Diethyl Chlorophosphite: A Versatile Reagent

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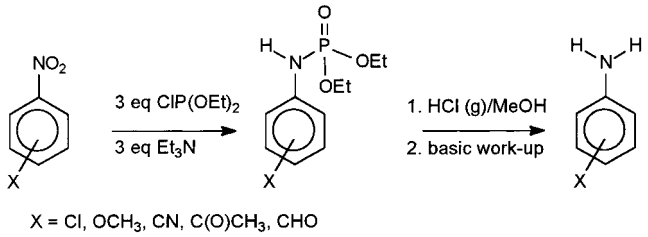
Diethyl chlorophosphite (DECP) was previously described as a reducing agent for nitro compounds to the corresponding amines (Fischer, B.; Sheihet, L. *J. Org. Chem.* **1998**, *63*, 393). Here, the utility of this reagent was extended to chemical conversions of other oxygenated functional groups. In this paper we report on the scope of the reaction of DECP with *N*-oxides, epoxides, sulfones, sulfoxides, hydroxylamines, ketoximes, and aldoximes. The chemoselectivity of DECP is described, and conditions for a stepwise multiple conversion of functional groups on the same molecule with this reagent are provided.

Introduction

Tervalent organophosphorus compounds (X_3P) such as trialkyl- or triarylphosphines and trialkyl phosphites are useful reagents in synthetic chemistry in several deoxygenation and dehydration reactions.[1] The major driving force for these reactions is the formation of a P═O bond and the release of 120−150 kcal/mol.

We previously reported on the utility of diethyl chlorophosphite (DECP) as an agent for the reduction of nitro compounds to the corresponding phosphoramides, which are further cleaved in situ, yielding amine derivatives (Scheme 1).[2] In this paper, we extend the scope of this reagent to the deoxygenation of other functional groups. Specifically, we report on the reaction of DECP with *N*-oxides, epoxides, sulfones, sulfoxides, hydroxylamines, ketoximes, and aldoximes. In addition, we report on the chemoselectivity of DECP, provide conditions for stepwise multiple conversion of functional groups on the same molecule with this reagent, and propose mechanistic explanations.

Scheme 1



Results

Various Chemical Conversions with Diethyl Chlorophosphite. The versatility and efficiency of $(EtO)_2PCl$, DECP, as a deoxygenating agent, was evaluated with various functional groups (Table 1). Thus, pyridine *N*-oxide was quantitatively reduced to pyridine with DECP in chloroform at room temperature (Table 1, entry 1). The reduction of methyl phenyl sulfoxide to the corresponding sulfide was readily accomplished by DECP at room temperature within 30 min (entry 2), providing a facile alternative to other phosphorus reagents previously proposed for the deoxygenation of sulfoxides.[3]

When an aliphatic acyclic epoxide is treated with the reagent, alone or in combination with triethylamine, a chlorohydrin is formed in 85% yield with complete regioselectivity (entry 3), rather than the corresponding olefin obtained with other phosphorus deoxygenating agents.[4] Cyclohexene oxide, however, gave a mixture of isomers of 2-chlorocyclohexyl ethyl hydrogen phosphonate in 88% yield (entry 4), as indicated by MS, ^1H, ^{31}P, and ^{13}C NMR, and DEPT spectra. These compounds exhibited the typical 700 Hz one-bond P−H coupling in ^{31}P and ^1H NMR.

Deoxygenation of hydroxylamines was reported to proceed at room temperature with medium yields upon treatment with triphenylphosphine derivatives.[5] DECP, however, is extremely reactive with phenylhydroxylamine, yielding a multitude of products even at −100 °C. The same high reactivity was observed also with (*p*-nitrophenyl)hydroxylamine and (*p*-methoxyphenyl)hydroxylamine (entry 5). However, no reaction occurred between DECP and methyl (phenylsulfonyl)acetate, allyl phenyl sulfone, or benzamide (entries 6 and 7) even after they were heated under reflux in acetonitrile for 24 h. Likewise, no reaction occurred with 2-indanone oxime and DECP, with or without triethylamine; the ketone isolated from the reaction mixture is the result of hydrolysis of the oxime during workup (entry 8). Aldoximes, on the other hand, proved to be efficiently converted by DECP to the corresponding nitrile, even in the absence of Et_3N (Table 2).

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(1) (a) Cadogan, J. I. G. *Q. Rev.* **1968**, *22*, 222. (b) Smith, D. J. H. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; pp 1127−1188. (c) Corbridge, D. E. C. *Phosphorus. An Outline of its Chemistry, Biochemistry and Uses*; Studies in Inorganic Chemistry 20; Elsevier: Amsterdam, 1995; pp 319−320 and 352−354.

(2) Fischer, B.; Sheihet, L. *J. Org. Chem.* **1998**, *63*, 393.

(3) (a) Olah, G. A.; Balaram Gupta, B. G.; Narang, S. C. *J. Org. Chem.* **1978**, *43*, 4503 and references therein. (b) Suzuki, H.; Sato, N.; Osuka, A. *Chem. Lett.* **1980**, 143.

(4) (a) Wong H. N. C.; Fok, C. C. M.; Wong, T. *Heterocycles* **1987**, *26*, 1345. (b) Yamada, K.; Goto, S.; Nagase, H.; Kyotani, Y.; Hirata, Y. *J. Org. Chem.* **1978**, *43*, 2076. (c) Paryzek, Z.; Wydra, R. *Tetrahedron Lett.* **1984**, *25*, 2601.

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Table 1. Conversions of Various Oxygenated Functions by DECP

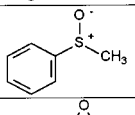
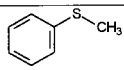
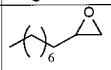
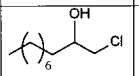
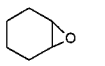
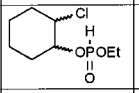
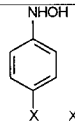
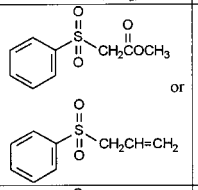
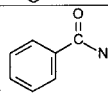
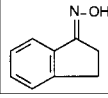
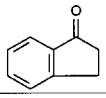
Entry	Reactant	Product	Reaction conditions	Yield (%)
1			$CHCl_3$, rt,3 h	89
2			$CHCl_3$, rt, 30 min	83
3			$CHCl_3$, rt, 12 h	85
4			$CHCl_3$, 3 h -40°C -> rt,	88
5	 X = H, NO_2, OMe	Multitude of products	$CHCl_3$, 3 h -100°C	----
6	 or	No reaction	CH_3CN, 24 h reflux	----
7		No reaction	CH_3CN, 24 h reflux	----
8			$CHCl_3$, rt, 30 min acidic work-up	100

Table 2. Conversion of Aldoximes to Nitriles by DECP:

RCH=NOH + 3DECP → RCN

Entry	R	Reaction conditions[a]	Yield (%)
1		rt, 30 min	83
2		-78°C- rt, 1.5 h	90
3		-40°C, 10 min	91
4		-40°C, 10 min	92
5		60°C, 6 h	95
6		rt, 30 min	95
7		-40°C, 30 min	90
8	$CH_3(CH_2)_3$-	rt, 6 h	76
9		rt, 1.5 h[b]	95
10		rt, 45 min	81
11		rt, 30 min	0[c]

[a] All reactions were performed in $CHCl_3$ unless otherwise stated. [b] The reaction was performed in acetonitrile. [c] The reactant precipitated upon addition of DECP as the diethyl (4-carboxaldoxime pyridinium)phosphite chloride salt.

