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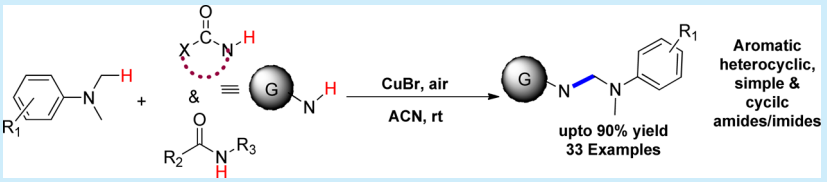
N-Mannich Bases of Aromatic Heterocyclic Amides: Synthesis via Copper-Catalyzed Aerobic Cross-Dehydrogenative Coupling under Ambient Conditions

Shailendra K. Singh,[†] Nisha Chandna,[†] and Nidhi Jain*

Department of Chemistry, Indian Institute of Technology, New Delhi 110016, India

Supporting Information

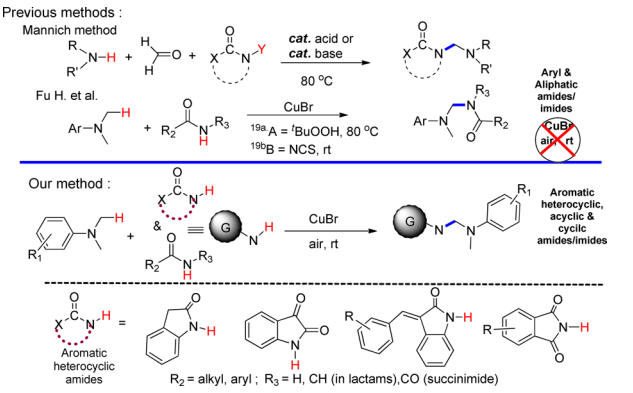


ABSTRACT: An efficient and facile method to synthesize *N*-Mannich bases has been developed using an inexpensive copper(I) bromide/air catalyst system at ambient temperature. A cross-dehydrogenative coupling of *N*,*N*-dimethylarylamines occurs efficiently with aromatic heterocyclic amides (oxindoles, isatins), cyclic amides (lactams), simple amides (benzamide), as well as imides (succinimide, phthalimide) to furnish the corresponding amidated/imidated derivatives in good to excellent yields. Preliminary mechanistic and isotope-labeling studies suggest the reaction follows a radical pathway and involves an iminium ion intermediate.

Aromatic heterocyclic amides/imides, particularly oxindoles, isatins, and phthalimides, are unique pharmacophores that form an integral part of various drugs or druglike molecules.[1] They are usually derivatized into *N*-Mannich bases since these molecules exhibit higher lipophilicity and absorption behavior than the parent amides, thus making them favorable prodrugs under physiological conditions.[2] The *N*-Mannich bases of these amides/imides exhibit important antimicrobial,[1a,3] antiviral,[4] anti-HIV,[5] anti-inflammatory,[6] analgesic,[7] and RSK2 inhibitory[8] properties (Figure S1). At this point in time, C−N bond formation through the multicomponent Mannich reaction remains the only reliable way to synthesize *N*-Mannich bases using amides, secondary amines, and formaldehyde. Intermolecular amidations that can directly convert an unactivated sp^3 C−H bond of an amine to C−N bond by reaction with amides/imides are particularly useful though challenging to achieve. While synthetic tools enabling C−N bond formation via sp^2 C−H activation are the most developed with metal catalysts such as palladium,[9] rhodium,[10] ruthenium,[11] and iron[12] using a variety of oxidants such as TBHP,[13] IBD,[14] NXS,[15] and DDQ,[16] similar reports on facile amidations at the sp^3 C−H bonds are rare.[17] Copper is an efficient and economical metal for C−H bond functionalizations. Copper-catalyzed intermolecular amidations of sp^3 C−H bonds have been reported with the benzylic, allylic, and secondary C−H bonds.[18] However, intermolecular amidation of an sp^3 C−H bond adjacent to a nitrogen atom in a tertiary amine has very few reports.[19]

In 2007, Fu and co-workers[19a] reported the first copper-catalyzed amidation of C−H bonds of *N*,*N*-dimethylanilines with simple aliphatic amides using TBHP at high temperature under nitrogen atmosphere. Attempts to perform the reaction at room temperature or under air did not yield any product. Following this, the same group later realized a more facile protocol on amidation via copper/*N*-halosuccinimide (NCS or NBS) assisted process under ambient conditions[19b] (Scheme 1).

