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β-Anomer Selectivity in 2'-Deoxynucleoside Synthesis: A Novel Approach Using an Acyl Carbamate Directing Group.

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Abstract: Glycosylation of silylated pyrimidines using a phenyl 2-deoxy-3-*O*-(*N*-benzoyl)carbamoyl-1-thio-D-erythro-pentofuranoside yielded 2-deoxy-β-*ribo*nucleosides in good yields with excellent anomeric selectivity. This prototype 3-*O*-carbamate directing group was readily formed and removed in high yields.

Base glycosylation, using the Vorbruggen method[1] and its variations, has been a much-exploited synthetic reaction in the formation of many important nucleoside analogues.[2] However, a major practical drawback has been the poor β-selectivity of some glycosylations; notably with 2-deoxy-*erythro*-furanosides, precursors to the biologically important 2-deoxy-β-*ribo*-nucleosides. This particular problem has been tackled by using a directing groups on the 3-hydroxyl[3] and by intramolecular delivery of a 5-*O*-tethered base.[4] We report here on a new approach, utilising a more amenable 3-*O*-directing group in a thioglycoside coupling.

In recent papers,[5] Sugimura and co-workers have reported glycosylation reactions, based on a number of thioglycosides, which exhibit marked selectivity in the formation of the *N*-glycosyl bond. These results have been explained by putative ion-pairing between the oxonium ion intermediate and the succinimide anion (Figure 1), which effectively shields one face from attack by the base: the resultant anomeric configuration is dependent on the substitution pattern of the thiofuranosyl donor. However, the desired β-selectivity was not observed with 2-deoxy-*erythro*-furanosyl donors.[5b]

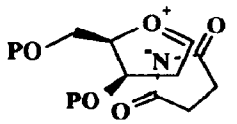


Figure 1.

Our solution was to mimic this putative intermediate in a 2-deoxy-*erythro*-furanosyl donor by providing an internally-tethered imide nitrogen through the use of an acyl carbamate on the 3-hydroxyl (Figure 2).

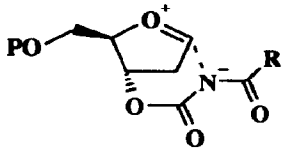
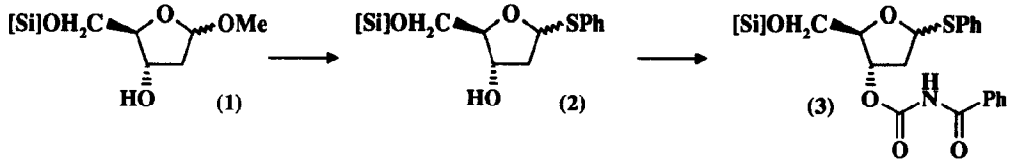


Figure 2.

The use of acyl carbamates as a potential directing groups was particularly attractive due to their ready formation: typically by direct treatment of an alcohol with an acyl isocyanate under mild conditions without the need for activation.[6] Subsequent removal, by simple base hydrolysis, enhanced this potential.

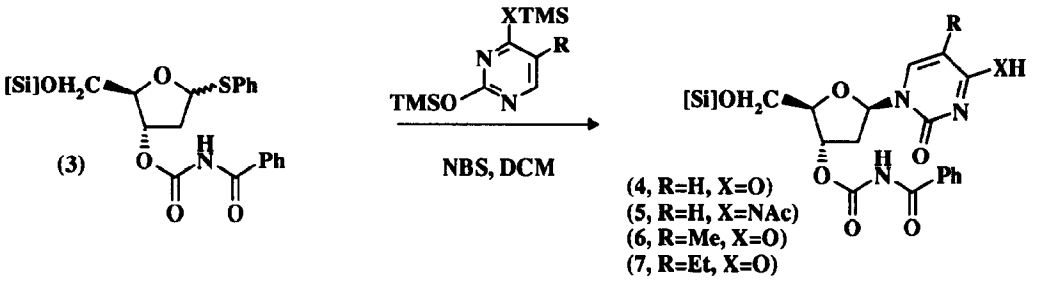
Methyl-5-*O*-*tert*-butyldiphenylsilyl-2-deoxy-*ribo*-furanoside (**1**)[7] provided a suitable starter for our required glycosyl substrate, and was converted to a thioglycoside before carbamoylation (Scheme 1). Thus reaction of (**1**) with TMS-SPh in dichloroethane, catalysed by BF_3-etherate[5a] gave thioglycoside (**2**), which was readily converted to its 3-*O*-(*N*-benzoyl)carbamoyl derivative (**3**)[8] by treatment with commercially available (Aldrich) benzoyl isocyanate in dry toluene.



