(14) M. Colapietro, A. Vaciago, D. C. Bradley, M. B. Hursthouse, and I. F. Rendall, *J. Chem. Soc., Dalton Trans.*, 1052 (1972).
(15) D. G. Bilght and D. L. Kepert, *Inorg. Chem.*, **11**, 1556 (1972).
(16) B. L. Edgar, D. J. Duffy, M. C. Palazzotto, and L. H. Pignolet, *J. Am. Chem. Soc.*, **95**, 1125 (1973), and references therein.
(17) C. E. Holloway and M. H. Gitlitz, *Can. J. Chem.*, **45**, 2659 (1967).

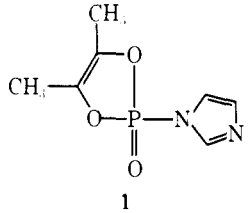
Robert C. Fay,* David F. Lewis, John R. Weir
Department of Chemistry, Cornell University
Ithaca, New York 14853
Received August 1, 1975

One-Flask Synthesis of Unsymmetrical Phosphodiesters. Selective Amine Catalysis of Phosphorylations of Primary vs. Secondary Alcohols

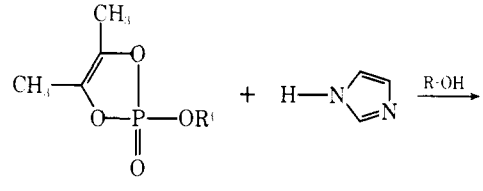
Sir:

We wish to describe a new procedure for the direct conversion of two different alcohols into an unsymmetrical phosphodiester without the isolation of any intermediate ("one-flask" reaction).

An acetonitrile solution of R^1OH is added to a solution of *N*-(1,2-dimethylethenylenedioxyphosphoryl)imidazole[1] (**1**) in the same solvent, and the mixture is stirred for 45 min (20°, 0.6 *M*). R^2OH is introduced, and the solution is stirred at 20° for periods which vary with the structure of the alcohols; reaction times are conveniently ascertained by ^1H NMR spectrometry. The solution is diluted with acetonitrile, mixed with twice its volume of water (final molarity ~0.1), treated with 2 mol equiv of triethylamine, and stirred at 70° for ca. 10 hr. The acetonitrile is evaporated, and the aqueous solution is treated with sodium carbonate, extracted with dichloromethane to remove by-products, acidified, and reextracted with dichloromethane. The phosphodiester, **4**, is obtained in high degree of purity and is converted into a crystalline amine salt, **4a**, for characterization.



1



2

$$(R^1O)(R^2O)P(O)OCH(CH_3)COCH_3 \xrightarrow{H_2O}$$

3

$$(R^1O)(R^2O)P(O)(OH) + HOCH(CH_3)COCH_3$$

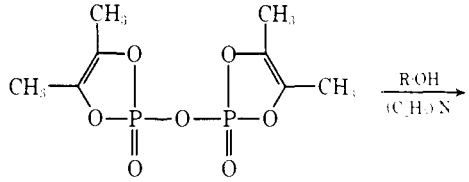
4

The following dicyclohexylammonium dialkyl phosphates,[2] **4a**, were isolated in 75–80% yield (based on R^1OH) by the above procedure: $(C_2H_5)_2CH$, $(CH_3)_2CHCHCH_2$; (±)3-*p*-menthanyl, $C_6H_5CH_2$; c-C_6H_{11}, $(CH_3)_2CH$; c-C_5H_9, $(CH_3)_2CHCHCH_2$.[3,4]

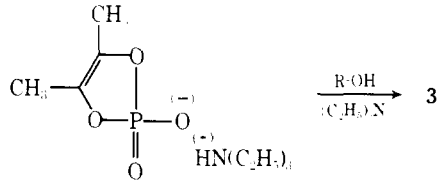
The phosphorylimidazole, **1**, can also be utilized for the conversion of the two alcohols into the acyclic triester, **3**, in one laboratory operation; **3** is then hydrolyzed[4a] to the diester, **4**, with or without an intervening purification step. The reaction is carried out as in the first procedure, but in dichloromethane solution; the latter is extracted with dilute hydrochloric acid to yield the virtually pure triester, **3**. The following dialkyl(1-methylacetonyl) phosphates,[2] **3**, were obtained in 92–96% yield (based on R^1OH): $(C_2H_5)_2CH$, $C_6H_5CH_2$; (±)3-*p*-menthanyl, $C_6H_5CH_2$; c-C_6H_{11}, $(CH_3)_2CH$; $[(CH_3)_2CH]_2CH$, $C_6H_5CH_2$; c-C_5H_9, $(CH_3)_2CHCH_2$.[3]

The syntheses are possible because alcohols react much faster with the phosphorylimidazole, **1**, than with the alkyl cyclic enediol phosphates, **2**. Imidazole[5] autocatalyzes the reaction of R^1OH with **1**, and is also an excellent catalyst for the reactions of primary and secondary alcohols (R^2OH) with the cyclic triesters, **2**. For example, when R^2 = $(CH_3)_2CHCH_2$, and R^1 = c-C_5H_9, $t_{1/2}$ for the phosphorylation is reduced from 8 hr to 2 min in 0.2 *M* $CDCl_3$, and from 12 hr to 30 min in 0.2 *M* CD_3CN by imidazole (equimolar amounts of reagents, at 25°). The rates of phosphorylation by the cyclic triesters **2** decrease significantly as the polarity of the solvent, and the size of R^1 and R^2, increase; therefore, the imidazole effect is essential for the success of the syntheses.

