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Synthesis, characterization and theoretical evaluations of HMDS promoted chemoselective O-alkylation of uracils

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ABSTRACT

The sodium salts of the conjugated bases of uracils undergo highly chemoselective O^4-monoalkylation when treated with various alkyl halides in dry DMF, while the use of methyl iodide results in N^1+N^3-dimethylation. Theoretical evaluations of the chemo- and regioselectivity along with X-ray crystallographic data are presented.

1. Introduction

Uracil (pyrimidine-2,4(1*H*,3*H*)dione) is a privileged molecule because it is a major component of ribonucleic acids.[1] In the past decades, uracil and its derivatives have attracted the interest of numerous researchers. Uracil is an important anticancer agent,[2–4] with great potential for treatment of HIV infection.[5,6]

The tetradentate nucleophilic nature of uracils or their conjugated bases have made their chemoselective alkylation an interesting subject for long debate. Uracils are susceptible to N/O alkylation and as a result a mixture of N^1, N^1+N^3 and some O^4-alkyl derivatives are obtained.[7]

The chemoselectivity in the alkylation of uracils has recently been reviewed by Krzyszto Walezac et al.[8] Most chemical efforts has been devoted in uracil participation towards selective N^1 and to some extent N^3 alkylation while the selective O^4-alkylation has been largely overlooked partly because the *O*-alkyluracil ethers isomerize to their *N*-alkyl derivatives in the presence of Lewis acids.[9,10] Recently, in the course of a study to prepare 4(6)-alkyluracils from 4(6)-methyl uracil, we noticed that 1,1,1,3,3,3-hexamethyldisilazane (HMDS) can assist the chemoselective O-alkylation of uracils. In this paper, we report the results of our study on the HMDS driven chemoselective O-alkylation of these compounds. In addition, we wish to present the results of our theoretical evaluation on the chemo- and regioselectivity of alkylation of 5-substituted 6-methyl uracils **1**(**a**–**c**) through computational ^{13}C NMR chemical shifts using the gauge invariant atomic orbital (GIAO) method.[11]

2. Results and discussion

While investigating the alkylation of 2,4-disilyloxy-pyrimidines **2**(**a**–**c**) via obtained from 6-methyl uracils **1**(**a**–**c**) by methyl iodide in the presence of a strong base, a wide spectrum of methylated products were obtained. When an equimolar amount of methyl iodide was used, a mixture of N^1, N^3 and N^1+N^3-methylated uracils were obtained, but in the case of excess methyl iodide, N^1+N^3-methylated uracils **3**(**a**–**c**) were observed (Scheme 1). A literature survey revealed the formation of the unexpected N^1+N^3-double alkylation products **3**(**a**–**c**).[12–16]

The above findings prompted us to further investigate the alkylation of uracils with other alkyl halides under the same conditions. Surprisingly, we noticed that substrates **1**(**a**–**c**) exclusively undergo the O^4-alkylation under the same conditions. As shown in Scheme 1, selected uracils **1**(**a**–**c**) were reacted with HMDS in the presence of a catalytic amount of ammonium sulfate to produce the corresponding 2,4-bis(trimethylsilyloxy)pyrimidines **2**(**a**–**c**). These products underwent chemoselective O^4-alkylation with alkyl halides (primary, benzylic and α-carbonyl halides) with the exception of methyl iodide in the presence of sodium hydride in DMF at −10 °C to give the related O^4-alkyluracil ethers **4**(**a**–**r**) (Table 1).

Moreover, we carried out a model study to investigate the effects of different bases and solvents on the formation of products arising from mono- or di-alkylation of the N- or O-group of the

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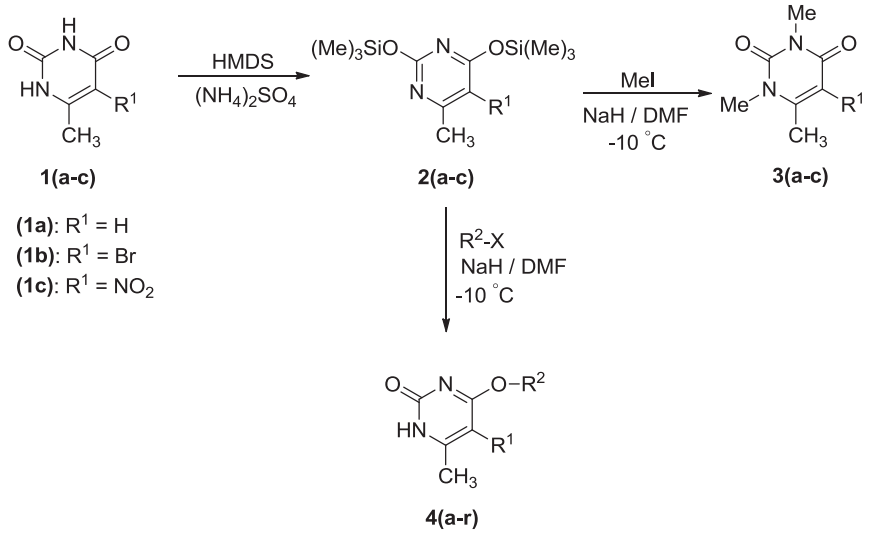

Scheme 1.

