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Phenylsulfenyl D-Ribofuranosides as Efficient Ribosyl Donors: Application to the Synthesis of [1'-^{13}C]-(Deoxy)Nucleosides

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Key Words: anomeric sulfoxides; silylated nucleobases; [1'-^{13}C]-nucleosides; 2'-deoxynucleosides

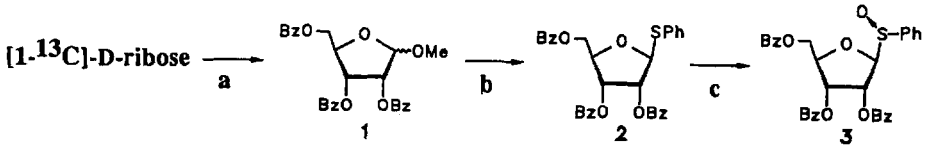
Abstract: Readily available phenylsulfenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside glycosylates silylated nucleobases in a fast, high-yielding and stereoselective reaction promoted by trimethylsilyl trifluoromethanesulfonate. The method has been applied to the synthesis of [1'-^{13}C] labelled nucleosides further transformed to building blocks ready for oligodeoxynucleotide construction.

NMR Spectroscopy has given the most useful parameters to study the conformational behavior of nucleic acids in solution. Introduction of a ^{13}C label in the (2-deoxy)-D-ribose moiety of nucleic acids would allow an increase of the dimensionality of the NMR experiment, thus greatly simplifying the structural analysis of these biomolecules in solution. Such a strategy should prove very useful to detect local conformational changes induced by a small (e.g., an antitumor drug) or a much larger molecule (e.g., a regulatory protein) when they interact with the target sequence of a nucleic acid. As a first step towards this goal, we report a reliable synthetic scheme which provides (deoxy)ribonucleosides labelled in the sugar moiety[1-5] with a good overall efficiency, starting from commercial [1-^{13}C]-D-ribose[6].

Anomeric sulfoxides of glucopyranosides were recently recognized as useful glucosylating agents of poor nucleophiles, using triflic acid as a promoter[7]. We now describe that phenylsulfenyl ribofuranosides, when employed using the Vorbrüggen procedure[8], represent highly active agents in nucleoside synthesis.

Acetolysis (Ac_2O, AcOH, H_2SO_4) of methyl ribofuranosides[9] according to Recondo and Rinderknecht[10] provided acetyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside, transformed to thiophenyl ribofuranoside **2**[11] (PhSH, $BF_3.Et_2O$, CH_2Cl_2) by the Ferrier procedure[12] (93% overall yield). This two-step procedure was conveniently shortened by treating directly methyl ribofuranoside **1** with thiophenol (95% yield, see Scheme 1).

Scheme 1

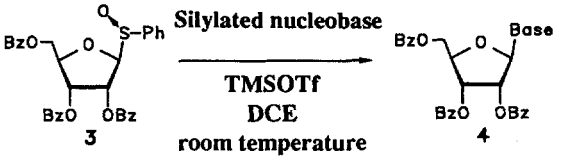


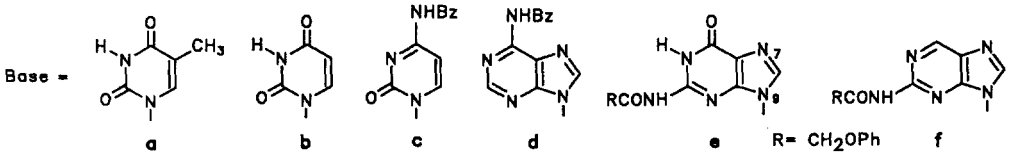
Reagents and Conditions: *a)* MeOH, H_2SO_4, 0°C, overnight; BzCl, pyridine, 0°C, overnight; 86%. *b)* PhSH, $BF_3.Et_2O$, CH_2Cl_2, 0°C, 1 h; 95%. *c)* *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0°C, 1 h; 95%.

The sulfoxides **3**[13] (isomeric ratio, 1:1) produced by *m*CPBA oxidation of **2**, were thus obtained in an overall yield of 77% from [1-^{13}C]-D-ribose.

