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Catalytic aza-Wittig Cyclizations for Heteroaromatic Synthesis

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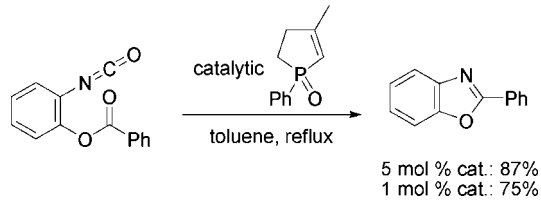
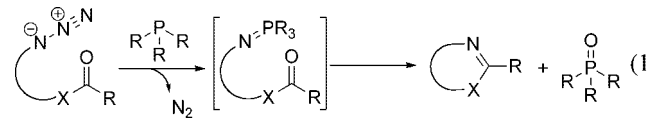
ABSTRACT



The first examples of heterocycle synthesis by iminophosphorane formation/intramolecular aza-Wittig cyclizations that are catalytic in the organophosphorus component are reported. The reaction has been demonstrated in the synthesis of both azine (phenanthridine) and azole (benzoxazole) heterocycles. Catalyst loadings down to 1 mol % have been used with little or no loss in reaction efficiency. The intimate involvement of the phosphine oxide in the catalytic cycle has been verified by in situ infrared spectroscopy.

Five- and six-membered aromatic heterocycles containing a C═N bond are important structural units in both natural products and synthetic pharmaceutical and agrochemical targets. Half of the small molecule drugs receiving FDA approval in 2005−2006 contain at least one azole (five-membered) or azine (six-membered) ring,[1] and a recent survey showed that 5% of all reactions carried out in the process research groups of three major pharmaceutical companies involve construction of a heteroaromatic ring.[2] The development of new methods for heteroaromatic synthesis is therefore the focus of intense and continuing interest.

The intramolecular aza-Wittig reaction (eq 1) has found widespread use[3] in the synthesis of C═N-containing heterocycles, due to the broad applicability of the mild, pH-neutral reaction conditions coupled with the ease of direct condensation to relatively unreactive carbonyl groups.



Nevertheless, there are some issues which disfavor use of this reaction, particularly on a large scale. First, as shown in eq 1, the iminophosphoranes are usually prepared from a phosphine by a Staudinger reaction, with associated safety risks in the synthesis and manipulation of organic azides. Second, the reactions generate stoichiometric quantities of high molecular weight phosphine oxide as a byproduct, creating separation and waste disposal problems. The development of a variant of the reaction catalytic in the organophosphorus reagent and utilizing alternative feedstocks would therefore represent a significant advance.

The potential for catalysis in the classical Staudinger/aza-Wittig sequence is poor. The enormous strength of the phosphine oxide P═O bond provides a driving force for the forward reaction, but its conversion back to a reactive P(III) species (to complete the catalytic cycle) would necessitate harsh, strongly reducing conditions incompatible with the existing functionality in the substrates (and potentially the

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(1) See http://www.centerwatch.com/patient/drugs/drugdirectories.html.

(2) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

(3) Recent reviews: (a) Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. *Tetrahedron* **2007**, *63*, 523. (b) Eguchi, S. *ARKIVOC* **2005**, 98. (c) Fresneda, P. M.; Molina, P. *Synlett* **2004**, 1.

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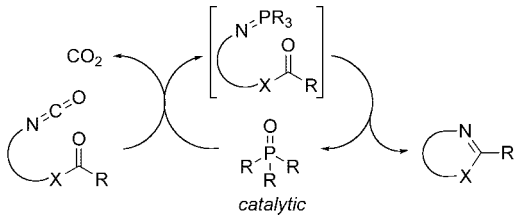
products). A solution to this impasse would be to utilize a method for iminophosphorane formation operating *solely at the P(V) oxidation state*. The self-condensation of isocyanates to give carbodiimides under phosphine oxide catalysis has been known since the 1960s.[4] The proposed mechanism[4c,5] involves generation of an iminophosphorane (and CO_2) by a slow metathesis reaction between phosphine oxide and isocyanate; the iminophosphorane then undergoes rapid aza-Wittig reaction with a second equivalent of isocyanate to give the carbodiimide, regenerating the phosphine oxide. We reasoned that isocyanates bearing a pendant carbonyl group would also react with phosphine oxide to generate an iminophosphorane which could then be intercepted by intramolecular aza-Wittig reaction with the carbonyl to generate a heterocycle (eq 2).



