

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

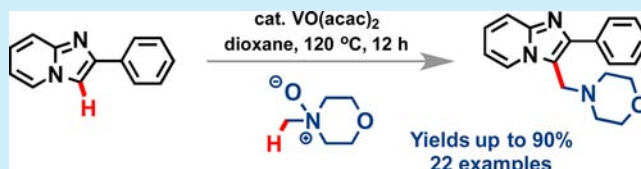
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S Supporting Information

ABSTRACT: The vanadium-catalyzed oxidative coupling of substituted 2-arylimidazo[1,2-*a*]pyridines to *N*-methylmorpholine oxide, which acts as both a coupling partner and an oxidant, has been achieved. This reaction was applied to various substituted imidazo[1,2-*a*]pyridine and indole 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 prefunctionalization 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 prefunctionalization 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 In contrast, 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-

Scheme 1. Oxidative Amination versus Aminomethylation

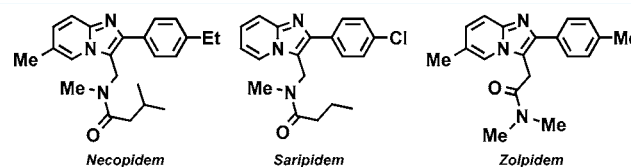


Figure 1. Pharmaceuticals with imidazo[1,2-*a*]pyridine backbone.


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 during the C(sp^3)–H activation step.⁴ Despite these challenges, we sought to develop a novel aminomethylation via the oxidative coupling of sp^3 - and sp^2 -hybridized C–H bonds.

Specifically, we sought to find a method for the aminomethylation of imidazo[1,2-*a*]pyridine substrates. Neuroactive pharmaceuticals such as necopidem, saripidem, and zolpidem contain a substituted imidazo[1,2-*a*]pyridine backbone (Figure 1).⁹ Providing a way to oxidatively couple the 3-position of 2-arylimidazo[1,2-*a*]pyridine with alkylamines would be a useful tool for the synthesis of derivatives of these nonbenzodiazepine GABA potentiators. Herein, we disclose the discovery of a vanadium-catalyzed oxidative coupling of imidazo[1,2-*a*]pyridines with *N*-methylmorpholine oxide (NMO), which serves as both the sp^3 -hybridized coupling partner and the oxidant.

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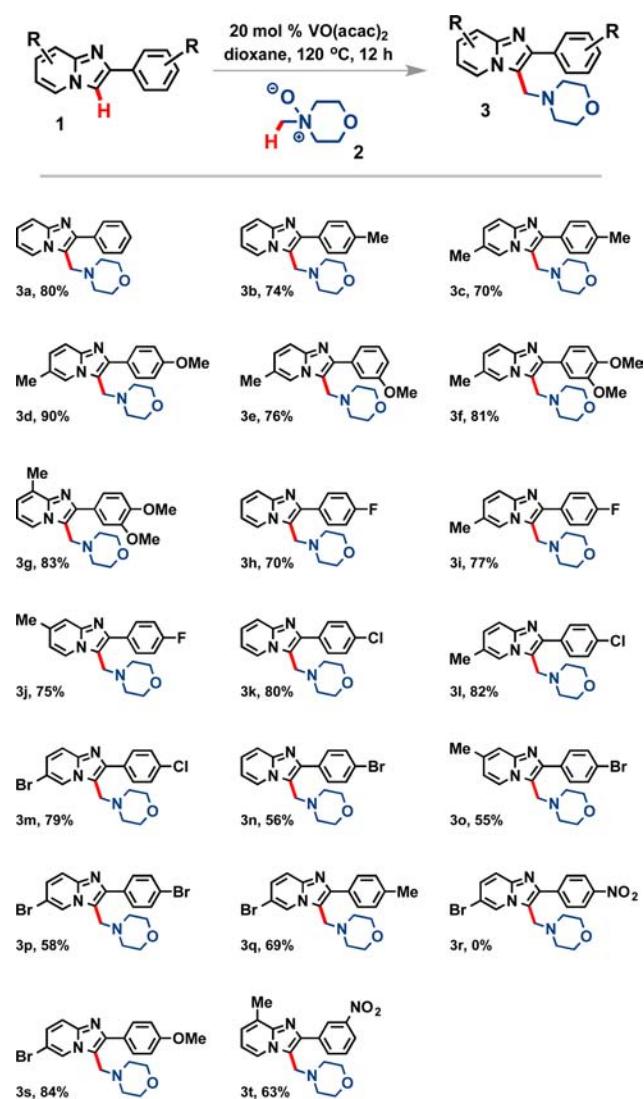
Table 1. Optimization of the Oxidative Aminomethylation Conditions



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	<i>b</i>
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 ₂ O 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

^aProduct yield determined by NMR. ^bTraces of 4 were observed. ^cIsolated yield.

