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Cu-Catalyzed Synthesis of 3-Formyl Imidazo[1,2-*a*]pyridines and Imidazo[1,2-*a*]pyrimidines by Employing Ethyl Tertiary Amines as Carbon Sources

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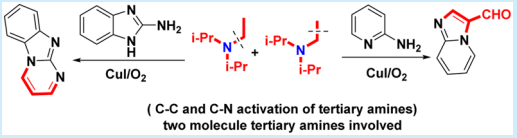
Supporting Information

ABSTRACT: A highly efficient synthesis of 3-formyl imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine, under Cu-catalyzed aerobic oxidative conditions and by utilizing ethyl tertiary amines as carbon sources, is disclosed. A novel activation mode of ethyl tertiary amines in which simultaneous selective cleavage of C−C bond and C−N bond of ethyl group with molecular oxygen as terminal oxidant in this one-pot protocol is reported for the first time. This reaction features broad substrate scope, good functional group tolerance, as well as diversified and valuable products.



Fused heterocyclic compounds constitute one of the privileged core structural motifs in pharmaceuticals and material sciences. Among them, imidazo[1,2-*a*]pyridines and imidazo[1,2-*a*]pyrimidines show prominent biological applications in pharmaceutical agents and natural products.[1] These two important frameworks have emerged in a variety of drugs, such as zolpidem (**A**),[2] alpidem (**B**),[3] olprinone (**C**),[4] p38 kinase inhibitor (**D**),[5] Fasiplon (**E**)[6] and Divaplon (**F**)[7] (Figure 1).

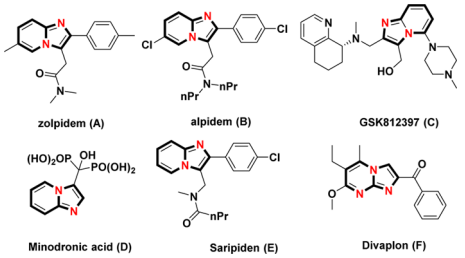


Figure 1. Biologically active or potent imidazo[1,2-*a*]pyrimidines and imidazo[1,2-*a*]pyridines.

Therefore, continued effort has been devoted to the development of new and efficient synthetic strategies for the preparation of 3-formyl imidazo[1,2-*a*]pyridine and imidazo-[1,2-*a*]-pyrimidine backbones. In 2011, Zhu's group developed a Cu-catalyzed intramolecular dehydrogenative aminooxygenation to produce various imidazo[1,2-*a*]pyridine-3-carbaldehydes from readily available *N*-allyl-2-aminopyridines.[8] In 2012, an aqueous synthesis of 3-formyl imidazo[1,2-*a*]pyridines via silver-catalyzed aminooxygenation was also achieved by Adimurthy.[9] In 2014, Cao and co-workers demonstrated a novel Cu-catalyzed selective formylation of imidazo[1,2-*a*]pyridines by using DMSO as the formylation reagent.[10] Herein, we report a Cu-catalyzed synthesis of 3-formyl imidazo[1,2-*a*]pyridines from commercially available 2-aminopyridines by using ethyl tertiary amines as both carbon source and formylation reagent. At the same time, we present access to diverse imidazo[1,2-*a*]pyrimidines from 2-aminobenzimidazoles and ethyl tertiary amines. Due to the high C−N bond dissociation energy and the stability of unactivated N-containing compounds, C−N bond activation has emerged as a great challenge in organic chemistry.[11] As one of most stable nitrogen-containing compounds, the application of ethyl tertiary amines as amino sources via C−N bond activation has aroused much attention in recent years. In 2011, Huang's group established a Cu-catalyzed oxidative amination of benzoxazoles via C−N bond activation of Et_3N (Scheme 1a).[12] In 2013, Bao and co-workers developed the first selective aminolysis of aryl esters using inert tertiary amines as nitrogen sources (Scheme 1b).[13] Later on, an effective supported gold nanoparticle-catalyzed aminolysis of esters using tertiary amines as amino donors was also reported by Bao et al. (Scheme 1c).[14] In 2016, Sun's group demonstrated a Cu-catalyzed coupling reaction of sulfonyl chlorides with tertiary amines via oxidative C−N bond cleavage of Et_3N (Scheme 1d).[15] Recently, selective synthesis of *β*-arylsulfonyl enamines from sodium sulfinates via C−H activation of tertiary amines has been achieved by Yuan and co-workers (Scheme 1e).[16] Although ethyl tertiary amines have been widely used as nitrogen sources via C−N bond activation, their usage as carbon sources via C−C bond activation has rarely been explored. In addition, simultaneous cleavage of C−C bond and C−N bond of ethyl group in ethyl tertiary amines followed by the formation of acrolein which was involved in the subsequent transformation has not been reported before. Herein, we report the synthesis of imidazo[1,2-*a*]pyridine and imidazo-[1,2-*a*]pyrimidine by utilizing ethyl tertiary amines as carbon sources via both C−C bond and C−N bond activation in one-pot protocol (Scheme 1f).

