JOC Article
pubs.acs.org/joc

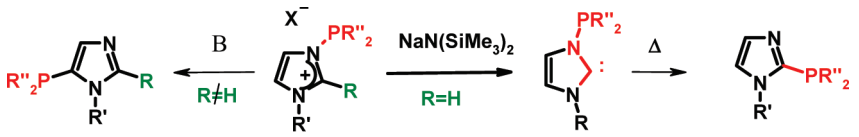
N-Phosphorylated Imidazolium Salts as Precursors to 2- and 5-Phosphorylated Imidazoles and New Imidazol-2-ylidenes Featuring the PNCN Unit

Anatolii P. Marchenko, Heorgii N. Koidan, Anastasiya N. Huryeva, Evgeniy V. Zarudnitskii, Aleksandr A. Yurchenko, and Aleksandr N. Kostyuk*

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanska Str. 5, Kyiv-94, 02094, Ukraine

a.kostyuk@enamine.net

Received June 25, 2010



It has been experimentally proven that the reaction of 1- or 1,2-disubstituted imidazoles with diorganylphosphorus(III) halides proceeds via initial formation of N-phosporylated imidazolium salts. Treatment of these salts with strong bases results in phosphorylation of the parent imidazoles at the 2- or 5-positions, correspondingly. In a previous case, imidazol-2-ylidenes are formed as intermediates. With both N1 and N3 atoms bearing sterically demanding or/and π-donating groups, deprotonation of 1,3-disubstituted imidazolium salts with $NaN(SiMe_3)_2$ afforded new stable N-phosphorus-substituted Arduengo-type carbenes.

Introduction

The chemistry of phosphorylated imidazoles has undergone intensive development due to increasing application of such compounds in metal complex catalysis, biochemistry, pharmacology, and agriculture. Among literature methods, direct phosphorylation of azaheterocycles[1] with phosphorus(III) halides is one of the most attractive and synthetically accessible methods.

In our previous work,[2,3] we studied in detail phosphorylation of 1- and 1,2-disubstituted imidazoles with phosphorus(III) mono-, di-, and trihalides in pyridine in the presence of triethylamine affording 2- and 5-phosphorylated imidazoles, respectively. As a result of exhaustive work, we have determined the optimum conditions (time, temperature, solvent) for running these reactions depending on substituents both at the phosphorus atom and at the imidazole ring. A few facts should be highlighted from these experimental studies. (a) Phosphorus bromides compared to phosphorus chlorides are much more active phosphorylating agents in these reactions. (b) Lithium halides act as catalysts in the phosphorylation, markedly increasing the rate of the reactions and their yields. (c) Reaction of 1,2-disubstituted imidazoles both with phosphorus halides and organolithium compounds (*n*-butyllithium, *tert*-butyllithium) proceeds at the fifth position of the imidazole ring probably by the same mechanism.

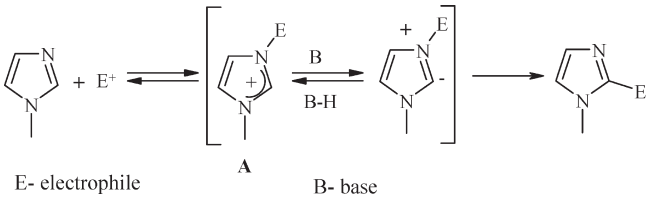
These data undoubtedly have positive value in a synthetic planning but are insufficient for understanding the mechanism of these reactions including the nature of intermediates and their role in the formation of the final products.

It is worth noting that the same is true for 1,3-azoles. For electrophilic substitution reactions of 1,3-azoles, the so-called "ylide" mechanism[4] is commonly accepted assuming, initial formation of *N*-acylazolium salts of type A[5] in the case

