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Copper-Mediated Selective C−H Activation and Cross-Dehydrogenative C−N Coupling of 2′-Aminoacetophenones

Andivelu Ilangovan* and Gandhesiri Satish

School of Chemistry, Bharathidasan University, Tiruchirappalli 620024, India

ilangovanbdu@yahoo.com

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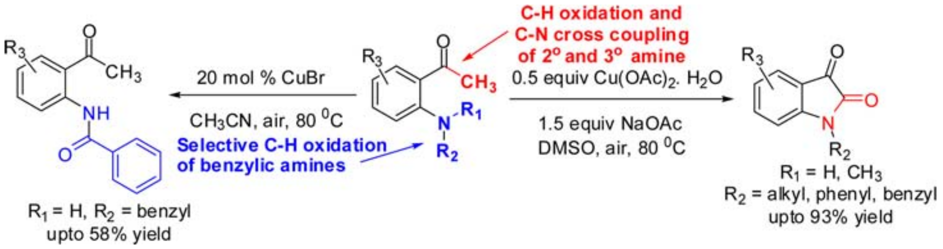
ABSTRACT



Isatins were obtained by cross-dehydrogenative C−N annulation and dealkylative C−N annulation of 2′-*N*-aryl/alkylaminoacetophenones and 2′-*N,N*-dialkylaminoacetophenones respectively in the presence of Cu(OAc)$_2$·H$_2$O/NaOAc/air. However, on reaction with CuBr, 2′-*N*-benzylaminoacetophenones underwent selective oxidation of an α-methylene group of amine rather than the 2-acetyl group to provide corresponding benzamides exclusively. Base played an important role in selective oxidation by lowering the temperature and time.

Organic transformations via transition-metal-catalyzed C−H bond activation have emerged as an exciting strategy for construction of C−C and C−heteroatom bonds.[1] Consequently, the processes concerning cross-coupling between C$_{sp3}$−H and N−H centers and dealkylation reactions have received much consideration.[2] However, such examples are only few.

Conversion of readily available tertiary amines into secondary amines and amides is considered as an important value addition process in the synthesis of pharmaceuticals and fine chemicals.[3] For demethylation of tertiary amine catalytic systems, such as Ru− and Ir−polypyridyl complexes,[4a] CuCl/TBHP,[4b] and Fe(II)-mediated Polonovski-type reaction,[4c] were found to be better over conventional methods.[5] Very recently, FeCl$_2$/TBHP was used as catalyst for intermolecular dealkylative amidation between tertiary amine and anhydride[6] or aldehyde.[7] However, to the best of our knowledge, intramolecular equivalents of such a reaction are not yet known. Similarly, oxidation of the α-methylene group of amine to primary amide was reported using catalysts such as RuCl$_3$,[8] Ru(OH)$_x$/Al$_2$O$_3$/air (5 bar),[9] CuBr−K$_2$CO$_3$/air,[10] manganese oxide octahedral molecular sieves (OMS-2),[11] and ZnBr$_2$/TBHP or FeCl$_3$/TBHP.[12] The majority of these reports deal with the coversion of benzylamine derivatives to the corresponding benzamides, and chemoselectivity is not addressed. This may be due to the requirement of high temperature/pressure or use of strong co-oxidant. Chemoselective

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oxidation of the C−H bond adjacent to nitrogen against the easily oxidizable acetophenone group is a challenging task.

