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Synthesis of substituted uracils by the reactions of halouracils with selenium, sulfur, oxygen and nitrogen nucleophiles under focused microwave irradiation

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Abstract—Under microwave irradiation, the nucleophilic substitution reactions of halouracils with selenium, sulfur, oxygen and nitrogen nucleophiles was complete within several minutes with yields up to 99%. The method using microwave irradiation is superior to those conducted under conventional heating processes.

1. Introduction

Several of the 5- and 6-substituted uracils exhibit significant antitumor activity against experimental mouse tumor.[1] Therefore, an efficient synthetic methodology for the preparation of these uracil derivatives will be crucial in developing new antitumor drugs. Our previous results have shown that the reaction rates of nucleophilic aromatic and heteroaromatic substitution can be accelerated under microwave irradiation.[2,3] We have been interested in developing new, more efficient, and synthetically useful reactions for the synthesis of biologically active molecules via microwave acceleration. As a result the development of more practical synthesis of 5-substituted and 6-substituted uracils will be examined in this proposal to further expand the utility and scope of our previous studies.

2. Results and discussion

Study was initiated of 5-bromouracil with amine nucleophiles. Microwave irradiation of 10 equiv of benzylamine and 5-bromouracil at 110 °C is found to yield 5-benzylaminouracil in 95% (Table 1, entry 1). The nucleophilic substituted reactions of 5-iodouracil, 5-chlorouracil and 5-fluorouracil were similarly performed. Of the four halouracils studied, the relative reactivity of 5-halouracils toward nitrogen-containing nucleophile (benzylamine) appeared to decrease in the order of Br > Cl > F > I (compared entries 1, 2, 4 with 5 in Table 1). There is little regularity in the relative replaceabilities of these substituents. The reason might be that iodine is too soft to react with hard nitrogen nucleophile.[4] As a comparison (entry 3, Table 1), 5-chlorouracil was heated with 20 equiv of benzylamine at 150 °C in an oil bath for 20 min to give only 34% yield of 5-benzylaminouracil, far less than 88% in microwave irradiation (entry 2, Table 1). We have now found that 5-substituted aminouracils were prepared by reaction of 5-bromouracil with appropriate amine in 95–98% yield within 10 min under microwave irradiation (Table 1, entries 8–12). Weak nucleophilic aromatic amine such as aniline also can react with 5-bromouracil to give 5-anilinouracil (92% yield) at 180 °C within 15 min (Table 1, entry 13). By conventional heating process, 5-anilinouracil was prepared at 195 °C in refluxing ethylene glycol for 2 h (76% yield).[5]

In order to investigate the efficacy of nucleophilic substitutions in different reaction conditions, we examined the solvent effect in the displacement reaction. 5-Chlorouracil, 5-bromouracil and 5-iodouracil were studied. When reacted with PhSNa under microwave irradiation, the substitution reaction could be realized by using NMP (*N*-methylpyrrolidone), HMPA, DMSO, DMF and DMAC (dimethylacetamide) as the solvent (Table 2). The better yields were obtained in HMPA for 5-chlorouracil and 5-bromouracil (93 and 86%, respectively. Table 2, entries 2 and 7). However, the reaction of 5-iodouracil with 2.2 equiv of PhSNa proceeded smoothly at 130 °C under microwave

Keywords: Microwave irradiation; Nucleophilic substitution; Halouracils.
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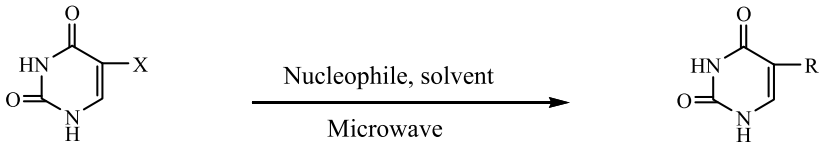
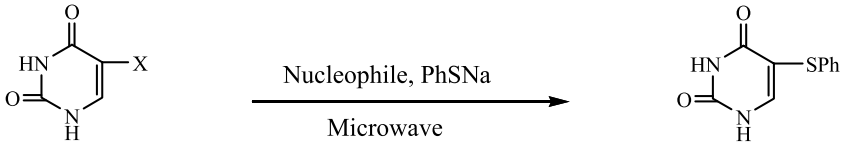
Table 1. Substitution of 5-halouracils with amines



