10-19-2015

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Citation/Publisher Attribution

Kaswan, P., Porter, A., Pericherla, K., Simone, M., Peters, S., Kumar, A., & DeBoef, B. (2015). Oxidative Cross-Coupling of sp^3- and sp^2-Hybridized C-H Bonds: Vanadium-Catalyzed Aminomethylation of Imidazo[1,2-*a*]pyridines. *Organic Letters, 17*(21), 5208-5211. doi: 10.1021/acs.orglett.5b02539
Available at: http://dx.doi.org/10.1021/acs.orglett.5b02539

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Oxidative Cross-Coupling of sp^3 and sp^2-Hybridized C–H Bonds: The Vanadium Catalyzed Aminomethylation of Imidazo[1,2-*a*]pyridines

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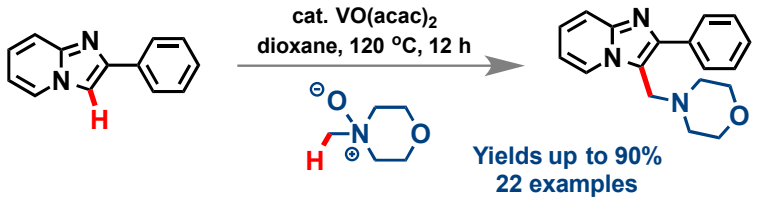
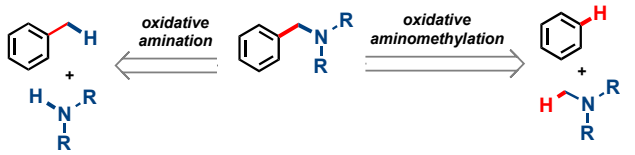
Supporting Information Placeholder



ABSTRACT: The vanadium-catalyzed oxidative coupling of substituted 2-arylimidiazo[1,2-*a*]pyridines to *N*-methylmorpholine, which acts as both a coupling partner and an oxidant, has been achieved. This reaction was applied to various substituted imidiazo[1,2-*a*]pyridine substrates, resulting in yields as high as 90%. Mechanistic investigations indicate that the reaction may proceed *via* a Mannich-type process. This work demonstrates how oxidative aminomethylation can be used as a useful method to introduce tertiary amines into heterocycles, thus providing an alternative method for conventional Mannich-type reactions.

Incorporating new carbon–carbon and carbon–nitrogen bonds into organic molecules is an apparent need in modern chemical industry. There have been many recent advances in this field, most using metal catalysis; however, these methods require pre-functionalization steps, thus diminishing the overall atom economy of the process.[1] The ability to oxidatively couple two carbon–hydrogen (C–H) bonds to form a carbon–carbon (C–C) bond with no pre-functionalization would be ideal.[2] The same is true for the synthesis of carbon–nitrogen (C–N) bonds from the coupling of C–H and nitrogen–hydrogen (N–H) bonds. One can envision the incorporation of new C–N bonds *via* cross-dehydrogenative coupling through either oxidative amination or oxidative aminomethylation (Scheme 1). The former process, direct oxidative amination, has been reported numerous times, though much work remains to be done.[3] Contrastingly, aminomethylation is a rare,[4-7] but attractive bond disconnection for the synthesis of tertiary amines. Two notable examples have been reported, to date: Hwang and Uang achieved the regioselective aminomethylation of naphthols,[6] and a team at Eli Lilly used an oxidative aminomethylation in the large-scale synthesis of an active pharmaceutical ingredient for the treatment of myeloproliferative disorders.[8]

There are numerous methods to oxidatively couple two sp^2 hybridized C–H bonds in high yields;[2] however, the cross-coupling of sp^3 and sp^2 hybridized C–H bonds is much less common, as sp^3 hybridized C–H bonds are generally less reactive.[4] In fact, in order to achieve sp^3 C–H bond activation, directing groups are often needed.[3] In the absence of such a directing group, and occasionally even when these groups are employed, β-hydride elimination, as opposed to cross-coupling is often observed flowing the C(sp^3)–H activation step.[4] Despite these challenges, we sought to develop a novel aminomethlation via the oxidative coupling of sp^3 and sp^2-hybridized C–H bonds.



