



## Synthesis of 3-halo-2,5-disubstituted furans via CuX mediated cyclization–halogenation reactions

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### ABSTRACT

The Cu(I) halide (X = I, Br, Cl) mediated reactions of Cbz-protected *cis*-2-phenylethenyl-3-hydroxypyrrolidine gave novel 3-halo-2,5-trisubstituted furans in good yields, via a cyclization–halogenation, ring-opening reaction sequence. In contrast, the reactions with CuCN gave mainly the corresponding 3-cyanofuro[3,2-*b*]pyrrole formed from a cyclization–cyanation reaction.

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We recently reported the CuX (X = I, Br, Cl, CN) mediated cyclization–halogenation and cyclization–cyanation reactions of  $\beta$ -hydroxyalkynes **1** (R = H, Ph) to give 3-halo-(X = Cl, Br, I) and 3-cyanofuro[3,2-*b*]pyrroles **2** (X = CN), respectively (Fig. 1).<sup>1</sup> These reactions were also extended to *ortho*-alkynyl phenol and aniline derivatives which gave rise to 3-iodo, 3-bromo and 3-cyanobenzofurans and 3-cyanoindoles, respectively.<sup>2</sup> As an extension of this work we have examined the reaction of the related  $\beta$ -hydroxyalkyne **3** with CuX. We report here that the reactions using Cu(I) halides under an oxygen atmosphere give rise to novel 3-halo-2,5-trisubstituted furans **6** (X = halogen) in good yields, via a cyclization–halogenation, ring-opening reaction sequence.<sup>3</sup> In contrast, the reactions with CuCN gave mainly the corresponding 3-cyanofuro[3,2-*b*]pyrrole **5** (X = CN) formed from a cyclization–cyanation reaction.

Racemic *N*-Cbz protected *cis*-2-alkynyl-3-hydroxypyrrolidine **3** was prepared by treatment of the known compound *N*-Cbz-4,5-

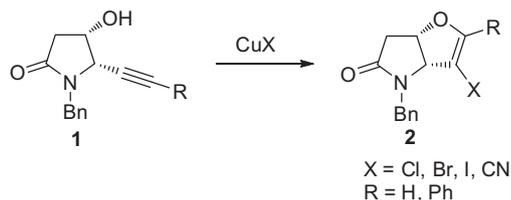
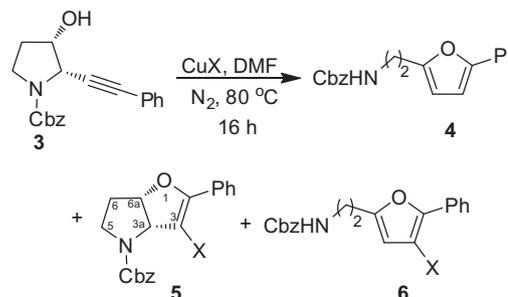


Figure 1. Reactions of  $\beta$ -hydroxyalkynes with Cu(I) salts.

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dihydroxypyrrolidine with potassium phenylacetylenetrifluoroborate.<sup>1</sup> Initially the reaction of **3** with CuI was tested. The use of 1 equiv of CuI in DMF at 80 °C under a nitrogen atmosphere resulted in formation of the products **4** and **5** in 55% and 20% yields, respectively (Table 1, entry 1). Increasing the amount of CuI to three equiv. yielded **4** and **5** in respective yields of 19% and 52% (Table 1, entry 2). However the use of 6 equiv of CuI afforded only

Table 1  
Reactions of **3** with Cu(I) salts under an N<sub>2</sub> atmosphere (compounds **3** and **5** are racemic)