Dehydration of Aldoximes to Nitriles by Diethyl Chlorophosphite. Dehydration of aldoximes to nitriles is a well-known transformation for which many reagents have been proposed.[6] The long list of reagents used for this transformation includes several phosphorus reagents: phosphonitrilic chloride,[7] polymer-supported triphenylphosphine/carbon tetrachloride,[8] tributylphosphine/DEAD,[9] dialkyl hydrogen phosphonate,[10] and diphosphorus tetraiodide.[11] Many of these methods have shortcomings such as low yields, hazardous reagents, harsh and long reaction conditions, and, in some cases, lack of generality for variously substituted aldoximes. Thus, the search for new and milder synthetic methodologies continues. Here we illustrate the usefulness of diethyl chlorophosphite for achieving this conversion in excellent yields under mild reaction conditions.

The dehydration reaction involves stirring the aldoxime with 3 equiv of $(EtO)_2PCl$ in dry chloroform at −40 °C or room temperature under argon. Some cases required heating for completion of the reaction (Table 2). After a short reaction time, usually between 10 and 90 min, an aqueous workup affords the nitrile in 76−95% yield. The method is general and is applicable for aromatic, heterocyclic, and aliphatic aldoximes. The advantage of this methodology lies both in the mildness of the procedure and in the selective conversion of an aldoxime functionality in the presence of other DECP-sensitive groups such as hydroxyl and nitro (Scheme 2d).

Dehydration of aldoxime to nitrile is best effected in aprotic polar solvents. For instance, the conversion of 3-methoxy-5-nitrosalicylaldehyde oxime (Table 2, entry 9) in toluene is complete after 12 h at 90 °C, whereas in chloroform and acetonitrile, the conversion is complete at room temperature within 3 and 1.5 h, respectively.

Conversion of benzaldoxime to benzonitrile in good yield was effected by DECP after 30 min at room temperature (entry 1). Electron-withdrawing groups such as chloro or nitro at either *para* or *ortho* positions accelerated the reaction (entries 2−4). A similar behavior was observed for cinnamaldehyde oxime (entry 7). Thus,

(6) (a) Lehnert, W. *Tetrahedron Lett.* **1971**, *6*, 559. (b) Clive, D. L. *J. Chem. Soc., Chem. Commun.* **1970**, 1014. (c) Rogic, M.; van Peppen, J. F.; Klein, K. P.; Demmin, T. R. *J. Org. Chem.* **1974**, *39*, 3424. (d) Foley, H. G.; Dalton, D. R. *J. Chem. Soc., Chem. Commun.* **1973**, 628. (e) Keumi, T.; Yamamoto, T.; Saga, T.; Kitajima, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1579. (f) Olah, G. A.; Vankar, Y. D. *Synthesis* **1978**, 702. (g) Olah, G. A.; Vankar, Y. D.; Garcia-Luna, A. *Synthesis* **1979**, 227. (h) Katrizky, A. R.; Zhang, G. F.; Fan, W. G. *Org. Prep. Proced. Int.* **1993**, *25*, 315. (i) Molina, P.; Alajarin, M.; Vilaplana, M. J. *Synthesis* **1982**, 106. (j) Arrieta, A.; Paloma, C. *Synthesis* **1983**, 472. (k) Kim, S.; Yi, K. Y. *Tetrahedron Lett.* **1986**, *27*, 1925. (l) Tamami, B.; Kiasat, A. R. *Synth. Commun.* **2000**, *30*, 235. (m) Sosnovsky, G.; Krogh, J. A. *Synthesis* **1978**, 703. (n) Babad, H.; Zeiler, A. G. *Chem. Rev.* **1973**, *73*, 75.

(7) Rossini, G.; Baccolini, G.; Cacchi, S. *J. Org. Chem.* **1973**, *38*, 1060.

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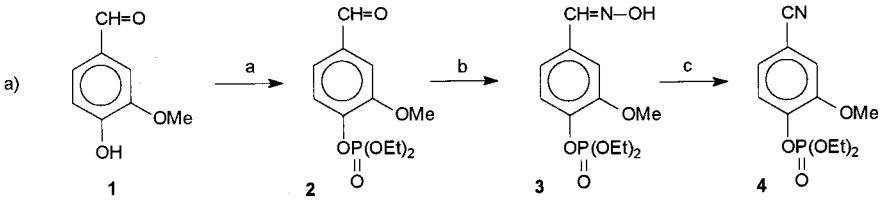
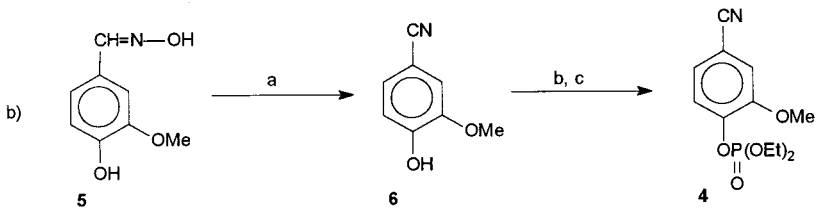
(11) Suzuki, H.; Fuchita, T.; Iwasa, A.; Mishina, T. *Synthesis* **1978**, 905.

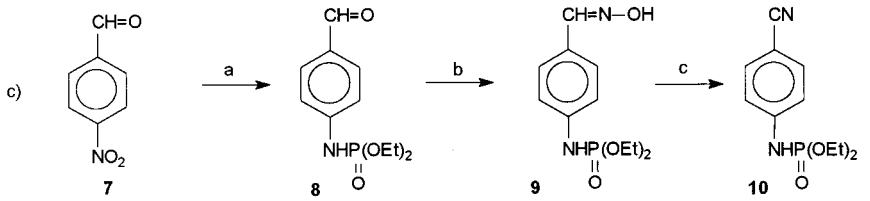
Scheme 2



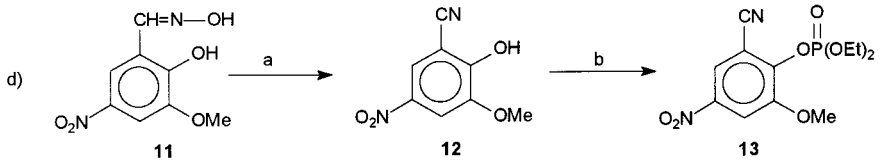
a. 1.5 eq DECP/ Et_3N, ether, rt, 2 h; I_2 / H_2O, 71% b. NH_2OH, EtOH, rt, 4 h, 81% c. 3 eq DECP, $CHCl_3$, 96%



