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Cupric Halide-Mediated Intramolecular Halocyclization of *N*-Electron-Withdrawing Group-Substituted 2-Alkynylanilines for the Synthesis of 3-Haloindoles

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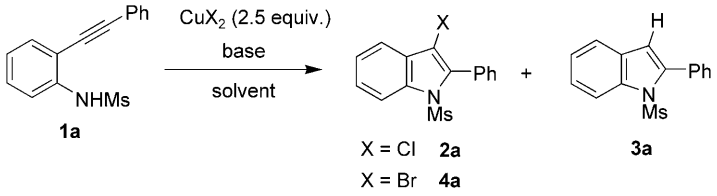
Abstract: A convenient and efficient method for the synthesis of 3-haloindoles has been developed. Both 3-chloro- and 3-bromoindole derivatives can be obtained in high yields by the reaction of *N*-electron-withdrawing group-substituted 2-alkynylanilines with cupric halide in dimethyl sulfoxide (DMSO) within a short period of time. Investigation of the reaction mechanism reveals that two equivalents of cupric halide are necessary.

Keywords: alkynes; copper; cyclization; halogenation; nitrogen heterocycles

Indoles are important compounds which exhibit a variety of biological activities.[1] It is well known that many naturally occurring compounds contain the indole skeleton as a backbone of their structural frameworks. Because of their applications in pharmaceutical fields, investigations on indole derivatives from aspects of both their reactivity and the development of efficient preparative methods have continuously attracted the attention of chemists. Especially, 3-haloindoles appear as a class of important building blocks for the connection of different types of R groups with indoles at the 3-position. Traditional methods for making 3-haloindoles involve direct halogenation of indoles with halogenating reagents, such as halogen,[2] *N*-halosuccinimides,[3] POX_3/imidazole[4] and others.[5] Recently, Barluenga,[6] Knight[7] and Larock,[8] reported the electrophilic cyclizations of 2-alkynylanilines to synthesize 3-iodoindoles using IPy_2BF_4/HBF_4, I_2/K_2CO_3 and I_2, respectively. However, the synthesis of 3-chloro- and 3-bromoindoles starting from 2-alkynylanilines was rarely reported.[9] More recently, the PdX_2-catalyzed halocyclization reaction of 2-alkynylanilines in the presence of CuX_2 (3 equiv., X = Cl, Br) to form 3-bromo- and 3-chloroindoles in moderate to good yields has been reported,[9a] while the employment of the noble-metal palladium and moderate yields in most cases prevent its industrial applications. Thus, the development of a practical and efficient approach to synthesize 3-haloindoles is still a challenge. Herein, we wish to report our recent results that 3-chloro- and 3-bromoindoles can be prepared conveniently and efficiently by CuX_2 (X = Cl, Br) mediated intramolecular halocyclization of *N*-electron-withdrawing group-substituted 2-alkynylanilines without the use of a Pd catalyst.

In the initial studies, we discovered that 3-chloroindole **2a** could be obtained in 73% yield in the presence of the catalytic amount of Pd species, 2.5 equivalents of $CuCl_2$ and 3 equivalents of LiCl (Table 1, entry 1). Subsequently, we found that the Pd catalyst was not necessary for the halocyclization (Table 1, entry 2). In the absence of LiCl, however, 3-chloroindole **2a** was also synthesized in 90% yield within 5 h (Table 1, entry 3). Furthermore, it was found that the solvent was important for the reaction. The use of polar solvents, such as DMSO, DMF and HMPA, afforded 3-chloroindole **2a** exclusively in 77–90% yields (Table 1, entries 3–5), and the rate of reaction in DMSO was faster than that in DMF and HMPA. Surprisingly, reactions in CH_3CN, acetone, or toluene all provided the protonolysis product **3a** in good yields (Table 1, entries 6–8). Strangely, neither 3-chloroindole **2a** nor the protonolysis product **3a** was formed in THF (Table 1, entry 9). Accordingly, the best conditions for the preparation of 3-chloroindoles were 2.5 equivalents of $CuCl_2$ and 1 equivalent of K_2CO_3 in DMSO at 50 °C. When $CuBr_2$ was used to generate 3-bromoindole, it was found that the base played an important role in promoting the formation of 3-bromo-

Table 1. CuX_2-mediated halocyclization of **1a**.[a]



