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Arife Yazici
University of Wollongong, arife@uow.edu.au

Stephen G. Pyne
University of Wollongong, spyne@uow.edu.au

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Abstract

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Keywords

Synthesis, halo, disubstituted, furans, via, CuX, mediated, cyclization, halogenation, reactions, CMMB

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Graphical Abstract

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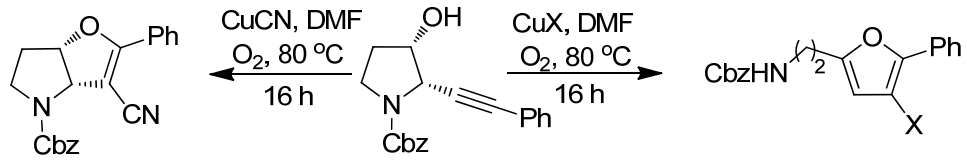

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Synthesis of 3-halo-2,5-disubstituted furans via CuX mediated cyclization-halogenation reactions

Arife Yazici, Stephen G. Pyne*

School of Chemistry, University of Wollongong, New South Wales, 2522, Australia

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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

* Corresponding author. Tel.: +61-2-42213511; fax: +61-2-42214287; e-mail: spyne@uow.edu.au

We recently reported the CuX (X = I, Br, Cl, CN) mediated cyclization-halogenation and cyclization-cyanation reactions of *β*-hydroxyalkynes **1** (R = H, Ph) to give 3-halo- (X = Cl, Br, I) and 3-cyanofuro[3,2-*b*]pyrroles **2** (X = CN), respectively (Figure 1).[1] 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.[2] As an extension of this work we have examined the reaction of the related *β*-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.[3] 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 from the treatment of the known compound *N*-Cbz-4,5-dihydroxypyrrolidine with potassium phenylacetylenetrifluoroborate.[1] 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 3 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 the 3-iodofuro[3,2-*b*]pyrrole **5** (X = I) in 65% yield (Table 1, entry 3).[4]

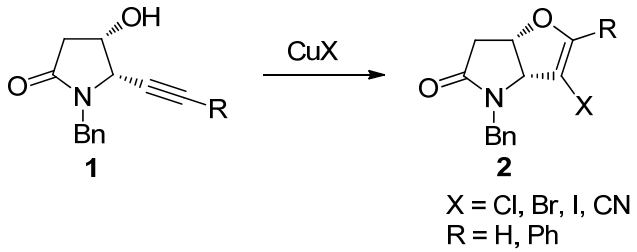
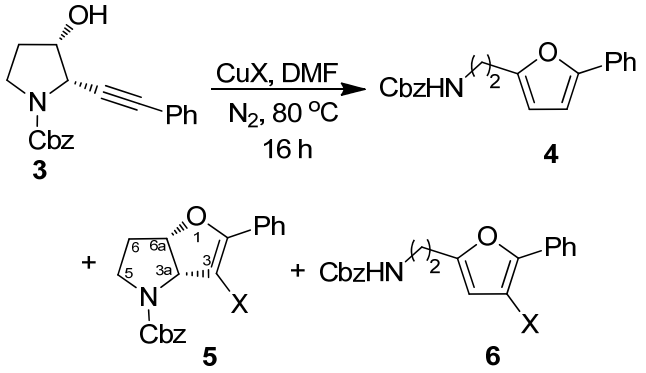


Figure 1. Reactions of *β*-hydroxyalkynes with Cu(I) salts.

