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Copper mediated oxidation of amides to imides by Selectfluor

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The combination of Selectfluor and copper(I) bromide has shown a strong oxidation ability, readily oxidizing amides into the corresponding imides in acetonitrile at room temperature in less than 1 h. This transformation under mild conditions gives good to excellent chemical yields. A possible reaction mechanism is proposed.

Imides are core structures in many therapeutic and agrochemical agents.[1] Although imides can be prepared through the condensation of carboxylic acid derivatives and ammonia or primary amine[2] or other protocols,[3] the most straightforward preparation would be the direct oxidation of amides into imides. Accordingly, several methodologies involving the direct oxidation of amides have been reported over the years.[4] Unfortunately, most protocols suffer from low yields or/and limited substrate scope.[4a–h] To the best of our knowledge, there are only two efficient methods to prepare imides from amides.[4i,j] And they still have some shortcomings like the use of toxic chromium reagent[4j] or use of Dess–Martin periodinane at elevated temperatures.[4i] We are now pleased to report a very mild synthesis of imides from amides using a combination of copper(I) bromide and Selectfluor.

Selectfluor is an easy-handling and bench stable electrophilic fluorinating agent.[5] In the course of our works on Selectfluor/gold mediated oxidative coupling[6] and copper mediated amination,[7] we found that a combination of copper(I) bromide and Selectfluor is a strong oxidation system that efficiently oxidizes amides into imides. First, we chose amide **1a** as substrate to find the best oxidation conditions (Table 1). Amide **1a**, Selectfluor (2.2 equiv), and copper bromide (10%) were mixed in acetonitrile at room temperature for 1 h, and afforded 10% yield of imide **2a**, the same yield as the load of copper salt, together with unreacted starting material (Table 1, entry 1). When the copper load was increased to 1 equivalent, we obtained a moderate yield of imide (Table 1, entry 2); however, 1 equivalent of Selectfluor gave a low yield (Table 1, entry 3). Entries 4 and 5 showed that both copper bromide and Selectfluor are indispensable to the oxidation. $CuCl_2$ alone, or together with Selectfluor (Table 1, entries 6 and 7), has no effect on the transformation. Similarly, the use of different copper salts, such as CuOTf, $CuBF_4$, CuCl, CuI, and $Cu(OTf)_2$ gave small amounts of imide (Table 1 entries 8–12). Since the main difference among these copper salts is the counteranion, which shows remarkably dissimilar results, and because it has been reported that bromide can be oxidized to bromine cation[8] we examined the role of bromide, and found that bromide itself (KBr) was not the active species (Table 1, entry 13). Inspired by White's work,[9] CuBr was added in five portions over 32 min, improving our results (Table 1, entry 14). Using a similar portion-wise addition, the highest yield of imide can be obtained by increasing the amount of both Selectfluor and CuBr (Table 1, entry 15); hence, this was chosen as our optimized condition for this oxidation. Although water may be a possible oxygen source in this oxidation, small amounts of water (Table 1, entry 16) have a deleterious effect on this reaction.

Next, we examined the substrate scope. Amide **1a** (Table 2, entry 1) was readily oxidized by the combination of copper bromide and Selectfluor to give imide **2a** in excellent yield after 1 h, together with small amounts of unreacted starting material. Similarly, amides **1b**, **1c**, **1d,** and **1e** all afforded the corresponding imides in high yields (Table 2, entries 2–5). Branched amide **1f** gave moderate yield (Table 2, entry 6); this may be due to steric hindrance; the unreacted amide can be recycled. Amide **1g** also gave moderate yield of **2g** together with small amount of unreacted **1g** (Table 2, entry 7) and the reason for this lower yield is unknown. The oxidation of **1h** gave **2h** in high yield (Table 2, entry 8); and the reaction with amidoesters **1i**, **1j** is chemoselective (Table 2, entries 9 and 10). Unfortunately, a hydroxyl group, double, or triple bonds are not tolerated due to possible over oxidation.

