 3. Optimization of the Base-Promoted Arylation of 1-*N*-Benzyl-5-iodouracil 1a with Thiophene[a]



entry	solvent	base	equiv	T (°C)	yield **2g** (%)[b,c]	yield **3** (%)[b]
1	DMF	K_2CO_3	2	100	–	80 (74)
2	DMF/H_2O[d]	K_2CO_3	2	100	75 (60)[e]	20
3	DMF/H_2O	K_2CO_3	1[f]	100	73 (61)	17
4	DMF/H_2O	NaOH	2	100	16	30
5	DMF/H_2O	CsF	2	100	37	35
6	DMF/H_2O	Ag_2CO_3	2	100	20	8
7	DMF/H_2O	Cs_2CO_3	2	100	61 (53)	32
8	DMF/H_2O	Cs_2CO_3	2	80	53 (41)	8
9	DMF/H_2O	Cs_2CO_3	2	60	15	2
10	DMF	Cs_2CO_3	2	100	76 (65)	11
11	DMF	Cs_2CO_3[g]	2	100	82 (76)[h]	4
12	DMF	Cs_2CO_3[g]	2	80	51 (43)	8

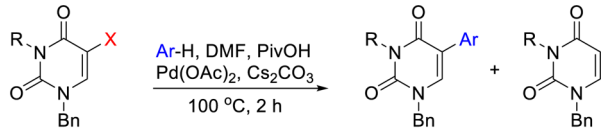
[a]Couplings were performed on 0.14 mmol scale of **1a** (0.07 M) in the presence of 0.05 equiv of $Pd(OAc)_2$ with thiophene to DMF ratio of 1:9 (v/v). [b]Determined by GC–MS of the crude reaction mixture. [c]Isolated yield in parentheses. [d]DMF/H_2O (5:1, v/v). [e]$Pd_2(dba)_3$ gave **2g** in 36% isolated yield. [f]4 equiv of K_2CO_3 gave **2g** in 50% isolated yield. [g]With addition of PivOH (1.25 equiv). [h]80% yield with addition of PivOH (1.25 equiv) and Ag_2CO_3 (1.0 equiv).

Base-promoted direct arylation of the 5 position of the uracil ring with other electron-rich heteroarenes are presented in Table 4. Thus, heating of **1a** with furan (ratio of furan to **1a**, 15:1) in DMF in the presence of Cs_2CO_3 (2 equiv) and PivOH at 100 °C for 2 h produced **2e** in addition to **3** (entry 1). Arylation proceeded smoothly with thiophene (entry 2) but failed with pyrrole (entry 3). The coupling of 5-bromouracil **1b** with furan and thiophene gave products but in lower yields (entries 4 and 5). Interestingly, contrary to the unsuccessful TBAF-promoted coupling of 3-*N*-methyl-5-iodouracil **1c** with heteroarenes (Table 2, entry 12), the base-promoted arylation of **1c** with furan or thiophene gave coupling products **5e** and **5g** (entries 6 and 7). Attempted 5-arylations of the 3-*N* unprotected **1a** and 3-*N* protected **1c** uracil substrates with simple arenes in the presence of Cs_2CO_3 were unsuccessful (entries 8 and 9).

Our methodology, which not only avoids the use of toxic tributyl(2-furyl)stannne[9a,b,11] but also works efficiently with the 3-*N* unprotected uracil substrates,[20b,21a,22] was applied to the synthesis of 5-heteroarylated uracil nucleosides. Thus, reaction of 2′,3′,5′-tri-*O*-acetyl-1-(β-D-arabinofuranosyl)-5-iodouracil **7** with furan in DMF (1:9, v/v) in the presence of TBAF (3.5 equiv) and $Pd_2(dba)_3$ afforded 5-(2-furyl)uracil analogue **12** (61%; Table 5, entry 1). Similarly, the protected 2′-deoxy-5-iodouridine **8** was converted to **13** (entry 2), confirming that direct arylation conditions are compatible with the commonly used acyl protection group.

Arylation proceeded also with the unprotected nucleosides. Thus, subjection of 1-(β-D-arabinofuranosyl)-5-iodouracil **9**, 2′-deoxy-5-iodouridine **10**, and 5-iodouridine **11** to TBAF-promoted/Pd-catalyzed coupling with furan gave the corresponding 5-(2-furyl) analogues **14**–**16** in high yields (entries

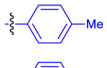
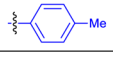
Table 4. Arylation of 5-Halouracils 1 with Electron-Rich Heteroarenes Promoted by Cs_2CO_3[a]



1a, R = H, X = I
1b, R = H, X = Br
1c, R = Me, X = I

2, R = H
5, R = Me

3, R = H
6, R = Me

Entry	Substrate	Product	Ar-	**2** or **5** Yield[b,c] (%)	**3** or **6** Yield[b] (%)
1	**1a**	**2e**		79 (73)[d]	12
2	**1a**	**2g**		82 (76)	4
3	**1a**	**2j**		-	11
4	**1b**	**2e**		13	14
5	**1b**	**2g**		16	13
6	**1c**	**5e**		71 (65)	15
7	**1c**	**5g**		70 (62)	15
8	**1a**	**2a**		-	65
9	**1c**	**5a**		-	74

[a]Couplings were performed on 0.14 mmol scale of **1** (0.07 M) with Cs_2CO_3 (2 equiv), PivOH (1.25 equiv), and $Pd(OAc)_2$ (0.005 equiv) with Ar–H to DMF ratio of 1:9 (v/v). [b]Determined by GC–MS of the crude reaction mixture. [c]Isolated yield in parentheses. [d]Coupling without addition of PivOH gave **2e** in 65% yield.

3–5). Coupling of **11** proceeded also with only a small excess of furan (1.75 equiv) affording **16** in 41% isolated yield (entry 5, footnote *c*). Deacetylation of **12** or **13** with methanolic ammonia also gave **14** (92%) and **15** (95%).

The 5-iodouridine **11** coupled efficiently with thiophene and 2-methylthiophene to give products **17** or **18** (entries 6 and 7). We found that the pyrrole also coupled with **11** to produce 5-(2-pyrrolyl)uridine **19** (entry 8), which can be purified on silica gel column but is somewhat unstable during storage and when exposed to air. Coupling of 2′-deoxyuridine **9** with benzimidazole failed to give 5-benzimidazolyl-2′-deoxyuridine.[25] Base-promoted 5-arylation of **11** with furan or thiophene preceded less efficiently giving products **16** or **17** in 23 and 17% isolated yield (entries 9 and 10). Instability of the glycosidic bond was noted during the 5-arylation of 3-*N*-benzyl-1-(tetrahydrofuran-2yl)uracil with bromobenzene.[21a] Subjection of 5-iodocytidine or 4-*N*-acetyl-2′,3′,5′-tri-*O*-acetyl-5-iodocytidine[26] to the TBAF- or base-promoted direct arylation with furan failed to provide 5-(2-furyl)cytidine products.

