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A CONVENIENT SYNTHESIS OF 6-, 7-, AND 8-MEMBERED CYCLIC PHOSPHODIESTERS

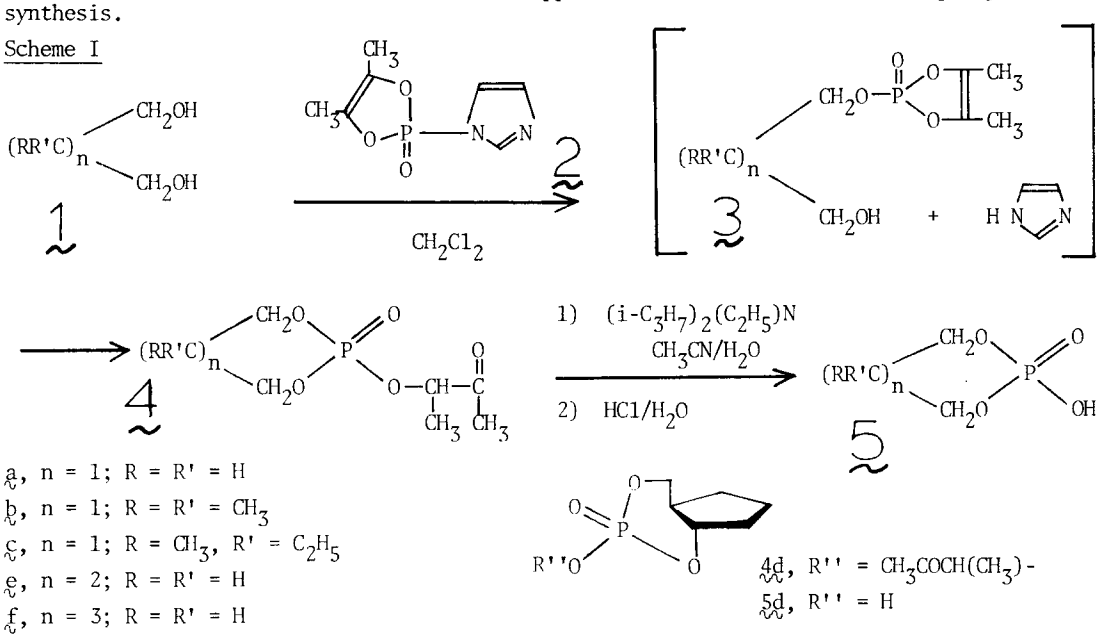
Fausto Ramirez*, Hikotada Tsuboi,
Hiroshi Okazaki and James F. Marecek
Department of Chemistry, State University of New York at Stony Brook
Stony Brook, New York 11794

Abstract

1,3-, 1,4-, and 1,5-Alkanediols are converted into the corresponding 6-, 7-, and 8-membered cyclic phosphodiesters in a two-step procedure utilizing N-(1,2-dimethylethenylenedioxyphosphoryl)imidazole (2) as the sole phosphorylating reagent.

Scheme I and Table I summarize a novel application of the CEP-method[1] of phosphodiester synthesis.

Scheme I



a, n = 1; R = R' = H
b, n = 1; R = R' = CH_3
c, n = 1; R = CH_3, R' = C_2H_5
e, n = 2; R = R' = H
f, n = 3; R = R' = H

4d, R'' = $CH_3COCH(CH_3)$-
5d, R'' = H

Separate solutions of diol 1 (10 mmol) and phosphoimidazole 2 (10 mmol) in dichloromethane (25 mL each) are added simultaneously, over a 1-hr period, to a relatively large volume (100 mL) of dichloromethane at 25° C. After an additional hr, the solution is extracted with dilute HCl, washed with water, dried and evaporated to yield the triester 4, which is purified by molecular distillation. The triester 4 (10 mmol) is dissolved in acetonitrile/water (1/2 v/v, 100 mL) containing diisopropylethylamine (20 mmol). The solution is kept 10-12 hr at

70° C and the acetonitrile evaporated. The aqueous solution is decanted from small amounts of acetoin polymers and treated with sodium carbonate (20 mmol). The solution is extracted with dichloromethane. The aqueous phase is acidified with dilute HCl (to pH ~ 1) and evaporated. The residue is triturated with dichloromethane to extract the phosphodiester 5. Evaporation and recrystallization (Table I) yields the pure sample of acid 5. Racemic 1d was used.