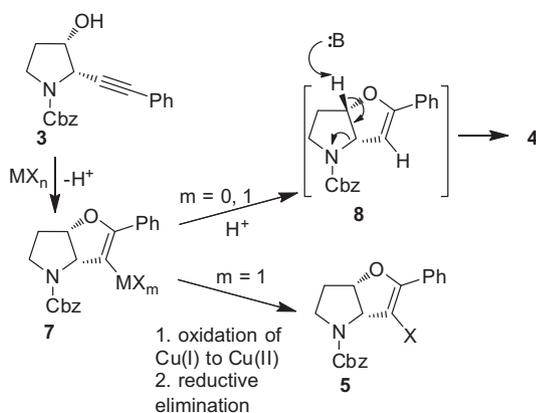
Entry	X (equiv)	Yield (%) of <b>4</b>	Yield (%) of <b>5</b>	Yield (%) of <b>6</b>
1	I (1.0)	55	20	0
2	I (3.0)	19	52	0
3	I (6.0)	0	65	0
4	Br (6.0)	25	0	41
5	Cl (6.0)	61	0	0
6	CN (6.0)	26	30	0

the 3-iodofuro[3,2-*b*]pyrrole **5** (X = I) in 65% yield (Table 1, entry 3).<sup>4</sup>

Attempts to prepare independently the product **5** from the reaction of **3** and I<sub>2</sub> or NIS produced a complex mixture of products.<sup>1</sup> We next focused on the CuBr and CuCl mediated reactions of **3** with the aim of preparing the corresponding 3-bromo- and 3-chloro-furo[3,2-*b*]pyrroles **5** (X = Br, Cl). Treatment of **3** with 6 equiv of CuBr under the same experimental conditions as described above resulted in a mixture of the 2,5-disubstituted furan **4** and the 3-bromofuran product **6** (X = Br) in 25% and 41% yields, respectively (Table 1, entry 4). Treatment of **3** with CuCl afforded only the furan **4** in 61% yield (Table 1, entry 5). The reaction of **3** with CuCN (6 equiv) yielded products **4** and **5** (X = CN) in yields of 26% and 30%, respectively (Table 1, entry 6).

We proposed that product **4** is formed by protonation of the RCu(I) intermediate **7** (M = Cu(I), *m* = 0) to give intermediate **8** which then undergoes a base-catalysed ring-opening reaction as shown in Scheme 1. Oxidation of the intermediate **7** (M = Cu(I), *m* = 0) with CuX gives the corresponding Cu(II)X intermediate **7** (M = Cu(II), *m* = 1) which upon reductive elimination would give product **5**.<sup>1</sup>

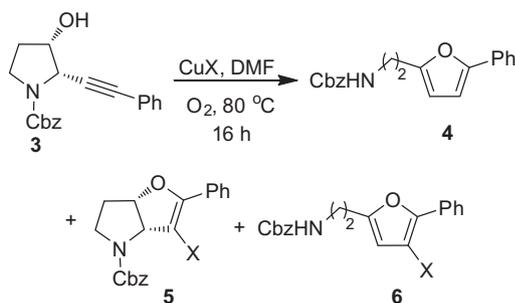
We speculated that if we enhanced the rate of oxidation of the Cu(I) intermediate **7** to the corresponding Cu(II) intermediate in situ, then we would increase the yield of the halogenated and cyanated products. This might also allow us to use lesser amounts of



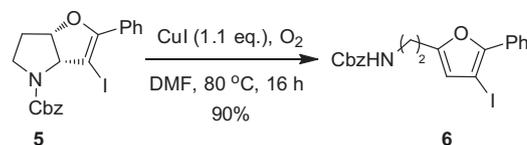
Scheme 1. Proposed mechanisms for the formation of products **4** and **5**.

Table 2

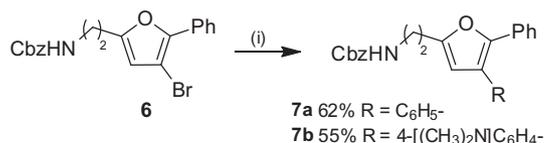
Reactions of **3** with Cu(I) salts under an O<sub>2</sub> atmosphere (compounds **3** and **5** are racemic)



Entry	X (1.1 equiv)	Yield (%) of <b>4</b>	Yield (%) of <b>5</b>	Yield (%) of <b>6</b>
1	I	5	0	74
2	Br	4	0	68
3	Cl	6	0	78
4	CN	35	40	0



Scheme 2. Reaction of **5** (X = I) with CuI/O<sub>2</sub>.



