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Synthesis of 2-Substituted Pyrazolo[1,5-*a*]pyridines through Cascade Direct Alkenylation/Cyclization Reactions

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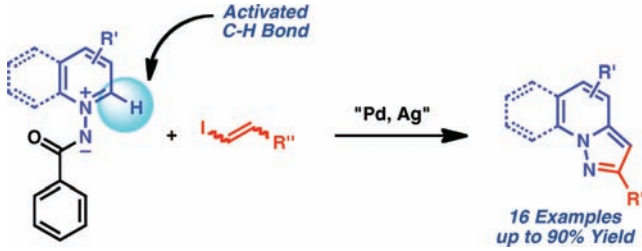
ABSTRACT



The synthesis of 2-substituted pyrazolo[1,5-*a*]pyridines from *N*-iminopyridinium ylides is described. These medicinally interesting compounds are formed through a cascade process involving a palladium-catalyzed direct alkenylation reaction followed by silver-mediated cyclization. The reaction can be performed with a wide range of electron-poor and electron-rich alkenyl iodides in good yields. This work represents perhaps the most direct route for the preparation of these compounds.

Nitrogen-containing heterocycles continue to receive much interest due to their ubiquity in Nature, as well as their extensive presence as part of the skeletal backbone of many therapeutic agents.[1] Of these heterocycles, 2-substituted pyrazolo[1,5-*a*]pyridines possess important biological activity (Figure 1). Derivatives of these compounds have been shown to be effective D3 and D4 agonists and antagonists.[2] Consequently, they are applicable in the treatment of several neurological disorders including schizophrenia, attention-deficit disorder, and Parkinson's disease.[2] In addition, they have been reported to exhibit potent antiherpetic and diuretic activity due to their ability to act as adenosine agonists and antagonists and may eventually be used in the treatment of cardiac arrhythmias.[3]

Although there have been several accounts of pyrazolo[1,5-*a*]pyridine synthesis, more often the resulting products possess substitution at the 3-position.[4] Substitution at the 2-position has

(1) (a) Zheng, G.; Dwoskin, L. P.; Deaciuc, A. G.; Zhu, J.; Jones, M. D.; Crooks, P. A. *Bioorg. Med. Chem.* **2005**, *13*, 3899. (b) Wilson, K. J.; van Niel, M. B.; Cooper, L.; Bloomfield, D.; O'Connor, D.; Fish, L. R.; MacLeod, A. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2643. (c) Campeau, L.-C.; Fagnou, K. *Chem. Soc. Rev.* **2007**, *36*, 1058. (d) Laird, T. *Org. Process Res. Dev.* **2006**, *10*, 851.

(2) (a) Lober, S.; Hubner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2377. (b) Hasen, J. B.; Weis, J.; Suzdak, P. D.; Eskesen, K. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 695. (c) Bettinetti, L.; Schlotter, K.; Hubner, H.; Gmeiner, P. *J. Med. Chem.* **2002**, *45*, 4594.

(3) (a) Johns, B. A.; Gudmundsson, K. S.; Turner, E. M.; Allen, S. H.; Samano, V. A.; Ray, J. A.; Freeman, G. A.; Boyd, F. L., Jr.; Sexton, C. J.; Selleseth, D. W.; Creech, K. L.; Moniri, K. R. *Bioorg. Med. Chem.* **2005**, *13*, 2397. (b) Akahane, A.; Katayama, H.; Mitsunaga, T.; Kato, T.; Kinoshita, T.; Kita, Y.; Kusunoki, T.; Terai, T.; Yoshida, K.; Shiokawa, Y. *J. Med. Chem.* **1999**, *42*, 779. (c) Kuroda, S.; Akahane, A.; Itani, H.; Nishimura, S.; Durkin, K.; Kinoshita, T.; Tenda, Y.; Sakane, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1979.

(4) For selected examples of synthesis of 3-substituted pyrazolo[1,5-*a*]pyridines, see: (a) Lober, S.; Hubner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 97. (b) Stevens, K. L.; Jung, D. K.; Alberti, M. J.; Badiang, J. G.; Peckham, G. E.; Veal, J. M.; Cheung, M.; Harris, P. A.; Chamberlain, S. D.; Peel, M. R. *Org. Lett.* **2005**, *7*, 4753. (c) Valenciano, J.; Cuadro, A. M.; Vaquero, J. J.; Builla, J. A.; Castaño, O. *J. Org. Chem.* **1999**, *64*, 9001.