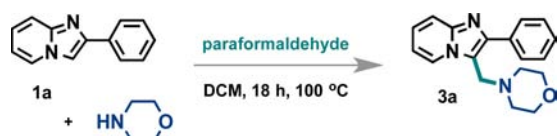
Based on the previous work of Hwang and Uang,⁶ we chose to commence our studies using vanadyl acetylacetonate, VO(acac)₂, as the catalyst for the oxidative aminomethylation shown in Table 1. We systematically studied the effect of solvent, catalyst loading, time, and NMO loading. Ethanol, toluene, and tetrahydrofuran were initially tested (Table 1 entries 4–6), but none had yields comparable to those with methylene chloride (DCM). To our surprise, the aminomethylation reactions consistently formed the acetylacetonate byproduct 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 the Supporting Information). This study indicated that the optimal yield of 3a could be achieved using 10 mol % VO(acac)₂ and 5 equiv of NMO for 6 h 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, V₂O₅ (entry 8), but the yield of 3a was lower. Finally, we found that changing the solvent to 1,4-dioxane and increasing the catalyst loading of VO(acac)₂ to 20 mol % allowed for the facile synthesis of 3a in 80% yield in high purity. Decreasing the

Scheme 2. Substrate Scope for Oxidative Aminomethylation of Imidazo[1,2-*a*]pyridines

Scheme 3. Oxidative Aminomethylation of Indoles



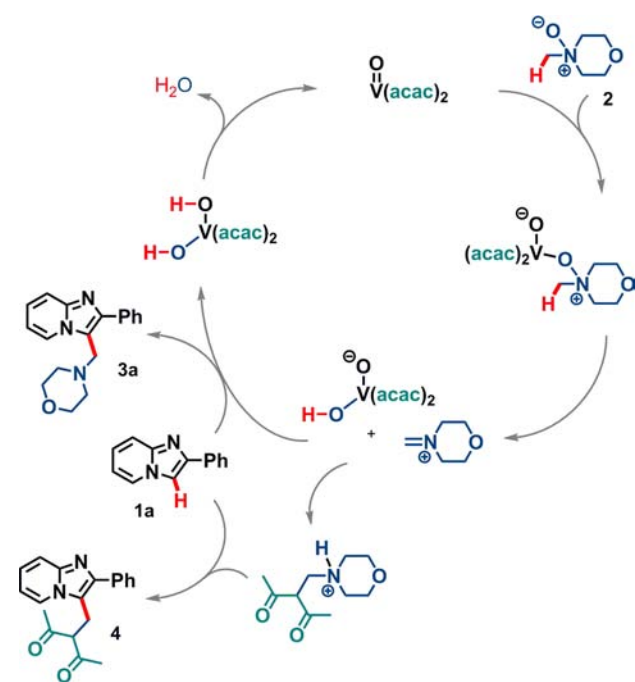
Scheme 4. Conventional Mannich Conditions



amount of NMO below 5 equiv decreased the yield of 3a, and when it became 1 equiv 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

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



aryl substituent resulted in diminished yields, while electron-donating groups in the para position generally led 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 C₆-position (entry 3f) to the C₈-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 imidazo[1,2-*a*]pyridines, 2-substituted indoles could also be aminomethylated. As shown in Scheme 3, both 2-phenyl and 2-methylindole were oxidatively aminomethylated in 60% and 73% yields (6a and 6b).

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 iminium ion in situ, resulting in 3a in a 98% yield (Scheme 4). Performing the aminomethylation 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.

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 an 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.

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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02539.

Experimental procedures as well as characterization of previously unknown compounds (PDF)

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Notes

The authors declare no competing financial interest.

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