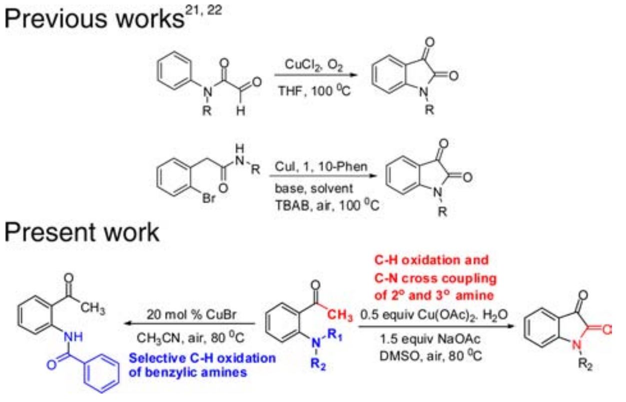
Isatins are privileged structural motifs found in pharmaceuticals and dyes,[13] find applications as precious synthetic intermediates,[14,15] and signal several promising applications. Two major approaches are followed for the synthesis of isatins. One involves the reaction of aniline with suitable carbonyl precursors,[16−18] and the other involves oxidation of a preexisting aromatic ring.[19] These methods are generally associated with harsh and tedious synthetic procedures. Although strategies such as reaction between 2-oxo-2-(arylamino)acetates and -arynes[20] and intramolecular oxidative cyclization of formyl-*N*-arylformamide[21] or *N*-arylacetamides[22] (Scheme 1) did provide access to *N*-arylisatins, typical starting materials which are difficult to prepare were needed.

During the final stages of preparing this manuscript, Cheng et al.[23] and Deng et al.[24] have independently reported the conversion of 2′-*N*-aryl/alkylaminoacetophenones into isatins using CuI and SeO_2, respectively. The former method requires very high temperature (140 °C), high boiling solvent (*o*-dichlorobenzene), and 2,2′-bipyridine ligand. SeO_2, which was used in the later method, is considered to be harmful even at residual level in pharmaceuticals. Moreover, both procedures studied only the C−N bond formation of 2′-*N*-aryl/alkylaminoacetophenones and did not consider the functionalization of 2′-*N*,*N*-dialkylaminoacetophenones, chemoselective oxidation of C−H bond adjacent to nitrogen, and the role of amine in the oxidation process.

In the present study, we observed a facile cross dehydrogenative and delalkylative C−N coupling of 2′-*N*-aryl/alkylaminoacetophenones and 2′-*N*,*N*-dialkylaminoacetophenones respectively in the presence of $Cu(OAc)_2.H_2O$ (0.5 equiv)/NaOAc (1.5 equiv)/air at relatively low temperature (80 °C). Thus isatins were produced in very good yield. It was also observed that secondary amines can be selectively oxidized to amides in the presence 2-acetyl group using catalytic quantity of CuBr. Further, this study provided clear evidence for the role of amine group in the C−H activation process. Herein, we portray our approach toward selective funtionalization of 2′-aminoacetophenones using Cu(II) and Cu(I) catalysts (Scheme 1).

Our optimization studies began with the examination of compound **1a** as a typical substrate for C−H bond activation. In the presence of $Cu(OAc)_2 \cdot H_2O$ (0.5 equiv)/air at 80 °C isatin was formed in low yield (Table 1, entry 1). It was envisaged that a base could be used for removal of proton from either acetyl group or amine.

Scheme 1. Methods for the Synthesis of Isatin



Among a set of bases screened, NaOAc furnished good yield (Table 1, entry 4), while use of K_2CO_3 and K_3PO_4 resulted only in moderate yield (Table1, entry 2 and 3). Et_3N as a base produced a complex mixture of products. In the absence of copper source, no product was obtained (Table 1, entry 5). Other copper catalysts such as $Cu(NO_3)_2$, $Cu(ClO_4)_2$, $CuCl_2$, $CuBr_2$, $CuSO_4$, CuI, and CuBr provided isatin only in low yield. This preliminary result indicates that Cu(II) catalysts are better than Cu(I) for isatin formation. DMSO was more effective among all the solvents such as toluene, DMF, DMA, CH_3CN, and IPA studied. It was found that 0.5 equiv of $Cu(OAc)_2 \cdot H_2O$ and 1.5 equiv of NaOAc in DMSO at 80 °C are a superlative combination to provide isatin in high yield (82%, entry 4).