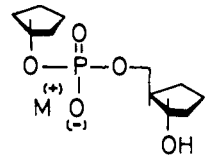
Triethylamine is an effective catalyst for the reaction of alcohols with the cyclic triesters, **2**, and the following procedure can also be used to prepare the acyclic triesters, **3**, in one flask. A dichloromethane solution of R^1OH containing 1 mol equiv of triethylamine is added to a solution of di(1,2-dimethylethenylene) pyrophosphate[4a] (**5**) in the same solvent, and the mixture is stirred for 30 min (20°, 0.6 *M*). R^2OH, together with 1 mol equiv of triethylamine, is introduced, and the mixture is stirred for the appropriate period of time (ca. 10 hr at 20°, in 0.5 *M* solutions, when R^1 = secondary alkyl and R^2 = primary alkyl). The dichloromethane solution is extracted with hydrochloric acid and sodium carbonate to yield the virtually pure acyclic triester **3**. The following triesters **3** were obtained in 92–95% yield (based on R^1OH): c-C_5H_9, $(CH_3)_2CHCH_2$[4a]; c-C_5H_9, $C_6H_5CH_2$.[4a] Without triethylamine these phosphorylations require ca. 30 hr for completion.[4a]



5



Triethylamine catalyzes the reactions of primary alcohols (R^2OH) with the cyclic triesters **2**, *but it does not catalyze the reactions of secondary alcohols with* **2**. This remarkable specificity can be exploited for the synthesis of compound **6** (M = $C_6H_{11}NH_3^{(+)}$) from cyclopentanol (R^1OH) and unprotected *trans*-2-hydroxymethylcyclopentanol (R^2OH). The selectivity in the phosphorylation of the pri-

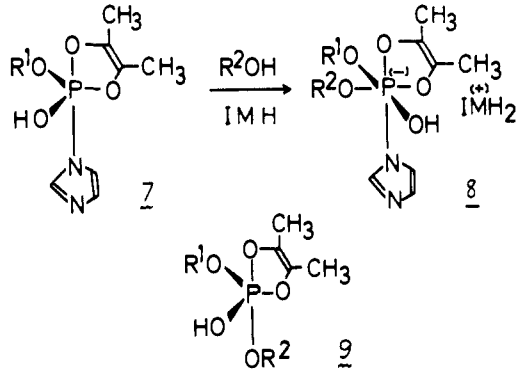


6

mary vs. the secondary hydroxyl functions of the diol is 98:2; the previous synthesis[4a] of **6**, without triethylamine, involved a 90:10 selectivity.

The best results in these procedures are obtained when the bulkier alcohol is introduced first (R^1OH), whenever possible. Although many alcohol pairs have been used successfully, some combinations of steric and electronic features in R^1 and R^2 result in the formation of some symmetrical acyclic triesters. Another limitation is the formation of some alkyl (1-methylacetonyl) phosphates in the hydrolysis of **3**.

We speculate that the amine catalysis of the phosphorylation involves intermediates with penta- and hexacoordinate[6] phosphorus, **7** and **8**, the former being involved in the rate-controlling step. Decomposition of **8** generates the phosphorane intermediate **9**, which is assumed to be formed in the uncatalyzed reaction. Triethylamine could act in



the same manner, but via dipolar ions[6] analogous to **7** and **8**. The selectivity and the lower efficiency of triethylamine (pK_B = 3.0) vs. imidazole (pK_B = 6.9) may be due in part to the higher steric requirements of the former; quinuclidine (pK_B = 2.9), in fact, resembles imidazole, rather than triethylamine, in catalytic pattern. Tetramethylguanidine (pK_B = 0.4) is also an effective catalyst in these reactions. The presence of histidine, arginine, and lysine residues in hydrophobic active sites of enzymes that catalyze reactions of phosphates could facilitate the addition of nucleophiles to tetracoordinate phosphorus by similar mechanisms.

The techniques described here, and others recently introduced,[4] provide considerable flexibility in approaches to complex biological phosphodiesters, such as oligonucleotides and phospholipids; the latter, in high degree of purity, are required for studies on membrane structure.