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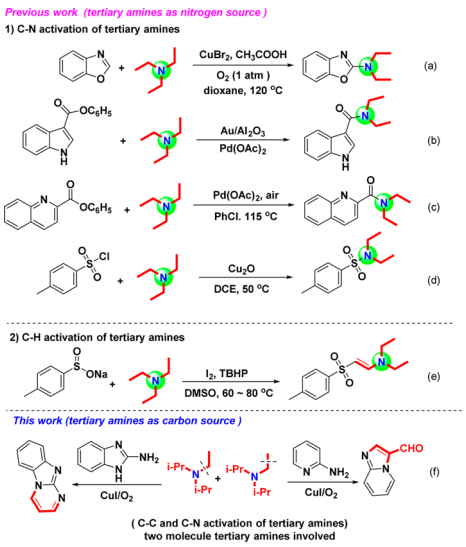
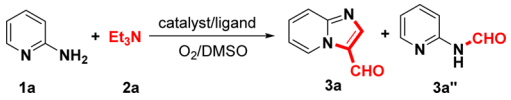
Scheme 1. Application of Tertiary Amines as Material to Synthesis of N-Containing Compounds



We began our investigation by treatment of 2-aminopyridine **1a** in the presence of 20 mol % CuI and 40 mol % DMEDA in DMSO using O_2 as the oxidant at 130 °C,[17] which delivered the product imidazo[1,2-*a*]pyridine-3-carbaldehyde (**3a**) in 20% yield along with 10% yield of *N*-(pyridin-2-yl)formamide (Table 1, entry 1). The results inspired us and indicated the feasibility of the envisioned strategy by employing ethyl tertiary amines as carbon sources albeit the low yield. Subsequently, when other metals such as CuBr, $Pd(OAc)_2$ or $Cu(OAc)_2$ were used instead of CuI, stagnant reactions were observed (see Supporting Information). Among the temperatures tested, the model reaction was performed at 100 °C rendering the best yield of **3a** (Table 1, entries 3−5). The effect of ligands was further explored in this transformation (Table 1, entries 6−9). To our delight, the yield of desired product **3a** was slightly increased to 66% by using TMEDA as ligand (Table 1, entry 9). Of note, only marginal improvements were obtained when we changed the amount of catalyst and the loading of ligand (Table 1, entries 10−14).

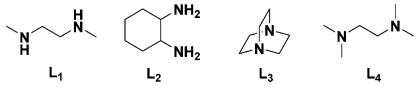
Inspired by the C−N activation of Et_3N to construct imidazo[1,2-*a*]pyridine-3-carbaldehyde, other variety of ethyl amines were further employed under the standard conditions to react with 2-aminopyridine **1a** (Scheme 2). To our delight,

Table 1. Optimization of the Reaction Conditions for the Reaction[a]

