Chemistry Letters

Phosphorylation of Isocyanates and Aldehydes Mediated by Multifunctional *N*-Phosphine Oxide-Substituted Imidazolylidenes

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doi:10.1246/cl.170475

Phosphorylation of Isocyanates and Aldehydes Mediated by Multifunctional *N*-Phosphine Oxide-Substituted Imidazolylidenes

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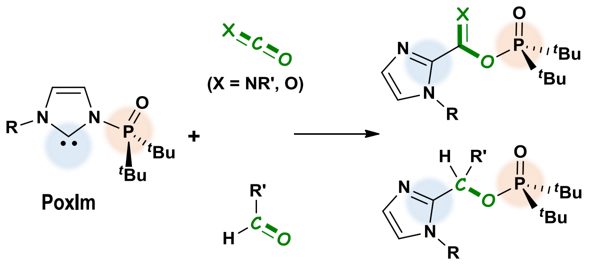
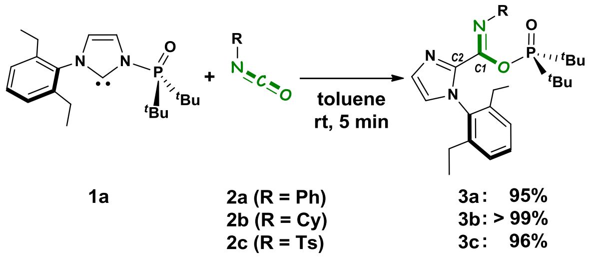
The direct syntheses of imidic-phosphinic mixed anhydrides and phosphinates were accomplished via phosphorylation of isocyanates or aldehydes with *N*-phosphine oxide-substituted imidazolylidenes (PoxIms) that are equipped with both nucleophilic carbene and electrophilic phosphorus moieties. In addition, the catalytic cyclotrimerization of phenyl isocyanate took place by employing a PoxIm having bis-*N*-phosphine oxide groups. The results presented in the current study demonstrate that judiciously designed multifunctional carbenes represent a promising potential for the phosphorylation of heterocumulenes and carbonyl compounds.

Over the past couple of decades, *N*-heterocyclic carbenes (NHCs) have found a multitude of applications in diverse research areas in organic, inorganic and organometallic chemistry.[1] The advancement of these research areas has largely benefitted from the advent of novel NHCs and other stable carbenes that exhibit unprecedented functionality.[2] Among these examples, NHC derivatives containing a phosphorus-based functional group have been extensively employed as multidentate ligands for transition metals.[3] However, there are only few reports on NHCs that contain a phosphine oxide moiety.[4,5] The reactivity of these carbenes should be of substantial interest as the phosphine oxide moiety could function as a hemi-labile coordination ligand,[4b,5c] as well as an electron-withdrawing substituent.[4a]

We developed *N*-phosphine oxide-substituted imidazolylidenes (PoxIms) as a novel type of isolable NHCs,[5a] that afforded carboxylic-phosphinic mixed anhydrides via direct phosphorylation of CO_2 (Scheme 1).[5b] The resulting mixed anhydride was subsequently transformed into a variety of unsymmetrical carbonyl compounds via the corresponding imidazolium salt followed by a sequential double substitution reaction. In this work, we envisioned that the direct syntheses of imidic-phosphinic mixed anhydrides and phosphinates could be achieved by the treatment of PoxIms with isocyanates and aldehydes, respectively (Scheme 1). These unprecedented transformations should offer novel and efficient methods for phosphorylation of carbonyl compounds.[6] Given the significant utility of these organophosphorus compounds that are frequently encountered in bioactive reagents as well as industrial commodities,[6a-d] development of an efficient phosphorylation method should be noteworthy. Herein, we report the phosphorylation of isocyanates and aldehydes by using PoxIms.



Scheme 1. Phosphorylation of heterocumulenes (X = O in the previous work; X = NR' in this work) and aldehydes mediated by PoxIm.



Scheme 2. Reaction of **1a** with isocyanates **2**. Isolated yields are given.

