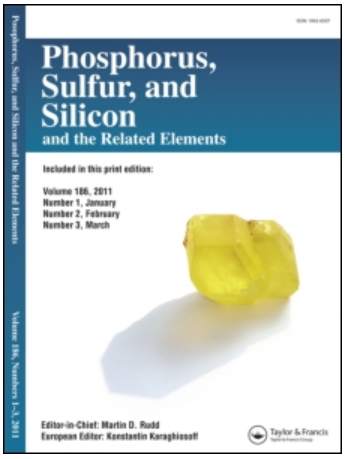

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Highly Efficient P(III)-to-P(V) Oxidative Rearrangement

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A rapid and efficient P(III)-to-P(V) intramolecular rearrangement of N-[(phosphino)oxy] amines is reported. This intermediate is generated in situ from the reaction of hydroxylamines with chlorophosphites or chlorophosphoramidites and with rearrangement via the cleavage of the weaker N—O bond to generate a more stable P═O bond. The reaction proceeds spontaneously in an excellent yield when the hydroxylamine is electron poor. Various substituents on the phosphorus are well-tolerated.

Keywords Chlorophosphite; chlorophosphoramidite; hydroxylamine; (phosphino)oxy amine; rearrangement

INTRODUCTION

P(III)-containing molecules are good nucleophiles due to the great polarizability of the phosphorus lone pair of electrons. This is especially true for di- or tri-alkyl/aryl/alkoxy substituted phosphines and favors the rearrangement of P(III) to P(V).[1,2]

A number of P(III)-to-P(V) transformations have been reported, the most common of which is the Arbuzov reaction.[2,3,4,5] This reaction is believed to proceed in two steps via the nucleophilic attack of the phosphorus on an alkyl halide to generate an alkylated phosphonium intermediate. This is followed by the cleavage of one of the alkoxy C—O bonds to form a phosphoryl (P═O). Owing to the relative high strength of C—O bonds, the second step is normally rate-determining and the

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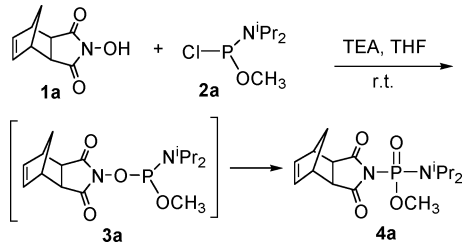
rearrangement usually requires a high temperature, yet offers moderate yields.[2]

It should be emphasized that most P(III)-to-P(V) rearrangements reported involve the formation of a P=O bond at the expense of C—O bond cleavage. We report here a highly efficient P(III)-to-P(V) rearrangement of *N*-[(phosphino)oxy] amines, where a P-O bond is formed at the expense of an N—O bond. Similar rearrangements were reported in 1976 with cyclic aminophosphines[6] and in 1989[7] with chlorophosphites; however, either the yields were low and/or a complex mixture was obtained. Bailly and Burgada reported a more extensive study of this rearrangement but only tested cyclic phosphines.[8] More recently, Sekine and coworkers have suggested that phosphites and H-phophonates may be oxidized by 1-hydroxybenzotriazole (HOBt) derivatives via an analogous rearrangement.[9] This oxidation was shown to be of use in the preparation of oligonucleotides using the N-unprotected approach.[10] We recently encountered a similar rearrangement between electron-poor hydroxylamines and various chlorophosphines. The high efficiency of our reaction prompted us to investigate its scope. It was envisioned that this P(III)-to-P(V) rearrangement could be used to synthesize a wide range of organophosphorus compounds such as phosphoramidates, phosphorodiamidates, phosphonamidates, phosphonic diamides, phosphinic amide, and phosphoric triamides. These organophosphorus compounds are often important synthetic reagents or biologically active molecules.[2,11,12] For example, phosphonates and their derivatives are important analogs of peptides,[13,14] nucleic acid,[15] and lipids.[16]

RESULTS AND DISCUSSION

In our initial experiment, the reaction of substituted hydroxylamine **1a** with chlorophosphoramidite **2a** in the presence of triethylamine proceeded rapidly and quantitatively to give the phosphorodiamidic acid ester **4a**, without detection of the expected phosphoramidite **3a** (Scheme 1). Although **3a** and **4a** cannot be differentiated by mass spectrometry, ^{31}P-NMR clearly revealed the difference. Trivalent phosphorus-containing molecules such as phosphite **3a** are expected to show ^{31}P chemical shifts around 140 ppm relative to 85% phosphoric acid, whereas the chemical shift of pentavalent phosphorus compounds like **4a** generally is at a higher field (*ca.* 1 ppm).[17,18,19] The expected range of ^{31}P chemical shifts for the products were confirmed using commercially available material. The formation of the intermediate phosphoramidite **3a** was observed when the reaction was monitored over time by ^{31}P NMR ($\delta = 141.56$ ppm). It was apparent for only about 5 min at r.t. before rearranging to the thermodynamically more stable product **4a** (Figure 1). To further confirm the structure of **4a**,