Table I. Properties of Cyclic Phosphodiesters, 5, and Their 3-Oxo-2-butyl Ester Precursors, 4.

Compd. No.	Ring Size	M.P.°, or B.P.° (mm) [a]	Yield %	$\delta^{31}P$ [b]	Molecular Formula	Calcd., % C	H	P	Found, % C	H	P
4a	6	95(0.1)	70	-8.0	$C_7H_{13}O_5P$	40.39	6.30	14.88	40.50	6.40	14.78
4b	6	95(0.05)	90	-8.5	$C_9H_{17}O_5P$	45.76	7.25	13.11	45.57	7.08	13.12
4c	6	95(0.05)	85	-8.1	$C_{10}H_{19}O_5P$	48.00	7.65	12.38	48.28	7.76	12.20
4d	6	105(0.05)	70	-7.5[c]	$C_{10}H_{17}O_5P$	48.39	6.90	12.48	48.60	6.92	12.24
4e	7	58-59[d]	82	+2.3	$C_8H_{15}O_5P$	43.25	6.81	13.94	43.11	6.82	13.87
4f	8	95(0.05)	43	-2.1	$C_9H_{17}O_5P$	45.76	7.25	13.11	45.90	7.39	12.92
5a	6	101-103[e,f]	77	-3.7	$C_3H_7O_4P$	26.10	5.11	22.43	25.99	5.00	22.36
5b	6	174-175[g,h]	80	-4.0	$C_5H_{11}O_4P$	36.15	6.67	18.65	36.28	6.80	18.40
5c	6	138-140[g]	74	-3.6	$C_6H_{13}O_4P$	40.01	7.27	17.19	39.93	7.26	17.27
5d	6	141-142[g]	68	-2.4	$C_6H_{11}O_4P$	40.46	6.22	17.39	40.64	6.38	17.49
5e	7	129-131[i,j]	86	+4.8	$C_4H_9O_4P$	31.59	5.96	20.37	31.44	5.81	20.49
5f	8	79-80[k]	82	0.0	$C_5H_{11}O_4P$	36.15	6.67	18.65	35.96	6.59	18.59

[a]B.p. = bath temp. in molecular distillation; [b]From 85% H_3PO_4 = 0; positive values are down field from the reference; triesters 1 in $CDCl_3$, diesters 2 in D_2O (except 2f in $CDCl_3$); [c]A minor signal at -5.1 is attributed to diastereomer; cf. ref. 5; [d]After sublimation at 0.05 mm (bath at 95° C); [e]Crystallized from dichloromethane/ether; [f]Lit. 102-102.5°, ref 3. [g]Crystallized from acetonitrile; [h]Lit. 174-176°, ref. 4; [i]Crystallized from dichloromethane; [j]Lit. 128-129°, ref. 6; [k]Crystallized from benzene-hexane.

In terms of simplicity and product yield, this application of the CEP-Imidazole (2) procedure[2] is competitive with others available for the same purpose[3-7].

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References

1. F. Ramirez and J. F. Marecek, Acc. Chem. Res. 11, 239 (1978).
2. F. Ramirez, J. S. Ricci, H. Okazaki, K. Tasaka and J. F. Marecek, J. Org. Chem., 43, 3635 (1978).
3. H. G. Khorana, G. M. Tener, R. S. Wright and J. G. Moffatt, J. Am. Chem. Soc., 79, 430 (1957).
4. R. L. McConnell and H. W. Coover, J. Org. Chem., 24, 630 (1959).
5. F. Ramirez, P. Stern, S. Glaser, I. Ugi and P. Lemmen, Phosphorus, 3, 165 (1973).
6. J. A. Gerlt, F. H. Westheimer and J. M. Sturtevant, J. Biol. Chem., 250, 5059 (1975).
7. C. L. Penney and B. Belleau, Can. J. Chem., 56, 2396 (1978).

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