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Synthesis of 3-Haloindolizines by Copper(II) Halide Mediated Direct Functionalization of Indolizines

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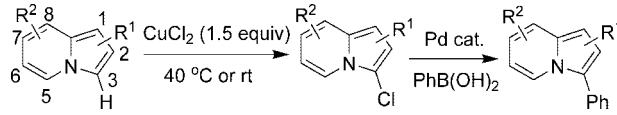
ABSTRACT



3-Haloindolizines were synthesized via Cu(II) halide mediated halogenation of indolizines. This C−H direct functionalization process occurred under mild conditions giving 3-haloindolizines in moderate to excellent yields, and the products obtained were tested under the Suzuki−Miyaura reaction providing 3-arylindolizines in high yields.

Indolizines are important *N*-fused heterocycles broadly found in biologically important natural products and synthetic pharmaceuticals.[1] Accordingly, synthesis and functionalization of indolizines have attracted considerable attention over the decades.[2] The 3-haloindolizines are particularly attractive since their analogues have been used as biologically interesting compounds[3] and their important role as the synthetic intermediates for 3-substituted indolizines is also apparent. In addition, transition-metal-catalyzed cross-coupling reactions would allow the installation of carbon−carbon and carbon−heteroatom bonds regioselectively upon the availability of 3-haloindolizines. Therefore, efforts toward the synthesis of 3-haloindolizines have been underway for a long time. For instance, reaction of pyridines with tetrachlorocyclopropene could lead to the formation of 3-chloroindolizines, but together with problematically separable 1,3-dichloroindolizines.[4] The reaction of dichlorocarbene with pyridines also led to 3-chloroindolizines but generally with low yields.[5] 3-Haloindolizines were also synthesized by the treatment of indolizines with Br_2/acetic acid, NOCl/acetic acid, or NCS/acetic acid; however, a mixture of mono- and dihalosubstituted products was given in low yields.[6] Despite the significance of 3-haloindolizines and many attempts so far, the efficient synthesis of 3-haloindolizines has not been documented yet.

(1) For reviews, see: (a) Michael, J. P. *Alkaloids* **2001**, *55*, 91. (b) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191. (c) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. For selected examples, see: (d) Molyneux, R. J.; James, L. F. *Science* **1982**, *216*, 190. (e) Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T.; Ueno, M.; Chikazawa, Y.; Yamada, K.; Ono, T.; Teshirogi, I.; Ohtani, M. *J. Med. Chem.* **1996**, *39*, 3636. (f) Millet, R.; Domarkas, J.; Rigo, B.; Goossens, L.; Goossens, J.-F.; Houssin, R.; Hénichart, J.-P. *Bioorg. Med. Chem.* **2002**, *10*, 2905. (g) Weide, T.; Arve, L.; Prinz, H.; Waldmann, H.; Kessler, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 59. (h) James, D. A.; Koya, K.; Li, H.; Liang, G.; Xia, Z.; Ying, W.; Wu, Y.; Sun, L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1784. (i) Oslund, R. C.; Cermark, N.; Gelb, M. H. *J. Med. Chem.* **2008**, *51*, 4708. (j) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3004.

(2) For reviews, see: (a) Uchida, T.; Matsumoto, K. *Synthesis* **1976**, 209. (b) Behnisch, A.; Behnisch, P.; Eggenweiler, M.; Wallenhorst, T. Indolizine. In *Houben-Weyl*; Thieme: Stuttgart, Germany, 1994; Vol. E6b/1, 2a, pp 323−450. For recent examples, see: (c) Shen, Y.-M.; Grampp, G.; Leesakul, N.; Hu, H.-W.; Xu, J.-H. *Eur. J. Org. Chem.* **2007**, 3718. (d) Surpateanu, G. G.; Landy, D.; Lungu, N. C.; Fourmentin, S.; Surpateanu, G. *J. Heterocycl. Chem.* **2007**, *44*, 783. (e) Schwier, T.; Sromek, A. W.; Yap, D. M. L.; Chernyak, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868. (f) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 3433. (g) Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323. (h) Chuprakov, S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 4463. (i) Hardin, A. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 4547. (j) Yan, B.; Zhou, Y.; Zhang, H.; Chen, J.; Liu, Y. *J. Org. Chem.* **2007**, *72*, 7783. (k) Przewloka, T.; Chen, S.; Xia, Z.; Li, H.; Zhang, S.; Chimmanamada, D.; Kostik, E.; James, D.; Koya, K.; Sun, L. *Tetrahedron Lett.* **2007**, *48*, 5739. (l) Kim, I.; Choi, J.; Won, H. K.; Lee, G. H. *Tetrahedron Lett.* **2007**, *48*, 6863. (m) Guazzelli, G.; Settambolo, R. *Tetrahedron Lett.* **2007**, *48*, 6034. (n) Kuznetsov, A. G.; Bush, A. A.; Babaev, E. V. *Tetrahedron* **2008**, *64*, 749. (o) Niyomura, O.; Yamaguchi, Y.; Sakao, R.; Minoura, M.; Okamoto, Y. *Heterocycles* **2008**, *75*, 297. (p) Chernyak, D.; Gadamsetty, S. B.; Gevorgyan, V. *Org. Lett.* **2008**, *10*, 2307.

