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Organophosphine-free copper-catalyzed isothiocyanation of amines with sodium bromodifluoroacetate and sulfur†

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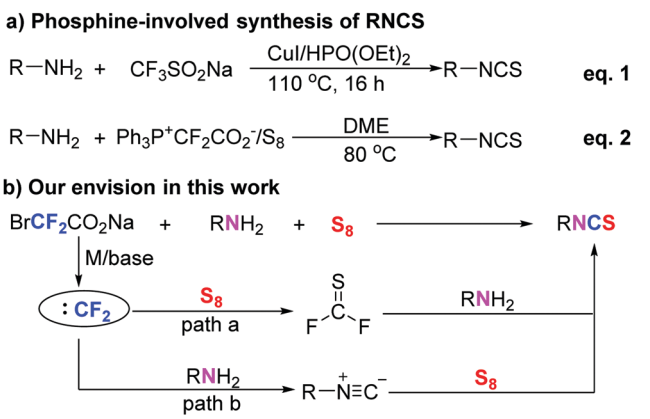
A copper-catalyzed isothiocyanation of amines with sodium bromodifluoroacetate and sulfur in the absence of organophosphine has been established. This approach represents a simple and efficient one-pot synthesis of isothiocyanates, and features excellent functional group tolerance and the use of a cheap, safe and odorless sulfur source. Moreover, this process could directly provide isothiocyanate analogous bioactive molecules, thiocarbonyl-containing pesticides and facile construction of benzoxazole and benzimidazole frames.

As a class of important organic molecules with excellent biological properties and chemical reactivity, isothiocyanates have wide applications in pharmaceuticals,[1] biochemistry[2] and organic synthesis.[3] For instance, many isothiocyanates exhibit anti-cancer, anti-inflammatory, anti-microbial and anti-platelet properties.[4] They are also widely used as a versatile synthetic building block for the construction of heterocycles,[5] food additives[6] and medicinal molecules.[7] Consequently, the synthetic strategies for isothiocyanates have gained increasing attention during the past few decades.[8] Traditionally, the highly flammable and volatile carbon disulfide and highly toxic thiophosgene are usually applied as isothiocyanation reagents for the synthesis of isothiocyanates from primary amines,[9] which violates the requirements of green chemistry. Therefore, the development of convenient, practical and environmentally friendly synthetic approaches for the synthesis of isothiocyanates is still highly desirable.[10] In 2017, Zheng and co-workers reported the synthesis of isothiocyanates using Langlois reagent in the presence of a copper catalyst and diethyl phosphonate (Scheme 1, eqn (1)).[11] Xiao's group also developed an isothiocyanation of primary amines with sulfur and (triphenylphosphonio)difluoroacetate,[12] which was prepared from triphenylphosphine and potassium bromodifluoroacetate[13] (eqn (2)). In consideration that sodium bromodifluoroacetate could directly afford difluorocarbene in the presence of a transition-metal and base,[14] we envisioned that the combination of the resulting difluorocarbene with sulfur might be utilized for the isothiocyanation of amines. As part of our continuous research interest in sulfur and fluorine chemistry,[15] herein we wish to report a copper-catalyzed three-component reaction for the one-pot synthesis of isothiocyanates in the absence of organophosphine (Scheme 1b).

We initiated our investigation by choosing β-naphthylamine **1a** as a model substrate for this isothiocyanation with $BrCF_2CO_2Na$ and S_8. The reaction was firstly carried out in the presence of 5 mol% CuCl and 2 equiv. Na_2CO_3 in CH_3CN at 100 °C. To our delight, the desired product **2a** was obtained in 22% yield (Table 1, entry 1). Then, various copper catalysts such as CuBr, CuI, $CuCl_2$ and $Cu(OTf)_2$ were screened (entries 2–5), and CuI afforded the best result with a 35% yield of **2a**. To further improve the yield, we then conducted this reaction by changing a variety of bases, including $NaHCO_3$, K_2CO_3, Cs_2CO_3, K_3PO_4, *t*-BuONa and organic base DABCO (1,4-diazabicyclo[2.2.2]octane) (entries 6–11). Among them, 2 equiv. of K_3PO_4 gave significantly enhanced reaction efficiency, and the product **2a** was isolated in 87% yield (entry 10). During the examination of the solvent



Scheme 1 Strategies towards the preparation of isothiocyanate.

