white crystalline solid: mp 148 °C; NMR δ 1.69 (s, 3 H), 2.20 (s, 3 H), 2.85 (s, 1 H), 6.13 (d, 2 H, J = 8.4 Hz), 6.95 (d, 2 H, J = 8.4 Hz), 7.33 (s, 5 H); IR (KBr) 1781, 1719 cm^{-1}. Anal. Calcd for $C_{19}H_{16}O_2NCl$: C, 70.04; H, 4.95; N, 4.30. Found: C, 70.15; H, 4.96; N, 3.97.

Preparation of Dimethyl 1-Chloro-2-isopropylmaleate (34Z). To a solution of **43** (30.0 mmol) in ether (30 mL) was added dropwise a solution of 1 (ca. 31.5 mmol) in ether (70 mL) at 0 °C. After 0.5 h, 100 mL of benzene was added to the reaction mixture and then ether was removed from the solution and the solution was refluxed for 30 min. Removal of solvent left an oil which was chromatographed on silica gel. Elution with ether-hexane (10:90) gave 1-chloro-2-isopropylmaleic anhydride (**45**) (76%): bp 104-106 °C (6 mmHg); NMR δ 1.35 (d, 6 H, J = 7.1 Hz), 3.09 (hep, 1 H, J = 7.1 Hz); IR (film) 1862, 1832, 1775, 1633 cm^{-1}. Anal. Calcd for $C_7H_7O_3Cl$: C, 48.15; H, 4.04. Found: C, 48.33; H, 4.32. **45** (9.99 mmol) was dissolved in methanol (40 mL) and refluxed for 5 h. Removal of methanol left an oil, which was dissolved in dichloromethane (10 mL) and treated with diazomethane (ca. 15 mmol) in ether. After few minutes, solvent was removed under reduced pressure and the residue was chromatographed on silica gel. Elution with ether-hexane (10:90) gave **34Z** (89%): bp 121.5-122.5 °C (6 mmHg); NMR δ 1.15 (d, 6 H, J = 6.9 Hz), 3.18 (hep, 1 H, J = 6.9 Hz), 3.82 (s, 3 H), 3.83 (s, 3 H); IR (film) 1735, 1610 cm^{-1}. Anal. Calcd for $C_9H_{13}O_4Cl$: C, 48.99; H, 5.94. Found: C, 48.91; H, 6.03.

Preparation of Dimethyl 1-Chloro-2-(1-phenethyl)maleate (36Z). To a solution of chloromaleic anhydride (**43**) (30.0 mmol) in ether (30 mL) was added dropwise a solution of 1-phenyldiazoethane (ca. 31.5 mmol) in ether (45 mL) for 15 min and was kept at 0 °C for 1 h. The precipitate was filtered and washed with cold ether/pentane, giving **47Z** (18%), which decomposed gradually at room temperature. **47Z** was refluxed in benzene (20 mL) for 30 min and then removal of solvent left an oil, the NMR spectrum of which showed 1:1 mixture of **48** and **49**. Elution with benzene-hexane (1:1) gave 1-chloro-2-(1-phenethyl)maleic anhydride (**48**) (39%): mp 52.5-53.5 °C; NMR δ 1.74 (d, 3 H, J = 7.2 Hz), 4.24 (q, 1 H, J = 7.2 Hz), 7.33 (s, 5 H); IR (KBr) 1860, 1796, 1634 cm^{-1}. Anal. Calcd for $C_{12}H_9O_3Cl$: C, 60.90; H, 3.83. Found: C, 60.66; H, 3.87. A solution of **48** (1.67 mmol) in methanol (40 mL) was refluxed for 5 h. Removal of methanol left an oil, which was dissolved in dichloromethane (10 mL) and reacted with diazomethane (2.5 mmol) in ether. After a few minutes, solvent was removed under reduced pressure and the residue was chromatographed on silica gel. Elution with benzene/hexane (1:1) gave **36Z** (96%): NMR δ 1.54 (d, 3 H, J = 7.2 Hz), 3.56 (s, 3 H), 3.75 (s, 3 H), 4.37 (q, 1 H, J = 7.2 Hz), 7.26 (s, 5 H); IR (film) 1737, 1608 cm^{-1}. Anal. Calcd for $C_{14}H_{15}O_4Cl$: C, 59.47; H, 5.35. Found: C, 59.36; H, 5.36.

Photochemical Isomerization of Dimethyl 1-Chloro-2-(1-phenethyl)maleate (36Z). A solution of **36Z** (1.48 mmol) in benzene (130 mL) was irradiated under nitrogen with a low pressure mercury lamp at room temperature for 1 h. Solvent was removed under reduced pressure, leaving an oil, the NMR spectrum of which showed a mixture of **36Z** and dimethyl 1-chloro-2-(1-phenethyl)fumarate (**36E**) (δ 1.56 (d, 3 H, J = 7.2 Hz), 3.53 (s, 3 H), 3.79 (s, 3 H), 4.75 (q, 1 H, J = 7.2 Hz), 7.29 (s, 5 H)).

Reactions of Carboxylic Acids with "Phosphonium Anhydrides"

James B. Hendrickson* and Md. Sajjat Hussoin

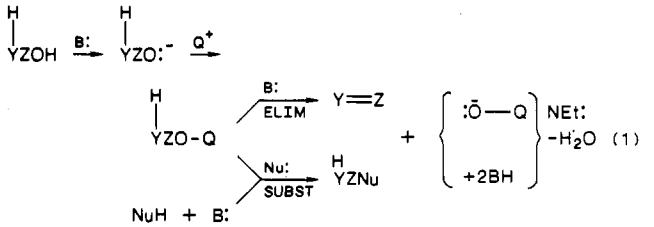
Edison Chemistry Laboratories, Brandeis University, Waltham, Massachusetts 02254

Received August 31, 1988

General considerations are outlined for a reagent to extract oxygen from organic molecules by an equivalent of dehydration. Reagents, $(R_3P^+)_2O$, $2OTf^-$, were created for the purpose and subjected to a preliminary study. They were found to convert carboxylic acids readily and rapidly to anhydrides, esters, amides, amidines, benzimidazoles, and cyclic aryl ketones in good yields.