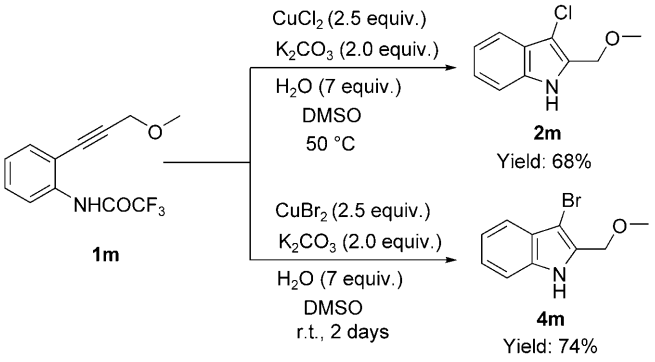
Entry	CuX_2	Additive	Solvent	Time [h]	Yield [%] (**2a** or **4a**)[b]	Yield [%] (**3a**)[b]
1	$CuCl_2$	$PdCl_2(CH_3CN)_2$ (10 mol%); LiCl (3 equiv.)	DMSO	3	73 (**2a**)	–
2	$CuCl_2$	LiCl (3 equiv.)	DMSO	1	92 (**2a**)	–
3	$CuCl_2$	none	DMSO	5	90 (**2a**)	–
4	$CuCl_2$	none	DMF	36	77 (**2a**)	–
5	$CuCl_2$	none	HMPA	28	90 (**2a**)	–
6	$CuCl_2$	none	CH_3CN	19	– (**2a**)	91
7	$CuCl_2$	none	acetone	21	trace (**2a**)	86
8	$CuCl_2$	none	toluene	3	– (**2a**)	94
9	$CuCl_2$	none	THF	36	N.R.	
10	$CuBr_2$	none	DMSO	4	54 (**4a**)	10
11[c]	$CuBr_2$	none	DMSO	32	83 (**4a**)	trace
12[d]	$CuBr_2$	none	DMSO	72	96 (**4a**)	–

[a] *Reaction conditions:* substrate (0.2 mmol, 0.1 M), CuX_2 (X = Cl, Br) (0.5 mmol, 2.5 equiv.), K_2CO_3 (0.2 mmol, 1 equiv.), DMSO (2 mL), 50 °C.
[b] Isolated yield.
[c] Cs_2CO_3 (0.1 mmol, 0.5 equiv.), room temperature.
[d] Et_3N (0.2 mmol, 1.0 equiv), room temperature.

indole **4a** (Table 1, entries 10–12). Et_3N gave the best result at room temperature (Table 1, entry 12).

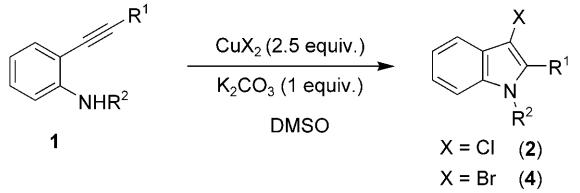
With the optimized reaction conditions in hand, we attempted to extend the scope of this halocyclization reaction by varying the substituents on the nitrogen atom and alkyne component (Table 2). When the substituent on the nitrogen atom was a tosyl or a mesyl group, a variety of alkynylanilines bearing an R^1 group, including Ph, *n*-Bu, CH_2OCH_3, and CH_2OH could afford 3-haloindoles **2** or **4** exclusively in 79–100% yields (Table 2, entries 1–6 and 9–16). However, the terminal acetylene **1j** gave 3-chloroindole **2j** and 3-bromoindole **4j** only in 22% and 23% yields, respectively (Table 2, entries 17 and 18). Compound **1k** with the sterically bulky TMS group on the alkyne could not form the desired 3-haloindoles (Table 2, entries 19 and 20). It is worth noting that when the substitutent on the nitrogen atom was an acetyl group (**1e)** or a hydrogen (**1l)**, the reactions did not occur, which may be due to the lower acidity of the N–H group as compared to those of *N*-trifluoroacetyl or *N*-sulfonyl analogues (Table 2, entries 7, 8, 21 and 22).

