A Facile Synthesis of Cyclic Phosphodiesters

Jadwiga JANKOWSKA, Jacek STAWIŃSKI*

Institute of Bioorganic Chemistry, Polish Academy of Sciences, Noskowskiego 12/14, 61-704 Poznań, Poland

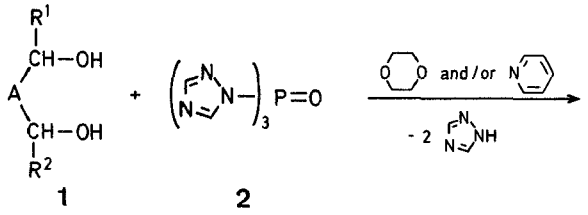
In principle, the reaction of an appropriate diol with phosphoryl chloride appears to be the most straightforward synthesis of cyclic phosphodiesters. Although this approach has been successfully used for diols with favourably constrained geometry[1], the reaction of diols with phosphoryl chloride cannot be applied as a general synthesis of cyclic phosphodiesters[2,3].

Therefore, for the preparation of cyclic phosphodiesters a number of synthetic methods have been developed; e.g. cyclization of acyclic phosphomono-[4], phosphodi-[5] or phosphotriesters[6] and, more recently, the phosphorylation of diols by means of phenyl phosphodichloridate[3] or cyclic enediol phosphoimidazole[7]. All these methods, however, require many reaction steps and the overall yield based on a starting diol is usually rather low. Moreover, some of these methods may be inconvenient on a large scale preparation[4,6].

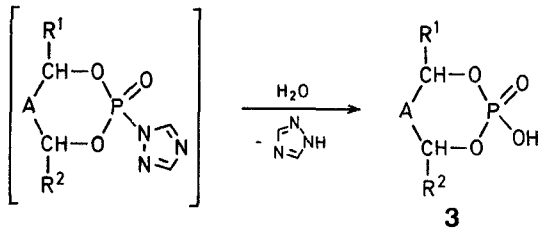
In search of a simple and general method for the synthesis of cyclic phosphodiesters **3** form diols **1**, we have investigated phosphoryl tris-triazole **(2)**[8] as a potential reagent for this conversion.

To obtain cyclic phosphotriesters **3a–g**, a solution of reagent **2** in dioxan is added to the corresponding diols **1a–g** dissolved in dioxan or pyridine. After a few minutes the mixture is decomposed with water or an aqueous solution of a base.

^{13}C-N.M.R. analysis reveals that all diols **1a–g** yield the corresponding ester **3** as single or at least main product. The cyclic phosphodiesters **3** are isolated either as free acids or as salts (Table).



1 **2**



3

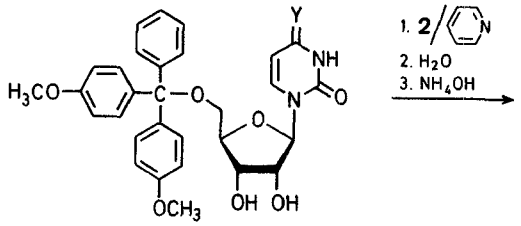
1,3	A	R^1	R^2	1,3	A	R^1	R^2
a	–	H	H	e	$-(CH_2)_2-$	H	H
b	–	CH_3	CH_3	f	$-(CH_2)_3-$	H	H
c	$-CH_2-$	H	H	g	$-CH_2-O-CH_2-$	H	H
d	$-CH_2-$	H	CH_3				

The advantages of this methods are:

- phosphorylation and cyclisation are performed in one step under mild conditions giving high yields of cyclic phosphodiesters **3**;
- no additional deprotection steps for the removal of phosphate protective groups are required;
- easy work-up of the reaction mixture.

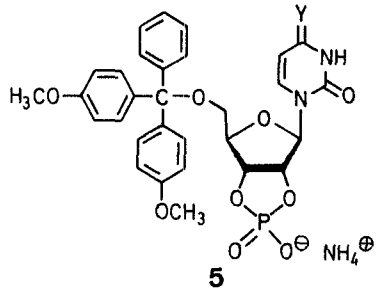
As can be seen from the Table, only in the case of **3f** is the yield of isolated product lower than 50%. This is mainly due to difficulties in obtaining **3f** in a crystalline form.