(i) RB(OH)<sub>2</sub> (1.5 eq), Pd(OAc)<sub>2</sub> (0.15 eq), PPh<sub>3</sub> (0.15 eq)  
Na<sub>2</sub>CO<sub>3</sub> (1.5 eq), EtOH/H<sub>2</sub>O, 100 °C, MW

Scheme 3. Suzuki reactions of **6** (X = Br).

copper salts. We thus repeated these reactions under an oxygen atmosphere. The reaction of **3** with 1.1 equiv of CuI in DMF at 80 °C under an oxygen atmosphere for 16 h yielded the 3-iodofuran **6** (X = I) in 74% yield and furan **4** in 5% yield (Table 2, entry 1).<sup>5</sup> The relative ratio of these compounds was 91:9 from <sup>1</sup>H NMR analysis of the crude reaction mixture. The reactions using CuBr and CuCl worked equally well to give the 3-bromo and 3-chlorofurans **6** (X = Br, Cl) in 68% and 78% yields, respectively (Table 2, entries 2 and 3). Treatment of **3** with CuCN under similar conditions provided the 3-cyanofuro[3,2-*b*]pyrrole **5** (X = CN) in 40% yield and furan **4** in 35% yield (Table 2, entry 4).

The formation of 3-halofurans **6** (X = I, Br, Cl), rather than the 3-halofuro[3,2-*b*]pyrroles **5** (X = I, Br, Cl), when these reactions were performed under an oxygen atmosphere, could be due to the formation of CuO from the reaction between Cu(I) and O<sub>2</sub>. CuO could act as a base to catalyse the ring-opening reaction of the 3-halofuro[3,2-*b*]pyrroles **5** (X = I, Br, Cl) to give 3-halogenated furans **6** (X = I, Br, Cl) (compare with the transformation of **8** into **4** in Scheme 1). Support for this proposal came from the reaction of **5** (X = I) with CuI/O<sub>2</sub> which yielded the corresponding iodofuran **6** (X = I) in 90% yield (Scheme 2).

The 3-iodo- and 3-bromo-furans **6** (X = I, Br) are potentially useful scaffolds for the synthesis of libraries of novel 2,3,5-trisubstituted furans. For example, the Suzuki coupling reactions of the 3-bromofuran **6** (X = Br) with phenylboronic acid or 4-dimethylaminophenylboronic acid gave the desired cross-coupling products **7a** and **7b** in yields of 62% and 55%, respectively (Scheme 3).<sup>6</sup>

In summary, an efficient synthesis of 2,3,5-trisubstituted furans has been developed using copper-mediated reactions. Such derivatives would be difficult to prepare in a regioselective fashion using more conventional methods.