Importantly, when substrate **1m** with a trifluoroacetyl group on nitrogen was treated with 2.5 equivalents of CuX_2 (X = Cl, Br), K_2CO_3 (2.0 equiv.) and H_2O (7.0 equiv.) in DMSO at room temperature or 50 °C, 3-haloindoles **2m** and **4m** with cleavage of the trifluoroacetyl group were obtained in moderate to good yields through the *in situ* hydrolysis of the $COCF_3$ group under basic conditions (Scheme 1). This method could be used to synthesize the 3-haloindoles with no substitutent on the nitrogen. In addition, owing to the autoxidation-reduction of $CuBr_2$ ($2\,CuBr_2 \rightarrow 2\,CuBr + Br_2$),[10] 1 equivalent of Br_2 instead of $CuBr_2$ was used to test the reaction under the typical bromocyclization conditions [Eq. (1)]. The reaction did not occur and most of the substrate **1d** was recovered, indicating that the bromocyclization reaction of 2-hexynylanilines is promoted by $CuBr_2$ but not Br_2.



Scheme 1. Synthesis of 3-haloindoles with no substitutent on nitrogen.

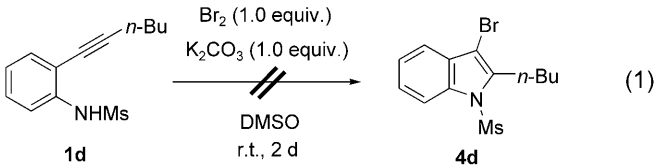
Table 2. Intramolecular halocyclization of **1** mediated by CuX_2.



Entry	R^1	R^2	Time [h]	Conditions[a]	X	Yield [%][b]
1	Ph (**1b**)	Ts	4	A	Cl	85 (**2b**)
2	Ph (**1b**)	Ts	48	B	Br	87 (**4b**)
3	*n*-Bu (**1c**)	Ts	1	A	Cl	96 (**2c**)
4	*n*-Bu (**1c**)	Ts	3	C	Br	94 (**4c**)
5	*n*-Bu (**1d**)	Ms	1	A	Cl	95 (**2d**)
6	*n*-Bu (**1d**)	Ms	5	C	Br	89 (**4d**)
7	*n*-Bu (**1e**)	Ac	72	A	Cl	N.R.
8	*n*-Bu (**1e**)	Ac	72	C	Br	N.R.
9	CH_2OCH_3 (**1f**)	Ms	1	A	Cl	88 (**2f**)
10	CH_2OCH_3 (**1f**)	Ms	1.5	C	Br	95 (**4f**)
11	CH_2OCH_3 (**1g**)	Ts	1	A	Cl	93 (**2g**)
12	CH_2OCH_3 (**1g**)	Ts	2	C	Br	100 (**4g**)
13	$CH_3(CH_2)_5$ (**1h**)	Ms	1	A	Cl	91 (**2h**)
14	$CH_3(CH_2)_5$ (**1h**)	Ms	5	C	Br	93 (**4h**)
15	CH_2OH (**1i**)	Ms	1	A	Cl	79 (**2i**)
16	CH_2OH (**1i**)	Ms	1.5	C	Br	95 (**4i**)
17	H (**1j**)	Ms	3	A	Cl	22 (**2j**)
18	H (**1j**)	Ms	3	C	Br	23 (**4j**)
19	TMS (**1k**)	Ms	48	A	Cl	N.R.
20	TMS (**1k**)	Ms	48	C	Br	N.R.
21	Ph (**1l**)	H	168	A	Cl	N.R.
22	Ph (**1l**)	H	168	B	Br	N.R.

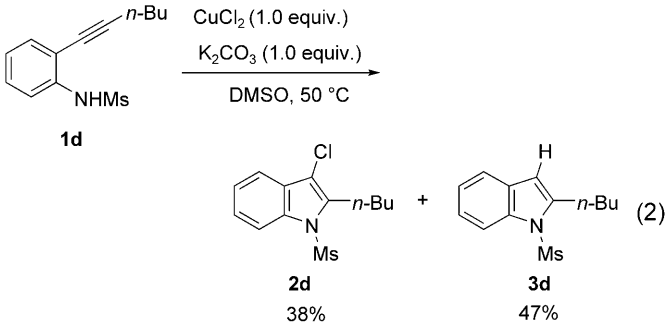
[a] *Conditions A:* substrates (0.22 mmol), $CuCl_2$ (0.55 mmol, 2.5 equiv.), K_2CO_3 (0.22 mmol, 1.0 equiv.), DMSO (1.1 mL), 50 °C; *B:* substrates (0.22 mmol), $CuBr_2$ (0.44 mmol, 2.0 equiv.), Et_3N (0.22 mmol, 1.0 equiv.), DMSO, room temperature; *C:* substrates (0.22 mmol), $CuBr_2$ (0.55 mmol, 2.5 equiv.), K_2CO_3 (0.22 mmol, 1.0 equiv.), DMSO, room temperature.