We wished to design a general reagent for the activation of oxygen in organic molecules to effect its removal in an isohypsic manner.[1] The synthetic importance of such a reagent lies in the ubiquitous presence of oxygen in common functional groups and the fact that many important organic transformations involve loss of water. Although many such reagents exist,[2] they are commonly either flawed in some aspect or narrow in their range of activity. The features we sought were (1) selectivity for oxygen; (2) enough reactivity for rapid reaction at moderate temperatures; (3) no potential for redox reactions; (4) no nucleophiles present or formed to create competitive substitution reactions; (5) utility in a range of common solvents and pH values.

The key to a general view of the utility of such a reagent is the summary of eq 1, which shows the reagent Q bonding first as electrophile to an oxygen atom electron pair. This in turn creates a good leaving group of that oxygen atom for elimination or nucleophilic substitution reactions. The



net effect is removal of the elements of H_2O from the reactants.

The design of the ideal reagent requires an element that forms an unusually strong bond to oxygen so that its initial bond formation and its final removal of the oxygen as R-O:$^-$ will be thermodynamically favored. Thus, the central work of the reagent may be seen as the extraction of the oxygen atom from the molecule, with two protons released in its wake to some base. The strongest bond oxygen forms is its bond to phosphorus in the phosphoryl group. Furthermore, although sulfur forms strong bonds also, it is more prone to oxidation-reduction changes, which can create unwanted side reactions (Martin's sulfurane reagent[3] is a powerful dehydrating reagent based on sulfur, which also initiates oxidation-reduction). We

(1) A preliminary report has appeared: Hendrickson, J. B.; Hussoin, S. M. *J. Org. Chem.* **1987**, *52*, 4137. Isohypsic ("equal level") indicates neither oxidative nor reductive, cf. Hendrickson, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 6847.

(2) Castro, B. R. *Org. React.* **1983**, *29*, 1. *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: New York, 1979.

(3) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003.

0022-3263/89/1954-1144$01.50/0

Table I. Acid Dehydrations[a]

entry	starting acid	product	% yield (mp, °C)	ref
1	cyclohexanecarboxylic	anhydride	88 (oil)	
2	*p*-toluic	anhydride	93 (92–3)	14
3	phenylacetic	anhydride	90 (oil)	
4	4-phenylbutanoic	anhydride	85 (45–6)	15
5	diphenylacetic	diphenylketene	72 (oil)[b]	7

[a] Conditions: 2:1:2:2 molar ratios of Ph_3PO:Tf_2O:RCOOH:Et_3N in $C_2H_4Cl_2$/25 °C/15 min. [b] 100% by IR; 72% isolated by tituration with hexane.

focused on a phosphorus–based reagent both because of the unusual strength of the P=O bond and also to avoid any redox side reactions.

Phosphonium Anhydride Reagents. These considerations led us to the set of "phosphonium anhydrides", $R_3P^+O^+PR_3$, as triflate salts. We report here preliminary studies on their reactions activating -COOH. The reagents are made from phosphoryl compounds with triflic anhydride[4] as in eq 2, and activation of carboxyl is presumably initiated as in eq 3. The reagents form instantly at −78

$$2R_3P{=}O + Tf_2O \rightarrow [R_3P^+OTf + R_3PO] \rightarrow R_3P^+O^+PR_3,\ 2OTf^- \quad (2)$$

$$R'COOH + R_3P^+O^+PR_3 \rightarrow R'COO^+PR_3 + R_3PO + H^+ \quad (3)$$

°C or room temperature on mixing in methylene chloride, partially precipitating as white crystalline solids, which are commonly used directly in situ owing to their very hygroscopic nature. As the activation of oxygens (eq 1) generates triflic acid, the acidity of the medium can be moderated with added nonnucleophilic bases if desired. The main reagent has been made with triphenylphosphine oxide (R = C_6H_5) and used with triethylamine, but, both to provide internal base and to facilitate removal of the R_3PO formed (eq 3), we have also used $(C_6H_5)_2PON(CH_2CH_2)_2NCH_3$, mp 109 °C, made from diphenylphosphinic chloride and *N*-methylpiperazine. With this reagent the returned phosphinamide, as its triflate salt, extracts completely into aqueous phase after reaction. The reagent from hexamethylphosphoramide (R = $N(CH_3)_2$ in eq 2 and 3), however, is much less reactive.[5,6]

Carboxylate Nucleophiles. If the carboxylic acid is activated as in eq 3, we expect either elimination from the α-CH to form a ketene or substitution by an added nucleophile; if no other nucleophile is added, substitution by carboxylate should form an anhydride. Thus, when 2 mol of acid are added in methylene chloride to 1 mol of reagent at room temperature with 2 mol of triethylamine as base, the anhydride is formed immediately in high yield. No other products (except triphenylphosphine oxide) are observed on TLC. Several such experiments are summarized in Table I. When no base is used, reaction between carboxylic acid and reagent is very slow at room temperature, chromatography indicating only the presence of substantial amounts of acid remaining with the anhydride after several hours.

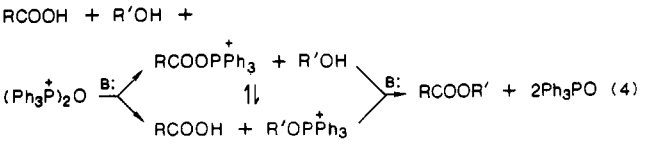
When the α-hydrogen is more acidic, however, the ketene is generated. Diphenylacetic acid immediately generates diphenylketene essentially quantitatively in the presence of triethylamine, but phenylacetic acid affords only the anhydride (Table I). This preparation of diphenylketene is simpler and more effective than the traditional one,[7] since simple evaporation of solvent and extraction with hexane affords pure ketene, avoiding distillation.