Entry	X	Nucleophile	Solvent	Molar proportions of nucleophile	Temp (°C)	Time (min)	Product, R=	Yield (%)
1	Br	NH_2CH_2Ph	[a]	10	110	12	$NHCH_2Ph$	95
2	Cl	NH_2CH_2Ph	[a]	20	150	20	$NHCH_2Ph$	88
3	Cl	NH_2CH_2Ph	[a]	20	150	20	$NHCH_2Ph$	34[b]
4	F	NH_2CH_2Ph	[a]	20	170	20	$NHCH_2Ph$	76
5	I	NH_2CH_2Ph	[a]	20	130	10	$NHCH_2Ph$	0
6	I	NH_2CH_2Ph	[a]	10	100	10	$NHCH_2Ph$	18
7	I	NH_2CH_2Ph	DMF	3.5	130	10	$NHCH_2Ph$	16
8	Br	$NH_2(CH_2)_3CH_3$	[a]	20	90	10	$NH(CH_2)_3CH_3$	96
9	Br	Piperidine	[a]	20	90	9	Piperidyl	95
10	Br	Morpholine	[a]	20	90	5	N-Morpholyl	96
11	Br	Cyclohexylamine	[a]	20	110	7	Cyclohexylamino	98
12	Br	$NH(CH_3)CH_2$ Ph	[a]	15	120	5	N (CH_3) CH_2 Ph	97
13	Br	$PhNH_2$	[a]	15	180	15	NHPh	92

[a] No solvent was used.
[b] Heating in an oil bath.

Table 2. Reaction conditions of 5-halorouracils

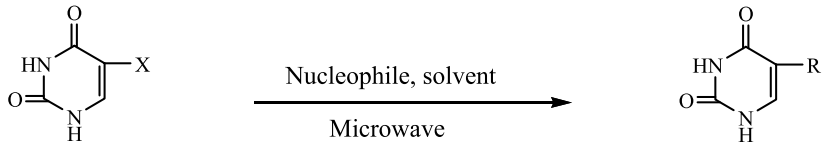


Entry	X	Solvent	Molar proportions of nucleophile	Temp (°C)	Time (min)	Product, R=	Yield (%)
1	Cl	NMP	4	140	5	SPh	81
2	Cl	HMPA	4	140	5	SPh	93
3	Cl	DMSO	4	140	5	SPh	56
4	Cl	DMF	4	140	5	SPh	74
5	Cl	DMAC	4	140	5	SPh	74
6	Br	NMP	4	140	5	SPh	75
7	Br	HMPA	4	140	5	SPh	86
8	Br	DMSO	4	140	5	SPh	65
9	Br	DMF	4	140	5	SPh	77
10	Br	DMAC	4	140	5	SPh	75
11	I	NMP	2.2	130	5	SPh	82
12	I	HMPA	2.2	130	5	SPh	72
13	I	DMSO	2.2	130	5	SPh	80
14	I	DMF	2.2	130	5	SPh	84

irradiation for 5 min in different solvents (Table 2, entries 11–14). Interestingly, the result indicated that DMF was the best solvent.

A detailed study of the reactions of 5-halouracils with O, S and Se containing nucleophiles in various amounts, reaction times, temperatures and solvents was investigated in order to find the optimized conditions for the preparation of uracil derivatives (Table 3). When 5-fluorouracil was treated with the oxygen, sulfur and selenium nucleophiles (PhONa, PhSNa and PhSeH) under microwave irradiation, the corresponding 5-substituted uracils were obtained in low yield (0–14%). The nucleophilic substitution reactions of 5-chlorouracil, 5-bromouracil and 5-iodouracil were similarly carried out (Table 3, entries 4–29). We might expect that with 5-iodouracil the order of reactivity is PhSeH > PhSNa > PhONa (compared entries 17, 21 with 29 in Table 3). Different 5-halouracils were studied in an attempt to appreciate the leaving group effect on reactivity and yields. Of the four halouracil tested, the relative reactivity of 5-halouracils toward selenium nucleophile (PhSeH) appeared to decrease in the order of I > Br > Cl > F (compared entries 3, 10, 15 with 29 in Table 3). The relative reactivity of 5-halouracils toward sulfur nucleophile (PhSNa) appeared to decrease in the order of I > Cl ~ Br > F (compared entries 2, 4, 12 with 22 in Table 3). Se and I are more polarizable in nucleophiles and halogens. The iodine would be expected to be easily attacked by nucleophilic

