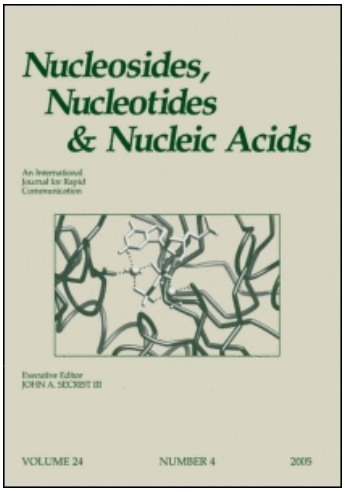

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Solid-Liquid Phase-Transfer Catalysis I: Studies of the N-Alkylation of Purines and Pyrimidines

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SOLID-LIQUID PHASE-TRANSFER CATALYSIS I: STUDIES OF THE N-ALKYLATION OF PURINES AND PYRIMIDINES

H.B. Lazrek,[1*] M. Taourirte,[1] J.-L. Barascut[2] and J.-L. Imbach[2]

ABSTRACT: N-alkylation with acyclic side chains of pyrimidine and purine heterocycles occurs regioselectively at N-1 and N-9 respectively under solid-liquid phase transfer catalysis by 18-crown-6 or tetraglyme in the presence of potassium tert-butoxide at 0°C.

Some acyclonucleosides such as acyclovir[1], DHPG[2,3], (ganciclovir) present well established antiviral activities. Their synthesis is usually performed using standard glycosylation procedures which could lead in some cases to isomeric mixtures and variable yields. Therefore we would like to report herewith a phase-transfer catalysis approach (PTC) for N-alkylation of purine and pyrimidine bases with acyclic side chains.

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PTC is one of the most attractive techniques in organic synthesis because of mild conditions, high yields of the products and convenience. Alkylation takes place by simply stirring a solution containing an alkylating agent, a heterocycle, a suitable base and a catalyst. However the corresponding mono or dialkylated products[4-6] or a mixture of isomers[7] are usually observed. In spite of the numerous advantages of the liquid-liquid PTC[5,6,8], several disadvantages decrease the usefulness of this procedure. For example, there are a number of solvents in which the commonly employed quaternary ammonium salts are insoluble[9] and consequently, reactions do not take place when these solvents are used[10]. However it has recently been shown that acetate[11], alkoxide[12] and indole[13] anions can be efficiently alkylated with the use of only one solvent in presence of catalytic amounts of quaternary ammonium salts. The alkylation of uracil, xanthine and adenine derivatives using PTC in such conditions has been reported[14] and the alkylation of adenine led to a mixture of 9-alkyladenine and 3-alkyladenine[15].

The aim of this study was to develop a general method for N-alkylation of a heterocycles possessing an ionizable hydrogen under phase-transfer conditions.

In the allopurinol series, the liquid-liquid PTC procedure gives rise to the formation of the expected alkylated derivatives isomer in a yield of 30 to 60% according to the nature of the C_4 substitution on the heterocyclic ring[16]. However when we used solid-liquid PTC with 18-crown-6 or tetraglyme as catalyst, the product yields increased to 50-80% and only N-1 isomers were formed.

We therefore decided to explore the use of 18-crown-6[17] tetraglyme[18] as solid-liquid phase-transfer catalyst for the N-alkylation of pyrimidines and purines using potassium tert-butoxide[17] as a base.

