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Efficient Synthesis of 2'-*O*-Alkyl Ribonucleosides Using Trichloroacetimidate D-Ribofuranosides as Ribosyl Donors

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Abstract: *Trichloroacetimidate-2-O-alkyl-3,5-O-TIPS-β-D-ribofuranoside glycosylates silylated nucleobases in a fast high-yielding and stereoselective reaction promoted by trimethylsilyl trifluoromethanesulfonate. This method has been applied to the synthesis of 2'-O-alkyl ribonucleosides further transformed to building blocks ready for oligo(2'-O-alkyl)ribonucleotide construction.*

Oligo(2'-*O*-alkyl)ribonucleotides are proving to be useful reagents for a variety of biological experiments. They have been developed recently as novel oligonucleotide analogues with properties that enhance their use as antisense probes. They possess high chemical stability and are resistant to hydrolysis by alkali and a wide range of DNA- or RNA-specific nucleases[1,2]. Many forms of oligo(2'-*O*-alkyl)ribonucleotides hybridize specifically and efficiently to complementary RNA sequences or to duplex DNA via triplex formation[3,4].

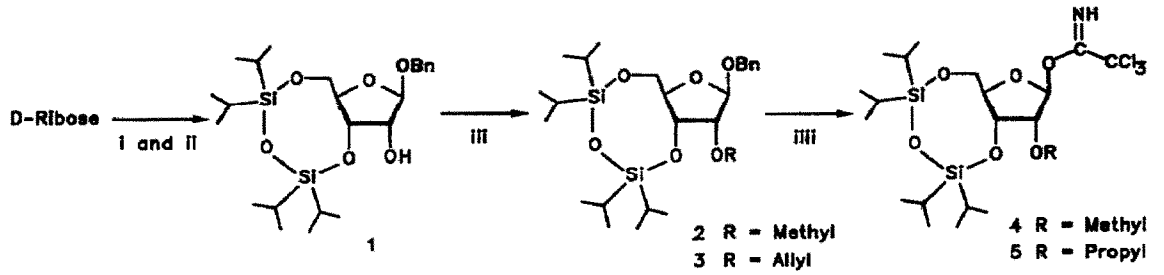
Considerable effort has been directed toward developing efficient alkylation of appropriately protected ribonucleosides. By this method the 2'-*O*-alkyl derivatives of some common ribonucleosides have been synthesized[5-9]. An attractive alternate route is the glycosylating reaction using an activated 2-*O*-alkyl ribose derivative and silylated bases[10]. This approach should be straightforward and would open general access to a wide variety of different nucleosides, since any base could be introduced later in the synthesis.

In carbohydrate chemistry, anomeric trichloroacetimidates of glycopyranosides were recognized as useful glycosylating agents towards nucleophiles, using Lewis acid as promoter[11,12]. We report here the use of 2-*O*-alkyl-β-ribosyl trichloroacetimidate **4** or **5** for the preparation of 2'-*O*-alkyl ribonucleosides.

Starting from D-ribose, the synthesis of the trichloroacetimidate derivative **4** or **5** was performed following Scheme 1. Selective protection of benzyl ribofuranoside[13] according to Markiewicz[14] provided benzyl-3,5-*O*-TIPS-ribofuranoside **1** (77%). For the synthesis of 2-*O*-methyl derivative **2**, the methylation of **1** was performed with methyl iodide in DMF after deprotonation with sodium hydride (70%). In an alternative procedure, the alkylation of **1** was achieved under neutral conditions, using an allyloxycarbonyl derivative and palladium catalysts[15] (87%). After hydrogenolysis of the benzyl derivative **2** or **3** (92%, allyl was also reduced

in propyl) and treatment by the Schmidt procedure[16], the stable 2-*O*-alkyl-β-D-ribofuranosyl trichloroacetimidates **4** or **5**[17] was obtained with a good yield (75%) (see Scheme 1).

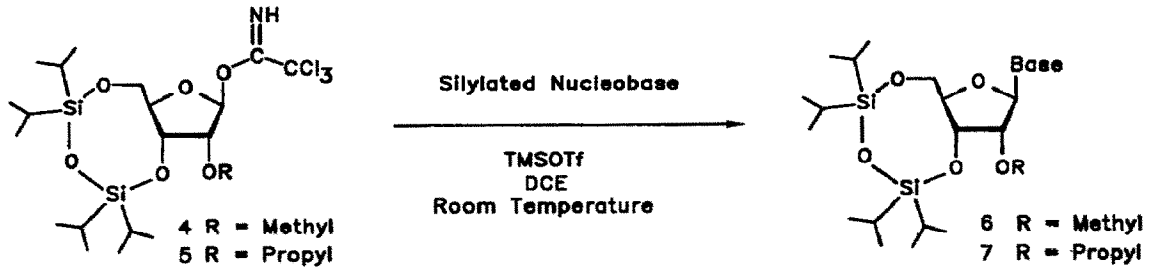
Scheme 1 ***Synthesis of Trichloroacetimidate Derivatives***