[Si] = *t*BuPh$_2$Si

Scheme 1

In line with our expectations, exploratory couplings, on a 0.1 mmol scale, between (**3**) and *bis*(trimethylsilyl)pyrimidines on treatment with *N*-bromosuccinimide in dichloromethane[9] gave the required 2'-deoxynucleosides (Scheme 2) in reasonable yields with marked β-selectivity (up to 14:1).[10] These findings were based on ^{1}H NMR analysis of the crude reaction products: ratios were readily assigned by the relative integration of peaks in the spectra, *eg* at 600 MHz for (**6**), 1' protons at δ 6.38 ppm (dd, *J* 9.6 and 5.1 Hz) for the β-anomer and at δ 6.34 ppm (dd, *J* 8.6 and 5.3 Hz) for the α-anomer.



Scheme 2

In light of the exploratory findings, an illustrative set of couplings was performed, using the optimised conditions, on a larger scale . These produced the 2'-deoxynucleoside products in good yields[11] whilst maintaining the excellent levels of anomeric selectivity as summarised in the table.

The carbamate group was easily removed, in each case, using 2 equivalents of sodium methoxide in methanol with overnight reflux; subsequent treatment of the crude 5'-*O*-silyl-2'-deoxynucleosides with tetraethylammonium fluoride in methanol-tetrahydrofuran furnished the 2'-deoxynucleosides in essentially

quantitative yields over the two steps, after flash chromatography on silica eluted with gradients of methanol-chloroform-ammonia. The predominant anomer in each product had spectral and chromatographic properties consistent with authentic 2'-deoxyuridine, thymidine, 2'-deoxycytidine or 2'-deoxy-5-ethyl-uridine.

Table: Illustrative results of pyrimidine couplings with (3).

Compound[a]	Temp. °C	R =	X =	Yield[b]	β:α Ratio[c]
4	0	H	O	68%	6.5:1
5	0	H	NAc[d]	78%	2.4:1
6	0	Me	O	72%	10:1
6	-78[e]	Me	O	50%	14:1
7	0	Et	O	73%	12:1
7	-78[e]	Et	O	49%	10:1

[a] All conditions/ratios used essentially identical to example given below, on 1 or 2 mmol scale;
[b] Isolated yields after chromatography; [c] ^{1}H NMR ratio of crude product;
[d] *Bis*(trimethylsilyl)cytosine coupled poorly under these conditions; [e] reaction time 2.5 hours.

Typical Experimental Procedure:

Thymine (504 mg, 4.0 mmol) was refluxed under nitrogen in 20 ml of dry dichloromethane with *N,O-bis*trimethylsilylacetamide (1.97 ml, 8.0 mmol) for 6 hours, when dissolution was complete. This solution was then cooled to 0 °C and the thioglycoside (3) (1.22 g, 2.0 mmol) was added in 20 ml of dry dichloromethane at 0 °C, followed immediately by *N*-bromosuccinimide in one portion (534 mg, 3.0 mmol). (A deep red brown colour is initially formed, which rapidly fades to give a pale orange solution). The mixture was stirred for 1 hour at 0 °C, then it was quenched by the addition of saturated aqueous sodium thiosulphate. The resulting suspension was filtered through hyflo®, layers were separated and two further ethyl acetate extractions were made. Combined organic fractions were washed twice with brine, then dried and evaporated to yield the crude nucleoside (6) as an off-white foam. A short column eluted with 1:1 to 3:1 ethyl acetate:petrol (b.p 40-60 °C), followed by trituration with ether gave crystalline (6) as essentially a single anomer in 72% yield.[11]

