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COMMUNICATION

t-BuONa-mediated direct C-H halogenation of electron-deficient (hetero)arenes†

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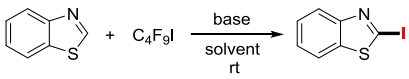
An efficient halogenation of electron-deficient (hetero)arenes is described. The reaction utilizes common *t*-BuONa as a catalyst (for iodination) or a promoter (for bromination and chlorination), and perfluorobutyl iodide, CBr_4 or CCl_4 as the readily-available halogenating agents, respectively. The protocol features broad scope, high efficiency, mild conditions and gram scalability. An ionic pathway involving halogen bond formation and halophilic attack is proposed. The utility of the resulting iodinated heteroarenes is demonstrated in visible light-mediated C_{aryl}—C_{aryl} cross-coupling reaction.

(Hetero)aromatic halides are valuable and fundamental building blocks that are used to construct new carbon–carbon and carbon–heteroatom bonds in organic synthesis and drug design.[1] Quite a few of important classical cross-coupling reactions such as the Heck reaction, the Suzuki reaction and the Buchwald–Hartwig reaction, require aryl halides as starting materials.[2] Recently developed metal-free and electron transfer-mediated cross-coupling occurs between halogenated (hetero)aromatics and aromatics.[3] Hence, it is always an important task to develop efficient preparation methods of (hetero)aromatic halides. Till now, there are many known methods for the preparation of haloarenes from aromatics especially from electron-rich systems. However, electron-deficient (hetero)arenes are difficult to be halogenated,[4] often suffering from harsh conditions (either strong alkyllithium bases at extremely low temperature or relatively weak bases upon heating), multi-steps and/or low yields. Among all the halogenated aromatics, aryl iodides are less accessible and particularly expensive due to the weakly electrophilic nature of iodine. Based on our prehension on halogen-bonding interaction/activation,[5] herein, we would like to report an efficient halogenation of electron-deficient (hetero)arenes under mild conditions, employing common *t*-BuONa as the catalyst[6] (for iodination) or the promoter (for bromination and chlorination) with broad halogen compatibility (Cl, Br and I).

The initial optimization started from benzothiazole and perfluorobutyl iodide (Table 1). The reaction with *t*-BuONa (1.2 equiv) proceeded efficiently in DMF at room temperature, giving 2-iodobenzothiazole (**3a**) in nearly quantitative yield in 20 min (entry 1). NaOH also worked well (entry 2), however, K_2CO_3 and DBU proved to be ineffective (entries 3 and 4). Solvent screening indicated that DMSO, MeCN, DCM and toluene were much less efficient than DMF (entries 5-8). It was interesting to note that catalytic amount of *t*-BuONa of 50 mol% loading can drive the reaction to completion, without sacrificing the yield (entry 9). Comparatively, in the absence of *t*BuONa, no reaction was observed (entry 10). All the reactions were conducted in the open air and no precaution needs to be taken to exclude moisture from the glassware.

The survey of alternative iodination reagents revealed that *N*-iodosuccinamide, iodine and C_6F_5I were not competent in the reaction (Table 2, entries 1-3). As for bromination reaction, 2-bromobenzothiazole (**4a**) could be obtained in 71% yield, using perfluorooctyl bromide (1.1 equiv) as the bromine source (entry 4). Thus, other brominating reagents including CBr_4, NBS and BrCN were tried (entries 5-7). Delightly, CBr_4 can be used as an efficient bromine source, giving **4a** in 93% yield (entry 5). Same case was observed when CCl_4 was employed as the chlorine source (entries 8 and 9).

Table 1. Optimization of the reaction conditions.[a,b]



1a 2a 3a

entry	base (equiv.)	solvent	t	yield (%)[b]
1	*t*-BuONa (1.2)	DMF	20 min	99
2	NaOH (1.2)	DMF	25 min	98
3	K_2CO_3 (2.2)	DMF	6 h	0
4	DBU (1.2)	DMF	6 h	trace

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†Electronic Supplementary Information (ESI) available: [Experimental procedure, and characterization data for all compounds (PDF)]. See DOI: 10.1039/x0xx00000x

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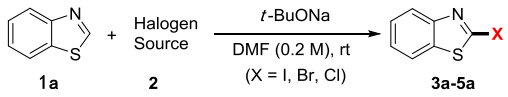
5	*t*-BuONa (1.2)	DMSO	6 h	50
6	*t*-BuONa (1.2)	MeCN	6 h	trace
7	*t*-BuONa (1.2)	DCM	6 h	0
8	*t*-BuONa (1.2)	toluene	6 h	0
9	***t*-BuONa (0.5)**	**DMF**	**25 min**	**99**
10	–	DMF	6 h	nr

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (1.1 equiv) and base in solvent (0.5 mL). [b] Isolated yield. nr = no reaction.