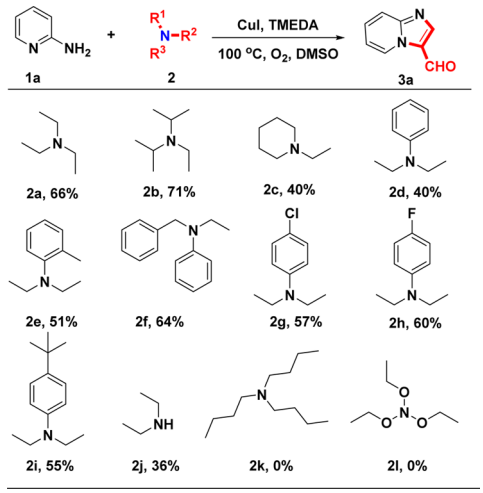


entry	catalyst	temp (°C)	ligand	yield (%) of **3a**	yield (%) of **3a**″
1	CuI	130	L_1	20	10
2	$Pd(OAc)_2$	130	L_1	N.D.	N.D.
3	CuI	80	L_1	25	49
4	CuI	100	L_1	41	33
5	CuI	120	L_1	32	10
6	CuI	100	L_1	63[b]	22
7	CuI	100	L_2	48	20
8	CuI	100	L_3	10	trace
9	CuI	100	L_4	66[b]	23
10[c]	CuI	100	L_4	58[b]	32
11[d]	CuI	100	–	44	20
12[e]	CuI	100	L_4	56	25
13[f]	CuI	100	L_4	47	12
14[g]	CuI	100	L_4	16	9

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (2.5 equiv), catalyst (20 mol %), ligand (40 mol %), DMSO (1 mL), under O_2, 24 h, GC yield. [b]Isolated yield. [c]CuI 40 mol %. [d]no TMEDA. [e]TMEDA 20 mol %. [f]TMEDA 60 mol %. [g]TMEDA 100.



Scheme 2. Scope of Tertiary Amines[a]



[a]Reaction conditions: **1a** (0.5 mmol), **2** (2.5 equiv), CuI (20 mol %), TMEDA (40 mol %), DMSO (1 mL), at 100 °C, under O_2, 24 h. The isolated yield of **3a** was based on **1a**.

various ethyl-containing tertiary amines (**2a**−**2i**) were suitable for this transformation, delivering the desired product **3a** in moderate to good yields. In addition to tertiary amines, secondary amine **2j** was also amenable to this reaction albeit with a low yield of **3a** (36% yield). No product **3a** was detected when **2k** or **2l** was submitted to the standard conditions, which indicated that the ethyl group installed on the amines was a prerequisite for this transformation.

Because the yield of **3a** was higher when DIPEA was used instead of Et_3N (Scheme 2), DIPEA was then employed as carbon sources for further assessment of the scope of 2-aminopyridine derivatives. As shown in Scheme 3, a variety of 2-aminopyridine derivatives bearing different substituents on the pyridine ring were well tolerated, giving the desired imidazo[1,2-*a*]pyridine-3-carbaldehydes in moderate to good yields (Scheme 3, **3a**−**3j**), among them, **3a** could be obtained in 60% yield in a 2 mmol-scale reaction. Interestingly, quinolin-2-amine **1k** was also amenable to this transformation, delivering the product **3k** in moderate yield. To our delight, 3-amino pyridazine (**1l**) could produce the corresponding imidazo[1,2-*b*]pyridazine-3-carbaldehyde (**3l**) as well, albeit with a relative low yield.

Next, the copper-catalyzed annulation reaction of the 2-aminobenzo[*d*]imidazole compounds **4** with DIPEA to provide imidazo[1,2-*a*]pyrimidines **5** was further performed with CH_3CN as the solvent (Scheme 4) after condition optimization (see SI for details). Among them, a variety of symmetrical bis-substituted 2-aminobenzo[*d*]imidazoles were first tested under