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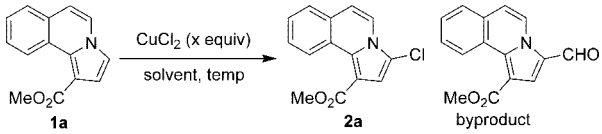
As part of our research program toward the development of a C−H activation process and direct functionalization of the indolizines,[7] we report in this paper that the Cu(II) halide mediated halogenation of indolizines affords regioselectively 3-haloindolizines. This work was inspired by the recent findings by Yu and co-workers where a catalytic amount of $CuCl_2$ was found to enable the chlorination of 2-arylpyridines in the presence of $Cl_2CHCHCl_2$ as the chlorine source.[8] Recently, in our laboratory the $CuCl_2$ alone was found to mediate the synthesis of 3-chloroindolizines under mild conditions for a wide range of substrates. The 3-chloroindolizines were demonstrated to be suitable for synthesis of 3-arylindolizines in high yields under the Suzuki−Miyaura reaction conditions.

In our initial studies, indolizine **1a** was chosen as the model substrate to test the direct chlorination process. To our delight, reaction of indolizine **1a** with 2.0 equiv of $CuCl_2$ in DMF at 60 °C gave 3-chloroindolizine **2a** in 27% yield with **1a** being recovered in 68% yield (entry 1, Table 1).

Table 1. Optimization of the Reaction Conditions[a]

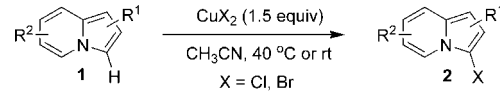


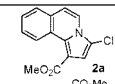
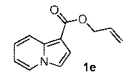
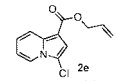
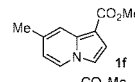
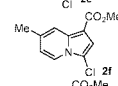
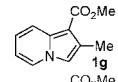
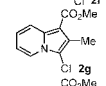
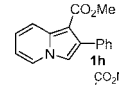
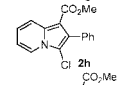
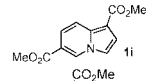
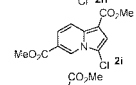
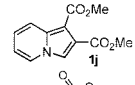
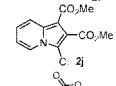
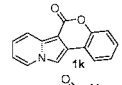
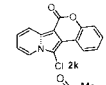
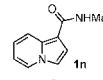
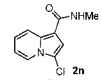
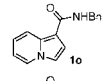
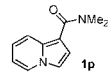
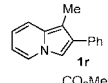
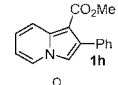
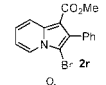
entry	$CuCl_2$ (x equiv)	solvent	T (°C)	time (h)	yield[b] (%)
1	2.0	DMF	60	24	27 (68)
2	3.0	DMF	60	96	46 (38)
3[c]	2.0	DMF	80	30	57 (36)
4	2.0	EtOH	60	36	91 (7)
5	2.0	THF	60	36	91
6	2.0	CH_3CN	60	12	87
7	2.0	dioxane	60	36	2 (89)
8	2.0	CH_3CN	40	12	89
9	2.0	CH_3CN	rt	24	90
10	2.0	CH_2Cl_2	rt	48	41 (50)
11	2.0	Et_2O	rt	48	41 (41)
12	**1.5**	**CH_3CN**	**40**	**20**	**93**
13	1.5	CH_3CN	rt	72	77
14	1.2	CH_3CN	rt	72	80 (8)

[a] 0.2 mmol of **1a** in solvent (1 mL). [b] Isolated yield and the numbers in the parenthesis indicate the yield of recovered **1a**. [c] 10% yield of byproduct was isolated.