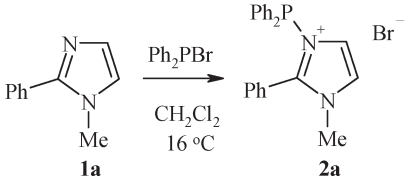
(1) Van der Jeught, S; Stevens, C. V. *Chem. Rev.* **2009**, *109*, 2672.
(2) Yurchenko, A. A.; Huryeva, A. N.; Zarudnitskii, E. V.; Marchenko, A. P.; Koidan, G. N.; Pinchuk, A. M. *Heteroatom Chem.* **2009**, *10*, 289.
(3) Huryeva, A. N.; Marchenko, A. P.; Koidan, G. N.; Yurchenko, A. A.; Zarudnitskii, E. V.; Pinchuk, A. M.; Kostyuk, A. N. *Heteroatom Chem.* **2010**, *3*, 103.
(4) Belenkii, L. I.; Chuvylkin, N. D. *Khim. Geterosikl. Soedin.* **1996**, *11*/*12*, 1535.
(5) (a) Grimmett, M. R. *Adv. Heterocycl. Chem.* **1980**, *27* (241), 297. (b) Regel, E.; Büchel, K.-H. *Justus Lieb. Ann. Chem.* **1977**, *1*, 145. (c) Bastiaansen, L. A.; Godefroi, E. F. *Synthesis* **1978**, 675.

DOI: 10.1021/jo101177h Published on Web 10/06/2010

SCHEME 1



SCHEME 2



of acylation of 1-substituted imidazoles[6] and their condensed derivatives[7] (Scheme 1).

Probably, in pyridine electrophilic substitution of imidazoles with phosphorus (P^{III}) halides the reaction also proceeds via initial formation of N-phosphorylated imidazolium salts of type A. In this paper, we report on the synthesis of such intermediates, their reactivity, and their role in the formation of the 2-and 5-phosphorylated imidazoles.

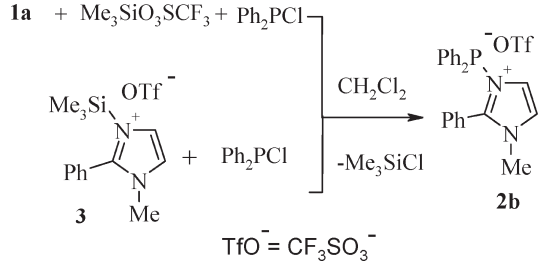
Results and Discussion

Determined by ^{31}P NMR spectroscopy, it has been found that chlorophosphines R_2PCl (R = Ph, *t*-Bu, *i*-Pr_2N) on mixing with 1,2-disubstituted imidazoles in methylene chloride, ether, or pyridine at room temperature do not form stable intermediates so that the starting materials are present in the reaction mixture. Heating the reaction mixture results in the final 5-phosphorylated imidazoles. Intermediary products were neither separated nor registered in the reaction mixture spectroscopically. We assumed that it was due to high nucleophilicity of a chloride anion. In using phosphorus bromides we found that diphenylbromophosphine easily reacts with imidazole **1a** in methylene chloride affording stable salt **2a** (Scheme 2) exhibiting the ^{31}P NMR chemical shift at the range 67−68 ppm as a sharp singlet. In pyridine, the signal has the same value but appears as a broad singlet. The salt **2a**, a colorless low melting crystalline compound, is partially soluble in ether and less soluble in pentane.

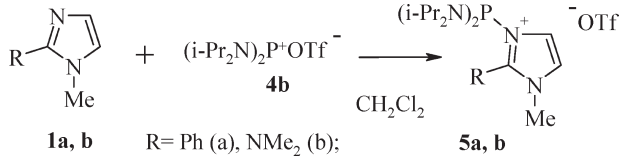
Bromophosphines such as *t*-Bu_2PBr and (*i*-$Pr_2N)_2PBr$ do not form analogous phosphonium salts probably because of increased steric hindrance of the substituents at the phosphorus atom.

One can expect that imidazolium salts of type **2a** bearing a triflate anion would be stable like triflate poly onio derivatives of pyridine and quinuclidine.[8] To this end, we have developed two approaches to these compounds using diphenylchlorophosphine. Imidazolium triflate **2b** can be easily prepared either by treatment of imidazole **1a** with trimethylsilyl triflate and diphenylchlophosphine or by the reaction of

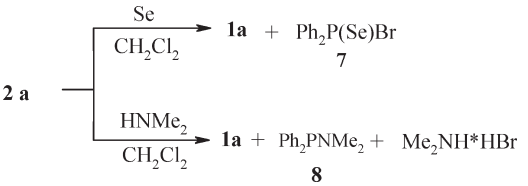
SCHEME 3



SCHEME 4



SCHEME 5



diphenylchlophosphine with *N*-silylimidazolium salt **3** prepared beforehand by the reaction of imidazole **1a** with trimethylsilyl triflate by the known procedure[10] (Scheme 3).

