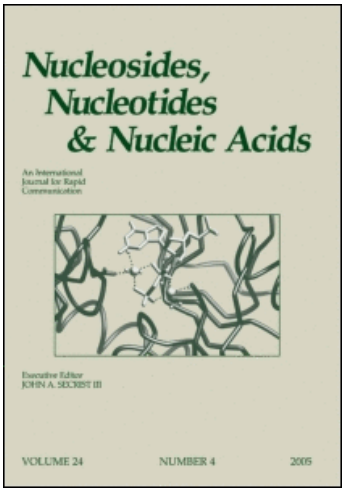

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Synthesis of 2'-Deoxypyrimidine Nucleosides via Copper (I) Iodide Catalysis

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SYNTHESIS OF 2'-DEOXYPYRIMIDINE NUCLEOSIDES VIA COPPER (I) IODIDE CATALYSIS

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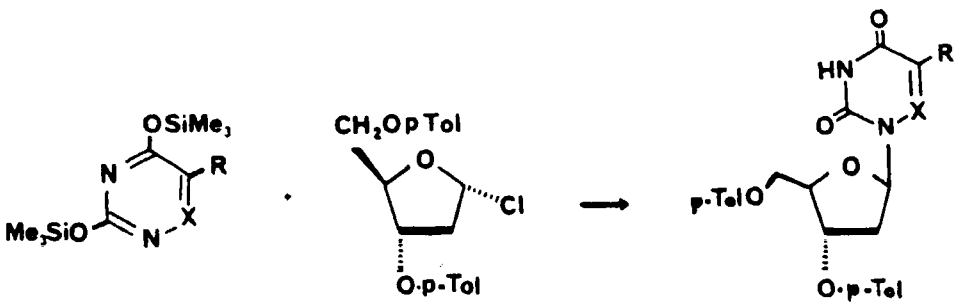
Abstract: The coupling of various 5-substituted-2,4- disilyl pyrimidines with α-2-deoxy-3,5-di-p-toluyl ribofuransyl chloride in the presence of copper (I) iodide in chloroform yields predominantly ß-nucleosides (>15/1 ß/α selectivity in some cases) in >90% overall yields.

Considerable effort has been expended in the synthesis of pyrimidine nucleosides over the past three decades.[1] Early synthetic efforts relied on the Hilbert-Johnson method[2], which involves coupling of a dialkoxypyrimidine or the more reactive and accessible disiloxypyrimidine[3] with a protected 1-halosugar, either thermally or via mercury catalysis. The scope of this reaction was greatly expanded when Vorbruggen and co-workers[4] demonstrated catalysis by a wide variety of Lewis acids, even when the less electrophilic 1-alkoxy or 1-acyloxysugars are employed. The Vorbruggen method typically gives high overall yields of the desired N-1-nucleosides.

In the synthesis of ribonucleosides, neighboring-group participation by a 2'-acyloxy group dictates exclusive formation of ß-anomers. Unfortunately, when Vorbruggen's method is extended to the synthesis of 2'-deoxyribonucleosides, 1:1 mixtures of α:ß anomers are usually obtained[4a,5]. Walker and co-workers[6] studied uncatalyzed 2'-deoxyribonucleoside synthesis by coupling protected

pyrimidines with α-2-deoxy-3,5-di-O-p-toluoyl-ribofuransyl chloride 2[7]. They observed that ß-selectivity increased when solvents of low dielectric constant were used, and reasoned that non-polar solvents promoted the S_N2 condensation and minimized anomerization of the glycosyl halide.[8] Using silyated thymine 1b as the base, Walker obtained a 5:1 ratio of ß:α anomers by carrying out the coupling in dry $CHCl_3$ (ϵ=4) without catalyst. With less reactive bases $ZnCl_2$ was found to be an effective catalyst.



1 2 3

a R=H, X=CH
b R=CH_3, X=CH
c R=C_2H_5, X=CH
d R=I, X=CH
e R=F, X=CH
f R=NO_2, X=CH
g R=H, X=N
h R=CH_3, X=N

Due to the current interest in the use of 2'-deoxypyrimidine nucleosides as potential anti-viral agents, a high-yield route favoring the biologically active ß-anomers would be useful. Initially I studied the coupling of pyrimidine 1b with 2 in dichloroethane (ϵ=10) or $CHCl_3$ using various weak Lewis acid catalysts. Reaction conditions and resulting anomeric ratios are presented in Table 1. Of the systems studied CuI gave the best overall yield and ß-selectivity. Surprisingly, neither other copper (I) salts nor other soft Lewis acid iodides gave ß-selective reactions.

TABLE I. Catalyst Effect on the Coupling of 1b and 2

Entry	Catalyst	Reaction Conditions	Ratio ß:α
1	1 eq CuI	RT, EDC	75:25
2	1 eq CuBr	RT, EDC	46:54
3	1 eq CuCl	RT, EDC	55:45
4	1 eq $CuBr_2$	RT, EDC	42:58
5	1 eq $Cu(OTf)_2$	RT, EDC	other products
6	1 eq ZnI_2	RT, EDC	51:49
7	0.2 eq ZnI_2	0°C, EDC	46:54
8	1 eq AgI	RT, $CHCl_3$	other products, slow reaction
9	0.2 eq AlI_3	0°C, EDC	35:65
10	uncatalyzed	EDC	60:40

To determine whether the observed selectivity increase was due to the presence of CuI or simply due to the solvent, coupling of 1b and 2 was carried out in $CDCl_3$ with and without catalyst. The resulting reaction products were analyzed by 360 MHz ^{1}H-NMR. The CuI-containing reaction gave 15:1 ß:α selectivity while the uncatalyzed reaction gave only 6:1 selectivity. This NMR study also showed that the CuI-catalyzed reaction was faster, a factor that might be important in explaining the increased ß-selectivity.