Scheme 1. Methods for Synthesizing *N*-Mannich Bases



Though useful, both methods employed only simple amides as coupling partners. There is no literature report on direct C−N bond formation utilizing biologically significant aromatic heterocyclic amides and imides. Cognizant of the importance of these molecules challenged by unavailability of mild synthetic routes, we sought an efficient and robust catalytic system for their synthesis. In this work, we demonstrate an oxidative amidation of

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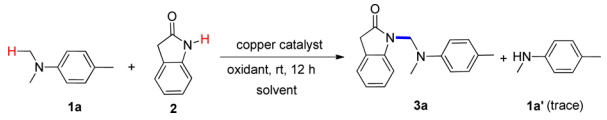
the sp^3 C−H bond adjacent to nitrogen using CuBr/air at room temperature. (Scheme 1) Compared to previous methods, this procedure is distinguished by using air as an oxidant, avoids the use of hydroperoxides and high temperatures, and furnishes the *N*-Mannich bases of aromatic heterocyclic amides in moderate to high yields.

We started our investigation with *N,N*-dimethyl-*p*-toluidine (**1a**) and oxindole (**2**) as model substrates in an attempt to synthesize *N*-Mannich bases of oxindole since we do not find any precedence in literature. In the presence of CuBr (10 mol %) and TBHP (1.5 equiv) in dioxane (2 mL) at 80 °C, the reaction mixture showed multiple spots on TLC with the formation of a trace amount of the desired product 1-((methyl(*p*-tolyl)amino)-methyl)indolin-2-one (**3a**). To enhance the product yield, we optimized the reaction with respect to solvent, catalyst, oxidant, and temperature. Lowering the reaction temperature facilitated the reaction and increased the yield of the desired product (Table 1, entries 1−4). The reaction performed best at room temperature, and **3a** was isolated in 52% yield (Table 1, entry 4).

Table 1. Optimization of Reaction Conditions[a,b]



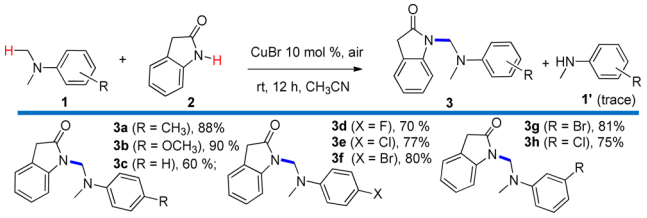
entry	catalyst	oxidant (equiv)	solvent	temp (°C)	yield[b] (%)
1	CuBr	TBHP (1.5)	dioxane	80	trace
2	CuBr	TBHP (1.5)	dioxane	60	20
3	CuBr	TBHP (1.5)	dioxane	50	40
4	CuBr	TBHP (1.5)	dioxane	rt	52
5	CuBr	air	dioxane	rt	65
6	**CuBr**	**air**	**ACN**	**rt**	**88**, 35[c]
7	CuBr	air	DCM	rt	40
8	CuBr	air	DMSO	rt	trace
9	CuBr	air	DMF	rt	10
10	CuBr	air	THF	rt	15
11	$CuBr_2$	air	ACN	rt	55
12	CuCl	air	ACN	rt	52
13	$CuCl_2$	air	ACN	rt	58
14	CuO	air	ACN	rt	trace
15	$Cu(OTf)_2$	air	ACN	rt	48
16	$Zn(OTf)_2$	air	ACN	rt	0
17		air	ACN	rt	0

[a]Reaction conditions: **1a** (1 mmol, 1 equiv), **2a** (1 mmol, 1 equiv), catalyst (10 mol %), and oxidant were taken in a solvent (3 mL) and stirred for 12 h. [b]Yield of **3a**. [c]5 mol % of CuBr.