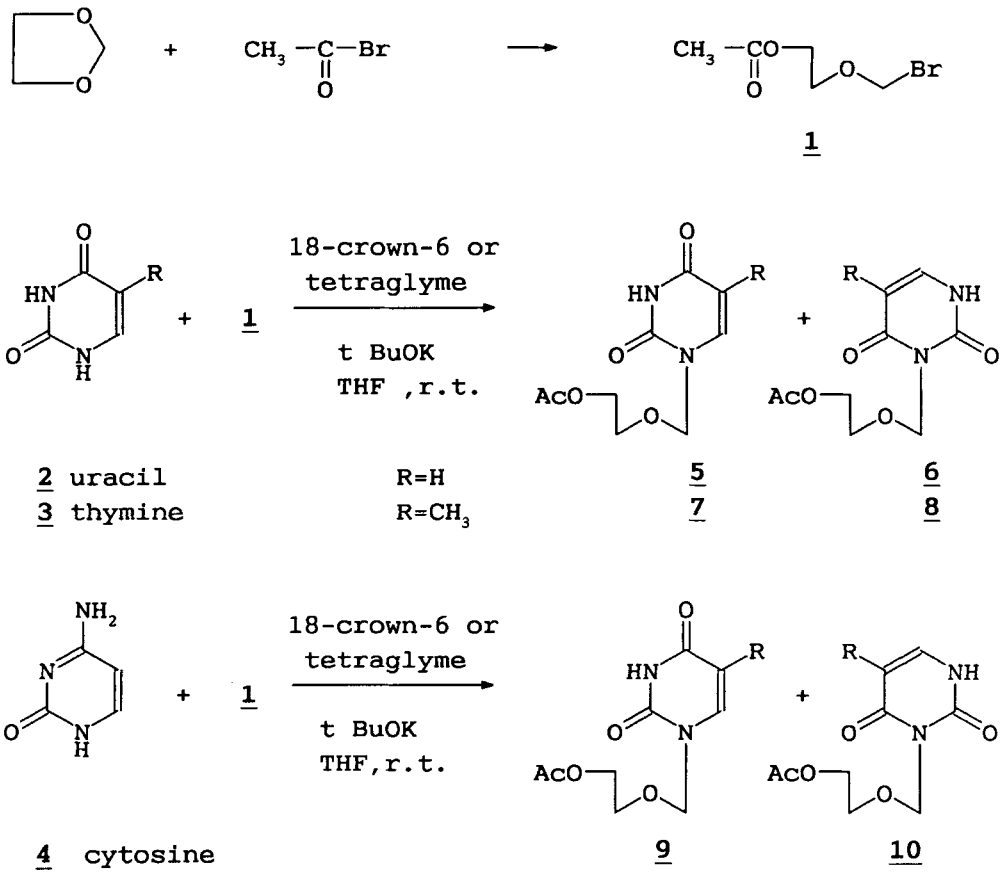

FIGURE 1

FIGURE 1 illustrates the sequence used to prepare the required acyclic chain[19] and an acyclonucleoside in the pyrimidine series and present some examples of acyclonucleoside synthesis in the pyrimidine series.

After various assays, THF was selected as solvent for this reaction. As an example, in the uracil series, when either 18-crown-6 or tetraglyme was used as catalyst at a temperature of 0°C, only the N-1 acyclonucleoside 5, 7, 9 were obtained (50% yield) after chromotagraphic purification. But when the same reaction was carried out at 25°C, the isomeric acyclonucleosides 5 and 6 were obtained.

- TABLE I -

Base	Solvent	Catalyst	Reaction time (*min*)	Temperature *	Yield N-1 Subst		N-3 Subst	
Uracil	THF	18-crown-6 or tetraglyme	45	0°C	5	50%	-	
2				25°C	5	34%	6	17%
Thymine	THF	18-crown-6 or tetraglyme	45	0°C	7	60%	-	
3				25°C	7	33%	8	16%
Cytosine	THF	18-crown-6 or tetraglyme	45	0°C	9	50%	-	
4				25°C	9	40%	10	20%
Adenine 11	THF	18-crown-6 or tetraglyme	45	0°C	13	50%	-	
				25°C	13	31%	14	19%
8-Bromo adenine 12	THF	18-crown-6 or tetraglyme	45	0°C	15	50%	-	
				25°C	15	41%	16	27%

** Reaction carried out at 0°C and 25°C with 18-crown-6 or tetraglyme.*

Similar data were observed with thymine and cytosine (TABLE 1).

The site of alkylation of the acyclonucleosides was established as N-1 for **5**, **7**, **9** (experimental data) and N-3 for **6** (λ_{max}^{MeOH} = 267 nm), **8** (λ_{max}^{MeOH} = 272 nm) and **10** ($\lambda_{max}^{0.1\ N\ HCl}$ = 282 nm) by U.V. spectroscopy.

