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Copper-Catalyzed Synthesis of Fused Imidazopyrazine *N*-Oxide Skeletons

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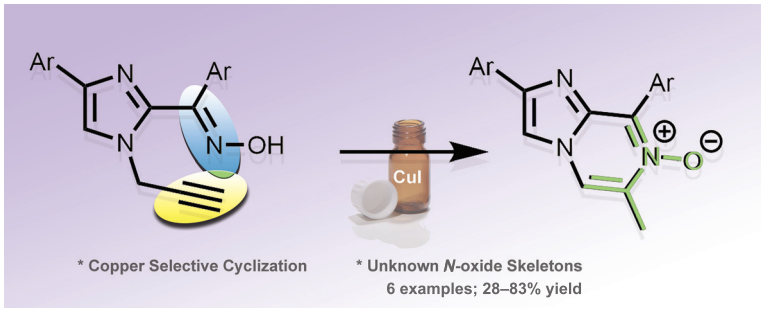

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Abstract *N*-Propargyl-2-aroylimidazoles synthesized and converted into the corresponding ketoximes. Under various conditions, several mono- and diketoxime imidazole derivatives were formed by converting the carbonyl or carbonyl and propargyl groups into oxime groups. *N*-Propargyl monooxime imidazole derivatives were cyclized by treatment with CuI to give various imidazopyrazine *N*-oxides. Several copper salts, such as CuOAc, $CuSO_4$, and CuOTf, formed the same cyclization product. This cyclization reaction occurred only in the presence of Cu(I) or Cu(II) salts; other transition metals such as Au, Ag, In, and Fe did not yield cyclic products. The nucleus-independent chemical shift method was used to calculate the aromaticity of the bicyclic rings.

Keywords alkynes, cyclization, copper catalysis, imidazopyrazine oxides, oximes

Fused bicyclic imidazole molecules have attracted considerable attention from researchers owing to their importance in the design of drugs, for example, zolpidem and alpidem. Despite the fact that many important compounds contain an imidazole ring, for example, protein kinase inhibitors,[1] antitubercular agents,[2] and cannabinoid receptor ligands,[3] certain members of this class are virtually unexplored, including substituted imidazopyrazine *N*-oxides. Heterocyclic *N*-oxide molecules are important structural moieties, because they are present in numerous natural and pharmacological compounds that display significant biological activities (Figure 1).[4a,b] To access such moieties, cyclization reactions of alkynes are of particular interest.[4c,5–7]

Although some heterocyclic *N*-oxide derivatives, such as isoquinoline *N*-oxides,[8,9] pyrrolo- and indolopyrazine *N*-oxides,[10] pyrazole *N*-oxides,[11] benzopyrazole *N*-oxides,[12] and benzimidazole *N*-oxides,[13] have been documented, this is the first study to report the synthesis of the highly substituted imidazo[1,2-*a*]pyrazine *N*-oxide skeleton. In the only

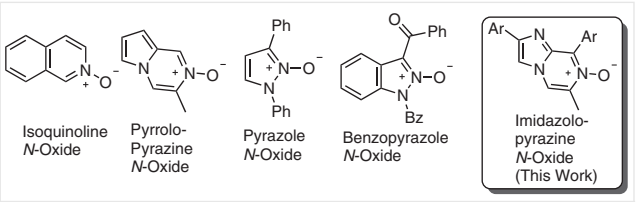
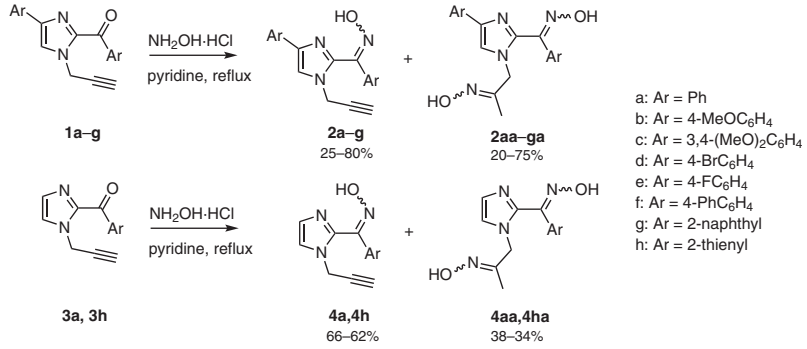