On the basis of the established mechanisms for the substitution of hydrogen in the arenes by Pd-activated aryl halides,[12b,d] it is expected that arylation of 5-iodouracils would occur via either electrophilic aromatic substitution (palladation) or direct proton abstraction (σ-bond metathesis). We do not have sufficient data to speculate on the mechanism or the role of TBAF. However, the fact that 1-*N*-benzyl-3-*N*-methyl-5-

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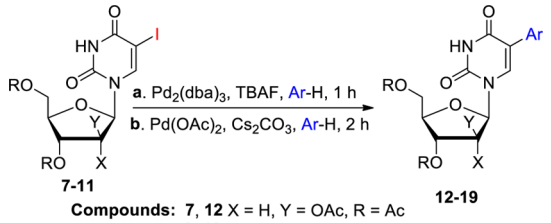
Table 5. Arylation of 5-Iodouracil Nucleosides with Electron-Rich Heteroaromatics[a]



Compounds: **7**, **12** X = H, Y = OAc, R = Ac
8, **13** X = H, Y = H, R = Ac
9, **14** X = H, Y = OH, R = H
10, **15** X = H, Y = H, R = H
11, **16-19** X = OH, Y = H, R = H

Entry	Substrate	Conditions	Product	Ar-	Yield[b]
1	**7**	a	**12**		61
2	**8**	a	**13**		72
3	**9**	a	**14**		70
4	**10**	a	**15**		73
5	**11**	a	**16**		80[c,d]
6	**11**	a	**17**		98
7	**11**	a	**18**		76
8	**11**	a	**19**		45
9	**11**	b	**16**		23
10	**11**	b	**17**		17

[a]Couplings were performed on 0.14 mmol scale of nucleosides (0.07 M) in the presence of 3.5 equiv of TBAF and 0.05 equiv of Pd catalyst with Ar−H to DMF ratio of 1:9 (v/v). Ratio of Ar−H to substrate nucleosides 15−20:1. [b]Isolated yields. [c]41% yield with 1.75:1 ratio of furan to **11**. [d]Coupling on 1 mmol scale of **11** gave **16** in 88% yield.

iodouracil (**1c**), which lacks the possibility to tautomerize to the enol form, did not undergo TBAF-promoted coupling with arenes indicates that the C4-alkoxide (enol form of uracil) may participate in the intramolecular processes of hydrogen abstraction as depicted in structures **A** and **B** (Figure 1). Fagnou and co-workers showed that direct arylation was facilitated by using Pd-coordinated carboxylate group, which assisted in intramolecular proton abstraction.[16]

In order to expand the TBAF-promoted arylation methodology of the uracil ring into the other heterocyclic systems,

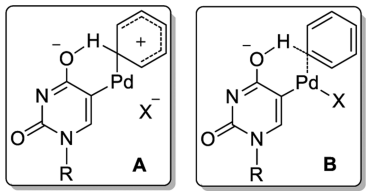
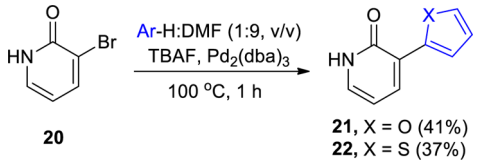


Figure 1. The plausible intermediates for the Pd-catalyzed direct arylation of 5-halouracils: (**A**) electrophilic aromatic palladation assisted by C4-alkoxide; (**B**) direct proton abstraction assisted by C4-alkoxide.

which have also possibility of tautomerization between oxo group and the hydrogen at the adjacent nitrogen atom, we subjected 3-bromo-2-pyridone **20** to our direct arylation protocol. Thus, heating of **20** with furan in the presence of TBAF and $Pd_2(dba)_3$ without other additives added gave product **21** in moderate yield (41%) in addition to unchanged **20** (35%, Scheme 1). Arylation of **20** with thiophene was also

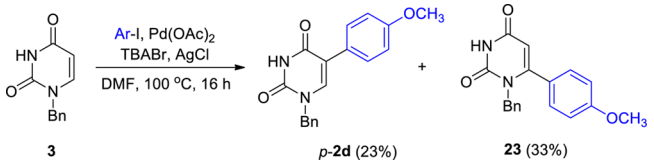
Scheme 1. Arylation of 3-Bromo-2-pyridone



successful to give **22** (37%) but essentially failed with benzene (5−10%, GC−MS). Also coupling of **20** with furan or thiophene in the presence of Cs_2CO_3/PivOH produced **21** or **22** in 68 and 63% isolated yields, respectively. Products **21** and **22** have UV (MeOH) λ maxima at 332 and 346 nm and are good candidates for development as fluorescence probes (λ_{em} 397 and 410 nm). There have been few reports on the arylation and/or vinylation of the *N*-alkylated 3-halo-2-pyridones at 3 position using Suzuki[27] or Stille[28] protocols as well as Negishi[29] reactions.

Hocek[20] and Kim[21a] and their co-workers recently reported the base-promoted direct C−H arylation of 1,3-*N*-diprotected uracils at C5 and/or C6 position(s) with aryl halides under the conditions that usually required higher temperature (130−160 °C) and longer reaction time (12−48 h) with noted instability of the glycosidic bond.[21a] In view of those results, we carried out direct C−H arylation of 1-*N*-benzyluracil **3** with aryl halides in the presence of TBAF. Thus, treatment of **3** with 4-iodoanisole with TBAF/$Pd_2(dba)_3$/DMF/100 °C/16 h failed to give arylated uracil products. However, heating (DMF/100 °C/16 h) of **3** with 4-iodoanisole (3 equiv) in the presence of TBABr/$Pd(OAc)_2$/AgCl[15f] produced mixture of the 5 and 6 arylated products *p*-**2d** (23%) and **23** (33%) in addition to the unchanged **3** (41%, Scheme 2).

Scheme 2. Direct C−H Arylation of Uracil with 4-Iodoanisole



In summary, we have demonstrated that 1-*N*-benzyl-5-iodo(or bromo)uracil undergoes Pd-catalyzed direct arylation with simple arenes and electron rich heteroarenes in the presence of TBAF in DMF to give 5-arylated uracil analogues. Analogues coupling of 1-(β-D-arabinofuranosyl)-5-iodouracil, 2′-deoxy-5-iodouridine, and 5-iodouridine with heteroarenes afforded the corresponding 5-(2-furyl, or 2-thienyl, or 2-pyrrolyl)uracil nucleosides that are important RNA and DNA fluorescent probes. The TBAF-promoted protocol developed here differs from the existing routes to 5-aryluracils in at least one of the following: (i) it avoids usage of the arylboronic acid or stannane precursors necessary for Suzuki or Stille couplings,

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(ii) it proceeds without the necessity of adding any ligands and additives, (iii) it works efficiently with the natural 3-*N*-unsubstituted uracils and uracil nucleosides, and (iv) it is compatible with the stability of the nucleoside glycosidic bond. The π-excessive heteroarenes couple also with 5-halouracils in the presence of Cs_2CO_3 in DMF. The yields for the 5-arylated products were improved with the addition of pivalic acid. The $Pd_2(dba)_3$ was the catalyst of choice for TBAF-promoted arylation of 5-halouracils, whereas $Pd(OAc)_2$ gave the best results for base-promoted couplings. Heteroarylation was extended into the other enolizable heterocyclic systems such as 3-bromo-2-pyridone

EXPERIMENTAL SECTION

^{1}H NMR spectra at 400 MHz and ^{13}C NMR at 100.6 MHz were recorded in $CDCl_3$ unless otherwise noted. All chemical shift values are reported in parts per million (ppm) and referenced to the residual solvent peaks [$CDCl_3$ (7.26 ppm) or DMSO-d_6 (2.54 ppm)] for ^{1}H NMR and the $CDCl_3$ (77.16 ppm) or DMSO-d_6 (39.52 ppm) for ^{13}C NMR spectra, with coupling constant (J) values reported in Hz. HRMS were obtained in TOF (ESI) mode. TLC was performed on Merck kieselgel 60-F_{254}, and products were detected with 254 nm light or by development of color with I_2. Merck kieselgel 60 (230−400 mesh) was used for column chromatography. Purity, yields and ratio of the products (crude and/or purified) were established using a GC−MS (EI) system [capillary column (30 m × 0.25 mm × 25 μm)] using calibrated standards. The 1.0 M TBAF solution in THF (catalog number: 216143) were purchased from Aldrich-Sigma Co., LLC.

