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N-Difluoromethylthiophthalimide: A Shelf-Stable, Electrophilic Reagent for Difluoromethylthiolation

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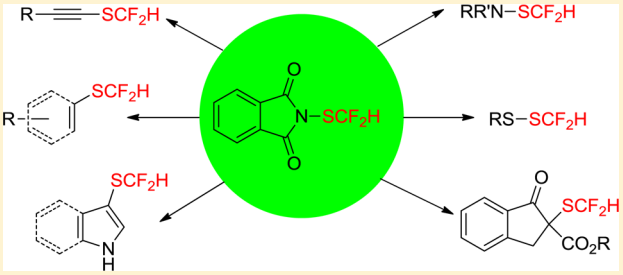
Supporting Information

ABSTRACT: A new, electrophilic difluoromethylthiolating reagent *N*-difluoromethylthiophthalimide **3** was developed. Reagent **3** can be readily synthesized in four steps from easily available starting materials phthalimide and $TMSCF_2H$. *N*-difluoromethylthiophthalimide **3** is a powerful electrophilic difluoromethylthiolating reagent that allows the difluoromethylthiolation of a wide range of nucleophiles including aryl/vinyl boronic acids, alkynes, amines, thiols, *β*-ketoesters, and oxindoles and electron-rich heteroarenes such as indole, pyrrole, 1*H*-pyrrolo[2,3-*b*]pyridine, imidazo[1,2-*a*]pyridine, aminothiazole, isoxazole, and pyrazole under mild conditions.



INTRODUCTION

Due to their intrinsic beneficial properties, fluorine and fluoroalkyl groups have been increasingly recognized and practiced by medicinal chemists as an important tool to improve drug's efficacy over the past three decades.[1] In particular, one of the fluoroalkyl groups, difluoromethylthio group ($-SCF_2H$) which is generally considered as a highly lipophilic weak hydrogen-bonding donor, is of great current interest.[2] Examples of drugs and agrochemicals bearing a difluoromethylthio unit include *β*-lactamase-resistant oxcephalosporin antibiotic Flomoxef sodium,[3] pesticide Pyriprole[4] and broad-spectrum paddy herbicide Pyrimisulfan[5] (Figure 1).

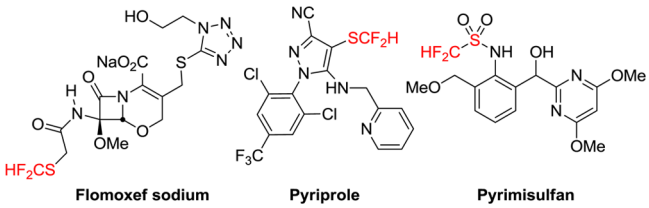


Figure 1. Drugs and agrochemicals containing a difluoromethylthio group.

One general and routinely used approach for the preparation of difluoromethylthiolated compounds typically involves the nucleophilic attack of the an *in situ* formed difluoromethyl carbene intermediate[6] by an appropriate thiolate. For example, formation of difluoromethylthioether using chlorodifluoromethane HCF_2Cl (Freon 22) as a difluoromethyl carbene source has been well-developed.[7] Yet, HCF_2Cl is a ozone-depleting gas, thus its future usage for the difluoromethylthioether formation is rather limitted. In this respect, a number of different difluoromethyl carbene precursors such as $BrCF_2P(O)(OEt)_2$, $ClCF_2CO_2Na$, $TMSCF_2Br$, HCF_2OTf, $PhS(O)(NTs)CF_2H$, etc.[8] have been developed. A less common approach for the preparation of difluoromethylthiolated compounds is the reaction of thiolate with either an electrophilic difluoromethylated reagent[9] or a reagent that can easily generate a difluoromethyl radical,[10] as reported by Prakash, Hu, and Baran, respectively. Nevertheless, both approaches were conducted under strong basic conditions, and many functional groups are not compatible. In addition, both approaches require the preformation of thiols that might be a problem for more complicated molecules. Very recently, Goossen and co-workers reported that difluoromethylthioethers could be accessed via a copper-mediated difluoromethylation of organothiocyanates, which represents a major step-forward.[11] Shortly after, we reported a copper-mediated Sandermeyer-type difluoromethylthiolation of aryl and heteroaryl diazo compounds under mild conditions.[12] However, the scope of both reactions was limited to the substrates that could form RSCN or $ArN_2^+BF_4^-$. Many other substrates including amines, thiols, alkynes, *β*-ketoesters, or oxindoles could not be difluoromethylthiolated via these methods.