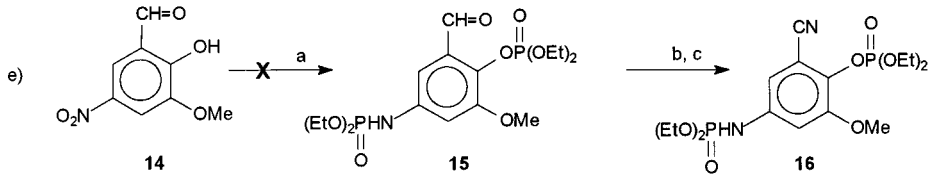
a. 3 eq DECP, $CHCl_3$, rt, 30 min 95% b . 1 eq DECP/Et_3N, THF, rt, 3 h c. I_2 / H_2O, 79%



a. 3 eq DECP/Et_3N, $CHCl_3$, 0°C, 3 h, 78% b. NH_2OH, EtOH, rt, 4 h, 91% c. 3 eq DECP/Et_3N, $CHCl_3$, 91%



a. 3 eq DECP, toluene, reflux, 12 h b. 4 eq DECP/Et_3N, toluene, reflux, 12 h ; I_2 / H_2O, 25% overall yield



a. 4 eq DECP/Et_3N, CH_3CN, reflux 24 h b. NH_2OH, EtOH, rt c. 3 eq DECP, $CHCl_3$

p- and *o*-nitrobenzonitrile were obtained from the corresponding aldoximes in high yield after 10 min at −40 °C. On the other hand, electron-donating groups such as methoxy or hydroxy at *ortho*/*para*/*meta* positions retarded the reaction (entries 5 and 6). For instance, conversion of 2,3-dimethoxybenzaldoxime was achieved in excellent yield only after 6 h at 60 °C. DECP-sensitive groups, such as nitro and hydroxyl, were not affected at all under the mild reaction conditions (entries 3, 4, 6, and 9). The reaction conditions proved to be general also for aliphatic and heterocyclic aldoximes (entries 8 and 10), although reaction with valeraldehyde was slower than with benzaldoxime.

When pyridine 4-carboxaldoxime was subjected to the reaction conditions, a precipitate was formed instantaneously and no nitrile product was obtained (entry 11). Apparently, the pyridine moiety reacts more favorably with DECP in comparison to the oxime moiety, thus forming the diethyl phosphitylpyridinium chloride salt.

When $P(OMe)_3$ (3 equiv) was used in place of DECP, no conversion of benzaldoxime to benzonitrile was effected even under reflux in chloroform for 12 h. With PCl_3 (3 equiv) conversion of benzaldoxime to benzonitrile was effected in 11% yield only after addition of Et_3N and heating under reflux in chloroform for 20 h. No conversion to a nitrile was effected upon treatment of *p*-nitrobenzaldoxime *O*-methyl ether with DECP.

Chemoselectivity of DECP. Conditions effecting the conversion of aldoximes to nitriles left DECP-sensitive substituents, such as nitro and hydroxyl, unaffected (Table 2, entries 3, 4, 6, and 9). We then performed competition studies designed to explore the chemoselectivity of DECP for aldoxime, nitro, and hydroxyl substituents in the same molecule. We also attempted to fine-

tune the conditions for the conversion of only a certain function in the presence of others (Scheme 2).

When vanillin, **1**, was treated with 1.5 equiv of DECP and Et_3N, followed by an oxidative workup with iodine/water, a smooth conversion of the hydroxyl group to the phosphoric acid triester **2** occurred. Aldoxime, **3**, prepared from **2**, was quantitatively converted to nitrile **4** with DECP in $CHCl_3$ without base (Scheme 2a).

Chemoselectivity was demonstrated in a reversed sequence (Scheme 2b). When 4-hydroxy-3-methoxybenzaldoxime, **5**, was treated with DECP at room temperature, the conversion to nitrile **6** was quantitative, with the hydroxyl remaining intact. However, upon the addition of 1 more equiv of DECP and triethylamine at room temperature, phosphitylation of the hydroxyl, followed by oxidation with iodine/water, was effected in 79% yield to afford the corresponding stable phosphoric acid triester **4** (Scheme 2b).

We then investigated the conversion by DECP of both nitro and aldoxime groups on the same molecule (Scheme 2c). Indeed, we found that conversion of *p*-nitrobenzaldoxime to the corresponding nitrile occurs in high yield (Table 2, entry 4). A one-pot conversion of both functions by first adding DECP to form the nitrile, followed by the addition of DECP/Et_3N to reduce the nitro function, would therefore seem an attractive pathway. However, this was not attempted, since in our earlier work we found that reduction of *p*-nitrobenzonitrile resulted in only a 20% yield after 4 days at room temperature.[2] Alternatively, these transformations were achieved in high yield in the reversed sequence of steps (Scheme 2c). Thus, the addition of 3 equiv of DECP/Et_3N to *p*-nitrobenzaldehyde afforded the reduced product **8** in 80% yield. After conversion of **8** to oxime **9** in high yield, another 3 equiv of DECP was added at room temperature to afford nitrile **10** in 91% yield after 3 h.

When 2-hydroxy-3-methoxy-5-nitrobenzaldoxime, **11**, was subjected to DECP, a complete conversion of the aldoxime to the nitrile was obtained at room temperature, with the nitro and hydroxyl groups unaffected (Table 2, entry 9). We then attempted the transformation of all three DECP-sensitive groups in a one-pot reaction. Thus, aldoxime **11** was completely converted to the nitrile upon the addition of DECP in toluene under reflux for 12 h (Scheme 2d). The addition of 4 more equiv of DECP and Et_3N and heating in toluene under reflux for 12 h effected the conversion of the hydroxyl to a phosphite. The latter was isolated as the stable phosphoric acid triester **13** after oxidative workup in 25% overall yield. Under these conditions, the nitro group did not react. Here, the order of chemical conversions with DECP is aldoxime > hydroxy > nitro.

One-pot sequential conversions of aldoxime, hydroxy, and nitro groups on the same molecule by DECP were found to be sluggish. Therefore, we attempted to reverse the sequence of DECP transformations starting from 2-hydroxy-3-methoxy-5-nitrobenzaldehyde, **14** (Scheme 2e). We planned to effect first both phosphitylation of the hydroxyl group and reduction of the nitro group of aldehyde **14** by 4 equiv of DECP/Et_3N to obtain **15**. After formation of the corresponding aldoxime, we planned to convert it by DECP treatment to nitrile **16**. However, upon the addition of 4 equiv of DECP/Et_3N, even under reflux in acetonitrile for 24 h, neither reduction of the nitro group nor phosphitylation of the hydroxyl group occurred. Apparently, the presence of a strong electron-withdrawing group *para* to the hydroxyl group reduces considerably its nucleophilicity and renders this function incapable of reaction with electrophilic DECP/Et_3N under these conditions. On the other hand, the presence of a hydroxy group *para* to the nitro group retards the reduction of this function to the corresponding phosphoroamidate (Scheme 1), as we found before.[2]

Discussion

In our earlier work with DECP as a reducing agent for nitro compounds, we noticed that this reagent, which is a hybrid of PCl_3 and $P(OEt)_3$, possesses a biphilic character.[2] Namely, DECP is capable of acting either as an electrophile or as a nucleophile.