Table 1
The different substituents of compounds **4**(**a**–**r**) via selective O^4-alkylation

Entry	R^1	R^2	Yield (%)
4a	H	Et	78
4b	H	*n*-Pr	85
4c	H	*n*-Bu	79
4d	H	CH_2Ph	89
4e	H	CH_2CO_2Et	79
4f	H	CH_2COPh	65
4g	Br	Et	80
4h	Br	*n*-Pr	87
4i	Br	*n*-Bu	75
4j	Br	CH_2Ph	70
4k	Br	CH_2CO_2Et	65
4l	Br	CH_2COPh	68
4m	NO_2	Et	82
4n	NO_2	*n*-Pr	79
4o	NO_2	*n*-Bu	69
3p	NO_2	CH_2Ph	77
4q	NO_2	CH_2CO_2Et	73
4r	NO_2	CH_2COPh	65

uracils **1**(**a**–**c**), but the results showed NaH in dry DMF at room temperature gave only the O^4-alkylated uracils and other bases such as *t*-BuOK, *n*-BuLi, $NaNH_2$, and solvents such as THF, toluene, CH_3CN did not led to the desired mono-alkyl derivatives.

The structural elucidation of all the synthesized compounds **4**(**a**–**r**) was achieved by their physical, chemical and spectroscopic data. For instance, the IR spectrum of compound (**4g**) displayed two distinguished absorption bands at 3203 and 1238 cm^{-1} due to NH and C–O moieties, respectively. Also, the ^1H NMR spectrum of this product showed a triplet peak at 1.41 ppm for the methyl protons as well as a quartet peak at 4.62 ppm (methylene group), both for the ethyl substituent, a singlet peak at 2.55 ppm for the methyl substituent, which is attached directly to the pyrimidine ring. Another broad singlet signal at 13.31 ppm was observed due to the NH group of the pyrimidine ring, which was removed on adding D_2O. The mass spectrum of compound (**4g**) showed a molecular ion peak at *m*/*z* 232 (M^+) and 234 (M^++2) corresponding to the molecular formula of $C_7H_9BrN_2O_2$. The micro analytical data of the new synthesized derivative (**4g**) was fully supportive of the corresponding molecular structure and confirmed the mono-alkylation pathway. Further proof for confirming the O^4-alkylated structure came from X-ray crystallographic analysis. A survey of the Cambridge Crystallographic Structure Database showed that no structures have been determined for 4-ethoxy-6-methylpyrimidin-2(1*H*)-one (**4g**). As shown in Fig. 1, this compound crystallizes in the triclinic space group *P*-1. Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (deposition no. CCDC 918052).[17]

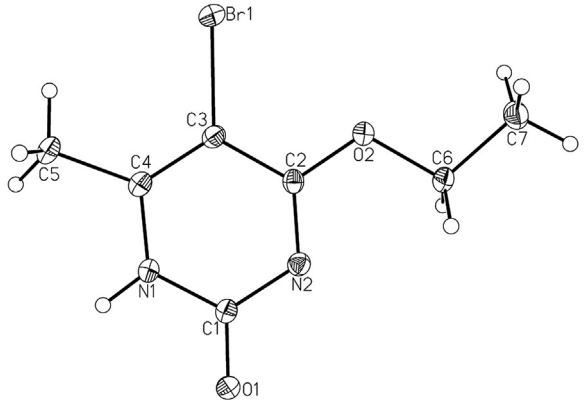

Fig. 1. ORTEP view of compound (**4g**). The thermal displacement ellipsoids are shown at 50% probability level.

A plausible mechanism for trimethylsilylation of uracils **1**(**a**–**c**) is shown in Scheme 2. It seems that the ammonium sulfate acts as a catalyst to convert HMDS into an activated silylating agent through polarization of the Si–N bond by proton transfer before any silylation occurs. Consequently, the oxygen of the carbonyl group is silylated.

The stepwise chemoselective O^4-alkylation of silylated uracils **2**(**a**–**c**) is also shown in Scheme 3. The anion obtained from the nucleophilic attack with hydride ion onto the silylated uracils undergoes monoalkylation with alkyl halides to yield the corresponding products.

As mentioned earlier, alkylation with methyl iodide only gave 1,3-dimethyl uracils **3**(**a**–**c**). The sharp prevalence of N^1+N^3-attack on methyl iodide and the lack of O-alkylation can be attributed to the very soft nature of methyl iodide as has been observed by earlier workers.[18–20] The ambiguity in alkylation of uracils **1**(**a**–**c**) can be explained by theoretical evaluations. The bond lengths and angles of compound (**4g**), derived from the optimization procedure at B3LYP/6-31+G(d,p) level of theory in a gas phase showed good agreement with the experimental data of X-ray analysis (see Table 2).

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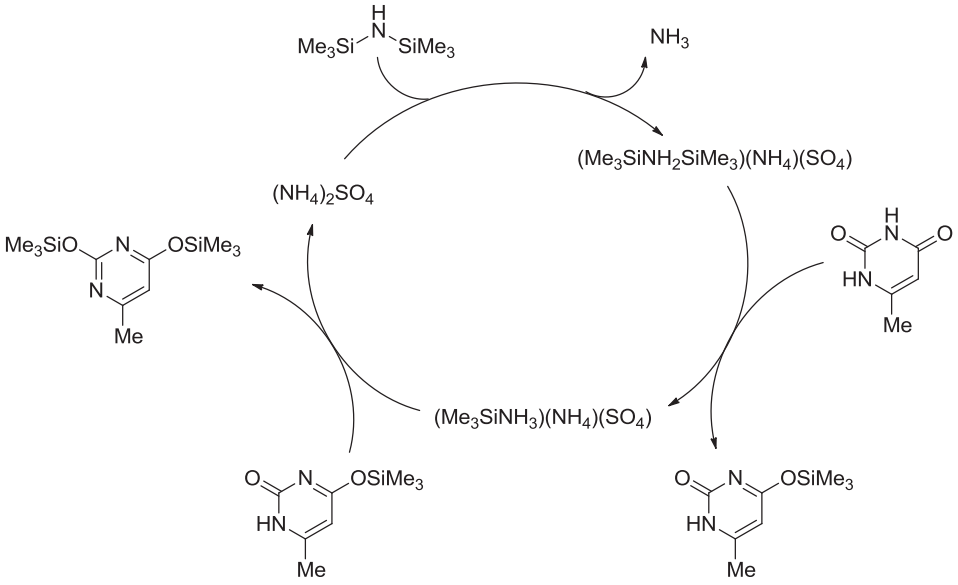
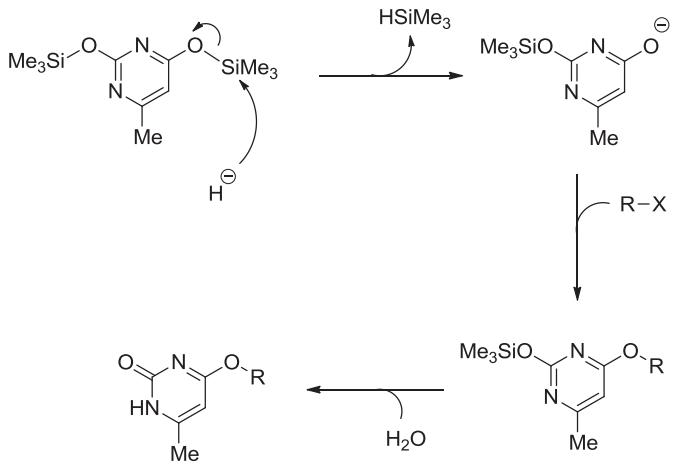


