

[A0009]

# Intramolecular Aza-Wittig Reaction of Iminophosphoranes with the $\beta$ -Lactam Carbonyl Group

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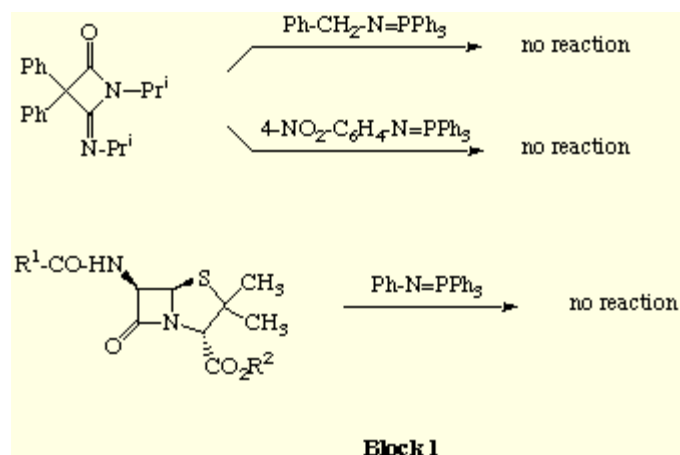
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The aza-Wittig reaction<sup>1</sup> of iminophosphoranes ( $[\lambda^5]$ -phosphazenes, phosphine imines) with carbonyl compounds, when carried out inter- or intramolecularly, leads to the formation of C=N double bonds, usually under neutral and mild reaction conditions. Several review articles<sup>1,2</sup> have appeared recently reporting the increasing significance of the aza-Wittig reaction in organic synthesis, basically in the preparation of nitrogen-containing heterocyclic compounds.

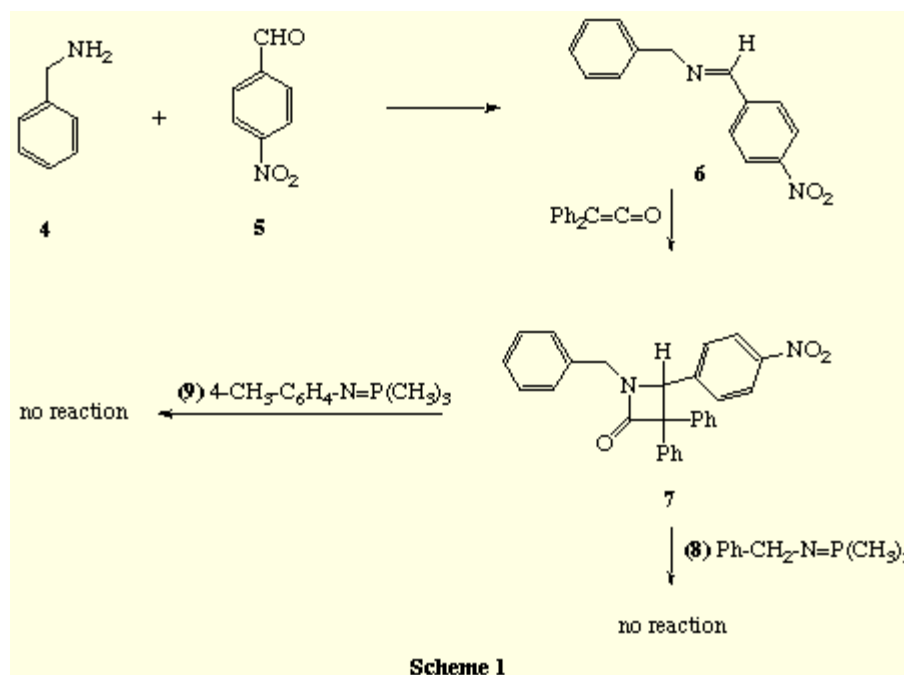
The intramolecular aza-Wittig reaction involving the carbonyl group of acyclic amides yields heterocycles containing an amidino function such as imidazolines,<sup>3</sup> quinazolinones,<sup>4</sup> 1,2,4-triazino[4,3-*b*]-1,2,4,5-tetrazines<sup>5</sup> and imidazo[1,5-*a*]benzimidazoles.<sup>6</sup>

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.<sup>7</sup> However, there are no reported examples of aza-Wittig reactions involving the carbonyl group of a  $\beta$ -lactam ring.