[b] Isolated yield.



(1)

To gain an insight into the mechanism of the CuX_2-mediated halocyclization reactions,[11] detailed studies toward our reaction were carried out. Firstly, the reaction of compound **1d** with less $CuCl_2$ (1 equiv.) under the chlorocyclization conditions provided 3-chloroindoles **2d** in 38% yield and the competing protonolysis



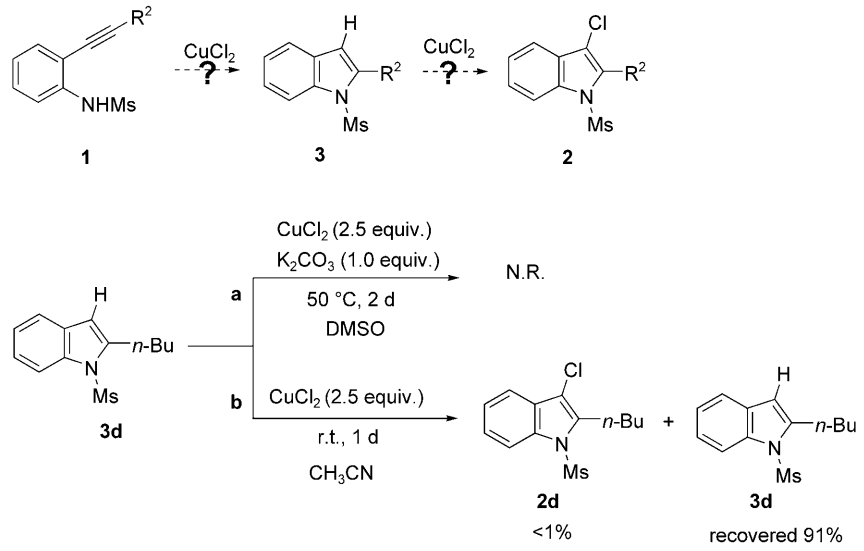
(2)

product **3d** in 47% yield [Eq. (2)], indicating that 2 equivalents of $CuCl_2$ are necessary in this reaction. Secondly, we found that the CuX_2-mediated reaction could not proceed in the absence of a base. Thirdly, the direct chlorination of 2-methyl-1*H*-indole mediated by $CuCl_2$ has been reported by Speier.[12] We wondered if the product **2** was derived from the intermediate **3d** bearing the electron-withdrawing methanesulfonyl group on nitrogen (Scheme 2). A control experiment showed that indole **3d** did not afford the desired 3-chloroindole **2d** under our standard chlorination conditions (Scheme 2, a) or under the conditions reported in the literature[12] (Scheme 2, b). These experiments indicated that the formation of 3-haloindoles mediated by CuX_2 did not proceed *via* the protonolysis product **3d**.

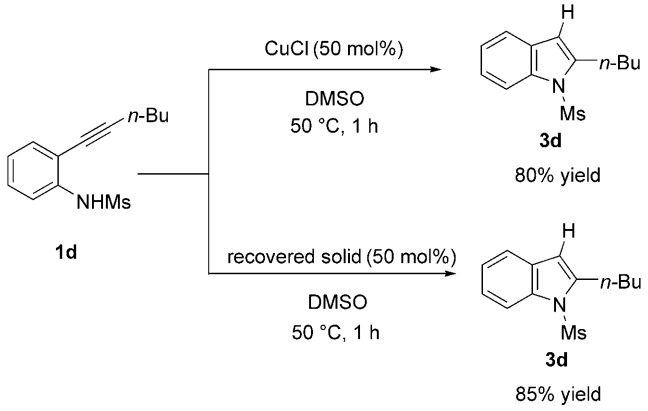
To further investigate the role of the two equivalents of CuX_2 in the reaction, electron paramagnetic resonance (EPR) experiments[13] were carried out. The EPR spectra of the $CuCl_2$ solution in DMSO have a strong absorption at 3200 gauss. The reaction of compound **1d** and $CuCl_2$ (2 equiv.) in DMSO was monitored by EPR. After 5 min, it was observed that the intensity of EPR signal was slowly decreasing and completely disappeared after 1 hour, implying that $CuCl_2$ might turn into CuCl at the end of the reaction. Similar EPR phenomena were observed in the bromocyclization reaction (see Supporting Information).