We found that imidazoles **1a**,**b** react readily with bis(diisopropylamino)phosphenium triflate **4b**[9] affording imidazolium triflates **5a**,**b** in high yields (Scheme 4). Structures **5a**,**b** are crystalline, high-melting compounds, insoluble in ether. In methylene chloride, the ^{31}P NMR signals appear in the range 106−115 ppm. In pyridine immediately after dissolving, compound **5a** has a broad signal at 106 ppm that gradually over 48 h shifts downfield to 145 ppm.

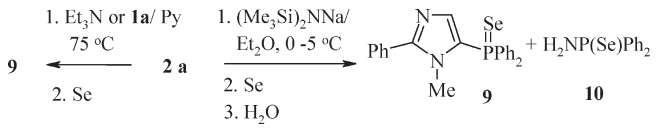
Imidazolium salts **2** and **5** feature highly labile P−N bonds demonstrated in the example of salt **2a**. It reacts with selenium and dimethylamine with cleavage of the P−N bond (Scheme 5).

We have studied the influence of other bases on salts **2** and **5**. Thus, the treatment of imidazolium salt **2a** with a sterically hindered base such as sodium hexamethyldisilazanide caused migration of the diphenylphosphino group from the N(3) atom to the fifth position affording (1-methyl-2-phenylimidazol-5-yl)diphenylphosphine (^{31}P NMR, $\delta = -33$ ppm) as the major product (75%) and amidophosphine (^{31}P NMR, $\delta = 29$ ppm) as a minor product.[2] To separate these compounds, the reaction mixture was treated with selenium giving selenides **9** and **10** that resulted from hydrolysis on further workup. The compounds were separated by crystallization (Scheme 6).

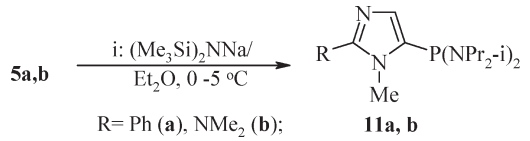
In the case of bulky diisopropylamino groups on the phosphorus atom, formation of amidophosphine of type **10** is completely suppressed. Thus, treatment of compounds **5a**,**b** with sodium hexamethyldisilazanide afforded phosphonite

(6) Hlasta, D. J. *Tetrahedron* **1990**, *31*, 5833.
(7) (a) Anders, E.; Gassner, T. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 289. (b) Anders, E.; Boldt, H.-G.; Fuchs, R.; Gassner, T. *Tetrahedron Lett.* **1984**, *25*, 1715–1716.
(8) Weiss, R.; Engel, S. *Synthesis* **1991**, 1077.
(9) Weiss, R.; Roth, R. *J. Chem. Soc., Chem. Commun.* **1987**, *5*, 317.
(10) (a) Roques, C.; Mazières, M.-R.; Majoral, J.-P.; Sanchez, M. *Inorg. Chem.* **1989**, *28*, 3931. (b) Kim, T. C.; Mazières, M.-R.; Sanchez, M. *Tetrahedron Lett.* **1990**, *31*, 4459.

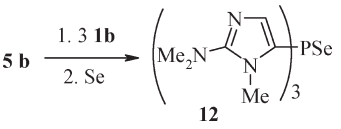
SCHEME 6



SCHEME 7



SCHEME 8



11a,**b** in high yields. These are distillable liquids that solidify on storage (Scheme 7).

Treatment of salt **2a** with tertiary bases led to 5-C-phosphorylated imidazoles similar to acylation of 2-unsubstituted imidazoles.[4,5] Thus, heating at 75 °C salt **2a** in pyridine in the presence of such tertiary bases as triethylamine or imidazole **1a** results in the phosphine that can be isolated as its selenide **9** in 65−72% yield (Scheme 6).

