RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2019, **9**, 8369

1-Alkyl-3-alkylindolin-2-imine hydrochlorides as useful building blocks in the copper-catalyzed synthesis of polycyclic indoline scaffolds†

Can Liu,[ab] Haijun Yang,[b] Changjin Zhu[a] and Hua Fu *[ab]

Received 7th February 2019
Accepted 6th March 2019

DOI: 10.1039/c9ra00995g

rsc.li/rsc-advances

A novel and efficient copper-catalyzed synthesis of dihydro-6*H*-indolo[2,3-*b*]quinoline derivatives has been developed by using 3-alkyl-1-alkylindolin-2-imine hydrochlorides as the building blocks. Furthermore, easy reduction of dihydro-6*H*-indolo[2,3-*b*]quinolines with diisobutylaluminum hydride provided tetrahydro-6*H*-indolo[2,3-*b*]quinoline derivatives in excellent yields. The present method shows some advantages including use of cheap cuprous chloride as the catalyst and tolerance of wide functional groups.

Indole alkaloids widely occur in nature and exhibit diverse and interesting biological and pharmacological activities.[1] For example, perophoramidine (**A**) and communesins (**B–I**), isolated from *Penicillium* species,[2] a marine fungal strain, and Philippine ascidian *Perophora namei*,[3] show important cytotoxicity and insecticidal properties (Fig. 1). Both intriguing structural complexity and interesting biological activities of these alkaloids attract much attention for organic synthetic chemists.[4]

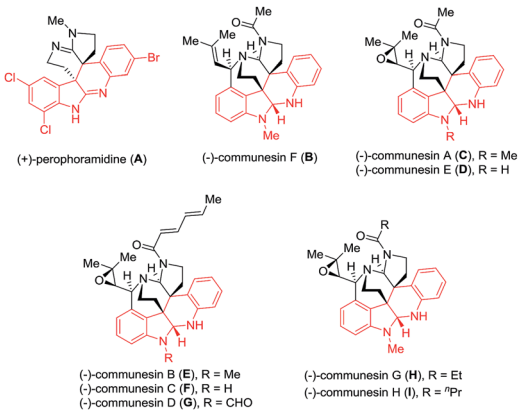
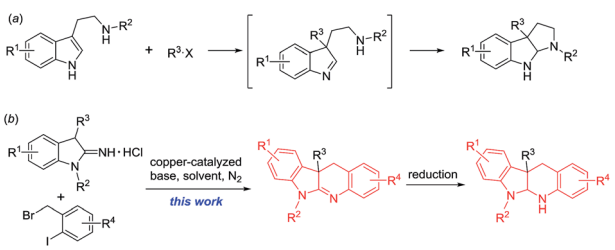


Fig. 1 Structures of representative perophoramidine and communesin alkaloids with diverse biological activities.

In previous synthesis of indole alkaloids, dearomatization of readily available indoles is often used in the construction of complex indole-containing structural motifs.[5] In particular, dearomatizing C3-alkylation/arylation of 3-substituted indoles first provides C3-quaternary indolenines, and then the indolenines are used as the versatile building blocks for the synthesis of complex indole alkaloids and related compounds.[6] However, this strategy often needs long multi-step and tedious processes. As an alternative, dearomatizing alkylation of tryptamine derivatives yields the C3-quaternary indolenines followed spontaneous cyclization to afford pyrroloindolines (Scheme 1a).[7] To the best of our knowledge, 1-alkyl-3-alkylindolin-2-imine hydrochlorides as a kind of indole derivatives have not been used in synthesis of indole alkaloids thus far. Herein, we report application of 1-alkyl-3-alkylindolin-2-imine hydrochlorides as the useful building blocks in copper-catalyzed synthesis of polycyclic indoline scaffolds (Scheme 1b).