In order to confirm whether CuCl was formed in the reaction, two control experiments were carried out. It was found that the residual solid of the chlorocyclization reaction (containing CuCl) and the commercially available CuCl could both efficiently promote the cyclization of the 2-hexynylaniline derivative **1d** to afford the protonolysis product **3d** in 80% and 85% yields, respectively (Scheme 3).[14] These control experiments indicated that CuX was formed indeed during the halocyclization reaction.

On the basis of the studies described above, the proposed reaction mechanism is shown in Scheme 4. The interaction of 2-alkynylaniline **1** and the solvated CuX_2 gives the coordination complex **5**. Under the assistance of a base, the nitrogen atom acts as a nucleophile and attacks the copper-coordinated alkyne



Scheme 2. Control experiments for the reaction of indoles in the presence of $CuCl_2$.



Scheme 3. Reactions of CuCl with **1d**.

moiety to give the indole-containing copper intermediate **6**. Reductive elimination of **6** can provide the 3-haloindole derivative **2** (or **4**) and Cu(0). The formed Cu(0) can be oxidized by CuX_2 to produce CuX.[15] Thus, two equivalents of CuX_2 are necessary in this reaction.

In conclusion, we have developed a convenient and efficient method for the synthesis of 3-haloindoles. Both 3-chloro- and 3-bromoindole derivatives can be obtained in high yields by the reaction of *N*-electron-withdrawing group-substituted 2-alkynylanilines with two equivalents of CuX_2 (X = Cl, Br) in DMSO in the presence of a base within a short period of time. Detailed investigation of the reaction suggests that two equivalents of CuX_2 are required and completely turned into Cu(I) halide at the end of the reaction.

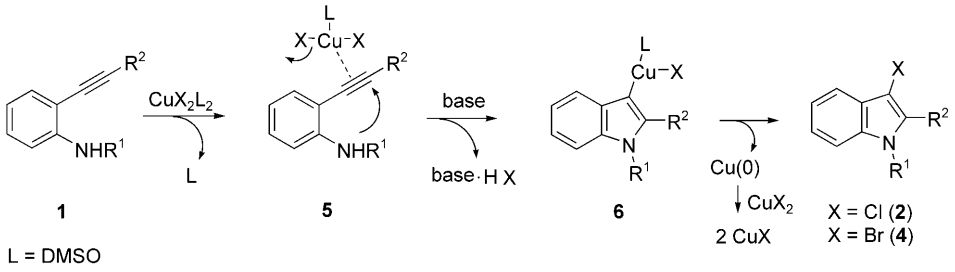
Experimental Section

General

All reactions were carried out under nitrogen atmosphere unless otherwise indicated. Reactions were monitored using thin-layer chromatography (TLC). All of copper reagents were purified according to the standard methods.

General Procedure for the Synthesis of 3-Chloroindoles Mediated by $CuCl_2$ (Conditions A)

Under nitrogen, a solution of 2-ethynylaniline **1** (0.22 mmol), $CuCl_2$ (74 mg, 0.55 mmol) and K_2CO_3 (30.5 mg, 0.22 mmol) in DMSO (1.1 mL) was stirred at 50 °C for 1–4 h. The mixture was then diluted with saturated NaCl solu-



Scheme 4. Proposed mechanism of CuX_2-mediated halocyclization reaction.

tion and extracted four times with diethyl ether. The organic layers were combined and dried over Na_2SO_4. After evaporation, the residue was purified by flash chromatography on silica gel with petroleum ether/ethyl acetate [20/1 (v/v)] as the eluent to afford 3-chloroindoles (**2**).

3-Chloro-*N*-methanesulfonyl-2-phenylindole (2a): white solid; yield: 90%; m.p 105–106 °C (recrystallization from petroleum ether-dichloromethane). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.79$ (s, 3H) 7.43–7.57 (m, 7H), 7.66–7.69 (m, 1H), 8.13–8.16 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 39.9, 115.3, 115.6, 119.0, 125.0, 126.4, 127.8, 128.2, 128.9, 129.4, 131.0, 135.6, 135.9; IR (KBr): $\nu = 3011$, 2929, 1448, 1365, 1176 cm^{-1}; MS (EI): $m/z = 307$ [M$^+$ (^{37}Cl)] (25.88), 305 [M$^+$(^{35}Cl)] (71.06), 228, 226, 201, 199, 190; anal. calcd. for $C_{15}H_{12}ClNO_2S$: C 58.92, H 3.96, N 4.58, Cl 11.59; found: C 58.93, H 4.22, N 4.43, Cl 11.31.