By reaction with phosphoryl tris-triazole **(2)** even aliphatic diols, which usually tend to yield polymers[2] or mono- and diphosphates[3] under conventional phosphorylation procedures are transformed into cyclic phosphodiesters **3**. Furthermore, 5′-protected ribonucleosides **4** react smoothly with reagent **2**. Quantitative yields of 5′-*O*-dimethoxytrityluridine 2′,3′-cyclic phosphate **(5a)** and 5′-*O*-dimethoxytrityl-*N*-benzoylcytidine 2′,3′-cyclic phosphate **(5b)**, respectively, and the experimental simplicity indicate that reaction with **2** can be the method of choice for the preparation of nucleoside 2′,3′-cyclic phosphates. However, attempts to extend this method to the preparation of nucleoside 3′,5′-cyclic phosphates failed. Instead of the desired products nucleoside diphosphates are formed.



4

4,5	a	b
Y	O	N–CO–C_6H_5



5

In conclusion, despite some limitations, the method described in this paper is at present the most general way for the synthesis of cyclic phosphodiesters **3** and **5**. In terms of simplicity and yield it is superior to other recently proposed methods for the same purpose[3,7].

Table. Phosphorylation of Diols **1** with Phosphoryl Tris-triazole **(2)**

Product	Yield[a] [%]	m.p. [°C]	Molecular formula[b] or Lit. m.p. [°C]	^{13}C-N.M.R.[c] δ [ppm]
3a	93[d]	159°[e]	168°[9]	(D_2O)[c]: 66.1 (d, J = 1.95 Hz, P—OCH_2—); 51.2, 31.2, 25.1, 24.6 (signals due to the cyclohexylammonium ion).
3b	91[d]	–	$C_8H_{16}O_8P_2Ba$	(D_2O)[f]: 77.7 (s, P—O—CH); 15.7 (d, J = 4.88 Hz, $-CH_3$)
3c	81[g]	102–103°	101–103°[7]	(D_2O): 69.2 (d, J = 6.84 Hz, P—OCH_2—); 26.8 (d, J = 5.86 Hz, $-CH_2$—)
3d	95[h]	159–160°[i]	160–161°[3]	(D_2O)[j]: 78.1 (d, J = 5.86 Hz, P—O—CH); 68.7 (d, J = 5.86 Hz, P—O—CH_2), 33.64 (d, J = 5.86 Hz, $-CH_2$—); 22.3 (d, J = 8.79 Hz, $-CH_3$)
3e	76[g]	128–129°	127–129°[3]	(D_2O): 68.0 (d, J = 5.86 Hz, P—O—CH_2—); 29.8 (s, $-CH_2$—)
3f	47[g]	79–80°	79–80°[7]	($CDCl_3$): 68.7 (d, J = 5.86 Hz, (P—O—CH_2—); 29.0 (s, P—O—CH_2—CH_2—); 23.7 (s, $-CH_2$—)
3g	60[g]	142–143°	$C_4H_9O_5P$	(D_2O): 68.5 (d, J = 6.80 Hz, P—O—CH_2—); 71.7 (s, $-CH_2$—)

[a] Yields of isolated products.
[b] Correct microanalysis obtained: C, ±0.06; H, ±0.06.
[c] Measured at 22.5 MHz.
[d] Isolated as barium salt; the free acid decomposes.
[e] Taken from the cyclohexylammonium salt of **3a** prepared from the barium salt.
[f] Taken from the barium salt of **3f**.
[g] Isolated as free acid.
[h] Isolated as benzylammonium salt; the free acid is obtained as an oil.
[i] m.p. of the benzylammonium salt.
[j] ^{13}C-N.M.R. taken from the free acid **3d**.

Reaction of Diols 1 and Nucleosides 4 with Phosphoryl Tris-triazole (2); General Procedure:
Phosphoryl tris-triazole (**2**; 5 mmol) – prepared from equimolar amounts of phosphoryl chloride, 1,2,4-triazole, and triethylamine in dioxan as described previously[8] – is added dropwise during 10 min to a stirred solution of the diol **1** or the nucleoside **4** (4.5 mmol) in pyridine (40 ml; **1c–g**, **4a, b**) or dioxan (40 ml; **1a, b**). After stirring for 10 min the mixture is decomposed and worked-up as described below.