Using 3.0 equiv of $CuCl_2$ or performing the reaction at 80 °C, the starting material **1a** could not be completely consumed (entries 2 and 3, Table 1). Notably, 10% aldehyde byproduct, likely formed by reacting with DMF, was isolated when the reaction was performed at 80 °C. Several other solvents were screened. Surprisingly, the reaction in dioxane afforded only trace amount of **2a** (entry 7, Table 1). Reaction in EtOH, THF, or CH_3CN all afforded **2a** in good yields. In

Table 2. Scope of Halogenation of Indolizines[a]



entry	substrate	product	temp (°C)	time (h)	yield (%)
1	 1a	 2a	40	20	93
2	 1b	 2b	40	2	58
3	 1c	 2c	40	2	56
4	 1d	 2d	rt	2	39
5	 1e	 2e	40	1.5	58
6	 1f	 2f	40	17	38
7	 1g	 2g	40	2	96
8	 1h	 2h	40	20	91
9	 1i	 2i	40	30	88
10	 1j	 2j	40	30	86
11	 1k	 2k	40	20	90
12	 1l	 2l	rt	2	77
13	 1m	 2m	40	17	89
14	 1n	 2n	40	2	78
15	 1o	 2o	40	2	81
16	 1p	 2p	40	2	55
17	 1q	 2q	40	2	81
18	 1r	 2r	40 or rt	-	0
19	 1h	 2r	rt	14	58
20	1n	2s	rt	2	62

[a] **1** (0.2 M) in CH_3CN at 40 °C or rt with the following molar ratio: **1**/CuX_2 = 1:1.5.

(3) Rogers, B. N.; Piotrowski, D. W.; Walker, D. P.; Jacobsen, E. J.; Acker, B. A.; Wishka, D. G.; Groppi, V. E. PCT Int. Appl. WO 2003070732, 2003.

(4) (a) Smith, K. A.; Streitwieser, A., Jr. *J. Org. Chem.* **1983**, *48*, 2629. (b) Smith, K. A.; Waterman, K. C.; Streitwieser, A., Jr. *J. Org. Chem.* **1985**, *50*, 3360.

particular, good yields could be obtained in CH_3CN even at 40 °C or room temperature (entries 8 and 9, Table 1). After testing the amount of $CuCl_2$, we found that the reaction with 1.5 equiv of $CuCl_2$ in CH_3CN at 40 °C gave the best result (93% yield, entry 12, Table 1).

Under the optimized conditions as described in entry 12, Table 1, the generality of the reaction was examined. Chlorination of indolizine esters **1b**−**f** gave moderate yields due to byproduct formation (entries 2−6, Table 2; also see Figure 1). Excellent yields were obtained when 2-substituted

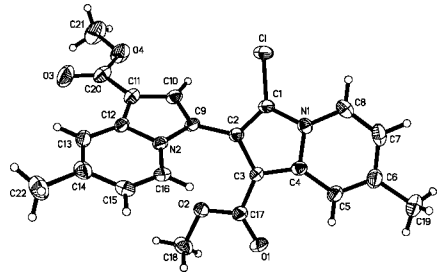
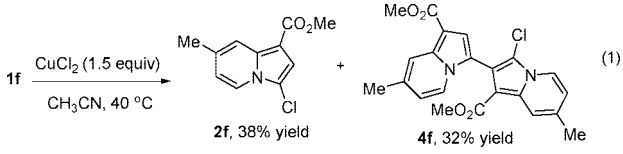


Figure 1. ORTEP representation of **4f**.

indolizines **1g**, **1h**, **1j**, and **1k** were employed (entries 7, 8 and 10, 11, Table 2). 6-Methoxycarbonyl-substituted indolizine **1i** was well tolerated and gave good yield (entry 9, Table 2). Chlorination of indolizine ketone **1l** afforded product in 77% yield at room temperature (entry 12, Table 2). Nitrile, amide, and Weinreb amide groups were tolerated, and chlorination of substrates **1m**−**q** gave their corresponding 3-chloroindolizines in moderate to good yields (entries 13−17, Table 2). However, reaction of indolizine **1r** with $CuCl_2$ did not give any desired product, presumably due to the instability of indolizine **1r** under the reaction conditions. In addition, bromination of indolizines **1g** and **1n** was tested under similar conditions using 1.5 equiv of $CuBr_2$, and the corresponding 3-bromoindolizines **2r** and **2s** were obtained in moderate yields (58 and 62% yield, entries 19 and 20, Table 2).