Table 2. Investigation of the halogen sources.[a]

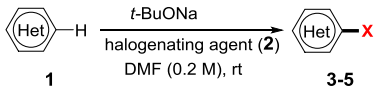


entry	halogen source	yield (%)	entry	halogen source	yield[b] (%)
iodine source			5	CBr_4	93[c]
1	NIS	0	6	NBS	0
2	I_2	0	7	BrCN	trace
3	C_6F_5I	90	chlorine source		
bromine source			8	CCl_4	88[c]
4	$C_8F_{17}Br$	71	9	NCP	0

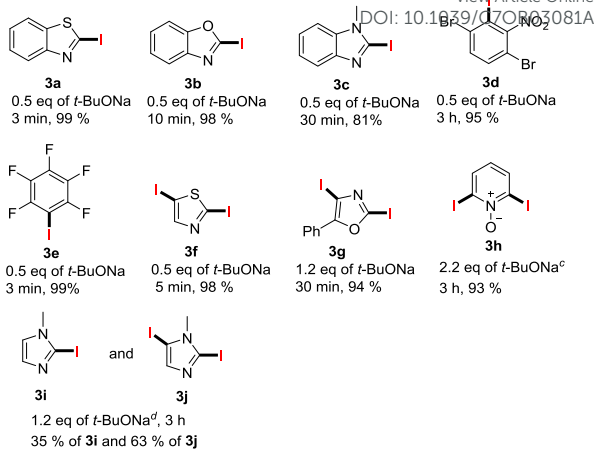
[a] Reaction conditions: **1a** (0.1 mmol), **2** (1.1 equiv) and *t*-BuONa (1.2 equiv) in DMF (0.5 mL). [b] Isolated yield. [c] *t*-BuONa (4 equiv) was used.

With the optimized conditions in hand, we examined the scope of the halogenation reaction (Table 3). Electron-deficient (hetero)aromatic hydrocarbons, such as benzothiazole, benzoxazole, *N*-methylbenzoimidazole and aromatics like pentafluorobenzene and 1,4-dibromo-2-nitrobenzene could be iodinated efficiently, giving products **3a-e** in high to excellent yields (81-99%). The amount of *t*-BuONa required can be as low as 50 mol%. Using 2.1 equiv of perfluorobutyl iodide, thiazole, 5-phenyloxazole and pyridine *N*-oxide afforded diiodination products **3f-h** as the main products in excellent yields. Differently, the iodination of *N*-methylimidazole did not proceed well in DMF solution. Instead, taking toluene as the solvent, the iodination reaction goes facilely, with monoiodination and diiodination as a mixture. We think the reaction performed in toluene may undergo a different pathway from that in DMF.

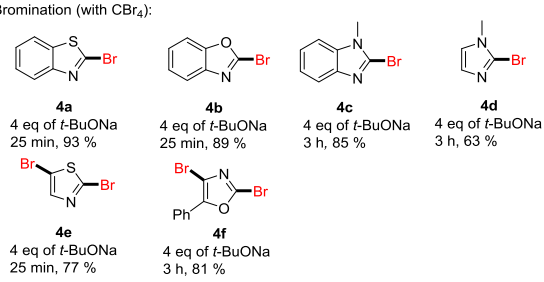
Table 3. Halogenation of heteroarenes.[a,b]



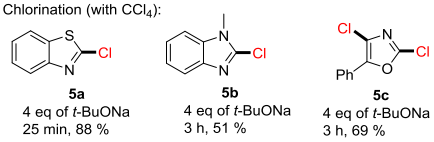
Iodination (with C_4F_9I):



Bromination (with CBr_4):



Chlorination (with CCl_4):



[a]Reaction conditions: **1** (0.1 mmol), *t*-BuONa and **2a** (1.1 or 2.1 equiv) in DMF (0.5 mL). [b]Isolated yields. [c] In dry DMF (0.5 mL). [d] In toluene (0.5 mL).

