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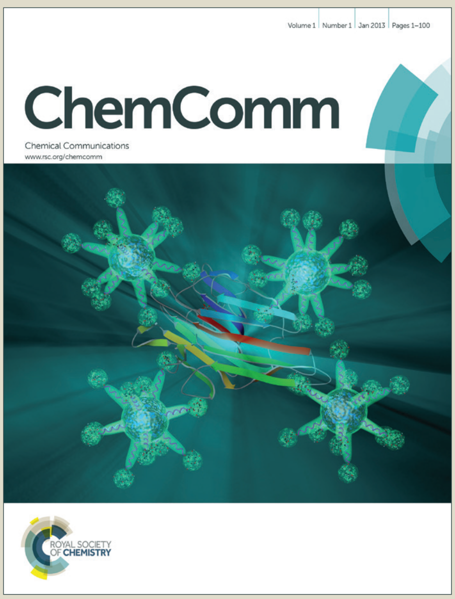

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ARTICLE TYPE

Cu-Catalyzed Selective C3-Formylation of Imidazo[1,2-a]pyridines C-H Bonds with DMSO using Molecular Oxygen

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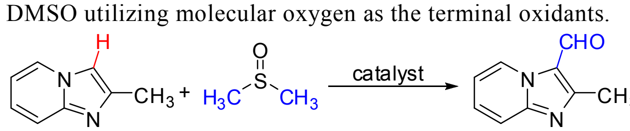
By the widely available DMSO as the formylation reagent under oxidative conditions, an efficient Cu-catalyzed C3-formylation reaction of imidazo[1,2-a]pyridines C-H bonds to directly generate structurally sophisticated 3-formyl imidazo[1,2-a]pyridine derivatives has been developed. The reaction proceed in good yields, and using the environmental friendly molecular oxygen as the oxidant.

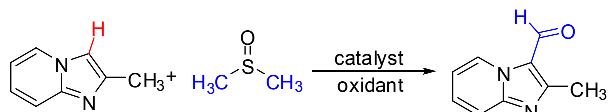
Formylheteroarenes are useful building blocks for preparation of a wide range of heteroarenes derivatives since their carbonyl groups can readily undergo various transformations, such as coupling reactions and reductions, for the formation of C-C and C-hetero bonds. The formylation of (hetero)arenes has attracted and continues to attract the interest of organic chemists due to their remarkable application value in chemistry. Generally, the traditional formylation methods for the construction of formylheteroarenes are mainly included Vilsmeier−Haack[1], Reimer−Tiemann,[2] Rieche[3] and Friedel Crafts acylations.[4] However, these transformations suffer from various problems, such as excess strong bases or acids, high temperatures, strict exclusion of moisture. Therefore, the development of efficient and facile formylation methods is a challenge for the synthetic organic chemists. Many elegant formylation process has been developed using anilines,[5] TMEDA,[6] DMF,[7] DMSO[8] as carbon source, which has provided new transformation for the formation of carbon-carbon bonds to prepare formylheteroarene molecules. DMSO is not only a common solvent but also an important carbon source for C=O,[8,9] Me,[10] SMe,[11] SO_2CH_3,[12] -CN[13] formation. Currently, our interests focused on developing an facile formylation of heteroarene using DMSO as carbon source.

Our recent efforts were including the construction of imidazo[1,2-a]pyridines by direct C-H functionalization[14] or multicompoent reaction[15]. Imidazo[1,2-a]pyridine and its derivatives as important fine chemicals[16] have been found to be key structural units in many natural products, drugs and exhibited a broad range of biological activities, such as zolpidem, alpidem, zolimidine, olprinone, saripidem, and necopidem. There has been long-standing interest in the development of new and efficient transformation[17] for the synthesis of imidazo[1,2-a]pyridines due to their great important applications. In continuation of our interest in preparing imidazo[1,2-a]pyridine derivatives by direct C-H functionalization, we reported a novel and facile copper-catalyzed C-3 formylation of imidazo[1,2-a]pyridines with DMSO utilizing molecular oxygen as the terminal oxidants.