Scheme 1. Oxidative amination verses aminomethylation

Specifically, we sought to find a method for the aminomethylation of imidiazo[1,2-*a*]pyridine substrates. Neuroactive pharmaceuticals such as Necopidem, Saripidem, and Zolpidem contain a substituted imidazo[1,2-a]pyridines backbone (Figure 1).[9] Providing a way to oxidatively couple the 3-position of 2-arylimidazo[1,2-*a*]pyridine with alkyl amines would be a useful tool for the synthesis of derivatives of these nonbenzodiazepine GABA potentiators. Herein, we disclose

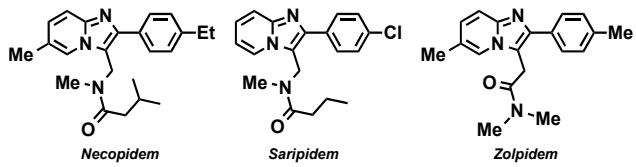
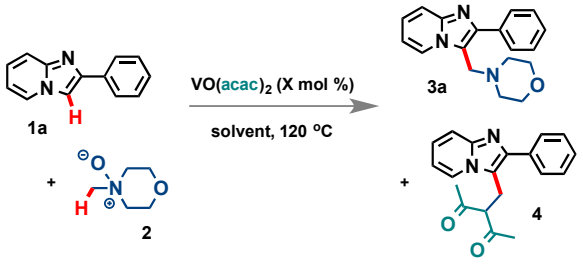


Figure 1. Pharmaceuticals with imidazo[1,2-*a*]pyridine backbone

Table 1. Optimization of the oxidative aminomethylation conditions



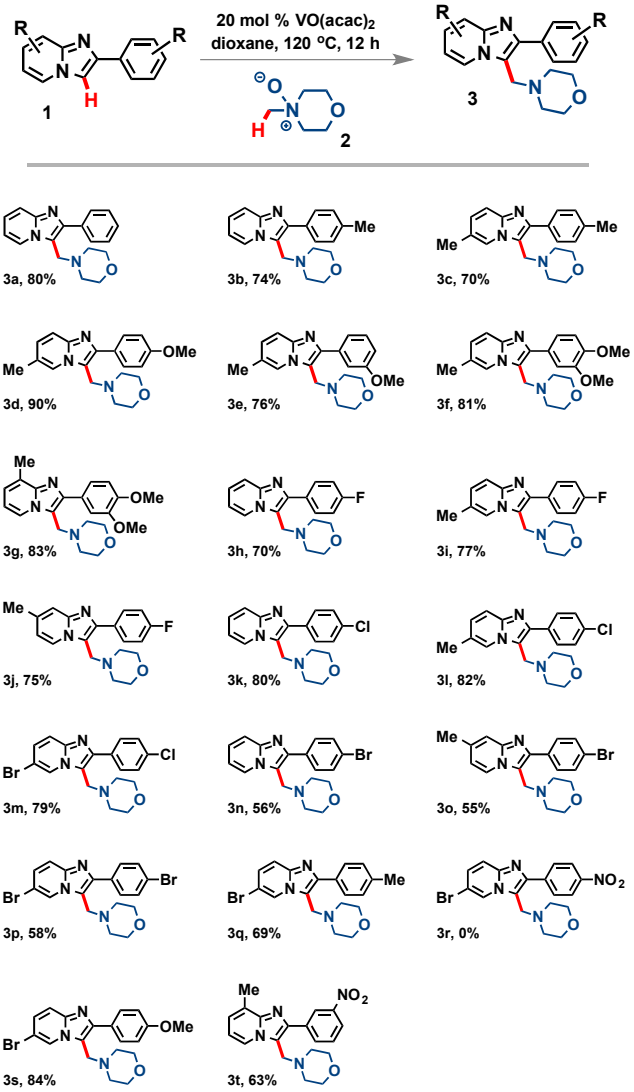
entry	$VO(acac)_2$ (mol %)	NMO (equiv)	solvent	time (h)	yield[a]	
					3a	**4**
1	$VO(acac)_2$ (25)	10	DCM	18	70 (59[c])	4
2	$VO(acac)_2$ (20)	10	DCM	18	65	3
3	$VO(acac)_2$ (10)	10	DCM	18	62	-[b]
4	$VO(acac)_2$ (20)	10	ethanol	18	33	2
5	$VO(acac)_2$ (20)	10	toluene	18	30	29
6	$VO(acac)_2$ (20)	10	THF	18	57	1
7	$VO(acac)_2$ (10)	5	DCM	6	88	6
8	V_2O_5 (20)	10	DCM	6	58[c]	0
9	$VO(acac)_2$ (20)	10	1,4-dioxane	12	80[c]	0
10	$VO(acac)_2$ (**20**)	**5**	**1,4-dioxane**	**12**	**80[c]**	**0**
11	$VO(acac)_2$ (20)	3	1,4-dioxane	12	69[c]	0
12	$VO(acac)_2$ (20)	1	1,4-dioxane	12	36[c]	7