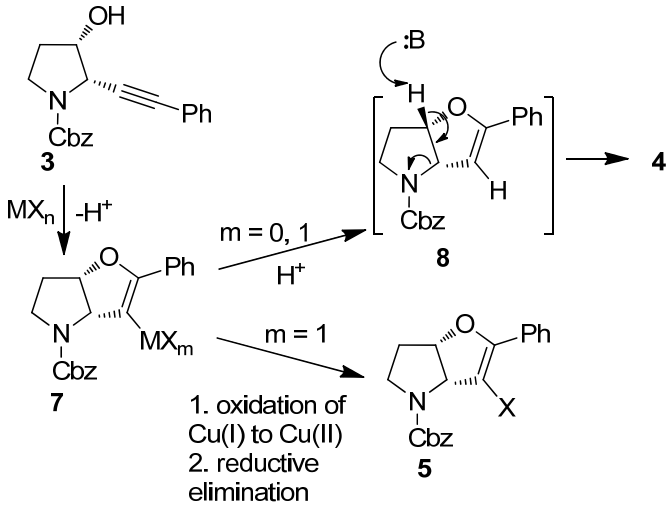
Attempts to prepare independently the product **5** from the reaction of **3** and I_2 or NIS produced a complex mixture of products.[1] We next focused on the CuBr and CuCl mediated reactions of **3** with the aim of preparing the corresponding 3-bromo- and 3-chloro-furo[3,2-*b*]pyrroles **5** (X = 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).

Table 1. Reactions of **3** with Cu(I) salts under an N_2 atmosphere (compounds **3** and **5** are racemic).



Entry	X (equiv.)	Yield (%) of **4**	Yield (%) of **5**	Yield (%) of **6**
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

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), by a redox reaction with CuX, gives the corresponding Cu(II)X intermediate **7** (M = Cu(II), m = 1) which upon reductive elimination would give product **5**.[1]

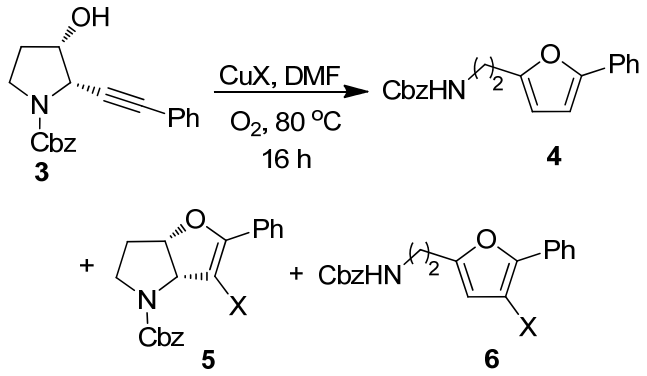


Scheme 1. Proposed mechanisms for the formation of products **4** and **5**.

We proposed 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 may also allow us to use less amounts of 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 hours yielded the 3-iodofuran **6** (X = I) in 74% yield and furan **4** in 5% yield (Table 2, entry 1).[5] The relative ratio of these compounds was 91:9 from ^{1}H NMR analysis of the crude reaction mixture. The reactions of CuBr and CuCl worked equally well to give the 3-bromo and 3-chlorofurans **6** (X = Br, Cl) in 68% and 78% yields, respectively

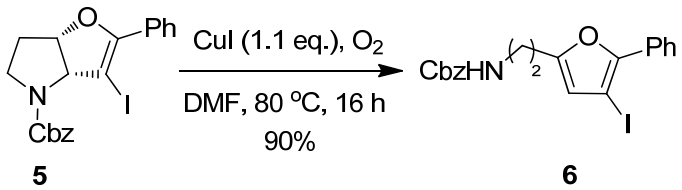
(Table 2, entries 2 and 3). Treatment of **3** with CuCN under similar conditions provided the 3-cyanofuro[3,2-*b*]pyrrole **5** (X = CN) in 40% yield and furan **4** in 35% yield (Table 2, entry 4).

Table 2. Reactions of **3** with Cu(I) salts under an O_2 atmosphere (compounds **3** and **5** are racemic).