1-*N*-Benzyl-3-*N*-methyl-5-iodouracil (1c). Freshly distilled diazomethane solution in ether (10 mL), generated from Diazald (3.0 g, 14.0 mmol), was added dropwise to a stirred solution of **1a**[30] (357 mg, 1.09 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After 18 h, the volatiles were evaporated to give **1c** (354 mg, 95%) as white powder: ^{1}H NMR δ 3.34 (s, 3H), 4.86 (s, 2H), 7.21−7.30 (m, 5H), 7.57 (s, 1H); ^{13}C NMR δ 29.7, 52.7, 68.0, 128.2, 128.8, 129.3, 135.0, 146.4, 151.5, 160.2; GC−MS (t_R 21.70 min) m/z 342 (85, M$^+$), 91 (100); HRMS calcd for $C_{12}H_{12}IN_2O_2$ [M + H]$^+$ 342.9938, found 342.9935.

1-*N*-Benzyl-5-(2-, 3-, and 4-methylphenyl)uracil (*o*/*m*/*p*-2a). Procedure A. Toluene (0.2 mL, 173 mg, 1.89 mmol), TBAF (1M/THF solution containing ca. 5 wt % of water; 980 μL, 0.98 mmol) and $Pd_2(dba)_3$ (6.4 mg, 0.007 mmol) were added to a stirring solution of 1-*N*-benzyl-5-iodouracil[30] (**1a**, 46 mg, 0.14 mmol) in DMF (1.8 mL) under the N_2 atmosphere at ambient temperature. The resulting suspension was stirred for 1 h at 100 °C (oil bath). Volatiles were evaporated, and the oily residue was dissolved in EtOAc or MeOH and filtrated through Celite or Whatman GF/A filter paper. The filtrate was partitioned (EtOAc/H_2O). The organic layer was then washed (brine), dried (Na_2SO_4) and evaporated. GC−MS of this material showed peaks at t_R 31.46, 32.38, and 32.70 min (m/z 292, M$^+$) for the three isomers of **2a** (*ortho*/*meta*/*para* with relative intensities of ∼3:2:1, respectively). Column chromatography (hexane/EtOAc, 8:2 → 6:4) gave a mixture of *o*/*m*/*p*-**2a** (*o*/*m*/*p*, 3:2:1; 29 mg, 71% overall yield) followed by **3** (1 mg, 4%; see Supporting Information, p S5). Mixture of *o*/*m*/*p*-**2a**: GC−MS t_R 31.46 (*o*-**2a**), 32.38 (*m*-**2a**) and 32.70 (*p*-**2a**) min (m/z 292, M$^+$); ^{1}H NMR δ 2.21 (s, 1.5H, *o*-**2a**), 2.35 (s, 0.5H, *p*-**2a**), 2.36 (s, 1H, *m*-**2a**), 4.97 (s, 1H, *o*-**2a**), 4.985 (s, 0.33H, *p*-**2a**), 4.990 (s, 0.67H, *m*-**2a**), 7.07−7.41 (m, 10H), 8.91 (s, 1H); HRMS calcd for $C_{18}H_{17}N_2O_2$ [M + H]$^+$ 293.1285, found 293.1294.

Attempted purification of the *o*/*m*/*p*-**2a** mixture on a long silica gel column (hexane/EtOAc, 8:2 → 7:3) gave partial separation of the *o*/*m*/*p* isomers of **2a** but failed to yield single isomers.

Note: Treatment of **1a** (46 mg, 0.14 mmol) with toluene/TBAF/$Pd_2(dba)_3$ in DMF for 18 h at 100 °C, as described above (column chromatography; hexane/EtOAc, 98:2 → 95:5) gave mixture of 1-*N*-benzyl-3-*N*-butyl-5-(2-methylphenyl)uracil (*o*-**4**), 1-*N*-benzyl-3-*N*-butyl-5-(3-methylphenyl)uracil (*m*-**4**) and 1-*N*-benzyl-3-*N*-butyl-5-(4-methylphenyl)uracil (*p*-**4**) (36.6 mg, 75% overall yield; *o*-**4**/*m*-**4**/*p*-**4**, 3:2:1): GC−MS t_R 27.29 (*o*-**4**), 28.27 (*m*-**4**) and 28.74 (*p*-**4**) min (m/z 348, M$^+$); ^{1}H NMR δ 0.92 (t, J = 7.3 Hz, 3H), 1.36 ("sextet", J = 7.4 Hz, 2H), 1.67 ("quint", J = 7.6, Hz, 2H), 2.18 (s, 1.5H, *o*-**4**), 2.30 (s, 0.5H, *p*-**4**), 2.32 (s, 1H, *m*-**4**), 4.00 ("t", J = 7.6 Hz, 2H), 4.94 (s, 1H, *o*-**4**), 4.95 (s, 0.33H, *p*-**4**), 4.96 (s, 0.67H, *m*-**4**), 7.02−7.37 (m, 10H); HRMS calcd for $C_{22}H_{25}N_2O_2$ [M + H]$^+$ 349.1911, found 349.1920.

1-*N*-Benzyl-5-(3-methylphenyl)uracil (*m*-2a). Suzuki coupling:[7c] 3-Tolylboronic acid (29 mg, 0.21 mmol) and PPh_3 (9 mg, 0.034 mmol) were added to a stirring solution of 1-*N*-benzyl-5-iodouracil (**1a**, 46 mg, 0.14 mmol) in CH_3CN/H_2O (3 mL; v/v, 2:1) under the N_2 atmosphere at ambient temperature, followed by the addition of Na_2CO_3 (22 mg, 0.21 mmol) and $Pd(OAc)_2$ (3 mg, 0.013 mmol). The resulting suspension was stirred for 4 h at 80 °C (oil bath). Volatiles were evaporated, and the residue was partitioned between EtOAc and H_2O. The organic layer was then washed (brine), dried (Na_2SO_4) and evaporated. Column chromatography (hexane/EtOAc, 6:4 → 5:5) gave *m*-**2a** (21.7 mg, 53%): ^{1}H NMR δ 2.38 (s, 3H), 5.01 (s, 2H), 7.16 (dt, J = 6.8, 2.0 Hz, 1H), 7.23−7.29 (m, 2H), 7.30 (t, J = 1.7 Hz, 1H), 7.32 (s, 1H), 7.34−7.46 (m, 5H), 9.35 (s, 1H); ^{13}C NMR δ 21.6, 51.5, 116.1, 125.3, 128.2, 128.5, 128.7, 128.97, 129.01, 129.3, 132.1, 135.4, 138.3, 141.2, 150.9, 162.5; GC−MS (t_R 32.38 min) m/z 292 (85, M$^+$), 91 (100); HRMS calcd for $C_{18}H_{17}N_2O_2$ [M + H]$^+$ 293.1285, found 293.1293.