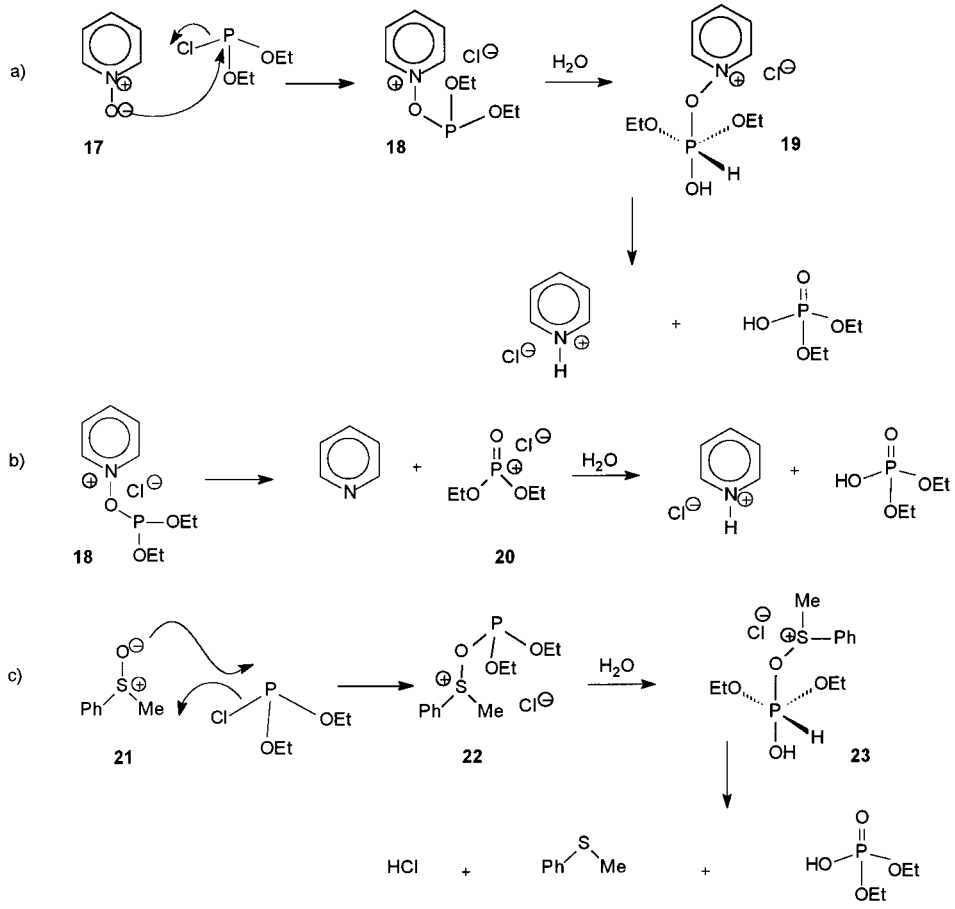
Benzamide and methyl (phenylsulfonyl)acetate or allyl phenyl sulfone are poor nucleophiles and electrophiles, and therefore, they do not undergo any reaction with DECP (Table 1, entries 6 and 7). Pyridine *N*-oxide and methyl phenyl sulfoxide, however, are sufficiently nucleophilic to undergo a facile deoxygenation with DECP as the electrophile (Table 1, entries 1 and 2). As an analogy, kinetic studies on the deoxygenation reaction of heterocyclic *N*-oxides by PCl_3 suggest a nucleophilic attack upon phosphorus by the *N*-oxide oxygen atom.[12] Replacement of chlorine atoms in phosphorus trichloride with an electron-releasing ethoxyl group decreases the rate of deoxygenation.[12] Investigations of intramolecular transfers of oxygen from nitrogen and sulfur to phosphines support the conclusion that the addition of *N*-oxide oxygen to phosphorus is the preferred mechanism.[13] In these cases, DECP acts as an electrophile being attacked by the oxygen of either the *N*-oxide or sulfoxide to form a phosphitylpyridinium or a phosphitylsulfonium chloride intermediate, **18** or **22**, respectively (Scheme 3). When the reaction of pyridine *N*-oxide with 3 equiv of DECP was performed without exclusion of water, pyridine was isolated in 90% yield after 3 h. However, when the reaction was repeated with severe exclusion of water for 12 h, the yield dropped below 50%. With only 1 equiv of DECP and no exclusion of water, the yield slightly decreased to 81%. ^1H and ^{31}P NMR and mass spectra of the latter crude reaction mixture indicated the formation of pyridinium hydrochloride and diethyl phosphate (typical acidic proton signal at 11.2 ppm), but no diethyl hydrogen phosphonate. The same phosphorus product was also obtained in the reaction of methyl phenyl sulfoxide with DECP.

On the basis of these observations, a mechanism involving a facile addition−elimination reaction of phosphitylpyridinium chloride intermediate **18** in the presence of water is proposed (Scheme 3a). The addition of water to the phosphitylpyridinium intermediate occurs by phosphorus octet expansion to form a pentavalent phosphorane intermediate, **19**.[5] This unstable trigonal bipyramidal species then collapses to diethyl phosphate and pyridinium hydrochloride.

Alternatively, a mechanism involving the elimination of diethyl metaphosphate, **20**, from the phosphitylpyridinium intermediate **18** followed by the addition of water to metaphosphate intermediate **20** could be considered (Scheme 3b). However, this mechanism is less likely, since there are no negative charges on the putative

(12) Emerson, T. R.; Rees, C. W. *J. Chem. Soc.* **1964**, 2319.
(13) Kurtzweil M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3426.

Scheme 3



metaphosphate oxygens to stabilize the developing positive charge on the phosphorus.[14]

DECP also plays the electrophile role with an epoxide moiety, effecting the formation of a chlorohydrin product rather than the expected olefin (Table 1, entry 3).[4] The observation that the addition of Et_3N to the reaction mixture (which brings about the formation of a highly electrophilic phosphorus species)[2] leads also to a chlorohydrin product supports DECP's electrophilic role. Thus, a reactive oxonium moiety, **25**, is formed by the attack of the epoxide oxygen on DECP (Scheme 4a). However, the mechanism of charge release of the oxonium moiety is different from that proposed for phosphitylpyridinium and phosphitylsulfonium ions **18** and **22** in Scheme 3 and occurs through the regiospecific attack of the chloride on the less hindered electrophilic carbon of intermediate **25**. The resulting trialkyl phosphite **26** is extremely sensitive to acid-catalyzed hydrolysis.[15] In the acidic medium produced by workup and hydrolysis of excess DECP, the trialkyl phosphite intermediate **26** is cleaved to form 1-chloro-2-hydroxydecane, **29**, and diethyl phosphite, which exists predominately as the hydrogen phosphonate.

