Synthesis of Imidazolidinone, Imidazolone, and Benzimidazolone Derivatives through Oxidation Using Copper and Air

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Supporting Information

ABSTRACT: A new synthetic method of urea derivatives using copper and air was developed. These mild conditions provided moderate to very good yields for 15 examples (53-93%), while low yields were obtained with sterically hindered substrates (3 examples). The reaction was found to go through an in situ generated copper-N-heterocyclic carbene, which was then oxidized into cyclic urea derivatives possessing alkyl, benzyl, aryl, hydroxy, Boc-protected, and tertiary amine groups.



rea derivatives play an important role in medicinal chemistry,^{1,2} as they show many biological and pharmacological activities, e.g., cofactor biotin,³ kealiiquinone from the Micronesian sponge,⁴ antagonist naamidine A,⁵ and cytotoxin agelastatin A (Figure 1).6 Among urea derivatives,





imidazolidinones and benzimidazolones are two important categories, e.g., antiviral agent DBPR103⁷ and RSV inhibitor BMS-433771 (Figure 1).^{8–10} For this reason, new approaches for the synthesis of urea derivatives remain of interest.^{2,11} In the course of our studies toward the synthesis of various copper-Nheterocyclic carbene complexes (Cu-NHC) from imidazolinium and benzimidazolium derivatives, the corresponding urea derivatives were advantageously isolated instead of the expected Cu-NHCs. We disclose herein a new synthetic method to prepare these ureas.

Among the previously described synthetic methods, the oxidation of imidazolium, imidazolinium, and benzimidazolium substrates into urea derivatives has been disclosed, using strong oxidants, such as $PhI(OAc)_{2,}^{12}$ NaOCl,^{13–15} di-*tert*-butyl peroxide,¹⁶ H₂O₂,^{17,18} and *m*-chloroperoxybenzoic acid (*m*-CPBA) (Scheme 1).^{19,20} A major disadvantage of using strong

Scheme 1. Synthesis of Urea Derivatives by Oxidation



oxidants is their incompatibility with oxidant-sensitive functionalities, thus hindering the substrate scope. Here, we report mild, easy, and practical conditions using copper metal and air for the oxidation of imidazolium, imidazolinium, and benzimidazolium substrates to obtain the corresponding urea derivatives. The conditions are applicable to substrates bearing alkyl, benzyl, aryl, primary hydroxy, acid-sensitive tert-butyloxycarbonyl group (-Boc), and tertiary amine groups.

While investigating reported procedures that describe the synthesis of related Cu–NHC under air in the presence of Cu₂O or Cu,^{21,22} it was found that for the chiral substrates targeted here the corresponding imidazolidinones and benzimidazolones were isolated instead (Scheme 2). The conditions using Cu_2O under reflux (Scheme 2, eq a) led to urea 2a in 39% yield, while the conditions using Cu powder at room temperature (Scheme 2, eq b) afforded the corresponding imidazolidinones and benzimidazolones in yields up to 85% (2b) and 45% (2c), respectively. These mild conditions using copper metal and air as oxidant were compatible with the hydroxyl group (2c). An iodo-substituted product 2cc was also obtained in 10% yield

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Scheme 2. Synthesis of Chiral Imidazolidinones and Benzimidazolones: Initial Attempts



(a proposed mechanism is available in the Supporting Information). Seeing that these conditions (eq b) were mild enough to tolerate an oxidant-sensitive functionality, further studies were pursued, including the effect of solvents and substrate scope.

Our first focus was to use the model substrate 1d to optimize the reaction conditions (Table 1). The reactions run in CH_2Cl_2 afforded the best yield in imidazolone 2d (83%, entry 1), while in other solvents, such as THF (low solubility of 2d and longer time), CH_3CN , EtOH, acetone, and MeOH, lower yields of 2d were obtained (entries 2–6). The reaction was also run on a gram scale, and a 67% yield of 2d was obtained (entry 1). The starting materials remained intact when Cu_2O , CuO, and Fe

Table 1. Oxidation of 1d: Optimization of the Reaction Conditions^a

	N Br solve 1d metal (1.1 e	nquiv), air ant 18 h 2d	
entry	metal/catalyst	solvent	yield 2d^b (%)
1	Cu	CH_2Cl_2	83 (67) ^c
2	Cu	THF	70 ^d
3	Cu	CH ₃ CN	42
4	Cu	EtOH	33
5	Cu	acetone	29
6	Cu	MeOH	24
7	Cu ₂ O	CH_2Cl_2	0 ^e
8	CuO	CH_2Cl_2	0 ^e
9	Fe	CH_2Cl_2	0 ^e
10	Cu (0.25 equiv)	CH ₂ Cl ₂	16

"Reaction conditions: imidazolium bromide 1d (0.30 mmol) and metal (0.33 mmol) in solvent (1 mL) under air (relative humidity 10–20%). ^bIsolated yields. ^c1 g scale of substrate 1d. ^d72 h of reaction time due to low solubility of the starting material. ^eStarting material intact. were used (entries 7–9). When a catalytic quantity of Cu was used (25 mol %, entry 10), 2d was afforded in only 16% yield. Thus, the conditions involving stoichiometric Cu in CH_2Cl_2 were chosen for further study.