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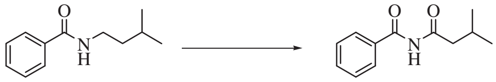
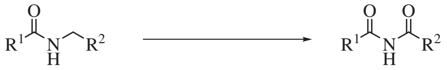
Table 1
Screening for best oxidation condition[a]

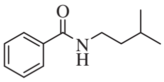
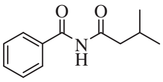
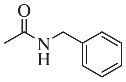
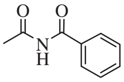
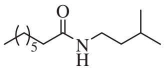
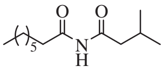
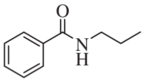
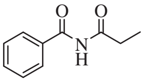
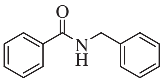
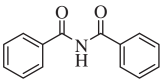
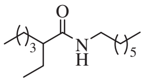
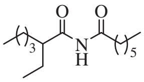
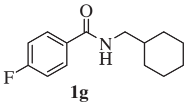
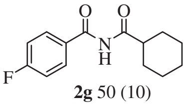
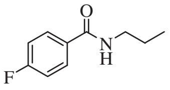
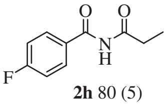
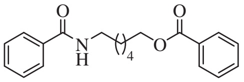
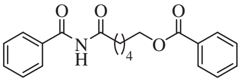
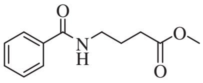
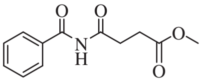

1a **2a**

Entry	Selectfluor (equiv)	Metal (or other) (equiv)	% Yield[b] (SM)[c]
1	2.2	CuBr (0.1)	10 (90)
2	2.2	CuBr (1.0)	66 (33)
3	1.0	CuBr (1.0)	12 (88)
4	2.2		0 (100)
5	–	CuBr (1.0)	0 (100)
6	–	$CuCl_2$ (1.0)	0 (100)
7	2.2	$CuCl_2$ (1.0)	0 (100)
8	2.2	CuOTf (1.0)	25 (75)
9[d]	2.2	$CuBF_4$ (1.0)	0 (100)
10	2.2	CuCl (1.0)	7 (93)
11	2.2	CuI (1.0)	6 (94)
12	2.2	$Cu(OTf)_2$ (1.0)	19 (81)
13	2.2	KBr (1.0)	0 (100)
14[e]	2.2	CuBr (1.0)	83 (17)
15[f]	2.5	CuBr (1.0)	92 (8)
16[f,g]	2.5	CuBr (1.0)	37 (63)

[a] All reactions were conducted in acetonitrile at room temperature for 1 h.
[b] NMR yield. Benzyl bromide as internal standard.
[c] Starting material.
[d] $CuBF_4$ was generated in situ.
[e] Copper bromide was added five portions over 32 min.
[f] Copper bromide was added six portions over 40 min.
[g] Acetonitrile/water = 100:3 (v/v).

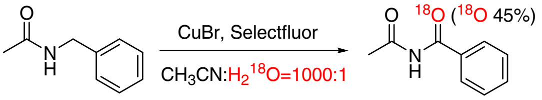
Table 2
Examination of substrate scope[a]


1 **2**

Entry	Amides	% Yield[b] (SM)[c]
1	 **1a**	 **2a** 88 (7)
2	 **1b**	 **2b** 83
3	 **1c**	 **2c** 79 (13)
4	 **1d**	 **2d** 77 (10)
5	 **1e**	 **2e** 84 (11)
6	 **1f**	 **2f** 66 (30)
7[d]	 **1g**	 **2g** 50 (10)
8[d]	 **1h**	 **2h** 80 (5)
9	 **1i**	 **2i** 84 (6)
10	 **1j**	 **2j** 82 (6)

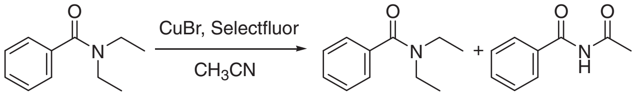
[a] Amide **1** (0.25 mmol), Selectfluor (0.625 mmol, 2.5 equiv) and CuBr (0.3 mmol, 1.2 equiv, added in six portions over 40 min) reacted in acetonitrile (5 mL) at room temperature for 1 h.
[b] Isolated yield based on starting material.
[c] Starting material recovered.
[d] Small amount of impurities were found in imides.

