

A Phosphine-Mediated Construction of 1,4-Oxazepines and 1,3-Oxazines

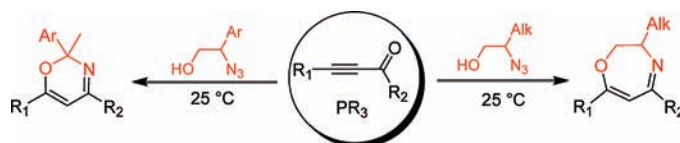
Céline François-Endelmond, Thomas Carlin, Pierre Thuery, Olivier Loreau,* and Frédéric Taran*

CEA, iBiTecS, Service de Chimie Bioorganique et de Marquage, Gif sur Yvette, F-91191, France, and CEA, IRAMIS, Service de Chimie Moléculaire, Gif sur Yvette, F-91191, France

frederic.taran@cea.fr; olivier.loreau@cea.fr

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ABSTRACT

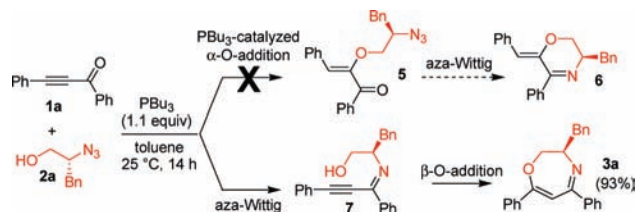


A simple and efficient method for constructing 1,4-oxazepines and 1,3-oxazines was developed with use of a phosphine-mediated tandem reaction of ynone with 2-azido alcohols. The method offers a promising route to synthetically useful as well as biologically active heterocycles under mild conditions and may be exploited for the preparation of interesting chiral ligands.

Small, “drug-like” heterocycles are predominant building blocks in medicinal chemistry.¹ Despite the numerous available methods, there is an ongoing search for simple and straightforward routes to heterocycles. Herein we disclose a new method for constructing 6- and 7-membered heterocycle products that are efficiently mediated by phosphines to generate 1,3-oxazines and 1,4-oxazepines in high yields. These new reactions were accidentally found during our work dealing with phosphine-catalyzed α -addition of pronucleophiles on activated alkynes.² Indeed, following our work on PBu₃-catalyzed α -addition of alcohols on arylpropiolates,³ we investigated the reaction of ynone **1a** with 2-azido alcohol **2a** in the presence of a substoichiometric amount of phosphine with the expectation to form the corresponding

α -O-adduct **5** that then should cyclize through an aza-Wittig reaction to afford **6** (Scheme 1).

Scheme 1. Reaction of **1a** with **2a** in the Presence of PBu₃



However, the monitoring of the reaction showed that imine formation was the first step of the process inducing the transitional formation of **7** that then underwent intramolecular Michael-type cyclization affording 2,3-dihydro-1,4-oxazepine **3a** as a sole product. The structure of compound **3a** was assigned by comparison to published analytical data⁴ and

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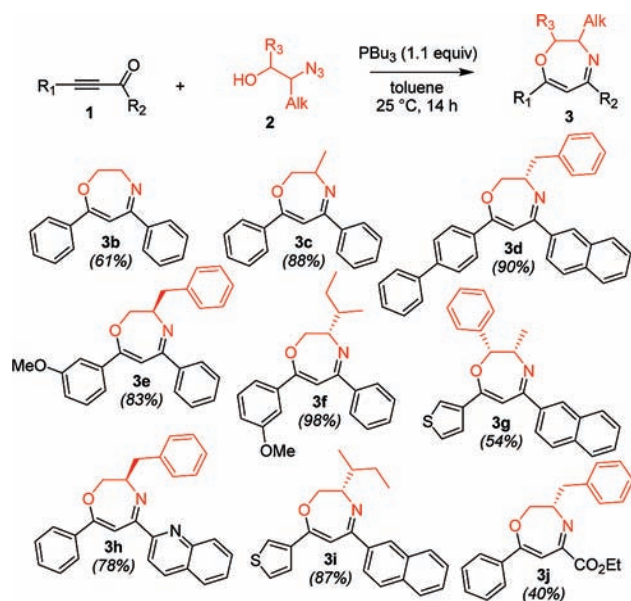
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further confirmed by DEPT ^{13}C NMR experiments conducted on ^{13}C -labeled **3a** prepared from ^{13}C -ynone **1a** (see the Supporting Information).