Scheme 1. Formylation of Imidazo[1,2-a]pyridines

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

Entry	Catalyst	Additive	Oxidant	T	Yield (%)[b]
1	$Cu(OAc)_2$	-	O_2	120	46
2	$CuBr_2$	-	O_2	120	24
3	$CuCl_2$	-	O_2	120	5<
4	CuO	-	O_2	120	trace
5	$CuSO_4$	-	O_2	120	13
6	$Cu(OTf)_2$	-	O_2	120	5<
7	$Cu(OAc)_2$	K_2CO_3	O_2	120	trace
8	$Cu(OAc)_2$	Na_2CO_3	O_2	120	trace
9	$Cu(OAc)_2$	DABCO	O_2	120	31
10	$Cu(OAc)_2$	AcOH	O_2	120	82
11	$Cu(OAc)_2$	TsOH	O_2	120	40
12	$Cu(OAc)_2$	AcOH	air	120	51
13	$Cu(OAc)_2$	AcOH	$K_2S_2O_8$	120	trace
14	$Cu(OAc)_2$	AcOH	BQ	120	trace
15	$Cu(OAc)_2$	AcOH	TBHP	120	23
16	$Cu(OAc)_2$	AcOH	Oxone	120	trace
17	$Cu(AcO)_2$	AcOH	O_2	100	68
18	$Cu(AcO)_2$	AcOH	O_2	50	N.P.
19	$Cu(AcO)_2$	AcOH	O_2	rt	N.P.
20	$Cu(AcO)_2$	AcOH	O_2	140	74
21	-	AcOH	O_2	120	N.P.

[a] Reaction conditions: **1a** (0.5 mmol), catalyst (5 mol %), additive (0.5 mmol), O_2 /air (with one balloon); other oxidant (1.2 mmol), solvent (3.0 mL). [b] Yields determinedby GC analysis using n-octadecane as internal standard.

With this in mind, we began the investigation by treatment of 2-tert-butylimidazo[1,2-a]pyridine **1a** in presence of $Cu(OAc)_2$ in DMSO using O_2 as oxidant at 120 ℃, which formed the desired product 2-tert-butylimidazo[1,2-a]pyridine-3-carbaldehyde **3a** in 46% yield (Table 1, entry 1).

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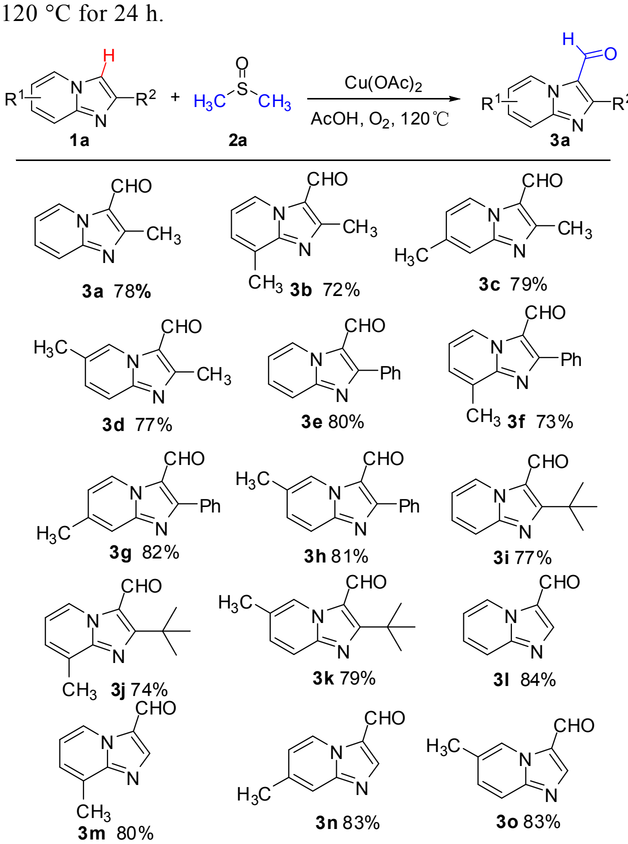
Despite low yield was obtained, the result showed the feasibility of the envisioned transformation. Further investigation, we focused on testing various conditions to improve the product yield. Unfortunately, low yields were also observed when using $CuBr_2$, $CuCl_2$, CuO, $CuSO_4$, $Cu(OTf)_2$ (Table 1, entries 2-6) as catalyst. Additives were next examined (Table 1, entries 7-11). To our delight, the corresponding formylation product **3a** was obtained in 82% yields in the presence of $Cu(OAc)_2$ and AcOH. Encouraged by those positive results, we then tested a variety of oxidant (Table 1, entries 12-16). The results indicated that other oxidants (e.g. air, $K_2S_2O_8$, TBHP, BQ, Oxone) provided low yields. Additional optimization revealed that the yield decreased gradually with increasing or decreasing temperature (Table 1, entries 17-20). The control experiment was carried out in the absence of $Cu(OAc)_2$ and no product **3a** was detected. It was found that the copper catalyst should play a predominate role in this formaylation of imidazo[1,2-a]pyridines. These preliminary experiments clearly revealed that the best way to proceed with the formylation of imidazo[1,2-a]pyridines is by using $Cu(OAc)_2$ as catalyst, and AcOH as additive, O_2 as oxidants, and DMSO as solvent at 120 °C for 24 h.

