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THE SILYL METHOD FOR THE SYNTHESIS OF 1[-2(PHENOXY)ETHYL]URACILS*

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A modification of the method for the synthesis of $N_{(1)}$-substituted derivatives of uracil is proposed using the Gilbert–Johnson reaction, which consists of the alkylation of 5-substituted 2,4-bis(trimethylsiloxy)pyrimidines with 1-bromo-2-(phenoxy)ethanes of low reactivity at 180-185° without solvent. The corresponding 1-[2-(phenoxy)ethyl]uracils, which were obtained in 55-74% yield, contained no impurities of the $N_{(1)}$,$N_{(3)}$-disubstituted compounds.

Keywords: 2,4-bis(trimethylsiloxy)pyrimidine, 1-bromo-2-(phenoxy)ethane, $N_{(1)}$-alkylation, the Gilbert–Johnson reaction.

The silyl modification of the Gilbert–Johnson reaction is widely used in the synthesis of pyrimidine nucleosides and their alkyl analogs. It is based on the alkylation of 2,4-bis(trimethylsiloxy)pyrimidines with highly reactive alkyl halides such as α-halo ethers [1-3] or α-halo sugars [4,5]. It is thought [6] that the first product of the interaction of the alkylating agent and 2,4-bis(trimethylsiloxy)pyrimidine is a quaternary salt which readily loses a trimethylsilyl halide to give the $N_{(1)}$-substituted 4-(trimethylsiloxy)pyrimidin-2(1H)-one. Hydrolysis of the latter leads to the required $N_{(1)}$-substituted derivative of uracil.

In the conditions of the silyl modification of the Gilbert–Johnson reaction α-halo ethers readily alkylate uracil in high yields even at room temperature in aprotic solvents of low polarity [1-3, 7].

The use of less reactive alkyl halides as alkylating agents has been studied considerably less. For example, $N_{(1)}$-substituted derivatives of uracil have been obtained by the condensation of 2,4-bis(trimethylsiloxy)pyrimidine with ethyl monobromoacetate and α-bromopropionate on boiling in dichloroethane in yields from 41 to 60% [8]. The reaction of 5-methyl-2,4-bis(trimethylsiloxy)pyrimidine with an excess of 1,4-dichlorobutane in methylene chloride at room temperature gave 1-(4-chloro-2-butyl)thymine in 47% yield [9].

The use of alkyl halides with medium reactivity has received still less attention. It is known that the reaction 2,4-bis(trimethylsiloxy)-5-methylpyrimidine with an excess of 1,3-dibromopropane or 1,6-dibromohexane at room temperature for 10 or 34 days gave 1-(3-bromopropyl)- and 1-(6-bromohexyl)thymine in 82 and 88 % yields [10].

Alkylation of uracil with alkyl halides of low reactivity, such as 2-chloroethoxyethyl acetate and 2-chloroethyl acetate, was carried out by heating in a polar solvent in the presence of a base, for example potassium carbonate or sodium hydride [11, 12]. The drawback of this method is the formation of a mixture of

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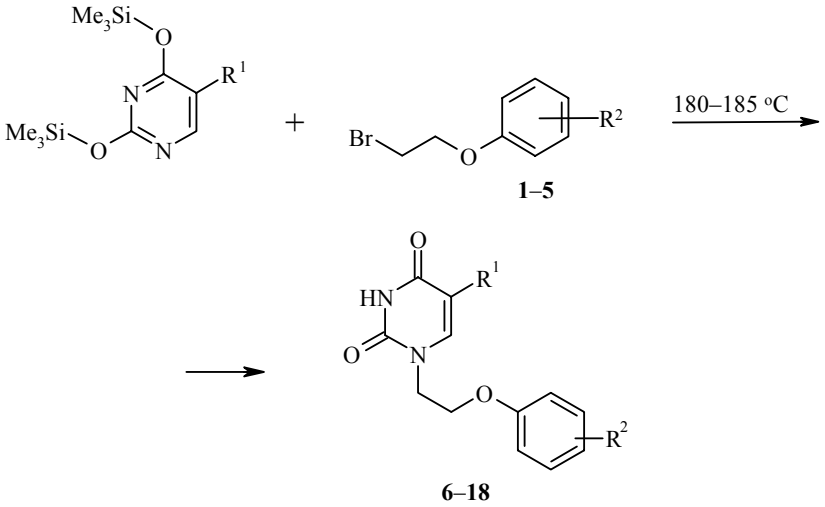
$N_{(1)}$-mono- and $N_{(1)},N_{(3)}$-dialkylated uracil which are usually separated by preparative chromatography. We previously obtained 1-[2-(phenoxy)ethyl] derivatives of uracil, thymine, 6-methyluracil [7], and 5-(arylamino)uracil [13] by this method.