To eliminate the use of hazardous TBHP, the reaction was carried out in an open atmosphere with air as the oxidant. To our delight, the reaction was much cleaner, and **3a** was isolated in 65% yield after 12 h. Screening of various solvents demonstrated that among dioxane, acetonitrile, DCM, DMSO, DMF, and THF acetonitrile was the solvent of choice and gave the highest yield of **3a** (Table 1, entries 5−10) with a trace amount of *N*-demethylated product **1a′**. Replacing CuBr with other salts such as $CuBr_2$, CuCl, CuO, $CuCl_2$, $Cu(OTf)_2$, and $Zn(OTf)_2$ (Table 1, entries 11−16) did not help the reaction, and CuBr was found to be the most effective catalyst at room temperature (Table 1, entry 6). Notably, the reaction did not proceed in the absence of copper catalyst (Table 1, entry 17). Further, on lowering the catalytic loading to 5 mol %, only 35% yield of **3a** was obtained (Table 1, entry 6). Thus, the best optimized conditions for a CDC between NH of oxindole and sp^3 C−H of tertiary amine required 10 mol % of CuBr and stirring at ambient temperature under air atmosphere for 12 h. It is noteworthy to mention that this protocol is much more effective and facile than the previously reported amidation[19a] using a CuBr/TBHP system wherein the reaction fails completely at room temperature and gives low yield in the absence of nitrogen atmosphere.

Following this initial success, we explored the conditions with a variety of *N,N*-dimethylanilines (Scheme 2). It was found that

Scheme 2. *N*-Mannich Bases of Oxindole with Various *N,N*-Dimethylanilines[a,b]

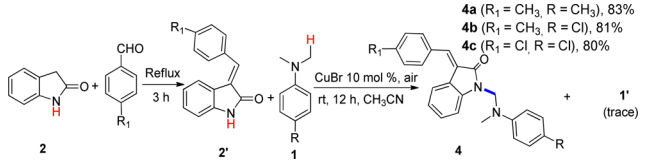


[a]Reaction conditions: **1** (1 mmol), **2** (1 mmol), and CuBr (10 mol %) in acetonitrile (3 mL), stirred at room temperature under air for 12 h. [b]Isolated yields.

anilines substituted with electron-donating groups showed higher reactivity than those with electron-withdrawing substituents or unsubstituted aniline, irrespective of their position (meta or para) on the benzene ring (Scheme 2, **3a,b** vs **3c−h**). Within the series, the relative reactivity of halogen-substituted anilines followed the order Br (**3f**) > Cl (**3e**) > F (**3d**), which is in accordance with the electronic influence exercised by electron-donating and -withdrawing groups on the reaction. Notably, with very strong electron-withdrawing groups like nitro and cyano, no product formation was seen. Further, the reaction was also attempted with other dialkylanilines such as *N*-methyl-*N*-ethyl- and *N,N*-diethylaniline. However, none of these amines worked under the optimized conditions, and the corresponding amidated products could not be obtained.

The alkylidene derivatives of oxindole are known to possess potent antiglycation activity, and some are even better than the standard drug rutin.[20] Instigated by the importance of these molecules, we attempted synthesis of *N*-Mannich bases of the alkylidene derivatives of oxindole using our protocol. For this, we first synthesized the alkylidene derivatives of oxindole by refluxing the aldehyde and oxindole[20] and then carried out the reaction with *N,N*-dimethylanilines under the optimized conditions (Scheme 3). Gratifyingly, the desired *N*-Mannich bases (**4a−c**) were formed in 80−83% yields. To the best of our knowledge, this is the first report on the synthesis of these novel derivatives.

Scheme 3. Substrate Scope with Alkylidene Derivatives of Oxindole[a,b]



[a]Reaction conditions: **2′** (1 mmol), **1** (1 mmol), CuBr (10 mol %) in acetonitrile (3 mL), stirred at room temperature under air for 12 h. [b]Isolated yields.