Thus, new approaches that could easily form the difluoromethylthioethers are still urgently needed and remain a significant challenge. Inspired by the recent development of powerful electrophilic trifluoromethylthiolating reagents,[13] especially the electrophilic trifluoromethylthiolating reagent *N*-trifluoromethylthiophthalimide which was initially developed by Munavalli and was further studied recently by Rueping and us,[14] we envisiged that if an analogous electrophilic difluoromethylthiolating reagent could be invented, a strategically new

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approach for the introduction of the difluoromethylthio group into small molecules would be created. This new approach could circumvent the harsh conditions and the requirement of preformation of thiols of the classical difluoromethyl carbene stratergy (Figure 2). Such a reagent would be valuable for the

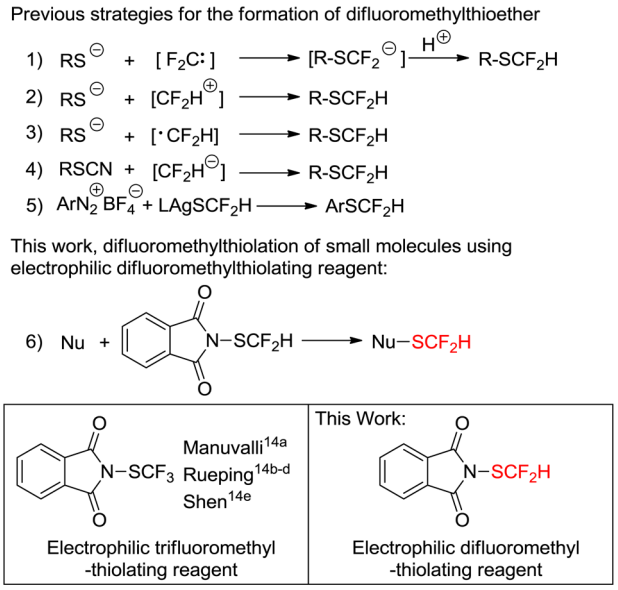

Figure 2. Strategies for the formation of difluoromethylthioether.

medicinal chemists since the difluoromethylthio group could be readily incorporated at the late-stage of the drug development process. Herein, we report the design and synthesis of *N*-difluoromethylthiophthalimide **3**, which can be efficiently synthesized from phthalimide in four-steps in high yields. The reactivity of compound **3** was demonstrated by difluoromethylthiolation of a wide range of nucleophiles including aryl/vinyl boronic acids, alkynes, amines, thiols, *β*-ketoesters, oxindoles, and electron-rich heteroarenes such as indole, pyrrole, 1*H*-pyrrolo[2,3-*b*]pyridine, imidazo[1,2-*a*]pyridine, aminothiazole, isoxazole, and pyrazole under mild conditions. To the best of our knowledge, reagent **3** represents the first shelf-stable electrophilic difluoromethylthiolating reagent.[15]

RESULTS AND DISCUSSION

Preparation of *N*-Difluoromethylthiophthalimide 3. Our efforts for the synthesis of difluoromethylthiophthalimide **3** began with the search for reaction conditions to assemble *N*-chlorophthalimide, sulfur, and $TMSCF_2H$ in the presence of different activators in different solvents. We expect that the *in situ* formed difluoromethyl anion could be trapped by sulfur to form difluoromethylthio anion, subsequent nucleophilic substitution with *N*-chlorophthalimide leading to the generation of reagent **3**. However, the formation of reagent **3** was not observed when various activators such as KO^{t}Bu, NaO^{t}Bu, CsF, AgF, and TBAF were used.[16] Instead, difluoromethane (CF_2H_2) was observed as the main product as determined by ^{19}F NMR spectroscopy. We then shifted our efforts for the synthesis of reagent **3** to the difluoromethylation of thoilated phthalimide substrates such as di(1-phthalimidy1)disulfane **1**[17] and *N*-(chlorosulfenyl)phthalimide **2**[18] that can be readily synthesized from phthalimide in excellent yields. Interestingly, reactions of compound **1** or **2** with $TMSCF_2H$ in the presence of activators such as NaO^{t}Bu, CsF, or AgF in solvents such as THF, CH_2Cl_2, CH_3CN, or DMF were messy. In contrast, reaction of compound **2** with [(SIPr)Ag(CF_2H)] (SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene),[19] a stable difluoromethylsilver complex discovered in our laboratory recently, formed cleanly difluoromethylthiophthalimide **3** in 81−83% yields when the reaction was conducted in solvents such as CH_2Cl_2, CH_3CN, or toluene. The reaction could be easily scaled up to 175 mmol to give reagent **3** in 66% yield (Figure 3). Notably, the silver product [(SIPr)AgCl] was

