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Acyl Carbamate Directing Groups in Nucleoside Synthesis: Applications in the Synthesis of 2'-Deoxy-5-Ethyl-4'-Thiouridine.

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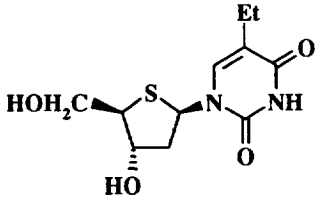
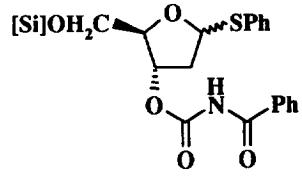
Abstract: The use of the 3-*O*-(*N*-acyl)carbamoyl directing groups in the synthesis of the potent anti-Herpes virus agent 2'-deoxy-5-ethyl-4'-thio-D-uridine is described. This includes details of experiments to optimise the carbamate substitution and a multi-gram exemplification of the key steps.

2'-Deoxy-4'-thionucleosides have received considerable recent interest due to potent biological activity in the series. In particular 2'-deoxy-5-ethyl-4'-thio-D-uridine (**1**) has shown considerable therapeutic promise due to potent anti-Herpes virus activity.[1] The published synthetic routes to such molecules[2] have been compromised, especially on a large scale, by either or both poor anomeric selectivity in the base glycosylation and difficulties in late stage deprotections. In this paper we describe further studies based on (**2**), our prototype 3-*O*-carbamoyl glycosylating agent, used in the anomer-selective synthesis of natural 2'-deoxy nucleosides.[3] This was applied to a multi-gram scale synthesis of 2'-deoxy-5-ethyl-4'-thio-D-uridine (**1**).

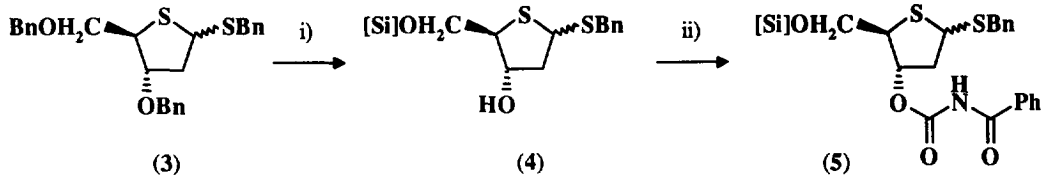


(**1**)



(**2**)

Construction of the appropriately substituted glycosylating agent was readily achieved (Scheme 1) from tribenzyl 2-deoxy-1,4-thio-D-*erythro*-pentofuranoside (**3**),[4] an intermediate available in kilogram quantities. The di-de-*O*-benzylation of (**3**), proved somewhat capricious and was best facilitated using titanium IV chloride in dichloromethane. This deblocking, followed by silylation, furnished (**4**) in about 40% yield, starting from 25 g of (**3**). This was readily converted to the required 3-*O*-(*N*-benzoyl)carbamoyl derivative (**5**)[5] in 85 % yield, by treatment with commercially available (Aldrich) benzoyl isocyanate in dry toluene.



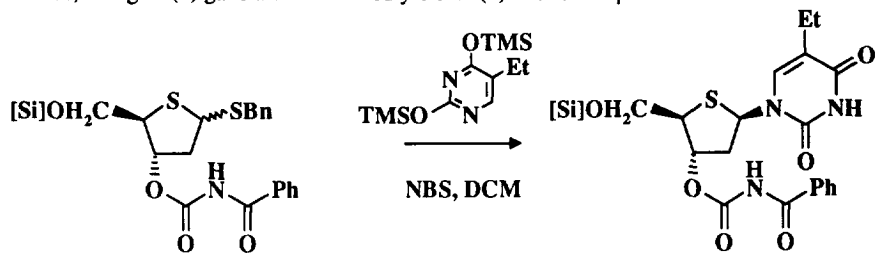
(3) (4) (5)

[Si] = tBuPh$_2$Si

i) $TiCl_4$, DCM; then [Si]Cl, DMAP, imidazole, DCM; ii) PhCONCO, toluene.

