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Facile synthesis of C-phosphanylformamidines via a carbene pathway

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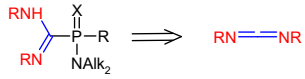
ABSTRACT

A direct synthetic approach to *C*-phosphanyl-*N*,*N*-dialkyl-*N*′-aryl(alkyl)-formamidines was developed. It was shown that phosphorylation of the formamidines proceeds at the nitrogen atom affording *N*-phosphanylformamidinium salts. Upon deprotonation, these salts gave *C*-phosphanylformamidines via formation of carbenes followed by a 1,2-phosphorus shift.

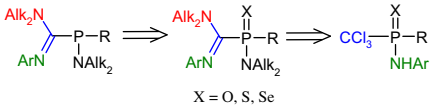
Formamidines are important organic compounds as starting materials for other syntheses, as well as being valuable in their own right.[1] *C*-Phosphanylformamidines are potential P,N-bidentate ligands because compounds of this class are actively utilized in various catalytic processes.[2] At the same time, *C*-phosphanylformamidines are only accessible with difficulty. The main method for their synthesis is via addition of either P(III)H or P(V)H compounds to carbodiimides, usually under basic catalysis. Thus, the method is limited by the availability of carbodiimides and affords only symmetrical *C*-phosphanylformamidines (Scheme 1).[3]

There are a few examples of the nucleophilic substitution with amines on *C*-phosphanylimidoyl chlorides and thioformimidic acid derivatives, but they are themselves not easily accessible compounds.[4] We have previously described a convenient approach to *C*-phosphanyl P(V) arylformamidines by the reaction of *N*-arylamidotrichloromethyl phosphoryl derivatives with secondary amines. On reduction of *N*-arylformamidino-phosphonoselenides, the corresponding *C*-phosphanyl P(III) arylformamidines were obtained (Scheme 2). This method was successfully applied to the synthesis of *C*-phosphanylformamidines bearing ferrocenyl substituents.[5]

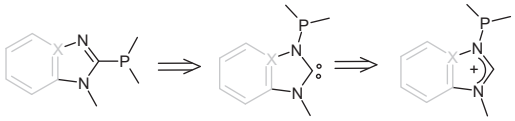
In our investigations directed at the synthesis of *C*-phosphanyl nitrogen-containing heterocycles we developed two convenient approaches via *N*-phosphanyl-substituted *N*-heterocyclic carbenes (NHCP ligands) (Scheme 3). The first involves a direct phosphanylation of the heterocycles (benzimidazoles, imidazoles, triazoles) with either di-*tert*-butylbromophosphane in tetrahydrofuran in the presence of sodium triflate, or with a phosphenium cation $(i\text{-Pr}_2\text{N})_2\text{P}^+\text{TfO}^-$ affording *N*-phosphanylazolium salts, followed by treatment with a strong base. The second occurs via deprotonation of *N*-substituted imidazoles (benzimidazoles) having bulky



Scheme 1. Synthesis of *C*-phosphanylformamidines based on addition of PH compounds to carbodiimides.



Scheme 2. Synthesis of *C*-phosphanylformamidines via *N*-arylamidotrichloromethyl phosphoryl derivatives.



Imidazole; ref. 6a and 6d; benzimidazole; ref. 6b and 6d; triazole; ref. 6c; formamidines; this work

Scheme 3. Available approaches to *C*-phosphanylheterocycles via *N*-phosphanylcarbenes.

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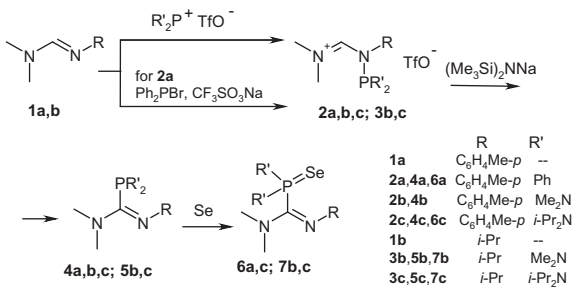


Scheme 4. Synthesis of *C*-phosphanylformamidines.

N-substituents with *n*-BuLi, followed by the reaction of the resulting Li-imidazolides with di-*tert*-butylchlorophosphane. Many of these NHCP ligands are quite stable and can be separated as individual compounds; some of them can be distilled under high vacuum. Nevertheless all these carbenes can be readily transformed into their corresponding *C*-phosphanylheterocycles.[6]

All these heterocycles (imidazole, benzimidazole, and 1,2,4-triazole) possess the formamidine moiety (N=CH–N–), on which phosphorylation proceeds. Based on this structural analogy, it might be expected that these approaches could be applied to *N*,*N*-dialkyl-*N*′-aryl(alkyl)formamidines as well.