Typical Procedure for the Preparation of 3-Bromoindoles Mediated by $CuBr_2$ (Conditions B). Synthesis of 3-Bromo-*N*-methanesulfonyl-2-phenylindole (4a) as an Example

Under nitrogen, a solution of **1a** (60 mg, 0.22 mmol), $CuBr_2$ (98 mg, 0.44 mmol) and Et_3N (31 μL, 0.22 mmol) in DMSO (1.1 mL) was stirred at room temperature for 3 days. The mixture was then diluted with saturated NaCl solution and extracted four times with diethyl ether. The organic layers were combined and dried over Na_2SO_4. After evaporation, the residue was purified by flash chromatography on silica gel with petroleum ether/ethyl acetate [20/1 (v/v)] as the eluent to afford the white solid **4a**; yield: 96%; m.p 116–118 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.82$ (s, 3H), 7.43–7.54 (m, 7H), 7.62–7.65 (m, 1H), 8.12–8.15 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 40.3$, 103.4, 115.4, 120.2, 124.9, 126.4, 127.8, 129.4, 129.5, 129.8, 131.1, 136.2, 137.4; IR (KBr): $\nu = 3009$, 1446, 1363, 1178 cm^{-1}; MS (EI): $m/z = 351$ [M$^+$ (^{81}Br)] (35.81), 349 [M$^+$ (^{79}Br)] (35.25), 172, 270, 191, 164, 88; anal. calcd. for $C_{15}H_{12}BrNO_2S$: C 51.44, H 3.45, N 4.00, Br 22.81; found: C 51.65, H 3.48, N 3.71, Br 22.48.

Typical Procedure for the Preparation of 3-Bromoindoles Mediated by $CuBr_2$ (Conditions C). Synthesis of 3-Bromo-2-*n*-butyl-*N*-(*p*-toluenesulfonyl)indole (4c) as an Example

Under nitrogen, a solution of **1c** (80 mg, 0.24 mmol), $CuBr_2$ (136 mg, 0.61 mmol) and K_2CO_3 (33.7 mg, 0.24 mmol) in DMSO (1.2 mL) was stirred at room temperature for 3 h. The mixture was then diluted with saturated NaCl solution and extracted four times with diethyl ether. The organic layer was combined and dried over Na_2SO_4. After evaporation, the residue was purified by flash chromatography on silica gel with petroleum ether/ethyl acetate [25/1 (v/v)] as the eluent to afford the white solid **4c**; yield: 94%; m.p 70–71 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.95$ (t, $J = 7.2$ Hz, 3H), 1.38–1.50 (m, 2H), 1.65–1.73 (m, 2H), 2.32 (s, 3H), 3.08 (t, $J = 7.2$ Hz, 2H), 7.16 (d, $J = 7.8$ Hz, 2H), 7.25–7.34 (m, 2H), 7.40–7.43 (m, 1H), 7.59 (d, $J = 7.8$ Hz, 2H), 8.16–8.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.8$, 21.5, 22.5, 27.3, 31.9, 101.8, 115.0, 119.2, 124.1, 125.1, 126.3, 129.2, 129.8, 135.5, 135.9, 138.9, 144.9; IR (KBr): $\nu = 3069$, 2959, 1598, 1450, 1374, 1176 cm^{-1}; MS (EI): $m/z = 407$ [M$^+$ (^{81}Br)] (6.31), 405 [M$^+$ (^{79}Br)] (6.86), 406 [(M−1)$^+$ (^{81}Br)] (31.46), 404 [(M−1)$^+$ (^{79}Br)] (27.59), 284, 210, 208, 171, 91, 65; HR-MS: $m/z = 428.0292$, calcd for ($C_{19}H_{20}BrNO_2S + Na^+$): 428.0290.

Acknowledgements

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References

[1] For reviews, see: a) M. Lounasmaa, A. Tolvanen, *Nat. Prod. Rep.* **2000**, *17*, 175–191; b) M. Somei, F. Yamada, *Nat. Prod. Rep.* **2004**, *21*, 278–311; c) J. A. Joule, in: *Science of Synthesis*, (*Houben-Weyl Methods of Molecular Transformations*), (Ed.: E. J. Thomas), Georg Thieme Verlag, Stuttgart, **2000**; Vol. 10, pp 361–652;.