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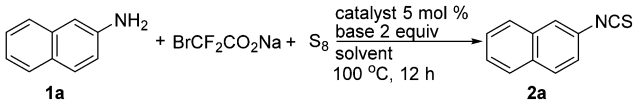
Table 1 Screening conditions[a]



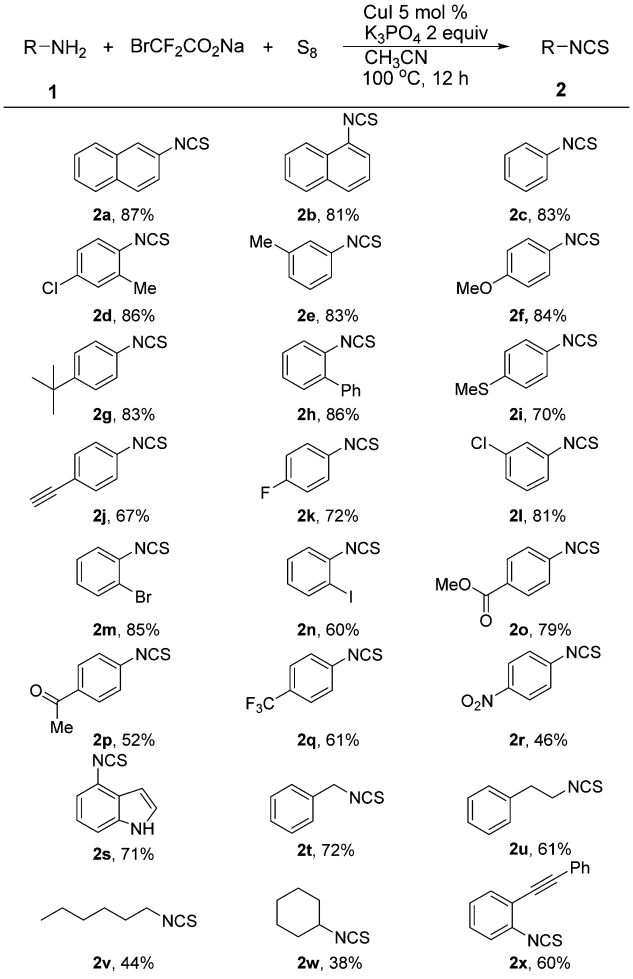
Entry	Catalyst	Base	Solvent	Yield[b] (%)
1	CuCl	Na_2CO_3	CH_3CN	22
2	CuBr	Na_2CO_3	CH_3CN	28
3	CuI	Na_2CO_3	CH_3CN	35
4	$CuCl_2$	Na_2CO_3	CH_3CN	20
5	$Cu(OTf)_2$	Na_2CO_3	CH_3CN	13
6	CuI	$NaHCO_3$	CH_3CN	49
7	CuI	K_2CO_3	CH_3CN	71
8	CuI	Cs_2CO_3	CH_3CN	34
9	CuI	K_3PO_4	CH_3CN	87
10	CuI	DABCO	CH_3CN	52
11	CuI	*t*-BuONa	CH_3CN	23
12	CuI	K_3PO_4	DMF	n.d.
13	CuI	K_3PO_4	DMSO	28
14	CuI	K_3PO_4	Toluene	n.d.
15	CuI	K_3PO_4	*n*-BuCN	Trace
16	—	K_3PO_4	CH_3CN	27
17[c]	CuI	K_3PO_4	CH_3CN	65
18[d]	CuI	K_3PO_4	CH_3CN	77
19[e]	CuI	K_3PO_4	CH_3CN	74

[a] Reaction conditions: **1a** (0.2 mmol), $BrCF_2CO_2Na$ (1.5 equiv.), S_8 (1.0 equiv.), catalyst (5 mol%), base (2 equiv.), solvent 2 mL at 100 °C for 12 h. [b] Isolated yields. [c] $BrCF_2CO_2Na$ (1.0 equiv.). [d] S_8 0.75 equiv. [e] At 80 °C.