Table 3. Reactions of 5-halouracil with nucleophiles



Entry	X	Nucleophile	Solvent	Molar proportions of nucleophiles	Temp (°C)	Time (min)	Product, R=	Yield (%)
1	F	PhONa	NMP	4	140	5	OPh	0
2	F	PhSNa	HMPA	4	180	30	SPh	17
3	F	PhSeH	HMPA	4	180	20	SePh	14
4	Cl	PhSNa	NMP	2	130	5	SPh	51
5	Cl	PhSNa	NMP	4	130	5	SPh	84
6	Cl	PhSNa	HMPA	4	130	5	SPh	86
7	Cl	PhSNa	HMPA	4	140	5	SPh	93
8	Cl	PhSNa	HMPA	4	150	5	SPh	97
9	Cl	PhSNa	HMPA	4	150	5	SPh	36[a]
10	Cl	PhSeH	HMPA	4	150	5	SePh	52
11	Cl	PhSeH	HMPA	4	160	10	SePh	43
12	Br	PhSNa	NMP	2	130	5	SPh	47
13	Br	PhSNa	NMP	4	140	5	SPh	75
14	Br	PhSNa	HMPA	4	140	5	SPh	86
15	Br	PhSeH	HMPA	4	150	5	SePh	70
16	Br	PhSeH	DMF	4	130	5	SePh	29
17	I	PhONa	NMP	3	160	20	OPh	0
18	I	PhSNa	NMP	4	130	5	SPh	39
19	I	PhSNa	NMP	3	130	5	SPh	69
20	I	PhSNa	NMP	2.5	130	5	SPh	81
21	I	PhSNa	NMP	2.2	130	5	SPh	82
22	I	PhSNa	NMP	2	130	5	SPh	82
23	I	PhSNa	HMPA	2	130	5	SPh	77
24	I	PhSNa	DMSO	2	130	5	SPh	76
25	I	PhSNa	DMF	2.2	130	5	SPh	84
26	I	PhSNa	DMF	2	130	5	SPh	82
27	I	PhSeH	DMF	3	130	5	SePh	58
28	I	PhSeH	DMF	2.5	130	5	SePh	75
29	I	PhSeH	DMF	2.3	130	5	SePh	96

[a] Heating in an oil bath.

selenium. So the trend of 5-halouracils toward selenium nucleophile is predictable.

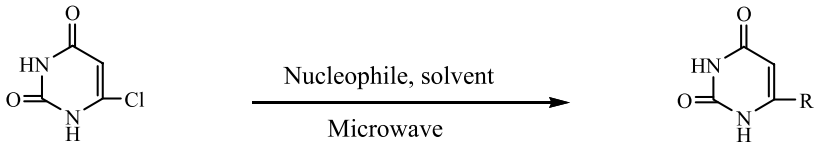
The product yield could be improved by running the reaction in a more polar solvent. The reaction of 5-chlorouracil with PhSNa afforded 5-phenylthiouracil in the yield up to 97% (Table 3, entry 8). The dipolar solvent HMPA might facilitate the substitution reaction. For comparing the efficacy of microwave irradiation with conventional heating, a HMPA solution of 5-chlorouracil and PhSNa (4 equiv) was heated at 150 °C in an oil bath for 5 min to give only 36% yield of 5-phenylthiouracil, far less than 97% in microwave irradiation (Table 3, entry 9). The reaction with PhONa nucleophile failed to give any appreciable quantities of the 5-phenoxyuracil in various reaction conditions.

When 2.2 equiv of PhSNa or 2.3 equiv of PhSeH were used, 5-iodouracil was converted to 5-phenylthiouracil or 5-(phenylselenenyl)uracil in good yields (84 and 96%, respectively. Table 3, entries 25 and 29). However, the yield of 5-phenylthiouracil or 5-(phenylselenenyl)uracil deteriorated when greater quantities of PhSNa or PhSeH were applied (Table 3, entries 18–22 and 27–29). Because iodine is the most replaceable of the halogens, it does not need too much amount of nucleophile.