It is noteworthy that compound **5b** does not react with triethylamine, but the reaction with an excess of imidazole **1b**, 3−4 equiv, at 75 °C results in tris(imidazol-5-yl)phosphine (^{31}P NMR δ = −85.6 ppm)[2] instead of the expected phosphonite **11b** (Scheme 8).

Thus, summarizing the data obtained, one can conclude that direct phosphorylation of 1,2-disubstituted imidazoles proceeds via formation of the N(3)-phosphorylated imidazolium salts. This process is reversible and is stipulated by weakness of the P−N bond and correlates with the above-mentioned instability of the imidazolium chlorides as well as weaker phosphorylating ability of chlorophosphines compared to bromophosphines.[2]

Broadening of the signals of salts **2** and **5** in pyridine shows that use of donor solvents (ether, THF, pyridine, and triethylamine) also facilitates dissociation of the intermediates on the starting components so that the rate of formation of 5-phosphorylated imidazoles decreases. At the same time, in basic medium the reaction thermodynamically shifts to formation of a carbanion at the C5 position of the imidazoles followed by intermolecular attack by a phosphorus group at N(3) or a halogenophosphine giving the final product (Scheme 9). Use of the starting imidazole as a base (instead of pyridine or triethylamine) as shown previously facilitates the reaction affording better yields of 5-phosphorylated imidazoles because dissociation of the salts of types **2** and **5** has a degenerate character.

Formation of 5-phosphorylated, not 4-phosphorylated, imidazoles can be rationalized by greater contribution of the resonance structure B in salts **2** and **5** so that removal of a proton from the C5 position is kinetically controlled (Scheme 9).

This regioselectivity probably does not depend on the nature of an electrophile at the nitrogen (N3). For example, the catalytic action of LiCl or LiBr on the rate of the reaction of 1,2-disubstituted imidazoles with phosphorus trihalides[2] would be logically explained by formation of highly reactive N(3)-Li imidazole derivatives. Therefore, it follows that the reaction of imidazoles with organolithium compounds initially gives N(3)-Li derivatives, and addition of LiCl would shift the equilibrium to the right increasing the overall rate of the reaction (Scheme 10).[11]

This assumption was confirmed by the following experiment. While lithiation of phosphonite **13** in the presence of 1 equiv of LiCl comes to completion in 4 h at −70 °C in almost quantitative yield (Scheme 11), in the absence of LiCl after 8 h the reaction mixture consists of ca. 60% of the unreacted phosphonite **13**.[3] 4,5-Diphosphorylated imidazole **14** was further oxidized with selenium to give selenide **15** in 89% yield. Further selenide **15** was reduced with metallic sodium in toluene to give pure **14**.

Previously unknown bis(dichlorophosphino)-4,5-imidazole **16** was prepared by the reaction of the corresponding diamide **14** with phosphorus trichloride. Diphosphine **16** is a distillable light-yellow crystalline compound. In ^{31}P NMR spectra it appears as a doublet of doublets at 114.4 and 134.6 ppm with coupling constant $^{3}J_{PP}$ = 324 Hz. It cannot be prepared by direct phosphorylation of imidazol-4-yldichlorophosphine with phosphorus trichloride in preparative quantities.[3]

Comparing our data on phosphorylation and lithiation of the 1,2-disubstituted imidazoles one can draw a conclusion that most probably both reactions proceed via the same mechanism.

As mentioned in the Introduction, imidazol-2-yldiphenylphosphine was prepared by the reaction of 1-methylimidazole with Ph_2PCl (Br, I) in pyridine at 20 °C.[12] In this work, the ^{31}P NMR signal at δ ~30 was mistakenly assigned to intermediate N-phosphorylated imidazolium salts. We now have found that 2-unsubstituted imidazole **17a**, like imidazole **1a**, reacts readily with Ph_2PBr in dichloromethane to afford imidazolium bromide **18** with the ^{31}P NMR signal at δ 67.8 (CH_2Cl_2, pyridine) (Scheme 12). In the case of diphenylchlorophosphine, stable imidazolium salts are not formed.

We have developed a method for the synthesis of *N*-imidazolium triflates using a mixture of sodium triflate and a phosphinous chloride. By this method, imidazolium triflate **19** bearing a sterically demanding di-tert-butylphosphino group was prepared (^{31}P NMR δ 116).