Reagents and Conditions: i) BnOH, H^+Cl^-, 20°C, overnight (85%). ii) $TIPSCl_2$, pyridine, room temperature (90%). iii) MeI, NaH, DMF, room temperature (70%) or $ClCO_2CH_2CH{=}CH_2$, DMAP, acetonitrile, room temperature then $Pd(OAc)_2$, PPh_3, toluene, reflux (87%). iiii) H_2, Pd/C-10%, ethyl acetate, room temperature (92%), then CCl_3CN, DBU, DCE, room temperature (75%).

Glycosylation under Vorbrüggen conditions[18] (trimethylsilyl trifluoromethanesulfonate as promoter, 1,2-dichloroethane as solvent) using imidate **4** or **5** and silylated base[19] furnished the required 2'-*O*-alkyl nucleosides in a very fast and high yielding reaction with good stereoselectivity (see Table).

Scheme 2 ***Synthesis of (2'-O-Alkyl)nucleosides from Imidate 4 or 5***



Base = **A**, thymine; **B**, N^4-Bz-5-Me-cytosine; **C**, lumichrome; **D**, N^2-phenoxyacetyl-2-aminopurine; **E**, N^2-isobutyryl-O^6-[2-(*p*-nitrophenyl)ethyl]guanine.

Entry	Silylated Base	Imidate	Product	α:β[a]	Yield[b] (%)
1	A	4	6A	5:95	94
2	B	4	6B	3:97	95
3	C	4	6C	β>99	80
4	D	5	7D	β>99	77
5	E	5	7E	β>99	86

a) Ratios were determined by ^{1}H-NMR analysis (H1'α 5,8 ppm and H1'β 6,4 ppm).

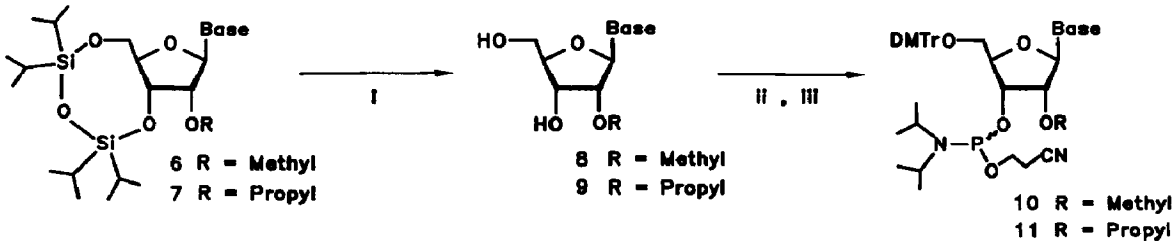
b) Total nucleoside yields isolated by column chromatography.

The following procedure is representative:

N^4-Bz-5-Me-cytosine, **B** (0.345 g, 1.6 mmol, 1.1 equiv.) was silylated in the usual way by reflux under argon in hexamethyldisilazane (5ml) for 2 h. To silylated cytosine was added a solution of imidate **4** (0.830 g, 1.5 mmol) in dry 1,2-dichloroethane (10 ml) and TMSOTf (291 µl, 1.5 mmol, 1 equiv.). 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 (500 µl) and diluted with CH_2Cl_2. The usual workup and column chromatography (3:1, toluene:ethyl acetate) provide nucleosides **6B** (0.880 g, 95%).

The 2'-*O*-alkyl nucleosides **6** or **7** were selectively deprotected at the 3'-and 5'-positions with tetrabutylammonium fluoride in THF[20] (95%) and transformed to the 5'-*O*-dimethoxytrityl-3'-*O*-[(β-cyanoethyl)-*N,N*-diisopropyl]-phosphoramidite building blocks[21] **10** or **11** (80%) ready for oligomerization (see scheme 3).

Scheme 3 ***Synthesis of Phosphoramidite Derivatives***



Reagents and Conditions: i) Bu_4NF, THF, room temperature (95%). ii) DMTrCl, pyridine, room temperature (88%). iii) i-$Pr_2NP(Cl)OCH_2CH_2CN$, i-Pr_2NEt, CH_2Cl_2, room temperature (90%).

This glycosylation using the trichloroacetimidate method, which no longer requires reflux temperature for several hours, should prove useful for the preparation of "exotic" 2'-*O*-alkyl ribonucleosides on a large scale in good overall yields and directly with protected aglycons ready for oligonucleotide construction.

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