Figure 1 Examples of *N*-oxide derivatives

example of an imidazo *N*-oxide reported in the literature, a carbaldehyde group attached at the C-2 position of the imidazole ring of an imidazopyrazine *N*-oxide was cyclized to an ethyne group by using hydroxylamine.[14] The addition of various groups to heterocyclic rings can change their pharmacological properties and the side-effects of candidate drugs; consequently, expedient strategies for synthesizing heterocyclic molecules are a welcome development. For example, the functional differences between zolpidem and alpidem derive from the different affinities of the peripheral benzodiazepine receptor subtype.[15] Efficient atom-economic synthetic routes that permit desirable diversification of such cores are proving to be of tremendous value, as they permit structure–activity relationship and quantitative structure–activity relationship studies to be performed more effectively.

Our research group has synthesized pyrrolo- and indolopyrazine *N*-oxide derivatives by a gold-catalyzed reaction.[10] In addition, we aimed to extend the range of heterocyclic *N*-oxides by replacing the heterocyclic ring in these compounds (i.e., pyrrole and indole) with imidazole.

We hypothesized that unknown imidazopyrazine *N*-oxides might be synthesized through a metal-catalyzed reaction of an oxime group with a propargyl group . This is the first report of synthesis of highly substituted imidazopyra-



Scheme 1 Synthesis of the desired condensation products.

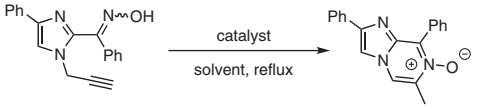
zine *N*-oxide derivatives in which an oxime group is used as a nucleophile to attack the propargyl group in a catalytic reaction.

N-Propargyl 2,4-disubstituted imidazoles **1a–g** and *N*-propargyl 2-substituted imidazoles **3a** and **3h** were synthesized by methods reported in the literature [for details of the reactions, see the Supplementary Information (SI), Scheme S3].[16–18] During the propargylation reaction to form **1a–g, 3a**, and **3h,** the N-1 atom was propargylated exclusively. To determine the structure of the favored *N*-propargylated isomer, we calculated their relative enthalpies and Gibbs free energies (SI; Figure S1).[19]

The *N*-propargylated derivatives **1a–g**, **3a**, and **3h** were converted into the corresponding *N*-propargylated ketoximes **2a–g**, **4a**, and **4h** in moderate yields by treatment with hydroxylamine under basic condition (Scheme 1). However, the attempted ketoximation of **1a** by using triethylamine as a base instead of pyridine did not give **2a**, but instead gave a mixture of products (SI; Scheme S1).

The cyclization reaction of the oxime derivative **2a** was optimized by screening various catalysts, bases, and solvents (Table 1). Gold salts did not catalyze the reaction (Table 1, entries 1–5, and 13), although they have been used for similar reactions reported in the literature. Most Lewis acids and bases were also unreactive except for the copper salts CuI, $CuSO_4$, CuOTf, and CuOAc (entries 15–17, 19, and 20).[20a] Both Cu(I) and Cu(II) salts gave a cyclized product **5a**, although $CuCl_2$ was ineffective (entry 18).[20b] Use of a hydrated copper salt decreased the yield of **5a** (entry 17). Moving from CuI to other counterions such as SO_4^{2-}, OTf^-, OAc^- had little effect on the yield of reaction.[20c] The observed yields of product **5a** suggest that the iodide ion might play an important role as a stabilizing ligand in the copper complex, thereby extending the lifetime of the formed intermediate.[20d] The choice of solvent was also found to be crucial for the efficiency of this process, and PrOH was found to be optimal (entry 14).