1-*N*-Benzyl-5-(4-methylphenyl)uracil (*p*-2a). Suzuki coupling:[7c] Treatment of **1a** (46 mg, 0.14 mmol) with 4-tolylboronic acid (29 mg, 0.21 mmol), as described above for *m*-**2a**, gave *p*-**2a** (20.0 mg, 49%): ^{1}H NMR δ 2.34 (s, 3H), 4.98 (s, 2H), 7.17 (d, J = 7.9 Hz, 2H), 7.28 (s, 1H), 7.32−7.41 (m, 7H), 9.03 (s, 1H); ^{13}C NMR δ 21.3, 51.5, 115.9, 128.1, 128.2, 128.7, 129.2, 129.3, 129.4, 135.4, 138.2, 140.8, 150.8, 162.4; GC−MS (t_R 32.70 min) m/z 292 (85, M$^+$), 91 (100); HRMS calcd for $C_{18}H_{17}N_2O_2$ [M + H]$^+$ 293.1285, found 293.1291.

1-*N*-Benzyl-5-phenyluracil (2b). Treatment of **1a** (46 mg, 0.14 mmol) with benzene (0.2 mL, 175 mg, 2.24 mmol) by procedure A gave **2b** (25.3 mg, 59%): ^{1}H NMR δ 4.99 (s, 2H), 7.32 (s, 1H), 7.33−7.49 (m, 10H), 9.02 (s, 1H); ^{13}C NMR δ 51.6, 115.9, 128.2, 128.3, 128.7, 128.8, 129.4, 132.2, 135.3, 141.2, 150.7, 162.3; GC−MS (t_R 24.52 min) m/z 278 (80, M$^+$), 91 (100); HRMS calcd for $C_{17}H_{14}N_2NaO_2$ [M + Na]$^+$ 301.0947, found 301.0945.

Analogues treatment of 1-*N*-benzyl-5-bromouracil[31] (**1b**, 39 mg, 0.14 mmol) with benzene (0.2 mL, 175 mg, 2.24 mmol) by procedure A (14 equiv of TBAF) gave **2b** (27.6 mg, 71%) with spectroscopic data as described above.

1-*N*-Benzyl-5-(2,4-dimethylphenyl)uracil (2c). Treatment of **1a** (46 mg, 0.14 mmol) with *m*-xylene (0.2 mL, 172 mg 1.62 mmol) by procedure A gave the desired product, which was recrystallized from hexane/EtOAc to give a single isomer **2c** (23.6 mg, 55%): ^{1}H NMR δ 2.16 (s, 3H), 2.31 (s, 3H), 4.95 (s, 2H), 6.95 (d, J = 8.0 Hz, 1H), 6.99 (br d, J = 8.1 Hz, 1H), 7.05 (s, 1H), 7.11 (s, 1H), 7.30−7.41 (m, 5H), 8.30 (s, 1H); ^{13}C NMR δ 20.1, 21.2, 51.4, 116.5, 126.8, 128.3, 128.7, 128.8, 129.4, 130.5, 131.4, 135.3, 137.6, 138.8, 142.2, 150.8, 161.9; GC−MS (t_R 27.34 min) m/z 306 (70, M$^+$), 91 (100); HRMS calcd for $C_{19}H_{19}N_2O_2$ [M + H]$^+$ 307.1441, found 307.1442.

GC−MS of the crude reaction mixture showed peaks for three isomers with t_R at 27.34, 27.90, and 28.33 min with relative intensities of 14:5:1 (m/z 306, M$^+$).

1-*N*-Benzyl-5-(2-, 3-, and 4-methoxyphenyl)uracil (*o*/*m*/*p*-2d). Treatment of **1a** (46 mg, 0.14 mmol) with anisole (0.2 mL, 199 mg, 1.84 mmol) by procedure A gave **2d** (*o*/*m*/*p*, 4:1:1; 29.3 mg, 68%): GC−MS t_R 25.52 (*o*-**2d**), 26.68 (*m*-**2d**) and 27.31 (*p*-**2d**) min (m/z 308, M$^+$); ^{1}H NMR δ 3.73 (s, 2H, *o*-**2d**), 3.80 (s, 0.5H, *p*-**2d**), 3.81 (s, 0.5H, *m*-**2d**), 4.96 (s, 1.3H, *o*-**2d**), 4.98 (s, 0.7H, *m*,*p*-**2d**), 6.86−7.34 (m, 10H), 9.01(s, 0.67H, *o*-**2d**) 9.14(s, 0.33H, *m*,*p*-**2d**); HRMS calcd for $C_{18}H_{17}N_2O_3$ [M + H]$^+$ 309.1234, found 309.1247.

1-*N*-Benzyl-5-(3-methoxyphenyl)uracil (*m*-2d). Suzuki coupling:[7c] Treatment of **1a** (46 mg, 0.14 mmol) with 3-methoxyphenylboronic acid (32 mg, 0.21 mmol), as described above for *m*-**2a**, gave *m*-**2d** (22 mg, 51%): ^{1}H NMR δ 3.80 (s, 3H), 4.98 (s, 2H), 6.88 (dd, J = 8.8, 2.5 Hz, 1H), 7.03 ("dt", J = 7.6, 2.0 Hz, 1H), 7.10 ("t", J = 2.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.33−7.40 (m, 6H), 9.33 (s, 1H); ^{13}C NMR δ 51.4, 55.3, 113.6, 114.0, 115.5, 121.4, 128.1, 128.6, 129.2, 129.5, 133.4, 135.2, 141.3, 150.7, 159.6, 162.2; GC−MS (t_R 26.68

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min) m/z 308 (75, M^+), 91 (100); HRMS calcd for $C_{18}H_{17}N_2O_3$ $[M + H]^+$ 309.1234, found 309.1238.

1-*N*-Benzyl-5-(4-methoxyphenyl)uracil (*p*-2d). Suzuki coupling:[7c] Treatment of **1a** (46 mg, 0.14 mmol) with 4-methoxyphenylboronic acid (32 mg, 0.21 mmol), as described above for *m*-**2a**, gave *p*-**2d** (23.7 mg, 55%): ^{1}H NMR δ 3.80 (s, 3H), 4.98 (s, 2H), 6.90 (d, J = 8.8 Hz, 2H), 7.25 (s, 1H), 7.32−7.39 (m, 7H), 8.64 (s, 1H); ^{13}C NMR δ 51.5, 55.5, 114.2, 115.7, 124.5, 128.2, 128.7, 129.3, 129.5, 135.4, 140.3, 150.8, 159.7, 162.5; GC−MS (t_R 27.31 min) m/z 308 (80, M^+), 91 (100); HRMS calcd for $C_{18}H_{17}N_2O_3$ $[M + H]^+$ 309.1234, found 309.1241.