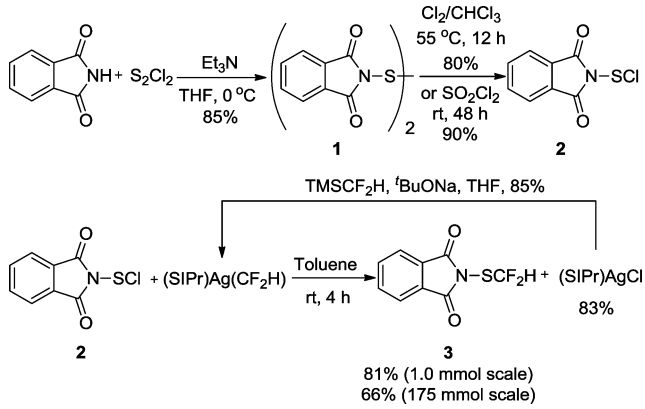

Figure 3. Preparation of *N*-difluoromethylthiophthalimide **3** and recovery of [(SIPr)AgCl].

recycled in 83% yield, which was reused for the preparation of [(SIPr)Ag(CF_2H)]. Even after three cycles, roughly half of [(SIPr)AgCl] still could be recovered.

Difluoromethylthiophthalimide **3** was fully characterized by ^{1}H, ^{13}C, ^{19}F NMR spectroscopies. The structure of compound **3** was unambiguously confirmed by X-ray analysis of its single crystals (Figure 4). Compound **3**, a white crystalline solid with

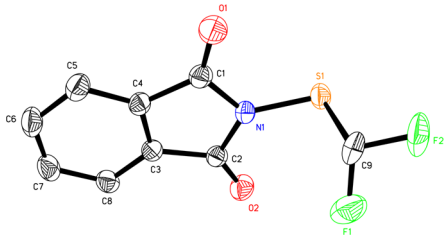

Figure 4. ORTEP diagrams of *N*-difluoromethylthiophthalimide **3**. Ellipsoids are shown at the 50% level.

a melting point 115−116 °C, is not air and light sensitive. No detectable decomposition was observed after more than a 2 month storage on a shelf at ambient temperature. Compound **3** is stable in solvents such as $ClCH_2CH_2Cl$, toluene, THF, acetone, and CH_3CN at 100 °C for at least 12 h as determined by ^{19}F NMR spectroscopy. Compound **3** is less stable in solvents such as DMF or methanol. It was completely decomposed after 5 min in methanol at room temperature and 12 h in DMF at 80 °C as determined by ^{19}F NMR spectroscopy.

Reaction of *N*-Difluoromethylthiophthalimide 3 with Electron-Rich Heteroarenes. With this new reagent in-hand, we first explored its reactivity with electron-rich arenes since Friedel−Crafts-type difluoromethylthiolation of electron-rich arenes represents a straightforward method for the introduction of difluoromethylthio group into arenes. It was found that