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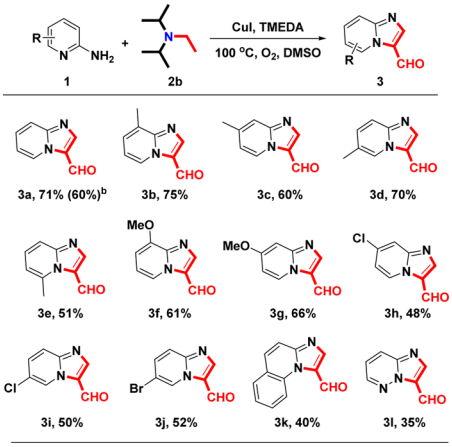
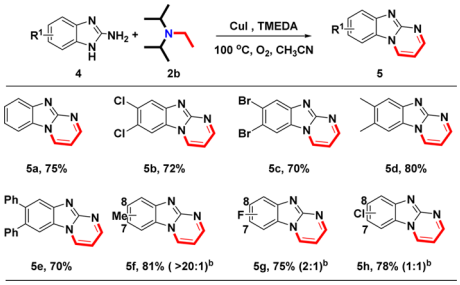
Scheme 3. Scope of 2-Aminopyridines toward C-3 Formyl-imidazo[1,2-*a*]pyridines[a]



[a]Reaction conditions: **1** (0.5 mmol), **2b** (2.5 equiv), CuI (20 mol %), TMEDA (40 mol %), DMSO (1 mL), at 100 °C, under O_2, 24 h. [b]2 mmol scale.

Scheme 4. Scope of 2-Aminobenzo[*d*]imidazoles toward Imidazo[1,2-*a*]pyrimidines[a]

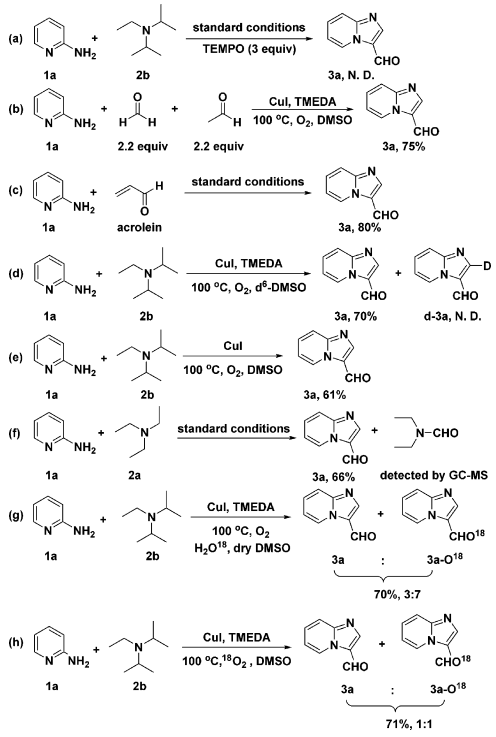


[a]Reaction conditions: **4a** (0.5 mmol), **2b** (2.5 equiv), CuI (20 mol %), TMEDA (40 mol %), CH_3CN (1 mL), at 100 °C, under O_2, 24 h. [b]Mixture ratio.

the optimized conditions (Scheme 4, **5a**−**5e**). Different 2-aminobenzo[*d*]imidazole compounds which bear Cl, Br, F, phenyl group on the benzene ring participated smoothly in this annulation process to render the corresponding imidazo[1,2-*a*]pyrimidines in good yields. Annulation reaction of the monosubstituted 2-amine-benzo[*d*]imidazol-2-amine can also provide corresponding imidazo[1,2-*a*]pyrimidines (**5f**−**5h**) in the mixture of C7 and C8 position. The ratio of C7 and C8 products were determined by ^{1}H NMR spectroscopy.

To gain further insight into the mechanism of this Cu(I)-catalyzed annulation reaction, a series of control reactions were carried out. First, radical inhibitor TEMPO was added to the reaction and it turned out that the reaction was completely inhibited (Scheme 5a) which inferred that this might be a radical-involved reaction. Then, to test the source of the three carbon units, we employed formaldehyde (concentration of 40% in water) and acetaldehyde aqueous solution (concentration of 40%) to take the place of DIPEA and the desired product **3a** was obtained in 75% isolated yield (Scheme 5b). This reaction suggested that the combination of formaldehyde and acetaldehyde play the same role as DIPEA. Given the fact that acrolein could be made from formaldehyde and acetaldehyde, we have reasons to believe that acrolein was generated in situ and became the key intermediate for this transformation, which was further