(2)

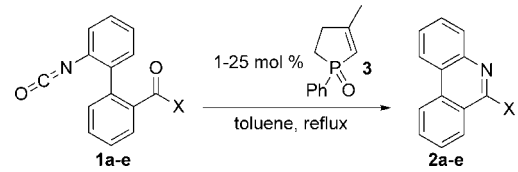
We report herein the first successful demonstration of iminophosphorane generation/aza-Wittig cyclizations in which the organophosphorus component is catalytic, exemplified in the context of both azine and azole synthesis.

We first focused on the assembly of six-membered (azine) heterocycles and specifically the 6-alkoxyphenanthridine system,[6] the heterocyclic core of many benzophenanthridine alkaloids.[7] In our preliminary experiments, isocyanates **1a** and **1b**[8] were treated with 25 mol % of the commercially available phospholene oxide **3** (as used in the catalytic carbodiimide syntheses[4]) in refluxing toluene, and to our delight, the desired phenanthridines **2a** and **2b** were formed in good yield (Table 1, entries 1 and 4).

Subsequent experimentation showed that improved yields were obtained with 5 mol % of catalyst at higher concentrations, even with the more hindered substrate **1c** (entries 2, 5, and 7). Catalyst loadings could be further reduced to 1 mol % without affecting yield, simply necessitating extended reaction times (entries 3 and 6). The less electrophilic amide substrates **1d**/**e** required higher catalyst loadings for efficient cyclization (entries 8 and 9) but still returned the desired 6-aminophenanthridines, a class of compounds with potent activity against mammalian prions[9] and as 5-HT_3 receptor agonists.[10]

Having demonstrated the potential utility of the new process, we next sought to extrapolate the reaction to the synthesis of azoles. Benzoxazoles[11] occur in a diverse range of natural products[12] and pharmaceutical targets,[13] and the current chemistry would provide a novel route to these valuable targets. The salicylic acid-derived[8] isocyanate esters **4a**−**n** were therefore treated under the standard reaction conditions outlined above, using a 5 mol % loading of catalyst **3**, and we were again delighted to observe efficient cyclization (Table 2). Gratifyingly, the reaction has been successful for every substrate surveyed thus far, returning good yields of benzoxazoles **5a**−**n**. Notably, the reaction

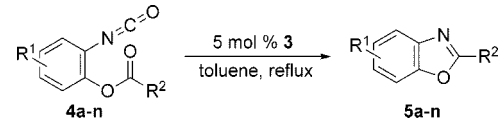
Table 1. Catalytic aza-Wittig Cyclizations: Phenanthridine Synthesis



entry	product	X	% **3**	concn (M)	time (h)	% yield[a]
1	**2a**	OMe	25	0.03	21	71
2		OMe	5	0.1	22	80
3		OMe	1	0.1	88	80
4	**2b**	OEt	25	0.03	16	67
5		OEt	5	0.05	42	78
6		OEt	1	0.1	44	82
7	**2c**	O^{i}Pr	5	0.1	22	72
8	**2d**	NC_5H_{10}	25	0.03	23	52
9	**2e**	NEt_2	25	0.03	23	30

[a] Isolated yield from acyl azide precursor to **1**.