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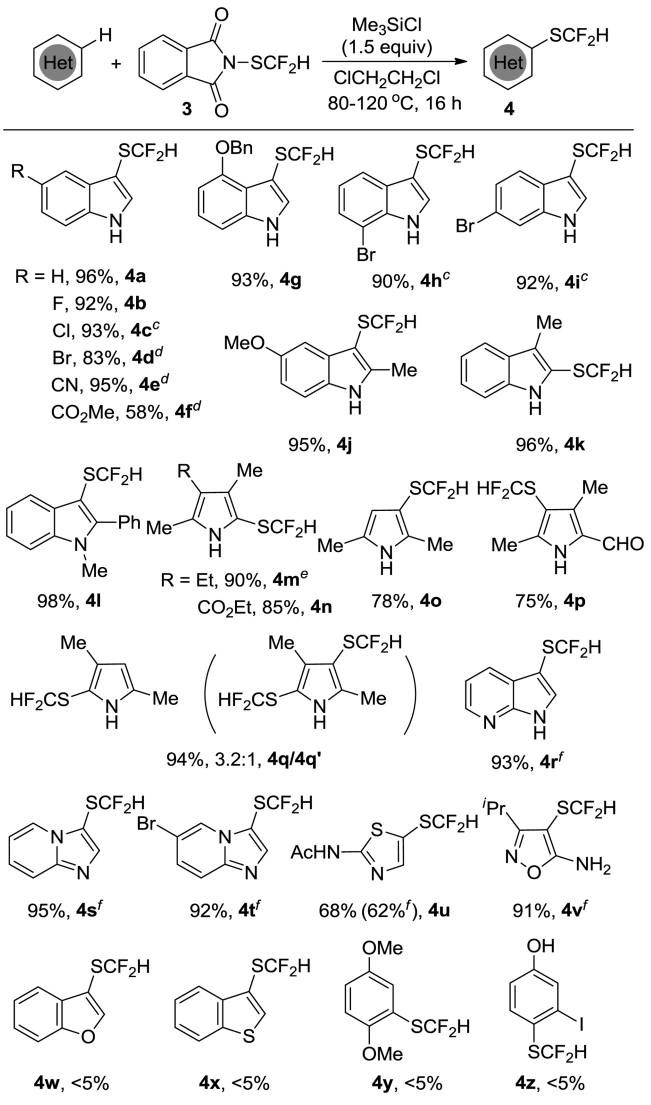
reaction of indole with reagent **3** in the presence of 1.5 equiv of Me_3SiCl[20] occurred smoothly after 16 h at 80 °C to give 3-difluoromethylthiolated indole in quantitative yield.[21] Reactions in the presence of other Lewis acid such as LiCl, $MgCl_2$, $MgBr_2$, $AlCl_3$, $ZnCl_2$, $TiCl_4$, or $BF_3{\cdot}OEt_2$ were much less effective, while reaction using LiBr as the activator occurred in high yield. Likewise, Brønsted acids such as triflic acid, *p*-toluenesulfonic acid, or camphorsulfonic acid were ineffective activators as well (see Supporting Information Table S1 for details).

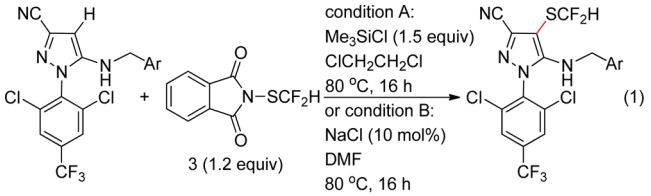
In general, reactions of a variety of other indoles with electron-donating or withdrawing groups occurred in good to excellent yields under slightly modified conditions (Scheme 1). Reactions of indoles with electron-rich substituted groups were much faster than those of indoles with electron-withdrawing groups. Reactions of indoles with electron-withdrawing groups were conducted at 100−120 °C for full conversion. Indoles with functional groups such as chloride, bromide, fluoride, aldehyde, ester, and cyano group reacted to generate the corresponding difluoromethylthiolated indoles in high yields (Scheme 1, **4b−f**, **4h−i**). Reaction of 3-methyl-indole formed the corresponding difluoromethylthiolated compounds in 96% yield (Scheme 1, **4k**). *N*-Methylindole also reacted under the optimized conditions to give the corresponding product in 98% yield (Scheme 1, **4l**). Similarly, reaction of pyrroles with different substituted groups occurred to give the corresponding difluoromethylthiolated pyrroles in 75−94% yield (Scheme 1, **4m−q**). Not only indoles and pyrroles but also other electron-rich heteroarenes such as 1*H*-pyrrolo[2,3-*b*]pyridine, imidazo-[1,2-*a*]pyridine, aminothiazole, and isoxazole reacted with *N*-difluoromethylthiophthalimide **3** in the presence of 1.5 equiv of Me_3SiCl or catalytic amount of NaCl[22] to give the corresponding difluoromethylthiolated heteroarenes in 62−95% yields (Scheme 1, **4r−v**). However, when other electron-rich heteroarenes or arenes such as benzothiophene, benzofuran, 1−4-dimethoxybenzene, or 3-iodophenol were subjected to these conditions, formation of the desired difluoromethylthiolated products was observed in <5% yields as determined by ^{19}F NMR spectroscopy (Scheme 1, **4w−z**).