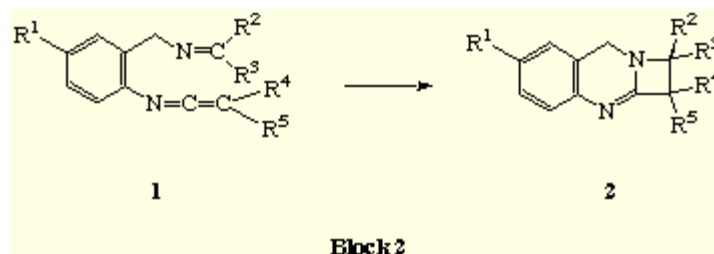
At this point, it is important to note that some attempts to achieve intermolecular aza-Wittig reactions of iminophosphoranes and the  $\beta$ -lactam carbonyl group have been described,<sup>8</sup> although all of them were unsuccessful (Block 1).



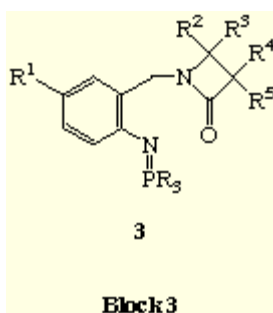
We started our study of the aza-Wittig reaction involving  $\beta$ -lactams carrying out several intermolecular attempts using  $N$ -substituted iminophosphoranes with higher reactivity than those used in the reactions described in Block 1. We prepared the 2-azetidinone **7**, as shown in Scheme 1, and 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<sup>9</sup> we have described the preparation of the new system azeto[2,1-*b*]quinazoline **2** by an intramolecular [2 + 2] cycloaddition of ketenimines with imines (Block 2).