SCHEME 1

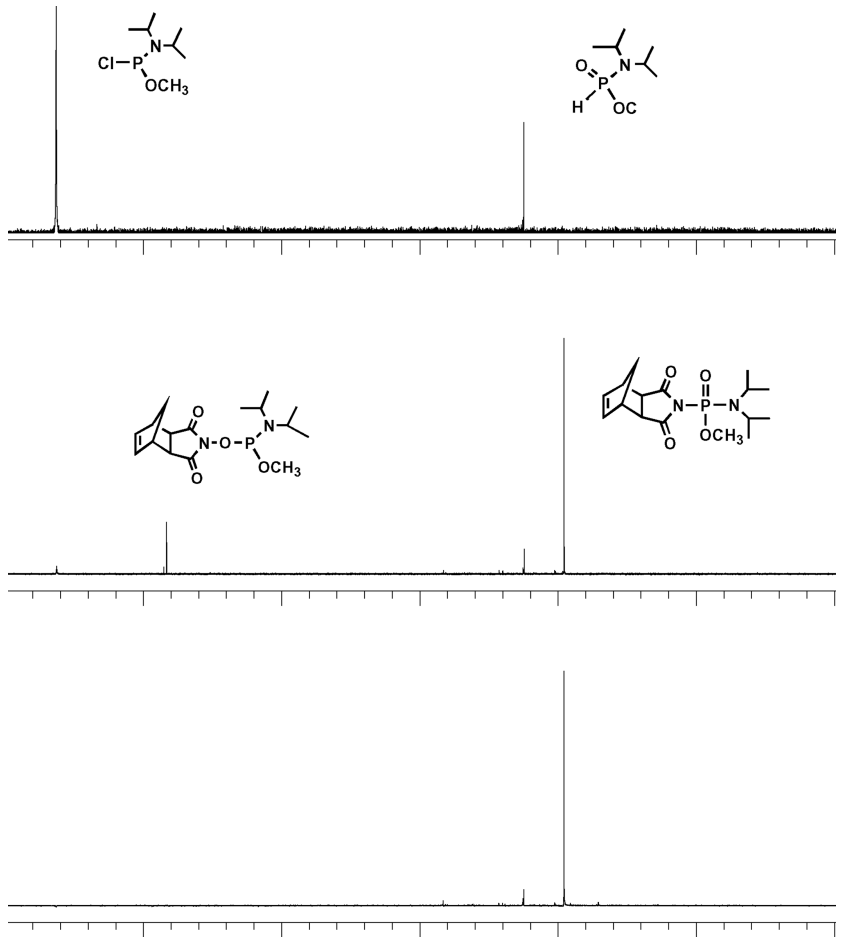
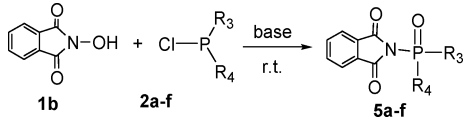


FIGURE 1 ^{31}P NMR spectra at different time points for the reaction shown in Scheme 1. (a) spectrum of **2a** (0.15 M) in CD_2Cl_2 before starting the reaction; (b) 5 min after the addition of **1a** (0.15 M) to **2a**; and (c) 2 h after starting the reaction.

tert-butylhydroperoxide and *m*-chloroperbenzoic acid were allowed to react separately with the product and as expected, no changes in ^{31}P chemical shift were apparent (data not shown).

The rearrangement was complete within 2 h. Surprisingly, the reaction was very clean and no chromatography was needed for purification. Acidic and basic aqueous washes of the crude product were sufficient to yield a product of >95% purity. Compound **4a** was quite stable, even when exposed to air at r.t. combined with the strong IR absorbance around 1270 cm^{-1}, this suggests conversion of P(III) to P(V).

When *N*-hydroxyphthalimide (**1b**) was used instead of **1a** (Scheme 2), the rearrangement proceeded to >92% for different chlorophosphites or chlorophosphoramidites (entries 1–5, Table I) except for bis(diisopropylamino)chlorophosphoramidite (entry 6, Table I). This reduced yield may be explained by a steric hindrance caused by the two diisopropylamino groups.



SCHEME 2

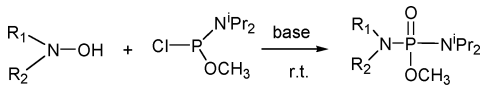
THF, acetonitrile, or dichloromethane could be used without any significant effect on the reaction yields, but polar solvents significantly increased the rate of the rearrangement process. Whether the transformation was carried out at −20°C or at r.t. also did not affect the results. However, the reaction appeared to be less tolerant towards substitutions at the hydroxylamine moiety. The results are summarized in Scheme 3 and Table II.