Initial glycosylation studies of silylated thymine by **3** under Kahne's conditions[7] (Tf_2O as a promoter in dichloroethane) led to the desired N^1-nucleoside in ~ 30% yield (see Table, entry 1). We found however that under Vorbrüggen conditions[8] (trimethylsilyl trifluoromethanesulfonate as a promoter, 1,2-dichloroethane as solvent) sulfoxides **3**[14] and silylated thymine furnished the required nucleoside in a very fast (less than one min) and high yielding (92%) coupling process (method A) provided that the reaction be conducted at *room temperature*[15] (Table, entry 2). Similar results were obtained with the silylated pyrimidines uracil and N^4-benzoylcytosine[17] (see Table).

Table ***Synthesis of Nucleosides from Sulfoxides 3***





Entry	Silylated Base	Conditions	Product	Yield* (%)	Selected NMR Coupling Constants[a] H_1'-H_2'	C_1'-H_1'	C_1'-H_2'
1	Thymine	Tf_2O[b]	**4a**	30	6.5	168	4.0
2	"	method A[c]	**4a**	92			
3	"	method B[c]	**4a**	~0[d]			
4	Uracil	method A	**4b**[e]	90	5.8	—	—
5	N^4-benzoyl cytosine	method A	**4c**	95	4.8	171	2.8
6	N^6-benzoyl adenine	method A	**4d**	40	5.2	166.2	4.1
7	"	method B	**4d**	90			
8	N^2-phenoxy-acetyl guanine	method B	**4e**	65[f] 22[g]	2.6 5.1	167.5 168	1 2.9
9	N^2-phenoxy-acetyl 2-amino-purine	method B	**4f**[e]	60	3.2	—	—

* Nucleoside yields isolated by column chromatography.

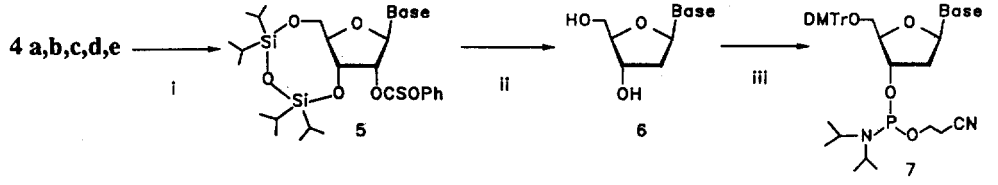
[a] ^{1}H-NMR spectroscopy was performed for $CDCl_3$ solutions at 300 MHz; values in hertz. [b] See Ref. 7; [c] The conditions are described under **representative procedures**; [d] 2,3,5-tri-*O*-benzoyl-D-ribofuranose and β-D-ribofuranosyl(1→1)β-D-ribofuranose are formed; [e] Unlabelled sulfoxides **3** were used; [f] N^9-isomer; [g] N^7-isomer.

The same conditions applied to silylated purines proved to be unreliable as seen by coupling **3** with silylated N^6-benzoyladenine which provided the required nucleoside in only 40% yield[18] (Table, Entry 6).

With N^6-benzoyladenine, N^2-phenoxyacetylguanine and N^2-phenoxyacetyl-2-aminopurine, the best yields were obtained however by combining silylation of the nucleobases and *N*-glycosylation in a single synthetic step (method B, see Table)[19]. Worthy of note is the use of the phenoxyacetyl protecting group[20] for guanine, which allowed a very easy separation of the N^7 (22%) and the N^9 (65%) regioisomer.

The [1'-^{13}C] labelled nucleosides **4a,c,d,e** were deoxygenated at C-2' using a standard procedure[21] and transformed to the 5'-*O*-dimethoxytrityl-3'-*O*-[(β-cyanoethyl)-*N*,*N*-diisopropyl]-phosphoramidite building blocks[22] for oligomerization. The results are shown in Scheme 2.