effect, we found that DMSO only provided a 28% yield and the reaction nearly did not work in DMF, toluene and butyronitrile (entries 12–15). Consistent with our hypothesis, only 27% yield of the product was obtained when the reaction was performed in the absence of a copper catalyst (entry 16), which suggested that the copper probably acted as a promoter for the decomposition of $BrCF_2CO_2Na$ and also as a partner to stabilize the active difluorocarbene.[14a,d] When the loading of sodium bromodifluoroacetate or elemental sulfur was decreased, the yields of target product obviously dropped to 65% and 77%, respectively (entries 17 and 18). Similarly, a lower yield of 74% was observed when this isothiocyanation was conducted at 80 °C (entry 19).

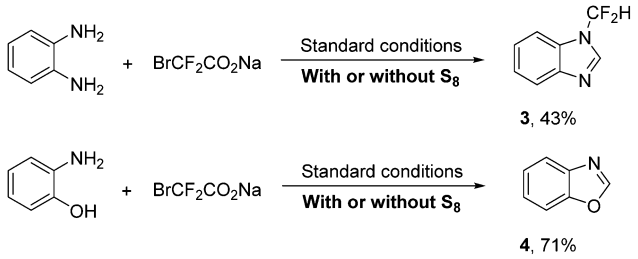
With the optimized conditions in hand, we explored the substrate scope of this isothiocyanation reaction and the results are displayed in Table 2. Both electron-rich and electron-poor aromatic amines could be tolerated well to afford aryl isothiocyanates in moderate-to-excellent yield. Anilines and naphthylamines provided **2a–2c** in 81–87% yields. Substituted anilines with different functional groups such as methyl, methoxy, *tert*-butyl, phenyl and methylthio were all suitable substrates to deliver the corresponding products **2d–2i** in 70–86% yields. Notably, 4-ethynylaniline bearing an active functional group underwent the isothiocyanation smoothly to give **2j** in 67% yield, and the ethynyl moiety remained unchanged during the reaction. Subsequently, the isothiocyanation was conducted under the standard conditions using halo-substituted anilines as substrates. The results showed that *para*-fluoro, *meta*-chloro, *ortho*-bromo, and *ortho*-iodine substituted anilines were all compatible and the corresponding halogenated isothiocyanates **2k–2n** were obtained in moderate to good yields. Especially for

Table 2 Scope of primary amines for one-pot isothiocyanation[a,b]



[a] Reaction conditions: **1a** (0.2 mmol), $BrCF_2CO_2Na$ (1.5 equiv.), S_8 (1.0 equiv.), CuI (5 mol%), K_3PO_4 (2 equiv.), CH_3CN 2 mL at 100 °C for 12 h. [b] Isolated yields.

bromide or iodide products **2m** and **2n**, they could provide potential handles for further modification in many reactions. To our delight, the reactions of anilines bearing electron-withdrawing groups, such as acetyl, methoxycarbonyl and trifluoromethyl, proceeded successfully under the standard conditions. Even the strong electron-withdrawing nitro group could afford 1-isothiocyanato-4-nitrobenzene **2r** in 46% yield. For heteroaryl amines, 4-aminoindole afforded product **2s** in 71% yield. As expected, the isothiocyanation of aliphatic primary amines also performed well under the standard conditions to give the corresponding products **2t–2w** in a yield of 38–72%. For example, phenylethyl isothiocyanate **2u**,[4h] an anticancer molecule, could be easily acquired in 61% yield through this three-component synthetic strategy. It is worth noting that *o*-alkynylaniline could be easily transformed to **2x** in 60% yield, which could be a useful building block in the synthesis of heterocyclic compounds. When *o*-phenylenediamine was used as the substrate, an interesting transformation was observed (Scheme 2). With or without S_8 under the optimized conditions, the reaction afforded 1-difluoromethyl benzoimidazole **3** in