Table II. Ester Formation[a]

entry	acid	+ alcohol	% yield/ester (mp, °C)
1	*p*-toluic	methanol	74 (oil)
2	*p*-toluic	ethanol	80 (oil)
3	*p*-toluic	1-propanol	78 (oil)
4	*p*-toluic	2-methyl-2-propanol	42 (oil)
5[a]	*p*-toluic	*p*-cresol	88 (90)[16]
5[b]	*p*-toluic	*p*-cresol	70 (90)
6	coumalic	ethanol	78 (35)[17]

[a] Conditions: 2:1:1:1:2 molar ratios of Ph_3PO:Tf_2O:RCOOH:R'OH:Et_3N in $C_2H_4Cl_2$/25 °C/15 min. Reagent made first in CH_2Cl_2 or $C_2H_4Cl_2$ and mixture of acid–alcohol–base in same solvent added: 25 °C/15 min. [b] Addition of cresol and amine to reagent first, followed by acid.

O- and N-Nucleophiles. When a mixture of alcohol and acid is added, with base, to the reagent, oxygen activation by the phosphonium anhydride may occur at either oxygen. If the carboxylate is activated first, the ester should form via acylation of the alcohol. If the alcohol is activated first, the carboxylate may still displace the $ROPR_3^+$ group to create ester by O-alkylation. If, however, there is a fast exchange of phosphonium between activated acid and alcohol, either mode of ester formation may proceed. These three paths are summarized in eq 4.



The experiment was carried out by mixing *p*-toluic acid, an alcohol, and triethylamine in methylene chloride in a molar ratio of 1:2:1. When this solution was added to the reagent suspension in methylene chloride, the precipitated reagent immediately clears and the solution is directly passed through a plug of silica and evaporated to yield the corresponding ester. Yields for methanol, ethanol, and 2-propanol were comparable and high (Table II). When *tert*-butyl alcohol was used, however, the yield of ester was only 40%; by using a 3-fold excess of *tert*-butyl alcohol, base, and reagent in an effort to overcome concurrent elimination of activated alcohol to isobutene, the yield of ester increased only to 47%.

The *tert*-butyl alcohol results imply some activation of the alcohol. A further test is provided by using a phenol since, if the phenol is preferentially activated, no ester can form unless there is subsequent exchange of the phosphonium activator. When *p*-cresol and *p*-toluic acid react, there is rapid ester formation in good yield, which therefore implies rapid exchange. This is confirmed by deliberate creation of the activated cresol first followed by subsequent addition of the acid, which still affords the ester (Table II). Studies on the formation of ethers from alcohols will be forthcoming soon.

N-Nucleophiles. In a similar vein, equimolar mixtures of acid and primary or secondary amines immediately dehydrate to form amides cleanly (Table III). Here, while

(4) Our earlier experiments with this combination[5] were based on incorrect stoichiometry and contained excess, and deleterious, triflic anhydride. The correct structure was adduced later.[6]

(5) Hendrickson, J. B.; Schwarzman, S. M. *Tetrahedron Lett.* **1975**, 277.

(6) Aaberg, A.; Gramstad, T.; Husebye, S. *Tetrahedron Lett.* **1979**, 2263.

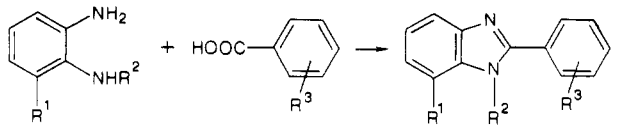
(7) Smith, L. I.; Hoehn, H. H. *Org. Syn. Coll. Vol. III*, **1955**, 356. Staudinger, H. *Chem. Ber.* **1911**, *44*, 1619.

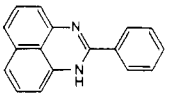
Table III. Amide and Amidine Formation[a]

entry	acid or amide	+	amine	product	% yield (mp, °C)
1	*p*-toluic acid		cyclohexylamine	*N*-cyclohexyl-*p*-toluamide	85 (152–3)
2	*p*-toluic acid		aniline	*N*-phenyl-*p*-toluamide	90 (150)
3	*p*-toluic acid		*p*-toluidine	*N*-*p*-tolyl-*p*-toluamide	78 (158–60)
4	*p*-toluic acid		benzylamine	*N*-benzyl-*p*-toluamide	90 (138–9)
5	*p*-toluic acid		*N*-methylbenzylamine	*N*-methyl-*N*-benzyl-*p*-toluamide	84 (66–7)
6	acetanilide		*N*-methylaniline	*N*-methyl-*N*,*N*′-diphenylacetamidine	94 (82)[18]
7	*n*-phenyl-*p*-toluamide		aniline	*N*,*N*′-diphenyl-*p*-toluamide	86 (167)[19]

[a] Conditions as in Table II except 8 h time for amidines/25 °C.

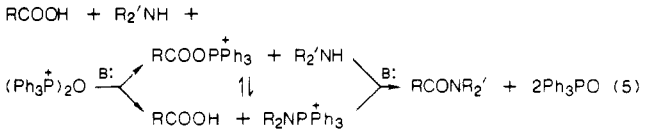
Table IV. Double Dehydration to Heterocycles



entry	starting materials R[1]	R[2]	R[3]	conditions[a]	product	% yield (mp, °C)	ref
1	H	H	H	A		85 (287)	20
2	H	C_6H_5	H	B		94 (109)	21
3	H	H	*o*-CH_3	A		95 (215)	22
4	H	C_6H_5	*o*-CH_3	A		90 (100)	
5	COOEt	H	*p*-CH_3	C		80 (77)	
6	COOEt	H	-N=S=N- (ortho)	A		86 (173)	
7	1,8-diaminonaphthalene		+ benzoic acid	D		71 (172)	11, 23
8	*o*-aminophenol		+ *p*-toluic acid	A	2-*p*-tolylbenzoxazole	81 (85)	
9	*o*-aminothiophenol		+ *p*-toluic acid	A	2-*p*-tolylbenzthiazole	82 (85)	