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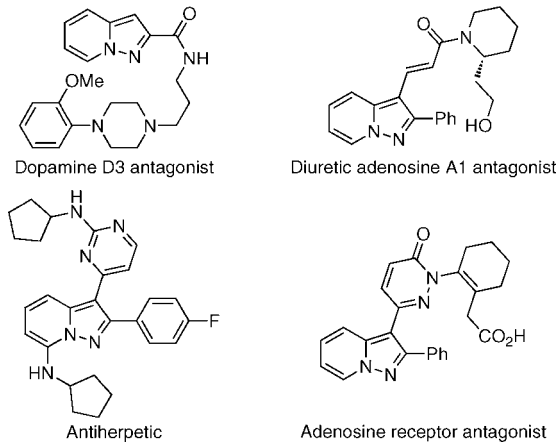


Figure 1. Examples of biologically relevant 2-substituted pyrazolo[1,5-*a*]pyridines.

been reported with limited scope and often requires lengthy syntheses, or is not possible without also including a group at the 3-position.[5] As such, the specific, site-selective synthesis of 2-substituted pyrazolo[1,5-*a*]pyridines remains a synthetic challenge.

Direct functionalization processes have emerged as extremely effective alternatives to traditional cross-coupling reactions.[6] In particular, whereas cross-coupling of both aryl electrophiles and nucleophiles at the 2-position of pyridine has historically been difficult, the direct arylation of pyridinium species has been proven to be remarkably efficient.[7] *N*-Iminopyridinium ylides have emerged as versitile scaffolds whereby complex pyridine derivatives can be prepared.[8] We have demonstrated that these activated pyridines can readily undergo a directed diastereoselective addition of Grignard reagents to yield 2,6-substituted tetrahydropyridines,[9] as well as asymmetric hydrogenation to give substituted piperidines with high levels of enantioselectivity.[10] Perhaps more pertinant to this account, we have also shown that they are amenable to direct arylation, and in the case of 2-alkylpyridinium ylides, direct benzylic arylation reactions.[11] However, to date these ylides have not been applied in cascade reactions. These processes have garnered much recent attention due to the high efficiency and cost effectiveness of performing several transformations within a single reaction vessel.[12] Herein we describe the synthesis of 2-substituted pyrazolo[1,5-*a*]pyridines in two steps from pyridine through a cascade direct alkenylation/cyclization reaction (Scheme 1).

During our work on developing a Pd-catalyzed direct alkenylation[13] reaction on *N*-iminopyridinium ylides we found that altering the base from K_2CO_3 to Ag_2CO_3 led to the formation of 2-phenylpyrazolopyridine **3a**. In the crude reaction mixture, no uncyclized product **4** was observed, and only unreacted **1a** along with **3a** and benzoic acid, presumably from the cleavage of the benzoyl moiety, were present.[14] Cognizant of the biological relavance of these compounds, we elected to optimize this transformation (Table 1). Screening of the silver source determined that AgOBz was ideal (entries 1−4). $PdBr_2$ was found to be superior to other sources of Pd (entries 4−6), and though the reaction was found to be relatively insensitive to the phosphine ligand employed (entries 6−9), P(4-MeOPh)$_3$ was optimal. Finally, etheral solvents (entries 10−12) were found to be superior with 1,4-dioxane chosen due to its relative low volatility. A slight increase in the loading of ylide **1a** gave the optimal reaction conditions (entry 13).

With these conditions in hand, we next explored the scope of the reaction (Table 2). Both *E* and *Z* styryl iodides

Scheme 1. Initial Synthesis of Pyrazolo[1,5-*a*]pyridines

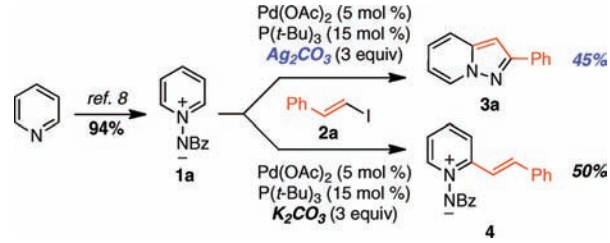
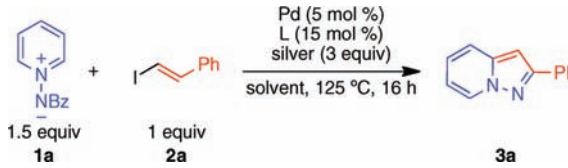