Table 2. Catalytic aza-Wittig Cyclizations: Benzoxazole Synthesis



entry	product	R^1	R^2	% yield[a]
1	**5a**	H	Ph	87
2	**5a**	H	Ph	75[b]
2	**5b**	H	4-FC_6H_4	70
3	**5c**	H	4-$MeOC_6H_4$	62
4	**5d**	H	2-furyl	77
5	**5e**	H	Me	82
6	**5f**	H	1-hexyl	45
7	**5f**	H	1-hexyl	69[c]
8	**5g**	H	2-pentyl	65[c]
9	**5h**	7-MeO	Ph	70
10	**5i**	7-MeO	4-FC_6H_4	62
11	**5j**	7-MeO	4-$MeOC_6H_4$	59
12	**5k**	6-MeO	Ph	46
13	**5k**	6-MeO	Ph	62[c]
14	**5l**	6-MeO	2-furyl	38
15	**5m**	5-F	Ph	51
16	**5n**	5-F	4-F C_6H_4	48

[a] Isolated yield from acyl azide precursor to **4**. [b] With 1 mol % catalyst loading. [c] With 3 mol % catalyst loading.

(4) (a) Campbell, T. W.; Monagle, J. J. *J. Am. Chem. Soc.* **1962**, *84*, 1493. (b) Campbell, T. W.; Monagle, J. J.; Foldi, V. S. *J. Am. Chem. Soc.* **1962**, *84*, 3673. (c) Monagle, J. J.; Campbell, T. W.; McShane, H. F. *J. Am. Chem. Soc.* **1962**, *84*, 4288. (d) Monagle, J. J. *J. Org. Chem.* **1962**, *27*, 3851. (e) Campbell, T. W.; Monagle, J. J. *Org. Synth.* **1963**, *43*, 31.

(5) (a) Monagle, J. J.; Mengenhauser, J. V. *J. Org. Chem.* **1966**, *31*, 2321. (b) Appleman, J. O.; DeCarlo, V. J. *J. Org. Chem.* **1967**, *32*, 1505.

functions well regardless of the nature of either the aryl substituent or the carboxyl substituent (primary and secondary alkyl, electron-poor and electron-rich aromatic, and heteroaromatic) in **4**.

In some cases (entries 6 and 12), reaction monitoring by IR spectroscopy revealed that formation of carbodiimide (by an intermolecular condensation process) was competing with the desired cyclization. In these cases, repeating the reaction with a lower catalyst loading/concentration eliminated formation of carbodiimide and gave much improved isolated yields of the benzoxazole (entries 7 and 13). Again, catalyst loadings down to 1 mol % were employed without significant loss in yield (entry 2).

While these results in their own right clearly demonstrate the synthetic utility of the reaction, we were keen to garner support for the proposed catalytic cycle. Confirmation of the involvement of the phosphine oxide was obtained from in situ IR monitoring of the reactions (e.g., the formation of 2-methylbenzoxazole **5e**, Figure 1). The absorbances from

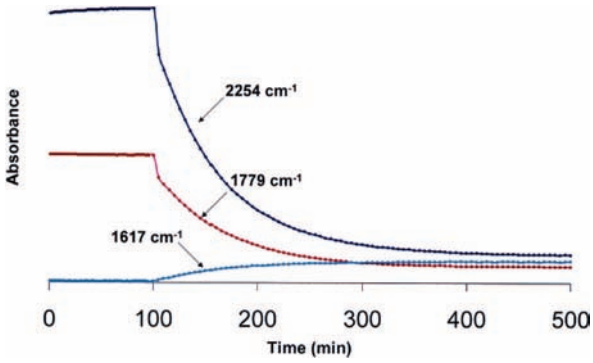


Figure 1. In situ IR data for formation of benzoxazole **5e**.

both the isocyanate (2254 cm^{-1}) and the ester (1779 cm^{-1}) functions remained constant until addition of phosphine oxide **3** (t = 100 min), whereupon the intensity of both signals rapidly decayed with first order kinetics. New signals corresponding to the product (e.g., 1617 cm^{-1}) also appeared and grew in intensity. We believe that this unambiguously demonstrates the involvement of the phosphine oxide in the catalytic cycle and also confirms that the first step of the reaction is rate-determining.

