Mendeleev Communications

Mendeleev Commun., 2025, **35**, 214–216

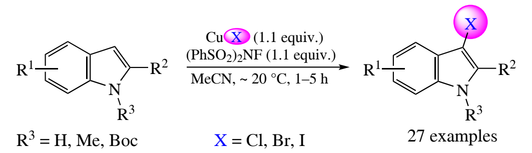
Mild cuprous halide mediated direct C^3 monohalogenation of indoles

Xin He,*[a] Jie Sui,[b] Jikuo Xu,[a] Ziyi Wang,[a] Tian Yuan,[a] Di Liu,[a] Liang Wang*[a] and Qihua Zhu*[c]

[a] *School of Chemical and Pharmaceutical Engineering, Changzhou Vocational Institute of Engineering, Changzhou 213164, China. E-mail: Peter_he2009@126.com; lwcczu@126.com*
[b] *Nanjing Customs Testing Center for Dangerous Goods and Packaging, Changzhou 213100, China*
[c] *Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, China. E-mail: zhuqihua@vip.126.com*

DOI: 10.71267/mencom.7609

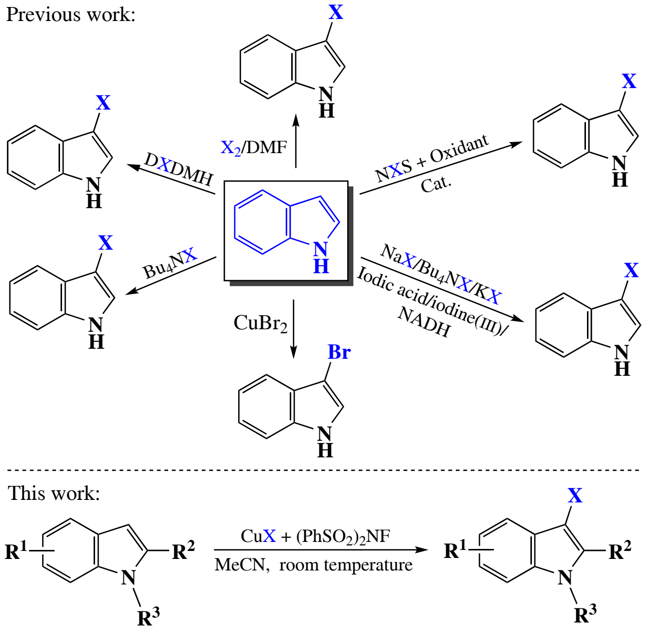
Treatment of indoles with cuprous halide–*N*-fluorobenzenesulfonimide system in MeCN at room temperature affords the corresponding C^3-halogenated derivatives. Cuprous halide acts as a dual-function reagent serving both as the halogen source and the promoter.



• CuX halogen source and promoter • Mild conditions • (PhSO$_2$)$_2$NF oxidant

Keywords: indole derivatives, halogenation, cuprous halide, *N*-fluorobenzenesulfonimide, mild conditions.

Halogenated indoles have attracted interest due to their extensive applications in biology and medicine.[1–7] They are also utilized as efficient motifs in pesticide[8] and general organic synthesis.[9] Typically, halogen atoms are introduced onto the indole ring through direct functionalization. Among all strategies, the halogenation of indoles on the C^3 position has garnered more interest due to its widespread applications in medicinal chemistry. Molecular iodine,[10–13] systems of sodium halides with phenyliodine diacetate [PIDA, PhI(OAc)$_2$],[14–18] NCS/catalyst,[19–25] 1,3-dichloro-5,5-dimethylhydantoin (DXDMH), Bu$_4$NX (under electrosynthesis conditions),[26–31] and copper(II) bromide or chloride[32] have been employed as halogen sources and catalysts (Scheme 1). However, some of the reported procedures required the use of solvents with high boiling point or special catalysts, and the substrate scope was limited.