[2] a) V. Bocchi, G. Palla, *Synthesis* **1982**, 1096–1097; b) P. Martin, *Tetrahedron Lett.* **1987**, *28*, 1645–1646; c) P. Martin, *Helv. Chim. Acta* **1988**, *71*, 344–347; d) G. H. Timms, D. E. Tupper, S. E. Morgan, *J. Chem. Soc. Perkin Trans. 1* **1989**, 817–822; e) A. D. Billimoria, M. P. Cava, *J. Org. Chem.* **1994**, *59*, 6777–6782; f) M. R. Brennan, K. L. Erickson, F. S. Szmalc, M. J. Tansey, J. M. Thornton, *Heterocycles* **1986**, *24*, 2879–2885.

[3] For representative papers on the synthesis of 3-haloindole mediated by *N*-halosuccinimides, see: a) M. G. Saulnier, G. W. Gribble, *J. Org. Chem.* **1982**, *47*, 757–761; b) M. G. Saulnier, G. W. Gribble, *J. Org. Chem.* **1983**, *48*, 2690–2695; c) A. G. Mistry, K. Smith, M. R. Bye, *Tetrahedron Lett.* **1986**, *27*, 1051–1054; d) Y. Kobayashi, T. Fujimoto, T. Fukuyama, *J. Am. Chem. Soc.* **1999**, *121*, 6501–6502; e) S. Katayama, N. Ae, R. Nagata, *J. Org. Chem.* **2001**, *66*, 3474–3483; f) C. Ma, X. Liu, X. Li, J. Flippen-Anderson, S. Yu, J. M. Cook, *J. Org. Chem.* **2001**, *66*, 4525–4542.

[4] a) K. Akinori, N. Tatsuya, *Synthesis* **1980**, 365–366; b) G. Tarzia, G. Diamantini, B. Di. Giacomo, G. Spadoni, *J. Med. Chem.* **2000**, *43*, 2449–2456.

[5] For selected papers for the synthesis of 3-haloindoles *via* other methods, see: a) J. Bergman, R. Carlsson, B. Sjoberg, *J. Heterocycl. Chem.* **1977**, *14*, 1123–1134; b) A. Kubo, K. Uchino, *Heterocycles* **1981**, *16*, 1441–1443; c) G. W. Gribble, B. D. Allison, S. C. Conway, M. G. Saulnier, *Org. Prep. Proced. Int.* **1992**, *24*, 649–654; d) B. Witulsk, N. Buschmann, U. Bergsträßer, *Tetrahedron* **2000**, *56*, 8473–8480; e) É. Balogh-Hergovich, G. Speier, *J. Chem. Soc. Perkin Trans. 1* **1986**, 2305–2308; f) S. Tang, J.-H. Li, Y.-X. Xie, N.-X. Wang, *Synthesis* **2007**, 1535–1541.

[6] J. Barluenga, M. Trincado, E. Rubio, J. M. González, *Angew. Chem.* **2003**, *115*, 2508–2511; *Angew. Chem. Int. Ed.* **2003**, *42*, 2406–2409.