In summary, we have developed the first variant of the aza-Wittig cyclization of iminophosphoranes, which is catalytic in the organophosphorus component, and used this novel process to prepare privileged phenanthridine and benzoxazole motifs. Low catalyst loadings (1−5 mol %) can be employed without any compromise in reaction yield. Furthermore, the use of carboxylic acid-derived isocyanates as progenitors of the ring nitrogen offers a novel disconnection for the rapid preparation of biologically relevant heterocycles. The reaction promises to have broad applicability to the synthesis of other (particularly azine and azole) heterocycles, and studies to explore both the scope of the process and its use in target-oriented synthesis are underway.

Acknowledgment. We thank the EPSRC and AstraZeneca for an Industrial CASE award to A.E.M., and Lai Chan, Brian Cox (AstraZeneca), Mark Blitz, and Professor Mike Pilling (Leeds) for assistance with the in situ IR experiments.

Supporting Information Available: Experimental procedures for acyl azide synthesis, isocyanate formation/catalytic cyclizations, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Synthesis of (hetero)aryl-fused alkoxypyridines by Staudinger/aza-Wittig cyclization: (a) Purwono, B.; Smalley, R. K.; Porter, T. C. *Synlett* **1992**, 231. (b) Luheshi, A.-B. N.; Salem, S. M.; Smalley, R. K.; Kennewell, P. D.; Westwood, R. *Tetrahedron Lett.* **1990**, *31*, 6561.

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(8) Isocyanates **1a**−**e** and **4a**−**n** were prepared by Curtius rearrangement of the corresponding acyl azides; see Supporting Information.

(9) Bach, S.; Talarek, N.; Andrieu, T.; Vierfond, J.-M.; Mettey, Y.; Galons, H.; Dormont, D.; Meijer, L.; Cullin, C.; Blondel, M. *Nat. Biotechnol.* **2003**, *21*, 1075.

(10) Cappelli, A.; Anzini, M.; Vomero, S.; Canullo, L.; Mennuni, L.; Makovec, F.; Doucet, E.; Hamon, M.; Menziani, M. C.; De Benedetti, P. G.; Bruni, G.; Romeo, M. R.; Giorgi, G.; Donati, A. *J. Med. Chem.* **1999**, *42*, 1556.

(11) Synthesis of benzoxazoles by Staudinger/aza-Wittig cyclization of azidoesters: (a) Klare, J. E.; Tulevski, G. S.; Nuckolls, C. *Langmuir* **2004**, *20*, 10068. (b) Klare, J. E.; Tulevski, G. S.; Sugo, K.; de Picciotto, A.; White, K. A.; Nuckolls, C. *J. Am. Chem. Soc.* **2003**, *125*, 6030. (c) Leyshon, L. J.; Saunders, D. G. *J. Chem. Soc., Chem. Commun.* **1971**, 1608.

(12) Benzoxazoles feature in, for example, the cytotoxic agent UK-1 (Ueki, M.; Ueno, K.; Miyadoh, S.; Abe, K.; Shibata, K.; Taniguchi, M.; Oi, S. *J. Antibiot.* **1993**, *46*, 1089), the antibiotic boxazomycins (Kusumi, T.; Ooi, T.; Wälchli, M. R.; Kakisawa, H. *J. Am. Chem. Soc.* **1998**, *110*, 2954), and the ionophore calcimycin (Chaney, M. O.; Demarco, P. V.; Jones, N. D.; Occolowitz, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 1932).

(13) Some recent examples include 5-HT3 receptor partial agonists (Yoshida, S.; Watanabe, T.; Sato, Y. *Bioorg. Med. Chem.* **2007**, *15*, 3515), mGluR5 antagonists (Wang, B.; Vernier, J.-M.; Rao, S.; Chung, J.; Anderson, J. J.; Brodkin, J. D.; Jiang, X.; Gardner, M. F.; Yang, X.; Munoz, B. *Bioorg. Med. Chem.* **2004**, *12*, 17), and LPAAT-b inhibitors (Gong, B.; Hong, F.; Kohm, C.; Bonham, L.; Klein, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1455).