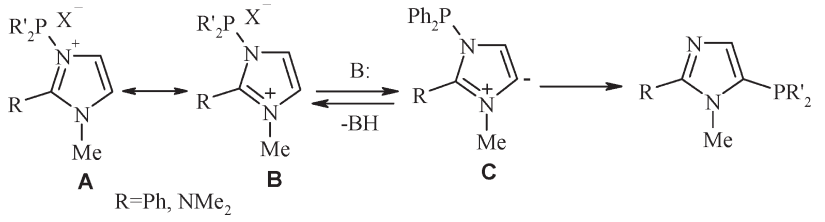
Salts **18** and **19** are crystalline compounds that are poorly soluble in ether and other nonpolar solvents. Treatment of compound **18** with triethylamine afforded the known compound phosphine **20** described by us previously (Scheme 12).[12] This compound has found wide application as a ligand in coordination chemistry and can also be prepared by the reaction of lithium imidazolide with diphenylchlorophosphine.[13]

(11) (a) Hill, C.; Bosold, F.; Harms, K.; Lohrenz, J. C. W.; Marsch, M.; Schmieczek, M.; Boche, G. *Chem. Ber.* **1997**, *130*, 1201. (b) Hilf, C.; Bosold, F.; Harms, K.; Marsch, M.; Boche, G. *Chem. Ber.* **1997**, *130*, 1213. (c) Gupta, L.; Hoepker, A. C.; Singh, K. J.; Collum, D. B. *J. Org. Chem.* **2009**, *74*, 2231.

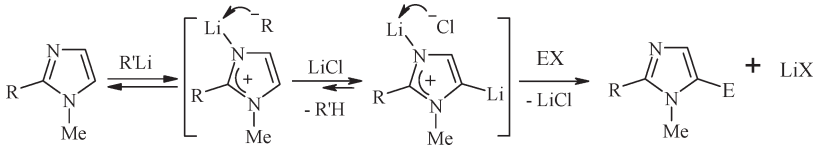
(12) Tolmachev, A. A.; Yurchenko, A. A.; Merkulov, A. S.; Semenova, M. G.; Zarudnitskii, E. V.; Ivanov, V. V.; Pinchuk, A. M. *Heteroatom Chem.* **1999**, *10*, 585.

(13) (a) Jalil, M. A.; Yamada, T.; Fujinami, S.; Honjo, T.; Nishikawa, H. *Polyhedron* **2001**, *20*, 627. (b) Chevykalova, M. N.; Manzhukova, L. F.; Artemova, N. V.; Luzikov, Yu. N.; Nifantiev, I. E.; Nifantiev, E. E. *Izv. Acad. Nauk. SSSR* [*Khim.*] **2003**, *1*, 75–80. (c) Díez, V.; Espino, G.; Jalón, F. A.; Manzano, B. R.; Pérez-Manrique, M. *J. Organomet. Chem.* **2007**, *692*, 1482.