The objective of the present work was the adaptation of the silyl method for the synthesis of 1-[2-(phenoxy)ethyl] derivatives of uracil, while excluding the formation of the 1,3-disubstituted compounds as side products. We have observed that heating equimolar amounts of 5-substituted 2,4-bis(trimethylsiloxy)pyrimidines with 1-bromo-2-(phenoxy)ethanes **1-5** at 180-185°C for 3 h gave the corresponding 1-[2-(phenoxy)ethyl]uracils in yields of 55-74%, while the 1,3-disubstituted products were not observed.



6, **9**, **12**, **15**, **17** R^1 = H; **7**, **10**, **13** R^1 = Me; **8**, **11**, **14**, **16**, **18** R^1 = Br; **1**, **6-8** R^2 = H; **2**, **9-11** R^2 = 4-Me; **3**, **12-14** R^2 = 4-Cl; **4**, **15**, **16** R^2 = 3,4-Me_2; **5**, **17**, **18** R^2 = 2,4-Cl_2

Note that, on the one hand, a decrease in the reaction time led to a considerable decrease in the yield of the required product. For example, the yield of 1-[2-(phenoxy)ethyl]uracil (**6**) obtained on heating for 3 h was 67%, while it was 37% on heating for 1.5 h. On the other hand the yield of compound **6** also decreased to 59% on prolonging the heating (5 h).

In a study of the effect of the solvent we observed that the alkylation of 2,4-bis(trimethylsiloxy)pyrimidine with 1-bromo-2-(phenoxy)ethane (**1**) in boiling 1,2-dichloroethane occurred slowly and the yield of compound **6** was only 16% after 24 h. Replacement of 1,2-dichloroethane by anhydrous acetonitrile, which has approximately the same boiling point but a considerably higher dielectric permeability, gave only trace amounts of compound **6**.

It was also observed that the steric bulk of the substituent at position 6 in the 2,4-bis(trimethylsiloxy)pyrimidine had a considerable effect on the reaction. For example, heating 2,4-bis(trimethylsiloxy)-6-methylpyrimidine with compound **1** at 180-185°C for 6 h gave a complex mixture of alkylation products, while the reaction with 2,4-bis(trimethylsiloxy)quinazoline did not occur at all under these conditions.

The structure of the compounds synthesized **6-18** was confirmed by ^{1}H NMR spectroscopy, their purity and individuality were demonstrated by TLC, and their composition by elemental analysis.