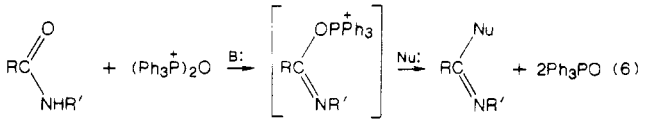
[a] Solution of mixed components in $C_2H_4Cl_2$ or CH_2Cl_2 added to 2 mol of reagent prepared in same solvent: A, 25 °C/30 min; B, 25 °C/60 min; C, 0 °C/30 min; D, reflux/$C_2H_4Cl_2$ (83 °C)/100 min.

the amines can react preferentially with the phosphonium anhydride reagent, the intermediate ($R_3P^+NR'_2$) should exchange even more effectively in order to bond phosphorus to oxygen, as in eq 5. The preference of phos-



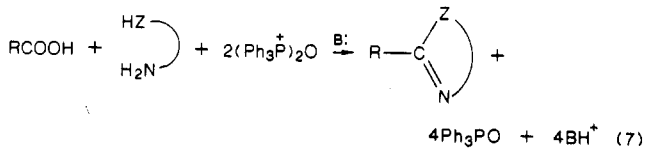
phonium bonding to oxygen over nitrogen is basic to the selectivity of the reagent for oxygen and is presumed to arise from there being two electron pairs on oxygen to back-donate into p orbitals on phosphorus and only one pair on nitrogen. In this connection it is instructive that the X-ray analysis[6] of the reagent $(Me_2N)_3P^+O^+P(NMe_2)_3$, $2OTf^-$ shows a P–O–P angle of 180°. It may be noted here that, while most methods for forming amides require *prior* activation of the acid, in this procedure the two components are simply mixed with the reagent.

Double Dehydration of Acids. Analogous to the carboxylic acids, the amide of a primary amine can be activated by the reagent at oxygen to produce a phosphonium imino ether with a leaving group for a second nucleophilic substitution as in eq 6. This constitutes two



successive "dehydrations" of the parent acid with attachment of two nucleophiles, but the second is much slower than the first. Amidine formation from amide + amine required 8 h at room temperature (eq 6).

Activation of acetanilide with the reagent and triethylamine followed by addition of an amine formed the corresponding amidines (Table IV). Since there appears to be free exchange of phosphonium from nitrogen to oxygen, it seemed likely that a diamine should form a cyclic amidine directly from the acid with 2 mol of reagent, i.e., a double dehydration as in eq 7 with $Z = NHR'$.[8]

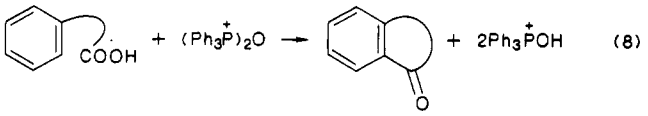


Our first explorations with aromatic acids and *o*-phenylenediamines[1,8] indeed formed the corresponding 2-arylbenzimidazoles smoothly at room temperature (Table IV) with 2 mol of reagent and triethylamine. This stands in sharp contrast to the traditional procedures,[10] which require high temperatures and afford much poorer yields. The monoacyl *o*-phenylenediamines of course could be formed first and then cyclodehydrated just as easily with 1 mol of reagent. Apart from requiring two steps, this procedure was flawed by formation of some diacyl derivative in the first traditional acylation (with acid chloride), but the intermediate amino amides cyclized smoothly. In contrast to the present reagent the use of $POCl_3$ or PCl_5 on the monoacyl derivative of entry 6 (Table IV) gave very

(8) The cyclizations of eq 7 in modest yields were reported[9] for aliphatic NH_2C_nZH components by using various phosphorus reagents.
(9) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1981**, 4471.
(10) (a) Philips, M. A. *J. Chem. Soc.* **1928**, 172, 2393, 2821. (b) Hein, D. W.; Alheim, R. J.; Leavitt, J. J. *J. Am. Chem. Soc.* **1957**, *79*, 427. (c) Kahaoka, Y. S.; Yohemitsu, O.; Tanizawa, K.; Bah, Y. *Chem. Pharm. Bull.* **1964**, *12*, 773.

poor yields of benzimidazole and considerable cleavage back to the two components. The direct double dehydration of eq 7 was similarly successful on *o*-aminophenol and thiophenol to afford the benzoxazole and benzothiazole directly (Table IV).

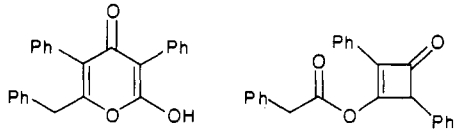
C-Nucleophiles. When several arylalkanoic acids were allowed to react with the reagent *without* base present, formation of anhydride was slow and in several hours at room temperature superceded by cyclodehydration to cyclic ketones in good yield, summarized in eq 8 and Table V. These internal C-acylations are generally milder and



(8)

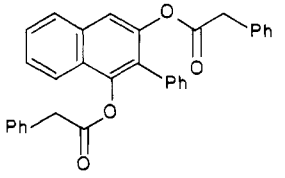
cleaner than the traditional polyphosphoric acid procedures[11] and without their attendant experimental problems of solubility, viscosity, higher temperatures, and workup neutralization. Without added base, the activation of carboxyl generates triflic acid (eq 3) and so there is strong acid catalysis for the intramolecular Friedel–Crafts reaction. The bimolecular acylation of *p*-toluic acid and toluene, however, yielded no ketone even on extended heating.