The reaction of phenyl isocyanate (**2a**) with PoxIm **1a** in toluene at room temperature afforded mixed anhydride **3a** in 95% yield through the formation of the oxygen-phosphorous bond (Scheme 2), which was unambiguously confirmed by single-crystal X-ray diffraction analysis (Figure 1a). In the ^{13}C NMR spectrum, the resonances for C1 and C2 are observed at δ_C 140.4 ($^2J_{C,P}$ = 12.0 Hz) and 129.2 ppm ($^3J_{C,P}$ = 12.0 Hz), respectively. In the ^{31}P NMR spectrum, the resonance for the phosphinate moiety is observed at δ_P 67.9 ppm, which is downfield-shifted relative to the phosphine oxide in **1a** (δ_P 61.4 ppm). These results are consistent with the formation of **3a**. Thus, an imidazolium-2-amidate intermediate, obtained from the reaction between **1a** and **2a**, was sufficiently reactive for the subsequent substitution of the *N*-phosphine oxide moiety. Cyclohexyl (**2b**) and tosyl (**2c**) isocyanates also reacted with **1a**, and furnished **3b** and **3c** in > 99 and 96% yield, respectively. Even though common NHCs have been reported to catalyse cyclotrimerization of isocyanates to isocyanurates,[7] a catalytic cyclotrimerization was not observed in the presence of **1a** under the applied reaction conditions in the present case. Thus, in the reactions between **1a** and **2a–c**, the intramolecular addition of the amidate moiety in the imidazolium-2-amidate intermediate to the phosphine oxide should occur far easier than the intermolecular addition to another isocyanate.

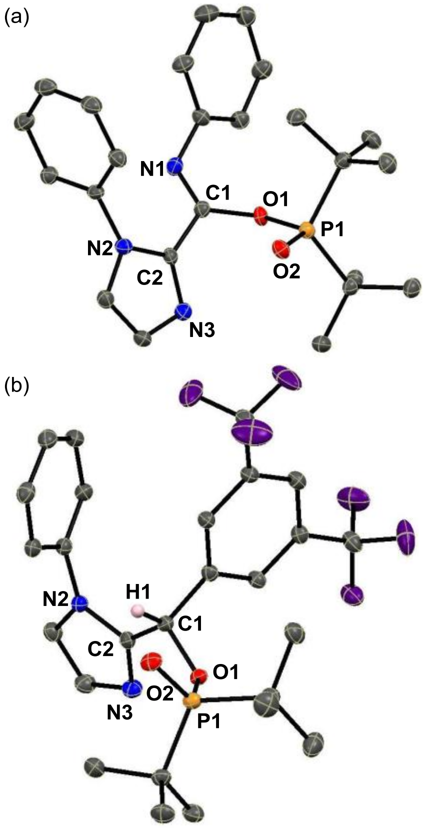
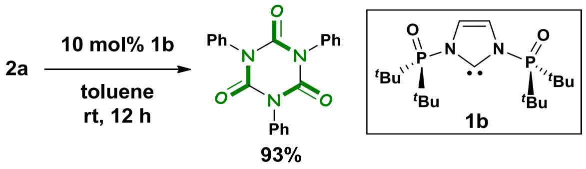
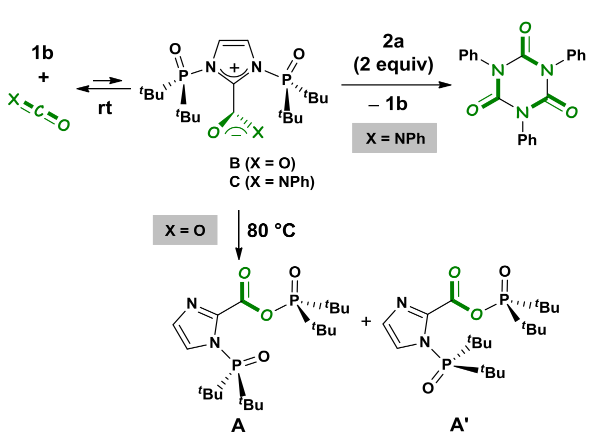


Figure 1. Molecular structures of (a) **3a** and (b) **5a**; ellipsoids are set at 30% probability. The substituent groups on the N2-Ar groups, and hydrogen atoms (except H1) are omitted for clarity.



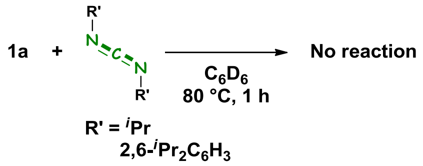
Scheme 3. Catalytic cyclotrimerization of **2a** with **1b**. Isolated yield is given.