The rate of acid hydrolysis of a phosphite is ca. 10^{12} times as great as that of the corresponding phosphate.[15] This is because a phosphite binds a proton with the unshared electrons and thus forms an electrophilic phosphorus[16] highly sensitive to nucleophilic attack by water. Thus, the protonated phosphite rapidly adds water to form a phosphorane, and this unstable intermediate then decomposes.[17] Phosphorane **28** (Scheme 4a) eliminates a chlorohydrin, rather than EtOH. It is well established that the leaving group in phosphorane is displaced from the axial position, and that the most electronegative ligand occupies preferentially axial sites.[18] The negative inductive effect of the adjacent chloro group, which stabilizes the incipient negative charge on the oxygen, makes the chlorohydrin a better leaving group. However, phosphorane **32**, derived from cyclohexene oxide (Scheme 4b), eliminates EtOH preferentially. This is a rare case of formation of "asymmetric" hydrogen phosphonate diester from a trivalent phosphorus precursor.[19] The preferential elimination of EtOH is probably due to the different positions of the cyclohexyloxy and ethoxy substituents in the bipyramidal phosphorane **32**, where the large cyclohexyl substituent prefers the less hindered equatorial position. However, elimination occurs from the axial position, where the ethoxy group is found.

A different mode of decomposition of phosphorane is proposed for the charged phosphoranes **19** and **23** in Scheme 3 and the neutral phosphoranes **28** and **32** in

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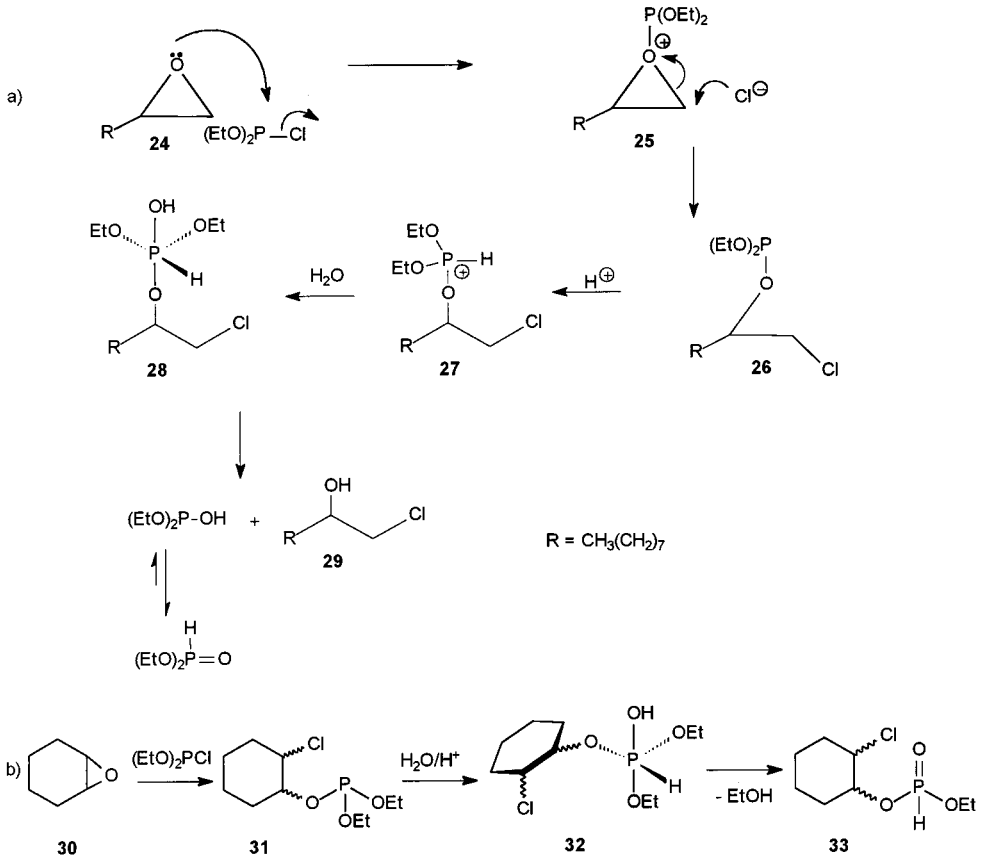
Scheme 4



Scheme 4. Whereas in Scheme 3 the charged species decomposes to diethyl phosphate and pyridine or sulfide by loss of proton and charge neutralization, in Scheme 4, the neutral phosphorane decomposes to hydrogen phosphonate and alcohol.

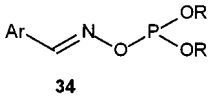
DECP effected efficiently the conversion of aldoximes to nitriles. Some observations were made concerning the role of DECP in the reaction: (a) the efficient conversion of aldoximes to the corresponding nitriles occurs even in the absence of base; (b) the reaction is accelerated by electron-withdrawing groups on the benzaldoxime (Table 2); (c) $P(OMe)_3$ does not effect the conversion to the nitrile, even under reflux in chloroform for 12 h; (d) with PCl_3 conversion to the nitrile occurs in low yield, only after addition of Et_3N and heating under reflux in chloroform for 20 h.

Elucidation of the reaction's mechanism was attempted by monitoring it using ^{31}P NMR. Thus, the reaction of 2,3-dimethoxybenzaldoxime with 3 equiv of DECP in $CDCl_3$ at 40 °C was followed, and the spectra were recorded in 10 min intervals. The signal of DECP at 166 ppm decreased gradually, while a typical signal for hydrogen phosphonate at 5 ppm with a $^1J_{P-H}$ of 700 Hz appeared. No phosphorus intermediates were observed. The formation and decomposition of the intermediates are apparently too fast to be observed on the NMR time scale.

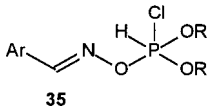
Oximes are expected to react as oxygen nucleophiles due to the α-effect of the adjacent nitrogen's lone pair. Ketoximes, indeed, react with PCl_3 in the presence of Et_3N, with the oxygen acting as the nucleophile, followed by an Arbuzov-type rearrangement.[20] On the other hand, an "amphoteric" behavior is most pronounced for tervalent phosphorus compounds. These compounds can act either as electrophiles or as nucleophiles, due to the high polarizability of the phosphorus atom that can be affected by both positive and negative charges.[21]

There are several precedents of nucleophilic reactions of tervalent phosphorus compounds (PCl_3 and $P(OMe)_3$) at an imine carbon or an electrophilic aldoxime ether carbon.[22] Hence, both the aldoxime and DECP bear electrophilic and nucleophilic sites, and are capable of reacting either way.

A mechanism consistent with the above-mentioned data involves the attack of aldoxime's oxygen at the electrophilic DECP phosphorus, rather than DECP attacking at the electrophilic aldoxime's carbon. In the former mechanism intermediates **34** and **35** are likely



34



35

formed. Collapse of phosphorane **35** will provide the nitrile product, HCl, and diethyl hydrogen phosphonate.