Isolation of the Cyclic Phosphodiesters 3a, b:
The mixture is brought to pH 8 by addition of aqueous barium hydroxide and evaporated to dryness. The residue is dissolved in water/ethanol (1/1) and insoluble material is removed. Addition of an excess of anhydrous ethanol precipitates the barium salt of **3a** or **3b**. Precipitation is repeated twice and then the precipitate is washed with ethanol, diethyl ether, and dried under vacuum.

Isolation of the Cyclic Phosphodiesters 3c–g:
After the addition of water (1 ml), the mixture is evaporated to an oil under reduced pressure. The residue is dissolved in water (5 ml) and passed through a column of Dowex 50W × 8/$H^{\oplus}$/resin (~ 5 ml). The column is washed with methanol and the effluent is controlled with pH paper. The methanolic solution is evaporated to an oil and the residue triturated with dichloromethane (4 × 30 ml) to extract the phosphodiesters **3c–g**. The solvent is removed by evaporation under reduced pressure. To obtain the phosphodiesters in crystalline form, the residue is dissolved in dichloromethane (~ 20 ml); **3e** crystallises from this solvent and **3c, f, g** after addition of anhydrous diethyl ether. Compound **3d** is obtained as an oil. The corresponding benzylammonium salt can be recrystallised from methanol/diethyl ether.

Isolation of 5′-*O*-Dimethoxytritylnucleoside 2′,3′-Cyclic Phosphodiesters 5a, b:
Water (1 ml) is added and the mixture left to stand for 1 h. The solvent is removed by evaporation under reduced pressure and the residue dissolved in *n*-butanol/ethyl acetate (1/2) and washed several times with water. The organic layer is evaporated and products **5** are converted into their ammonium salts by evaporation with 5% aqueous ammonia (2 ml) and pyridine (15 ml). Then the residue is evaporated twice with anhydrous pyridine (15 ml). The residue is dissolved again in pyridine (2 ml) and mixed with anhydrous diethyl ether (300 ml) under vigorous stirring. The precipitate is centrifuged, washed with diethyl ethr and dried under vacuum. Chromatographically pure 5′-*O*-dimethoxytrityluridine 2′,3′-cyclic phosphate **(5a)** and 5′-*O*-dimethoxytrityl-*N*-benzoylcytidine 2′,3′-cyclic phosphate **(5b)**, respectively, are obtained in more than 95% yield. The identity with authentic samples prepared independently[10] has been proved by microanalysis. U.V. spectra, chromatographic mobilities on cellulose plates in isopropanol/concentrated ammonia/water (7/1/2 v/v) and ethanol/1 molar ammonium acetate (7/3 v/v) and enzymatic hydrolysis with pancreatic ribonuclease.

This work was supported by the Polish Academy of Sciences, project MR I.12.1.7.11.

Received: September 20, 1983
(Revised form): November 11, 1983

*Address for correspondence

[1] R.I. McConnell, H.W. Coover, *J. Org. Chem.* **24**, 630 (1959). S. Van der Meer, H. Pouwels, *J. Med. Chem.* **12**, 534 (1969). M. Hubert, L. Goodman, *J. Chem. Soc. Chem. Commun.* **1969**, 740.
[2] R.S. Edmundson, *Chem. Ind. (London)* **1962**, 1828.
[3] C.L. Penney, B. Belleau, *Can. J. Chem.* **56**, 2396 (1978).
[4] H.G. Khorana, G.H. Tener, J.G. Moffat, *J. Am. Chem. Soc.* **79**, 430 (1957).
[5] J.H. van Boom, J.F.M. de Rooy, C.B. Reese, *J. Chem. Soc. Perkin Trans. 1* **1973**, 2513.
[6] J.H. van Boom, P.M.J. Burgers, P. van Deursen, C.B. Reese, *J. Chem. Soc. Chem. Commun.* **1974**, 618.
[7] F. Ramirez, H. Tsuboi, H. Okazaki, J.F. Marecek, *Tetrahedron Lett.* **23**, 5375 (1982).
[8] A. Kraszewski, J. Stawiński, *Tetrahedron Lett.* **21**, 2935 (1980).
[9] J. Kumato, J.R. Cox, F.H. Westheimer, *J. Am. Chem. Soc.* **78**, 4858 (1956).
[10] R. Lohrmann, D. Söll, H. Hayatsu, E. Ohtsuka, H.G. Khorana, *J. Am. Chem. Soc.* **88**, 819 (1966).