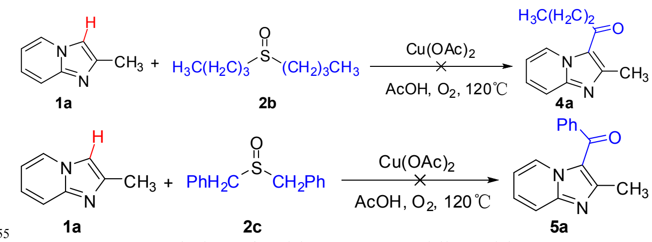


[a] Isolated yields

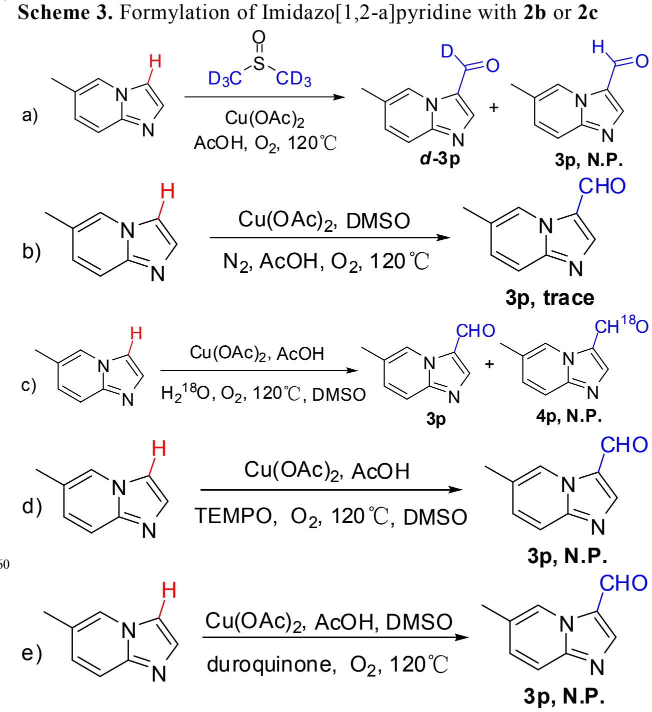
Scheme 2. Copper-Catalyzed Formylation of Imidazo[1,2-a]pyridine