Under the above optimized conditions the substrate scope was examined. As summarized in Table 2, the substrates **1a**−**h** with no substitution on the 2′-aminoacetophenone ring afforded isatins **3a**−**h** in good yield. Compounds **1d**−**g** with *N*-alkyl substituents reacted slowly compared to *N*-benzyl substituent. However, compound **1i**, a primary amine, afforded the desired product **3i** only in traces even after a long time. Notably, substrate **1h** with a phenyl group attached to amine gave a very high yield of the product **3h** in the shortest time, indicating that the electronic factor has significant influence in the reaction. Halogen substituents on the phenyl ring are well tolerated, and 5-halo-*N*-substituted isatins **3j**−**p** were obtained in good yields. There was an increase in the rate of the reaction and yield when electron-donating substituents such as 3,5-dimethoxy and 3,4,5-trimethoxy groups are present on the phenyl ring (**3q**−**u**). Compounds **1v** and **1w** with acetyl and benzoyl amide groups did not undergo reaction to give expected products **3v** and **3w**. Overall, this method has been prove to be versatile for the synthesis of *N*-alkyl- as well as *N*-aryl-substituted isatins.

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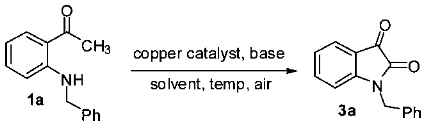
Table 1. Optimization of the Reaction Conditions[a]



entry	Cu catalyst	base	solvent	time (h)	yield[b] (%)
1	$Cu(OAc)_2 \cdot H_2O$		DMSO	24	55
2	$Cu(OAc)_2 \cdot H_2O$	K_2CO_3	DMSO	15	69
3	$Cu(OAc)_2 \cdot H_2O$	K_3PO_4	DMSO	15	56
4	$\mathbf{Cu(OAc)_2 \cdot H_2O}$	**NaOAc**	**DMSO**	**4**	**82**
5		NaOAc	DMSO	24	nd[c]
6	$Cu(OAc)_2 \cdot H_2O$	NaOAc	DMF	20	52
7	$Cu(OAc)_2 \cdot H_2O$	NaOAc	DMA	20	54
8	$Cu(OAc)_2 \cdot H_2O$	NaOAc	CH_3CN	20	trace
9	$Cu(OAc)_2 \cdot H_2O$	NaOAc	toluene	20	nd[c]
10	$Cu(OAc)_2 \cdot H_2O$	NaOAc	IPA	20	nd[c]
11	$Cu(NO_3)_2$	NaOAc	DMSO	12	63
12	$Cu(ClO_4)_2$	NaOAc	DMSO	16	nd[c]
13	$CuSO_4$	NaOAc	DMSO	16	nd[c]
14	$CuCl_2$	NaOAc	DMSO	12	58
15	$CuBr_2$	NaOAc	DMSO	12	70
16	CuI	NaOAc	DMSO	12	64
17	CuBr	NaOAc	DMSO	12	68

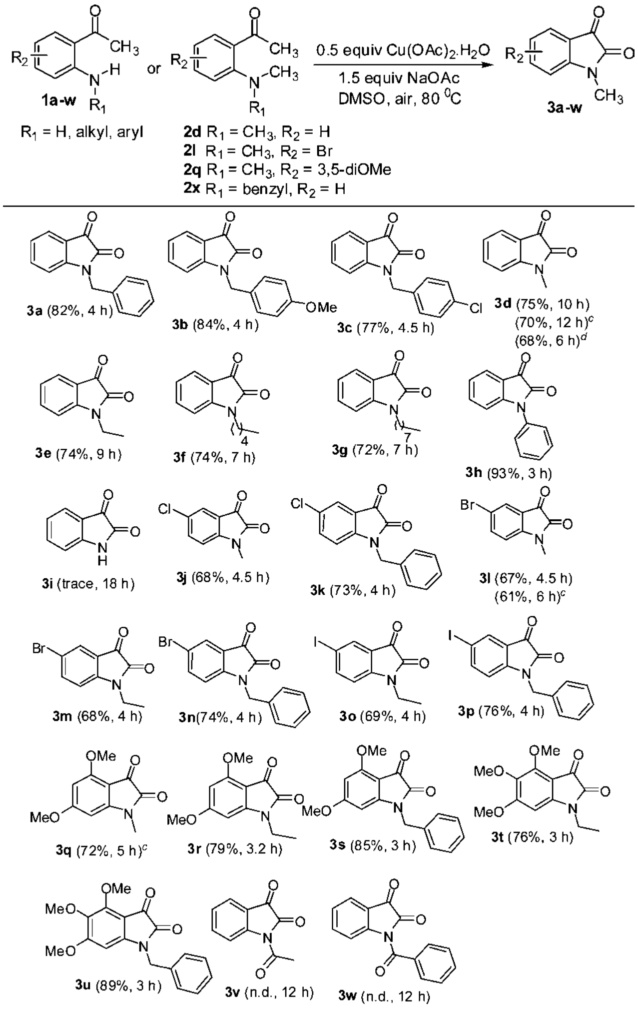
[a] Reaction conditions: 1-(2-benzylaminophenyl)ethanone **1a** (1 mmol), [Cu] (0.5 mmol), base (1.5 mmol) in solvent (2 mL) at 80 °C under air atmosphere. [b] Isolated yield. [c] Not determined.