At the outset, copper-catalyzed reaction of 3-benzyl-1-methylindolin-2-imine hydrochloride (**1h**) with 2-iodobenzyl bromide (**2a**) leading to 10*b*-benzyl-6-methyl-10*b*,11-dihydro-6*H*-indolo[2,3-*b*]quinoline (**3h**) was selected as the model to optimize conditions including catalysts, base, solvents and temperature. As shown in Table 1, six catalysts, CuI, CuBr, CuCl,



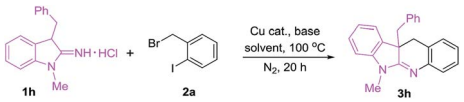
Scheme 1 Synthesis of polycyclic indoline scaffolds using tryptamine derivatives (a) or 1-alkyl-3-alkylindolin-2-imine hydrochlorides (b) as the useful building blocks.

[a]*School of Chemistry and Chemical Engineering, Beijing Institute of Technology, Beijing 100081, P. R. China. E-mail: fuhua@mail.tsinghua.edu.cn; Fax: +86 10 62781695*

[b]*Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P. R. China*

† Electronic supplementary information (ESI) available: Synthetic procedures, characterization data and ^{1}H, ^{13}C, ^{19}F NMR spectra of these synthesized compounds. See DOI: 10.1039/c9ra00995g

Table 1 Optimization of conditions for copper-catalyzed reaction of 3-benzyl-1-methylindolin-2-imine hydrochloride (**1h**) with 2-iodobenzyl bromide (**2a**) leading to 10*b*-benzyl-6-methyl-10*b*,11-dihydro-6*H*-indolo[2,3-*b*]quinoline (**3h**)[a]



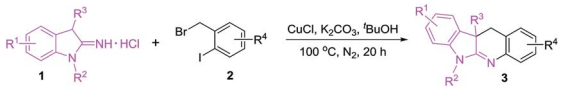
Entry	Cat.	Base	Solvent	Yield[b] (%)
1	CuI	^{t}BuONa	^{t}BuOH	73
2	CuBr	^{t}BuONa	^{t}BuOH	78
3	CuCl	^{t}BuONa	^{t}BuOH	90
4	Cu_2O	^{t}BuONa	^{t}BuOH	75
5	$Cu(OAc)_2$	^{t}BuONa	^{t}BuOH	83
6	$Cu(TFA)_2$	^{t}BuONa	^{t}BuOH	81
7	CuCl	^{t}BuONa	CH_3CN	46
8	CuCl	^{t}BuONa	^{i}PrOH	81
9	CuCl	^{t}BuONa	Toluene	42
10	CuCl	^{t}BuONa	1,4-Dioxane	38
11	CuCl	^{t}BuOLi	^{t}BuOH	89
12	**CuCl**	**K_2CO_3**	**^{t}BuOH**	**91**
13	CuCl	Cs_2CO_3	^{t}BuOH	88
14	CuCl	K_3PO_4	^{t}BuOH	86
15	CuCl	NaOAc	^{t}BuOH	43
16	CuCl	DIPEA	^{t}BuOH	Trace
17[c]	CuCl	K_2CO_3	^{t}BuOH	80
18[d]	CuCl	K_2CO_3	^{t}BuOH	91

[a] Reaction conditions: under nitrogen atmosphere, 3-benzyl-1-methylindolin-2-imine hydrochloride (**1h**) (0.33 mmol, 1.1 equiv.), 2-iodobenzyl bromide (**2a**) (0.3 mmol, 1.0 equiv.), catalyst (30 μmol, 10 mol%), base (1.2 mmol, 4.0 equiv.), solvent (3.0 mL), temperature (100 °C), time (20 h) in a sealed Schlenk tube. [b] Isolated yield. [c] Temperature (80 °C). [d] Temperature (120 °C).