In cases that are sterically or entropically less favored for cyclization, some anhydride was also found with the ketone, as in entries 2 and 8 in Table V. When the reaction was performed on phenylacetic acid, an intermolecular condensation apparently intervened, followed by cyclization and acylation. The crystalline product (mp 129–30 °C) that formed analyzed as a multiple of phenylketene $(C_8H_6O)_n$. The mass spectrum with a parent peak at 355 implied a trimer (M_r 354) but an osmotic molecular weight determination yielded a value of 418, between trimer and tetramer. The two known trimers[12] **1** and **2** were independently prepared and found not to be identical with our product, and acylation of **1** with phenylacetyl chloride led to a tetramer ester (an oil), which was also not identical in its spectra. The NMR spectra (^1H and ^{13}C) of the product were, however, consistent with tetramer **3**; apart



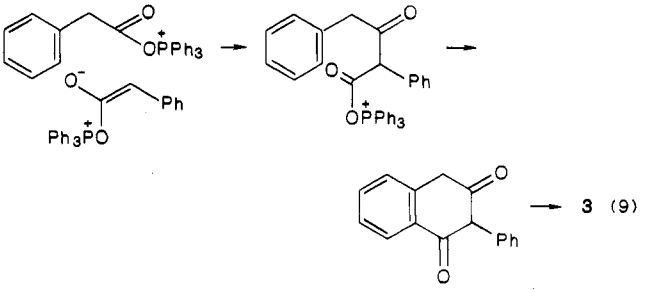
1

2



3

from the aromatic multiplet the proton spectrum showed two $PhCH_2CO$- peaks at δ 3.5 and 3.6 and the attached-proton test in the ^{13}C spectrum yielded 32 carbons as 2 CO, 2 CH_2, 20 CH, and 8 carbons with no hydrogen. The formation of **3** is reasonably formulated via an initial Claisen condensation summarized in eq 9. We were, however, unsuccessful in several attempts to repeat the literature preparation[13] of 2-phenylnaphthalene-1,3-diol.



Conclusion

This preliminary study of phosphonium anhydride reagents shows considerable promise that they will meet the desired conditions outlined at the beginning. The focus of simple reactions on carboxylic acids generally performed well as designed and they are very easy to carry out. In our experience other functionality such as simple ketones, esters, or ethers is unaffected; alcohols are of course activated by the reagent and their subsequent reactions are currently under study.

Experimental Section

Infrared spectra were determined with a P-E 683 spectrometer, NMR spectra with either Varian EM-390 or XL-300 spectrometers (vs Me_4Si), mass spectra on the H-P 5958 spectrometer, and melting points (uncorrected) with a Fisher-Johns apparatus. Analyses were performed by Galbraith Labs, Knoxville, TN. Column chromatography utilized Kieselgel 60 silica, commonly via flash techniques, and TLC utilized Analtech (GHLF) glass-backed silica plates. Solvents were dried and distilled fresh by common practice, flasks were dried at 150 °C and flushed with dry nitrogen just before use, and reactions were routinely run under nitrogen. Product solutions were dried over anhydrous magnesium sulfate. Triflic anhydride was prepared[24] from triflic acid (3M Company) and maintained in a still over P_2O_5 for distillation prior to use.

***N*-(Diphenylphosphinyl)-*N'*-methylpiperazine.** A solution of 1.12 mL (10 mmol) of *N*-methylpiperazine in 10 mL of methylene chloride was added dropwise to a solution of 1.90 mL (10 mmol) of diphenylphosphinic chloride in 10 mL of methylene chloride at 0 °C. After 10 min the solution was washed with water (2×), dried, and evaporated to 2.86 g (95%) of solid, recrystallized from toluene to mp 108–109 °C: ^1H NMR ($CDCl_3$) δ 8.0–7.7 (m, 4 H), 7.5–7.3 (m, 6 H), 3.2–3.0 (m, 4 H); IR (CH_2Cl_2) 3060, 3000, 2960, 2860, 2800, 1460, 1450, 1190 cm^{-1}; MS (70 eV) 300 (M^+), 200. Anal. Calcd for $C_{17}H_{21}N_2PO$: C, 68.00; H, 7.00; N, 9.30; P, 10.33. Found: C, 67.70; H, 7.00; N, 8.91; P, 10.92.

Dehydration of Acids to Anhydrides: Formation of *p*-Toluic Anhydride. To a solution of 5.56 g (20 mmol) of triphenylphosphine oxide in 30 mL of ethylene dichloride at 0 °C

(11) Uhlig, F.; Snyder, H. R. *Adv. Org. Chem.* **1960**, *1*, 85.
(12) Farnum, D. G.; Johnson, R. J.; Hess, R. E.; Marshall, T. B.; Webster, B. *J. Am. Chem. Soc.* **1965**, *87*, 5191.
(13) (a) Zabovics, V. Z.; Wittman, H. *Ann.* **1972**, *760*, 171. (b) Runge, F.; Koch, U. *Chem. Ber.* **1958**, *91*, 1217.
(14) Berliner, E.; Altschul, L. H. *J. Am. Chem. Soc.* **1952**, *74*, 4110.
(15) Reppe, V. W. *Ann.* **1955**, *596*, 158.
(16) Neeman, M.; Modiano, A.; Shor, Y. *J. Org. Chem.* **1956**, *21*, 671.
(17) Pechmann, V. H. V. *Ann.* **1891**, *264*, 281.
(18) Haunter, L.; Marriott, J. A. *J. Chem. Soc.* **1941**, 777.
(19) Shirsatt, M. V.; Shah, R. C. *J. Indian Chem. Soc.* **1950**, *27*, 1.
(20) Hein, D. W.; Alheim, R. J.; Leavitt, J. J. *J. Am. Chem. Soc.* **1957**, *79*, 427.
(21) Martshoka, B. K.; Pozharaskii, A. F.; Simonov, A. M. *Zh. Obsch. Khim.* **1964**, *34*, 1317.
(22) Wayts, M. H.; Vaerenberg, J. V. *Bul. Chem. Soc. Belg.* **1939**, *48*, 329.
(23) Morita, N.; Dickstein, J. J.; Miller, S. I. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2013.
(24) Hendrickson, J. B.; Judelson, D. A.; Chancellor, T. *Synthesis* **1984**, *4*, 320.
(25) Wedekind, V. E. *Ann.* **1902**, *323*, 255.
(26) Pfeiffer, V. P.; Waal, H. L. *Ann.* **1935**, *520*, 189.
(27) Koelsch, C. F.; Lecaire, C. D. *J. Org. Chem.* **1941**, *6*, 516.
(28) Graeber, V. C.; Rateanu, A. S. *Ann.* **1894**, *279*, 254.
(29) Vorlander, D.; Drescher, B. *Ber.* **1901**, *34*, 1856.