Under microwave irradiation, 6-chlorouracil also reacted with PhSNa, PhSeH and some amino nucleophiles to give the corresponding 6-substituted uracils in varied yields (38–98%, Table 4). The reaction with PhSNa (4 equiv) in HMPA and DMSO at 90 °C for 3 min afforded an excellent yield of 6-phenylthiouracil (98 and 96%, respectively. Table 4, entries 11 and 12). The substitution with PhSeH was achieved in DMF to provide an 86% yield of 6-phenylselenenyluracil (entry 18, Table 4). The results indicated that the reactivity is 6-chlorouracil > 5-chlorouracil. For example, the substitution reaction of 6-chlorouracil with PhSNa occurred at 90 °C in 3 min (98% yield, Table 4, entry 11), whereas the reaction of 5-chlorouracil occurred at 150 °C in 5 min (97% yield, Table 3, entry 8).

Similar experiments were performed with another two substrates, 1,3-dimethyl-5-bromouracil and 1,3-dimethyl-6-chlorouracil (Tables 5 and 6). 1,3-Dimethyl-5-bromouracil was less reactive than 5-bromouracil toward nitrogen-containing nucleophiles. Only the reaction with piperidine gave the desired substitution product in a good yield of 94% (entry 8, Table 5). When 1,3-dimethyl-6-chlorouracil was treated with the sulfur, oxygen and nitrogen nucleophiles (PhSNa, PhONa, EtONa, MeONa, aniline, benzylamine and piperidine) under microwave irradiation, the corresponding

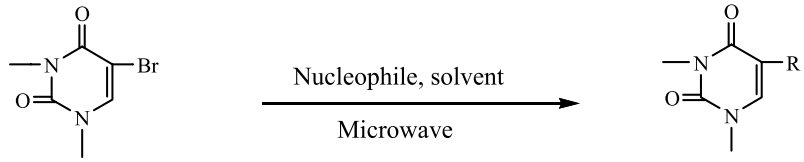
Table 4. Substitutions of 6-chlorouracil with nucleophiles



Entry	Nucleophile	Solvent	Molar proportions of nucleophiles	Temp (°C)	Time (min)	Product, R=	Yield (%)
1	NH_2CH_2Ph	[a]	15	130	15	$NHCH_2Ph$	94
2	NH_2CH_2Ph	[a]	15	130	15	$NHCH_2Ph$	41[b]
3	$NH_2(CH_2)_3CH_3$	[a]	15	90	20	$NH(CH_2)_3CH_3$	62
4	Cyclohexylamine	[a]	20	130	35	Cyclohexylamino	88
5	Piperidine	[a]	20	100	15	Piperidyl	96
6	Morpholine	[a]	20	100	15	N-Morpholyl	94
7	NH (CH_3) CH_2 Ph	[a]	10	130	20	N (CH_3) CH_2 Ph	92
8	$PhNH_2$	[a]	30	160	20	NHPh	95
9	PhONa	NMP	4	90	3	OPh	0
10	PhSNa	NMP	4	90	3	SPh	86
11	PhSNa	HMPA	4	90	3	SPh	98
12	PhSNa	DMSO	4	90	3	SPh	96
13	PhSNa	DMF	4	90	3	SPh	90
14	PhSNa	DMAC	4	90	3	SPh	85
15	PhSeH	NMP	4	90	3	SePh	83
16	PhSeH	HMPA	4	90	4	SePh	63
17	PhSeH	DMSO	4	90	4	SePh	38
18	PhSeH	DMF	4	90	4	SePh	86

[a] No solvent was used.
[b] Heating in an oil bath.

Table 5. Substitutions of 1,3-dimethyl-5-bromouracil with nucleophiles



Entry	Nucleophile	Solvent	Molar proportions of nucleophiles	Temp (°C)	Time (min)	Product, R=	Yield (%)
1	PhSNa	NMP	3	130	3	SPh	79
2	PhSNa	HMPA	3	130	3	SPh	52
3	PhSNa	DMSO	3	130	3	SPh	45
4	PhSNa	DMF	3	130	3	SPh	78
5	PhONa	NMP	3	130	2	OPh	0
6	$PhNH_2$	[a]	20	180	30	NHPh	0
7	NH_2CH_2Ph	[a]	20	180	30	$NHCH_2Ph$	0
8	Piperidine	[a]	15	100	40	Piperidyl	94

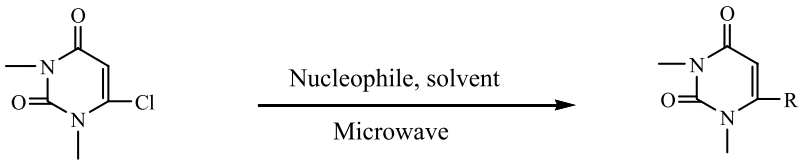
[a] No solvent was used.