We have developed a modification of the Gilbert–Johnson reaction which permits a considerable broadening of the range of use of the method and the preparation of sufficiently high yields of 1-[2-(phenoxy)ethyl] derivatives of uracil which are potentially biologically active compounds.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f*	Yield, %
		C	H	N			
6	$C_{12}H_{12}N_2O_3$	62.28 / 62.06	5.33 / 5.21	11.89 / 12.06	156-158	0.15	67
7	$C_{13}H_{14}N_2O_3$	63.12 / 63.40	5.55 / 5.73	11.14 / 11.38	193-195	0.21	69
8	$C_{12}H_{11}BrN_2O_3$	46.54 / 46.32	3.66 / 3.56	9.21 / 9.00	203-205	0.44	71
9	$C_{13}H_{14}N_2O_3$	63.59 / 63.40	5.90 / 5.73	11.01 / 11.38	150-152	0.19	68
10	$C_{14}H_{16}N_2O_3$	64.76 / 64.60	6.20 / 6.20	10.59 / 10.76	196-197	0.37	70
11	$C_{13}H_{13}BrN_2O_3$	48.26 / 48.02	4.10 / 4.03	8.43 / 8.62	193-195	0.48	69
12	$C_{12}H_{11}ClN_2O_3$	53.87 / 54.05	4.10 / 4.16	10.77 / 10.50	219-221	0.11	74
13	$C_{13}H_{13}ClN_2O_3$	55.68 / 55.62	4.40 / 4.67	9.95 / 9.98	207-209	0.16	68
14	$C_{12}H_{10}BrClN_2O_3$	41.90 / 41.71	3.23 / 2.92	8.00 / 8.11	220-222	0.28	70
15	$C_{14}H_{16}N_2O_3$	64.21 / 64.60	6.08 / 6.20	10.80 / 10.76	168-170	0.20	55
16	$C_{14}H_{15}BrN_2O_3$	49.80 / 49.57	4.64 / 4.46	8.41 / 8.26	192-195	0.45	64
17	$C_{12}H_{10}Cl_2N_2O_3$	47.93 / 47.86	3.40 / 3.35	9.40 / 9.30	207-209	0.10	67
18	$C_{12}H_9BrCl_2N_2O_3$	38.28 / 37.93	2.55 / 2.39	7.50 / 7.37	203-205	0.24	65

* 1:1 ethyl acetate–chloroform.

EXPERIMENTAL

^{1}H NMR spectra were recorded with Bruker DRX500 (500 MHz) and Tesla BS-567A (100 MHz) spectrometers in 1:1 DMSO-d_6–acetone-d_6 solutions with TMS as internal standard. The spectra were interpreted using licensed ACD/HNMR Predictor 3.0 programs (Advanced Chemistry Development, Canada). TLC was carried out on Silufol UV-254 plates, developed with iodine vapor. Melting points were determined in glass capillaries with a Mel-Temp 3.0 apparatus (Laboratory Devices Inc., USA).

1-[2-(Phenoxy)ethyl]uracil (6). 1-Bromo-2-(phenoxy)ethane (**1**) (3.6 g, 17.91 mmol) was added at ~20°C to 2,4-bis(trimethylsiloxy)pyrimidine, obtained by boiling uracil (2.9 g, 17.87 mmol) in HMDS (50 ml) in the presence of NH_4Cl (0.3 g), and the mixture was heated for 3 h at 180-185°C in the absence of moist air. The reaction mixture was cooled to room temperature, dissolved in ethyl acetate (30 ml), and treated with ethanol (10 ml). The precipitate was recrystallized twice from ethanol to give compound **6** (2.8 g, 67%) as a white finely crystalline substance. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.79-4.37 (4H, m, CH_2CH_2); 5.53 (1H, d, *J* = 8, H-5); 6.59-7.27 (6H, m, C_6H_5).

Compounds 7-18 were prepared analogously.

1-[2-(Phenoxy)ethyl]thymine (7). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.74 (3H, s, CH_3); 3.98 (2H, t, *J* = 7, CH_2); 4.12 (2H, t, *J* = 7, CH_2); 6.60-7.29 (5H, m, C_6H_5); 7.36 (1H, s, H-6).

5-Bromo-1-[2-(phenoxy)ethyl]uracil (8). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.98-4.20 (4H, m, CH_2CH_2); 6.77-7.30 (5H, m, C_6H_5); 8.06 (1H, s, H-6); 11.48 (1H, br. s, NH).