Table 1 Optimization Experiments for the Cyclization[a]



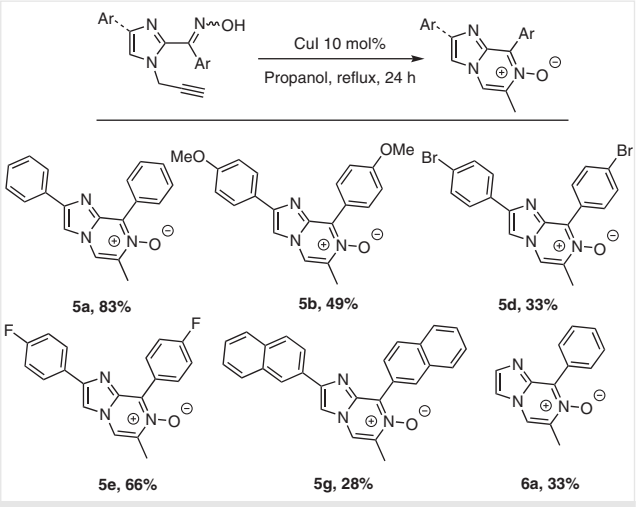
Entry	Catalyst	Solvent	Yield (%)
1	AuCl + $AgSbF_6$	DCE	ND[b]
2	$AuCl_3$	acetone	ND
3	$AuCl_3$	MeCN	ND
4	$AuCl_3$	$CHCl_3$	ND
5	$AuBr_3$	$CHCl_3$	ND
6	$InCl_3$	acetone	ND
7	$InCl_3$	$CHCl_3$	ND
8	$InCl_3$	MeCN	ND
9	$InCl_3$	MeOH	ND
10	AgOTf	MeCN	ND
11	$Yb(OTf)_3$	MeCN	ND
12	Cs_2CO_3	MeOH	ND
13	AuCl	PrOH	ND
14	CuI	PrOH	83
15	CuI	MeCN	59
16	$CuSO_4$	PrOH	69
17	$CuSO_4·5H_2O$	PrOH	49
18	$CuCl_2·2H_2O$	PrOH	ND
19	CuOTf	PrOH	66
20	CuOAc	PrOH	63
21	$FeCl_3·6H_2O$	MeCN	ND
22	$FeCl_3·6H_2O$	PrOH	ND

Entry	Catalyst	Solvent	Yield (%)
23[c]	$TiCl_4$	MeCN	ND
24[c]	$BF_3{\cdot}OEt_2$	MeCN	ND
25	CuI	$CHCl_3$	48%

[a] 10 mol% of the metal salt was used. All reactions were performed in the refluxing solvent.
[b] ND = not detected.
[c] An equivalent amount of the Lewis acid was used.

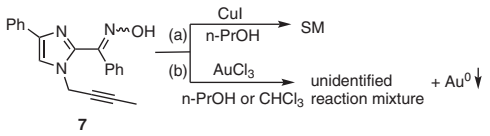
As an alternative cyclization route, we attempted to carry out the oxime formation before the propargylation reaction. All attempts at cyclization of a dipropargylated ketoxime derivative with various catalysts and bases failed to give any cyclic product (SI; Scheme S2).

Next, we examined the scope of the cyclization reaction, and various unknown imidazopyrazine *N*-oxide derivatives were obtained (Scheme 2).[21] The diphenyl, bis(4-methoxyphenyl), bis(4-bromophenyl), bis(4-fluorophenyl), and di-2-naphthyl derivatives **5a**, **5b**, **5d, 5e**, and **5g**, respectively, and the monophenyl *N*-oxide derivatives **6a** were obtained in moderate yields. Other products (not shown) were obtained only as crude products. The scope of this cyclization reaction was limited to aryl substituents, because the reaction by which we prepared the *N*-propargyl-2-aroylimidazole derivatives did not permit the preparation of alkyl-substituted (ketone or aldehyde) imidazole derivatives.



Scheme 2 Extension of the cyclization reaction to various derivatives

To examine the effect of an internal alkyne on the cyclization, we treated compound **7** with CuI under the same cyclization conditions as discussed above; however, only the starting material was obtained (Scheme 3; Path a). When we attempted to cyclize compound **7** with $AuCl_3$ in PrOH or $CHCl_3$, as in our previous work,[10] we obtained a yellow precipitate. Extended stirring at room temperature led to further reduction of the Au(III) to Au(0) (Scheme 3; Path b) and, although we checked all the reaction media, we did not see any sign of the starting material. This might be due to the formation of a coordination complex of gold(III) with a reaction intermediate, which might occur as a result of the presence of the internal alkyne unit. A similar reduction has been reported for a reaction between benzothiazole and $AuCl_3$.[22]



Scheme 3 Testing of an internal alkyne for cyclization. SM = starting material.