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The latter is clearly observed in ^1H and ^{31}P NMR spectra of the crude reaction mixture. Elimination of hydrogen phosphonate is the driving force for this reaction.

The nucleophilic role of the aldoxime is supported by the absence of any reaction of *p*-nitrobenzaldoxime *O*-methyl ether with DECP. Furthermore, acceleration of the reaction by electron-withdrawing groups on the aromatic aldoxime (Table 2, entries 2−4) indicates the nucleophilic nature of the aldoxime's oxygen. Electron-withdrawing groups increase the acidity of the aldoxime.[23] Furthermore, linear relationships often exist between nucleophilic rates and the pK_a of the nucleophiles.[24] This mechanism also explains the lack of reactivity of $P(OMe)_3$, due to its low electrophilicity.

Conclusions

DECP was shown to be an effective deoxygenating agent for *N*-oxide and sulfoxide functions. For the deoxygenation of the sulfoxide function, the use of DECP is an attractive alternative to known phosphorus reagents.

Unlike other phosphorus reagents, DECP does not effect deoxygenation of an epoxide to the corresponding olefin. However, DECP effects the efficient formation of a chlorohydrin or a chloro hydrogen phosphonate product, depending on the nature of the leaving group. This reagent proved to be too reactive with arylhydroxylamines, and was completely unreactive with benzamide and sulfones.

An attractive application of DECP is the transformation of aldoximes to nitriles, which is effected under mild conditions in high yields. This reaction is of a wide scope, and applies to aliphatic, heterocyclic, and aromatic aldoximes bearing various substituents (Cl, NO_2, OH, OMe), however with no basic nitrogen function.

Among the various reagents for aldoxime's dehydration, DECP provides some significant advantages: DECP is a commercially available compound; DECP is conveniently used, unlike hazardous dehydration agents, such as selenium dioxide[6m] or phosgene;[6n] unlike the reaction with ortho esters[6c] or P_2I_4[6] and chlorothionoformate,[6b] the reaction does not require acid or base catalysis; DECP effects a chemoselective conversion of an aldoxime to the nitrile, under conditions that leave intact functions such as hydroxyl, nitro, amide, and sulfone. This is in contrast to reagents such as Bu_3P/DEAD[9] and 1,1′-carbonylbenztriazole,[6h] which, in addition to their reaction with aldoxime, react with nitro and amide functions, respectively.

Although DECP is completely chemoselective for aldoximes in the presence of nitro and hydroxyl, conditions for the stepwise transformation of those DECP-sensitive groups were explored. Thus, 2-hydroxy-3-methoxy-5-nitrobenzaldoxime, **11**, was completely converted to the nitrile upon addition of DECP in toluene under reflux. The addition of 4 more equiv of DECP and Et_3N and heating in toluene under reflux effected the conversion of the hydroxyl to a phosphite, which was isolated as the phosphoric acid triester **13**. Under these conditions, the nitro group did not react. Here, the order of chemical conversions with DECP is aldoxime > hydroxy > nitro.

Deoxygenation of *N*-oxide and sulfoxide by electrophilic DECP is probably water-assisted, involving charged phosophoranes. These putative phosphoranes decompose to the deoxygenated product, HCl, and diethyl phosphate. With epoxides, neutral phosphoranes are likely formed and decompose to a hydrogen phosphonate and an alcohol. Nitrile formation from aldoxime and DECP is accelerated by electron-withdrawing groups which, together with the lack of reactivity of $P(OMe)_3$, support the electrophilic role of DECP.

Experimental Section

General Procedures. All reagents were of analytical grade. Chloroform was distilled over CaH_2, and stored over 4 Å molecular sieves under Ar. Diethyl chlorophosphite, benzaldoxime, 2-nitrobenzaldoxime, and 4-nitrobenzaldoxime were used as received from commercial sources. Other oximes were prepared from the corresponding aldehydes and $NH_2OH{\cdot}HCl$ in the presence of NaOH in boiling EtOH. The oximes were dried under vacuum prior to use. *N*-arylhydroxylamines were prepared from the corresponding nitro compounds according to a literature procedure.[25] All reactions were carried out in flame-dried flasks under dry Ar, unless otherwise mentioned. The reagents were handled under Ar with airtight syringes. The reactions' progress was monitored by TLC on precoated Merck silica gel plates (60F-254). Flash column chromatography was performed with Merck silica gel 60 (230−400 mesh). ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX300 machine and ^{31}P NMR spectra on a Bruker AC-200 machine in $CDCl_3$ with TMS as internal standard. J_{PC} values are given in parentheses in the ^{13}C NMR spectral data. The products were also characterized on an AutoSpec-E fision VG high-resolution mass spectrometer. For known compounds the ^1H/^{13}C NMR and mass spectra are consistent with the given structure and literature data.

Reaction with Pyridine *N*-Oxide. DECP (213 μL, 1.5 mmol, in 10 mL of $CHCl_3$) was added dropwise to a solution of pyridine *N*-oxide (48 mg, 0.5 mmol) in $CHCl_3$ (5 mL). The solution was stirred at room temperature for 3 h, and then concentrated under reduced pressure while the bath was cooled to 0 °C. The residue was extracted with 5% NaOH and purified by column chromatography (MeOH/$CHCl_3$, 1:9). Pyridine was obtained in 89% yield (35 mg).

Reaction with Methyl Phenyl Sulfoxide. A solution of DECP (213 μL, 1.5 mmol, in $CHCl_3$, 5 mL) was added dropwise over 5 min at room temperature to a solution of methyl phenyl sulfoxide (70 mg, 0.5 mmol) in $CHCl_3$ (5 mL). The solution was stirred for 30 min till the reactant was completely consumed. The reaction mixture was separated by silica gel chromatography (hexane), and methyl phenyl sulfide was obtained in 83% yield (51 mg).

Reaction with 1,2-Epoxydecane. DECP (213 mL, 1.5 mmol) was added dropwise to a solution of 1,2-epoxydecane (78 mg, 0.5 mmol) in $CHCl_3$ (5 mL) at 0 °C under Ar, and the solution was stirred for 12 h at room temperature. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$, washed with saturated NH_4Cl solution (3 × 25 mL), and dried over $MgSO_4$. 1-Chloro-2-hydroxydecane, **29**, was obtained after chromatography on silica gel and elution with hexane/$CHCl_3$ (3:1) in 83% yield (80 mg).