The preparation of such 7-membered heterocycles **3** has been only sporadically described despite their reported biological activities.⁵ To the best of our knowledge, the condensation of 2-amino alcohols with β -diketones is the only reported one-step method leading to 2,3-dihydro-1,4-oxazepines.⁶ This method suffers, however, from severe drawbacks: yields are often low and only symmetrical β -diketones should be used. Another simple route to oxazepines would have been the direct condensation of 2-amino alcohols with ynones. However, all attempts conducted in our laboratory to run such a reaction failed. Treatment of **1a** with 2-benzylaminoethanol in the presence or absence of catalytic amounts of Brønsted or Lewis acids gave complex mixtures. *N*-Michael adduct was the major isolated product (5–30% yield), and no trace of oxazepine **3a** was observed.

Consequently, we decided to explore further the scope and limitation of this phosphine-mediated reaction using a panel of starting reagents (Scheme 2). The reaction proceeded

Scheme 2. Phosphine-Mediated Synthesis of 2,3-Dihydro-1,4-oxazepines **3**



smoothly at room temperature with a series of substrates including heterocyclic ynones and disubstituted azido alcohols. It is quite remarkable that in all cases only one product

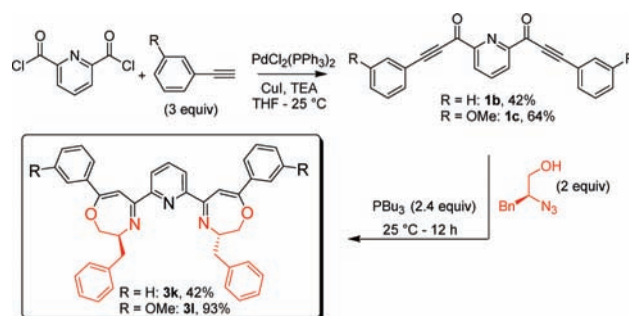
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was observed in the crude reaction mixture although many other reactions, such as [2+2] cycloaddition of iminophosphorane with ynone⁷ or aziridine formation from intramolecular reaction of 2-iminophosphorane alcohols,⁸ might have occurred.

Chiral HPLC analysis of products **3a** and **3g** confirmed that no racemization of the chiral centers occurred during the reaction. We contemplated that a possible application of this chemistry would be found in the synthesis of chiral ligands by using diynones as starting material.

Our interest was focused on the preparation of 2,6-bis(oxazepinyl)pyridines that are interesting 7-membered analogues of the well-known pybox ligands.⁹ 2,6-(diynone)-pyridines **1b** and **1c** were therefore prepared from 2,6-pyridinedicarbonyl dichloride according to a described protocol¹⁰ and reacted with (*S*)-2-azido-3-phenyl-1-propanol in the presence of PBu_3 . Double cyclization occurred efficiently affording the desired chiral ligands **3k** and **3l** with moderate to excellent yields (Scheme 3).

Scheme 3. Preparation of Bis-oxazepines Pybox Analogues



During the course of this study an unexpected rearrangement was discovered when 2-phenyl-2-azido-1-ethanol **2b** was used as starting reagent. Upon reaction with ynone **1a** and PBu_3 at room temperature, no trace of oxazepine derivative was observed and 1,3-oxazine **4a** was obtained in high yield (Scheme 4). The structure of **4a** was assigned by comparison to published NMR data¹¹ and further proven by X-ray crystallography (see the Supporting Information).