Scheme 2.



Scheme 3.

Table 2
Some of calculated and experimental bond lengths and angles of compound (**4g**) (numbering, according to Fig. 1)

	Calculated	X-ray		Calculated	X-ray
Bond length (Å)					
Br1–C3	1.894	1.881	N2–C2	1.309	1.314
O1–C1	1.223	1.243	N2–C1	1.376	1.365
O2–C2	1.333	1.330	C2–C3	1.437	1.425
O2–C6	1.452	1.458	C3–C4	1.369	1.364
N1–C4	1.365	1.363	C4–C5	1.500	1.497
N1–C1	1.418	1.383	C6–C7	1.516	1.506
Bond angle (°)					
C2–O2–C6	118.1	116.1	O2–C2–C3	115.8	116.4
C4–N1–C1	125.0	123.5	C4–C3–C2	117.5	117.8
C2–N2–C1	120.3	118.8	C4–C3–Br1	121.4	122.0
O1–C1–N2	125.3	121.8	C2–C3–Br1	121.1	120.1
O1–C1–N1	118.8	119.7	N1–C4–C3	117.3	117.6
N2–C1–N1	115.9	118.6	N1–C4–C5	117.8	115.9
N2–C2–O2	120.2	120.1	C3–C4–C5	124.9	126.4
N2–C2–C3	123.9	123.5	O2–C6–C7	107.0	107.3

The experimental and calculated bond lengths and angles are between 0.002 and 0.035 Å (except C–H and N–H bonds, due to systematically being too long predicting by DFT methods) and 0.1–3.5°, respectively.

Moreover, GIAO ^{13}C chemical shifts for the compounds shown in Fig. 2 were calculated by two approaches using Eq. 1: (1) using TMS as a single reference and (2) using multiple reference compounds that was proposed in 2009 by Sarotti and Pellegrinet.[21] They used methanol as the reference for sp^3 hybridized carbons and benzene for sp and sp^2 hybridized carbons [the multi-standard (MSTD) approach].

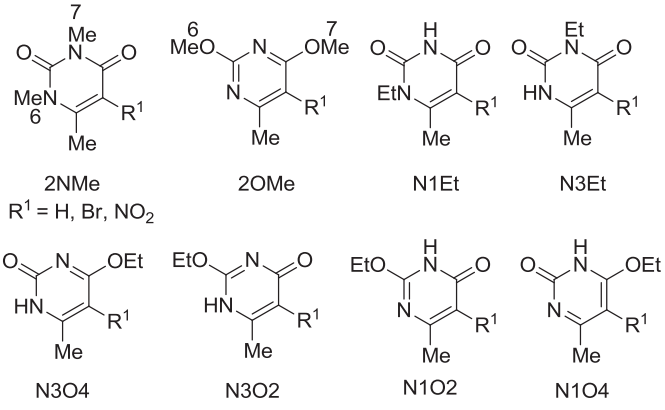


Fig. 2. Structures of the considered compounds for GIAO ^{13}C NMR calculations.

$$\delta_i = \sigma_{ref} - \sigma_i + \delta_{ref} \quad (1)$$

In Eq. 1, the chemical shifts relative to TMS for each nucleus in the molecule of interest (δ_i) are determined from the shielding constants computed for the same nucleus type in the reference compound (σ_{ref}), the computed shielding constants for each nucleus in the molecule of interest (σ_i), and the known experimental chemical shift for the reference compound (δ_{ref}). Chemical shifts calculated in this way often benefit from a fair amount of error cancellation. Computed shielding constants and experimental chemical shifts for the reference compounds are shown in Table 3.

The comparison of calculated chemical shifts of carbons attached to O or N atoms with their experimental data shows N-methylation and O-ethylation are preferred in the reaction of compounds **2**(**a**–**c**) with methyl or ethyl iodide, respectively

Table 3
Experimental chemical shifts and GIAO isotropic magnetic shielding values of the standards in $CDCl_3$ and $(CD_3)_2CO$ calculated at different levels of theory for B3LYP/6-31+G(d,p) optimized structures

Level of theory	In $(CD_3)_2CO$			In $CDCl_3$		
	TMS	Methanol	Benzene	TMS	Methanol	Benzene
B3LYP/6-31+G(d,p)	193.12	140.15	67.76	193.32	140.04	67.68
mPW1PW91/6-31+G(d,p)	196.67	144.11	70.21	196.87	144.02	70.12
mPW1PW91/6-311+G(2d,p)	187.01	133.31	52.82	187.18	133.22	52.70
Experimental[a]	0	50.41	128.37	0	49.77	129.15

[a] Data chosen from Ref. 22.