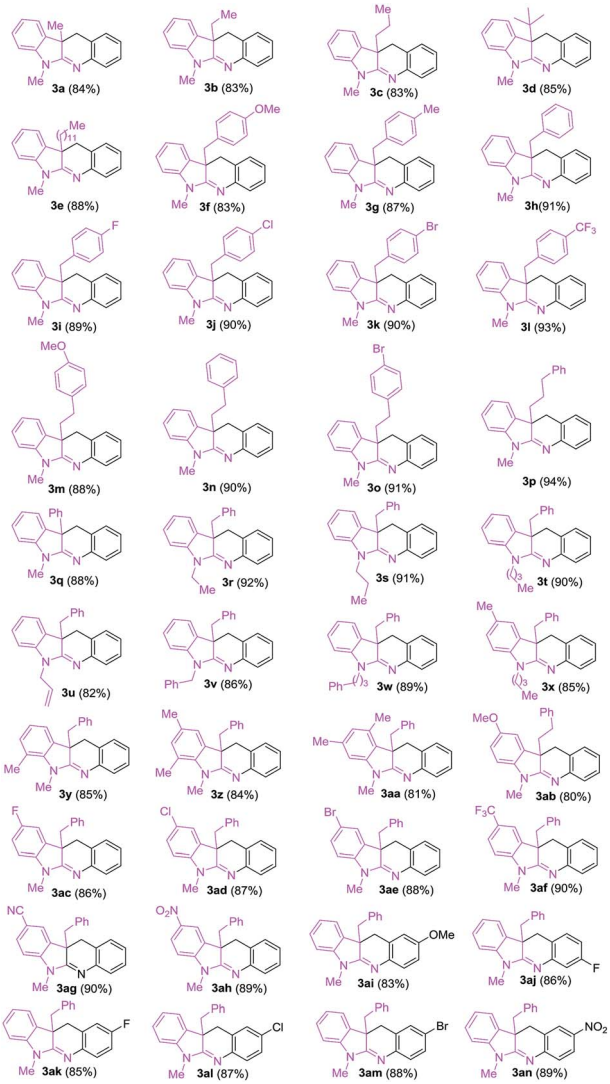
Cu_2O, $Cu(OAc)_2$ and $Cu(TFA)_2$, were tested using $NaOBu^t$ as the base and $HOBu^t$ as the solvent under nitrogen atmosphere at 100 °C for 20 h (entries 1–6), and CuCl gave the highest yield (90%) (entry 3). Subsequently, other four solvents, MeCN, $HOPr^i$, toluene and 1,4-dioxane, were attempted (entries 7–10), and they were inferior to $HOBu^t$ (compare entries 3, 7–10). Next, effect of bases including $LiOBu^t$, K_2CO_3, Cs_2CO_3, K_3PO_4, NaOAc and diisopropylethylamine (DIPEA) was investigated (entries 11–16), and the results showed that K_2CO_3 was a suitable base (entry 12). Finally, we attempted variation of temperature and found that 100 °C was an optimal temperature (compare entries 12, 17 and 18). Therefore, the copper-catalyzed optimal conditions for synthesis of 10*b*-benzyl-6-methyl-10*b*,11-dihydro-6*H*-indolo[2,3-*b*]quinoline are as follows: 10 mol% CuCl as the catalyst, K_2CO_3 as the base, and $HOBu^t$ as the solvent under nitrogen atmosphere at 100 °C for 20 h.

After obtaining the optimized conditions, we surveyed substrate scope for the copper-catalyzed reactions of 1-alkyl-3-alkylindolin-2-imine hydrochlorides (**1**) with substituted 2-iodobenzyl bromides (**2**) leading to dihydro-6*H*-indolo[2,3-*b*]quinolines (**3**). As shown in Table 2, we first surveyed reactivity of substrates (**1**) using 2-iodobenzyl bromide (**2a**) as the partner. When substituents R^3 in **1** were aliphatic alkyls (see **3a–3e**), substituted benzyls (see **3f–3l**), substituted phenylethyls (see **3m–3o**), phenylpropyl (see **3p**) and phenyl (see **3q**), and the reactions were performed well. Subsequently, variation of substituent groups R^2 including ethyl (see **3r**), propyl (see **3s**), butyl (see **3t**), allyl (see **3u**), benzyl (see **3v**) and phenylpropyl (see **3w**) in **1** was investigated, and the substrates provided the corresponding target products (**3r–3w**) in 82–92%. Next, several substrates **1** containing different R^1 substituents including electron-donating (see **3x–3ab**), poor electron-withdrawing (see **3ac–3ae**), strong electron-withdrawing (see **3af–3ah**) groups