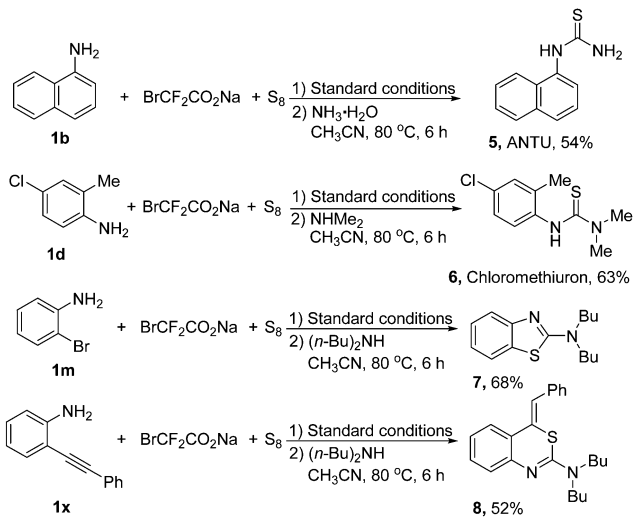


Scheme 2 Facile construction of benzoxazole and benzimidazole.

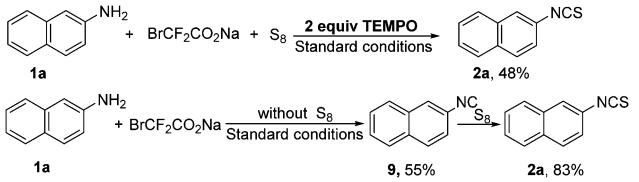
43% yield, which provided a new method for the synthesis of fluorinated benzoimidazoles. Similarly, benzoxazole **4** was achieved in 71% yield when *o*-hydroxyaniline was applied, affording a facile approach for the construction of benzoxazole scaffolds.

To demonstrate the significant applications of this protocol, two pesticides were directly synthesized from commercially available starting materials by this one-pot tandem process (Scheme 3). Rodenticide ANTU **5**[16] was isolated in 54% yield by adding aqueous ammonia in the reaction. Chloromethiuron **6**,[12] as an insecticide, could be directly obtained in a 63% isolated yield through the combination of this isothiocyanation of 4-chloro-2-methyl aniline **1d** and following addition with dimethylamine. Moreover, the isothiocyanation of *o*-bromoaniline **1m** followed by the attack of dibutylamine could give the corresponding benzothiazole **7** in 68% yield. Similarly, benzothiazine derivative **8**[15e] could be prepared in 52% yield through this one-pot synthetic strategy from the reaction of *o*-alkynylaniline **1x** with dibutylamine.

In order to support our original description of this organophosphine-free isothiocyanation, a series of control experiments have been conducted as shown in Scheme 4. Firstly, 2 equiv. TEMPO was added into the model reaction mixture under standard conditions, and the product **2a** was still isolated in 48% yield, indicating that this reaction might not involve a free radical pathway. Furthermore, when the reaction



Scheme 3 The synthetic applications of this isothiocyanation.



Scheme 4 Control experiments.

was carried out in the absence of elemental sulfur, 2-isocyanonaphthalene **9** could be detected (or isolated in 55% yield). Then, S_8 was added into the above reaction mixture, and the desired product **2a** was obtained in 83% yield. These results suggested that isocyanide might be a probable intermediate in the isothiocyanation.

Based on our experimental evidence and previous reports,[14,17] two pathways in the reaction mechanism previously proposed by us might be reasonable and compatible (Scheme 1b). Firstly, difluorocarbene is generated from the decomposition of sodium bromodifluoroacetate in the presence of copper and base, and immediately stabilized by the copper catalyst,[14d] then, directly combined with elemental sulfur to afford thiocarbonyl fluoride, which could be instantly trapped by primary amines to deliver isothiocyanate (Scheme 1, path a). Meanwhile, as a reactive species, difluorocarbene can also react with primary amines to give another intermediate isocyanide, which then undergoes addition with S_8 to provide the target product (Scheme 1, path b).

In summary, we have developed an organophosphine-free copper-catalyzed isothiocyanation from readily available starting materials under mild reaction conditions. A variety of primary amines underwent this reaction to give aryl or alkyl isothiocyanates in moderate to excellent yields. Importantly, as an operationally easy and simple procedure, this method provides a straightforward and efficient route to isothiocyanates, benzimidazole and benzoxazole, as well as some thiocarbonyl-containing pesticides, which potentially allows it to be applied in further synthetic applications.

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Conflicts of interest

There are no conflicts to declare.

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