(Table 4). For example, unscaled calculated chemical shifts for C6 attached to N2 or O2 in the ethylated compound (R^1=Br) are 38.58 ppm and 64.32 ppm, respectively, while the experimental chemical shift for this carbon is 64.76 ppm. Therefore, O-ethylation is preferred with ethyl iodide. It is notable that more thermodynamically stable products are formed in the case of methylation (N-methylation) and less thermodynamically stable isomers in ethylation (O-ethylation) (Table 5). Hence, chemoselectivity of compounds **2**(**a**–**c**) with ethyl iodide is controlled kinetically.

Table 4
Experimental and unscaled GIAO chemical shift values of all the compounds shown in Fig. 3, calculated at mPW1PW91/6-31+G(d,p)-PCM[a]//B3LYP/6-31+G(d,p) level of theory using MSTD approach (numbering is according to Figs. 1 and 3)

Compound	R^1	C7	C5	C6	C3	C1	C4	C2	Max $\lvert\Delta\delta\rvert$[b]
N3O4	H	13.44	18.83	62.52	94.72	154.30	156.31	170.50	4.51
	Br	13.25	20.91	64.32	104.14	152.37	156.05	165.97	2.88
	NO_2	12.35	20.02	64.43	127.73	151.79	161.44	163.72	5.67
N1O4	H	13.55	25.69	61.05	90.59	153.39	177.92	161.97	7.06
	Br	13.43	27.29	62.71	99.60	151.76	176.58	157.66	8.16
	NO_2	12.55	25.61	63.62	126.23	151.03	175.22	159.91	11.80
N3O2	H	13.32	18.01	63.74	107.11	155.78	148.98	168.65	12.20
	Br	13.46	18.05	64.48	121.57	154.46	147.69	163.56	7.44
	NO_2	12.53	16.37	64.85	137.96	155.05	152.50	160.89	14.56
N1O2	H	13.83	24.53	61.34	105.29	155.42	170.16	160.39	10.38
	Br	13.96	23.54	61.91	117.56	153.23	168.24	156.72	3.86
	NO_2	13.06	22.77	62.62	137.08	155.88	169.97	154.65	13.68
N1Et	H	13.13	19.70	40.47	103.47	150.25	156.01	159.63	22.49
	Br	12.89	19.25	42.36	114.56	148.81	155.30	156.54	22.40
	NO_2	12.00	15.92	41.50	129.58	143.75	152.49	148.57	22.46
N3Et	H	12.18	18.42	36.74	101.79	150.16	151.06	161.72	26.22
	Br	12.03	18.24	38.58	113.5	148.62	150.45	158.55	26.18
	NO_2	11.43	18.30	37.67	133.07	149.10	155.84	156.45	26.29
Experimental[c]	*H*	*14.28*	*18.63*	*62.96*	*94.91*	*156.31*	*160.82*	*173.12*	—
	Br	*14.19*	*19.68*	*64.76*	*90.21*	*155.13*	*158.93*	*168.42*	—
	NO_2	*13.35*	*16.15*	*63.96*	*123.40*	*153.27*	*155.77*	*163.42*	—
2NMe	H	26.74	19.85	29.13	102.19	151.84	154.24	160.27	2.59
	Br	28.61	19.76	30.65	114.27	150.64	153.75	157.42	2.90
	NO_2	27.20	16.20	29.75	134.74	151.10	155.77	155.26	5.37
2OMe	H	52.31	23.90	53.35	100.67	165.56	170.45	170.82	24.33
	Br	55.70	26.90	55.98	112.41	161.35	167.22	163.79	26.16
	NO_2	56.57	25.24	57.19	130.99	161.73	166.76	161.52	28.75
Experimental[c]	*H*	*27.98*	*20.25*	*31.72*	*101.25*	*151.44*	*152.62*	*162.47*	—
	Br	*29.54*	*20.69*	*33.55*	*98.21*	*149.96*	*151.36*	*158.87*	—
	NO_2	*27.82*	*15.41*	*31.85*	*129.69*	*150.34*	*155.04*	*150.40*	—

[a] Acetone for R^1=NO_2 and chloroform for other compounds.
[b] Maximum absolute deviation chemical shift from experimental data.
[c] Experimental chemical shifts are ordered only based on values and not assigned.

Table 5
Relative Gibbs free energies (kcal mol^{-1}) in B3LYP/6-31+G(d,p) level of theory in a gas phase

Compound	Methylation						Ethylation	
	N1Et	N3Et	N1O2	N3O2	N1O4	N3O4	2NMe	2OMe
R^1=H	3.48	0.00	20.39	21.65	24.27	14.60	0.00	21.75
R^1=Br	4.47	0.00	19.57	20.55	24.48	14.32	0.00	20.23
R^1=NO_2	4.22	0.00	18.95	20.06	23.49	13.97	0.00	19.59

By considering the differences between calculated and experimental chemical shifts of all the regioisomers/tautomers of a compound, we conclude that N3O4 regioisomers are preferred. For example, these differences for compound (**4g**) are shown in Fig. 3. We did not calculate the ^{13}C shielding constants for brominated carbons because of the requirement of relativistic and spin–orbit coupling correction[23] that makes the calculations too lengthy. Without these corrections, the calculations for *ipso*-brominated carbons yield meaningless results. So we excluded those carbons from further considerations.