Identical results were also obtained in the case of purine acyclonucleosides (adenine, 8-bromoadenine and guanine)[20].

For example (FIG. 2), the alkylation of adenine (X = H, **11**) by solid-liquid PTC in THF at room temperature afforded a mixture of 9-(2-acetoxyethoxy)methyladenine **13** and 3-(2-acetoxyethoxy)methyladenine **14**. No N-7 isomer were detected. In contrast, when the same reaction was carried out at 0°C, only the 9-acycloderivatives **13** or **15** were obtained in 50% yield after chromatography purification.

All the synthesized compounds were fully characterized using usual analytical methods.

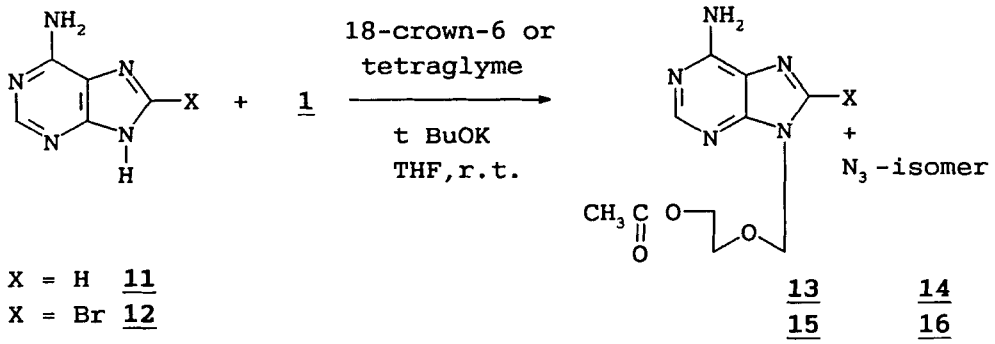

FIGURE 2

In conclusion, we have shown that solid-liquid PTC gives only one isomer in either pyrimidine or purine series provided this procedure is carried out in anhydrous THF at 0°C. Under these PTC conditons, alkylation of purine or pyrimidine bases appears to be regioselective and gives only the thermodynamically stable isomers. This approach provides a new alternative route to synthesize acyclonucleosides.

EXPERIMENTAL:

All melting points were determined with a Buchi apparatus and are uncorrected. Ultraviolet spectra were recorded with a Cary 219 spectrophotometer. The ^{1}H NMR spectra were recorded with a 80 MHz Varian FT 80A spectrometer chemical shifts are reported in parts per million (δ) using internal TMS standard. Thin layer chromatography (t.l.c) was performed on plates of Kiesegel 60 F_{254} (Merck). Column chromatography was performed on silica gel (0.063-0.2 mm Merck).

General alkylation procedure:

To a solution of 0.02 mmole (5.28 mg) of 18-crown-6 or 0.02 mmole (0.25 ml) of tetraglyme in 4 ml of anhydrous THF,

0.11 mmole (12.34 mg) of potassium tert-butoxide is added. Then 0.1 mmole of the heterocycle is added to this solution and the reaction mixture is stirred at room temperature.

At Room Temperature:

After 15 min, 0.11 mmol (21.66 mg) of (2-acetoxyethoxy) methyl bromide 1 in 2 ml of THF is added dropwise. When the addition is finished, the reaction mixture is stirred for 30 min at room temperature.

At 0°C:

After 15 min the reaction mixture is cooled to 0°C. And 0.11 mmol (21.66 mg) of (2-acetoxyethoxy)methyl bromide in 2 ml of anhydrous THF is added dropwise with stirring.
When the addition is finished, the reaction mixture is stirred at 0°C for 30 min.
The reaction mixture is then filtered and the filtrate is evaporated *in vaccuo* to dryness (bath temp. 30-35°C).

The residue is then chromatographed on a silica gel column to obtain the expected acyclonucleosides.