Scheme 1

Application of cuprous halides as cost-effective and readily available metal catalysts have garnered significant attention, rendering them crucial sources of halogens.[33] Herein, we propose a novel approach to the direct monohalogenation of the C–H bond at the C^3 position of the indole scaffold, employing cuprous halides as both the halogen sources and promoter, while utilizing *N*-fluorobenzenesulfonimide (PhSO$_2$)$_2$NF (NFSI) as an oxidant. It is noteworthy that (i) our operations are conducted at room temperature and (ii) cuprous halides, functioning as inorganic salts, play dual roles as halogen sources and promoters. This strategic approach showcases exceptional regioselectivity by employing cost-effective halogen sources with high reactivity, while also applying to a broad range of substrates with straightforward execution.

Initially, we optimized the reaction conditions with indole **1a** (1.0 mmol) and cuprous chloride (1.0 mmol) as the model reactants (see Scheme 1) at room temperature in acetonitrile as the solvent. A range of oxidants was screened including PIDA and phenyliodine bis(trifluoroacetate) (PIFA), with NFSI having been identified as the most favorable choice (Table 1, entries 1–5). Solvents such as 1,4-dioxane, THF, deionized water, dichloromethane, and DMF (entries 6–10) were evaluated; however, these provided lower yields of product **2a** compared to acetonitrile. When amounts of NFSI and cuprous chloride were raised to 1.1 equiv., the substrate **1a** was completely transformed into the desired product (entry 11). The impact of reaction temperature on chlorination was further investigated. Conducting the reaction at reflux resulted in decreased yields due to impurity formation, while lower temperatures (0–5 °C) caused incomplete conversion of substrate **1a** to **2a**. Additionally, our study showed that chlorination could be completed within 1 h (see entry 11). Finally, with extending the chlorination protocol to bromination (CuBr) and iodination (CuI) the corresponding products **2′a** and **2″a** were obtained (entries 12, 13).

Based on the optimized reaction conditions, a series of indole derivatives were synthesized under these refined parameters (Scheme 2).† This approach exhibited excellent tolerance towards various substituted indole compounds **1b–i**. Halogenation of *N*-methyl-substituted indole **1b** resulted in C^3-

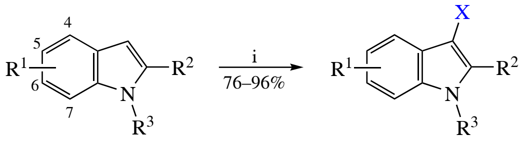
Table 1 Optimization of CuX-mediated halogenation of indole **1a** at C(3) position.[a]

Entry	Oxidant	Solvent	CuX	Product	Yield of **2a** (%)[b]
1	PIDA	MeCN	CuCl	**2a**	35
2	H_2O_2	MeCN	CuCl	**2a**	55
3	$K_2S_2O_8$	MeCN	CuCl	**2a**	20
4	PIFA	MeCN	CuCl	**2a**	30
5	NFSI	MeCN	CuCl	**2a**	85
6	NFSI	Dioxane	CuCl	**2a**	70
7	NFSI	THF	CuCl	**2a**	30
8	NFSI	H_2O	CuCl	**2a**	trace
9	NFSI	CH_2Cl_2	CuCl	**2a**	25
10	NFSI	DMF	CuCl	**2a**	30
11	NFSI	MeCN	CuCl	**2a**	95[c] (88,[d] 45,[e] 96[f,g])
12	NFSI	MeCN	CuBr	**2′a**	82
13	NFSI	MeCN	CuI	**2″a**	82

[a] *Reaction conditions*: **1a** (1.0 mmol), CuX (1.0 mmol, 1.0 equiv.), oxidant (1.0 mmol, 1.0 equiv.), solvent (5 ml), room temperature, 12 h. [b] Isolated yield. [c] CuCl (1.1 equiv.), NFSI (1.1 equiv.). [d] Under reflux. [e] At 0 °C. [f] Reaction time was 6 h. [g] Reaction time was 1 h.

halogenated *N*-methyl indoles **2b**, **2′b** and **2″b** with yields ranging from 94 to 96% (for particular values, see Online Supplementary Materials). Analogous *N*-Boc derivative **1c** was transformed into products **2c/2′c/2″c** in somewhat lower yields, so the reaction time had to be increased to 5 h. Indole substrates **1d–g** bearing nitro substituents on the phenyl ring underwent smooth halogenation within 5 h achieving good to excellent yields of the corresponding halogeno derivatives. The introduction of an electron-donating group, such as 5-methoxy, at the 5 position yielded satisfactory yields (**2h**, **2′h** and **2″h**) within 1 h. Additionally, 2-methylindole **1i** was converted into the desired products **2i/2′i/2″i** with yields ranging from 76 to 87%.