As a part of the study the reactivity of different tertiary amines such as **2d**, **2l**, **2q**, and **2x** was examined under the optimized reaction conditions (Scheme 2). Remarkably, compound **2d** underwent facile dealkylative C–N bond formation to provide isatin **3d** in good yield (70%). To the best of our knowledge, this is the first example of intramolecular C–N bond cleavage and C–N bond formation taking place in single step in the presence of copper catalyst. Further, 4-bromo- and 3,5-dimethoxy-substituted 2′-aminoaectophnones **2l** and **2q**, respectively, underwent reaction to provide isatin **3l** and **3q** in good yield. Notably, compound **2x** afforded *N*-methylisatin **3d** in 68% yield, indicating debenzylation takes place faster than demethylation. During the course of formation of **3d** from **2x**, intermediate **1d** was isolated indicating that the reaction proceeds via mono-demethylation followed by oxidative cyclization. This study proves that even tertiary amines can be used as starting materials for isatin synthesis.

Next, we examined the effect of copper(I) catalyst on 2′-*N*-benzylaminoacetophenones in CH_3CN and air oxidant (Scheme 3). Compound **1a** underwent selective oxidation of benzylic C–H bond adjacent to amine, over another easily oxidizable acetyl group, in the presence of CuBr (20 mol %) in CH_3CN solvent and air oxidant at relatively low temperature (80 °C)[22,23] to produce *N*-(2-acetylphenyl)benzamide (**4a**) in 52% isolated yield. There was no need for the use of base and co-oxidant.[10]

Considering the importance of converting amine to amide,[13,14] other benzyl amines **1a**–**c**, **1n**, **1s**, and **1u**

Scheme 2. Synthesis of Highly Substituted *N*-Alkyl- and *N*-Arylisatins Using Copper(II) Catalyst from Secondary and Tertiary Amines[a]

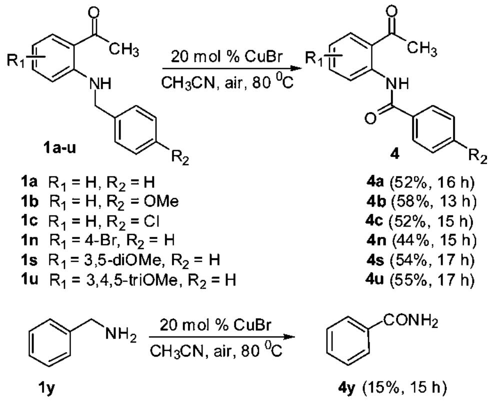


[a] Reaction conditions: **1a**–**w** (1 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.5 mmol), NaOAc (1.5 mmol), DMSO (2 mL). [b] Isolated yield. [c,d] Tertiary amine as starting material.

were converted into the corresponding amides **4b**, **4c**, **4n**, **4s**, and **4u**, respectively, in good yield. None of these reactions produced isatin at all. Under the same reaction conditions, simple a benzylamine underwent oxidation to benzamide, only slowly in low yield (15%, 15 h), which indicates that the acetyl group plays a role in oxidation step. As expected, 1-(2-(ethylamino)phenyl)-ethanone (**1e**) did not undergo reaction under the same conditions.