Table 2 Substrate scope for copper-catalyzed synthesis of dihydro-6*H*-indolo[2,3-*b*]quinolines (**3**)[a]



3 (time, yield[b])

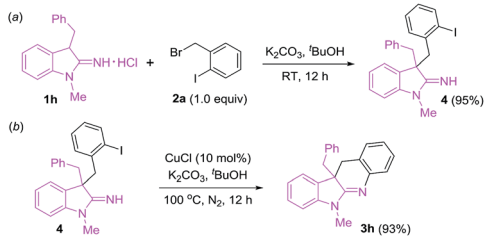


[a] Reaction conditions: under nitrogen atmosphere, 3-alkyl-1-alkylindolin-2-imine hydrochloride (**1**) (0.33 mmol, 1.1 equiv.), substituted 2-iodobenzyl bromide (**2**) (0.3 mmol, 1.0 equiv.), CuCl (30 μmol, 10 mol%), K_2CO_3 (1.2 mmol, 4.0 equiv.), ^{t}BuOH (3.0 mL), temperature (100 °C), time (20 h) in a sealed Schlenk tube. [b] Isolated yield.

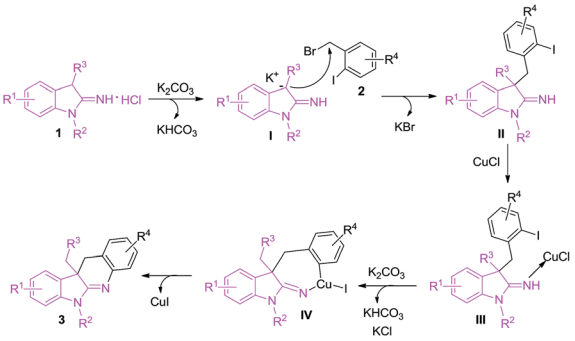
were tested, and they afforded **3x–3ah** in 80–90%. Finally, several substituted 2-iodobenzyl bromide (**2**) were applied with 3-benzyl-1-methylindolin-2-imine hydrochloride (**1h**) as the partner, and the target products (**3ai–3an**) were obtained in high yields. The copper-catalyzed reactions showed tolerance of various functional groups including C–F (see **3i**, **3ac**, **3aj** and **3ak**), C–Cl (see **3j**, **3ad** and **3al**), C–Br (see **3k**, **3o**, **3ae** and **3am**) bonds, ether (see **3f**, **3m**, **3ab** and **3ai**), trifluoromethyl (see **3l** and **3af**), cyano (see **3ag**) and nitro (see **3ah** and **3an**) groups.

To explore mechanism on the copper-catalyzed reactions of **1** with **2**, two control experiments were carried out as follows: (a) reaction of 3-benzyl-1-methylindolin-2-imine hydrochloride (**1h**) with 2-iodobenzyl bromide (**2a**) produced **4** in 95% yield in the absence of copper catalyst at room temperature (Scheme 2a). (b) Copper-catalyzed intramolecular *N*-arylation of **4** gave the target product (**3h**) in 93% yield under the standard conditions (Scheme 2b). According to the results above, the copper-catalyzed reaction mechanism is proposed in Scheme 3.[8] First, **1** transforms into anion **I** in the presence of base (K_2CO_3), and nucleophilic attack of **I** to **2** yields **II**. Coordination of CuCl with nitrogen in imine group of **II** provides **III**, and oxidative addition of **III** forms **IV** in the presence of base. Finally, reductive elimination of **IV** gives the target product (**3**) freeing copper catalyst.