With the optimized conditions in hand, we explored the scope of this novel copper-catalyzed formylation of imidazo[1,2-a]pyridine with DMSO. And the results are summarized in Scheme 2. A variety of different 2-CH_3 substituted imidazo[1,2-a]pyridines were firstly tested under the optimized condition. Different position substituted group on the pyridine ring, having 6-CH_3, 7-CH_3, 8-CH_3 substitution, were smoothly participated in this formylation process to provide the corresponding imidazo[1,2-a]pyridines in good yields. This new methodology was further found to be successfully applied to catalyze the formylation of 2-Ph substituted imidazo[1,2-a]pyridines, affording the desired products in moderate to good. Interestingly, the reaction also worked well under the standard reaction condition when sterically hindered 2-$C(CH_3)_3$ substituted imidazo[1,2-a]pyridines as substrates were employed. Furthermore, 2-unsubstituted imidazo[1,2-a]pyridines were next employed. To our delight, the selective C-3 formylation products were also obtained in good yields. No regioisomeric products were observed by GC-MS and ^1H NMR spectroscopy. The results clearly indicated that this strategy provided a new route for selective C-3 formylation of imidazo[1,2-a]pyridines.

For further investigation, we attempted to prepare products by using 1-(butylsulfinyl)butane **2b** or sulfinylbis(methylene) dibenzene **2c** as regents. (Scheme 3.) Disappointingly, other sulfones substrates (**2b**, **2c**) failed to work under the standard reaction condition.



Scheme 3. Formylation of Imidazo[1,2-a]pyridine with **2b** or **2c**



Scheme 4. Control experiments for investigation of the mechanism

To gain further insight into the mechanism of this Cu(II)-catalyzed formylation, a serials of control reactions were carried out. An isotope experiment was performed to prove the source of aldehydic hydrogen in deuterated d_6-DMSO

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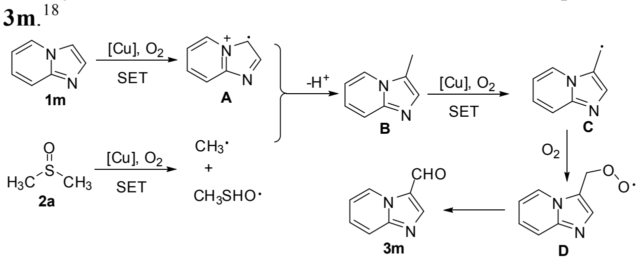
under the optimized conditions in (Scheme **4a**). The completely deuterated product ***d*-3p** was formed, while **3p'** was not detected by ^{1}H NMR. The reaction was run under nitrogen atmosphere, and as a result, only a trace amount of **3p** was detected (Scheme **4b**). The product **4p** with ^{18}O in the carbonyl group was not detected using the combination of DMSO and $H_2{}^{18}O$ (Scheme **4c**). Subsequently, radical inhibitors(e.g.TEMPO and duroquinone) were added to the reaction and it was found that the reaction was completely inhibited (Scheme **4d** and **4e**). These results clearly indicated that: i) a radical process was involved in this formylation; ii) oxygen sources of aldehyde product were from from the O_2 rather than H_2O via aradical process; iii) hydrogen sources of aldehyde were from the DMSO rather than others.

On the basis of all of the results described above together with precious literature reports,[5a,6b,8b-c, 9, 11c] a plausible mechanism of this formylation proces has been proposed in Scheme 5. First, The reaction starts from a single electron transfer(SET) oxidation by Cu(II) species to give radical intermediate **A** and methyl radical, respectively from **1m** and **2a**. And then intermediate **B** is formed via radical coupling of radical intermediate **A** and methyl radical. Intermediate **B** undergos a single electron-transfer oxidation to generate intermediate **C** which is trapped by dioxygen to give peroxy radical **D**. Finally, the intermediate **D** is converted into desired product **3m**.[18]



Scheme 5. Proposed mechanism

In summary, we have succeeded in developing a novel Cu-catalyzed selective formylation of imidazo[1,2-a]pyridines with DMSO by using O_2 as oxidant, which provided a practical approach to access 3-formylimidazo[1,2-a]pyridine derivatives. Advantageously, the employment of cheap copper as catalyst, O_2 as clean oxidant and DMSO as carbon source significantly improved the practicality of this C-H formylation transformation. Compared to the traditional methods for preparing 3-formylimidazo[1,2-a]pyridine, our method is more convenient and environmental friendly.

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Notes and references

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