To gain deeper insights into the reaction mechanism, a series of control experiments were subsequently conducted. Initially, to verify the role of copper(I) salt in the halogenation reaction, cuprous chloride was replaced with sodium chloride. In this case, no conversion of indole **1a** substrate into the target product **2a** was detected through TLC analysis, indicating that cuprous salt truly promoted the reaction. Subsequently, upon addition of 5.0 equiv. of 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) into the reaction system, no suppression effect was observed and product **2a** was formed in 82% yield, thus suggesting that the reaction did not proceed *via* a radical pathway.

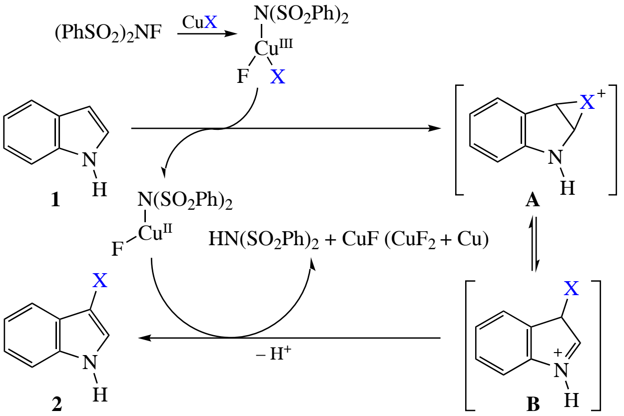


1a–i

2a–i X = Cl
2′a–i X = Br
2″a–i X = I

a $R^1 = R^2 = R^3 = H$
b $R^1 = R^2 = H$, $R^3 = Me$
c $R^1 = R^2 = H$, $R^3 = Boc$
d $R^1 = 4\text{-}NO_2$, $R^2 = R^3 = H$
e $R^1 = 5\text{-}NO_2$, $R^2 = R^3 = H$
f $R^1 = 6\text{-}NO_2$, $R^2 = R^3 = H$
g $R^1 = 7\text{-}NO_2$, $R^2 = R^3 = H$
h $R^1 = 5\text{-}OMe$, $R^2 = R^3 = H$
i $R^1 = R^3 = H$, $R^2 = Me$

Scheme 2 *Reagents and conditions*: i, **1a–i** (1.0 mmol), CuX (1.1 mmol, 1.1 equiv.), NFSI (1.1 mmol, 1.1 equiv.), MeCN (5 ml), room temperature, 1 h (or 5 h for substrates **1c–g**).



Scheme 3 Proposed mechanism.

Based on the control experiments and the relative literature,[29] a plausible mechanism was proposed (Scheme 3). Initially, cuprous halide is oxidized with NFSI to form a copper(III) complex.[34] Subsequently, this complex reacts with indole substrate **1** to generate an intermediate halogen cation **A**, simultaneously, bis(phenylsulfonyl)imidocopper(II) fluoride is produced. The intermediate product **A** subsequently transforms into a more stable cationic species **B**.[35] After eliminating a proton, it yields 3-halo indole **2**, bis(phenylsulfonamide), and cuprous fluoride. The latter is unstable and decomposes into cupric fluoride and copper metal.

In summary, we have developed a cuprous-mediated synthesis for 3-halogenated indoles from indole derivatives under mild conditions. In this reaction, cuprous halide acts not only as the source of the halogenated reagent but also as the promoter, with NFSI serving as an effective oxidant. Most indole substrates displayed excellent reactivity and regioselectivity. The process is straightforward and amenable to scale-up. Further mechanistic studies and bi-functionalization based on this method are in progress in our laboratory.

This project was financially supported by the Research Fund of Changzhou Vocational Institute of Engineering.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7609.

References

1 T. B. Ahmad, D. Rudd, J. Smith, M. Kotiw, P. Mouatt, L. M. Seymour, L. Liu and K. Benkendorff, *Mar. Drugs*, 2017, **15**, 133; https://doi.org/10.3390/md15050133.