1-(2-acetoxyethoxy)methyluracil 5.
Eluant chloroform/methanol 95/5 (V/V)
Mp: 77-78°C (chloroform/diethyl ether) lit.[19]: 77-78°C.
U.V.: 0.1 N HCl λ_{max} = 259 nm ϵ = 9 800
0.1 N NaOH λ_{max} = 259 nm ϵ = 6 800
^{1}H NMR, $CDCl_3$: 2.07 (s, 3H, CH_3COO) ; 3.81 (m, 2H, $AcOCH_2CH_2$); 4.23 (m, 2H, $AcOCH_2CH_2$); 5.21 (s, 2H, OCH_2N); 5.80 (d, J = 8 Hz, 1H, H-5); 7.33 (d, 1H, H-6).
M.S. m/z calc : 228.0742 found: 228.0747
Elem. Anal. calc: C 45.17, H 5.41, N 15.05
found: C 44.93, H 5.33, N 15.06

1-(2-acetoxyethoxy)methylthymine 7:
Eluant chloroform/MeOH 98/2 (V/V)
Mp: 123-125°C (chloroform/diethyl ether) lit.[19]: 123-125°C.

U.V.: 0.1 N HCl λ_{max} = 264 nm ϵ = 9 600
0.1 N NaOH λ_{max} = 265 nm ϵ = 7 000
^{1}H NMR, DMSO-d_6 : 1.78 (s, 3H, CH_3); 2.01 (s, 3H, CH_3COO); 3.70 (m, 2H, $AcOCH_2CH_2$); 4.11 (m, $AcOCH_2CH_2$); 5.08 (s, 2H, OCH_2N); 7.56 (s, 1H, H-6).
M.S. m/z calc: 242.0903, found 242.0903
Elem. Anal. calc: C 49.59, H 5.83, N 11.57
found: C 49.32, H 5.72, N 11.57

1-(2-acetoxyethoxy)methylcytosine 9:
Eluant chloroform/methanol 98/2 (V/V)
Mp: 184-186°C (methanol/diethyl ether) lit.[19]: 181-186°C.
U.V.: 0.1 N HCl λ_{max} = 275 nm ϵ = 1 200
0.1 N NaOH λ_{max} = 266 nm ϵ = 7 700
^{1}H NMR: DMSO-d_6: 1.98 (s, 3H, CH_3COO); 3.66 (m, 2H, $AcOCH_2CH_2$); 4.06 (m, 2H, $AcOCH_2CH_2$); 5.06 (s, 2H, OCH_2N); 5.68 (d, J = 7.5 Hz, 1H, H-5); 7.15 (2H, NH_2); 7.58 (d, 1H, H-6).
M.S. m/z calc: 227.0907, found 227.0907
Elem. Anal. calc: C 47.58, H 5.77, N 18.49
found: C 47.43, H 5.71, N 18.42

9-(2-acetoxyethoxy)methyladenine 13:
Eluant chloroform/methanol 98/2 (V/V).
Mp: 156-158°C (chloroform/diethyl ether) lit.[19]: 156-158°C.
U.V.: 0.1 N HCl λ_{max} = 256 nm ϵ = 16 600
0.1 N NaOH λ_{max} = 260 nm ϵ = 16 900
^{1}H NMR DMSO-d_6: 1.92 (s, 3H, CH_3COO); 3.72 (m, 2H, $AcOCH_2CH_2$); 4-06 (m, 2H, $AcOCH_2CH_2$); 5.56 (s, 2H, OCH_2N); 7.23 (2H, NH_2); 8.16 (s, 1H, H-2); 8.26 (s, 1H, H-8).
M.S. m/z calc: 228.0742, found 228.0747
Elem. Anal. calc: C 47.81, H 5.22, N 27.88
found: C 47.51, H 5.05, N 28.01

9-(2-acetoxyethoxy)methyl 8-bromo-adenine 15:
Eluant chloroform/methanol 98/2 (V/V).
Mp: 150-152°C (methanol/diethyl ether)
U.V.: 0.1 N HCl λ_{max} = 262 nm ϵ = 10 500

^{1}H NMR DMSO-d_6 : 2.01 (s, 3H, CH_3COO); 3.66 (m, 2H, AcO CH_2CH_2); 4.1 (m, 2H, AcO CH_2CH_2); 5.5 (s, 2H, OCH_2N); 7.46 (2H, NH_2); 8.16 (s, 1H, H-2).

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