[7] M. Amjad, D. W. Knight, *Tetrahedron Lett.* **2004**, *45*, 539–541.
[8] a) D. Yue, R. C. Larock, *Org. Lett.* **2004**, *6*, 1037–1040; b) D. Yue, T. Yao, R. C. Larock, *J. Org. Chem.* **2006**, *71*, 62–69.
[9] a) S. Tang, Y.-X. Xie, J.-H. Li, N.-X. Wang, *Synthesis* **2007**, 1841–1847; b) Y. Yin, Z. Chai, W.-Y. Ma, G. Zhao, *Synthesis* **2008**, 4036–4040; c) C. Koradin, W. Dohle, A. L. Rodriguez, B. Schmid, P. Knochel, *Tetrahedron* **2003**, *59*, 1571–1588; d) Y. Yin, W. Ma, Z. Chai, G. Zhao, *J. Org. Chem.* **2007**, *72*, 5731–5736.
[10] J. C. Barnes, D. N. Hume, *Inorg. Chem.* **1963**, *2*, 444–448.
[11] Some examples for the CuX_2-mediated halogenation reactions, see: a) C. E. Castro, J. G. Gaughan, D. C. Owsley, *J. Org. Chem.* **1965**, *30*, 587–592; b) W. C., Jr. Baird, J. H. Surridge, M. Buza, *J. Org. Chem.* **1971**, *36*, 3324–3330; c) S. Uemura, A. Onoe, M. Okano, *J. Chem. Soc. Chem. Commun.* **1975**, 925–926; d) S. Uemura, H. Okazaki, A. Onoe, M. Okano, *J. Chem. Soc. Perkin Trans. 1* **1977**, 676–680; e) S. Uemura, H. Okazaki, M. Okano, *J. Chem. Soc. Perkin Trans. 1* **1978**, 1278–1282; f) R. Rodebaugh, J. S. Debenham, B. Freiser-Reid, J. P. Synder, *J. Org. Chem.* **1999**, *64*, 1758–1761; g) S. Ma, S. Wu, *J. Org. Chem.* **1999**, *64*, 9314–9317; h) S. Ma, S. Wu, *Chem. Commun.* **2001**, 441–442; i) S. Ma, H. Xie, *Tetrahedron* **2005**, *61*, 251–258; j) Y. Liang, S. Tang, X. Zhang, L. Mao, Y. Xie, J. Li, *Org. Lett.* **2006**, *8*, 3017–3020; k) F. Yu, X. Lian, J. Zhao, Y. Yu, S. Ma, *J. Org. Chem.* **2009**, *74*, 1130–1134; l) J.-B. Xia, S.-L. You, *Org. Lett.* **2009**, *11*, 1187–1190.
[12] É. Balogh-Hergovich, G. Speier, *J. Chem. Soc. Perkin Trans. 1* **1986**, 2305–2308.
[13] The cupric(II) ion ($3d^9$) is a paramagnetic ion, but the cuprous(I) ion ($3d^{10}$) has no EPR signal. See: a) D. Cavallini, C. D. Marco, S. Dupre, G. Rotilio, *Arch. Biochem. Biophys.* **1969**, *130*, 354–361; b) H. Liu, Y. Pang, *Acta Pharm. Sinica* **1989**, *24*, 155–158; c) Y. K. K. Mohammed, J. Mathew, *Indian J. Chem. Sect. A* **1997**, *36 A*, 303–306; d) T. M. Das, C. P. Rao, E. Kolehmainen, R. M. Kadam, M. D. Sastry, *Carbohydr. Res.* **2002**, *337*, 289–296; e) B. S. Prabhananda, M. H. Kombrabail, *J. Magn. Reson. Ser B* **1994**, *105*, 167–171; f) P. Strauch, S. Abram, U. Drutkowski, *Inorg. Chim. Acta* **1998**, *278*, 118–121.
[14] Some examples for the synthesis of indoles mediated by copper, see: a) J. Ezquerra, C. Pedregal, C. Lamas, J. Barluenga, M. Pérez, M. A. García-Martín, J. M. González, *J. Org. Chem.* **1996**, *61*, 5804–5812; b) S. Kamijo, Y. Sasaki, Y. Yamamoto, *Tetrahedron Lett.* **2004**, *45*, 35–38; c) S. Cacchi, G. Fabrizi, L. M. Parisi, *Org. Lett.* **2003**, *5*, 3843–3846; d) F. J. Reboredo, M. Treus, J. C. Estévez, L. Castedo, R. J. Estévez, *Synlett* **2003**, 1603–1606; e) J. Soloducho, *Tetrahedron Lett.* **1999**, *40*, 2429–2430; f) V. Kumar, J. A. Dority, E. R. Bacon, B. Singh, G. Y. Lesher, *J. Org. Chem.* **1992**, *57*, 6995–6998; g) D. Villemin, D. Goussu, *Heterocycles* **1989**, *29*, 1255–1261; h) C. E. Castro, E. J. Gaughan, D. C. Owsley, *J. Org. Chem.* **1966**, *31*, 4071–4078; i) C. E. Castro, R. D. Stephens, *J. Org. Chem.* **1963**, *28*, 2163–2164; j) N. T. Patil, Y. Yamamoto, *J. Org. Chem.* **2004**, *69*, 5139–5142; k) L. Ackermann, *Org. Lett.* **2005**, *7*, 439–442; l) K. Hiroya, S. Itoh, T. Sakamoto, *J. Org. Chem.* **2004**, *69*, 1126–1136; m) S. Kamijo, T. Jin, Y. Yamamoto, *Angew. Chem.* **2002**, *114*, 1858–1860; *Angew. Chem. Int. Ed.* **2002**, *41*, 1780–1782.
[15] a) A.-Y. Peng, F. Hao, B. Li, Z. Wang, Y. J. Du, *J. Org. Chem.* **2008**, *73*, 9012–9015; b) J. K. Kochi, *J. Am. Chem. Soc.* **1955**, *77*, 5274–5278.