Table V. Intramolecular Aryl Acylations

entry	acid	conditions[a]	product	% yield (mp, °C)
1	3-phenylpropanoic	A	indanone	83 (39–40)[25]
2	3-phenylbutanoic	A	3-methylindanone	62 (oil) + 15[b]
3	3,3-diphenylpropanoic	B	3-phenylindanone	92 (76–7)[26]
4	3,3,3-triphenylpropanoic	C	3,3-diphenylindanone	95 (128–9)[27]
5	*o*-phenylbenzoic	C	fluorenone	92 (77–9)[28]
6	4-phenylbutanoic	A	1-tetralone	93 (oil)
7	5-phenylpentanoic	A	1-benzosuberone	63 (oil) +12[b]
8	*N*-phenylglycine	D	indoxyl	92 (84)[29]

[a] Conditions ($C_2H_4Cl_2$): A, 25 °C/4 h; B, reflux (83 °C)/30 min; C, 25 °C/30 min; D, Et_3N/(25 °C)/2 min. [b] Isolation of anhydride as minor component.

was added dropwise a solution of 1.57 mL (10 mmol) of triflic anhydride in 30 mL of ethylene dichloride. After 15 min when precipitate appeared, a solution containing 2.72 g (20 mmol) of *p*-toluic acid in 20 mL of ethylene dichloride was added, followed by 2.84 mL (20 mmol) of anhydrous triethylamine. After being stirred for 15 min, everything dissolved, giving a light brown solution that was concentrated and passed through a short column of silica (4:1 hexane/ethyl acetate) to remove triphenylphosphine oxide. Evaporation of the solvent gave 2.36 g (93%) of *p*-toluic anhydride, mp 92–93 °C.

Other acid dehydrations were done in analogous fashion (Table I).

Diphenylketene. To the reagent prepared as above from 6.00 g (20 mmol) of *N*-(diphenylphosphinyl)-*N'*-methylpiperazine in methylene chloride was added a solution containing 2.12 g (10 mmol) of diphenylacetic acid in 10 mL of methylene chloride. The mixture was stirred at room temperature for 2 h, by which time acid was consumed completely (monitored by IR). The solvent was evaporated on an aspirator and the gummy residue was washed with hexane (50 × 3). On evaporation of solvent this gave 1.40 g (72%) of oil: IR (CH_2Cl_2) 2100, 1600, 1450, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4–7.2 (m).

***p*-Cresyl *p*-Toluate.** To the reagent prepared as above from 5.56 g (20 mmol) of triphenylphosphine oxide was added a solution containing 1.08 g (10 mmol) of *p*-cresol and 1.36 g (10 mmol) of *p*-toluic acid in 15 mL of ethylene dichloride, followed by 2.84 mL (20 mmol) of anhydrous triethylamine. After 15 min when everything dissolved, giving a light yellow solution, it was washed (3×) with 5% sodium bicarbonate, water, and brine, dried, and evaporated. The residue was passed through a short column of silica (6:1 hexane/ethyl acetate) to remove triphenylphosphine oxide. Evaporation gave 1.99 g (88%) of ester, mp 90–92 °C.

When the experiment was repeated with only one component added first to the reagent, followed by the triethylamine, and the other component added only after the precipitate dissolved (~15 min) and stirred a further 15 min., the results were essentially the same (Table II).

Other acid dehydrations to esters were done in analogous fashion (Table II).

Acid Dehydrations to Amides: Preparation of *N*-(*p*-Tolyl)-*p*-toluamide. To the reagent prepared as above from 5.56 g (20 mmol) of triphenylphosphine oxide was added a solution containing 1.07 g (10 mmol) of *p*-toluidine in 10 mL of ethylene dichloride, followed by a solution containing 1.36 g (10 mmol) of *p*-toluic acid in 10 mL of ethylene dichloride. Then 2.84 mL (20 mmol) of anhydrous triethylamine was added immediately. After stirring for 15 min at room temperature, when everything dissolved, it was washed (3×) with 5% aqueous sodium bicarbonate solution, water (2×), and brine, dried, and evaporated. The residue was passed through a short column of silica (4:1 hexane/ethyl acetate) to remove triphenylphosphine oxide. Evaporation yielded 1.8 g (78%) of amide, mp 158–160 °C.

Other amides were prepared in analogous fashion (Table III).

Preparation of *N*-Methyl-*N*,*N'*-diphenylacetamidine. To the reagent prepared as above from 5.56 g (20 mmol) of triphenylphosphine oxide was added a solution containing 1.35 g (10 mmol) of acetanilide in 10 mL of ethylene dichloride. After stirring for 30 min at room temperature, when everything dissolved, a solution containing 1.1 mL (10 mmol) of *N*-methylaniline was added. The mixture was stirred at room temperature for 8 h and extracted with 5% hydrochloric acid; the acidic solution was made basic with aqueous sodium bicarbonate and extracted with methylene chloride (50 × 3), washed with water (2×) and brine, and dried. Evaporation yielded 2.10 g (94%) of solid, recrystallized to mp 82 °C.

2-Phenylbenzimidazole. To the reagent prepared as above from 5.56 g (20 mmol) of triphenylphosphine oxide was added a solution containing 0.44 g (4 mmol) of *o*-phenylenediamine and 0.61 g (5 mmol) of benzoic acid in 10 mL of ethylene dichloride. After being stirred for half an hour, the solution was washed (3×) with 5% aqueous sodium bicarbonate solution, water, and brine, dried, and evaporated. The residue was passed through a short column of silica (3:1 hexane/ethyl acetate) to remove triphenylphosphine oxide. Evaporation yielded 0.66 g (85%) of 2-phenylbenimidazole, mp 287 °C.