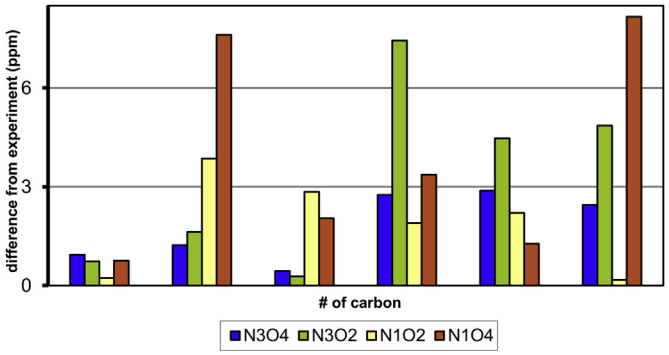


Fig. 3. Absolute differences (ppm) between experimental and calculated ^{13}C NMR chemical shifts (unscaled) for regioisomers/tautomers of compound (**4g**) at mPW1PW91/6-31+G(d,p)-PCM//B3LYP/6-31+G(d,p) level of theory with an implicit chloroform solvent model and MSTD approach.

In order to compare the efficiency of various methods and basis sets in predicting the calculated chemical shifts of our studied compounds, we also calculated ^{13}C chemical shifts for six main regioisomers (2MeN and N3O4 with R^1=H, Br, NO_2) at B3LYP/6-31+G(d,p) and mPW1PW91/6-311+G(2d,p) levels of theory according to the mentioned conditions. As can be seen in Table 6, mPW1PW91 hybrid functional reproduce smaller MADs of ^{13}C chemical shifts relative to B3LYP with the same basis sets (6-31+G(d,p)). Surprisingly, MAD values on large 6-311+G(2d,p) basis set with the same functional (mPW1PW91) are greater than standard 6-31+G(d,p) basis set, specially for unscaled values.

Table 6
The average of mean absolute deviations (MAD) of GIAO ^{13}C chemical shifts for all the calculated compounds at different levels of theory

Level of theory	MSTD		TMS	
	Unscaled	Scaled	Unscaled	Scaled
B3LYP/6-31+G(d,p)	1.74	1.38	2.51	1.38
mPW1PW91/6-31+G(d,p)	1.64	1.31	2.24	1.28
mPW1PW91/6-311+G(2d,p)	1.83	1.37	2.63	1.29

The most general approach to reduce systematic errors is empirical scaling, namely, the application of corrections derived from linear regression procedures. Therefore, empirically scaled calculated chemical shifts were computed according to Eq. 2:

$$\delta_{scaled} = (\delta_{calcd} - b)/m \quad (2)$$

where m and b are the slope and intercept, respectively, resulting from a regression calculation on a plot of calculated (δ_{calcd}) against experimental (δ_{exp}) chemical shifts. Fig. 4 shows the correlation between the experimental and the calculated ^{13}C chemical shifts (except C–Br) of all computed compounds at mPW1PW91/6-31+G(d,p)-PCM//B3LYP/6-31+G(d,p) level of theory based on TMS single reference. A good linear relationship is observed (R^2=0.9987)

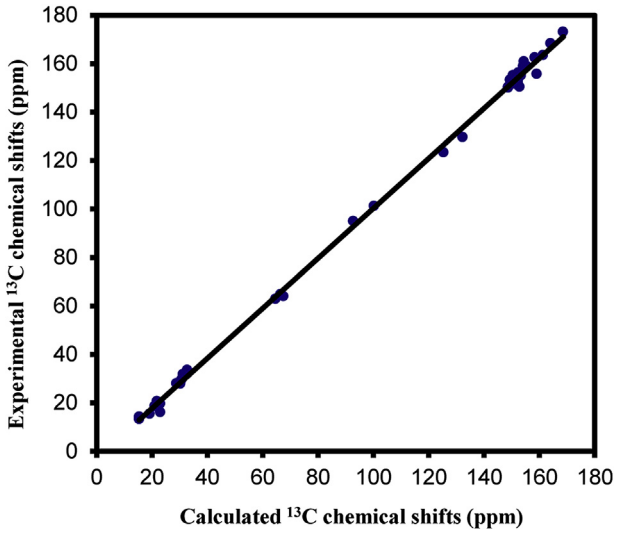


Fig. 4. Graph showing the linear correlation between the experimentally measured and calculated [GIAO mPW1PW91/6-31+G(d,p)-PCM//B3LYP/6-31+G(d,p)] ^{13}C NMR chemical shifts.

fitted by $\delta_{exp}=1.0323\delta_{calcd}-2.9313$. As shown in Table 6, if the linear regression approach for empirical scaling of the calculated ^{13}C chemical shifts is used, the single reference approach with TMS has lower MAD values, while without scaling of results, the multi-standard (MSTD) approach has better values as has been observed by other workers.[21]

3. Conclusion

HMDS promoted O-alkylation of uracil is a high yielding chemoselective and regioselective mono-alkylation strategy. The use of various alkyl halides in the presence of aprotic solvents such as DMF results in chemoselective mono-O^4-alkylation except with methyl iodide, which gave the N^1+N^3-dimethylated uracil derivatives. GIAO/^{13}C NMR calculations with mPW1PW91 hybrid functional and 6-31+G(d,p) standard basis set is preferred for elucidation of chemo- and regioselectivity in these reactions.

4. Experimental

4.1. General procedure for the preparation of *O*-alkylated uracils 4(a–r)

To a mixture of 5-substituted uracils **1**(**a**–**c**) (1 mmol) and ammonium sulfate (0.06 mmol, 0.008 g), HMDS (4 mL) was added and refluxed until the precipitate was dissolved. Then, the solvent was removed under reduced pressure and the resulting oily liquid was dissolved in dry DMF (4 mL) and NaH (2 mmol, 0.048 g) was added at −10 °C. After stirring of the reaction mixture for 1 h, various alkyl halides (1 mmol) were added. The progress of the reaction was monitored by TLC using chloroform/methanol as eluent (20:1). After the completion of the reaction, the mixture was neutralized by 2 N HCl and extracted by CH_2Cl_2 (2×30 mL). The combined organic phase was dried over Na_2SO_4 and removed under reduced pressure. The resulting solid was recrystallized in EtOAc and *n*-hexane.