After the optimization of reaction conditions, the substrate scope was studied (Scheme 3). The reaction conditions were





^{*a*}Reaction conditions: imidazolium halide (0.30 mmol) and Cu (0.33 mmol) in CH_2Cl_2 (1 mL) under air (relative humidity 10–20%). ^{*b*}Isolated yields. ^{*c*}CH_2Cl_2/EtOH (10:1) was used due to low solubility of imidazolium and 72 h of reaction time. ^{*d*}3.0 equiv of Cu used. ^{*c*}Yields determined by ¹H NMR. ^{*f*}CH₂Cl₂/MeOH (10:1) was used, and the product was obtained as a mixture of rotamers. ^{*g*}The tertiary amino groups in the starting materials were present as ammonium salt of HCl and 72 h of reaction time. ^{*h*}4.0 equiv of Cu used in CH₂Cl₂/MeOH (10:1).

suitable for the synthesis of urea derivatives bearing saturated (2e, 2h, 2i, 2l, and 2m), unsaturated (2g, 2j), and aromatic backbones (2f, 2n-r). Except for the sterically hindered substrates (2i-k), the reactions proceeded to give moderate to very good yields (53–93%). ¹H NMR analysis of the crude reaction mixtures obtained from 1j and 1k indicated that the major products were the corresponding Cu–NHCs. For 1j, the crude reaction mixture contained 70% of Cu–NHC, 22% of urea 2j, and 8% of imidazolinium, while for 1k, the crude reaction mixture contained 71% of Cu–NHC along with 29% of remaining imidazolium and no detection of urea derivative. This was attributed to the combination of steric and electronic factors of the Cu–NHCs, exhibiting trends similar to those of their Ni–

NHCs analogues,²³ i.e., being stable toward any oxidation into ureas or decomposition into imidazoliums. Actually, these two Cu-NHCs from 1j and 1k could be isolated as pure compounds in air.²¹ The current conditions are suitable for substrates containing different N-substituents, including benzyl (2e-g), aryl (2h, 2i, 2m, 2p), -Boc group (2l, acid-sensitive), alkyl (2m, 2n), and the substituents tethered to tertiary amino groups (2o-r). The case of 2g showed that the oxidation was chemoselective toward the imidazolium, while the hydroxy group remained intact. Subsequently, the synthesis of DBPR103 (Figure 1) was attempted. Unfortunately, due to the unsuccessful synthesis of the corresponding N-pyridylimidazolinium (see the Supporting Information), the oxidation using the current conditions could not be carried out. Hence, an N-phenyl analogue of DBPR103, which may also show bioactivities,^{24,25} was synthesized from simple starting materials. The oxidation of N-phenyl imidazolinium 1s gave the DBPR103 analogue 2s in 87% vield.

Originally, the imidazolium was thought to be oxidized by Cu_2O or CuO, which was previously formed through Cu oxidation under air. However, the fact that the use of Cu_2O or CuO at room temperature did not lead to any desired products (Table 1, entries 8 and 9) ruled out this hypothesis. In fact, the reaction of imidazolium with Cu_2O (under reflux) was believed to first generate Cu–NHC according to the findings by Cazin.²² However, the present study demonstrated that the urea derivatives were generated through the oxidation of corresponding Cu–NHCs, which was confirmed by high resolution mass spectrometry (HRMS, see the Figures S1–S3) and ¹H NMR (see the Supporting Information). The reaction pathway was presented below using 1d as a model substrate (Scheme 4).

Scheme 4. Proposed Reaction Pathway of the Formation of Urea through Oxidation of Cu–NHCs





When the reaction was run under argon atmosphere, Cu–NHC **3d** was indeed obtained. After the reaction mixture was exposed to air, the Cu–NHC decomposed quickly to give the oxidation product **2d** and the corresponding hydrolysis product. For the decomposition of Cu–NHCs bearing saturated backbones with *N*-aryl substituents, ring-opening products were also detected in addition to imidazoliniums (Scheme 4).

To further support this reaction pathway, three other Cu– NHC solutions (Scheme 5) were exposed to air and monitored





^{*a*}Reactions were monitored by ¹H NMR and HRMS. Because the solutions were not agitated in the NMR tube, longer times were needed.

by ¹H and ¹³C NMR (see Figures S4–S7). More information about the decomposition of Cu-NHC and the proposed mechanism for the oxidation of Cu-NHC by air and for the formation of iodo-substituted product 2cc is also available in the SI. As expected, the Cu-NHCs were oxidized smoothly to give the corresponding urea derivatives. The new ¹³C NMR signals at 150–160 ppm clearly showed the formation of urea structures. It is important to mention that the urea synthesis using the current method relies on the instability of Cu-NHCs. The reaction time increased with the robustness of the Cu-NHCs (3e vs 3n vs 3t, Scheme 5). The low yields of 2i, 2j, and 2k (Scheme 3) indicated that the current method is not suitable for the substrates possessing large steric hindrance at the urea core. In fact, the preparation of such sterically hindered ureas requires strong oxidizing conditions from free carbenes instead of from imidazoliums.^{26–29} In addition, the results obtained in this study also shed light on the low yields obtained with some Cu–NHCs in the literature,²¹ which have not been rationalized before.

In conclusion, a new synthetic method of imidazolidinone, imidazolone, and benzimidazolone derivatives using copper and air as oxidant was developed, which provided moderate to very good yields for sterically unhindered substrates. The mild oxidation conditions are suitable for the synthesis of urea derivatives possessing alkyl, benzyl, aryl, primary hydroxy, acidsensitive *tert*-butyloxycarbonyl group (-Boc), and tertiary amine groups. The formation of the urea derivatives was confirmed to occur through the oxidation of the corresponding Cu-NHCs, even though the sometimes tedious preparation of Cu-NHC complexes is avoided in our method. Further applications in the synthesis of potent compounds will be disclosed in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00973.

Details of the synthetic procedures of the urea derivatives, imidazoliums, imidazoliniums, and benzimidazoliums and copies of 1 H, 13 C, and 19 F NMR spectra for 1a–t and 2a–t (PDF)

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Notes

The authors declare no competing financial interest.

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