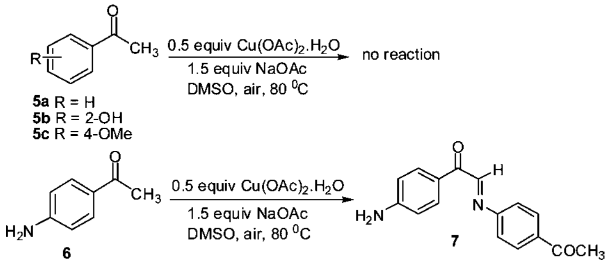
To deepen our understanding on the role of the amine group in the reaction mechanism, substrates **5a**, **5b**, **5c**, and **6** containing substituents H, 2-OH, 4-OMe, and 4-NH_2, respectively, were identified and subjected to oxidation using $Cu(OAc)_2 \cdot H_2O$ (0.5 equiv)/NaOAc (1.5 equiv)/air in DMSO at 80 °C (Scheme 4). Except for compound **6** undergoing oxidation to compound **7**, no other substrate underwent oxidation of the acetyl group. This result and dealkylative C–N bond-forming reactions of tertiary

Scheme 3. Copper-Catalyzed Oxidation of *N*-Benzyl-2′-aminoacetophenones[a,b]

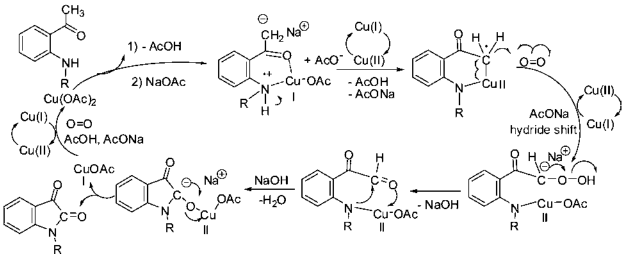


[a] Reaction conditions: **1a**–**u** (1 mmol), CuBr (20 mol %), CH_3CN (2 mL). [b] Isolated yields based on conversion (70% conversion).

Scheme 4. $Cu(OAc)_2 \cdot H_2O$-Catalyzed Oxidation of Some Acetophenones



Scheme 5. Plausible Mechanism for Cu(II)-Catalyzed C–N Bond Formation



amines confirms that the amine group plays an important role and the 2-amino group may provide anchiomeric assistance during the C–H bond activation. This also confirms the role of a base.

Considering the role of amine and base, a suitable mechanism is proposed. It has recently been established that the imines or iminium ions, generated by oxidation of C–H bonds adjacent to nitrogen using transition-metal catalysts, are key intermediates in various organic transformations.[4] As shown in Scheme 5, on reaction with basic and electron-rich amine, Cu(II) undergoes reduction to Cu(I) and substrate activation takes place.[25] Further, the deprotonation of acetyl group by a base helps the formation of C–N bond faster. Cu(I) formed in the process is reoxidized to Cu(II) in the presence of air, and this forms a comfortable catalytic cycle.

In conclusion, we have successfully developed an efficient copper(II)-catalyzed cross-dehydrogenative intramolecular C–N coupling of an acetyl group and an amine to furnish isatins at relatively lower temperature. We have also observed for the first time that tertiary amines undergo intramolecular C–H bond oxidation, C–N bond cleavage, as well as C–N bond formation to produce isatins in the presence of Cu(II) catalysts. Cu(I) in the presence of air selectively oxidized benzyl amines over acetophenone to the corresponding amides in CH_3CN solvent. Application of copper catalysts for oxidative transformations in organic synthesis is currently underway in our laboratory.

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Supporting Information Available. Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.