*4.1.1. 4-Ethoxy-6-methylpyrimidin-2(1H)-one (**4a**).* Mp 187–189 °C; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, t, *J* 9.0 Hz, CH_3), 2.33 (3H, s, CH_3), 4.50 (2H, q, *J* 9.0 Hz, CH_2O), 5.75 (1H, s, CH), 12.89 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 14.3, 18.6, 62.0, 94.9, 156.3, 160.8, 173.1; ν_{max} (KBr disk): 3141, 3031, 2987, 2945, 2882, 2819, 2766, 1664, 1634, 1617 cm^{-1}; *m*/*z* 154 (M^+). Found: C, 54.49; H, 6.44; N, 18.12. $C_7H_{10}N_2O_2$ requires C, 54.54; H, 6.54; N, 18.17%.

*4.1.2. 6-Methyl-4-propoxypyrimidin-2(1H)-one (**4b**).* Mp 107–108 °C; δ_H (400 MHz, $CDCl_3$) 1.00 (3H, t, *J* 7.6 Hz, CH_3), 1.71–1.81 (2H, m, CH_2), 2.33 (3H, s, CH_3), 4.35 (2H, t, *J* 6.8 Hz, CH_2O), 5.76 (1H, s, CH), 12.85 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 10.4, 18.7, 21.0, 68.6, 94.9, 156.3, 160.7, 173.3; ν_{max} (KBr disk): 3145, 2970, 2937, 2872, 1672, 1632 cm^{-1}; *m*/*z* 168 (M^+). Found: C, 57.02; H, 7.03; N, 16.60. $C_8H_{12}N_2O_2$ requires C, 57.13; H, 7.19; N, 16.66%.

*4.1.3. 4-Butoxy-6-methylpyrimidin-2(1H)-one (**4c**).* Mp 125–127 °C; δ_H (400 MHz, $CDCl_3$) 1.00 (3H, t, *J* 7.5 Hz, CH_3), 1.7–1.8 (4H, m, CH_2CH_2), 2.18 (3H, s, CH_3), 4.41 (2H, t, *J* 8.5 Hz, CH_2O), 5.61 (1H, s, CH), 9.85 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 10.3, 19.0, 19.6, 21.8, 68.6, 89.9, 155.0, 158.9, 168.5; ν_{max} (KBr disk) 3120, 2955, 2933, 2871, 2765, 1669, 1632, 1324 cm^{-1}; *m*/*z* 182 (M^+). Found: C, 59.12; H, 7.63; N, 15.20. $C_9H_{14}N_2O_2$ requires C, 59.32; H, 7.74; N, 15.37%.

*4.1.4. 4-(Benzyloxy)-6-methylpyrimidin-2(1H)-one (**4d**).* Mp 179–180 °C; δ_H (400 MHz, $CDCl_3$) 2.29 (3H, s, CH_3), 4.45 (2H, s, CH_2O), 6.08 (1H, s, CH), 7.28–7.40 (5H, m, phenyl), 12.87 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 18.6, 67.5, 99.2, 128.5, 128.6, 128.9, 136.8, 157.4, 164.5, 172.1; ν_{max} (KBr disk) 3199, 3076, 3031, 3011, 2917, 2824, 1654, 1572, 1546, 1494, 1454, 1393 cm^{-1}; *m*/*z* 216 (M^+). Found: C, 66.54; H, 5.50; N, 12.91. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.59; N, 12.96%.

*4.1.5. Ethyl 2-((6-methyl-2-oxo-1,2-dihydropyrimidin-4-yl)oxy)acetate (**4e**).* Mp 197 °C; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 10.0 Hz, CH_3), 2.34 (3H, s, CH_3), 4.25 (2H, q, *J* 7.5 Hz, OCH_2CH_3), 4.99 (2H, s, OCH_2CO), 5.91 (1H, s, CH), 12.80 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 14.1, 18.8, 61.5, 62.4, 94.7, 157.4, 160.2, 167.8, 172.2 cm^{-1}; ν_{max} (KBr disk): 3145, 2998, 2965, 2883, 1751, 1676, 1635, 1453, 1334; *m*/*z* 212 (M^+). Found: C, 50.82; H, 5.66; N, 13.03. $C_9H_{12}N_2O_4$ requires C, 50.94; H, 5.70; N, 13.20%.

*4.1.6. 6-Methyl-4-(2-oxo-2-phenylethoxy)pyrimidin-2(1H)-one (**4f**).* Mp 210–211 °C; δ_H (400 MHz, $CDCl_3$) 2.23 (3H, s, CH_3), 4.95 (2H, s, CH_2O), 7.21–7.44 (5H, m, phenyl), 11.75 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 14.5, 68.5, 83.2, 128.6, 133.0, 134.5, 138.7, 155.2, 159.0, 160.4, 168.5; ν_{max} (KBr disk) 3113, 3061, 3012, 2929, 2846, 2735, 1701, 1661, 1616, 1446, 1386, 1357 cm^{-1}; *m*/*z* 244 (M^+). Found: C, 63.90; H, 4.92; N, 11.45. $C_{13}H_{12}N_2O_3$ requires C, 63.93; H, 4.95; N, 11.47%.

*4.1.7. 5-Bromo-4-ethoxy-6-methylpyrimidin-2(1H)-one (**4g**).* Mp 247–248 °C; δ_H (400 MHz, $CDCl_3$) 1.42 (3H, t, *J* 7.5 Hz, CH_3), 2.48 (3H, s, CH_3), 4.52 (2H, q, *J* 7.5 Hz, CH_2O), 13.12 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 14.2, 19.7, 64.8, 90.2, 155.1, 158.9, 168.4; ν_{max} (KBr disk) 3113, 2970, 2929, 2892, 2819, 1651, 1608, 1421, 1382 cm^{-1}; *m*/*z* 232 (M^+), 234 (M^++2). Found: C, 35.01; H, 3.86; N, 12.04. $C_7H_9BrN_2O_2$ requires C, 36.07; H, 3.89; N, 12.02%.

