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Letter

A Cautionary Note on the Use of 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) in Conjunction with Chlorophosphates

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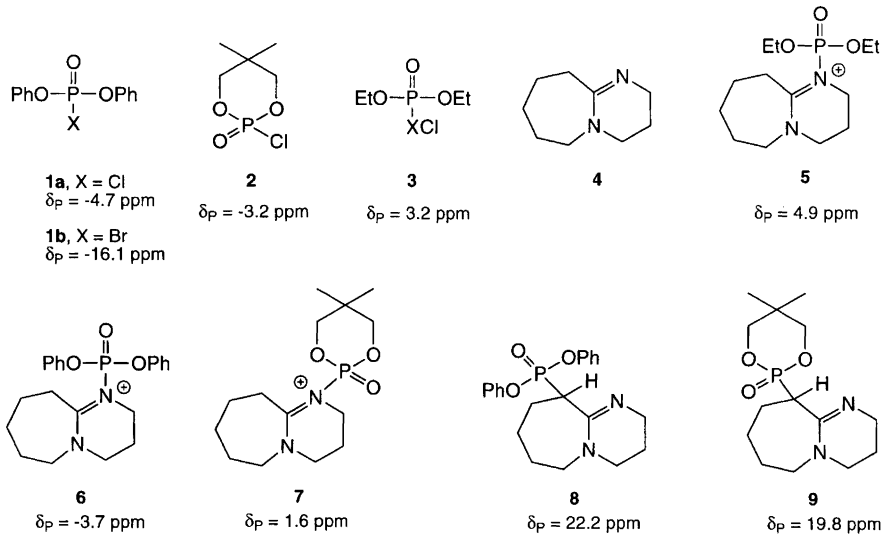
Bicyclic amidines, usually referred to as 'non-nucleophilic strong bases', are of great synthetic importance because of their efficiency in promoting various transformations that otherwise are difficult to carry out.[1–6] There is a growing body of evidence that strong catalytic effects of bicyclic amidines, e.g. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) **4** (Scheme 1), is probably not only due to their high basicity, but also to the profound nucleophilicity of nitrogen centers in these species.[2–4,6] Indeed, X-ray analysis of some complexes of DBU (and other bicyclic amidines) with P^{III} compounds clearly shows the presence of the P–N bonds.[7] Recently, using ^{31}P NMR spectroscopy, we have also detected the formation of amidines of type **5** and **6** during oxidative transformation of H-phosphonate derivatives that further supports the possibility of strong nucleophilic properties of DBU.[8]

In this letter we describe our preliminary studies on the reaction of DBU with various phosphorochloridate diesters **1–3**, which might be relevant to a variety of other transformations of phosphorus compounds, when bicyclic amidine bases are used as catalysts.

^{31}P NMR experiments showed that diphenyl phosphorochloridate **1a** ($\delta_P = -4.7$) reacted rapidly in acetonitrile upon the addition of 2 equiv. of DBU (**4**) producing within 10 min a major product (>95%), with a signal resonating at 22.2 ppm, which was identified



Scheme 1.

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as diphenyl-1,8-diazabicyclo[5.4.0]undec-7-en-6-ylphosphonate **8**.† The incremental addition of DBU revealed the formation of the putative amidine derivative **6** ($\delta_P = -3.7$),[8] that underwent gradual transformation into compound **8**. The same course of reaction (the formation of intermediate **6** and its conversion into product **8**) was observed for diphenyl phosphorobromidate **1b** ($\delta_P = -16.1$).

Alkyl phosphorochloridate diesters **2** ($\delta_P = -3.2$) and **3** ($\delta_P = 3.2$) also reacted rapidly with DBU (2 equiv.) in acetonitrile, tetrahydrofuran, or pyridine, affording the amidine derivatives **7** ($\delta_P = 1.6$) and **5** ($\delta_P = 4.9$), respectively, as major phosphorus-containing species (>95%). Although no visible changes occurred in the reaction mixtures within 15 min, when left to stand overnight, the amidine **5** produced a complicated mixture of products, while **7** was cleanly converted into a product with a signal resonating at 19.8 ppm. The latter was isolated by silica gel chromatography and identified (^1H, ^{13}C, ^{31}P, ^1H–^1H, ^1H–^{13}C, ^1H–^{31}P NMR) as the phosphonate **9**.[9]

The formation of 6-substituted phosphinoyl derivatives of DBU **8** and **9**, probably occurs via an intramolecular nucleophilic attack of the C-6 carbon of the DBU moiety on the electron-deficient phosphorus center in **6** or **7**. This is consistent with the observed reactivity of the C-6 position in the DBU cation.[10] The reaction was significantly faster in the instance of amidine **6**, most likely due to the presence of two electron-withdrawing substituents (two phenoxy groups) attached to the phosphorus center. Formation of the complicated mixture of products from diethoxyphosphinoyl derivative **5** might be due to a competing dealkylation reaction, and some subsequent transformations of the produced reactive species.

† Compound **8** was isolated from the reaction mixture as its hydrochloride using silica gel column chromatography and its structure determined using ^1H, ^{13}C, ^{31}P, and ^1H–^{31}P correlated NMR spectroscopy. ^1H and ^{13}C NMR spectra showed resonances due to DBU and aryl moieties in the expected ratio. Some diagnostic spectral data: ^1H NMR δ ($CDCl_3$) 7.12–7.32 (m, 10 H), 5.05 (*J* 30.4, 5.5 Hz, ^1H; cross peak in ^1H–^{31}P), 4.85 (*J* 12.3, 14.3 Hz, 1 H), 3.5 (m, 2 H), 3.3 (m, 1 H), 3.1 (m, 2 H), 2.1 (m, ^1H; cross peak in ^1H–^{31}P), 1.5–2.0 (m, 7 H). ^{13}C NMR δ ($CDCl_3$) 159.8, 150.4 (*J* 9.2 Hz), 149.7 (*J* 11.0 Hz), 129.8 (*J* 12.9 Hz), 125.5 (*J* 14.6 Hz), 120.5 (*J* 5.5 Hz), 120.4 (*J* 5.5 Hz), 53.2, 50.1 42.5 (*J* 135.7 Hz), 38.4, 26.1, 24.4 (*J* 3.7 Hz), 23.6 (*J* 5.5 Hz), 19.1.

In conclusion, one should exercise caution when using DBU as a catalyst during the synthesis of phosphorus compounds, especially, in the reactions where nucleophilic properties of DBU can become more important than its basicity. Since amidine derivatives of type **6** have been directly or indirectly postulated as intermediates in a variety of transformations involving phosphorus compounds,[2–8] it is important to be aware of the existence of this low energy reaction pathway which may lead to stable *C*-phosphonates of type **8** under exceedingly mild conditions. On the other hand, since the formation of phosphonates **8** and **9** is a clean reaction, these findings might also be of synthetic value for the functionalisation of DBU (and possibly other bicyclic amidines) at the C-6 position. Further studies on this subject are in progress in this laboratory.

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