6-substituted uracils were obtained in excellent yields (90–99%, Table 6).

3. Conclusion

In conclusion, our present study demonstrated that microwave irradiation can greatly facilitate the synthesis of various substituted uracils by nucleophilic substitution. This new synthetic tool is definitely valuable for the quick access of these bioactive compounds. The substitution reactions under conventional heating take many hours and low yields desired products were obtained. For example, the substitution reaction of 5-bromouracil with PhSNa by heating at 140 °C for 2 h gave a low yield (11%) of 5-phenylthiouracil,[6] whereas the reaction was promoted significantly by microwave irradiation at 140 °C for 5 min gave a good yield (86%) of the desired product (Table 3, entry 14). The relative reactivity of halouracils in substitution reactions follows 1,3-dimethyl-6-chlorouracil > 5-bromouracil > 6-chlorouracil > 1,3-dimethyl-5-bromouracil. For example, the reaction of 1,3-dimethyl-6-chlorouracil with PhONa afforded 90% yield of the desired product under microwave irradiation at 60 °C for 0.5 min (Table 6, entry 2).

Table 6. Substitutions of 1,3-dimethyl-6-chlorouracil with nucleophiles



Entry	Nucleophile	Solvent	Molar proportions of nucleophiles	Temp (°C)	Time (min)	Product, R=	Yield (%)
1	PhSNa	NMP	3	60	0.5	SPh	93
2	PhONa	NMP	3	60	0.5	OPh	90
3	EtONa	EtOH	3	60	0.5	OEt	97
4	MeONa	MeOH	3	60	0.5	OMe	99
5	$PhNH_2$	[a]	15	160	30	NHPh	98
6	NH_2CH_2Ph	[a]	5	130	3	$NHCH_2Ph$	98
7	piperidine	[a]	15	60	0.5	piperidyl	99
8	NH (CH_3) CH_2 Ph	[a]	5	130	1	N (CH_3) CH_2 Ph	94

[a] No solvent was used.

4. Experimental

^{1}H NMR spectra were measured in DMSO-d_6 or $CDCl_3$ solutions on a Bruker 300 spectrometer. Reactions were monitored by analytical thin-layer chromatography using silica gel 60 F-254 (0.2 mm layer thickness). Flash chromatography was carried out by utilizing silica gel 60 (70–230 mesh ASTM).

4.1. General procedure for reaction of halouracil nucleophile

In a reaction vessel (12 mL) were placed a nucleophile and a halouracil (0.1 mmol) in an appropriate solvent (1 mL). *t*-BuOK (1.1 equiv vs. nucleophile) could be added as the base if needed. The reaction vessel was then placed into the cavity of a focused monomode microwave reactor (CEM Discover) and irradiated for the period listed in the tables. The reaction temperature was maintained by modulating the power level of the reactor. The desired product precipitates after the pH was adjusted to 6 with 6 N HCl. The product was collected, washed with H_2O. Then was purified by recrystallization. Products **19**, **21**, **22**, **23**, **24**, **26** and **27** were purified by silica gel chromatography eluting with a mixture of hexane, ethyl acetate and acetone.

4.1.1. 5-Benzylaminouracil.[7] Pale white solid, mp 301–305 °C (dec) (lit. 285 °C dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.34 and 10.02 (2s, 2H, 2NH), 7.31–7.19 (m, 5H, Ph), 6.08 (s, 1H, 6-H), 4.97 (t, J=6.2 Hz, 1H, NH), 4.08 (d, J=6.2 Hz, 2H).

4.1.2. 5-Butylaminouracil.[8] Pale yellow solid, mp 285–288 °C (dec) (lit. 286–288 °C dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.11 and 10.13 (2s, 2H, 2NH), 6.26 (d, J=6.0 Hz, 1H, 6-H), 4.10 (t, J=5.8 Hz, 1H, NH), 2.76 (m, 2H), 1.47 (m, 2H), 1.30 (m, 2H), 0.87 (t, J=7.4 Hz, 3H).