*4.1.8. 5-Bromo-6-methyl-4-propoxypyrimidin-2(1H)-one (**4h**).* Mp 214–216 °C; δ_H (400 MHz, $CDCl_3$) 1.02 (3H, t, *J* 7.5 Hz, CH_3), 1.82–1.91 (2H, m, CH_2), 2.47 (3H, s, CH_3), 4.41 (2H, t, *J* 7.5 Hz, CH_2O), 13.12 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 10.3, 19.6, 21.9, 70.3, 90.3, 154.9, 158.9, 168.5; ν_{max} (KBr disk) 3113, 2970, 2921, 2872, 2831, 1658, 1611, 1358 cm^{-1}; *m*/*z* 246 (M^+), 248 (M^++2). Found: C, 38.82; H, 4.41; N, 11.30. $C_8H_{11}BrN_2O_2$ requires C, 38.89; H, 4.49; N, 11.34%.

*4.1.9. 5-Bromo-4-butoxy-6-methylpyrimidin-2(1H)-one (**4i**).* Mp 159–161 °C; δ_H (400 MHz, $CDCl_3$) 1.02 (3H, t, *J* 7.5 Hz, CH_3), 1.72–1.87 (4H, m, CH_2CH_2), 2.48 (3H, s, CH_3), 4.42 (2H, t, *J* 7.5 Hz, CH_2O), 13.12 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 10.3, 19.1, 19.6, 21.9, 68.7, 90.3, 155.1, 159.0, 168.5; ν_{max} (KBr disk) 3121, 2961, 2932, 2873, 2828, 1658,

1612, 1338 cm^{-1}; *m/z* 260 (M^+), 262 (M^++2). Found: C, 41.35; H, 5.03; N, 10.60. $C_9H_{13}BrN_2O_2$ requires C, 41.40; H, 5.02; N, 10.73%.

*4.1.10. 4-(Benzyloxy)-5-bromo-6-methylpyrimidin-2(1H)-one (**4j**).* Mp 228–230 °C; δ_H (400 MHz, $CDCl_3$) 2.21 (3H, s, CH_3), 4.98 (2H, s, CH_2O), 7.24–7.37 (5H, m, phenyl), 11.71 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 18.6, 67.5, 99.2, 128.6, 128.6, 128.9, 136.8, 157.5, 164.6, 172.2; ν_{max} (KBr disk) 3237, 3183, 3031, 2970, 2922, 1708, 1643, 1619 cm^{-1}; *m/z* 294 (M^+), 296 (M^++2). Found: C, 48.61; H, 3.66; N, 9.39. $C_{12}H_{11}BrN_2O_2$ requires C, 48.84; H, 3.76; N, 9.49%.

*4.1.11. Ethyl 2-((5-bromo-6-methyl-2-oxo-1,2-dihydropyrimidin-4-yl)oxy)acetate (**4k**).* Mp 218–219 °C; δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.5 Hz, CH_3), 2.48 (3H, s, CH_3), 4.22 (2H, q, *J* 7.5 Hz, OCH_2), 5.02 (2H, s, OCH_2CO), 13.01 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 14.2, 19.7, 61.2, 62.6, 84.4, 139.1, 161.2, 169.8, 182.2; ν_{max} (KBr disk) 2998, 2928, 2847, 2761, 1748, 1668, 1613, 1443, 1395, 1209 cm^{-1}; *m/z* 290 (M^+), 292 (M^++2). Found: C, 37.04; H, 3.76; N, 9.59. $C_9H_{11}BrN_2O_4$ requires C, 37.13; H, 3.81; N, 9.62%.

*4.1.12. 5-Bromo-6-methyl-4-(2-oxo-2-phenylethoxy)pyrimidin-2(1H)-one (**4l**).* Mp 245 °C; δ_H (400 MHz, $CDCl_3$) 2.29 (3H, s, CH_3), 5.78 (2H, s, OCH_2CO), 7.75 (3H, m, phenyl), 8.00 (2H, m, phenyl), 11.89 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 14.4, 68.5, 83.3, 128.6, 133.1, 134.6, 138.7, 155.2, 159.0, 160.4, 168.5; ν_{max} (KBr disk) 3116, 3063, 3010, 2932, 2843, 2745, 1705, 1665, 1614, 1445, 1386, 1356 cm^{-1}; *m/z* 322 (M^+), 324 (M^++2). Found: C, 48.23; H, 3.40; N, 8.46. $C_{13}H_{11}BrN_2O_3$ requires C, 48.32; H, 3.43; N, 8.67%.

*4.1.13. 4-Ethoxy-6-methyl-5-nitropyrimidin-2(1H)-one (**4m**).* Mp 239–240 °C; δ_H (400 MHz, acetone-d_6) 1.30 (3H, t, *J* 7.5 Hz, CH_3), 2.51 (3H, s, CH_3), 4.42 (2H, q, *J* 7.5 Hz, CH_2O); δ_C (400 MHz, acetone-d_6) 13.3, 16.1, 63.9, 123.4, 153.2, 155.7, 163.4. FTIR (KBr disk) 3141, 2986, 2933, 2855, 2761, 1665, 1623, 1567, 1529, 1384, 1353 cm^{-1}; *m/z* 199 (M^+). Found: C, 42.17; H, 4.58; N, 21.03. $C_7H_9N_3O_4$ requires C, 42.21; H, 4.55; N, 21.10%.