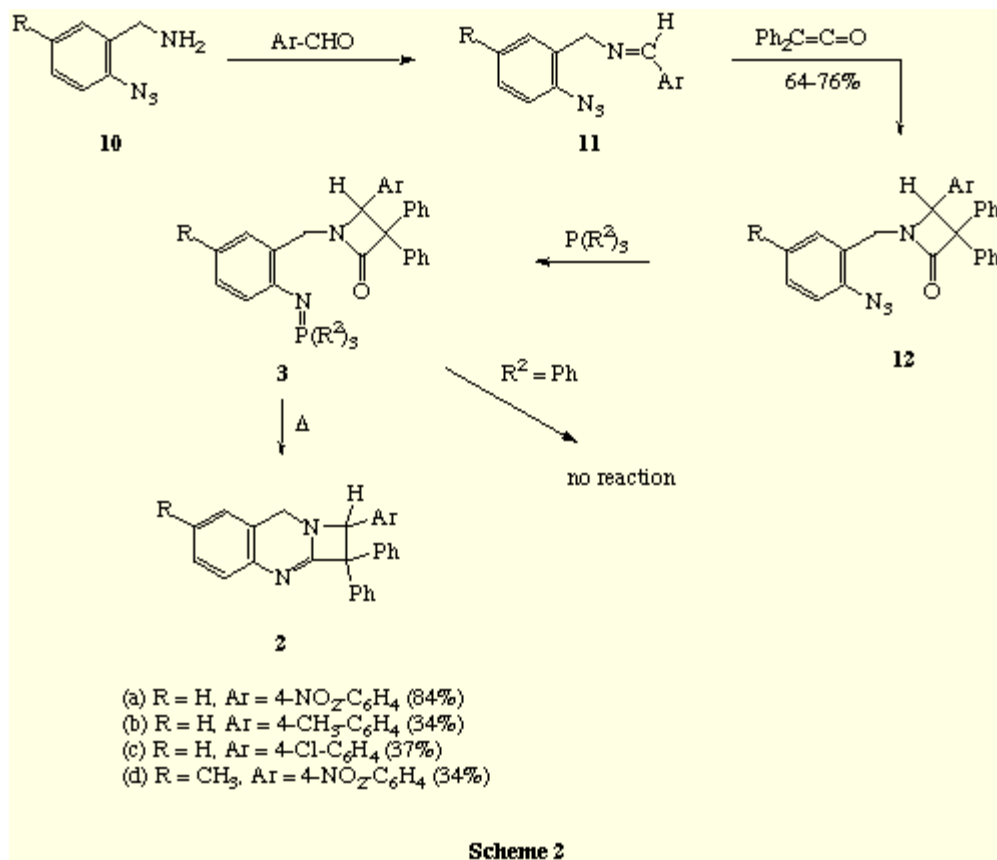


We reasoned that the amidino grouping of azetoquinazolines **2** could be also formed by an intramolecular aza-Wittig reaction between an iminophosphorane group and the C=O double bond of a  $\beta$ -lactam ring, both functionalities being present in suitable forerunners **3** (Block 3).

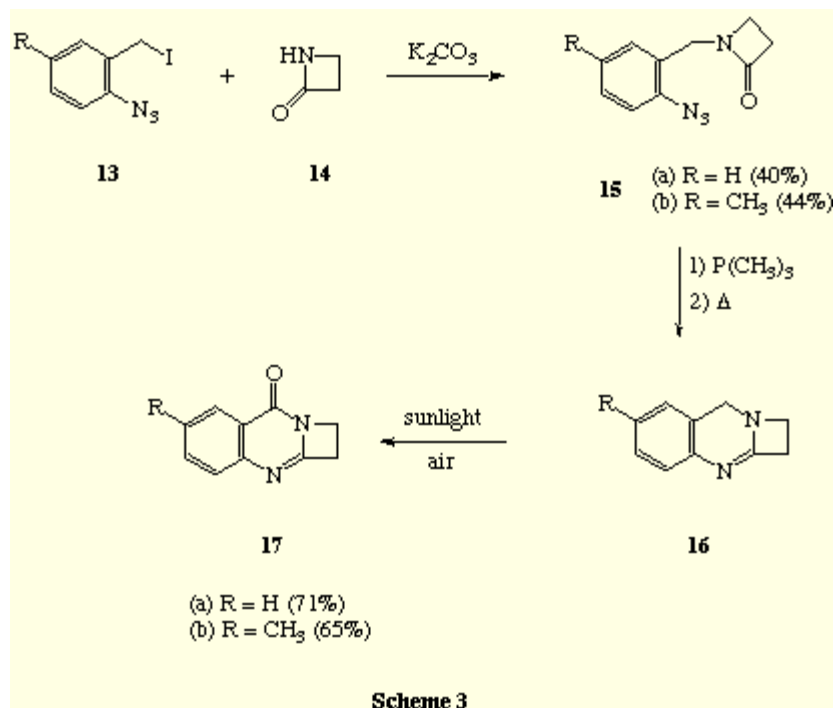


The preparation of the target iminophosphoranes **3** was achieved by two different synthetic routes depending on the degree of substitution of the two  $sp^3$  carbon atoms of the  $\beta$ -lactam ring.

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)- $\beta$ -lactams **12** (Scheme 2). When the azides **12** react with triphenylphosphane the corresponding triphenyliminophosphoranes **3** ( $R^2 = \text{Ph}$ ) were formed. When these compounds were heated in solution, under a variety of experimental conditions, the iminophosphoranes **3** ( $R^2 = \text{Ph}$ ) 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** ( $R^2 = \text{CH}_3$ ), 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)- $\beta$ -lactams **15**. When compounds **15** were treated with trimethylphosphane followed by thermal treatment of the resulting trimethyliminophosphanes yielded the azetoquinazolines **16** (Scheme 3), which were identified by <sup>1</sup>H-NMR and <sup>13</sup>C-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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