[a]Product yield determined by NMR, [b]Traces of **4** were observed, [c]Isolated yield.

the discovery of a vanadium catalyzed oxidative coupling of imidiazo[1,2-*a*]pyridines with *N*-methylmorpholine oxide (NMO), which serves as both the sp^3-hybridized coupling partner and the oxidant.

Based on the previous work of Hwang and Uang,[6] we chose to commence our studies using vanadyl acetylacetonate, $VO(acac)_2$, as the catalyst for the oxidative aminomethylation shown in Table 1. We systematically studied the effect of solvent, catalyst loading, time, and NMO loading. Ethanol, toluene, and tetrahydrofuran were initially tested (Table 1 entries 4-6), but none had comparable yields to methylene chloride (DCM). To our surprise, the aminomethylation reactions consistently formed the acetylacetonate-containing side product **4** which was very difficult to remove from the desired product **3a** by flash chromatography. The loading of $VO(acac)_2$ was varied from 25% to 10%, showing that lower catalyst loading provided lower yields but also lower impurities (entries 1-3). Performing a careful study of the reaction over time gave further insight into the reaction's profile (see supporting information). This study indicated that the optimal yield of **3a** could be achieved using 10 mol% $VO(acac)_2$ and 5 equivalents of NMO for six hours in methylene chloride (entry 7), but, as previously mentioned, the product **3a** was nearly impossible to purify from the byproduct **4**. Consequently, we chose to study a vanadyl catalyst that did not contain organic ligands, V_2O_5 (entries 8) but the yield of **3a** was lower. Finally, we found that changing the solvent to 1,4-dioxane and increasing the catalyst, $VO(acac)_2$, loading to 20 mol% allowed for the facile synthesis of **3a** in 80% yield in high purity. Decreasing the amount of NMO below 5 equivalent decreased the yield of **3a**, and when it became 1 equivalent the yield of the unwanted byproduct **4** increased to 7% (table 1, entries 10-12).

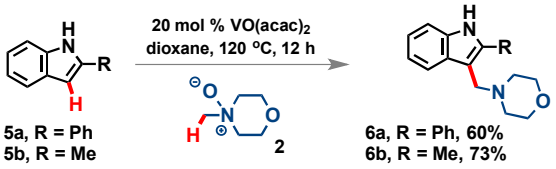
Once the optimal conditions were obtained, the oxidative aminomethylation was performed on a wide variety of substrates (Scheme 2). 2-Arylimidazo[1,2-*a*]pyridines containing electron withdrawing groups on the para-position of the aryl substituent resulted in diminished yields, while electron



Scheme 2. Substrate scope for oxidative aminomethylation of imidazo[1,2-*a*]pyridines

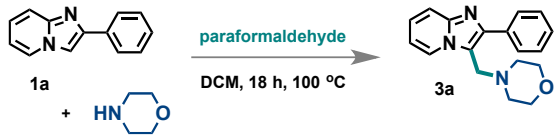
donating groups in the para-position generally lead to higher yields. For example **3r**, which contains a nitro substituent in the para-position, could not be formed, while **3s,** with a methyl ether substituent in the same position, was easily synthesized in 84% yield. The addition of a second electron donating substituent at the meta-position did not improve the yield of the reaction, rather it produced a slightly lower yield (compare **3d** and **3f**). Changing the position of an electron donating methyl group on the imidazo[1,2-*a*]pyridine ring from the C_6-position (entry **3f**) to the C_8-position (entry **3g**) did not appear to significantly effect the reaction. Importantly, halogens could be tolerated by the reactions, indicating that subsequent coupling reactions could be performed on the aminomethylated products.

In addition to imidazlo[1,2-*a*]pyridines, 2-substituted indoles could also be aminomethylated. As shown in Scheme 2, both 2-phenyl and 2-methylindole were oxidatively aminomethylated in 60% and 73% yields (**6a** and **6b**).