Scheme 1. Me_3SiCl-Mediated Difluoromethylthiolation of Electron-Rich Heteroarenes[a,b]



[a]Reaction conditions: heteroarene (0.5 mmol), reagent **3** (0.60 mmol), Me_3SiCl (0.75 mmol) in 3.0 mL of 1,2-dichloroethane 80 °C for 16 h. [b]Isolated yields. [c]Reaction was conducted at 100 °C for 16 h. [d]Reaction was conducted at 120 °C for 24 h. [e]Reaction was conducted at room temperature for 24 h. [f]Reaction conditions: heteroarene (0.70 mmol), reagent **3** (0.84 mmol), NaCl (0.07 mmol) in DMF (4.0 mL) at 80 °C for 16 h.

Pleasingly, it was discovered that conditions for Friedel−Crafts-type difluoromethylthiolation of electron-rich heteroarenes were also able to difluoromethylthiolate the Pyriprole precursor. Under the standard conditions, Pyriprole **4aa**[15b] was generated in 93% yield (eq 1). Furthermore, the same reaction could be achieved when the reaction was conducted in the presence of 10 mol % of NaCl as the catalyst in DMF.[22] Likewise, a furyl-substituted analog of Pyriprole **4ab** could also be synthesized in 94% yield under the similar reaction conditions (eq 1).



Copper-Catalyzed Difluoromethylthiolation of Aryl/Vinyl Boronic Acids with *N*-Difluoromethylthiophthalimide 3. Although reagent **3** is highly reactive for Friedel−Crafts-type difluoromethylthiolation of electron-rich heteroarenes, reactions of electron-rich or poor arenes with reagent **3** under the same conditions were much less effective. To overcome the limitation of the Lewis acid-mediated electrophilic difluoromethylthiolation reaction, we seek to use easily available, bench stable aryl boronic acids to couple with reagent **3** in the presence of a copper catalyst for the formation of difluoromethylthiolated arenes. A careful screening of the reaction conditions for the copper-catalyzed difluoromethylthiolation of biphenyl boronic acid revealed that the base was crucial for the formation of the difluoromethylthiolated biphenyl. High yields were observed when KF, Li_2CO_3, or Na_2CO_3 was used as the base, whereas no product was formed when slightly stronger base K_2CO_3 or Cs_2CO_3 was used (Scheme 2).

Scheme 3 summarized the scope of the copper-catalyzed difluoromethylthiolation of aryl and vinyl boronic acids under

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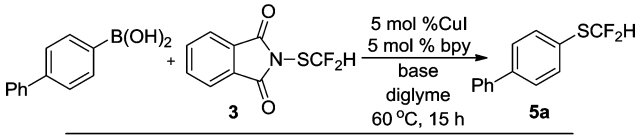
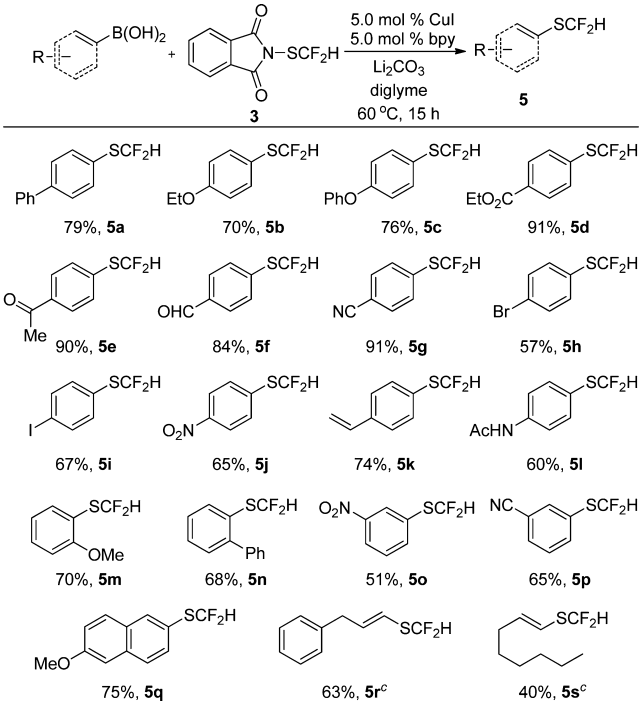
Scheme 2. Effects of Bases on Copper-Catalyzed Difluoromethylthiolation of Biphenylboronic Acid[a,b]



entry	base	yield (%)
1	KF	86
2	K_2CO_3	-
3	K_3PO_4	54
4	Li_2CO_3	89
5	$LiOH·H_2O$	30
6	Cs_2CO_3	-
7	Na_2CO_3	84