Table 1. Selected Optimization of 2-Substituted Pyrazolo[1,5-*a*]pyridine Synthesis



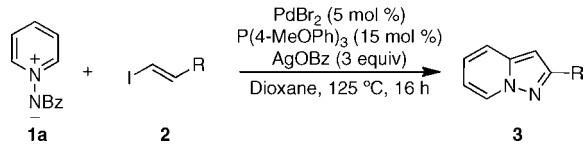
entry	Pd	L	Ag	solvent	yield[a] (%)
1	$Pd(OAc)_2$	P(*t*-Bu)$_3$	AgOTf	PhMe	0
2	$Pd(OAc)_2$	P(*t*-Bu)$_3$	AgOAc	PhMe	13
3	$Pd(OAc)_2$	P(*t*-Bu)$_3$	Ag_2CO_3	PhMe	45
4	$Pd(OAc)_2$	P(*t*-Bu)$_3$	AgOBz	PhMe	50
5	Pd_2dba_3	P(*t*-Bu)$_3$	AgOBz	PhMe	31
6	$PdBr_2$	P(*t*-Bu)$_3$	AgOBz	PhMe	52
7	$PdBr_2$	PPh_3	AgOBz	PhMe	59
8	$PdBr_2$	P(2-MePh)$_3$	AgOBz	PhMe	60
9	$PdBr_2$	P(4-MeOPh)$_3$	AgOBz	PhMe	63
10	$PdBr_2$	P(4-MeOPh)$_3$	AgOBz	DMF	46
11	$PdBr_2$	P(4-MeOPh)$_3$	AgOBz	THF	64
12[b]	$PdBr_2$	P(4-MeOPh)$_3$	AgOBz	DME	63
13	$PdBr_2$	P(4-MeOPh)$_3$	AgOBz	1,4-diox.	69
14[c]	$PdBr_2$	P(4-MeOPh)$_3$	AgOBz	1,4-diox.	80

[a] The yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b] 1 equiv of ylide **1a** was used. [c] 2 equiv of ylide **1a** was used.

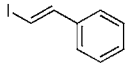
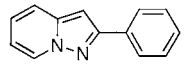
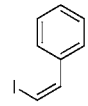
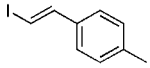
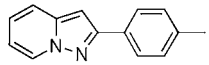
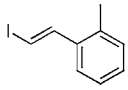
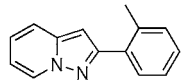
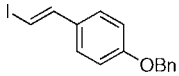
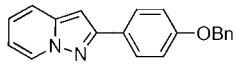
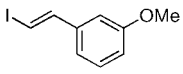
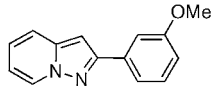
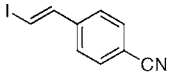
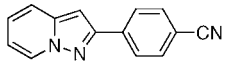
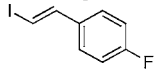
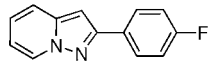
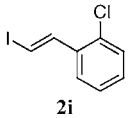
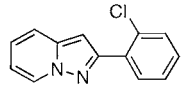
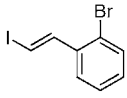
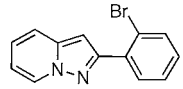
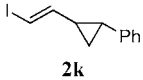
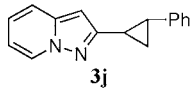
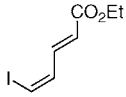
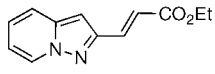
(5) (a) Takashi, T.; Haruki, S. *J. Chem. Soc., Chem. Commun.* **1980**, 1109. (b) Csanyi, D.; Hajos, G.; Riedl, Z.; Timari, G.; Bajor, Z.; Cochard, F.; Sapi, J.; Laronze, J.-Y. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1767. (c) Johns, B. A.; Gudmundsson, K. S.; Turner, E. M.; Allen, S. H.; Jung, D. K.; Sexton, C. J.; Boyd, F. L.; Peel, M. R. *Tetrahedron* **2003**, *59*, 9001. (d) Nunez, A.; Garcia de Viedna, A.; Martinez-Barrasa, V.; Burgos, C.; Alvarez-Builla, J. *Synlett* **2002**, 1093. (e) Chen, Z.; Su, M.; Yu, X. *Org. Biomol. Chem.* **2009**, *7*, 4641.

(6) For selected reviews, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Miura, M.; Satoh, T. *Top. Organomet. Chem.* **2005**, *14*, 55. (c) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (d) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (e) Seregin, I. Y.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (f) Ellman, J. *Science* **2007**, *316*, 1131.