2 M. Akhtar, L. Lai, T. Tian, X. Zhang, H. Cheng and L. Lin, *Eur. J. Med. Chem.*, 2024, **70**, 116376; https://doi.org/10.1016/j.ejmech.2024.116376.

3 A. Kumari and R. K. Singh, *Bioorg. Chem.*, 2019, **89**, 103021; https://doi.org/10.1016/j.bioorg.2019.103021.

4 C. Lechner, M. Flaßhoff, H. Falke, L. Preu, N. Loaëc, L. Meijer, S. Knapp, A. Chaikuad and C. Kunick, *Molecules*, 2019, **24**, 4090; https://doi.org/10.3390/molecules24224090.

5 J. King, V. H. Woolner, R. A. Keyzers and R. J. Rosengren, *Toxicol. Rep.*, 2022, **9**, 1198; https://doi.org/10.1016/j.toxrep.2022.05.016.

6 E. A. Lafayette, S. M. V. de Almeida, R. V. Cavalcanti Santos, J. F. de Oliveira, C. A. da Cruz Amorim, R. M. F. da Silva, M. G. D. R. Pitta, I. D. R. Pitta, R. O. de Moura, L. B. de Carvalho, Jr., M. J. B. de Melo Rêgo and M. D. C. A. de Lima, *Eur. J. Med. Chem.*, 2017, **136**, 511; https://doi.org/10.1016/j.ejmech.2017.05.012.

7 J. J. Soldevila-Barreda, K. B. Fawibe, M. Azmanova, L. Rafols, A. Pitto-Barry, U. B. Eke and N. P. E. Barry, *Molecules*, 2020, **25**, 4540; https://doi.org/10.3390/molecules25194540.

[†] *General procedure for the synthesis of* **2**. To a 25 ml flask equipped with a magnetic stirring bar and condenser tube, indole derivatives **1** (1.0 mmol), cuprous halide (1.1 mmol), *N*-fluorobenzenesulfonimide (1.1 mmol), and acetonitrile (5 ml) were added under air atmosphere. The reaction mixture was stirred at room temperature for 1–5 h, and then the mixture was filtered through a plug of celite, the filtrate was concentrated in a vacuum and purified by chromatography (light petroleum/EtOAc) as an eluent to give products **2**.

8 P. Jeschke, *Pest Manage Sci.*, 2017, **73**, 1053; https://doi.org/10.1002/ps.4540.

9 M. Luo, X. Zhu, R. Liu, S. Yu and W. Wei, *J. Org. Chem.*, 2020, **85**, 3638; https://doi.org/10.1021/acs.joc.9b03300.

10 K. Orito, T. Hatakeyama, M. Takeo, H. Suginome and M. Tokuda, *Synthesis*, 1997, 23; https://doi.org/10.1055/s-1997-1504.

11 F. De Simone, T. Saget, F. Benfatti, S. Almeida and J. Waser, *Chem. – Eur. J.*, 2011, **17**, 14527; https://doi.org/10.1002/chem.201102583.

12 L. Gu, C. Jin, J. Liu, H. Zhang, M. Yuan and G. Li, *Green Chem.*, 2016, **18**, 1201; https://doi.org/10.1039/C5GC01931A.

13 M.-N. Zhao, L. Ran, M. Chen, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *ACS Catal.*, 2015, **5**, 1210; https://doi.org/10.1021/cs5019106.

14 A. Khazaei, M. A. Zolfigol, E. Kolvari, N. Koukabi, H. Soltani and F. Komaki, *Synthesis*, 2009, **21**, 3672; https://doi.org/10.1055/s-0029-1216994.

15 A. Khazaei, M. A. Zolfigol, E. Kolvari, N. Koukabi, H. Soltani and L. S. Bayani, *Synth. Commun.*, 2010, **40**, 2954; https://doi.org/10.1080/00397910903349992.

16 V. Himabindu, S. P. Parvathaneni and V. J. Rao, *New J. Chem.*, 2018, **42**, 18889; https://doi.org/10.1039/C8NJ03822H.

