Intramolecular Aza-Wittig Reaction of Iminophosphoranes with the β-Lactam Carbonyl Group

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The aza-Wittig reaction of iminophosphoranes (λ5-phosphazenes, phosphine imines) with carbonyl compounds, when carried out inter- or intramolecularly, leads to the formation of C=N double bonds, usually under neutral and mild reaction conditions. Several review articles have appeared recently reporting the increasing significance of the aza-Wittig reaction in organic synthesis, basically in the preparation of nitrogen-containing heterocyclic compounds.

The intramolecular aza-Wittig reaction involving the carbonyl group of acyclic amides yields heterocycles containing an amidino function such as imidazolines, quinazolinones, 1,2,4-triazino[4,3-b]-1,2,4,5-tetrazines and imidazo[1,5-a]benzimidazoles.

On the other hand, the intramolecular reaction of amides and iminophosphoranes has also been explored using amides in which the carbonyl group belongs to a ring (succinimide or phthalimide) giving rise to fused heterocycles. However, there are no reported examples of aza-Wittig reactions involving the carbonyl group of a β-lactam ring.

At this point, it is important to note that some attempts to achieve intermolecular aza-Wittig reactions of iminophosphoranes and the β-lactam carbonyl group have been described, although all of them were unsuccessful (Block 1).
We started our study of the aza-Wittig reaction involving β-lactams carrying out several intermolecular attempts using N-substituted iminophosphoranes with higher reactivity than those used in the reactions described in Block 1. We prepared the 2-azetidinone 7, as shown in Scheme 1, and tested the reactions of this compound with the trimethylphosphazenes 8 and 9. We found that in both cases the starting materials were recovered unaltered.

In a recent publication we have described the preparation of the new system azeto[2,1-b]quinazoline by an intramolecular [2 + 2] cycloaddition of ketenimines with imines (Block 2).
We reasoned that the amidino grouping of azetoquinazolines 2 could be also formed by an intramolecular aza-Wittig reaction between an iminophosphorane group and the C=O double bond of a β-lactam ring, both functionalities being present in suitable forerunners 3 (Block 3).

The preparation of the target iminophosphoranes 3 was achieved by two different synthetic routes depending on the degree of substitution of the two sp³ carbon atoms of the β-lactam ring.

The 2-azidobenzylamines 10 reacted with aldehydes under standard conditions giving rise to the corresponding N-(2-azidobenzyl)imines 11 in almost quantitative yields. Their reactions with diphenyl ketene yielded the N-(2-azidobenzyl)-β-lactams 12 (Scheme 2). When the azides 12 react with triphenylphosphane the corresponding triphenyliminophosphoranes 3 (R² = Ph) were formed. When these compounds were heated in solution, under a variety of experimental conditions, the iminophosphoranes 3 (R² = Ph) were recovered unaltered and in the reaction mixture the formation of the azetoquinazolines 2 could not be detected. The expected intramolecular aza-Wittig reaction was observed when trimethylphosphane was used to prepare compounds 3 (R² = CH₃), and these were heated in a toluene solution at reflux temperature for 24 h, leading to the isolation of the azeto[2,1-b]quinazolines 2 in variable yields (34-84%). The hydrolytic sensitivity of the trimethylphosphazene grouping probably accounts for the low yields observed in some examples.
On the other hand, the reactions of 2-azetidinone 14 with 2-azidobenzyl iodides 13 led to the N-(2-azidobenzyl)-ß-lactams 15. When compounds 15 were treated with trimethylphosphane followed by thermal treatment of the resulting trimethyliminophosphoranes yielded the azetoquinazolines 16 (Scheme 3), which were identified by 1H-NMR and 13C-NMR of the crude reaction mixture, since during purification attempts compounds 16 underwent the oxidation of the benzylic methylene to give the azeto[2,1-b]quinazolin-9-ones 17.
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References

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