Other benzimidazoles were prepared in an analoguous fashion (Table IV).

α-Tetralone. To the reagent prepared as above from 5.56 g (20 mmol) of triphenylphosphine oxide was added a solution containing 1.64 g (10 mmol) of 4-phenylbutyric acid. The reaction mixture was brought to room temperature and stirred for 4 h. When everything dissolved, the clear light brown solution was washed (3×) with sodium bicarbonate, water (2×), and brine, dried, and evaporated. The residue was passed through a short column of silica (3:1 hexane/ethyl acetate). Evaporation of the solvent gave 1.36 g (93%) of α-tetralone.

Other ketones were prepared in analogous fashion (Table V).

2-Phenylnaphthalene-1,3-diol Diester 16. To the reagent prepared as above from 5.56 g (20 mmol) of triphenylphosphine oxide was added a solution containing 1.36 g (10 mmol) of phenylacetic acid in 10 mL of ethylene dichloride. The reaction mixture was stirred at room temperature for 3 h, when everything dissolved, giving a clear solution. TLC (3:1 hexane/ethyl acetate) revealed the disappearance of the acid and the presence of two compounds, one major and the other in very small amount. The solution was washed with 5% aqueous sodium bicarbonate, then water, and brine. After drying, the solution was concentrated and passed through a column of silica (3.5:1 hexane/ethyl acetate). Evaporation of the solvent gave 1.05 g of off-white crystals, which on recrystallization from ether gave bright, big colorless crystals, mp 129–130 °C: ^1H NMR ($CDCl_3$) δ 7.8–7.0 (m, 10 H), 3.6 (s, 1 H), 3.5 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 169.5, 169.2, 146.2, 145.3, many between 133–126, 122.3, 118.4, 40.1; ^{13}C NMR ($CDCl_3$) (APT) δ carbonyls, 169.5, 169.2; quaternary, 146.2, 145.3, 133.1–132.2; methines, 130–126, 122.3, 118.4; methylene, 40.1; IR (CH_2Cl_2) 1770, 1550, 1350, 1230, 1210, 1110 cm^{-1}; MS (70 eV) 355; M_r (THF) 418. Anal. Found: C, 81.02; H, 5.30 (calcd for C_8H_6O: C, 81.35; H, 5.08).

Registry No. $(C_6H_5)_2PON(CH_2CH_2)_2NCH_3$, 109744-89-0; HO_2CPh, 65-85-0; *o*-$HO_2CC_6H_4CH_3$, 118-90-1; *N*-methylpiperazine, 109-01-3; diphenylphosphinic chloride, 1499-21-4; triphenylphosphine oxide, 791-28-6; triflic anhydride, 358-23-6; *p*-toluic acid, 99-94-5; *p*-cresyl *p*-toluate, 15024-08-5; *p*-cresol, 106-44-5; *N*-(*p*-tolyl)-*p*-toluamide, 620-93-9; *p*-toluidine, 106-49-0; *N*-methyl-*N*,*N'*-diphenylacetamidine, 65957-22-4; acetanilide, 103-84-4; *N*-methylaniline, 100-61-8; 2-phenylbenzimidazole, 716-79-0; 4-phenylbutyric acid, 1821-12-1; 2-phenylnaphthalene-1,3-diol diester, 118514-43-5; cyclohexanecarboxylic acid, 98-89-5; phenylacetic acid, 103-82-2; 4-phenylbutanoic acid, 1821-12-1; diphenylacetic acid, 117-34-0; cyclohexanecarboxylic anhydride, 22651-87-2; *p*-toluic anhydride, 13222-85-0; phenylacetic anhydride, 1555-80-2; 4-phenylbutanoic anhydride, 1940-02-9; diphenylketene, 525-06-4; coumalic acid, 500-05-0; *p*-toluic acid

methyl ester, 99-75-2; *p*-toluic acid ethyl ester, 94-08-6; *p*-toluic acid propyl ester, 6976-69-8; *p*-toluic acid *tert*-butyl ester, 13756-42-8; coumalic acid ethyl ester, 5942-96-1; *N*-phenyl-*p*-toluamide, 620-84-8; *N*-cyclohexyl-*p*-toluamide, 10386-93-3; *N*-benzyl-*p*-toluamide, 5405-15-2; *N*-methyl-*N*-benzyl-*p*-toluamide, 69267-39-6; *N,N*-diphenyl-*p*-toluamide, 4316-53-4; cyclohexylamine, 108-91-8; benzylamine, 100-46-9; *N*-methylbenzylamine, 103-67-3; 2,1,3-benzothiadiazole-2-5^{IV}, 118514-40-2; 1,2-phenyldiamine, 95-54-5; *N*-phenyl-1,2-phenyldiamine, 534-85-0; 2,3-diaminobenzoic acid ethyl ester, 37466-88-9; 1,8-diaminonaphthalene, 479-27-6; *o*-aminophenol, 95-55-6; *o*-aminothiophenol, 137-07-5; *N*,2-diphenylbenzimidazole, 2622-67-5; 2-(2-methylphenyl)benzimidazole, 2963-64-6; *N*-phenyl-2-(2-methylphenyl)benzimidazole, 109744-85-6; 2-(4-methylphenyl)-4-benzimidazolecarboxylic acid ethyl ester, 109744-86-7; 2-(4-(2,13-benzothiadiazolyl))-4-benzimidazolecarboxylic acid ethyl ester, 109744-87-8; 2-*p*-tolylbenzoxazole, 835-71-2; 2-*p*-tolylbenzothiazole, 16112-21-3; 2-phenyl-1*H*-perimidine, 15666-84-9; 3-phenylpropanoic acid, 501-52-0; 3-phenylbutanoic acid, 4593-90-2; 3,3-diphenylpropanoic acid, 606-83-7; 3,3,3-triphenylpropanoic acid, 900-91-4; *o*-phenylbenzoic acid, 947-84-2; 5-phenylpentanoic acid, 2270-20-4; *N*-phenylglycine, 103-01-5; indanone, 83-33-0; 3-methylindanone, 6072-57-7; 3-phenylindanone, 16618-72-7; 3,3-diphenylindanone, 55010-17-8; fluorenone, 486-25-9; 1-tetralone, 529-34-0; 1-benzosuberone, 826-73-3; indoxyl, 480-93-3; 5-phenylpentanoic anhydride, 118514-42-4.

