A Convenient Method for the Selective Acylation of Guanine Nucleosides

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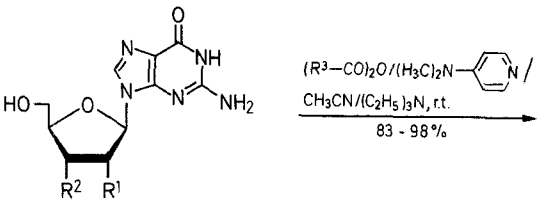
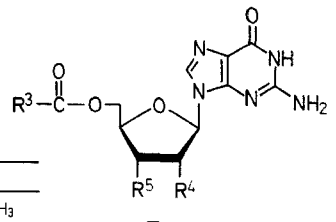
Fully acylated guanine nucleosides have most frequently been used in the preparation of oligonucleotide blocks. However, a selective acyl protection of the sugar hydroxy groups in guanine nucleosides is still troublesome in large scale works. Protected guanine nucleosides bearing a free 2-amino group have been known to be one of the most important starting materials for synthesizing antileukemic 2-haloadenine nucleosides[1], since non-aqueous diazotization methods were effectively applied in nucleoside chemistry[2,3,4,5]. Recently, we have also reported on the introduction of aryl and phenylthio groups to the C-2 position of 6-chloropurine ribosides through a similar radical processes[6,7] and have found that 2-iodoadenosine could couple with a variety of terminal alkynes via organopalladium intermediates[8].

A selective acylation of the sugar hydroxy groups in guanine nucleosides under conventional acylating conditions using an acid anhydride/pyridine, sometimes with *N,N*-dimethylformamide as a cosolvent, often required extended periods of time or elevated temperatures and even then the product was contaminated with incompletely acylated impurities. Replacement of pyridine by 4-dimethylaminopyridine[9] as catalyst in nonpolar solvents has rendered the reaction extremely sluggish due to their insolubilty.

After a series of attempts to find a suitable solvent, we have found acetonitrile offered a good chance. We now report a procedure by 4-dimethylaminopyridine catalysis using acetonitrile containing triethylamine as a solvent which gives excellent yields on acylation of sugar hydroxy groups in several sugar derivatives of guanine nucleosides. Guanosine **(1a)** was treated with acetic anhydride in acetonitrile/triethylamine in the presence of a catalytic amount of 4-dimethylaminopyridine at room temperature. Within 30 min, a clear solution was obtained. At this time, only a trace amount of N^2,2′,3′,5′-tetraacetylguanosine was detected by thin layer chromatographic analysis. After being quenched with methanol to decompose an excess amount of acetic anhydride, the mixture was evaporated to dryness under reduced pressure and the residue was crystallized from isopropyl alcohol to give 2′,3′,5′-tri-*O*-acetylguanosine **(2a)** in 98% yield.



1a $R^1 = R^2 = OH$
b $R^1 = H, R^2 = OH$
c $R^1 = OH, R^2 = H$



7a-f

2	R^3	R^4	R^5
a	CH_3	O—CO—CH_3	O—CO—CH_3
b	CH_3	H	O—CO—CH_3
c	C_6H_5	H	O—CO—C_6H_5
d	*i*-C_3H_7	H	O—CO—C_3H_7-*i*
e	CH_3	O—CO—CH_3	H
f	*i*-C_3H_7	O—CO—C_3H_7-*i*	H

It should be noted that the presence of triethylamine accelerated the reaction, since anhydride reacted very slowly in the absence of triethylamine. Similar reactions starting from 2′- or 3′-deoxyguanosines **(1b, c)** with benzoic or

Table. *O*-Acylated Guanine Nucleosides **2a–f** prepared

Product	Reaction Time	Yield [%]	m.p. [°C][b] (solvent)	M.S. m/e (re.int. %)	Molecular Formula[c] or Lit. m.p. [°C]
2a	0.5 h	98	225–227° (i-C_3H_7OH)	410 (M^+, 1); 151 (B^+, 17)	232°[10]
2b	2 h	97	300°	351 (M^+, 1); 151 (B^+, 53)	222° (dec)[11]
2c	14 h	84	214° (dec) (CH_3OH)	151 (B^+, 5)	dec[12]
2d	3 h	83	219–221° (H_2O)	407 (M^+, 3); 151 (B^+, 100)	$C_{18}H_{25}N_5O_6$ (407.4)
2e	3 h	89	226–229° (C_2H_5OH)	351 (M^+, 2); 151 (M^+, 2)	$C_{14}H_{17}N_5O_6$ (351.3)
2f	2 h	97	221–224° (H_2O)	407 (M^+, 2); 151 (B^+, 12)	$C_{18}H_{25}N_5O_6$ (407.4)

[a] Yield of isolated product.
[b] Uncorrected.
[c] Satisfactory microanalysis obtained: C ±0.29, H ±0.10, N ±0.24.

isobutyric anhydrides proceeded analogously with the formation of selectively acylated guanine nucleosides **2b–f** in high isolated yields without contamination by N^2-acylated products (Table).

This simple and convenient procedure provides a selective acylation method which is easily applicable for larger scale works as well as for the protection of sugar hydroxyl groups of other nucleosides.

Acylated Guanine Nucleosides 2; General Procedure:
To a suspension of guanine nucleosides **1a–c** (40 mmol) and 4-dimethylaminopyridine (366 mg, 3 mmol) in a mixture of acetonitrile (500 ml) and triethylamine (1.1 molar equivalents to acid anhydride used) is added the acid anhydride (1.2 molar equivalents for each hydroxy group of **1a–c**) at room temperature. After stirring for appropriate periods of time (Table), methanol (5 ml) is added to the mixture and stirring is continued for further 5 min. The mixture is evaporated to dryness under reduced pressure and the resulting oil or solid is crystallized from an appropriate solvent (Table). The crystals obtained are washed well with ethanol and ether. In the case of **2b**, the reaction does not give a clear solution and the suspended crystalline materials are collected directly by filtration and washed with ethanol and ether.

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