1-*N*-Benzyl-5-(fur-2-yl)uracil (2e). Method A. Treatment of **1a** (46 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A (3.5 equiv of TBAF) gave **2e** (30.4 mg, 81%): ^{1}H NMR δ 5.01 (s, 2H), 6.43 (dd, J = 3.0, 1.9 Hz, 1H), 7.05 (d, J = 3.0 Hz, 1H), 7.28−7.43 (m, 6H), 7.69 (s, 1H), 9.19 (s, 1H); ^{13}C NMR δ 51.9, 107.6, 109.7, 112.1, 128.2, 128.8, 129.3, 135.3, 137.7, 141.3, 145.7, 150.2, 160.4; GC−MS (t_R 27.41 min) m/z 268 (60, M^+), 91 (100); HRMS calcd for $C_{15}H_{13}N_2O_3$ $[M + H]^+$ 269.0921, found 269.0934.

Analogues treatment of **1b** (39 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A (14 equiv of TBAF) gave **2e** (31.9 mg, 85%) with spectroscopic data as described above.

Method B. Procedure B. Furan (0.2 mL, 187 mg, 2.75 mmol), Cs_2CO_3 (91.2 mg, 0.28 mmol) and $Pd(OAc)_2$ (1.6 mg, 0.007 mmol) were added to a stirring solution of **1a** (46 mg, 0.14 mmol) in DMF (1.8 mL) under the N_2 atmosphere at ambient temperature. The resulting suspension was stirred for 2 h at 100 °C (oil bath) and after cooling down to ambient temperature was diluted with EtOAc (3 mL). The resulting mixture was vacuum filtered using Whatman GF/A filter paper, and the filtrates were evaporated. The oily residue was dissolved in EtOAc and partitioned (EtOAc/H_2O). The organic layer was then washed (brine), dried (Na_2SO_4) and evaporated. Column chromatography (hexane/EtOAc, 8:2 → 6:4) gave **2e** (24.5 mg, 65% yield) with the spectroscopic data as above and **6** (4 mg, 12%).

Procedure C. Analogous treatment of **1a** (46 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) and Cs_2CO_3 (91.2 mg, 0.28 mmol) in the presence of PivOH (17.9 mg, 0.175 mmol) and $Pd(OAc)_2$ (1.6 mg, 0.007 mmol) by procedure B gave **2e** (27 mg, 73% yield).

Analogues treatment of **1b** (39 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure B gave **2e** (5 mg, 13% yield) with the spectroscopic data as above.

1-*N*-Benzyl-5-(benzo[*b*]fur-2-yl)uracil (2f). Treatment of **1a** (46 mg, 0.14 mmol) with benzo[*b*]furan (23.1 μL, 24.8 mg, 0.21 mmol) by procedure A (3.5 equiv of TBAF) gave **2f** (29.4 mg, 66%): ^{1}H NMR δ 5.06 (s, 2H), 7.2 (td, J = 7.3, 1.2 Hz, 1H), 7.26 (dt, J = 7.3, 1.4 Hz, 1H), 7.37−7.42 (m, 6H), 7.47 (d, J = 0.6 Hz, 1H), 7.56 (ddd, J = 7.3, 1.5, 0.8 Hz, 1H), 7.95 (s, 1H), 8.67 (s, 1H); ^{13}C NMR δ 52.2, 106.1, 107.0, 110.7, 121.6, 123.3, 124.8, 128.2, 128.9, 129.3, 129.4, 135.1, 139.5, 147.6, 149.9, 153.9, 160.1; HRMS calcd for $C_{19}H_{15}N_2O_3$ $[M + H]^+$ 319.1077, found 319.1081.

1-*N*-Benzyl-5-(thiophen-2-yl)uracil (2g). Method A. Treatment of **1a** (46 mg, 0.14 mmol) with thiophene (0.2 mL, 210 mg, 2.5 mmol) by procedure A (3.5 equiv of TBAF) gave **2g**[32] (36.2 mg, 91%): ^{1}H NMR (DMSO-d_6) δ 4.98 (s, 2H), 7.06 (dd, J = 5.1, 3.7 Hz, 1H), 7.29−7.32 (m, 1H), 7.34−7.37 (m, 4H), 7.44−7.47 (m, 2H), 8.45 (s, 1H), 11.72 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 50.8, 108.1, 122.7, 125.6, 126.4, 127.4, 127.6, 128.6, 133.7, 136.7, 140.9, 149.9, 161.7; HRMS calcd for $C_{15}H_{13}N_2O_2S$ $[M + H]^+$ 285.0692, found 285.0691.

Method B. Analogues treatment of **1a** (46 mg, 0.14 mmol) with thiophene (0.2 mL, 210 mg, 2.5 mmol) by procedure C gave **2g** (30.2 mg, 76% yield) with the spectroscopic data as above.

Analogues treatment of **1b** (39 mg, 0.14 mmol) with thiophene (0.2 mL, 210 mg, 2.5 mmol) by procedure C gave **2g** (6 mg, 16% yield) with the spectroscopic data as above.

1-*N*-Benzyl-5-(5-methylthiophen-2-yl)uracil (2h). Treatment of **1a** (46 mg, 0.14 mmol) with 2-methylthiophene (0.2 mL, 203 mg, 2.1 mmol) by procedure A (3.5 equiv of TBAF) gave **2h** (29.2 mg, 70%): ^{1}H NMR δ 2.46 (d, J = 0.8 Hz, 3H), 4.98 (s, 2H), 6.66 (dd, J = 3.6, 1.1 Hz, 1H), 7.15 (d, J = 3.6 Hz, 1H), 7.30−7.40 (m, 5H), 7.42 (s, 1H), 9.06 (s, 1H); ^{13}C NMR δ 15.3, 51.7, 110.9, 125.0, 125.5, 128.2, 128.8, 129.4, 130.8, 135.2, 138.2, 140.4, 152.2, 161.4; HRMS calcd for $C_{16}H_{14}N_2O_2SNa$ $[M + Na]^+$ 321.0668, found 321.0674.

1-*N*-Benzyl-5-(5-acetylthiophen-2-yl)uracil (2i). Treatment of **1a** (46 mg, 0.14 mmol) with 2-acetylthiophene (0.2 mL, 234 mg, 2.1 mmol) by procedure A (3.5 equiv of TBAF) gave **2i** (25 mg, 54%): ^{1}H NMR (DMSO-d_6) δ 2.50 (s, 3H), 4.99 (s, 2H), 7.29−7.34 (m, 1H), 7.37 (d, J = 4.3 Hz, 4H), 7.59 (d, J = 4.1 Hz, 1H), 7.87 (d, J = 4.1 Hz, 1H), 8.76 (s, 1H), 11.89 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 26.4, 51.2, 107.1, 123.0, 127.4, 127.7, 128.6, 133.1, 136.5, 141.9, 142.5, 143.2, 149.7, 161.5, 190.6; GC−MS (t_R 31.00 min) m/z 326 (20, M^+), 91 (100); HRMS calcd for $C_{17}H_{15}N_2O_3S$ $[M + H]^+$ 327.0798, found 327.0801.

1-*N*-Benzyluracil (3). Treatment of **1a** (46 mg, 0.14 mmol) with toluene (0.2 mL, 173 mg, 1.89 mmol) by procedure A [using $KOSiMe_3$ (53.8 mg, 0.42 mmol) instead of TBAF] gave **3**[33] (18.4 mg, 65%): ^{1}H NMR δ 4.92 (s, 1H), 5.70 (dd, J = 7.9, 1.5 Hz, 1H), 7.16 (d, J = 7.9 Hz, 1H), 7.25−7.44 (m, 3H), 9.46 (s, 1H); ^{13}C NMR δ 51.4, 102.8, 128.2, 128.7, 129.3, 135.2, 144.0, 151.3, 163.7; GC−MS (t_R 24.38 min) m/z 202 (35, M^+), 91 (100); HRMS calcd for $C_{11}H_{11}N_2O_2$ $[M + H]^+$ 203.0815, found 203.0817.