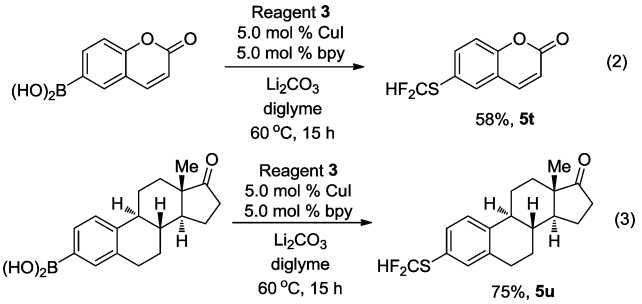
[a]Reaction conditions: biphenyl boronic acid (0.1 mmol), reagent **3** (0.12 mmol), CuI (0.005 mmol), bpy (0.005 mmol), base (0.05 mmol) in diglyme (1.0 mL) at 60 °C for 15 h. [b]Yields were determined by ^{19}F NMR spectroscopy with $PhCF_3$ as the internal standard.

Scheme 3. Scope for Copper-Catalyzed Difluoromethylthiolation of Aryl and Vinyl Boronic Acids.[a,b]



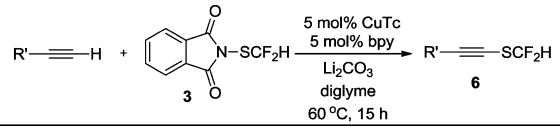
[a]Reaction conditions: aryl or vinyl boronic acid (0.7 mmol), reagent **3** (0.84 mmol), Li_2CO_3 (0.35 mmol), CuI (0.035 mmol), bpy (0.035 mmol) in diglyme (5.0 mL) at 60 °C for 15 h. [b]Isolated yields. [c]The reactions were conducted at 80 °C for 20 h.

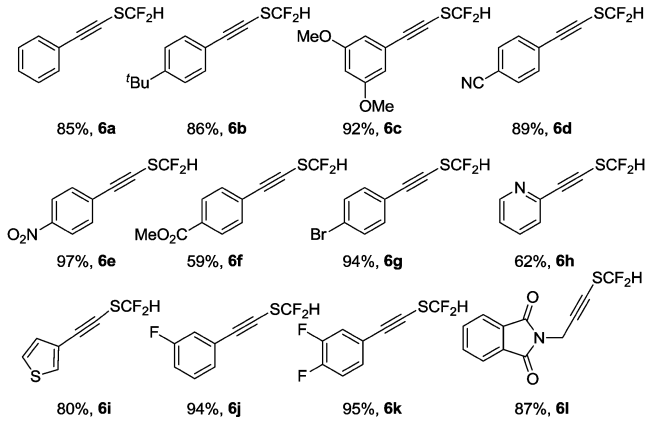
the reaction conditions described above. In general, in the presence of a combination of 5.0 mol % of CuI and 5.0 mol % of bipyridine (bpy), a variety of aryl boronic acids with ortho-, meta-, or para-substituents were able to couple with reagent **3** to give the difluoromethylthiolated arenes in good to excellent yields (Scheme 3, **5a**–**q**). Likewise, alkenyl boronic acids also converted effectively into difluoromethylthio-substituted olefins in reasonable yields (Scheme 3, **5r**–**s**). Challenging functional groups were compatible with the reaction conditions. Reactions of aryl boronic acids with functional groups such as enolizable ketone, ester, aldehyde, amide, olefin, cyano, bromo, iodo, and nitro group occurred in good yields (Scheme 3, **5d**–**l**). Notably, two difluoromethylthiolated analogs of natural products were generated from their corresponding boryl derivatives in 58% and 75% yields, respectively (eqs 2–3). Thus, the copper-catalyzed method for the formation of difluoromethylthiolated arenes and alkenes provides a complementary method for the introduction of the difluoromethylthio group into the medicinally important arene subunit.



