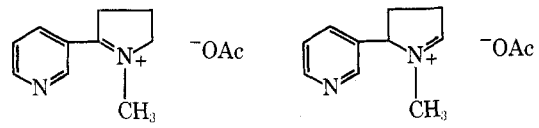
formation of cotinine, as well as varying amounts of 5′-cyanonicotine, probably occurs by way of **9**. If this is indeed



8 **9**

the case, then not only must one be concerned with the apparent preferential formation of **9**, but also with its subsequent facile oxidation.

Acknowledgments. We would like to express our thanks to Dr. Jerry Whidby for his assistance with NMR spectra and to Dr. Jeffrey Seeman for helpful discussions. We would also like to thank Dr. P. J. Murphy for his cooperation.

References and Notes

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(2) We thank Dr. Murphy for providing a detailed description of his experimental procedure.
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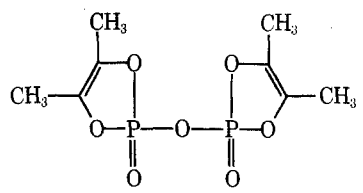
One-Flask Phosphorylative Coupling of Two Different Alcohols

Summary. Aryl (1,2-dimethylethenylenedioxy) phosphates are effective reagents for the "one-flask" conversion of two different alcohols, R^1OH and R^2OH, into dialkylacetoinyl phosphates, $(R^1O)(R^2O)P(O)[OCH(CH_3)COCH_3]$, which are readily hydrolyzed to unsymmetrical dialkyl phosphates, $(R^1O)(R^2O)P(O)(OH)$.

Sir: We would like to describe experiments of practical and theoretical importance for the synthesis of unsymmetrical dialkyl phosphates, $(R^1O)(R^2O)P(O)(OH)$, and for studies on the mechanism and the biological functions of phosphate esters.

Crystalline aryl (1,2-dimethylethenylenedioxy) phosphates, e.g., the known[1,2] *p*-nitrophenyl ester (**2**) and the new[3] pentafluorophenyl ester (**3**, mp 54–56°; $\delta_{^{31}P}$ −8.0 ppm, τ 7.98, both in $CDCl_3$) are obtained in 90–95% yield from the reaction of phenols with oxybis(1,2-dimethylethenylenedioxyphosphoryl)[1,2] (**1**).



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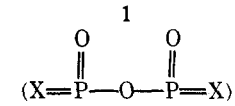


The reagents, X=P(O)OAr [**2** (Ar = p-$NO_2C_6H_4$) and **3** (Ar = C_6F_5)], are capable of converting two different alcohols, R^1OH and R^2OH, into dialkylacetoinyl phosphates, $(R^1O)(R^2O)P(O)[OCH(CH_3)COCH_3]$, without isolation of intermediates ("one-flask" reactions), in high yields by simple isolation techniques and within short periods of time; see Table I. The hydrolysis has already been described.[2]

$$(R^1O)(R^2O)P(O)[OCH(CH_3)COCH_3] + HO^- \rightarrow (R^1O)(R^2O)P(O)O^- + CH_3COCH(CH_3)OH$$

The synthesis consists of two steps (1 and 2), both of which are effectively catalyzed by salts of the phenols, e.g., $ArO^-(C_2H_5)_3NH^+$. The catalyst is generated by the introduction of the amine together with the first alcohol, R^1OH, since the phenol is a by-product of the reaction 1.

Table I
One-Flask Phosphorylative Coupling of Two Different Alcohols

No.	R^1 in R^1OH	R^2 in R^2OH	Yield of triester,[b] %
		X=P(O)OC$_6$H$_4$NO$_2$-*p*[a]	
1	c-C_5H_9	*i*-C_4H_9	93
2	c-C_5H_9	$C_6H_5CH_2$	91
3	c-C_5H_9	CH_2=$C(CH_3)CH_2CH_2$	93[c]
		X=P(O)OC$_6$F$_5$[d]	
4	c-C_5H_9	$BrCH_2CH_2$	97
5	$(CH_3)_3CCH_2$	*i*-C_4H_9	98[e]
6	c-C_5H_9	*i*-C_4H_9	90