1-*N*-Benzyl-3-*N*-methyl-5-(fur-2-yl)uracil (5e). Treatment of **1c** (48 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure C (column chromatography; hexane/EtOAc, 8:2 → 7:3) gave **5e** (26 mg, 65% yield): GC−MS (t_R 17.67 min) m/z 282 (75, M^+), 91 (100); ^{1}H NMR δ 3.45 (s, 3H), 5.03 (s, 2H), 6.45 (dd, J = 3.4, 1.8 Hz, 1H), 7.06 (d, J = 3.3 Hz, 1H), 7.35 (d, J = 5.9 Hz, 1H), 7.33−7.39 (m, 3H), 7.36 (d, J = 8.1 Hz, 2H), 7.72 (s, 1H); ^{13}C NMR δ 28.5, 53.0, 106.6, 109.3, 112.0, 128.1, 128.7, 129.3, 135.4, 136.0, 141.2, 146.3, 151.0, 160.2; HRMS calcd for $C_{16}H_{15}N_2O_3$ $[M + H]^+$ 283.1077, found 283.1065.

1-*N*-Benzyl-3-*N*-methyl-5-(thiophen-2-yl)uracil (5g). Treatment of **1c** (48 mg, 0.14 mmol) with thiophene (0.2 mL, 210 mg, 2.5 mmol) by procedure C (column chromatography; hexane/EtOAc, 8:2 → 7:3) gave **5g** (26 mg, 62% yield): GC−MS (t_R 23.66 min) m/z 298 (75, M^+), 91 (100); ^{1}H NMR δ 3.46 (s, 3H), 5.03 (s, 2H), 7.02 (dd, J = 5.1, 3.7 Hz, 1H), 7.28−7.39 (m, 7H), 7.55 (s, 1H). ^{13}C NMR δ 28.7, 52.8, 109.6, 124.0, 125.8, 126.9, 128.2, 128.8, 129.3, 134.9, 135.3, 137.0, 151.1, 161.4; HRMS calcd for $C_{16}H_{15}N_2O_2S$ $[M + H]^+$ 299.0849, found 299.0852.

1-*N*-Benzyl-3-*N*-methyluracil (6). Treatment of **1c** (48 mg, 0.14 mmol) with toluene (0.2 mL, 173 mg, 1.89 mmol) by procedure A (column chromatography; hexane/EtOAc, 6:4 → 4:6) gave **6**[34] (29 mg, 73%): ^{1}H NMR δ 3.36 (s, 3H), 4.94 (s, 2H), 5.75 (d, J = 7.9 Hz, 1H), 7.17 (d, J = 7.9 Hz, 1H), 7.2−7.48 (m, 5H); ^{13}C NMR δ 28.0, 52.4, 102.0, 128.1, 128.6, 129.2, 135.4, 141.7, 152.0, 163.2; GC−MS (t_R 20.49 min) m/z 216 (50, M^+), 91 (100); HRMS calcd for $C_{12}H_{13}N_2O_2$ $[M + H]^+$ 217.0972, found 217.0976.

Analogous treatment (TBAF 3.5 equiv) of **1c** (48 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A gave **6**[34] (24 mg, 60%).

1-(2,3,5-Tri-*O*-acetyl-β-D-arabinofuranosyl)-5-(fur-2-yl)uracil (12). Treatment (TBAF 3.5 equiv) of 1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-5-iodouracil[35] (**7**, 69.5 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A (column chromatography; hexane/EtOAc, 6:4 → 5:5) gave **12** (37.3 mg, 61%) as a slightly yellow solid: ^{1}H NMR δ 2.01 (s, 3H), 2.18 (s 3H), 2.19 (s, 3H), 4.24 (dt, J = 5.2, 3.9 Hz, 1H), 4.44 (dd, J = 12.0, 5.2 Hz, 1H), 4.53 (dd, J = 12.0, 4.2 Hz, 1H), 5.22 (dd, J = 3.6, 1.7 Hz, 1H), 5.48 (dd, J = 4.1, 1.7 Hz, 1H), 6.43 (d, J = 4.1 Hz, 1H), 6.49 (dd, J = 3.4, 1.8 Hz, 1H), 7.09 (d, J = 3.2 Hz, 1H), 7.39 (dd, J = 1.8, 0.6 Hz, 1H), 7.97 (s, 1H), 9.39 (s, 1H); ^{13}C NMR δ 20.4, 20.65, 20.68, 62.7, 74.7, 76.5, 80.5, 84.2, 106.6, 109.7, 112.0, 134.1, 141.3, 145.5, 149.0, 159.6, 168.6, 169.6, 170.5; HRMS calcd for $C_{19}H_{21}N_2O_{10}$ $[M + H]^+$ 437.1191, found 437.1176.

3′,5′-Di-*O*-acetyl-5-(fur-2-yl)-2′-deoxyuridine (13). Treatment of 3′,5′-di-*O*-acetyl-2′-deoxy-5-iodouridine[36] (**8**, 61.3 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A (column chromatography; hexane/EtOAc, 6:4 → 5:5) gave **13**[37] (38.1 mg,

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72%): ^{1}H NMR δ 2.12 (s, 3H), 2.15 (s, 3H), 2.54 (ddd, J = 14.4, 6.5, 2.1 Hz, 1H), 2.54 (ddd, J = 14.2, 5.6, 1.6 Hz, 1H), 4.31 ("q", J = 2.7 Hz, 1H), 4.38−4.39 (m, 2H), 5.28 (dt, J = 6.6, 1.7 Hz, 1H), 6.44 (dd, J = 6.5, 5.6 Hz, 1H), 6.45 (dd, J = 3.4, 1.8 Hz, 1H), 7.08 (d, J = 3.2 Hz, 1H), 7.32 (dd, J = 1.8, 0.6 Hz, 1H), 7.99 (s, 1H), 9.63 (s, 1H); ^{13}C NMR δ 20.8, 21.0, 38.1, 64.2, 74.6, 82.7, 85.4, 107.9, 109.9, 112.2, 132.5, 141.2, 145.8, 149.6, 160.0, 170.4, 170.5; HRMS calcd for $C_{17}H_{19}N_2O_8$ $[M + H]^+$ 379.1136, found 379.1136.