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

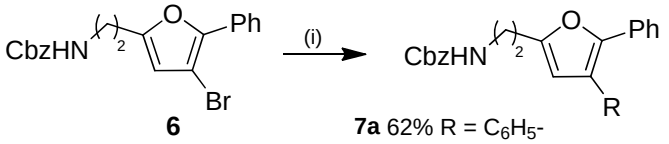
The formation of 3-halofurans **6** (X = I, Br, Cl), rather than the 3-halofuro[3,2-*b*]pyrroles **5** (X = I, Br, Cl), when these reactions were performed under an oxygen atmosphere, could be due to the formation of CuO from the reaction between Cu(I) and O_2. CuO could act as a base to catalyse the ring-opening reaction of the 3-halofuro[3,2-*b*]pyrroles **5** (X = I, Br, Cl) to 3-halogenated furans **6** (X = I, Br, Cl) (compare with the transformation of **8** to **4** in to Scheme 1). Support for this proposal came from the reaction of **5** (X = I) with CuI/O_2 which yielded the corresponding iodofuran **6** (X = I) in 90% yield (Scheme 2).



Scheme 2. Reaction of **5** (X = I) with CuI/O_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).[6]

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.



i) $RB(OH)_2$ (1.5 eq), $Pd(OAc)_2$ (0.15 eq), PPh_3 (0.15 eq) Na_2CO_3 (1.5 eq), EtOH/H_2O, 100 °C, MW

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

Acknowledgements

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References and notes

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2. Nalivela, K. S.; Yazici, A.; Pyne, S. G. *J. Org. Chem.* **2010**, *75*, 3412-3419.
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4. General procedure for the CuX mediated reactions of **3** under an N_2 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_2O (10 mL) was added and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Column chromatography (CH_2Cl_2 as eluent) of the crude residue furnished product **5** (X = I) (0.020 g, 65%) as a light pink oil. ^{1}H NMR ($CDCl_3$, 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*$_2$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). ^{13}C NMR ($CDCl_3$, 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*$_2$Ph), 56.5 (C3a) 42.8 (C5), 33.1 (C6). EIMS *m/z* 447 (M^+, 40%). HREIMS calculated for $C_{20}H_{18}NO_3I$ ($M^{+\cdot}$) 447.0331, found 447.0318.
5. General procedure for the CuX mediated reactions of **3** under an O_2 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_2O (5 mL) was then added and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$), 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. ^{1}H NMR ($CDCl_3$, 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*$_2$Ph), 4.90 (1H, br. s, NH), 3.54 (2H, dd, *J* = 7.0, 13.0 Hz, *CH*$_2$NH), 2.90 (2H, t, *J* = 7.0 Hz, *CH*$_2$CH$_2$). ^{13}C NMR ($CDCl_3$, 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*$_2$Ph), 61.4 (C3), 39.6 (*CH*$_2$NH), 28.8 (*CH*$_2$CH$_2$). EIMS *m/z* 447 (M^+ , 50%); HREIMS calculated for $C_{20}H_{18}NO_3I$ ($M^{+\cdot}$) 447.0320, found 447.0331.
6. General procedure for Suzuki reaction: Compound **6** (X = Br) (20 mg, 0.05 mmol), 4-dimethylaminophenylboronic acid (13 mg, 0.075 mmol), $Pd(OAc)_2$ (1.7 mg, 7.5 μmol), PPh_3 (2 mg, 7.5

μmol) and Na_2CO_3 (7.9 mg, 0.075 mmol) were placed into a microwave reactor tube and H_2O/EtOH (2 mL, 1 : 1) was added. The reaction mixture was heated to 100 ^oC over 5 min (100 W, 5 bar, closed vessel) and stirred at this temperature for 10 min in a CEM microwave reactor. CH_2Cl_2 (5 mL) was added to the cooled reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL). The combined organic extracts were dried ($MgSO_4$), 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. ^1H NMR ($CDCl_3$, 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_2Ph), 5.01 (1H, br s, NH), 3.57 (2H, dd, *J* = 6.0, 13.0 Hz, CH_2NH), 2.98 (6H, s, 2 x CH_3), 2.93-2.90 (2H, t, *J* = 6 Hz, CH_2CH_2). ^{13}C NMR ($CDCl_3$, 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_2Ph), 39.8 (CH_2NH), 28.9 (CH_2CH_2). ESIMS *m/z* 441 ($M+H^+$, 100%); HRESIMS calculated for $C_{28}H_{29}N_2O_3$ ($M+H^+$) 441.2178, found 441.2180.