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

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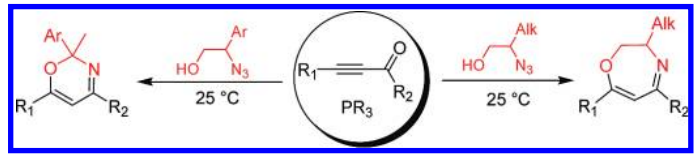
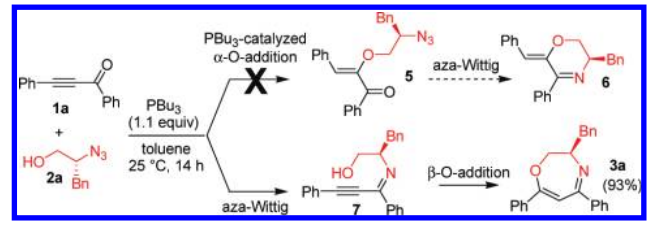
ABSTRACT



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 ynones 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 PBu_3-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 PBu_3



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 data[4] and

(1) See, for example: (a) Hansch, C.; Sammes, P. G.; Taylor, J. B. *Comprehensive Medicinal Chemistry*; Pergamon Press: Oxford, UK, 1990; Vol. 2, Chapter 7.1. (b) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239–2258. (c) Baladan, A. T.; Oniciu, D. C.; Katritzky, A. R. *Chem. Rev.* **2004**, *104*, 2777–2812.

(2) (a) Lecerclé, D.; Sawicki, M.; Taran, F. *Org. Lett.* **2006**, *8*, 4283–4285. (b) Carboni, M.; Gomis, J.-M.; Loreau, O.; Taran, F. *Synthesis* **2008**, *3*, 417–424. (c) Gabillet, S.; Lecerclé, D.; Loreau, O.; Carboni, M.; Dézard, S.; Gomis, J.-M.; Taran, F. *Org. Lett.* **2007**, *9*, 3925–3927. (d) Hanedanian, M.; Loreau, O.; Taran, F.; Mioskowski, C. *Tetrahedron Lett.* **2004**, *45*, 7035–7038. (e) Hanedanian, M.; Loreau, O.; Sawicki, M.; Taran, F. *Tetrahedron* **2005**, *61*, 2287–2294.

(3) Gabillet, S.; Lecerclé, D.; Loreau, O.; Dézard, S.; Gomis, J.-M.; Taran, F. *Synthesis* **2007**, *4*, 515–522.

(4) Lozada, M. C.; Lobato, C. E.; Enriquez, R. G.; Ortiz, B.; Toscano, R. A.; Gnecco, D.; Galindo, A.; Reynolds, W. F. *Magn. Reson. Chem.* **2003**, *41*, 975–982.

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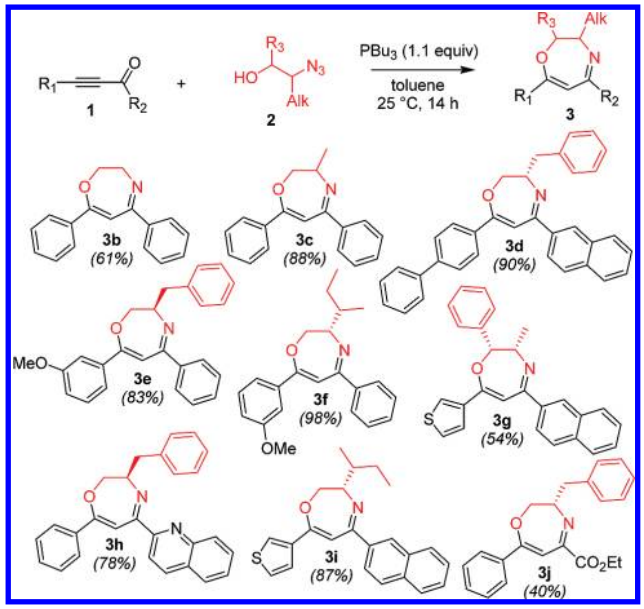
further confirmed by DEPT ^{13}C NMR experiments conducted on ^{13}C-labeled **3a** prepared from ^{13}C-ynone **1a** (see the Supporting Information).

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 attemps 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 Brönsted 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**

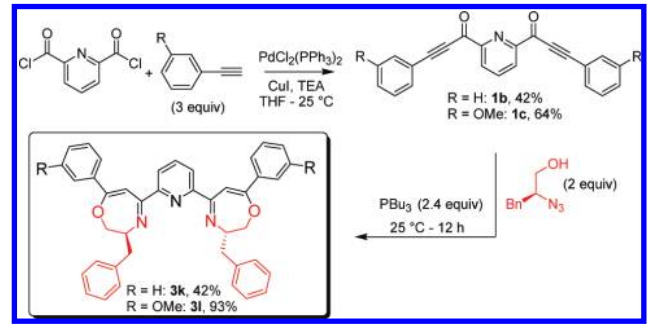


smoothly at room temperature with a series of substrates including heterocyclic ynones and disubstituted azido alcohols. It is quite remarkable that in all cases only one product was observed in the crude reaction mixture although many other reactions, such as [2+2] cycloaddition of iminophosphorane with ynone[7] 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 protocole[10] 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 **3*l*** 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 data[11] 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