TABLE I Results for the Reactions of Scheme 2

Entry	R_3	R_4	Product	Yield[a,b]	δ ^{31}P (ppm)
1	OCH_3	$N[CH(CH_3)_2]_2$	**5a**	98%	1.73
2	OCH_2CH_2CN	$N[CH(CH_3)_2]_2$	**5b**	96%	0.56
3	OCH_2CH_3	OCH_2CH_3	**5c**	95%	−7.55
4	$CH(CH_3)_2$	$CH(CH_3)_2$	**5d**	97%	63.40
5	Ph	Ph	**5e**	92%	17.93
6	$N[CH(CH_3)_2]_2$	$N[CH(CH_3)_2]_2$	**5f**	31%	6.99

[a]all reactions were carried at room temperature for 2 h in dichloromethane and using the base diisopropylethylamine. No chromatography was required to purify except for 5f.

[b]Isolated yield.



1a-h **2a** **4a, 5a, 6a-f**

SCHEME 3

Although formation of the intermediate remains extremely rapid (based on NMR studies), the efficiency of the rearrangement appears to be significantly dependent on the electron density at the nitrogen atom of the hydroxylamine. Electron-poor hydroxylamine derivatives undergo rapid and efficient (92–99%) rearrangement within a few hours (entries 1–5 in Table I and entry 7 in Table II). This suggests a weakening of the hydroxylamine N—O bond by electron-withdrawing groups. Greater electron density around the nitrogen atom, e.g., with a single carbonyl or sulfonyl substituent (entries 8 and 9, Table II), does not affect the formation of the P—O—N-containing intermediate but leads to a slower rearrangement.

This confirms earlier data for the reaction between *N*-methyl-*N*-*p*-tolyl-hydroxylamine and chlorophosphites, chlorophosphonites, or chlorophosphinites (with phenyl, ethoxy, or ethylenedioxy substituents) for which multiple nonrecoverable products were reported in addition to the desired rearrangement product.[7] Based on CIDNP NMR studies,

TABLE II Results for the Reactions of Scheme 3

Entry	N-hydroxyl-amines	R_1 and R_2	Product	Yield[a]	δ ^{31}P (ppm)
7	**1a**	See **1a**	**4a**	95%[b]	1.38
1	**1b**	See **1b**	**5a**	98%[b]	1.73
8	**1c**	$PhSO_2$- and H	**6a**	58%[b]	3.75
9	**1d**	PhCO- and H	**6b**	≤30%[c]	2.31
10	**1e**	iPr and H	**6c**	≤30%[c]	13.55
					12.41
					12.12
11	**1f**	Et and Et	**6d**	≤30%[c]	19.86
					5.78
12	**1g**	$(CH_3)_2C$=	**6e**	≤50%[c]	7.50
13	**1h**	Ph_2C=	**6f**	≤30%[c]	2.90

[a]All reactions were carried at room temperature for 2 h in dichloromethane and using the base diisopropylethylamine except for **4a**, where triethylamine was used.

[b]Isolated yield.

[c]by ^{31}P NMR (data not shown).

the authors suggested that the rearrangement proceeded by a radical mechanism. The observed reactivity trend reported here suggests the importance of using electron-poor hydroxylamines (e.g. **1a** or **1b**). Table II demonstrates that the presence of an *N*-benzosulfonyl (**1c**) substituent on the hydroxylamine moiety accelerates the rearrangement more than that of a *N*-benzocarbonyl (**1d**) group. Finally, in the absence of any electron-withdrawing substituents the rearrangement is even slower and yields a complex mixture (entries 10 and 11, Table II).

Others have previously reported that cyclic aminophosphines react almost as efficiently as cyclic chlorophosphines in similar rearrangements,[8] hence, aminophosphines were not tested here. The use of oximes instead of hydroxylamine derivatives have also been reported[6] and was briefly tested here. Acetone oxime and benzophenone oxime proceeded with a moderate-to-low yield as expected from a previous report[8] (entries 12 and 13, Table II), whereas *syn*-benzaldehyde oxime proceeded *via* a Beckman rearrangement[20,21] to yield benzonitrile and *N*, *N*-diisopropyl-methyl-phosphonamidic acid ester as the major products. These results are consistent with the reactivity trend observed for hydroxylamine derivatives.

In summary, we have explored the scope of the P(III)-to-P(V) rearrangement of phosphites prepared from hydroxylamines and chlorophosphites. Our results demonstrate that various substituents are well-tolerated on the phosphorus atom, and when electron-poor hydroxylamines are used, the reaction proceeds very rapidly (<2 h) and cleanly (>95% purity) to give excellent yields (>90%) of rearranged products.

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