Scheme 1

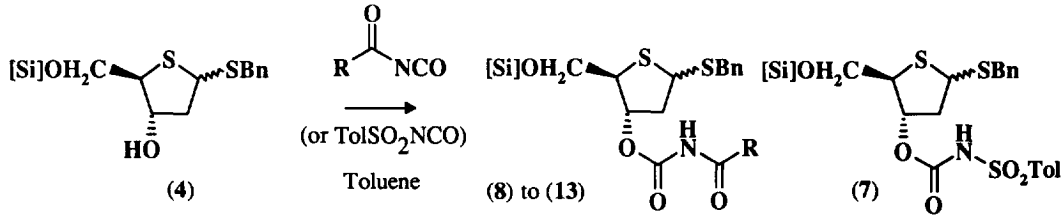
Small scale couplings between (**5**) and *bis*(trimethylsilyl)-5-ethyluracil (Scheme 2) were used to investigate the applicability of conditions from our prototype oxygen series[3] to furnish the diprotected 4'-thio nucleoside (**6**). Pleasingly, the coupling yields were reproduced, though the directing effect produced with the thiosugar was slightly diminished, giving ratios in the region of 3:1 β:α; changing the conditions produced similar trends in the observed coupling ratios. Scaling up the procedure, using essentially the same conditions as in the oxa- series, 10.9g of (**5**) gave a 72% isolated yield of (**6**) with 3.2:1 β:α ratio.[6]



(**5**) (**6**) β:α 3.2:1

Scheme 2

In an effort to optimise the directing effect and to investigate possible alternatives to the unstable and hazardous benzoyl isocyanate, a number of analogues were synthesised with variation in the carbamate substituent. To this end, (**4**) was reacted with *para*-toluenesulphonyl isocyanate and a number of acyl isocyanates,[7] furnishing *para*-toluenesulphonyl carbamate (**7**) and the variously acylated (**8**) to (**13**) (Scheme 3).



(**4**) (**8**) to (**13**) (**7**)

Scheme 3

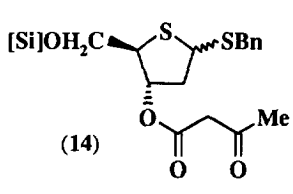
Bis-Trimethylsilyl-5-ethyl uracil was glycosylated by each donor (**7**) to (**13**) on a 1 mmol scale utilising the conditions described above (entries 2 to 8 in the table); which were compared to an averaged ratio (entry 1) for the benzoylated donor (**5**). The generality of the directing effect was apparent from these experiments,

whilst the *tert*-butanoyl derivative (**10**) emerged as the most viable alternative, with slightly improved anomer ratios and comparable yields to the prototype benzoyl (**5**).[8]

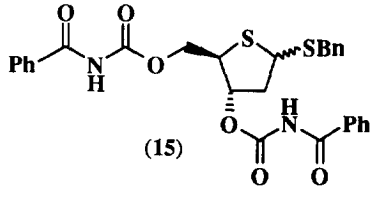
Table: Illustrative Average Coupling Ratios Between Variously Substituted Carbamates (7) to (13) with *Bis*(TMS)-5-ethyl-uracil Under the Conditions of Scheme 2.

Entry	Compound	R =	Ratio β:α
1	(**5**)	Ph	3.7:1
2	(**7**)	(SO_2pTol)	3.1:1
3	(**8**)	CCl_3	3.7:1
4	(**9**)	Me	2.5:1
5	(**10**)	CMe_3	4.2:1
6	(**11**)	CH_2Ph	2.9:1
7	(**12**)	*n*Hexyl	2.8:1
8	(**13**)	*c*Hexyl	2.3:1

Two further compounds gave interesting and informative results. The role of the nitrogen in the directing effect was corroborated by the ~2:3 β:α ratio obtained on coupling the acetoacetate (**14**), which was prepared by DCC coupling of (**4**) and acetylacetic acid. A potential short cut, utilising *bis*-*O*-carbamoyl (**15**), formed by treatment of the debenzylation product from (**3**) with excess benzoyl isocyanate; was precluded by a coupling ratio of 1:3 β:α; presumably due to preferential interaction by the 5-*O*-carbamoyl group.

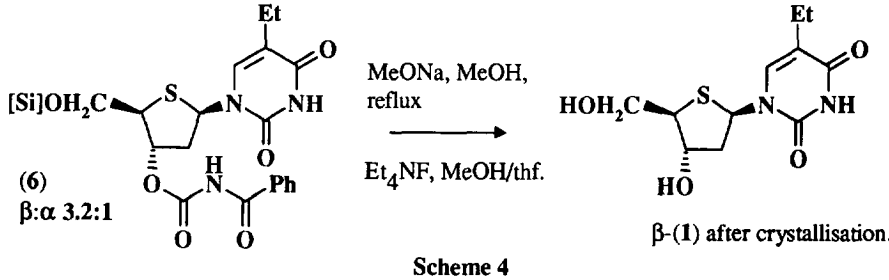


(14)



(15)

Deblocking of the 3' and 5' hydroxyls of (**6**) completed the synthesis. The carbamate groups were readily removed using sodium methoxide in refluxing methanol. Surprisingly, these conditions also produced up to 60% cleavage of the 5'-*O*-silyl protection. Although attempts were made to fully deprotect (**6**) in one pot, separate treatment of the 5'-*O*-silylated derivative with tetraethylammonium fluoride in thf-methanol proved most efficient. Ultimately, 11.0 g of (**6**) was deblocked quantitatively and >90% of the available pure β-(**1**), identical to authentic samples,[1b,2d] was recovered from the anomeric mixture following repeated crystallisations from ethanol.