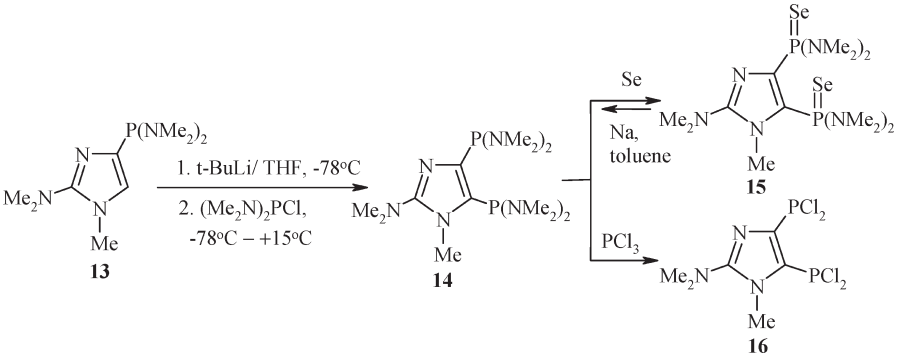
SCHEME 9



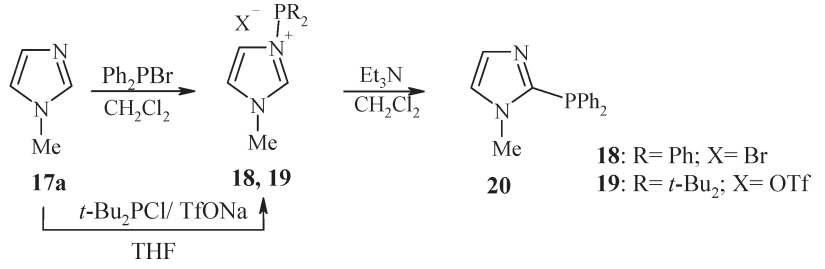
SCHEME 10



SCHEME 11



SCHEME 12



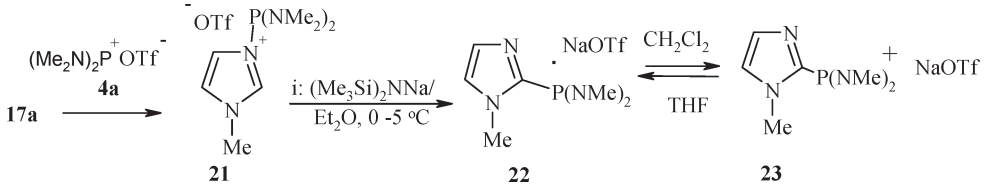
Imidazole **17a** readily reacts with bis(dimethylamino)-phosphenium triflate **4a** giving imidazolium salt **21**, a crystalline high-melting compound (Scheme 13). Treatment of compound **21** with sodium hexamethyldisilazanide gave an adduct of 2-phosphorylated imidazole **22** with sodium triflate insoluble in ether. On dissolving in methylene chloride, the adduct **22** decomposes, precipitating the sodium triflate and leaving compound **23** in ether. This process is reversible so the adduct can be prepared by dissolving phosphonite **23** and sodium triflate in THF.

Analogous salts **24a**–**c** were prepared by the reaction of imidazoles **17a**–**c** with more sterically hindered bis(diisopropylamino)phosphenium triflate **4b**. Salts **19** and **24** bearing bulky substituents at the phosphorus atom proved to be inert to bases such as triethylamine. At the same time, the reaction of salts **24a**–**c** with sodium hexamethyldisilazanide afforded previously unknown carbenes of new type **25a**–**c**. Likewise, salt **19** having a di-*tert*-butylphosphino group gave carbene **26** upon treatment with the same base (Scheme 14).

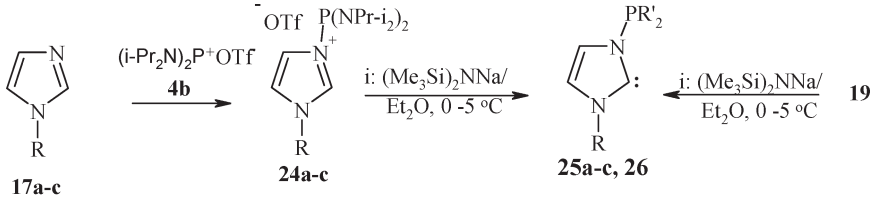
Stability of these carbenes varies widely.[14] In ^{31}P NMR spectra, carbene **25a** exhibits as a singlet at δ 81.0. In solution it is stable below 0 °C but completely transforms into 2-substituted imidazole **27a** in 24 h at 20 °C (Scheme 15). Like *N*,*N*′-dialkylimidazol-2-ylidenes,[15] it readily reacts with trimethylchlorosilane affording 2-trimethylsilyl-*N*-imidazole **29**[16] and bis(diisopropylamino)chlorophosphine in quantitative yield. Solid carbenes **25b**,**c** and oil **26** were separated as individual compounds, with carbene **26** being so stable that it can be distilled. On heating higher than ≥150 °C, carbenes **25b**,**c** and **26** completely transformed into 2-phosphorylated imidazoles **27b,c** and **28**.[17]

(14) Andreas A. Danopoulos, A. A.; Winston, S.; Gelbrich, T.; Hursthousea, M. B.; Toose, R. P. *Chem. Commun.* **2002**, 482.
(15) Kuhn, N.; Kratz, T.; Bläser, D.; Boese, R. *Chem. Ber.* **1995**, *128*, 245.
(16) Jutzi, P.; Sakriss, W. *Chem. Ber.* **1973**, *106*, 2815.
(17) Grotjahn, D. B.; Gong, Yi; Zakharov, L.; Golen, J. A.; Rheingold, A. L. *J. Am. Chem. Soc.* **2006**, *128*, 438.