Our cyclization reaction gave pyrazine *N*-oxides containing two different aromatic rings. We therefore desired to investigate the aromaticity of these rings by means of the nucleus-independent chemical shift (NICS) index method. The aromaticities of bicyclic compounds **5a**, **5b**, **5e**, **5g**, and **6a** were therefore calculated by using the NICS method.[19,23,24] NICS(1) values were chosen for this investigation. The imidazole and the pyrazine *N*-oxide rings were found to possess aromatic character (Table 2). The bicyclic disubstituted *N*-oxide derivatives **5a**, **5b**, **5e**, and **5g** all displayed similar aromatic properties, even though they possess different functional groups with different electronic properties. The imidazole rings exhibited more-aromatic character than did the *N*-oxide rings. The monosubstituted imidazopyrazine *N*-oxide **6a** exhibited the most aromatic traits for the imidazole ring; conversely, it showed the least aromatic character for the pyrazine *N*-oxide ring among the various cyclic derivatives (Table 2).

Table 2 Aromaticities of the Imidazopyrazine *N*-Oxides[a]

Ring	5a	5b	5e	5g	6a
imidazole	–12.0	–11.0	–11.9	–12.6	–12.7
N-oxide	– 5.9	– 6.1	– 6.2	– 6.2	– 5.2

[a] Values are expressed in ppm.

It is obvious that there are marked differences between the two aromatic rings. To test the effects of this variation on a cyclization reaction, we attempted a simple [3+2] cyclization reaction of compound **5a** with dimethyl acetylenedicarboxylate (DMAD) (SI; Scheme S4). However, this reaction did not proceed in refluxing xylene, and the starting material was recovered. Note that the phenyl ring adjacent to the quaternary nitrogen atom might cause steric hindrance resulting in an unfavorable geometrical position for the DMAD molecule. With this knowledge, this reaction might be fully optimized by adopting different reaction conditions.[25]

In conclusion, we investigated the oximation of *N*-propargyl-2 aroylimidazole derivatives. When pyridine was used as both base and solvent, the product of oximation of the carbonyl group was obtained exclusively. Monooxime derivatives were subjected to alkyne cyclization by copper salts to yield imidazopyrazine *N*-oxides. Both copper(I) and copper(II) salts gave the same cyclization products in different yields. However, the optimal reaction was achieved with CuI, which is a cheap and low-toxicity catalyst. Silver, gold, and iron salts were ineffective for the cyclization, possibly because of the higher catalytic activity of copper in C–X (X = C, N, O) coupling reactions. The developed cyclization protocol afforded novel bicyclic imidazole skeletons containing aryl substituents. Aromaticity values were calculated, and the aromaticities of the imidazole and N-oxide rings were found to be different. This feature of these bicyclic molecules might provide an opportunity for selective reactions.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610859.

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(21) **Imidazo[1,2-*a*]pyrazine *N*-Oxides 5a–g and 6a; General Procedure**
The appropriate *N*-propargylimidazole oxime derivative **2a–g**, **4a**, or **4h** (1 mmol) was dissolved in PrOH (5 mL) in a 25 mL flask. A catalytic amount of CuI (10 mol%) was added, and the mixture was refluxed for the appropriate time until the reaction was completed (TLC). The mixture was then extracted with EtOAc–H_2O (3 × 40 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a crude product that was purified by column chromatography. The products were further purified by preparative TLC (hexane–EtOAc, 5:1).
6-Methyl-2,8-diphenylimidazo[1,2-*a*]pyrazine 7-Oxide (5a)
Reaction time: 3 h; eluent for column chromatography: hexane–EtOAc (1:1).
Brown solid; yield: 250 mg (83%); mp 193–195 °C. FTIR (ATR): 3140, 3038, 2969, 2925, 2163, 1732, 1660, 1604, 1576, 1496, 1489 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 6.91 Hz, 2 H, Ar-H), 7.93–7.89 (m, 3 H, Ar-H), 7.78 (s, 1 H, Ar-H), 7.55–7.48 (m, 4 H, Ar-H), 7.41 (t, *J* = 7.36 Hz, 2 H, Ar-H), 2.51 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9, 132.6, 131.0, 130.3, 128.7, 128.6, 127.9, 127.8, 126.3, 116.9, 108.8, 15.5. LCMS: *m/z* [M + H]$^+$ Calcd for $C_{19}H_{16}N_3O$: 302.12879; found: 302.12958.
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