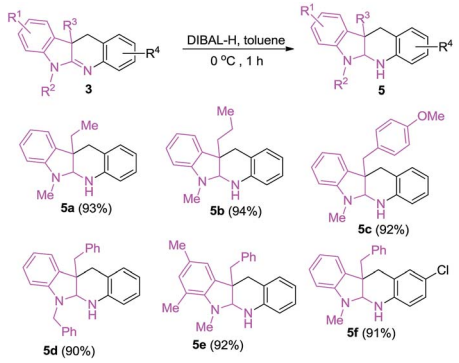
Furthermore, easy reduction of dihydro-6*H*-indolo[2,3-*b*]quinolines (**3**) with diisobutylaluminum hydride (DIBAL-H) in toluene at 0 °C led to another kind of N-heterocycles, tetrahydro-6*H*-indolo[2,3-*b*]quinolines (**5a–5f**) with wide biological activities[2,3] (Scheme 4). However, the traditional methods for synthesis of this kind of compounds need long multi-step processes by using common indoles as the starting materials. Therefore, the present method using 3-alkyl-1-alkylindolin-2-imine hydrochlorides as the building blocks is very simple and practical strategy for construction of dihydro-6*H*-indolo[2,3-*b*]quinoline and tetrahydro-6*H*-indolo[2,3-*b*]quinoline derivatives.



Scheme 2 (a) Reaction of 3-benzyl-1-methylindolin-2-imine hydrochloride (**1g**) with 2-iodobenzyl bromide (**2a**) in the absence of copper catalyst leading to **4**. (b) Copper-catalyzed intramolecular cyclization of **4** under the standard conditions.



Scheme 3 Reaction mechanism for the copper-catalyzed synthesis of dihydro-6*H*-indolo[2,3-*b*]quinolines (**3**).



Scheme 4 Reduction of dihydro-6*H*-indolo[2,3-*b*]quinolines (**3**) with DIBAL-H leading to tetrahydro-6*H*-indolo[2,3-*b*]quinolines (**5**).

In summary, we have developed a novel and efficient copper-catalyzed synthesis of dihydro-6*H*-indolo[2,3-*b*]quinoline derivatives by using 3-alkyl-1-alkylindolin-2-imine hydrochlorides as the building blocks. Furthermore, easy reduction of dihydro-6*H*-indolo[2,3-*b*]quinolines with DIBAL-H provided tetrahydro-6*H*-indolo[2,3-*b*]quinolines. The present method shows some advantages including use of cheap CuCl as the catalyst, and tolerance of wide functional groups. We believe that 3-alkyl-1-alkylindolin-2-imine hydrochlorides as the building blocks will find wide application in synthesis of complex polycyclic indoline scaffolds.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Natural Science Foundation of China (Grant No. 21772108) for financial support.

Notes and references

1 (*a*) U. Anthoni, C. Christophersen and P. H. Nielsen, in *Alkaloids: Chemical and Biological Perspectives*, ed. S. W.Pelletier, Wiley, New York, 1999, vol. 13, p. 163; (*b*) H. L. Pearce, in *The Alkaloids*, ed. A.Brossi and M.Suffness, Academic, San Diego, CA, 1990, vol. 37, p. 145.

2 (*a*) P. W. Dalsgaard, J. W. Blunt, M. H. G. Munro, J. C. Frisvad and C. Christophersen, *J. Nat. Prod.*, 2005, **68**, 258; (*b*) B. Andersen, J. Smedsgaard and J. C. Frisvad, *J. Agric. Food Chem.*, 2004, **52**, 2421; (*c*) H. Hayashi, H. Matsumoto and K. Akiyama, *Biosci., Biotechnol., Biochem.*, 2004, **68**, 753; (*d*) R. Jadulco, R. A. Edrada, R. Ebel, A. Berg, K. Schaumann, V. Wray, K. Steube and P. Proksch, *J. Nat. Prod.*, 2004, **67**,

78; (*e*) A. Numata, C. Takahashi, Y. Ito, T. Takada, K. Kawai, Y. Usami, E. Matsumura, M. Imachi, T. Ito and T. Hasegawa, *Tetrahedron Lett.*, 1993, **34**, 2355.