Scheme 2



Reagents and Conditions: *i) 1.* pyridine, MeOH, 2M NaOH, 0°C, 5 min; *2.* $TIPSCl_2$, pyridine, room temperature; *3.* PhOCSCl, DMAP, CH_3CN, room temperature. *ii) 1.* Bu_3SnH, AIBN, $PhCH_3$, reflux; *2.* Bu_4NF, THF, 75°C. *iii) 1.* DMTrCl, pyridine, Et_3N, 4°C; *2.* *i*-$Pr_2NP(Cl)OCH_2CH_2CN$, *i*-Pr_2NEt, CH_2Cl_2, room temperature.
Yields: **7a:** *i)* 79%; *ii)* 72%; *iii)* 58%. **7c:** *i)* 76%; *ii)* 68%; *iii)* 75%. **7d:** *i)* 42%; *ii)* 39%; *iii)* 63%. **7e:** *i)* 35%; *ii)* 51%; *iii)* 82%.

The following procedures are representative:

Method A: Thymine (0.85 g, 6.7 mmol, 1.1 equiv.) was silylated in the usual way by reflux under argon in hexamethyldisilazane (10 mL) for 2 h. To silylated thymine were added a solution of sulfoxides **3** (3.5 g, 6.1 mmol) in dry 1,2-dichloroethane (10 mL) and TMSOTf (1.1 mL, 6.1 mmol). The reaction was complete after stirring at room temperature under argon in less than 1 min (as judged by TLC). After 5 min, the reaction mixture was cooled to 0°C, treated by triethylamine (1 mL) and diluted with CH_2Cl_2. The usual workup and column chromatography (10:3, toluene:ethyl acetate) afforded nucleoside **4a** (3.23 g, 92%).

Method B: To a stirred solution of N^6-benzoyladenine (1.62 g, 6.77 mmol, 1.1 equiv.) in dry 1,2-dichloroethane (20 mL)* was added TMSOTf (2.74 mL, 14.16 mmol, 2.3 equiv). After stirring at room temperature for 0.5 h, a solution of sulfoxides **3** (3.5 g, 6.1 mmol) in 1,2-dichloroethane (20 mL) was added. The reaction was essentially complete in less than 1 min. Workup as described under Method A and column chromatography (2:1, toluene:ethyl acetate) provided nucleoside **4d** (3.77 g, 90%).

*10% (v/v) DMF was added in the case of N^2-phenoxyacetylguanine.

This glycosylation, which no longer requires reflux temperature (~ 80°C) for several hours, should prove useful for the *N*-ribosylation of sensitive bases or in the synthesis of complex nucleoside antibiotics[23].

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13. Selected ^1H-NMR data (300 MHz): **2** ($CDCl_3$) δ 5.61 (dd, $J_{1,2}$ 4.9, $J_{1,C1}$ 168 Hz, H-1); **3** ($CDCl_3$), one isomer: δ 5.04 (dd, 1 H, $J_{1,2}$ 3.7, $J_{1,C1}$ 169.2 Hz, H-1); other isomer: δ 5.05 (dd, 1 H, $J_{1,2}$ 2.4, $J_{1,C1}$ 168.8 Hz, H-1); **6a** (D_2O) δ 6.29 (dt, 1 H, $J_{1',2'} \sim J_{1',2''} = 6.9$ $J_{1',C1'}$ 168 Hz, H-1'); **6c** (DMSO-d_6) δ 6.15 (dt, 1 H, $J_{1',2'} \sim J_{1',2''} = 6.3$, $J_{1',C1'}$ 171.5 Hz, H-1'); **6d** (DMSO-d_6) δ 6.48 (dt, 1 H, $J_{1',2'}$ 6.3, $J_{1',2''}$ 7.2, $J_{1',C1'}$ 167 Hz, H-1'); **6e** (DMSO-d_6) δ 6.22 (ddd, 1 H, $J_{1',2'}$ 6.1, $J_{1',2''}$ 7.8, $J_{1',C1'}$ 168 Hz, H-1').
14. No difference in rate was observed when the R or S isomer of **3** were taken separately.
15. At 0°C, the same reaction conditions led to nucleoside **4a** (52%) and variable amounts of 2,3,5-tri-*O*-benzoyl-D-ribofuranose and disaccharide β-D-ribofuranosyl (1→1)β-D-ribofuranoside (45% total) as a result of an intramolecular rearrangement of **3** to the corresponding anomeric sulfenate[16].
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18. We suspect an inefficient activation of the silylated purine under these conditions. See also Note 15.
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