Reaction with Cyclohexene Oxide. DECP (426 μL, 3 mmol) was added to a solution of cyclohexene oxide (98 mg, 1 mmol) in dry $CHCl_3$ at −40 °C. The solution was then stirred at room temperature for 3 h. Workup with aqueous NH_4Cl, followed by silica gel chromatography (EtOAc), gave a mixture of isomers of 2-chlorocyclohexyl ethyl hydrogen phosphonate, **33**, as an oil (visible with I_2, R_f 0.78 with EtOAc as the eluent) in 88% yield (199 mg). ^1H NMR ($CDCl_3$): 8.19, 5.83 (d, J = 705 Hz, 1H, one isomer), 8.10, 5.75 (d, J = 705 Hz, 1H, second

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isomer), 4.40 (m, 1H), 4.20 (m, 2H), 3.95 (m, 1H), 2.25 (m, 2H), 1.71 (m, 6H), 1.35 (m, 3H) ppm.^{13}C NMR: 79.8 (d, J_{PC} = 2.5 Hz), 79.6 (d, J_{PC} = 2.5 Hz), 62.5 (d, J_{PC} = 4 Hz), 62.4 (d, J_{PC} = 4 Hz), 62.0, 61.9, 35.2, 34.9, 33.7, 33.0, 24.9, 24.6, 23.7, 23.5, 16.7, 16.6 ppm. ^{31}P NMR: +7.6 (d, J = 700 Hz, P−H) ppm. MS: *m*/*z* 244 (M + NH_4^+), 227 (MH^+). HRMS (DCI, isobutane): calcd for $C_8H_{17}O_3PCl$ 227.0604, found 227.0584.

Preparation of Nitriles from Aldoximes. A Typical Procedure. DECP (430 μL, 3 mmol) in $CHCl_3$ (15 mL) was added to a solution of the benzaldoxime (121 mg, 1 mmol) in $CHCl_3$ (20 mL) at 0 °C. When the reaction was complete, the solvent was removed in a rotary evaporator. The residue was dissolved in ether, washed several times with saturated NH_4Cl, and dried over Na_2SO_4. Pure benzonitrile was obtained in 83% yield (85 mg) after flash chromatography upon elution with hexane/EtOAc (1:1). Spectroscopic data (^{1}H and ^{13}C NMR and mass spectra) for the nitriles shown in Table 2 were consistent with the given structure and literature data.

Phosphoric Acid Diethyl Ester 4-Formyl-2-methoxyphenyl Ester (2). A solution of vanillin, **1** (152 mg, 1.0 mmol), in dry ether (40 mL) was cooled to 0 °C. DECP (213 μL, 1.5 equiv) and Et_3N (210 μL, 1.5 equiv) were added to the solution dropwise. After the reaction mixture was stirred at room temperature under Ar for 2 h, a solution of I_2 (304 mg, 1.2 equiv) in water/diethyl ether (3:1, v/v, 80 mL) was added. The mixture was stirred for another 40 min at room temperature. Then, the water phase was removed, and the organic phase was washed three times with 10% NaOH and once with water and dried over Na_2SO_4. Pure product **2** was obtained after solvent evaporation in 71% yield (206 mg). ^{1}H NMR ($CDCl_3$): 9.87 (s, 1H), 7.44 (m, 3H), 4.24 (m, 4H), 3.88 (s, 3H), 1.32 (dt, J = 6.5, 1 Hz, 6H) ppm. ^{13}C NMR: 190.9, 151.4, 145.9, 134.0, 124.9, 121.4, 110.9, 64.9, 56.1, 16.0 ppm. ^{31}P NMR: −6.1 ppm. MS: *m*/*z* 289 (MH^+), 288 (M^+), 154 ($[(EtO)_2P(O)OH]^+$).

Phosphoric Acid Diethyl Ester 4-((Hydroxyimino)-methyl)-2-methoxyphenyl Ester (3). A mixture of $NH_2OH\cdot HCl$ (154 mg, 4 equiv) and NaOH (89 mg, 4 equiv) in absolute EtOH (7 mL) was warmed to 70 °C. A solution of **2** (160 mg, 0.55 mmol) in absolute EtOH (8 mL) was added. After the resulting mixture was heated under reflux for 4 h, the solvent was removed under vacuum. The residue was partitioned between ether and water. The organic phase was washed three times with water and dried over Na_2SO_4. After evaporation of the solvent and drying of the compound in a vacuum oven overnight, product **3** was obtained in 81% yield (135 mg). ^{1}H NMR ($CDCl_3$): 7.95 (s, 1H), 7.22 (dd, J = 8, 1.9 Hz, 1H), 7.16 (br "t", 1H), 6.92 (dd, J = 8, 1.9 Hz, 1H), 4.18 (m, 4H), 3.78 (s, 3H), 1.28 (dt, J = 6.5, 1 Hz, 6H) ppm.

Phosphoric Acid 4-Cyano-2-methoxyphenyl Ester Diethyl Ester (4) (Scheme 2a). A solution of **3** (101 mg, 0.33 mmol) in dry $CHCl_3$ (18 mL) was cooled to 0 °C, DECP (142 μL, 3 equiv) was added dropwise, and then the reaction mixture was stirred at room temperature under Ar for 2 h. The mixture was evaporated to dryness in vacuo followed by addition of ether and water (20 mL of each) to the residue. After the mixture was stirred for another 30 min, the organic phase was washed five times with 10% NaOH, dried over Na_2SO_4, and evaporated. Pure phosphoric acid triester **4** was obtained as an oil (R_f 0.40 with hexane/EtOAc, 3:2) in 96% yield (91 mg). ^{1}H NMR ($CDCl_3$): 7.35 (dd, J = 8.5, 1.5 Hz, 1H), 7.20 (ddd, J = 8.5, 1.6, 0.4 Hz, 1H), 7.14 (m, 1H), 4.24−4.13 (dq, 4H), 3.83 (s, 3H), 1.36−1.21 (dt, J = 6.5, 1 Hz, 6H) ppm. ^{13}C NMR: 151.1 (d, J_{PC} = 6.0 Hz), 143.7 (d, J_{PC} = 6.8 Hz), 125.5, 122.0 (d, J_{PC} = 3.0 Hz), 118.3, 115.8, 109.2, 65.0 (d, J_{PC} = 6.0 Hz), 56.3, 16.0 (d, J_{PC} = 6.0 Hz) ppm. ^{31}P NMR: −6.1 ppm. MS: *m*/*z* 303 (M + NH_4^+), 286 (MH^+). HRMS (DCI, isobutane): calcd for $C_{12}H_{16}NO_5P$ 285.0766, found 285.0749.

Phosphoric Acid 4-Cyano-2-methoxyphenyl Ester Diethyl Ester (4) (Scheme 2b). DECP (120 μL, 1.2 equiv, 0.80 mmol) in dry THF (5 mL) was added to a solution of 3-methoxy-4-hydroxybenzonitrile, **6** (100 mg, 0.67 mmol, the preparation of **6** is described in the typical procedure and in Table 2), in dry THF (10 mL) under Ar at 0 °C, followed by addition of solution of Et_3N (113 μL, 1.2 equiv, 0.80 mmol) in THF (5 mL). The solution was stirred for 3 h at room temperature, then treated with a solution of I_2 (200 mg, 0.80 mmol, 1.2 equiv) in water/THF (1:1, v/v, 15 mL), and stirred for another hour. Excess I_2 was removed by washing with 10% $Na_2S_2O_3$ solution, and the organic phase was dried over Na_2SO_4. Evaporation of the solvent followed by chromatography (silica gel, EtOAc) gave pure phosphoric acid triester **4** in 79% yield (151 mg).