3 S. M. Verbitski, C. L. Mayne, R. A. Davis, G. P. Concepcion and C. M. Ireland, *J. Org. Chem.*, 2002, **67**, 7124.

4 For a recent review, see: (*a*) B. M. Trost and M. Osipov, *Chem. –Eur. J.*, 2015, **21**, 16318; For selected papers, see: (*b*) J. Yang, H. Wu, Y. Shen and Y. Qin, *J. Am. Chem. Soc.*, 2007, **129**, 13794; (*c*) P. Liu, J. H. Seo and S. M. Weinreb, *Angew. Chem., Int. Ed.*, 2010, **49**, 2000; (*d*) J. H. Seo, G. D. Artman III and S. M. Weinreb, *J. Org. Chem.*, 2006, **71**, 8891; (*e*) J. Belmar and R. L. Funk, *J. Am. Chem. Soc.*, 2012, **134**, 16941; (*f*) J. R. Fuchs and R. L. Funk, *J. Am. Chem. Soc.*, 2004, **126**, 5068; (*g*) S.-J. Han, F. Vogt, S. Krishnan, J. A. May, M. Gatti, S. C. Virgil and B. M. Stoltz, *Org. Lett.*, 2014, **16**, 3316; (*h*) S.-J. Han, F. Vogt, J. A. May, S. Krishnan, M. Gatti, S. C. Virgil and B. M. Stoltz, *J. Org. Chem.*, 2015, **80**, 528; (*i*) Z. Zuo, W. Xie and D. Ma, *J. Am. Chem. Soc.*, 2010, **132**, 13226; (*j*) Z. Zuo and D. Ma, *Angew. Chem., Int. Ed.*, 2011, **50**, 12008; (*k*) A. Sabahi, A. Novikov and J. D. Rainier, *Angew. Chem., Int. Ed.*, 2006, **45**, 4317.

5 For reviews of dearomatization reactions, see: (*a*) S. P. Roche and J. A. Porco Jr, *Angew. Chem., Int. Ed.*, 2011, **50**, 4068; (*b*) C.-X. Zhuo, W. Zhang and S.-L. You, *Angew. Chem., Int. Ed.*, 2012, **51**, 12662.

6 For selected examples, see: (*a*) R. Robinson and H. Suginome, *J. Chem. Soc.*, 1932, 298; (*b*) R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker and K. Schenker, *J. Am. Chem. Soc.*, 1954, **76**, 4749; (*c*) G. Stork and J. E. Dolfini, *J. Am. Chem. Soc.*, 1963, **85**, 2872; (*d*) F. He, Y. Bo, J. D. Altom and E. J. Corey, *J. Am. Chem. Soc.*, 1999, **121**, 6771; (*e*) S. A. Kozmin, T. Iwama, Y. Huang and V. H. Rawal, *J. Am. Chem. Soc.*, 2002, **124**, 4628.

7 For a recent review, see: (*a*) P. Ruiz-Sanchis, S. A. Savina, F. Albericio and M. Álvarez, *Chem.–Eur. J.*, 2011, **17**, 1388; For selected papers, see: (*b*) M. Kawahara, A. Nishida and M. Nakagawa, *Org. Lett.*, 2000, **2**, 675; (*c*) G. H. Tan, X. Zhu and A. Ganesan, *Org. Lett.*, 2003, **5**, 1801; (*d*) J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao and D. W. C. MacMillan, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5482.

8 For selected reviews on copper-catalyzed reactions, see: (*a*) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400; (*b*) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337; (*c*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054; (*d*) D. Ma and Q. Cai, *Acc. Chem. Res.*, 2008, **41**, 1450; (*e*) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6954; (*f*) D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2010, **1**, 13; (*g*) H. Rao and H. Fu, *Synlett*, 2011, 745; (*h*) T. Liu and H. Fu, *Synthesis*, 2012, **44**, 2805 and references cited therein.