4.1.3. 5-Piperidyluracil.[8] White solid, mp 303–305 °C (dec) (lit. 285–290 °C dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.89 and 10.40 (2s, 2H, 2NH), 6.66 (s, 1H, 6-H), 2.71 (m, 4H), 1.54–1.43 (m, 6H).

4.1.4. 5-Morpholinouracil.[8] White solid, mp 329–334 °C (dec) (lit. >310 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.05 and 10.46 (2s, 2H, 2NH), 6.72 (s, 1H, 6-H), 3.63 (t, J=4.5 Hz, 4H), 2.77 (t, J=4.5 Hz, 4H).

4.1.5. 5-Cyclohexylaminouracil.[8] Pale yellow solid, mp 327–333 °C (dec) (lit. >305 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.13 and 10.15 (2s, 2H, 2NH), 6.36 (d, J=5.2 Hz, 1H, 6-H), 3.78 (d, J=8.4 Hz, 1H, NH), 2.87 (m, 1H), 1.84–1.05 (m, 10H).

4.1.6. 5-(Benzylmethylamino)uracil.[8] White solid, mp 269–271 °C (lit. 267–269 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.08 and 10.40 (2s, 2H, 2NH), 7.33–7.20 (m, 5H, Ph), 6.60 (s, 1H, 6-H), 4.04 (s, 2H), 2.39 (s, 3H).

4.1.7. 5-Anilinouracil.[5] Pale white solid, mp 318–320 °C (dec) (lit. 317–319 °C dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.25 (s, H, NH), 10.63 (d, J=4.8 Hz, 1H, NH), 7.29 (d, J=5.8 Hz, 1H, 6-H), 7.12–6.62 (m, 5H, Ph), 6.90 (s, 1H, NH).

4.1.8. 5-Phenylthiouracil.[9] White solid, mp 273–274 °C (lit. 269–271 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.40 (s, 2H, 2NH), 7.92 (s, 1H, 6-H), 7.29–7.14 (m, 5H, SPh).

4.1.9. 5-Phenylselenenyluracil.[9] White solid, mp 250–252 °C (lit. 249–251 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.36 and 11.01 (2s, 2H, 2NH), 7.79 (s, 1H, 6-H), 7.36–7.19 (m, 5H, SePh).

4.1.10. 6-Benzylaminouracil.[10] Pale white solid, mp 318–320 °C (dec) (lit. 316–317 °C dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.19 and 10.03 (2s, 2H, 2NH), 7.38–7.24 (m, 5H, Ph), 6.60 (t, J=5.7 Hz, 1H, NH). 4.37 (s, 1H, 5-H). 4.25 (d, J=5.7 Hz, 2H, –CH_2Ph).

4.1.11. 6-Cyclohexylaminouracil.[11] Yellow solid, mp 327–329 °C (lit. 327–328 °C); ^{1}H NMR (300 MHz,

DMSO-d_6) δ 10.15 and 9.66 (2s, 2H, 2NH), 6.03 (d, J= 7.9 Hz, 1H, NH), 4.43 (s, 1H, 5-H), 3.18 (m, 1H), 1.83–1.14 (m, 10H).

4.1.12. 6-Piperidyluracil.[12] White solid, mp 307–309 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.33 and 10.22 (2s, 2H, 2NH), 4.60 (s, 1H, 5-H), 3.23 (m, 4H), 1.51 (m, 6H).

4.1.13. 6-Morpholinouracil.[13] White solid, mp 322–326 °C (dec) (lit. >310 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.45 and 10.24 (2s, 2H, 2NH), 4.65 (s, 1H, 5-H), 3.61 (t, J=4.8 Hz, 4H), 3.12 (t, J=4.8 Hz, 4H).

4.1.14. 6-(Benzylmethylamino)uracil.[11] White solid, mp 273–275 °C (lit. 273–275 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.35 and 10.13 (2s, 2H, 2NH), 7.40–7.15 (m, 5H, Ph), 4.58 (s, 2H), 4.47 (s, 1H, 5-H), 2.92 (s, 3H).

4.1.15. 6-Anilinouracil.[10] Pale white solid, mp 326–327 °C (dec) (lit. 325–327 °C dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.46 and 10.17 (2s, 2H, 2NH), 8.25 (s, 1H, NH). 7.29 (d, J=5.8 Hz, 1H, 6-H), 7.40–7.12 (m, 5H, Ph), 4.68 (s, 1H, 5-H).