Monobromination for benzothiazole, benzoxazole, *N*-methylimidazole and *N*-methylimidazole (**4a-d**), as well as dibromination for thiazole and 5-phenyloxazole (**4e** and **4f**) were achieved in 63-93% yields. In the presence of 1.1 equiv of CCl_4 and 4 equiv of *t*-BuONa, 2-chloro benzothiazole (**5a**) and 2-chloro-1-methylbenzoimidazole (**5b**) were obtained in 88% and 51% yields, respectively. 2,4-Dichloro-5-phenyloxazole (**5c**) were prepared with 2.1 equiv of CCl_4 and 4 equiv of *t*-BuONa. It is a major problem for bromonation and chlorination that *t*-BuONa could not be loaded with catalytic amount, contrary to that of iodination. Noteworthy that when pentafluorobenzene was subjected to the reaction sequence, pentafluoro-6-(tribromomethyl)benzene (**6**) and pentafluoro-6-(trichloromethyl)benzene (**7**), rather than the corresponding brominated and chlorinated products, were achieved in 92% and 77% yields, respectively (eqs 1 and 2).[7,8]

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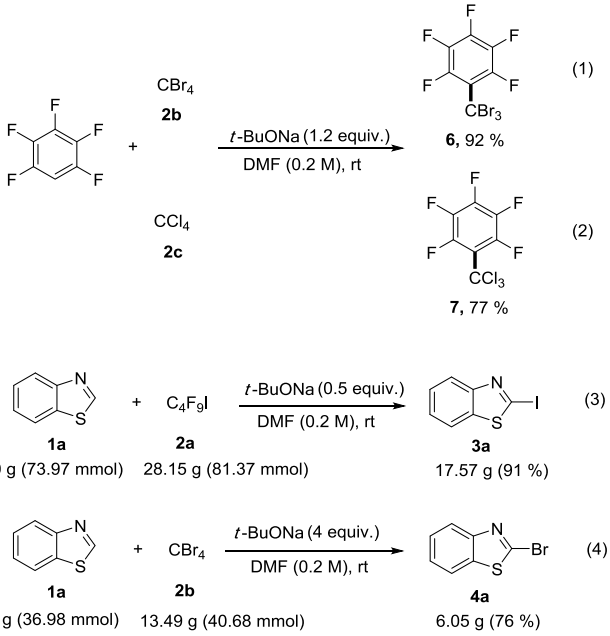
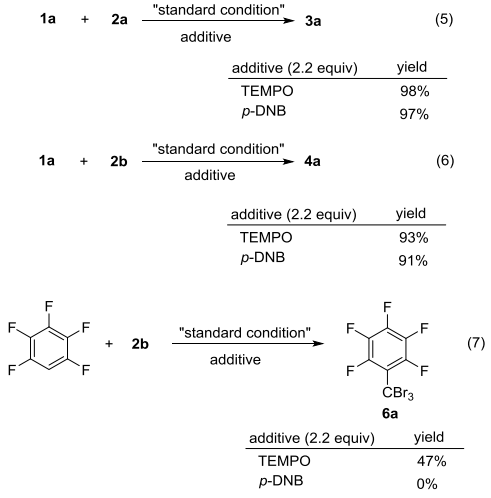


Scheme 1. Gram-scale reaction

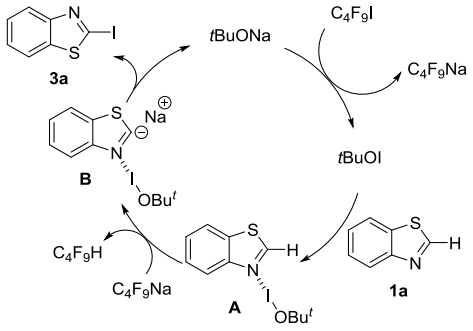


Scheme 2. Control experiment

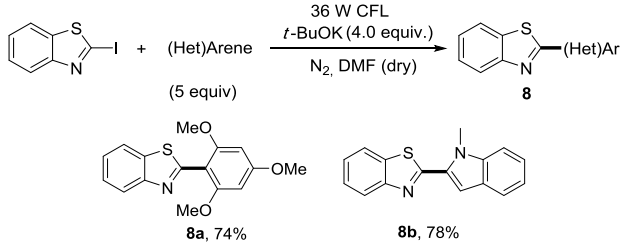
To demonstrate the practicality of this protocol, large scale reactions were conducted under otherwise identical conditions (Scheme 1). 10 g **1a** reacted with perfluorobutyl iodide (28.15 g) to give **3a** (17.57 g) in 91% yield (eq 3). In the mixture of **1a** (5 g, 36.99 mmol) with CBr_4 (13.49 g, 40.68 mmol) and *t*-BuONa (4 equiv) in DMF, product **4a** (6.05 g) was obtained in 76% yield (eq 4).