Given the excellent β-selectivity observed, we are undertaking further experiments to investigate the scope of this reaction in similar and related glycosylations, whilst further probing the mechanistic details.

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8. Data for phenyl 5-*O*-*tert*-butyldiphenylsilyl-3-*O*-benzoylcarbamoyl-2-deoxy-1-thio-α/β-D-*erythro*-furanoside (**3**), isolated as a white foam (*ca* 3:2 α/β): ^{1}H NMR (200 MHz, $CDCl_3$, δ_H, integration refers to sum for the two anomers): 1.05 and 1.10 (9H, 2s, CMe_3), 2.20 to 3.05 (2H, m, H-2), 3.65 to 4.05 (2H, m, H-5), 4.25 and 4.45 (1H, m, H-4), 5.45 (1H, m, H-3), 5.60 and 5.80 (1H, dd, H-1), 7.20 to 7.80 (20H, m, Ar-H), 8.00 and 8.10 (1H, brs, NH); Infra Red ν_{max} (KBr disc): 3 300, 1 757 cm^{-1}; (m/z) (FAB+): 612 ($M+H^+$, 10%), 634 ($M+Na^+$, 50%); Microanalysis: Found, C, 68.40; H, 6.30; N, 1.94; $C_{35}H_{37}O_5NSSi$ requires C, 68.71; H, 6.10; N, 2.29%.

9. During exploratory tests of the reaction system, in agreement with Sugimura and co-workers' findings, the use of a polar, non-co-ordinating, solvent such as dichloromethane was essential. Use of acetonitrile, more commonly used in nucleobase glycosylations, gave little anomeric selectivity.

10. General trends, i) Lowering the coupling temperature slowed the reaction rate, with equivocal evidence of further anomer ratio enhancement; however, such experiments gave reduced yields (See table). ii) *In situ* formation of the silylated base using *N,O-bis*trimethylsilylacetamide (BSA) was not only more convenient but also gave a slightly enhanced anomer ratio compared with silylated base formed using the hexamethyldisilazide method[1] in a tandem experiment. iii) A large excess of BSA in the reaction diminished anomeric selectivity. iv) The order of mixing was also important: if NBS was added to (**3**) prior to the base, yields were substantially reduced.

11. All coupled products, isolated as white hygroscopic solids, gave satisfactory spectroscopic and analytical data: *eg*, 5'-*O*-*tert*-butyldiphenylsilyl-3'-*O*-benzoylcarbamoyl-thymidine: M.p. 130-131 °C; ^{1}H NMR spectrum (200 MHz, $CDCl_3$, δ_H): 1.08 (9H, s, CMe_3), 1.54 (3H, m, CH_3), 2.20 to 2.45 (2H, m, H-2'), 3.98 (2H, brm, H-5'), 4.16 (1H, brm, H-4'), 5.53 (1H, m, H-3), 6.38 (1H, dd, *J* 9.6 and 5.1 Hz, H-1), 7.35 to 7.95 (16H, m, Ar-H, H-6), 9.25 and 9.65 (each 1H, brs, NH); Infra Red ν_{max} (KBr disc): 3 200, 1 780, 1 743, 1 695 cm^{-1}; (m/z) (FAB+): 650 ($M+Na^+$, 20%); Microanalysis: Found, C, 62.39; H, 5.70; N, 6.39; $C_{34}H_{37}N_3O_7Si.1.3H_2O$ requires C, 62.71; H, 6.12; N, 6.45%.

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