(5) (a) McEvoy, F. J.; Greenblatt, E. N.; Osterberg, A. C.; Allen, G. R., Jr. *J. Med. Chem.* **1970**, *13*, 295–297. (b) Yale, H. L.; Sowinski, F. *J. Med. Chem.* **1964**, *7*, 609–614. (c) Yale, H. L.; Beer, B.; Pluscec, J.; Spitzmiller, E. R. *J. Med. Chem.* **1970**, *13*, 713–722. (d) Yale, H. L.; Sowinski, F. *J. Med. Chem.* **1967**, *10*, 1022–1025. (e) Allen, R. C.; Reitano, P. A.; Urbach, H. *J. Med. Chem.* **1978**, *21*, 838–841. (f) Pan, W.; Liu, H.; Xu, Y.-J.; Chen, X.; Kim, K. H.; Milligan, D. L.; Columbus, J.; Hadari, Y. R.; Kussie, P.; Wong, W. C.; Labelle, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5474–5477.

(6) (a) Soloshonok, V. A.; Ohkura, H.; Yasumoto, M. *J. Fluor. Chem.* **2006**, *127*, 708–711. (b) Soloshonok, V. A.; Ohkura, H.; Yasumoto, M. *Mendeleev Commun.* **2006**, *16*, 165–167. (c) Lozada, M. C.; Enriquez, R. G.; Soriano-Garcia, M.; Toscano, R. A.; Gnecco, D. *J. Chem. Crystallogr.* **2007**, *37*, 119–133.

(7) (a) Palacios, F.; Alonso, C.; Pagalday, J.; Ochoa de Retana, A. M.; Rubiales, G. *Org. Biomol. Chem.* **2003**, *1*, 1112–1118. (b) Palacios, F.; Ochoa de Retana, A. M.; Pagalday, J. *Tetrahedron* **1999**, *55*, 14451–14458.

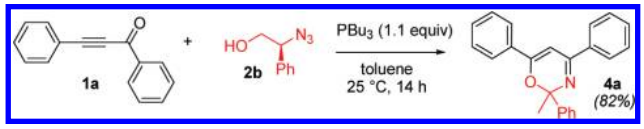
(8) Ittah, Y.; Sasson, Y.; Shahak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* **1978**, *43*, 4271–4273.

(9) For a review on pybox ligands see: (a) Nishiyama, H. *Adv. Catal. Processes* **1997**, *2*, 153–188. (b) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119–3154.

(10) Cox, R. J.; Ritson, D. J.; Dane, T. A.; Berge, J.; Charmant, J.; Kantacha, A. *Chem. Commun.* **2005**, 1037.

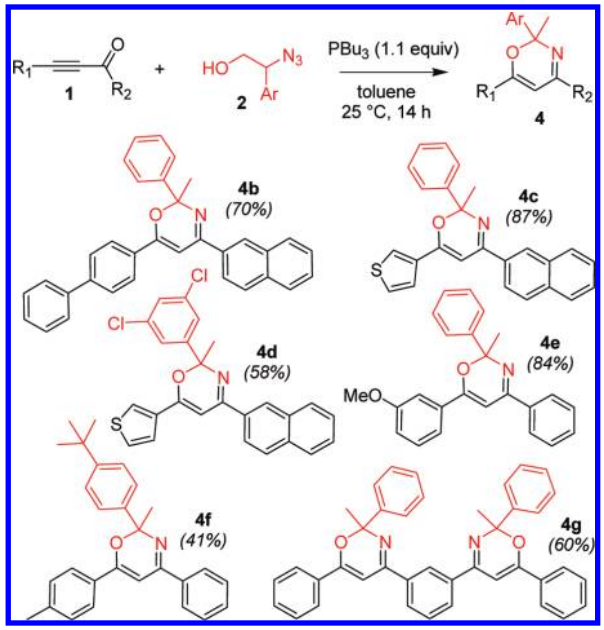
(11) Manning, J. R.; Davies, H. M. L. *Tetrahedron* **2008**, *64*, 6901–6908.

Scheme 4. PBu_3-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**



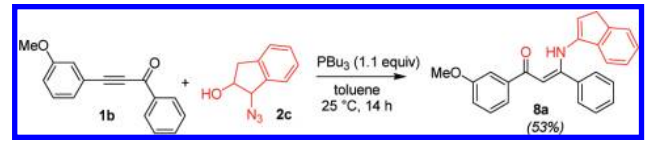
systematically obtained with use of these kinds of substrates.

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 PBu_3-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

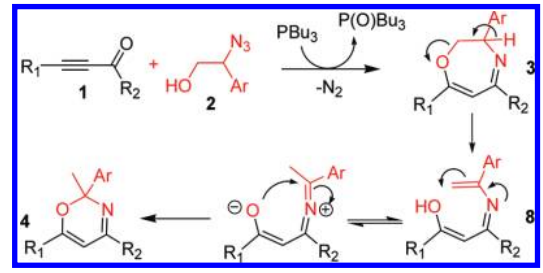
(12) Krapcho, A. P.; Shaw, K. J. *J. Org. Chem.* **1983**, *48*, 3341–3343.

Scheme 6. PBu_3-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*Bu_3P-mediated tandem aza-Wittig reaction and intramolecular cyclization. This synthetic methodology offers a straighforward 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.

Acknowledgment. We thank D. Buisson (CEA) for experimental assistance with MS and LC/MS measurements.

Supporting Information Available: Experimental procedures for the synthesis and full characterization for compounds, ^{1}HNMR and ^{13}CNMR 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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