4.1.16. 6-Phenylthiouracil.[9] White solid, mp 272–274 °C (lit. 270–272 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.58 and 10.98 (s, 2H, 2NH), 7.65–7.51 (m, 5H, SPh), 4.51 (s, 1H, 5-H).

4.1.17. 6-Phenylselenenyluracil.[9] White solid, mp 241–243 °C (lit. 238–240 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.54 and 10.97 (2s, 2H, 2NH), 7.70–7.47 (m, 5H, SePh), 4.68 (s, 1H, 5-H).

4.1.18. 1,3-Dimethyl-5-phenylthiouracil.[14] White solid, mp 134–136 °C (lit. 136 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.34 (s, 1H, 6-H), 7.29–7.12 (m, 5H, SPh), 3.35 (s, 3H), 3.18 (s, 3H).

4.1.19. 1,3-Dimethyl-5-piperidyluracil. Colorless oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.10 (s, 1H, 6-H), 3.27 (s, 3H), 3.14 (s, 3H), 2.76 (t, J=5.1 Hz, 4H), 1.60–1.45 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.3, 150.2, 130.1, 126.7, 51.1 (2C), 36.2, 27.7, 25.5 (2C), 23.8; IR (MeOH): 2931, 1700, 1650 cm^{-1}; MS *m/e* 223 (M^+), 194, 140, 84, 69; HRMS *m/e* calcd for 223.2782, found 223.1329.

4.1.20. 1,3-Dimethyl-6-phenylthiouracil.[15] Colorless needles, mp 131–132 °C (lit. 129–130 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.66–7.56 (m, 5H, SPh), 4.71 (s, 1H, 5-H), 3.45 (s, 3H), 3.10 (s, 3H).

4.1.21. 1,3-Dimethyl-6-phenoxyuracil.[15] Colorless needles, mp 109–110 °C (lit. 107–108 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.56–7.30 (m, 5H, OPh), 4.44 (s, 1H, 5-H), 3.41 (s, 3H), 3.13 (s, 3H).

4.1.22. 1,3-Dimethyl-6-ethoxyuracil.[16] White solid, mp 136–137 °C (lit. 134 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.19 (s, 1H, 5-H), 4.12 (q, J=7.0 Hz, 2H), 3.20 (s, 3H), 3.11 (s, 3H), 1.34 (t, J=7.0 Hz, 3H).

4.1.23. 1,3-Dimethyl-6-methoxyuracil.[17] Colorless needles, mp 164–166 °C (lit. 165–166 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.21 (s, 1H, 5-H), 3.86 (s, 3H), 3.20 (s, 3H), 3.12 (s, 3H).

4.1.24. 1,3-Dimethyl-6-anilinouracil.[18] Yellow solid, mp 186–188 °C (lit. 187 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53 (s, 1H, NH), 7.45–7.21 (m, 5H, Ph), 4.62 (s, 1H, 5-H), 3.42 (s, 3H), 3.10 (s, 3H).

4.1.25. 1,3-Dimethyl-6-benzylaminouracil.[19] Colorless needles, mp 159–163 °C (lit. 158–159 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.55 (t, J=5.9 Hz, NH), 7.34–7.21 (m, 5H, Ph), 4.49 (s, 1H, 5-H), 4.32 (d, J= 5.9 Hz, 2H), 3.36 (s, 3H), 3.04 (s, 3H).

4.1.26. 1,3-Dimethyl-6-piperidyluracil.[20] Colorless solid, mp 78–79 °C (lit. 77 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.10 (s, 1H, 5-H), 3.24 (s, 3H), 3.11 (s, 3H), 2.84 (t, J= 4.7 Hz, 4H), 1.62–1.52 (m, 6H).

4.1.27. 1,3-Dimethyl-6-(benzylmethylamino)uracil. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.24 (m, 5H, Ph), 5.27 (s, 1H, 5-H), 4.10 (s, 2H), 3.4 7 (s, 3H), 3.34 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ163.3, 160.0, 153.3, 135.4, 129.0 (2C), 128.2 (3C), 88.7, 58.1, 39.4, 33.4, 27.9; IR (MeOH): 2924, 2854, 1699, 1655, 1606 cm^{-1}; MS *m/e* 259 (M^+), 244, 137, 91, 69; HRMS *m/e* calcd for 259.2989, found 259.1322.

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