(6)
β:α 3.2:1

β-(**1**) after crystallisation.

Scheme 4

Thus we have facilitated the incorporation of two important features into a synthesis of 2'-deoxy-5-ethyl-4'-thio-D-uridine (**1**), namely the introduction of anomeric selectivity during the coupling step, followed by deprotection using conditions more amenable to large scale production. A new approach to the glycosyl donor is described in the following paper.

Acknowledgements.

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References and Notes

1. a) Rahim, S.G., Trivedi, N, Hardy, G.W., Mills, G., Littler, E., Purifoy, D.J.M., Dyson, M.R., Coe, P.L., Basnak, I., Whale, R.F., and Walker, R.T., Presented at the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy 4-7th Oct 1994, session 102, abstract H49; Walker, R.T., Dyson, M.R., Whale, R.F., Coe, P.L., *Ibid.* abstract H51; Littler, E., Lowe, D., Collins, P., Snowden, B.W., Ertl, P., and Alderton, W., *Ibid.* abstract H53. b) Rahim, S.G., Trivedi, N, Bogunovic-Batchelor, M.V., Hardy, G.W., Mills, G., Selway, J.W.T., Snowden, B.W., Littler, E., Coe, P.L., Basnak, I., Whale, R.F., and Walker, R.T., *J. Med. Chem., in press.*

2. a) Secrist, J.A. III, Riggs, R.M., Tiwari, K.N., and Montgomery, J.A., *J. Med. Chem.*, **1991**, *34*, 2361-2366; b) Dyson, M.R., Coe, P.L., and Walker, R.T., *J. Med Chem.*, **1991**, *34*, 2782-2786; c) Uenishi, J., Motoyama, M., and Takakashi, K., *Tetrahedron Asym.*, **1994**, *5*, 101-110; d) Jandhu, K.S. and Selwood, D.L., *J. Org. Chem.*, **1995**, *60*, 5170-5173.

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5. All new compounds gave satisfactory spectroscopic and analytical data. Data for Benzyl 5-*O*-*tert*butyldiphenylsilyl-3-benzoylcarbamoyl-2-deoxy-1,4-dithio-α/β-D-*erythro*-pentofuranoside (*ca* 1:4 α:β mixture of anomers): ^{1}H NMR ($CDCl_3$) δ_H, (integration refers to sum for the two anomers) 1.05 and 1.10 (9H, 2s, CMe_3), 2.25 to 2.60 (2H, m, H-2), 3.65 to 4.05 (3H, m, H-4/5), 4.40 (1H, dd, H-1), 5.55 (1H, m, H-3), 7.20 to 7.85 (20H, m, Ar-H), 8.05 and 8.15.(1H, brs, NH). Infra red spectrum ν_{max} (KBr disc) 3 300, 1 771, 1 753 cm^{-1}. Mass spectrum (m/z) (FAB+) 664 ($M+Na^+$, 25%); Microanalysis: Found, C, 67.73; H, 6.15; N, 2.30; $C_{36}H_{39}NO_4S_2Si$ requires C, 67.36; H, 6.12; N, 2.18%.

6. Ratios were assigned by characteristic ^{1}H NMR peaks due to the 1' protons at 6.33 ppm (dd, J = 7.9 and 2.4 Hz) for the α-anomer and 6.50 ppm (dd, J = 10.1 and 6.2 Hz) for the β-anomer.

7. Compounds (**7**) and (**8**) were produced from commercially available *para*-toluenesulphonyl isocyanate and trichloromethyl isocyanate respectively. Acyl isocyanates used to produce compounds (**9**) to (**13**) were prepared as toluene solutions *in situ* by refluxing the appropriate acid chloride with silver cyanate for 30 minutes and decanting aliquots from the cooled, settled, suspension.

8. An 83% yield of (**10**) was isolated after column chromatography from a 1 mmol scale reaction. The other carbamates gave coupled products in comparable yields, which was evident from hplc/NMR analysis.

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