Table 2. Synthesis of 2-Subsituted Pyrazolo[1,5-*a*]pyridines through a Tandem Direct Alkenylation/Cyclization Reaction[a]



1a 2 3

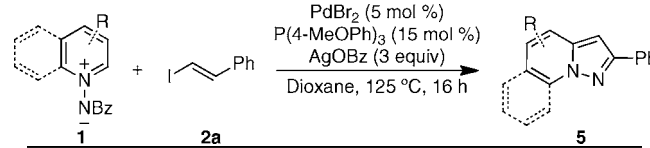
entry	vinyl iodide	product	yield (%)[b]
1	 **2a**	 **3a**	78
2	 **2b**		64
3	 **2c**	 **3b**	79
4	 **2d**	 **3c**	70
5	 **2e**	 **3d**	87
6	 **2f**	 **3e**	65
7	 **2g**	 **3f**	61
8	 **2h**	 **3g**	86
9	 **2i**	 **3h**	63
10	 **2j**	 **3i**	70
11	 **2k**	 **3j**	62
12	 **2l**	 **3k**	49

[a] Reaction conditions: **1a** (2 equiv), **2** (1.0 equiv), $PdBr_2$ (5 mol %), $P(4\text{-MeOPh})_3$ (15 mol %), AgOBz (3 equiv), 1,4-dioxane (0.2 M), 125 °C, 16 h. [b] Yield of isolated product.

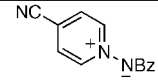
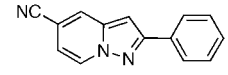
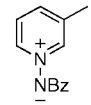
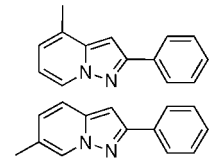
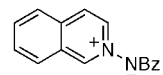
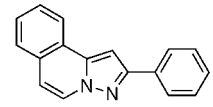
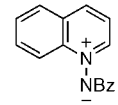
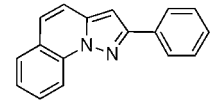
provided the desired pyrazolo[1,5-*a*]pyridine (entries 1 and 2), though improved yields for the cascade were observed with the *E* alkenes. Substitution on the aryl ring was well tolerated (entries 3 and 4) giving the desired products in good yields, though slightly lower yields were noted with the 2-methylstyryl iodide presumably due to increased steric hindrance. Electron-rich styryl iodides were operable (entries 5 and 6) as were electron-poor substrates (entries 7 and 8). Chemoselectivity was noted with β-iodostyrenes bearing halides on the aromatic moiety. As seen in entries 9 and 10, the pyazolo[1,5-*a*]pyridines were obtained in good yield with no evidence of arylation occurring on the phenyl group. Furthermore, these substrates represent interesting scaffolds whereby further structural elaboration can be performed. Although alkenyl iodides bearing alkyl groups proved ineffective in the transformation, those containing a cyclopropyl unit were quite reactive (entry 11), likely due to the high *s* character of the cyclopropane ring. Finally, *Z*/*E* dienes provided the corresponding product in moderate yield (entry 12). It should be noted that in call cases the crude reaction mixture contains primarily the unreacted ylide and the desired product. In cases where the observed yields were moderate, no unreacted alkenyl iodides were noted, suggesting their degradation during the course of the reaction.

Next, we investigated the scope with regards to the pyridinium ylide (Table 3). A nitrile group at the 4-position of the pyridinium ring had little effect on the reaction (entry 1). In the case of 3-methyl-*N*-iminopyridinium ylide there was a 3:1 preference of reaction at the less hindered site of

Table 3. Scope of the Pyridinium Ylide[a]