There are two possible sources of oxygen for the newly incorporated oxygen in imide **2**, namely dioxygen in air and trace amounts of water in the reaction media. We conducted the reaction under nitrogen, and found that 50% of imide was formed.[10] Since commercial Selectfluor always contains trace amounts of water,[11] we could not conduct the reaction under strictly anhydrous conditions. On the other hand, when substrate **1b** was oxidized in acetonitrile (dried shortly before use) containing 0.1% $H_2^{18}O$, we observed ^{18}O (45%) incorporation in imide **2b** (confirmed by high resolution mass spectroscopy and ^{13}C NMR of **2b**), which clearly demonstrated that trace water in the reaction acts as the oxygen source (Eq. (1)).[12]



1b **2b**, 70% (1)

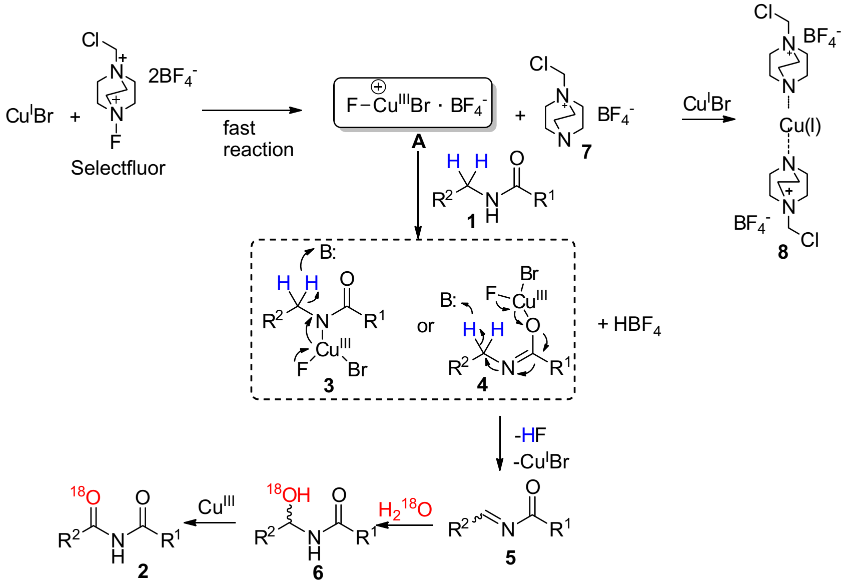
Since all amides in Table 2 are secondary amides, a tertiary amide **1k** was employed for examining whether N–H is important (Eq. (2)). Most of the starting amide **1k** was recycled and only small amounts of oxidation product **2b** (20%) could be isolated with some unknown product, the yield being much lower than a similar product in entry 2 of Table 1, indicating that N–H probably plays a role in the oxidation.



1k **1k**, 60% **2b**, 20% (2)

At first we thought that some of Cu(I)Br could be oxidized into Cu(II) species, which may disproportionate into Cu(I) and Cu(III).[13] Attempts to monitor the reaction by ^1H NMR spectroscopy was complicated by line broadening effects when Selectfluor was added; this phenomenon may be due to the presence of paramagnetic species in the reaction, which seemed to hint toward the existence of Cu(II). However, electron paramagnetic resonance (EPR) analysis showed that there was no Cu(II) formed in the course the reaction. Also Cu(II) salt along is not an effective oxidant in this transformation (Table 1, entry 12), so we rule out the possibility that the Cu(II) is the active species in this transformation.