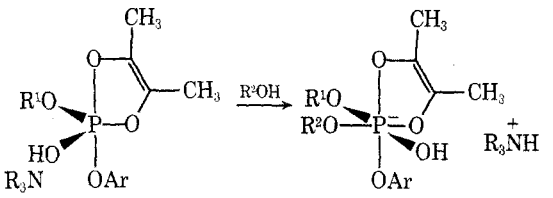
[a] A dichloromethane solution containing R^1OH (1 mol equiv) and triethylamine (1 mol equiv) was added dropwise in 5 min to a stirred dichloromethane solution of X=P(O)$C_6H_4NO_2$-*p* (1 mol equiv; 0.4–0.6 *M*) at 25°. After 15–30 min at 25°, a dichloromethane solution of R^2OH was added dropwise in ~5 min to X=P(O)OR^1. The reaction was allowed to proceed for ~1–2 hr at 25° (0.3–0.5 *M*). The solution was diluted with dichloromethane to ~0.2 *M* and was repeatedly extracted with cold, dilute aqueous alkali (Na_2CO_3 or NaOH) to remove the *p*-nitrophenol. The organic layer was washed first with 5% hydrochloric acid and then with water, dried over Na_2SO_4, filtered, and evaporated in vacuo to yield the dialkylacetoinyl phosphate. The triester was hydrolyzed to the dialkyl phosphate by known procedures.[2] [b] Crude triester, based on R^1OH. Purity >98% based on ^1H NMR spectrometry (in $CDCl_3$) and on conversion to amine salt of diester.[2] [c] Triester purified by short-path distillation (at 0.05 mm, bath temp ~100°), yield 81%. [d] As in the previous procedure (footnote *a*) except using X=P(O)OC_6F_5. The reaction of eq 2 was allowed to proceed for ~5 hr at 25° (0.5 *M*). [e] Triester purified by short-path distillation (at 0.10 mm, bath temp ~95°), yield 94%.

$$X{=}P(O)OAr + R^1OH \rightarrow X{=}P(O)OR^1 + ArOH \quad (1)$$

$$X{=}P(O)OR^1 + R^2OH \rightarrow CH_3COCH(CH_3)OP(O)(OR^1)(OR^2) \quad (2)$$

Alcohol R^1OH reacts much faster with $X{=}P(O)OAr$ than with the product $X{=}P(O)OR^1$, and, therefore, the symmetrical phosphates, $CH_3COCH(CH_3)OP(O)(OR^1)_2$, are not formed in any appreciable extent. Moreover, the phenols with electron-withdrawing substituents are much less reactive than alcohols toward both $X{=}P(O)OAr$ and $X{=}P(O)OR^1$, and hence the corresponding aryl phosphates are not produced.

The effective catalysis of reaction 2 by the phenol salts [e.g., a factor of ~140 in the reaction of i-C_4H_9OH with $X{=}P(O)O$-c-C_5H_9 by p-$N_2C_6H_4{}^-O(C_2H_5)_3NH^+$ in 0.2 M $CDCl_3$ at 25°] could involve 5- and 6-coordinate phosphorus intermediates[4] **4** and **5**; the latter, **5**, is analogous to



4 **5**

compounds isolated from the reaction of stable pentaoxyphosphoranes, phenols and tertiary amines.[4,5]

These results may have a bearing on the mechanism of action of enzymes that catalyze the reactions of phosphates and pyrophosphates, since the presence of tyrosine, lysine, arginine, and histidine residues could facilitate the addition of nucleophiles to 4-coordinate phosphorus by analogous mechanisms.

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(2) F. Ramirez, J. F. Marecek, and I. Ugi, *J. Am. Chem Soc.*, **97**, 3809 (1975).
(3) The elemental analyses of all new compounds agree with the calculated values. ^1H NMR signals are in parts per million vs.TMS = 10 (τ); ^{31}P NMR signals are in parts per million vs. H_3PO_4 = 0.
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Synthesis of DL-γ-Carboxyglutamic Acid Derivatives[1]