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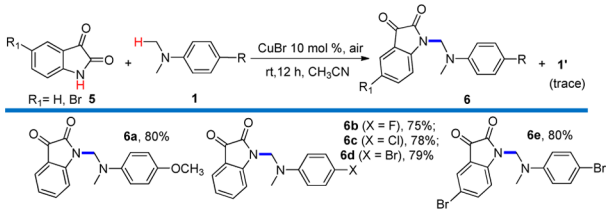
The scope of this strategy was further extended to isatins (**5**) as the amide substrate. It is known that 1-aminomethylisatins, also known as isatin *N*-Mannich bases, serve as efficient agents for the treatment of tuberculosis, oncological diseases, malaria, and infections caused by Gram-positive and Gram-negative bacteria.[21] In view of the medicinal importance of these compounds, the synthesis of isatin *N*-Mannich bases (**6a−d**) was carried out under optimized reaction conditions, and the desired products were obtained in good yields (Scheme 4). With 5-bromoisatin,

Scheme 4. Synthesis of *N*-Mannich Bases of Isatins[a,b]

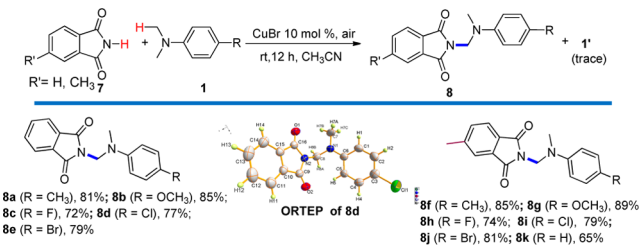


[a]Reaction conditions: **5** (1 mmol), **1** (1 mmol), CuBr (10 mol %) in acetonitrile (3 mL), stirred at room temperature under air for 12 h. [b]Isolated yields are given.

the corresponding bromo-substituted derivative (**6e**) was obtained in 80% yield, providing a handle for subsequent functionalizations. To ascertain the synthetic utility of the developed protocol for practical purposes, the reaction was also carried out on a gram scale. One gram of isatin (**5**) was treated with 6.8 mmol of 4-chloro-*N*,*N*-dimethylaniline under the standard reaction conditions, and the coupled product **6c** was isolated in 81% yield (1.62 g).

The copper-catalyzed CDC was next explored with phthalimides as the substrates since they constitute an essential structural motif in medicinal chemistry. As shown in Scheme 5, the coupling

Scheme 5. Substrate Scope with Phthalimides[a,b]

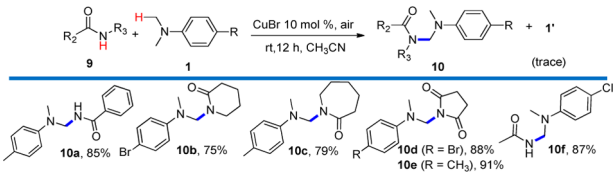


[a]Reaction conditions: **7** (1 mmol), **1** (1 mmol), CuBr (10 mol %) in acetonitrile (3 mL), stirred at room temperature under air for 12 h. [b]Isolated yields are given.

reaction worked well with a variety of substituted *N*,*N*-dimethylanilines (**1**) and phthalimides (**7**) and gave the desired imidated products (**8a−k**) in good to excellent yields (65−89%). These molecules are the new analogues of RSK2 inhibitors[8] and might exhibit potential inhibitory activity. The substituted anilines containing electron-rich groups showed higher reactivity than those with electron-deficient ones. The structure of 2-(((4-chlorophenyl) (methyl)amino)methyl)isoindoline-1,3-dione (**8d**) (Scheme 5) was also confirmed by X-ray crystallography (see the Supporting Information). In general, methyl-substituted phthalimide gave a slightly higher yield of the *N*-Mannich bases (**8f−k**) than the unsubstituted phthalimide (**8a−e**).

The reaction scope was also investigated with simple amides and imides as shown in Scheme 6. Aryl amide (benzamide) as well

Scheme 6. Scope with Simple Amides and Imides[a,b]

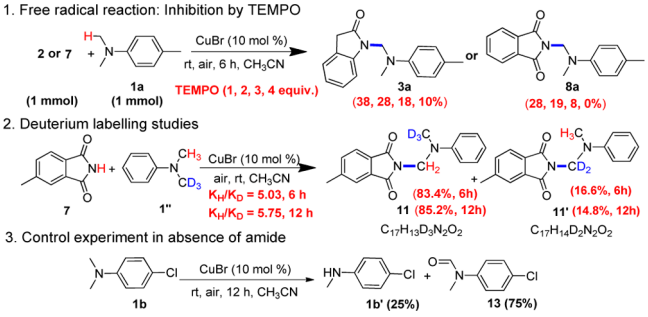


[a]Reaction conditions: **1** (1 mmol), **9** (1 mmol), CuBr (10 mol %) in acetonitrile (3 mL), stirred at room temperature under air for 12 h. [b]Isolated yields are given.