Scheme 5. Control Experiments to Elucidate the Reaction Pathway



confirmed by the reaction between **1a** and acrolein, since **3a** was afforded in 80% yield (Scheme 5c). When the reaction was performed in DMSO-d_6 under the optimized conditions, **3a**-*d* was not detected by ^{1}H NMR (Scheme 5d), which indicated that the aldehyde group of **3a** did not originate from DMSO. In order to exclude the source of formaldehyde from TMEDA, the reaction was run without TMEDA and the target product was obtained in 61% isolated yield (Scheme 5e). Remarkably, when trimethylamine (**2a**) was employed with **1a** under the standard conditions, **3a** was obtained in 66% yield along with the formation of *N*,*N*-diethyl formamide (detected by GCMS). This is strong evi- dence that the C−C bond of the ethyl group in trimethylamine was cleaved under the standard conditions and formaldehyde was generated during this process (Scheme 5f). In order to understand the origin of oxygen in aldehyde, H_2O^{18} was added to the system in anhydrous DMSO, and **3a** was obtained in 70% yield with 3:7 ratio of **3a** and **3a-O^{18}** (detected by GCMS) (Scheme 5g). This result infers that water is involved in the transformation and most likely is involved in the formation of acetaldehyde (see Scheme 5 for details). Noteworthily, when the reaction was performed under $^{18}O_2$ in anhydrous DMSO, **3a** was afforded in 71% yield with 1:1 ratio of **3a** and **3a-O^{18}** (detected by GCMS) (Scheme 5h). This result was also expected since one equivalent of H_2O^{18} was generated in situ when N−CH_2 bond of iPr_2NEt was oxidized into N=C bond in the presence of CuI and $^{18}O_2$; the H_2O^{18} eventually could be introduced into final product by hydrolysis of N=C bond to release CH_3CHO.

On the basis of earlier reports as well as our own experimental observation, a plausible mechanism for the formation of **3a** and **5a** is depicted in Scheme 6.[17,18] Formation of the immonium salt from tertiary amine oxidations is the first step of this cascade process under the standard condition. The immonium salt can go through two different pathways and render acetaldehyde as well as formaldehyde. The immonium salt is readily hydrolyzed to

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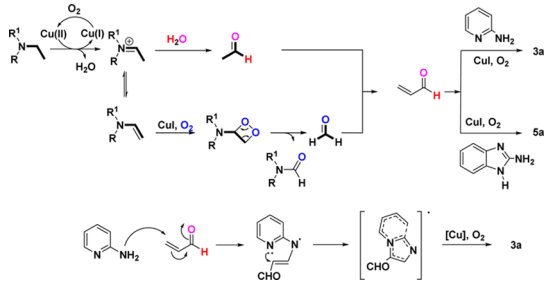
Scheme 6. A Plausible Mechanism for the Formation of Desired Products 3 and 5



yield a secondary amine and acetaldehyde in the presence of water. Deprotonation of the immonium salt can yield a *N*-vinyl-tertiary amine which reacts with O_2 to render a dioxygen-containing four-membered ring, subsequent rearrangement of the four-membered ring eventually leads to formaldehyde and the corresponding formamide.[19] Finally, condensation of formaldehyde and acetaldehyde forms acrolein which reacts with 2-aminopyridines and 2-aminobenzo[*d*]imidazoles as versatile synthons to construct imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine.[20]

In conclusion, we have exploited a copper-catalyzed one-pot strategy for the synthesis of five and six member fused heterocyclic compounds by utilizing ethyl-containing tertiary amines as carbon sources via both C−C bond and C−N bond activation in one-pot strategy. A series of C-3 formyl-imidazo-[1,2-*a*]pyridines and benzoimidazo[1,2-*a*]imidazolones were obtained in moderate to high yields by the sequential C−N, C−C bond cleavage on the same molecule and on the same ethyl group. Most importantly, the substrate scope was extended by successful execution of 2-aminopyridine and 2-aminobenzimidazoles as suitable substrates for this transformation. The present protocol provides a versatile method to establish two important heterocyclic frameworks that are key structural elements and are frequently encountered in many natural products and biomolecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02015.

Experimental procedure, characterization of all of the products (PDF)

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Notes

The authors declare no competing financial interest.

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