1 2a 5

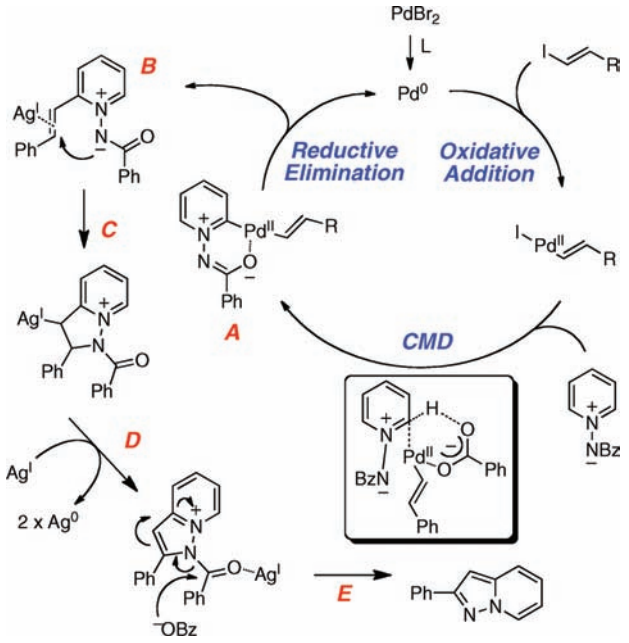
entry	pyridinium	product	yield (%)[b]
1	 **1b**	 **5a**	62
2	 **1c**	 **5b**	77
3	 **1d**	 **5c**	60
4	 **1e**	 **5d**	90

[a] Reaction conditions: **1** (2 equiv), **2a** (1.0 equiv), $PdBr_2$ (5 mol %), $P(4\text{-MeOPh})_3$ (15 mol %), AgOBz (3 equiv), 1,4-dioxane (0.2 M), 125 °C, 16 h. [b] Yield of isolated product.

the ring (entry 2). Isoquinolonium ylide **1d** was operative, and quinolonium ylide **1e** proved to be exceptionally reactive (entries 3 and 4). These results correlate with what was observed in the previously reported direct arylation reaction with exception of the 3-methylpyridinium, where complete selectivity was noted.[11a]

We believe that the reaction proceeds as shown in Scheme 2. The first step involves oxidative addition of the Pd catalyst into the alkenyl iodide. This is followed by insertion of the catalyst into the pyridinium ylide (**A**). Given that acetate/carbonate silver compounds are required, it is thought that this plays a role in the carbopalladation involving a concerted metalation/deprotonation (CMD) sequence.[15] Furthermore, as $PdBr_2$ is employed in the reaction in the presence of excess silver, we cannot discount the possible formation of a more reactive cationic Pd species. Reductive elimination (**B**) then gives the alkenylated pyridinium which undergoes a cyclization (**C**). This transient intermediate is thought to exist as when the 2-styrylpyridinium is subjected to the reaction conditions **3a** is obtained in 56% yield. Interestingly, however, the application of Ag or Pd alone prove ineffective in promoting the cyclization. Though Ag is known to promote such cyclizations, the role of Pd in this process is under investigation. Elimination of silver with disproportionation generates Ag(0) that is observed in the reaction vessel (**D**). Rearomatization via the explusion of benzoyl moeity (**E**) gives the observed product. This may also be assisted by silver, explaining the requirement of 3 equiv of AgOBz for the reaction to proceed.

Scheme 2. Proposed Reaction Pathway



In summary, we have described the synthesis of 2-substituted pyrazolo[1,5-*a*]pyridines in two steps from pyridine. The products are obtained in good yields, and the process is believed to proceed through a tandem direct alkenylation/cyclization pathway. The full scope, mechanistic investigations, and applications toward the synthesis of complex biologically relevant molecules is underway and will be reported in due course.

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Supporting Information Available: Experimental procedures, sample spectra, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902710F

(7) For direct functionalization of pyridiniums, see: (a) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8872. (b) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (c) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. (d) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (e) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781. (f) Schipper, D. J.; El-Salfiti, M.; Whipp, C. J.; Fagnou, K. *Tetrahedron* **2009**, *65*, 4977.

(8) Legault, C. Y.; Charette, A. B. *J. Org. Chem.* **2003**, *68*, 7119.

(9) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 6360.

(10) (a) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966. (b) Legault, C. Y.; Charette, A. B. *Heterocycles* **2008**, *76*, 1271.

(11) (a) Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52. (b) Mousseau, J. J.; Larivée, A.; Charette, A. B. *Org. Lett.* **2008**, *10*, 1641.

(12) For examples of cascade processes, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Parsons, P. J.; Perkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (c) Tourée, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439.

(13) (a) Mousseau, J. J.; Bull, J. A.; Charette, A. B. *Angew Chem., Int. Ed.* **2010**, ASAP (DOI: 10.1002/anie.200906020). (b) Bull, J. A.; Mousseau, J. J.; Charette, A. B. *Org. Lett.* **2008**, *10*, 5485.

(14) Determined by ^{1}H NMR.

(15) For a discussion on CMD pathways, see: (a) Cárdenas, D. J.; Martín-Matute, B.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 5033. (b) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (c) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (d) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.