as cyclic amides (lactams) tolerated the reaction conditions well and gave the desired amidated products **10a−c** in 75−85% yields. With cyclic imide (succinimide), the corresponding imidated products (**10d,e**) were obtained in 88% and 91% yields, respectively. The reaction was equally facile with simple acetamide as substrate and furnished **10f** in 87% yield.

Studies probing into the mechanisms involved in the oxidation of tertiary amines have been reported by several research groups over the years.[22−25] To gain insight into the reaction mechanism, several control experiments were carried out (Scheme 7).

Scheme 7. Preliminary Mechanistic Studies



The involvement of free-radical species in the reaction was ascertained by performing quenching studies with a radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO). It was found that the reaction of **1a** with **2** or **7** in the presence of TEMPO gave the corresponding products **3a** or **8a** in lower yields, and the yields were found to decrease in a dose-dependent manner (Scheme 7 (1)). The inhibitory effect of TEMPO indicated the reaction to proceed via radical intermediate(s). Since the reaction was facilitated in acetonitrile as the solvent, it also suggested the formation of a radical against a carbocationic species, as acetonitrile is known to trap carbocations by a Ritter-type reaction.[26] The kinetics of the reaction were monitored by deuterium-labeling studies (Scheme 7 (2)). *N*-methyl-*N*-trideuteriomethylaniline (**1″**) was prepared and treated with **7** under the optimized reaction conditions. The ratio of the products **11**/**11′** was determined at 6 and 12 h of reaction time by LC−MS yield analysis. The intramolecular kinetic isotope effect (k_H/k_D) calculated from the product ratio was found to be 5.03 and 5.75 respectively, which suggested hydrogen atom abstraction to be involved in the rate-determining step.[27,28] A similar k_H/k_D was reported by Miura et al. during [Fe(salen)]OAc-catalyzed oxidation of *N*,*N*-dimethylaniline with molecular oxygen.[23a] It is noteworthy to mention that the

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formation of trace amounts of *N*-demethylated product (**1′**) from the amine was inevitable with all of the different amides and imides employed in the reaction. To understand its formation, a control experiment of **1b** was carried out in the absence of amide, wherein a mixture of products, 4-chloro-*N*-methylaniline (**1b′**) and *N*-(4-chlorophenyl)-*N*-methylformamide (**13**), were obtained in 25 and 75% yields, respectively (Scheme 7 (3)). This is consistent with the previous observation by Miura et al., who reported the formation of these two products during the oxidation of amine with [Fe(salen)]OAc and suggested oxygen insertion in to the alkyl radical of *N,N*-dimethylaniline as the most probable pathway leading to their formation.[23a,29]

On the basis of these experimental findings and the available literature, a plausible mechanism for the reaction has been proposed (Figure S2).

In conclusion, we have developed an unprecedented copper-catalyzed direct sp^3 α-C−H amidation/imidation of *N,N*-dimethylarylamines with aromatic heterocyclic amides/imides under ambient conditions using air as the oxidant. A wide range of substrates including oxindoles, isatins, phthalimides, and aryl amides as well as cyclic amides/imides respond to this C−N bond formation and furnish the biologically useful amidated/imidated heterocycles in good to high yields. The reaction is believed to follow a radical pathway involving an iminium ion intermediate. The protocol is atom-economic, does not require toxic oxidants or additives, and can be executed efficiently at ambient temperature.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00125.

Experimental procedures and spectroscopic data of all new compounds (PDF)

X-ray crystal structure data for compound **8d** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: njain@chemistry.iitd.ac.in.

ORCID

Nidhi Jain: 0000-0001-8645-430X

Author Contributions

†S.K.S. and N.C. contributed equally.

Notes

The authors declare no competing financial interest.

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