Copper-Catalyzed Difluoromethylthiolation of Alkynes With *N*-Difluoromethylthiophthalimide 3. To further expand the scope of reagent **3**, we studied the copper-catalyzed difluoromethylthiolation of alkynes. To our delight, after initial optimization of the reaction conditions, we obtained phenylacetynyldifluoromethylthioether (**6a**) in 85% yield after 15 h at 60 °C in diglyme when a combination of 5.0 mol % copper(I)-thiophen-2-carboxylate (CuTc) and 5.0 mol % 2,2′-bipyridine (bpy) was used as the catalyst. Various alkynes could be readily converted into the difluoromethylthiolated alkynes in high yields, as summarized in Scheme 4.

Scheme 4. Scope for Copper-Catalyzed Difluoromethylthiolation of Alkynes[a,b]





[a]Reaction conditions: alkyne (0.6 mmol), reagent **3** (0.78 mmol), Li_2CO_3 (0.30 mmol), CuTc (5.0 mol %), bpy (5.0 mol %) in diglyme (4.0 mL) at 60 °C for 15 h. [b]Isolated yields.

In general, reactions of both electron-rich and electron-poor aryl-substituted alkynes with reagent **3** occurred in high yields. In addition, heteroaryl alkynes such as 2-ethynylpyridine and 3-ethynylthiophene were also converted to the corresponding difluoromethylthiolated alkynes in 62% and 80% yields, respectively (Scheme 4, entries **6h**–**i**). Because a weak base Li_2CO_3

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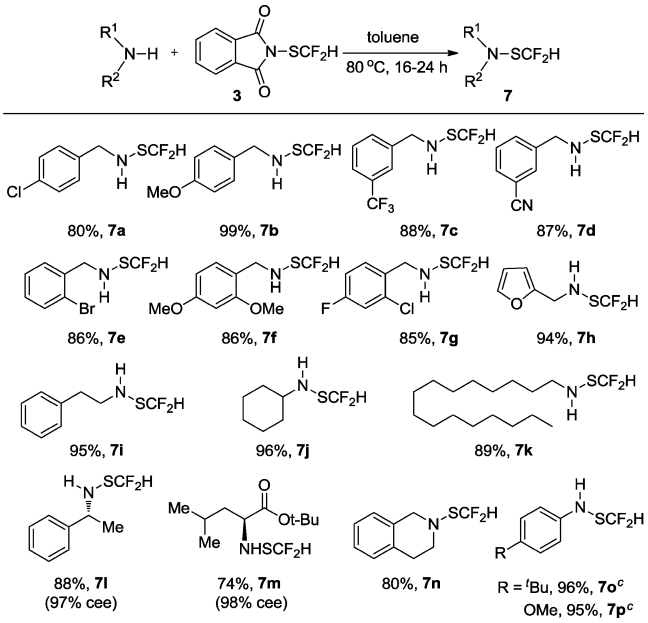
was used as the base, the reaction was compatible with a variety of functional groups such as cyano, nitro, ester, bromo, fluoro, and amide (Scheme 4, entries **6d–g**, **6j–l**). These compounds could not be accessed by the classic method via a difluoromethyl carbene intermediate.

Reaction of Amines with *N*-Difluoromethylthiophthalimide 3. With the successful development of methods for the formation of difluoromethylthiolated arenes, heteroarenes, and alkynes, we next sought to investigate the nucleophilic difluoromethylthiolation of amines since the fluoroalkylthiolated amino group is also considered as an important structural moiety with increased lipophilicity.[23] Reactions of aliphatic amines with reagent **3** occurred smoothly at 80 °C after 16–24 h to generate the corresponding difluoromethylthiolated amines in high yields, as summarized in Scheme 5.

Scheme 5. Scope for Difluoromethylthiolation of Amines with Reagent 3[a,b]