1-(β-D-Arabinofuranosyl)-5-(fur-2-yl)uracil (14). Method A. Treatment of 1-(β-D-arabinofuranosyl)-5-iodouracil[38] (**9**, 52 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A (column chromatography; CH_2Cl_2/MeOH, 15:1 → 10:1) gave **14** (30.5 mg, 70%) as off-white solid. The analytical sample was obtained by precipitation from minimum amount of MeOH:CH_2Cl_2 (1:1, v/v) with hexane: ^{1}H NMR (DMSO-d_6) δ 3.60 (dt, J = 10.3, 5.0 Hz, 1H), 3.68 (dt, J = 10.3, 5.1 Hz, 1H), 3.78 ("q", J = 4.6 Hz, 1H), 3.97 (dd, J = 7.3, 3.8 Hz, 1H), 4.04 (dt, J = 7.8, 3.9 Hz, 1H), 5.09 (t, J = 5.2 Hz, 1H), 5.51 (d, J = 4.4 Hz, 1H), 5.64 (d, J = 5.0 Hz, 1H), 6.07 (d, J = 4.3 Hz, 1H), 6.52 (dd, J = 3.3, 1.9 Hz, 1H), 6.85 (dd, J = 3.3, 0.5 Hz, 1H), 7.63 (dd, J = 1.8, 0.7 Hz, 1H), 8.07 (s, 1H), 11.65 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 60.7, 75.3, 75.6, 84.8, 85.3, 104.0, 107.6, 111.5, 136.5, 141.4, 146.5, 149.4, 160.2. HRMS calcd for $C_{13}H_{15}N_2O_7$ $[M + H]^+$ 311.0784, found 311.0811.

Method B. Compound **12** (43.6 mg, 0.10 mmol) was dissolved in NH_3/MeOH (3 mL) at 0 °C (ice bath), and the resulting solution was stirred overnight. Volatiles were removed under the reduced pressure and the residue was column chromatographed (CH_2Cl_2/MeOH, 15:1 → 10:1) to give **14** (28.5 mg, 92%) with the spectroscopic data as above.

5-(Fur-2-yl)-2′-deoxyuridine (15). Method A. Treatment of 2′-deoxy-5-iodouridine[36] (**10**, 49.6 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A (column chromatography; CH_2Cl_2/MeOH, 15:1 → 10:1) gave **15**[37] (30.1 mg, 73%) as yellow solid: ^{1}H NMR (DMSO-d_6) δ 2.18 (dd, J = 6.6, 4.8 Hz, 2H), 3.61 (dd, J = 8.8, 5.0 Hz, 2H), 3.84 (q, J = 3.3 Hz, 1H), 4.28 ("quint", J = 4.0 Hz, 1H), 5.08 (t, J = 4.8 Hz, 1H), 5.27 (d, J = 4.2 Hz, 1H), 6.22 (t, J = 6.7 Hz, 1H), 6.52 (dd, J = 3.3, 1.8 Hz, 1H), 6.85 (dd, J = 3.3, 0.5 Hz, 1H), 7.61 (dd, J = 1.8, 0.7 Hz, 1H), 8.33 (s, 1H), 11.62 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 40.1, 61.1, 70.4, 84.7, 87.6, 105.6, 107.8, 111.5, 134.6, 141.5, 146.4, 149.4, 160.1. HRMS calcd for $C_{13}H_{13}N_2O_6$ $[M - H]^-$ 293.0779, found 293.0788.

Method B. Treatment of **13** (38 mg, 0.10 mmol) with NH_3/MeOH, as described for **14** (Method B), gave **15** (28.0 mg, 95%) with the spectroscopic data as above.

5-(Fur-2-yl)uridine (16). Method A. Treatment of 5-iodouridine[36] (**11**, 52 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A (column chromatography; CH_2Cl_2/MeOH, 15:1 → 10:1) gave **16**[9b] (34.7 mg, 80%) as off-white solid. Precipitation of **16** from MeOH:CH_2Cl_2 (1:1, v/v) solution with hexane gave analytical sample of **16**: UV (MeOH) λ_{max} = 314 nm; ^{1}H NMR (DMSO-d_6) δ 3.60 (ddd, J = 11.9, 4.6, 2.9 Hz, 1 H), 3.68 (ddd, J = 11.9, 4.7, 2.9 Hz, 1H), 3.90 ("q", J = 3.2 Hz, 1H), 4.02 ("q", J = 4.5 Hz, 1H), 4.12 ("q", J = 5.1 Hz, 1H), 5.11 (d, J = 5.0 Hz, 1H), 5.21 (t, J = 4.7 Hz, 1H), 5.43 (d, J = 5.5 Hz, 1H), 5.87 (d, J = 5.1 Hz, 1H), 6.52 (dd, J = 3.3, 1.8 Hz, 1H), 6.86 (dd, J = 3.3, 0.6 Hz, 1H), 7.60 (dd, J = 1.8, 0.7 Hz, 1H), 8.42 (s, 1H), 11.64 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 60.6, 69.9, 74.0, 85.0, 88.2, 105.7, 108.0, 111.6, 134.9, 141.6, 146.4, 149.7, 160.1; HRMS calcd for $C_{13}H_{13}N_2O_7$ $[M - H]^-$ 309.0728, found 309.0734.

Analogous treatment of **11** (310 mg, 1.0 mmol) with furan (1.1 mL, 1.03 g, 15 mmol) by procedure A gave **16** (273 mg, 88%).

Method B. Treatment of **11** (52 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure C (column chromatography; CH_2Cl_2/MeOH, 15:1 → 10:1) gave **16** (10 mg, 23% yield) with the spectroscopic data as above.

5-(Thiophen-2-yl)uridine (17). Method A. Treatment of 5-iodouridine (**11**, 52 mg, 0.14 mmol) with thiophene (0.2 mL, 210 mg, 2.5 mmol) by procedure A (column chromatography; CH_2Cl_2/MeOH, 15:1 → 10:1) gave **17** (44.7 mg, 98%) as off-white solid. Precipitation of **17** from MeOH:CH_2Cl_2 (1:1, v/v) solution with hexane gave analytical sample of **17**: UV (MeOH) λ_{max} = 318 nm; ^{1}H NMR (DMSO-d_6) δ 3.64 (ddd, J = 12.0, 4.4, 2.3 Hz, 1H), 3.76 (ddd, J = 12.0, 4.7, 2.8 Hz, 1H), 3.92 (dt, J = 4.8, 2.7 Hz, 1H), 4.06 ("q", J = 5.1 Hz, 1H), 4.13 ("q", J = 4.8 Hz, 1H), 5.09 (d, J = 5.5 Hz, 1H), 5.42 (t, J = 4.6 Hz, 1H), 5.46 (d, J = 5.3 Hz, 1H), 5.84 (d, J = 4.2 Hz, 1H), 7.05 (dd, J = 5.1, 3.7 Hz, 1H), 7.40 (dd, J = 3.7, 1.1 Hz, 1H), 7.46 (dd, J = 5.1, 1.1 Hz, 1H), 8.65 (s, 1H), 11.69 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 60.2, 69.4, 74.3, 84.7, 88.7, 108.3, 122.5, 125.7, 126.4, 133.9, 135.7, 149.6, 161.3; HRMS calcd for $C_{13}H_{14}N_2NaO_6S$ $[M + Na]^+$ 349.0465, found 349.0465.

Method B. Treatment of **11** (52 mg, 0.14 mmol) with thiophene (0.2 mL, 210 mg, 2.5 mmol) by procedure C (column chromatography; CH_2Cl_2/MeOH, 15:1 → 10:1) gave **17** (8 mg, 17% yield) with the spectroscopic data as above.