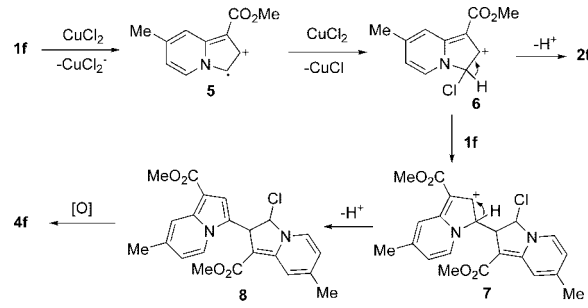
During the chlorination of **1f**, the byproduct was isolated in 32% yield and its structure was disclosed as a monochloride dimeric product **4f**, which was further confirmed by an X-ray analysis (eq 1 and Figure 1).[9] With the formation of the side product, a plausible mechanism was proposed for this chlorination process, as depicted in Scheme 1.[10] Indolizine **1f** reacts with $CuCl_2$ by an electron-transfer giving the radical cation **5**. Compound **5** takes a chloride from $CuCl_2$ resulting in cation intermediate **6**, which loses a proton to give chlorinated product **2f**. In addition, indolizine **1f** can react with **6** giving **7** by a Friedel−Crafts reaction. Compound **7** loses a proton giving **8**, which can be oxidized to **4f** under the reaction conditions.



(1)

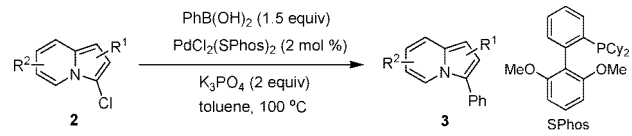
Since the 3-arylindoliznes are biologically important compounds[11] and of great synthetic importance,[2,12] we

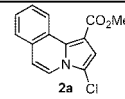
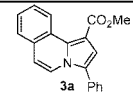
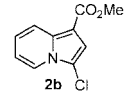
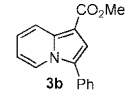
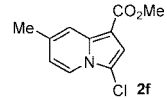
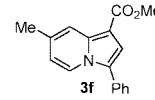
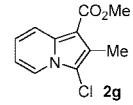
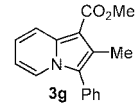
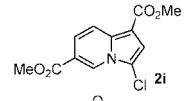
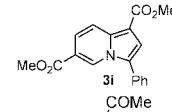
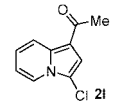
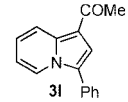
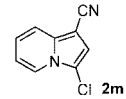
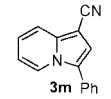
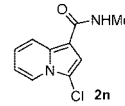
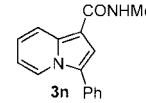
Scheme 1. Plausible Mechanism of the Chlorination of Indolizine **1f**



decided to test their synthesis from 3-chloroindolizines under the Suzuki−Miyaura conditions. This will be a simple demonstration of the utility of these 3-chloroindolizines. With the above 3-chloroindolizines in hand, we have screened the Suzuki−Miyaura conditions using phenyl boronic acid.

Table 3. Cross-Coupling of 3-Chloroindolizines with Phenyl Boronic Acid[a]



entry	substrate	product	time (h)	yield (%)
1	 **2a**	 **3a**	1	95
2	 **2b**	 **3b**	24	88
3	 **2f**	 **3f**	3	88
4	 **2g**	 **3g**	12	95
5	 **2i**	 **3i**	5	93
6	 **2l**	 **3l**	3	88
7	 **2m**	 **3m**	5	87
8	 **2n**	 **3n**	7	82

[a] **2** (0.2 M) in toluene at 100 °C with the following molar ratio: **2**/$PhB(OH)_2$/$PdCl_2(SPhos)_2$/K_3PO_4 = 1:1.5:0.02:2.

Interestingly, $PdCl_2(SPhos)_2$ was found to be an efficient catalyst.[13] As shown in Table 3, in the presence of 2 mol % of $PdCl_2(SPhos)_2$, various 3-chloroindolizines underwent smoothly the coupling with phenylboronic acid, affording 3-phenylindolizines in excellent yields. It was worthy of note that the reaction could tolerate various functional groups such as CO_2Me, COMe, CN, and CONHMe on indolizines (entries 6−8, Table 3).

In summary, we have found that the $CuCl_2$ alone efficiently mediated the synthesis of 3-chloroindolizines under mild conditions for a wide range of substrates. The utility of 3-chloroindolizines have been demonstrated in the synthesis of 3-arylindolizines under the Suzuki−Miyaura reaction conditions.

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Supporting Information Available: Experimental procedures, characterization of the products, and the crystallographic data of compound **4f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) CCDC 716176 contains the supplementary crystallographic data for byproduct **4f**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

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