Conversely, PoxIm **1b** containing bis-*N*-phosphine oxide groups catalysed the cyclotrimerization of **2a** at room temperature in toluene to afford triphenyl isocyanurate, which was isolated in 93% yield (Scheme 3). We previously reported the production of a mixture of **A** and **A′** from the reaction of CO_2 and **1b** at 80 °C, yet the formation of this mixture was not confirmed at room temperature (Scheme 4).[5b,8] Based on the results of this previous and the present studies, the addition of **1b** to CO_2 or **2a** would afford an imidazolium-2-carboxylate (**B**) or –amidate (**C**) intermediate at room temperature. However, the subsequent substitutions of *N*-phosphine oxide moiety via cleavage of the N–P bonds might hardly proceed at room temperature. Thus, decarboxylation from **B** or intermolecular addition to another **2a** from **C** would occur predominantly at room temperature.



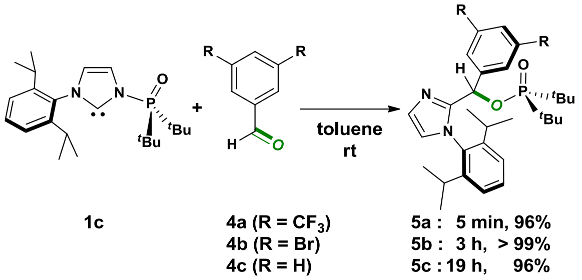
Scheme 4. Possible reaction pathways to afford triphenyl isocyanurate and a mixture of **A** and **A′**.

Treatment of **1a** with carbodiimides resulted in no reaction even at 80 °C, which was confirmed by NMR analyses (Scheme 5). It has previously been reported that NHCs with *N*-^{i}Pr groups (NHC^{iPr}) react with ^{i}PrN=C=N^{i}Pr to afford an amidinate, while a bulky cyclic (alkyl)(amino)carbene (CAAC) do not react under these conditions.[9] The steric bulkiness of these carbenes might determine whether the reaction between carbenes and carbodiimides occurs. The steric demand of these carbenes can be quantified by the $\%V_{\text{bur}}$ values ($\%V_{\text{bur}}$: **1a** = 49.9; CAAC = 50.7; NHC^{iPr} = 28.1. All of these values were given by Samb*V*ca program).[10,11]



Scheme 5. Reaction of **1a** with carbodiimides, monitored by NMR.

Subsequently, aldehydes **4** were employed instead of heterocumulenes (Scheme 6).[12] Phosphinate **5a** was obtained in 96% yield via phosphorylation of 3,5-ditrifluoromethylbenzaldehyde (**4a**) by **1c** in toluene within 5 minutes. The molecular structure of **5a** was unambiguously determined by single-crystal X-ray diffraction analysis (Figure 1b). The time required for the completion of these reactions decreased with increasing electron-withdrawing property of the substituents on aldehydes. Complete consumption of 3,5-dibromobenzaldehyde (**4b**) and benzaldehyde (**4c**) to furnish **5b** (> 99%) and **5c** (96%) thus required 3 and 19 h, respectively.



Scheme 6. Reaction of **1c** with aldehydes **4**. Isolated yields are given.

In conclusion, we developed a synthetic route to imidic-phosphinic mixed anhydrides and phosphinates via direct phosphorylation of isocyanates and aldehydes, respectively, by *N*-phosphine oxide-substituted imidazolylidenes (PoxIms). PoxIms served as i) a nucleophile to activate the carbonyl groups in isocyanates and aldehydes, as well as ii) an electrophile to transfer the phosphine oxide moieties, which lead to the formation of the mixed anhydrides and phosphinates. In addition, a PoxIm with bis-*N*-phosphine oxide groups worked as a catalyst in the cyclotrimerization of phenyl isocyanate. The current study illustrates that strategically designed multifunctional carbene reagents offer unprecedented utility for phosphorylation of carbonyl compounds in organic synthesis.

This work was supported by Grants-in Aid for Young Scientists (A) (JSPS KAKENHI Grant Number JP25708018), Encouragement for Young Scientists (B) (JSPS KAKENHI Grant Number JP15K17824), and Scientific Research on Innovative Areas “Stimuli-responsive Chemical Species (JSPS KAKENHI Grant Number JP15H00943)” and “Precisely Designed Catalysts with Customized Scaffolding (JSPS KAKENHI Grant Number JP15H05803).” Y.H. acknowledges support from the Frontier Research Base for Global Young Researchers, Osaka University, on the program of MEXT.

Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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