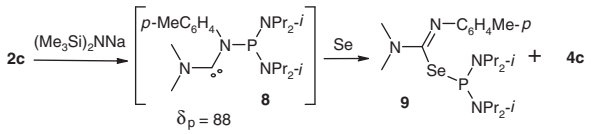
It should be noted that the direct phosphanylation of formamidines has been described using phosphorus tribromide.[7] We have found that the phosphanylation of *N*,*N*-dimethyl-*N*′-arylformamidines by PBr_3 in dichloromethane yields instead of the claimed *C*-phosphanylformamidines, cyclic zwitterionic phosphoranides as intermediate products, which were isolated.[8] It is worth mentioning that no other phosphinohalides take part in this reaction.

In contrast to 1,3-azoles, which can be deprotonated with strong bases and then enter into reactions with electrophiles, *N*,*N*-dialkyl-*N*′-aryl(alkyl)formamidines bearing the same moiety (–N=CH–N–) cannot be deprotonated as proton removal proceeds either at the α-position of the *N*,*N*-dialkylamino group, or at the α-position of the *N*′-alkyl group.[9,10] This property was successfully utilized for the synthesis of substituted amino acids[10] and flumazenil.[11]

Thus, the structural similarity of *N*,*N*-dialkyl-*N*′-aryl(alkyl)formamidines with *N*-alkylimidazoles, *N*-alkylbenzimidazoles, and *N*-alkyltriazoles allows us to assume that the approaches developed for the synthesis of *N*-phosphanylhetero-cyclic carbenes and the corresponding *C*-phosphanylheterocycles might be applied to formamidines. This Letter describes the exploration of these methods.

Indeed, we found that the previously developed method for the preparation of *N*-phosphanylazolium salts could be applied to *N*,*N*-dialkyl-*N*′-arylformamidines. Thus, diphenylbromophosphine reacts easily with *N*,*N*-dimethyl-*N*′-arylformamidine **1a** in THF in the presence of sodium triflate, affording *N*-phosphanylformamidinium triflate **2a** (Scheme 4). It is a crystalline powder, unstable in air, and insoluble in THF, petroleum ether, and diethyl ether, but soluble in methylene chloride and acetonitrile. The ^{31}P NMR signal for **2a** appears at 102.7 ppm, almost 40 ppm downfield compared to analogous imidazolium salts (61.6 ppm). The ^{1}H NMR signals of the NMe_2 group are not equivalent occurring as broad singlets at 2.56 and 3.43 ppm. The N=CH–N proton resonates at 8.2 ppm (J_{PH} 5.5 Hz), being downfield compared to the same proton in the starting formamidine **1a** (7.51 ppm). The same trend was observed for the ^{13}C signals for the N=CH–N carbon, which appears at 159 ppm as a doublet ($^{1}J_{PC}$ 53 Hz), downfield from the same carbon of the starting formamidine **1a** at 153.1 ppm.

Unfortunately, we failed to extend this approach to other phosphinohalides [tBu$_2$PBr, $(Me_2N)_2$PBr], as they did not react with formamidines **1**.



Scheme 5. The trapping reaction of carbene **8**.

We have also demonstrated that various 1,3-azoles react readily with bis-(dialkylamino)phosphenium triflate giving analogous *N*-phosphanylimidazolium triflates.[6a–c] This procedure was found to fit well for the formamidines.

It is also worth noting that azomethines react with bis-(dialkylamino)phosphenium triflate in a totally different way giving cyclic products.[12]

Formamidines **1** reacted readily with (dialkylamino)-phosphonium triflates at −90 °C to afford triflates **2b**, **2c**, **3b**, and **3c** in high yields. These compounds are white solids, and were not very soluble in ether or hydrocarbons, and were highly sensitive to air. The range of ^{31}P NMR chemical shifts for the iminium salts extends from 124.1 to 143.0 ppm. The ^{1}H NMR chemical shift for the formamidine proton ranges between 7.51 and 8.03 ppm, a downfield shift compared to the starting formamidines **1a** (7.51 ppm) and **1b** (7.28 ppm). The ^{13}C NMR chemical shift for the formamidine carbon was observed at 153–157 ppm with small or no splitting to phosphorus (Scheme 4).