17 V. M. Lakshmireddy, Y. Naga Veera, T. J. Reddy, V. J. Rao and B. China Raju, *Asian J. Org. Chem.*, 2019, **8**, 1380; https://doi.org/10.1002/ajoc.201900296.

18 X. Ge, L. Cheng, F. Sun, X. Liu, X. Chen, C. Qian and S. Zhou, *Catal. Commun.*, 2019, **123**, 32; https://doi.org/10.1016/j.catcom.2019.01.015.

19 H. Xu, L. Hu, G. Zhu, Y. Zhu, T. Wang, Z.-H. Wu. Y. Zi and W. Huang, *RSC Adv.*, 2022, **12**, 7115; https://doi.org/10.1039/D2RA00197G.

20 C. A. Kuttruff, P. Mayer and D. Trauner, *Eur. J. Org. Chem.*, 2012, 5151; https://doi.org/10.1002/ejoc.201200712.

21 P. K. Chhattise, A. V. Ramaswamy and S. B. Waghmode, *Tetrahedron Lett.*, 2008, **49**, 189; https://doi.org/10.1016/j.tetlet.2007.10.126.

22 P. Huang, X. Peng, D. Hu, H. Liao, S. Tang and L. Liu, *Org. Biomol. Chem.*, 2017, **15**, 9622; https://doi.org/10.1039/C7OB02312J.

23 P. P. Singh, T. Thatikonda, K. A. A. Kumar, S. D. Sawant, B. Singh, A. K. Sharma, P. R. Sharma, D. Singh and R. A. Vishwakarma, *J. Org. Chem.*, 2012, **77**, 5823; https://doi.org/10.1021/jo300731z.

24 D. A. Rogers, M. D. Hopkins, N. Rajagopal, D. Varshney, H. A. Howard, G. LeBlanc and A. A. Lamar, *ACS Omega*, 2020, **5**, 7693; https://doi.org/10.1021/acsomega.0c00631.

25 N. Bhardwaj, A. K. Singh, N. Tripathi, B. Goel, A. Indra and S. K. Jain, *New J. Chem.*, 2021, **45**, 14177; https://doi.org/10.1039/D1NJ02777H.

26 J. Yan, T. Ni and F. Yan, *Tetrahedron Lett.*, 2015, **56**, 1096; https://doi.org/10.1016/j.tetlet.2015.01.080.

27 S. Bhatt, Y.-N. Wang, H. T. P. Pham and K. L. Hull, *Org. Lett.*, 2022, **24**, 5746; https://doi.org/10.1021/acs.orglett.2c02190.

28 P. Liang, H. Zhao, T. Zhou, K. Zeng, W. Jiao, Y. Pan, Y. Liu, D. Fang, X. Ma and H. Shao, *Adv. Synth. Catal.*, 2021, **363**, 3532; https://doi.org/10.1002/adsc.202100234.

29 Y. Jian, P. Liang, X. Li, H. Shao and X. Ma, *Org. Biomol. Chem.*, 2023, **21**, 179; https://doi.org/10.1039/D2OB01951e.

30 L. Sun, X. Zhang, Z. Li, J. Ma, Z. Zeng and H. Jiang, *Eur. J. Org. Chem.*, 2018, 4949; https://doi.org/10.1002/ejoc.201800267.

31 M. Vayer, M. Pastor, C. Kofink and N. Maulide, *Org. Lett.*, 2021, **24**, 27; https://doi.org/10.1021/acs.orglett.1c03569.

32 S. Tang, J.-H. Li, Y.-X. Xie and N.-X. Wang, *Synthesis*, 2007, 1535; https://doi.org/10.1055/s-2007-966030.

33 C. E. Castro, E. J. Gaughan and D. C. Owsley, *J. Org. Chem.*, 1965, **30**, 587; https://doi.org/10.1021/jo01013a069.

34 S. Wang, Z. Ni, X. Huang, J. Wang and Y. Pan, *Org. Lett.*, 2014, **16**, 5648; https://doi.org/10.1021/ol502724u.

35 T. Zheng, J. Xu, S. Cheng, J. Ye, S. Ma and R. Tong, *J. Org. Chem.*, 2023, **88**, 11497; https://doi.org/10.1021/acs.joc.3c00638.

Received: 2nd September 2024; Com. 24/7609