To gain insight into the reaction mechanism, a control experiment was conducted (Scheme 2). The main question is whether radical intermediates are involved in the reaction. Thus, 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), an efficient free radical scavenger, was introduced as an additive under the standard conditions.[9] As a result, compounds **3a** and **4a** were produced with almost same efficiency, suggesting that TEMPO has no effect on the reactions (eq. 5 and 6). Furthermore, we examined the reactions in the presence of a single electron transfer (SET) inhibitor, *p*-dinitrobenzene (*p*-DNB), and no yield decrease was observed. On the contrary, in the case of trihalogenative methylation reaction to form compounds **6** and **7**, the reactions were partly or completely quenched in the presence of TEMPO or *p*-DNB (eq 7, Scheme 2).

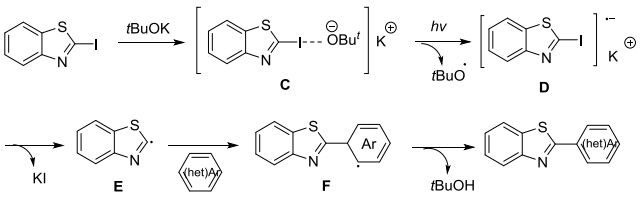
On the basis of all the experimental results, as well as literature report,[4e] an ionic mechanism was proposed, which involves the formation of *t*-butyl hypohalide from the metathesis of *t*BuONa and C_4F_9I[10] and subsequent halogen bond adduct **A** leading to the α C-H of **1a** more acidic.[11,12] Thus, hydrogen abstraction by C_4F_9Na becomes feasible, and carboanion **B** is generated. The final iodinated product **3a** is formed via halophilic attack (for example, via an three-membered iodonium ion intermediate),[13] along with the liberation of *t*-BuONa, to finish the catalytic cycle (Scheme 3).



Scheme 3. Proposed mechanism for the halogenation



Scheme 4. Visible light-mediated cross-coupling of halogenated heteroaryls



Scheme 5. Possible mechanism for the cross-coupling

Finally, the utility of the halogenated heterocycles was illustrated by performing visible-light mediated cross-coupling reaction, which is quite attractive in current organic synthetic chemistry.[14] In the presence of *t*-BuOK (4 equiv), the cross-coupling of 2-iodobenzothiazole with 1,3,5-trimethoxybenzene

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and *N*-methylindole was successful, giving the coupled products **8a** and **8b** in moderate yields. (Scheme 4). The possible mechanism for the metal-free cross-coupling reaction was given in Scheme 5. A halogen bond adduct **C** can be formed between sodium *t*-butoxide and 2-iodobenzothiazole. Under the action of visible light, single-electron-transfer occurs, yielding radical anion **D** with the liberation of *t*-BuO radical. C—I bond cleavage leads to persistent benzothiazole radical **E**,[15] which would add to (hetero)aromatics, giving carbon radical **F**. Hydrogen abstraction by *t*-BuO radical, affords the final C—C coupling products. The role of *t*-BuOK in the cross-coupling is a halogen bond acceptor as well as an electron donor.[16]

Conclusions

In conclusion, we have developed a novel method for the halogenation of an array of electron-deficient (hetero)arenes. The protocol exhibits broad scope and is efficient and practical. Among them, t-BuONa-catalyzed iodination by harnessing perfluorobutyl iodide as the iodination reagent was unprecedented. The utility of the halogenated products is demonstrated by visible light-mediated and metal-free cross-coupling reaction with (hetero)arenes.

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Conflicts of interest

The authors declare no competing financial interest.

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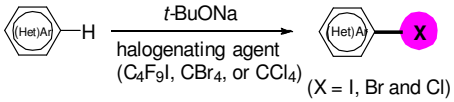

- broad scope
- high efficiency
- mild conditions
- gram scalable

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