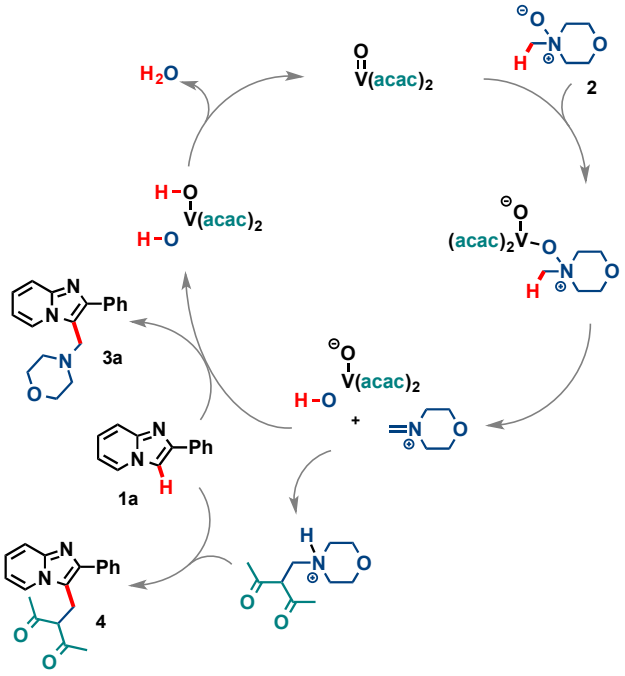
Scheme 3. Oxidative aminomethylation of indoles

Previous studies of vanadium-catalyzed oxidative coupling of structures similar to **1** proposed a radical mechanism,[8] while others hypothesized that the product was formed by way of a Mannich-type reaction.[5] We propose that a Mannich-type mechanism is responsible for the formation of both **3** and **4** (Scheme 5). This was determined by running a conventional Mannich reaction using **1**, formaldehyde, and morpholine to make the imminium ion in situ resulting in **3a** in a 98% yield (Scheme 4). Performing the aminomethyation for the synthesis of **3a** using our optimal reaction conditions in the presence of TEMPO, a radical inhibitor, did not prevent product formation, further indicating that the reaction is likely not radical-mediated.



Scheme 4. Conventional Mannich Condition

Consequently, we propose that the product **3** and byproduct **4** are formed by the mechanism shown in Scheme 5. The *N*-methylmorpholine oxidizes the $VO(acac)_2$ catalyst, resulting in the formation of the iminium ion. The vanadium species extracts a proton from **1** which then attacks the iminium ion, forming **3.** The elimination of water from vanadium regenerates the catalyst. We believe **4** is formed when the iminium ion reacts with one of the ligands from the vanadium catalyst, thus formally incorporating the acac ligand and the methyl from the NMO in the observed byproduct.



Scheme 5. Proposed mechanism of formation of both product **3** and byproduct **4**

In summary, the vanadium catalyzed oxidative coupling of substituted imidazo[1,2-*a*]pyridines to *N*-methylmorpholine was achieved in yields up to 90%. Despite the ability to produce this product using conventional Mannich conditions, we believe this is a useful, orthogonal method to synthesize tertiary amines.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures as well as characterization of previously unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

‡These authors contributed equally. †These authors contributed equally. The manuscript was written by M.S., A.K. and B.D.B. The majority of the data shown in Table 1 and Scheme 4 was obtained at URI, while the majority of the data shown in Scheme 2 and 3was obtained at BITS Pilani.

ACKNOWLEDGMENT

This work was supported by the National Science Foundation (CAREER 0847222), and the National Institutes of Health (NIGMS, 1R15GM097708-01). BDB is the recipient of a Pfizer Green Chemistry Award. PK and KP are thankful to CSIR, New Delhi and UGC, New Delhi, respectively, for senior research fellowships.

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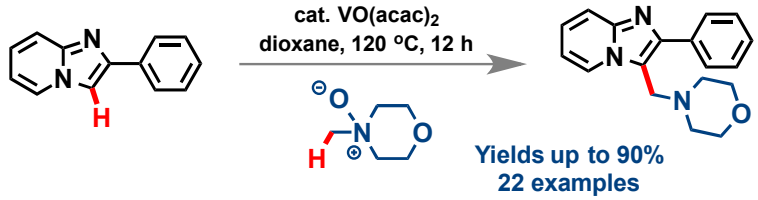
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dioxane, 120 °C, 12 h
Yields up to 90%
22 examples