Treatment of salts **2** and **3** with sodium hexamethyldisilazide gave *C*-phosphanylformamidines **4** and **5** in high yields. These compounds were separated and characterized. They are crystalline compounds, sensitive to moisture and oxygen, and readily soluble in many organic solvents such as diethyl ether, benzene, and hexane. These reactions are characterized by the disappearance of the signal due to the formamidine proton in the ^{1}H NMR spectrum and, in the ^{13}C NMR spectrum, the appearance of a signal due to the formamidine carbon, the most downfield (~160 ppm) coupled to phosphorus. Compounds **4** and **5** reacted readily with selenium to give stable pentavalent phosphorus derivatives **6** and **7**. The molecular structures of **6** and **7** were confirmed unambiguously by full sets of solution NMR spectroscopic data. In the ^{31}P NMR spectra the phosphorus signals coupled to selenium (J_{PSe} = 744–756 Hz) were indicative of these compounds.[13]

Phosphanylformamidines **4** and **5** are thought to form via a 1,2-phosphorus shift in the intermediate carbenes of type **8**. In our study on *N*-phosphanylheterocyclic carbenes, it was shown that the $(i\text{-}Pr_2N)_2P$ group stabilizes the carbenes much better compared to Ph_2P. Hence, we proposed to either isolate or detect carbene **8**. Indeed, at −95 °C, on treatment of salt **2c** with sodium hexamethyldisilazide (Scheme 5), the ^{31}P NMR spectrum exhibited a signal (δ_P 88 ppm) which could be attributed to carbene **8**. The ^{31}P NMR chemical shift for *N*-phosphanylimidazol-2-ylidenes ranges between 78 and 98 ppm.[6a]

In order to confirm the formation of carbenes, deprotonation of salt **2c** was carried out in the presence of an equimolar amount of selenium. The reaction of carbenes with group 16 elements affords stable adducts, formation of which can serve as a proof for transient and persistent carbenes.[14] Besides compound **4c**, we have separated compound **9** (Scheme 5). Its formation confirmed our hypothesis that deprotonation led to carbenes that reacted with selenium followed by a phosphorus shift from nitrogen to selenium. Although there are no previous examples of the nitrogen-selenium phosphorus shift, a similar nitrogen to sulfur shift is described in the literature, both for trivalent and pentavalent phosphorus groups.[15] Compound **9** is a stable, distillable compound. Its structure was confirmed by single crystal X-ray crystallography[16] (Fig. 1) and multinuclear NMR spectroscopy (^{1}H, ^{13}C, ^{31}P). The ^{31}P NMR signal occurred at 107.9 ppm (J_{PSe} = 240 Hz) with splitting to selenium typical for a P–Se single bond.

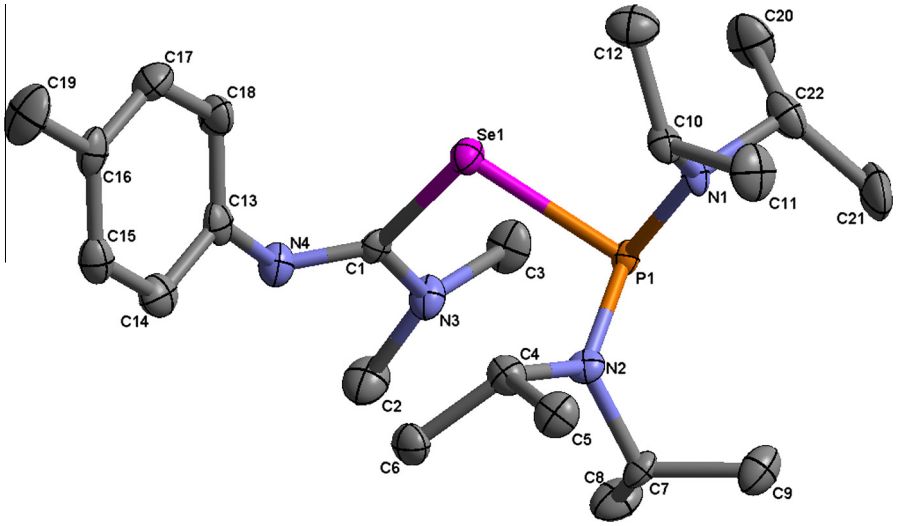


Figure 1. ORTEP plot of **9**.

In summary, our new synthetic route to *C*-phosphanyl-*N*,*N*-dialkyl-*N*′-aryl(alkyl)formamidines greatly expands the availability of compounds of this class. The accessibility of these compounds is limited only by the availability of the starting formamidines, making possible fine-tuning of the steric and electronic characteristics. Deprotonation of formamidinium triflates proceeds via the formation of carbenes followed by a 1,2-phosphorus shift.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.160.

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16. Crystallographic data (excluding structure factors) for the structure of **9** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 927183. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).