*4.1.14. 6-Methyl-5-nitro-4-propoxypyrimidin-2(1H)-one (**4n**).* Mp 225–227 °C; δ_H (400 MHz, acetone-d_6) 0.98 (3H, t, *J* 7.5 Hz, CH_3), 1.70–1.85 (2H, m, CH_2), 2.55 (3H, s, CH_3), 4.45 (2H, t, *J* 7.5 Hz, CH_2O); δ_C (400 MHz, acetone-d_6) 10.3, 19.6, 21.9, 70.2, 90.3, 154.9, 158.9, 168.6; ν_{max} (KBr disk) 3133, 2957, 2927, 2879, 2853, 1665, 1625, 1566, 1527, 1437, 1361, 1322 cm^{-1}; *m/z* 213 (M^+). Found: C, 44.98; H, 5.11; N, 19.65. $C_8H_{11}N_3O_4$ requires C, 45.07; H, 5.20; N, 19.71%.

*4.1.15. 4-Butoxy-6-methyl-5-nitropyrimidin-2(1H)-one (**4o**).* Mp 142–144 °C; δ_H (400 MHz, $CDCl_3$) 1.00 (3H, t, *J* 7.5 Hz, CH_3), 1.20–1.90 (4H, m, CH_2CH_2), 2.48 (3H, s, CH_3), 2.61 (3H, s, CH_3), 4.55 (2H, t, *J* 5.0 Hz, CH_2O); δ_C (100 MHz, $CDCl_3$) 11.0, 13.4, 15.7, 16.2, 35.9, 64.0, 148.8, 150.3, 153.3, 155.5, 155.8; ν_{max} (KBr disk) 3166, 3120, 2958, 2927, 2868, 1735, 1657, 1522, 1441, 1355, 1315 cm^{-1}; *m/z* 227 (M^+). Found: C, 47.51; H, 5.72; N, 18.45. $C_9H_{13}N_3O_4$ requires C, 47.57; H, 5.77; N, 18.49%.

*4.1.16. 4-(Benzyloxy)-6-methyl-5-nitropyrimidin-2(1H)-one (**4p**).* Mp 273–274 °C; δ_H (400 MHz, acetone-d_6) 2.29 (3H, s, CH_3), 4.98 (2H, s, CH_2O), 7.25–7.40 (5H, m, phenyl), 12.21 (1H, br s, NH); δ_C (400 MHz, acetone-d_6) 18.6, 67.6, 99.3, 128.6, 128.7, 128.9, 136.8, 157.5, 164.6, 172.2; ν_{max} (KBr disk): 3206, 3137, 3056, 3031, 2978, 2933, 2827, 1723, 1654, 1525, 1360, 1311 cm^{-1}; *m/z* 261 (M^+). Found: C, 55.03; H, 4.19; N, 16.01. $C_{12}H_{11}N_3O_4$ requires C, 55.17; H, 4.24; N, 16.09%.

*4.1.17. Ethyl 2-((6-methyl-5-nitro-2-oxo-1,2-dihydropyrimidin-4-yl)oxy)acetate (**4q**).* Mp 203–205 °C; δ_H (400 MHz, acetone-d_6) 1.22 (3H, t, *J* 7.5 Hz, CH_3), 2.49 (3H, s, CH_3), 4.20 (2H, q, *J* 7.5 Hz, OCH_2CH_3), 4.61 (2H, s, OCH_2CO); δ_C (400 MHz, acetone-d_6) 14.2, 19.7, 61.2, 62.6, 84.4, 139.2, 161.2, 169.8, 182.2; ν_{max} (KBr disk) 3208, 3051, 3000, 1737, 1658, 1520, 1433, 1354 cm^{-1}; *m/z* 257 (M^+). Found: C, 41.97; H, 4.28; N, 16.30. $C_9H_{11}N_3O_6$ requires C, 42.03; H, 4.31; N, 16.34%.

*4.1.18. 6-Methyl-5-nitro-4-(2-oxo-2-phenylethoxy)pyrimidin-2(1H)-one (**4r**).* Mp 243–245 °C; δ_H (400 MHz, acetone-d_6) 2.28 (3H, s, CH_3), 5.79 (2H, s, OCH_2CO), 7.73 (3H, m, phenyl), 8.04 (2H, m, phenyl), 11.92 (1H, br s, NH); δ_C (400 MHz, acetone-d_6) 14.5, 68.6, 83.3, 128.7, 133.2, 134.6, 138.8, 155.2, 159.1, 160.4, 168.5; ν_{max} (KBr disk) 3115, 3060, 3013, 2934, 2842, 2743, 1701, 1663, 1612, 1445, 1387, 1356 cm^{-1}; *m/z* 289 (M^+). Found: C, 53.94; H, 3.80; N, 14.49. $C_{13}H_{11}N_3O_5$ requires C, 53.98; H, 3.83; N, 14.53%.

4.2. Computational methods

All the structures shown in Fig. 2 and references (TMS, benzene and methanol) were fully optimized without any symmetric restriction at DFT B3LYP/6-31+G(d,p) theoretical level for single molecules in the gas phase. Analytic frequency calculations were done at the same level to confirm the optimized structures to be an energy minimum. The magnetic isotropic shielding tensors were calculated using the gauge invariant atomic orbital (GIAO) method at the mPW1PW91/6-31+G(d,p) level of theory. This functional is better than B3LYP functional for predicting ^{13}C NMR chemical shifts.[21,24,25] To reduce errors associated with solvent effects in chemical shift calculations, we utilized the polarizable continuum model (PCM) with UFF radii in the single-point calculation of NMR isotropic shielding constants in the solvents used for experimental spectrum (acetone for X=NO_2 and chloroform for other compounds). All calculations reported in this work were carried out with the GAUSSIAN 03 package.[26]

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.07.025.

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