Structure Determination of Lysobactin, a Macrocyclic Peptide Lactone Antibiotic[1]

Adrienne A. Tymiak,* Terrence J. McCormick, and Steve E. Unger

The Squibb Institute for Medical Research, Princeton, New Jersey 08543-4000

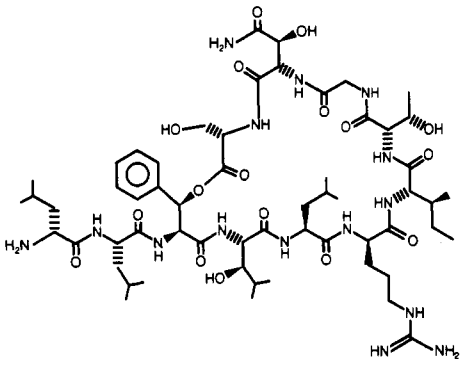
Received August 12, 1988

A new antibiotic, lysobactin (**1**), was isolated from fermentations of *Lysobacter* sp. ATCC 53042. Lysobactin was shown to be a potent agent against Gram-positive aerobic and anaerobic bacteria in vitro, and its efficacy in vivo was found to compare favorably with the clinically useful antibiotic vancomycin. Physicochemical characterization identified the antibiotic as a dibasic peptide of nominal mass 1275 Da. The structure of lysobactin, including stereochemical details, was determined by a combination of chemical and enzymatic degradations that were analyzed primarily by mass spectrometry. On the basis of synthetic modifications, the macrocyclic lactone and N-terminal D-amino acid of lysobactin are important structural elements contributing to the antibacterial activity.

Introduction

Inhibition of bacterial cell wall synthesis has proven to be a desirable mode of action for antimicrobial chemotherapeutic agents.[2] Notable examples of antibiotics having this mode of action are the penicillins, cephalosporins, bacitracin, and vancomycin. Microbial resistance to β-lactam antibiotics, however, is a widely occurring phenomenon. Recently, a clinically important increase in the incidence of methicillin-resistance Gram-positive infections has been noted.[3] The drug of choice for such infections,[4] vancomycin, is a natural product isolated from streptomycete fermentations. In contrast to the enzyme inhibitory activity of the β-lactams, vancomycin and related glycopeptide antibiotics inhibit bacterial cell wall biosynthesis by specific binding to D-alanyl-D-alanine cell wall precursors.[5] This mode of antibacterial action is consistent with the observed selectivity and potency of the vancomycin-type antibiotics.

Strains of vancomycin-resistant bacteria, although rare, have now been isolated and have been shown to cause infections.[6] Consequently, an alternative antibacterial agent with the same or similar cell wall precursor binding ability could be medically useful. In order to find such an agent, microbial fermentations were screened for antibiotics with biological activity antagonized by a *Staphylococcus aureus* cell wall preparation. Using this approach, *Lysobacter* sp. SC13,067 (ATCC 53042) was identified as a producer of a novel antibiotic having preferential activity against Gram-positive bacteria.[7] The structure determination of lysobactin (**1**) and structural requirements for its biological activity are the subjects of this paper. An independent structure elucidation of lysobactin, illustrating the utility of 2D NMR techniques, will be presented in a separate report.[8]



1

(1) This paper is dedicated to Professor Kenneth L. Rinehart Jr. on the occasion of his 60th birthday. Portions of this work were presented previously: (a) Tymiak, A. A.; McCormick, T. J.; Unger, S. E. 193rd National Meeting of the American Chemical Society, Denver 4/87, ORGN-56. (b) Tymiak, A. A.; Kirsch, D. R.; O'Sullivan, J.; McCullough, J. E. U.S. Patent 4,754,018; June 28, 1988.

(2) Gale, E. F.; Cundliffe, E.; Reynolds, P. E.; Richmond, M. H.; Waring, M. J. *The Molecular Basis of Antibiotic Action*, 2nd ed.; John Wiley & Sons: New York, 1972; pp 49–174.

(3) Thompson, R. L.; Wenzel, R. P. *Ann. Int. Med.* **1982**, *97*, 925–926.

(4) (a) Watanakunakorn, C. *Rev. Inf. Dis* **1981**, *3*, S210–215. (b) Cafferkey, M. T.; Hone, R.; Keane, C. T. *J. Antimicrob. Chemother.* **1982**, *9*, 69–74. (c) Cook, F. V.; Farrar, W. E., Jr. *Ann. Int. Med.* **1978**, *88*, 813–818. Levine, J. F. *Med. Clinics North Am.* **1987**, *71*, 1135–1145.

(5) (a) Barna, J. C. J.; Williams, D. H. *Ann. Rev. Microbiol.* **1984**, *38*, 339–357. (b) Williams, D. H.; Waltho, J. P. *Biochem. Pharmacol.* **1988**, *37*, 133–141.

(6) (a) Shlaes, D. M.; Marino, J.; Jacobs, M. R. *Antimicrob. Agents Chemother.* **1984**, *25*, 527–528. (b) Horowitz, H. W.; Handwerger, S.; van Horn, K. G.; Wormser, G. P. *Lancet* **1987**, Vol. II(8571), 1329–1330.

(7) O'Sullivan, J.; McCullough, J. E.; Tymiak, A. A.; Kirsch, D. R.; Trejo, W. H.; Principe, P. A. *J. Antibiot.*, in press.

(8) Andersen, N. H.; Hammen, P.; Banks, K.; Pratum, T.; Porubcan, M. A.; Tymiak, A. A. *J. Am. Chem. Soc.*, submitted.

(9) Arijoshi, Y.; Sato, N. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3435–3437.

0022-3263/89/1954-1149$01.50/0