## Acknowledgements

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4. General procedure for the CuX mediated reactions of **3** under an N<sub>2</sub> atmosphere: To a suspension of CuI (0.077 g, 0.411 mmol) in DMF (4 mL) was added **3** (0.022 g, 0.068 mmol) and the resulting mixture was heated at 80 °C for 16 h under a nitrogen atmosphere. The reaction mixture was then cooled to rt, H<sub>2</sub>O (10 mL) was added and the aqueous layer was extracted with Et<sub>2</sub>O (3 × 10 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo to give the crude product. Column chromatography (CH<sub>2</sub>Cl<sub>2</sub> as eluent) of the crude residue furnished product **5** (X = I) (0.020 g, 65%) as a light pink oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.85 (2H, br s, ArH), 7.46–7.25 (8H, m, ArH), 5.46 (1H, br s, H6a), 5.22 (1H, s, H3a), 5.18 (2H, s, CH<sub>2</sub>Ph), 3.99 (1H, br s, H5), 3.21 (1H, ddd, J = 9.5, 9.5, 19.5, Hz, H5), 2.22 (1H, dd, J = 9.5, 19.5 Hz, H6), 2.07 (1H, m, H6). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 155.3 (CO), 129.8 (ArC), 129.7 (ArC), 129.3 (ArCH), 128.9 (ArCH), 128.8 (ArCH), 128.4 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 83.3 (C3), 71.7 (C6a), 67.2 (CH<sub>2</sub>Ph), 56.5 (C3a), 42.8 (C5), 33.1 (C6). EIMS m/z 447 (M<sup>+</sup>, 40%). HREIMS calculated for C<sub>20</sub>H<sub>18</sub>NO<sub>3</sub>I (M<sup>+</sup>) 447.0331, found 447.0318.
5. General procedure for the CuX mediated reactions of **3** under an O<sub>2</sub> atmosphere: To a solution of **3** (0.040 g, 0.125 mmol) in DMF (1.5 mL) under an oxygen atmosphere (balloon) was added CuI (0.026 g, 0.173 mmol) and the reaction vessel was placed in a pre-heated oil bath at 80 °C. The mixture was stirred at this temperature for 16 h. H<sub>2</sub>O (5 mL) was then added and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo. The crude product was purified by column chromatography (1:5, EtOAc/petrol) to give compound **6** (X = I) (0.041 g, 74%) as a pink oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.92 (1H, d, J = 8.0 Hz, ArH), 7.40–7.31 (8H, m, ArH), 7.25 (1H, d, J = 7.0 Hz, ArH), 6.27 (1H, s, H4), 5.10 (2H, s, CH<sub>2</sub>Ph), 4.90 (1H, br s, NH), 3.54 (2H, dd, J = 7.0, 13.0 Hz, CH<sub>2</sub>NH), 2.90 (2H, t, J = 7.0 Hz, CH<sub>2</sub>CH<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 156.4 (CO), 151.6 (ArC), 136.4 (ArC), 130.3 (ArC), 128.7 (ArC), 128.6 (ArCH), 128.4 (ArCH), 128.2 (ArCH), 127.8 (ArC), 127.1 (ArC), 126.2 (ArCH), 117.6 (C4), 67.0 (CH<sub>2</sub>Ph), 61.4 (C3), 39.6 (CH<sub>2</sub>NH), 28.8 (CH<sub>2</sub>CH<sub>2</sub>). EIMS m/z 447 (M<sup>+</sup>, 50%); HREIMS calculated for C<sub>20</sub>H<sub>18</sub>NO<sub>3</sub>I (M<sup>+</sup>) 447.0320, found 447.0331.
6. Typical procedure for the Suzuki reaction: Compound **6** (X = Br) (20 mg, 0.05 mmol), 4-dimethylaminophenylboronic acid (13 mg, 0.075 mmol), Pd(OAc)<sub>2</sub> (1.7 mg, 7.5 μmol), PPh<sub>3</sub> (2 mg, 7.5 μmol) and Na<sub>2</sub>CO<sub>3</sub> (7.9 mg, 0.075 mmol) were placed into a microwave reactor tube and H<sub>2</sub>O/EtOH (2 mL, 1: 1) was added. The reaction mixture was heated to 100 °C over 5 min (100 W, 5 bar, closed vessel) and stirred at this temperature for 10 min in a CEM microwave reactor. CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added to the cooled reaction mixture and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 3 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo. The crude product was purified by column chromatography (1:9, EtOAc/petrol) to give compound **7b** (12 mg, 55%) as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.54 (2H, d, J = 7.5 Hz, ArH), 7.35–7.25 (10H, m, ArH), 7.22 (2H, d, J = 8.5 Hz, ArH), 6.20 (1H, s, H4), 5.12 (2H, s, CH<sub>2</sub>Ph), 5.01 (1H, br s, NH), 3.57 (2H, dd, J = 6.0, 13.0 Hz, CH<sub>2</sub>NH), 2.98 (6H, s, 2 × CH<sub>3</sub>), 2.93–2.90 (2H, t, J = 6 Hz, CH<sub>2</sub>CH<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 156.8 (CO), 151.8 (ArC), 149.8 (ArC), 146.8 (ArC), 131.8 (ArC), 129.4 (ArCH), 128.7 (ArCH), 128.6 (ArCH), 128.6 (ArC), 128.5 (ArCH), 128.3 (ArCH), 127.3 (ArC), 127.1 (ArCH), 126.0 (ArCH), 123.3 (ArC), 112.7 (ArCH), 111.3 (C4), 66.9 (CH<sub>2</sub>Ph), 39.8 (CH<sub>2</sub>NH), 28.9 (CH<sub>2</sub>CH<sub>2</sub>). ESIMS m/z 441 (M+H<sup>+</sup>, 100%); HRESIMS calculated for C<sub>28</sub>H<sub>29</sub>N<sub>2</sub>O<sub>3</sub> (M+H<sup>+</sup>) 441.2178, found 441.2180.