SCHEME 13



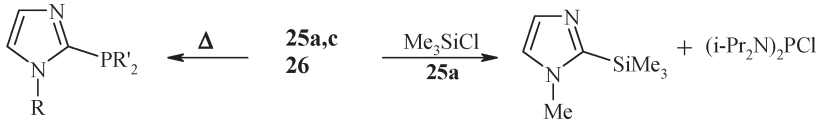
SCHEME 14



17a, 24a, 25a, 26 R=Me
17b, 24b, 25b R= t-Bu
17c, 24c, 25c R= $P(NPr\text{-}i_2)_2$

25a, 25b, 25c R'= $NPr\text{-}i_2$
26 R'= t-Bu

SCHEME 15



27a R= Me, **27b** R= t-Bu, **27c** R= $P(NPr_2\text{-}i)_2$ R'= $P(NPr_2\text{-}i)_2$
28 R= Me, R' = t-Bu

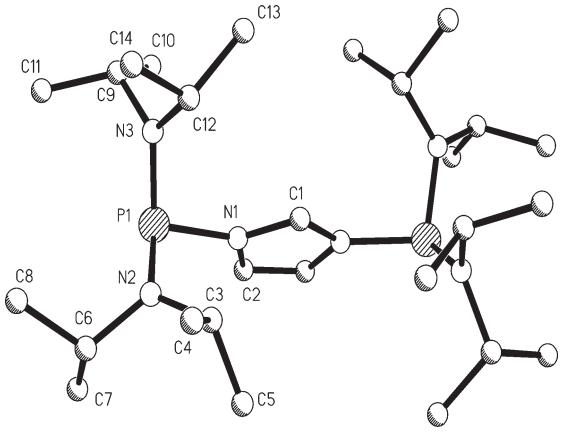


FIGURE 1. Molecular structure of **25c**.

The thermal stability of the carbenes depends on steric and electronic effects of substituents at the nitrogen atoms of imidazoles increasing in a row Me < $(i\text{-}Pr_2N)_2P$ < *t*-Bu. It is noteworthy that compared to the bis(diisopropylamino)phosphino group, the di-*tert*-butylphosphino group has a greater stabilizing effect on the imidazol-2-ylidenes.

In ^{13}C NMR spectra chemical shift of the divalent carbon is found in the region typical for singlet imidazolidin-2-ylidenes (δ 223−224).[18] The X-ray diffraction study carried out on **25c** allows comparison with numerous known imidazolidin-2-ylidenes (Figure 1).

The $N-C_{carbene}$ bond distance [1.3770(19) Å] and the carbene bond angle (102.96°) for **25c** are in the typical ranges observed for the imidazolidin-2-ylidenes (1.36−1.38 Å) and (101−103°).

Conclusion

We have developed a new method for the synthesis of 2- and 5-phosphorylated imidazoles based on 1- and 1,2-disubstituted imidazoles and diorganylphosphorus(III) halides. We have shown experimentally that N-phosphorylated imidazolium salts are intermediates in the reaction. Based on found results, we can assume that both phosphorylation and lithiation of imidazoles proceed via the same mechanism. Both reactions experience marked acceleration upon addition of lithium halides. N-Phosphorylated imidazolium salts are precursors to stable imidazol-2-ylidenes that on heating at 20−150 °C transform into 2-phosphorylated imidazoles. These data strongly suggested that phosphorylation of azines and azole bearing a pyridine nitrogen atom will proceed via the same "carbene mechanism".

Supporting Information Available: Experiemntal details and NMR spectra. X-ray data for **25** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

(18) (a) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39–91. (b) Tapu, D; Dixon, D. A.; Roe, C. *Chem. Rev.* **2009**, *109*, 3385–3407.