Based on the above observations, we proposed the copper(III) mechanism (Scheme 1). Recently, we have demonstrated that Selectfluor has the ability to oxidize gold(I) species to fluorinated



Scheme 1. Proposed copper(III) mechanism.

gold(III) species in a gold catalyzed oxidative coupling reaction.[6] Considering that copper(I) is a stronger reductant compared to gold(I), we propose that a similar chemistry will occur in copper(I) species. The copper(I) salt can be oxidized to generate a fluorinated copper(III) species A and 7 (Scheme 1).[14] Then, copper(III) species A may coordinate with oxygen or nitrogen in **1** to form complex **3** or **4**, followed by elimination of HF and copper(I) from **3** or **4** to give the imine intermediate **5**. Compound **5** may react with water to generate hemiaminal **6**; **6** can be further oxidized by **A** or Selectfluor itself to give the final product **2**. Considering that copper(III) species **A** may not be very stable (isolable only with specific ligands), a multi portion addition of CuBr could reduce the decomposition of A and thus improve the yield of **2** (Table 1, entries 2 and 14). A premixed solution of CuBr and Selectfluor is still active, albeit it gives lower yields.[15]

The proposed mechanism also helps to explain why stoichiometric amounts of copper(I) are needed to complete the reaction. Selectfluor loses its fluorine to generate **7** after oxidation, **7** has a free amine which may coordinate with copper(I) to generate a rather stable copper(I) complex **8**[16] thereby losing its catalytic activity. In theory, the addition of a ligand with a high affinity for copper(I) should prevent the oxidation of copper(I) to copper(III) and thus inhibit the reaction. This hypothesis was supported by the addition of 1,10-phenanthroline, a strong bidentate ligand to copper(I), which completely suppressed the reaction.

Alternatively, a single electron transfer (SET) mechanism[17–19] can also be a viable mechanism, based on the facts that tertiary amide **1k** (Eq. (2)) can also be oxidized into imide (albeit in low yield).

Cu(II) salts are well known oxidants in many transformations,[20] in our case, the combination of copper(I) bromide and Selectfluor can oxidize the stable amides into imides[21]. The broader implications of this oxidation system, including exploring other metal/Selectfluor combinations, are being investigated by our group.

Acknowledgment

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Supplementary data

Supplementary data (the ^{1}H, ^{13}C NMR spectroscopic data, MS and analytic data of the compounds shown in Tables 1 and 2, and the detailed description of experimental procedures) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.059.

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11. The trace amount of water in commercial Selectfluor can't be removed by 50 °C/1 mmHg vacuum overnight.
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21. *General procedure for copper mediated oxidation of amides to imides by Selectfluor*: Amide **1a** (48 mg, 0.25 mmol, 1 equiv), and Selectfluor (221 mg, 0.625 mmol, 2.5 equiv) were dissolved in 5 mL of acetonitrile at room temperature, and CuBr (42.6 mg, 0.3 mmol, 1.2 equiv) was added over a 40 min period in six portions. After all CuBr was added, the resulting mixture was stirred for extra 20 min, and then acetonitrile was evaporated under reduced pressure. Then, 20 mL of a saturated ammonium chloride solution was added into the reaction mixture and extracted by diethyl ether (25 mL × 4), the ether layers were combined and dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the crude product. Silica gel flash chromatography of the crude product (hexanes–ethyl acetate (10:1) to hexanes–ethyl acetate (4:1)) yielded pure imide **2a** (45 mg, 0.22 mmol, 88% yield) together with unreacted **1a** (3.2 mg, 0.017 mmol, 7%). *N*-(3-Methyl-butyryl)-benzamide,[3a] (**2a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (br s, 1H), 7.82 (d, J = 7.6 Hz, 2H), 7.51 (t, J = 6.4 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 2.82 (d, J = 6.8 Hz, 2H), 2.18 (m, 1H), 0.96 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 165.6, 133.1, 132.9, 128.9, 127.7, 46.2, 24.8, 22.52.