(4-Formylphenyl)phosphoramidic Acid Diethyl Ester (8). DECP (286 μL, 3 equiv) and Et_3N (278 μL, 3 equiv) were added to a solution of 4-nitrobenzaldehyde (100 mg, 0.66 mmol) in dry $CHCl_3$ (3 mL) under Ar at −10 °C. The solution was warmed to 0 °C and stirred at this temperature for 3 h. The solvent was removed under reduced pressure, and the residue was purified by chromatography (silica gel, EtOAc) to give the pure product **8** in 78% yield (131 mg). ^{1}H NMR ($CDCl_3$): 9.79 (s, 1H), 7.70 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 9 Hz, 1H), 7.08 (d, J = 8.5 Hz, 2H), 4.10 (m, 4H), 1.26 (dt, J = 6.5, 1 Hz, 6H) ppm. ^{13}C NMR: 191.1, 176.9, 146.2, 131.6, 130.2, 117.1 (7.5 Hz), 97.5, 63.2 (4.5 Hz), 16.1 (7.0 Hz) ppm. ^{31}P NMR: 1.9 ppm. MS: *m*/*z* 275 (M + NH_4^+), 258 (MH^+).

[4-((Hydroxyimino)methyl)phenyl]phosphoramidic Acid Diethyl Ester (9). NaOH (15.0 mg, 4 equiv) and $NH_2OH\cdot HCl$ (26.0 mg, 4 equiv) were added to a solution of **8** (24 mg, 0.093 mmol) in absolute EtOH (8 mL). The solution was heated under reflux for 4 h. The solvent was removed under reduced pressure, and the residue was partitioned between diethyl ether and water (10 mL of each). The organic phase was washed three times with water and dried over Na_2SO_4, and the solvent was removed under vacuum. Product **9** was obtained as a white solid, mp 135 °C, in 91% yield (23 mg) after being dried in a vacuum oven overnight (R_f 0.50 with EtOAc as the eluent). ^{1}H NMR ($CDCl_3$): 8.00 (s, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.15 (br. s, 1H), 6.93 (d, J = 8.4 Hz, 2H), 4.13 (m, 4H), 1.23 (t, J = 6 Hz, 6H) ppm. ^{13}C NMR: 149.4, 141.5, 128.1, 125.6, 117.4 (7.5 Hz), 63.10 (4.5 Hz), 16.05 (7.0 Hz) ppm. ^{31}P NMR: 3.1 ppm. MS: *m*/*z* 272 (M^+), 227 (M^+ − OEt). HRMS (DCI, isobutane): calcd for $C_{11}H_{17}N_2O_4P$ 272.0926, found 272.0912.

4-(Cyanophenyl)phosphoramidic Acid Diethyl Ester (10). Et_3N (35.5 μL, 3 equiv) was added to a solution of **9** (23 mg, 0.084 mmol) in dry $CHCl_3$ (3 mL) under Ar at −40 °C, followed by the addition of DECP (36 μL, 3 equiv) and stirring for 20 min at −40 °C. Then the solution was washed once with water and three times with 10% NaOH, dried over Na_2SO_4, and evaporated to dryness. Pure product **10** was obtained as a white solid, mp 108 °C, in 91% yield (20 mg) (R_f 0.71 with EtOAc as the eluent). The product was obtained in a comparable yield when the reaction was repeated without the addition of Et_3N. ^{1}H NMR ($CDCl_3$): 7.50 (br d, J = 9 Hz, 1H), 7.47 (d, J = 9 Hz, 2H), 7.04 (d, J = 9 Hz, 2H), 4.13 (m, 4H), 1.27 (dt, J = 6.5, 1 Hz, 6H) ppm. ^{13}C NMR: 144.5, 133.5, 132.1, 131.6, 128.9, 119.2, 117.5 (J_{PC} = 7.5 Hz), 104.3, 63.2 (J_{PC} = 4.5 Hz), 16.1 (J_{PC} = 7.0 Hz) ppm. ^{31}P NMR: 1.7 ppm. MS: *m*/*z* 272 (M + NH_4^+), 255 (MH^+). HRMS (CI, isobutane): calcd for $C_{11}H_{15}N_2O_3P$ 254.0820, found 254.0816.

2-Cyano-6-methoxy-4-nitrophenol (12). DECP (362 μL, 6 equiv) was added to dry **11** (90 mg, 0.425 mmol) in dry CH_3CN (20 mL) at 0 °C. Then, the reaction mixture was stirred at room temperature for 3 h. TLC, eluted with EtOAc, showed that starting material disappeared and a new yellow spot appeared at R_f 0.43. The solution was evaporated to dryness under high vacuum (most of the DECP and hydrogen phosphonate were removed), and the residue was purified on a silica gel column eluted with EtOAc. The yellow solid obtained was dried under high vacuum overnight to give pure product **12** in 95% yield (77 mg).^{1}H NMR (acetone-d_6): 8.06 (d, J = 1.5 Hz, 1H), 7.75 (d, J = 1.5 Hz, 1H), 4.03 (s, 3H) ppm. ^{13}C NMR: 150.0, 122.3, 116.3, 108.1, 98.2, 56.2 ppm. MS: *m*/*z* 194 (M^+). HRMS (DCI, isobutane): calcd for $C_8H_6N_2O_4$ 194.0327, found 194.0322.

Phosphoric Acid 2-Cyano-6-methoxy-4-nitrophenyl Ester Diethyl Ester (13). DECP (213 μL, 1.5 mmol) in dry toluene (5 mL) was added to a solution of **11** (98 mg, 0.46 mmol) in toluene (35 mL) at 0 °C. The mixture was stirred at 90 °C under Ar. After 12 h starting material was completely

consumed. An additional 4 equiv of DECP and Et_3N in toluene were added while the reaction mixture was cooled to 0 °C. The contents were then stirred at 90 °C for 12 h. The solvent was removed under vacuum, and the residue was treated with I_2 (140 mg, 1.2 equiv in water/diethyl ether, 3:1, v/v, 80 mL). After being dried over Na_2SO_4, the residue was separated on silica gel (EtOAc) to give pure **13** as a yellow semisolid in 25% yield (38 mg). ^{1}H NMR ($CDCl_3$): 8.13 (d, J = 1.5 Hz, 1H), 8.02 (d, J = 1.5 Hz, 1H), 4.40 (m, 4H), 4.04 (s, 3H), 1.25 (dt, J = 6.0, 1.5 Hz, 6H) ppm. ^{31}P NMR: −7.3 ppm. MS: m/z 331 (MH^+). HRMS (DCI, isobutane): calcd for $C_{12}H_{16}N_2O_7P$ 331.0695, found 331.0703.

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Supporting Information Available: Copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra and high-resolution mass spectra of **4**, **6**, **9**, **10**, **12**, **13**, and **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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