1-[2-(4-Methylphenoxy)ethyl]uracil (9). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.19 (3H, s, CH_3); 4.05 (2H, *J* = 6, N–CH_2); 4.12 (2H, *J* = 6, CH_2O); 5.45 (1H, dd, *J* = 8 and 2, H-5); 6.69-7.05 (4H, m, C_6H_4); 7.49 (1H, d, *J* = 8, H-6); 11.02 (1H, br. s, NH).

1-[2-(4-Methylphenoxy)ethyl]thymine (10). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.71 (3H, s, CH_3); 2.15 (3H, s, CH_3); 3.89-4.22 (4H, m, CH_2CH_2); 6.66-7.05 (4H, m, C_6H_4); 7.35 (1H, s, H-6); 11.17 (1H, br. s, NH).

5-Bromo-1-[2-(4-methylphenoxy)ethyl]uracil (11). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.26 (3H, s, CH_3); 4.08 (2H, t, *J* = 6, N–CH_2); 4.14 (2H, t, *J* = 6, CH_2O); 6.74-7.06 (4H, m, C_6H_4); 8.02 (1H, s, H-6); 11.60 (1H, br. s, NH).

1-[2-(4-Chlorophenoxy)ethyl]uracil (12). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.06 (2H, t, *J* = 6, N–CH_2); 4.18 (2H, t, *J* = 6, CH_2O); 5.46 (1H, dd, *J* = 8 and 2, H-5); 6.89-7.30 (4H, m, C_6H_4); 7.53 (1H, d, *J* = 8, H-6); 11.07 (1H, br. s, NH).

1-[2-(4-Chlorophenoxy)ethyl]thymine (13). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.81 (3H, s, CH_3); 4.02 (2H, t, *J* = 6, N–CH_2); 4.16 (2H, t, *J* = 6, CH_2O); 6.88-7.25 (4H, m, C_6H_4); 7.46 (1H, s, H-6); 11.04 (1H, br. s, NH).

5-Bromo-1-[2-(4-chlorophenoxy)ethyl]uracil (14): ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.09 (2H, t, *J* = 6, N–CH_2); 4.19 (2H, t, *J* = 6, CH_2O); 6.89-7.25 (4H, m, C_6H_4); 8.05 (1H, s, H-6); 11.63 (1H, br. s, NH).

1-[2-(3,4-Dimethylphenoxy)ethyl]uracil (15): ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.17 (3H, s, CH_3); 2.20 (3H, s, CH_3); 4.04 (2H, t, *J* = 6, N–CH_2); 4.12 (2H, t, *J* = 6, CH_2O); 5.46 (1H, dd, *J* = 8 and 2, H-5); 6.58 (1H, m, H-2'); 6.67 (1H, m, H-6'); 6.96 (1H, m, H-3'); 7.50 (1H, d, *J* = 8, H-6); 11.01 (1H, br. s, NH).

5-Bromo-1-[2-(3,4-dimethylphenoxy)ethyl]uracil (16): ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.21 (3H, s, CH_3); 2.24 (3H, s, CH_3); 4.08 (2H, t, *J* = 6, N–CH_2); 4.14 (2H, t, *J* = 6, CH_2O); 6.61 (1H, m, H-2'); 6.69 (1H, m, H-6'); 6.94 (1H, m, H-3'); 8.06 (1H, H-6); 11.52 (1H, br. s, NH).

1-[2-(2,4-Dichlorophenoxy)ethyl]uracil (17): ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.08 (2H, t, *J* = 6, N–CH_2); 4.13 (2H, t, *J* = 6, CH_2O); 5.44 (1H, dd, *J* = 8 and 2, H-5); 6.92-7.33 (3H, m, C_6H_3); 7.49 (1H, d, *J* = 8, H-6); 11.21 (1H, br. s, NH).

5-Bromo-1-[2-(2,4-dichlorophenoxy)ethyl]uracil (18): ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.11 (2H, t, *J* = 6, N–CH_2); 4.15 (2H, t, *J* = 6, CH_2O); 6.98-7.30 (3H, m, C_6H_3); 8.10 (1H,s, H-6); 11.68 (1H, br. s, NH).

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