Couplings of 2 with other silated pyrimidines were conducted using CuI in $CHCl_3$, and the results are shown in Table II. Generally, nucleosides were obtained in $\geq$ 90% yields and high ß:α ratios by using freshly prepared silyl bases and distilled $CHCl_3$. When reactive bases (i.e., 1a-c,g,h) were employed, fast reactions with high ß:α selectivity were observed. However, like the uncatalyzed reaction, rate and selectivity decreases as the electronegativity of the substituent in the 5-position increases[9]. For example, the coupling of 1e and 2 occurred with the same selectivity whether CuI was present or not. The catalyzed reaction was faster, proceeding to ~ 80% conversion in 4 hours at room temperature vs 55% conversion in the same time for the uncatalyzed reaction.

TABLE II. Yields and Anomeric Ratios of CuI Catalyzed Reactions of Protected Uracils with 2 in $CHCl_3$.

Base	Overall Yield	ß:α Ratio[a]
1a	93	92:8
1b	92	93:7
1c	92	93:7
1d	b	88:12
1e	90	73:27
1f	b	mainly ß
1g	92	92:8
1h	92	97:3

(a) determined by 360 MHz ^{1}H-NMR integration of anomeric protons

(b) Not determined

The couplings involving protected 5-iodouracil, 1d, and protected 5-nitrouracil, 1f, were NMR-scale experiments run in $CDCl_3$. After 5 hours, the uncatalyzed reaction of 1d and 2 was 77% complete with a 72:28 ß:α ratio while the CuI catalyzed reaction was 87% complete with a 90:10 ß:α ratio. After 20 hours, both reactions were greater than 97% complete. Again the CuI catalyzed reaction exhibited greater ß:α selectivity; 88:12 vs 65:35.

The couplings involving bis-trimethylsiloxy-5-nitrouracil, 1f, are much harder to analyze due to overlap of the ß and α anomeric protons in the NMR spectrum. The uncatalyzed reaction was extremely slow, showing only starting α-chlorosugar after 5 hours and 35% conversion after 24 hours. Walker et al. reported high conversions in the uncatalyzed reaction but the product was primarily the α-anomer.[10] With CuI a 90% conversion was achieved after 5 hours yielding mainly the ß-anomer.[11]

In summary, the use of CuI as a catalyst in the synthesis of various 2'-deoxypyrimidine nucleosides often results in improved ß:α selectivity and increased reaction rates. The ability of CuI to catalyze other glycosylation reactions is currently being studied.

Experimental

^{1}H-NMR spectra were recorded at 360 MHz on a GE/Nicolet NT-360 spectrometer and chemical shifts are reported in parts per million relative to tetramethylsilane. $CDCl_3$ was used as received. $CHCl_3$ was distilled from P_2O_5 and stored over 4Å molecular sieves. The parent uracils were purchased from Aldrich except for 5-ethyluracil which was prepared according to the procedure of Burkhalter and Scarborough.[12] Silylations were performed according to standard methods[4a] and the silylated nitrogen bases were distilled and used immediately. TLC analyses were performed on silca gel plates (Analtech). Melting points were determined on a Mel-Temp melting point apparatus in open capillary tubes and are uncorrected. NMR experiments were run on 50 mg scale in $CDCl_3$ and aliquots were removed at various intervals for analysis.

General Procedure

To a stirred solution of chlorosugar 2 (1.2 g, 3.1 mmol), bis-trimethylsilyloxythymine 1b (1.0 g, 3.4 mmol), and 80 mL of dry $CHCl_3$ was added CuI (0.60 g, 3.1 mmol). The slurry was stirred for 2 h at room temperature, at which time TLC analysis (2% $MeOH/CH_2Cl_2$ eluent) indicated complete reaction. The mixture was treated with 60 mL of saturated $NaHCO_3$ and filtered through Celite. The aqueous layer was washed with 50 mL of CH_2Cl_2. The combined organic layers were washed with 60 mL of saturated NaCl, dried over Na_2SO_4, and concentrated to give 1.4 g (92%) of white solid which had a ß:α ratio of 93:7 by ^{1}H-NMR. This solid was slurried with 40 mL EtOH, filtered, and washed twice

with 15 mL EtOH to yield pure β anomer, 1.1 g (71%): mp 195-196°C, lit mp 197°C[13]. Similarly the following were obtained: 1a: mp 209-210°C, lit mp 216-217°C[3]; 1c: mp 195-197°C, lit mp 197-198[4a]; 1e: mp 225-227°C, lit mp 229°C[13]; 1g: mp 175-177°C, lit mp 178-179[4h,13]; 1h: mp 170-172, lit mp 175-176.[14]

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(9) This implies that CuI is not acting as a Friedel Crafts catalyst as Vorbruggen has shown[4g] that electron withdrawing substituents in the 5 position give faster reactions.

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