References and Notes

(1) F. Ramirez, H. Okazaki, and J. F. Marecek, *Synthesis*, 637 (1975).
(2) Elemental analyses and integrated ^1H NMR signals of new compounds agree with expected values.
(3) Compound previously made by a different procedure (ref 4a).
(4) (a) F. Ramirez, J. F. Marecek, and I. Ugi, *J. Am. Chem. Soc.*, **97**, 3809 (1975); (b) F. Ramirez and J. F. Marecek, *J. Org. Chem.*, **40**, 2849 (1975).
(5) (a) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms", W. A. Benjamin, New York, N.Y., 1966: Vol. 1, p 46; Vol. 2, pp 29, 80; (b) P. Haake and G. Allen, *J. Am. Chem. Soc.*, **95**, 8080 (1973); (c) R. Blakeley, F. Kerst, and F. H. Westheimer, *ibid.*, **88**, 112 (1966).
(6) F. Ramirez, V. A. V. Prasad, and J. Marecek, *J. Am. Chem. Soc.*, **96**, 7269 (1974), and references therein.
(7) Research supported by Grant GM-20672 from the Cancer Institute of the National Institutes of Health, and, partially, by Grant 7136 from the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Fausto Ramirez,*[7] James F. Marecek, Hiroshi Okazaki
Department of Chemistry
State University of New York at Stony Brook
Stony Brook, New York 11794
Received July 10, 1975

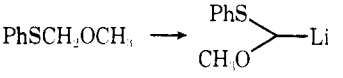
New Synthetic Methods. A Ring Expansion Approach to α-Methylene δ-Lactones

Sir:

Attention has been focused on the synthesis of α-methylene γ-butyrolactones because of their importance as a structural unit of many antitumor agents.[1] The presence of an α-methylene δ-lactone in the growth inhibitory elemanolide sesquiterpenes vernolepin, vernodalin, and vernomenin[2] has led to several approaches to this system too,[1,3] but most commonly by cleavage of cycloalkanone rings. Our interest in these terpenes, as well as related biologically important natural products like pentalenolactone[4] and the quassinoids,[5] led us to consider new approaches based upon the ring expansion of the easily accessible γ-butyrolactones. This work delineates three such approaches as well as demonstrates the utility of lithiated methoxymethyl phenyl thioether as an acyl anion equivalent.[6]

The γ-butyrolactone **1a** was readily available by the metal hydride reduction of the Diels–Alder adduct of 2,3-dimethylbutadiene and maleic anhydride[7] (see Scheme I). Methylation of the corresponding enolate utilizing lithium diisopropylamide in THF (−78°) and methyl iodide[8] provided **1b**, mp 30–31°.[9] Addition of bis(phenylthio)methyllithium[10] to **1a** in THF at 0° caused mainly enolization, but **1b** gave the adduct **2b**[9] (X = PhS) quantitatively. Conversion of the latter to **3b**[9] was effected with silver nitrate and *N*-chlorosuccinimide in methanol buffered with collidine at 0° (40%).[11a] *p*-Toluenesulfonic acid monohydrate (PhH, 50°) rearranged **3b** to **4b**,[9] mp 74–75° (ir 1735 cm^{-1}; NMR two methines at δ 4.30 and 4.34 and two CH_3O at δ 3.36 and 3.39, 36%). Methylenation to **5b** via the Wittig reaction (DME, room temperature), hydrolysis (5% aqueous HCl:THF 1:4, room temperature), and oxidation (manganese dioxide, methylene chloride, room temperature) completed the sequence in 54% overall yield of pure isolated product[9] (**6b**, ir 1733 cm^{-1}; NMR CH_2O at δ 4.24 and $=CH_2$ at δ 5.54 and 6.38).

The use of methoxyphenylthiomethyllithium (**7**), available by treatment of methoxymethyl phenyl thioether[12] with *n*-butyllithium in THF at −30°, proved superior.[13] It added in 88% yield to **1a** and in quantitative yield to **1b** to give **2a**[9] and **2b**[9] (X = OCH_3), respectively. Mercuric chloride–red mercuric oxide[11] in methanol at room temperature transacetalized the latter to give **3b** (60%) identical with the material obtained by the previous route.



7

Addition of **7** to **1d**[9] (mp 43–47°), available from **1c** by a sequence analogous to that for **1b**,[7] gave **2d**[9] (X = OCH_3) in 91% yield. Heating a solution of the latter in methanol containing iodine at 50° gave **3d**[9] in 71% yield.[14] Ring expansion as above gave the key tetrahydropyran-3-one (**4d**)[9] in 69% yield (ir 1735 cm^{-1}; NMR two methines at δ 4.32 and 4.35 and two methoxyls at δ 3.39 and 3.37). Conversion of **4d** to **6d**[9] proceeded in identical fashion to the preparation of **6b** in an overall yield of 56% (**6d**, ir 1733 cm^{-1}; NMR CH_2O at δ 4.20 and $=CH_2$ at δ 5.52 and 6.31).

An alternative approach makes use of the Pummerer reaction[15] as the key step. Dimsyllithium, prepared by the addition of *n*-butyllithium to a solution of DMSO in THF,[16] adds to **1d** in THF at 10°. Treatment of this adduct **8**[9] with iodine in refluxing methanol gives **3d** which, when subjected to a catalytic amount of TsOH in benzene at 50°, is converted into the key tetrahydropyran-3-one (**4d**) exclu-