5-(5-Methylthiophen-2-yl)uridine (18). Treatment of 5-iodouridine (**11**, 52 mg, 0.14 mmol) with 2-methylthiophene (0.2 mL, 203 mg, 2.1 mmol) by procedure A (column chromatography; CH_2Cl_2/MeOH, 15:1 → 10:1) gave **18** (36.5 mg, 76%) as off-white solid. Precipitation of **18** from MeOH:CH_2Cl_2 (1:1, v/v) solution with hexane gave analytical sample of **18**: ^{1}H NMR (DMSO-d_6) δ 2.42 (s, 3H), 3.63 (ddd, J = 12.0, 4.4, 2.3 Hz, 1H), 3.74 (ddd, J = 12.0, 4.6, 2.8 Hz, 1H), 3.91 ("dt", J = 4.8, 2.4 Hz, 1H), 4.05 ("q", J = 5.0 Hz, 1H), 4.11 ("q", J = 4.8 Hz, 1H), 5.08 (d, J = 5.4 Hz, 1H), 5.38 (t, J = 4.6 Hz, 1H), 5.44 (d, J = 5.4 Hz, 1H), 5.83 (d, J = 4.4 Hz, 1H), 6.72 (dd, J = 3.6, 1.1 Hz, 1H), 7.19 (d, J = 3.6 Hz, 1H), 8.53 (s, 1H), 11.63 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 14.7, 60.2, 69.4, 74.2, 84.7, 88.6, 108.6, 122.6, 124.7, 131.5, 134.9, 138.8, 149.5, 161.3; HRMS calcd for $C_{14}H_{17}N_2O_6S$ $[M + H]^+$ 341.0802, found 341.0803.

5-(Pyrrol-2-yl)uridine (19). Treatment of 5-iodouridine (**11**, 52 mg, 0.14 mmol) with pyrrole (0.2 mL, 193 mg, 2.88 mmol) by procedure A [reaction was carried out in a flask covered in aluminum foil under N_2 atmosphere; column chromatography (CH_2Cl_2/MeOH, 15:1 → 10:1)] gave **19** (19.4 mg, 45%) as brownish amorphous powder. This material is stable when stored in refrigerator under the inert condition for at least 1 month: ^{1}H NMR (DMSO-d_6) δ 3.60 (ddd, J = 12.0, 4.4, 3.3 Hz, 1H), 3.70 (ddd, J = 11.8, 4.6, 3.5 Hz, 1H), 3.87 ("q", J = 3.5 Hz, 1H), 4.03 ("q", J = 4.7 Hz, 1H), 4.14 ("q", J = 5.2 Hz, 1H), 5.10 (d, J = 5.2 Hz, 1H), 5.27 (t, J = 4.8 Hz, 1H), 5.42 (d, J = 5.6 Hz, 1H), 5.83 (d, J = 5.1 Hz, 1H), 6.03 (dd, J = 5.8, 2.6 Hz, 1H), 6.39 (dd, J = 4.5, 2.7 Hz, 1H), 6.76 (dd, J = 4.1, 2.5 Hz, 1H), 8.22 (s, 1H), 10.85 (s, 1H), 11.54 (bs, 1H); ^{13}C NMR (DMSO-d_6) δ 60.6, 69.6, 73.6, 84.7, 88.2, 105.5, 107.2, 108.0, 118.2, 123.8, 133.6, 149.7, 162.0; HRMS calcd for $C_{13}H_{16}N_3O_6$ $[M + H]^+$ 310.1034, found 310.1034.

3-(Fur-2-yl)pyridin-2(1*H*)-one (21). Method A. Treatment of **20** (24.36 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A (14 equiv of TBAF) gave **21**[39] (9.3 mg, 41%) followed by **20** (8.5 mg, 35%). Compound **21**: UV (MeOH) λ_{max} = 332 nm; ^{1}H NMR (CD_3CN) δ 6.33 (t, J = 6.9 Hz, 1H), 6.53 (dd, J = 3.3, 1.8 Hz, 1H), 7.27−7.29 (m, 2H), 7.54 (dd, J = 1.8, 0.7 Hz, 1H), 7.89 (dd, J = 7.1, 2.0 Hz, 1H), 10.33 (s, 1H); ^{13}C NMR (CD_3CN) δ 106.5, 111.1, 112.7, 122.2, 133.7, 134.6, 143.0, 150.4, 160.2; HRMS calcd for $C_9H_8NO_2$ $[M + H]^+$ 162.0550, found 162.0553.

Method B. Treatment of **20** (24.36 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure C gave **21** (15.3 mg, 68% yield) with the spectroscopic data as above.

3-(Thiophen-2-yl)pyridin-2(1*H*)-one (22). Treatment of **20** (24.36 mg, 0.14 mmol) with thiophene (0.2 mL, 210 mg, 2.5 mmol) by procedure A (14 equiv of TBAF) gave **22**[39] (9 mg, 37%) followed by **20** (8 mg, 33%). Compound **22**: UV (MeOH) λ_{max} = 346 nm; ^{1}H NMR (CD_3CN) δ 6.32 (dd, J = 7.0, 6.6 Hz, 1H), 7.09 (dd, J = 5.1, 3.8 Hz, 1H), 7.28 (dd, J = 6.5, 1.9 Hz, 1H), 7.40 (dd, J = 5.1, 1.1 Hz, 1H), 7.67 (dd, J = 3.8, 1.1 Hz, 1H), 7.97 (dd, J = 7.1, 1.9 Hz, 1H), 9.98 (s, 1H); ^{13}C NMR (CD_3CN) δ 105.4, 123.6, 126.2, 126.4, 128.2, 129.2, 132.4, 134.5, 159.6; HRMS calcd for C_9H_8NOS $[M + H]^+$ 178.0321, found 178.0320.

Method B. Treatment of **20** (24.36 mg, 0.14 mmol) with thiophene (0.2 mL, 210 mg, 2.5 mmol) by procedure C gave **22** (15.6 mg, 63% yield) with the spectroscopic data as above.

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1-*N*-Benzyl-6-(4-methoxyphenyl)uracil (23). AgCl (60 mg, 0.42 mmol), $Pd(OAc)_2$ (3.2 mg, 0.014 mmol) and tetrabutylammonium bromide (TBABr, 67.7 mg, 0.21 mmol) were added to a stirred solution of 1-*N*-benzyluracil[33] (**3**, 28.3 mg, 0.14 mmol) and 4-iodoanisole (98.3 mg, 0.42 mmol) in DMSO (1 mL) under the N_2 atmosphere at ambient temperature. The resulting suspension was stirred for 16 h at 100 °C (oil bath). Volatiles were evaporated, and the oily residue was dissolved in EtOAc and filtrated through Whatman GF/A filter paper. The filtrate was column chromatographed (hexane/EtOAc, 5:5 → 4:6) to give *p*-**2d** (10 mg, 23%) and **23** (14 mg, 33%) followed by **3** (12 mg, 41%). Compound **23**: ^{1}H NMR δ 3.84 (s, 1H), 4.96 (s, 1H), 5.65 (s, 1H), 6.87 (d, J = 8.6 Hz, 1H), 6.90−6.95 (m, 1H), 7.08 (d, J = 8.5 Hz, 1H), 7.19−7.26 (m, 1H), 9.73 (s, 1H); ^{13}C NMR δ 48.6, 55.5, 104.1, 114.2, 125.3, 127.0, 127.7, 128.7, 129.5, 136.5, 152.3, 157.3, 161.0, 163.1; GC−MS (t_R 24.77 min) m/z 308 (70, M^+), 91 (100); HRMS calcd for $C_{18}H_{17}N_2O_3$ $[M + H]^+$ 309.1234, found 309.1229.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all compounds and GC−MS spectra for **2a** and **2d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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