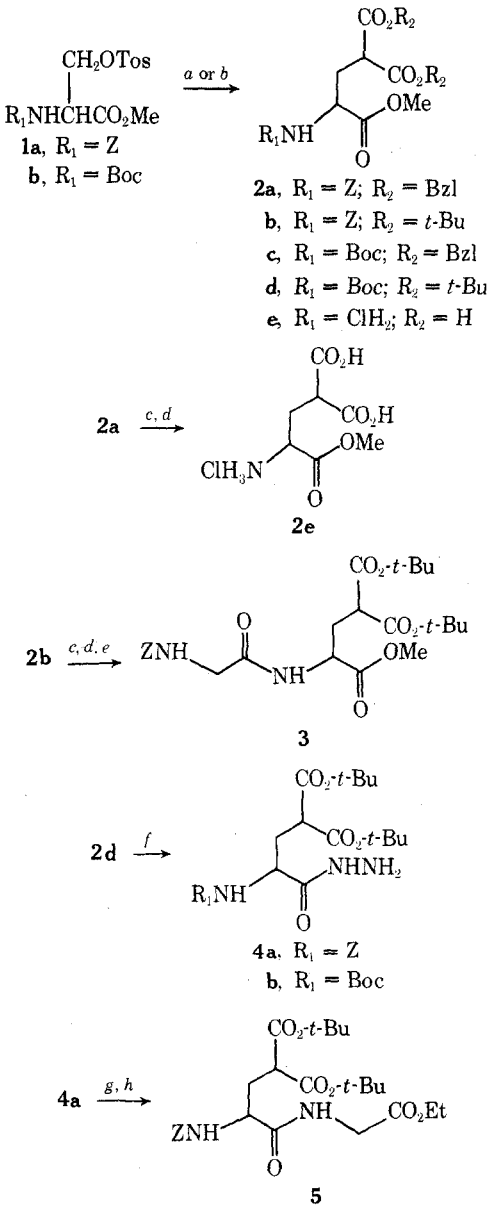
Summary: A method of synthesis of DL-γ-carboxyglutamic acid derivatives has been developed involving the reaction between *O*-tosyl serine derivatives and esters of malonic acid.

Sir: We wish to report the synthesis of derivatives of γ-carboxyglutamic acid (Gla),[1b] a new amino acid recently identified in prothrombin[2] and factor X,[2e] two of the four vitamin-K-dependent blood clotting factors. The success of the preparation of side chain protected cysteine[4,5] derivatives by displacement reactions on corresponding serines and alanines, and the DL-glutamic acid synthesis of Wieland et. al.[6] suggested the sequence of reactions outlined below for the preparation of Gla derivatives.[7]

Compounds **2a** and **2d** were prepared by the tosylate displacement[8] shown; yields and physical data are listed in Table I. Hydrolysis of aliquots of each reaction mixture followed by amino acid analysis[9] indicated the presence of glutamic acid in all cases.

Attempts to achieve SN2 displacement of the tosylate group were unsuccessful under a variety of conditions.[10] *Rather, the reaction seems to proceed in a stepwise fashion:* elimination to a dehydroalanine derivative, followed by conjugate addition of the malonate anion to the α,β-unsaturated ester. The optical rotations for the Gla derivatives obtained via this procedure were usually between +1 and +2°, indicating probable racemization. This was confirmed by acidic hydrolysis of **2c** to glutamic acid, which was shown to be totally racemized.

That appropriately protected Gla derivatives could be selectively deprotected and incorporated into peptides at either the α-amino or the α-carboxyl positions was shown



1a, $R_1 = Z$
b, $R_1 = Boc$

2a, $R_1 = Z$; $R_2 = Bzl$
b, $R_1 = Z$; $R_2 = t$-Bu
c, $R_1 = Boc$; $R_2 = Bzl$
d, $R_1 = Boc$; $R_2 = t$-Bu
e, $R_1 = ClH_2$; $R_2 = H$

2e

3

4a, $R_1 = Z$
b, $R_1 = Boc$

5

[a] $Li^+ {}^-CH(CO_2R_2)_2$, THF. [b] $Na^+ {}^-CH(CO_2R_2)_2$, DMF. [c] H_2, Pd/C, HOAc. [d] HCl/Et_2O. [e] Z-Gly-OH, THF, isobutyl chloroformate, *N*-methylmorpholine. [f] Hydrazine hydrate, methanol, 3 hr. [g] HCl/THF, *n*-butyl nitrite, −23°, 15 min. [h] Et_3N, H-Gly-OEt, THF, 0°, 2.5 hr.