To investigate whether or not this rearrangement is general, we conducted a series of reactions involving azido

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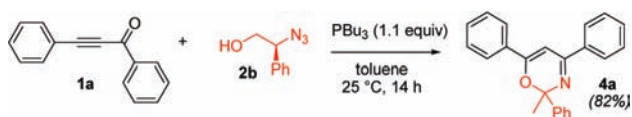
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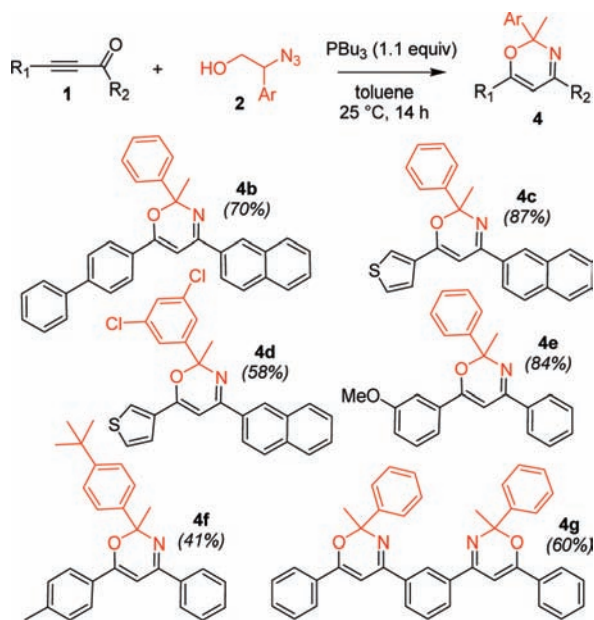
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Scheme 4. PBU₃-Mediated Reaction of **1a** with **2b**



alcohols bearing aryl moieties in the α position of the azido group. As shown in Scheme 5, oxazines **4** were

Scheme 5. Phosphine-Mediated Synthesis of 1,3-Oxazines **4**

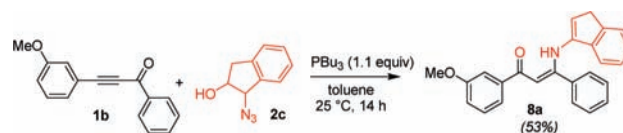


systematically obtained with use of these kinds of substrates.

While some examples of similar rearrangements have been reported in the literature,¹² a plausible mechanism for the formation of **4** was rather unclear. Therefore, we focused on isolation of any possible intermediates that would give us a valuable clue to a possible mechanism leading to compounds **4**. To this end, we conducted the PBU₃-mediated reaction between ynone **1b** and bicyclic 2-azido alcohol **2c** (Scheme 6) and fortunately were able to isolate enamine **8a**, which structure was determined by X-ray analysis (see the Supporting Information).

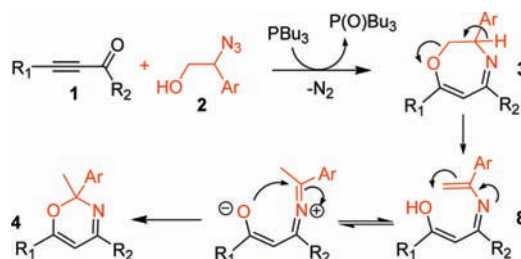
With enamine **8a** in hand as an intermediate, we can suggest the following sequence of transformations leading

Scheme 6. PBU₃-Mediated Reaction of **1b** with **2c**



to oxazines **4**. Once formed, 2-aryl-1,4-oxazepine **3** may undergo proton abstraction at the benzylic position and then β -elimination yields enamine **8**. Intramolecular nucleophilic attack of the enolate to the iminium form of **8** then affords **4** (Scheme 7).

Scheme 7. Proposed Mechanism for the Formation of **4**



In conclusion, we have developed a simple and practical method for the preparation of 1,4-oxazepines and 1,3-oxazines derivatives via an *n*Bu₃P-mediated tandem aza-Wittig reaction and intramolecular cyclization. This synthetic methodology offers a straightforward route to 7-membered heterocycles whose synthesis is poorly reported and that might attract biological interest. The reaction has been successfully extended to the preparation of chiral ligands that are 7-membered analogues of pybox structures. Preliminary results conducted in our laboratory showed that these ligands are very interesting in a series of Cu-catalyzed asymmetric transformations. These results will be published in due time.

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Supporting Information Available: Experimental procedures for the synthesis and full characterization for compounds, ¹HNMR and ¹³CNMR spectra of products **3** and **4**, and RX structure of product **8a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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