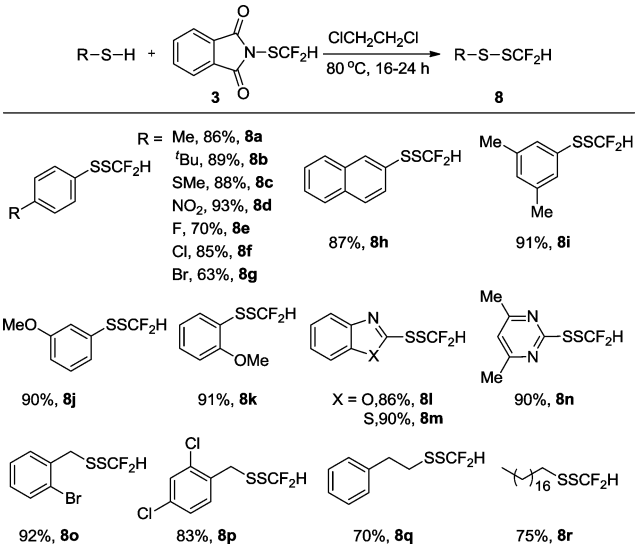


[a]Reaction conditions: amines (0.7 mmol), reagent **3** (1.05 mmol) in toluene (4.0 mL) at 80 °C for 16–24 h. [b]Isolated yields. [c]Reaction was conducted at 120 °C for 16 h.

In general, primary alkyl amines reacted with reagent **3** to generate difluoromethylthiolated amines in excellent yields (Scheme 5, **7a–k**). Reaction of a secondary alkylamine 1,2,3,4-tetrahydroisoquinoline also occurred in high yield (Scheme 5, **7n**). Notably, optically active amines such as (*R*)-1-phenylethanamine or α-amino ester were readily converted into the corresponding difluoromethylthiolated amines in 88% and 74% yields, respectively, without erosion of the optical purity (Scheme 5, **7l–m**). Reaction of electron-rich aniline derivatives such as 4-*tert*-butylaniline and 4-methoxyaniline occurred smoothly to give the difluoromethylthiolated anilines in 96% and 95% yields, respectively (Scheme 5, **7o–p**), when the reactions were conducted at 120 °C for 16 h. Under the same reaction conditions, aniline derivatives with electron-withdrawing group such as 4-nitroaniline occurred in <5% yield.

Reaction of Thiols with *N*-Difluoromethylthiophthalimide 3. Previously, we have established that thiols were able to be trifluoromethylthiolated to form trifluoromethyl substituted disulfides when thiols were treated with an electrophilic trifluoromethylthiolating reagent in the presence of triethylamine.[13c] To probe if difluoromethyl substituted disulfides could similarly be generated, we studied the reaction of thiols with reagent **3**. It was found that heating of a mixture of 4-methylbenzenethiol with 1.5 equiv of reagent **3** occurred smoothly at 80 °C after 16 h to give 1-(difluoromethyl)-2-(*p*-tolyl)disulfane **8a** in 86% yield (Scheme 6, **8a**). Likewise, a

Scheme 6. Scope for Difluoromethylthiolation of Thiols with Reagent 3[a,b]



[a]Reaction conditions: thiols (0.7 mmol), reagent **3** (1.05 mmol) in 1,2-dichloroethane (4.0 mL) at 80 °C for 16–24 h. [b]Isolated yields.

variety of electron-rich and electron-poor arylthiols were subjected to the reaction conditions to give the corresponding difluoromethylated disulfides in good yields (Scheme 6, **8a–k**). Heteroaryl thiols also reacted with reagent **3** in excellent yields (Scheme 6, **8l–n**). In addition, reactions of various alkylthiols with reagent **3** occurred smoothly to afford the difluoromethyl substituted disulfides in high yields (Scheme 6, **8o–r**).

Reaction of β-Ketoesters and 2-Oxindoles with *N*-Difluoromethylthiophthalimide 3. To further expand the scope and utility of reagent **3**, we studied the reaction of reagent **3** with soft nucleophiles such as β-ketoesters and 2-oxindoles. After a quick screening of the reaction conditions, it was discovered that reaction of methyl 6-methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate with reagent **3** in CH_2Cl_2 occurred smoothly at room temperature to afford the desired difluoromethylthiolated product in 96% yield when K_2CO_3 was used as the base. As summarized in Scheme 7, under these reaction conditions, reactions of various β-ketoesters derived from indanone or tetralone with reagent **3** gave the corresponding difluoromethylthiolated products in good to excellent yields (Scheme 7, **8a–j**). Likewise, *N*-Boc-2-substituted-oxindoles were also difluoromethylthiolated in excellent yields (Scheme 7, **8k–l**).

CONCLUSION

In summary, a new electrophilic reagent *N*-difluoromethylthiophthalimide for direct difluoromethylthiolation has been developed. Reagent **3** can be efficiently synthesized in four steps from cheap commodity chemical phthalimide. In the presence of Lewis acid Me_3SiCl, reagent **3** was able to efficiently

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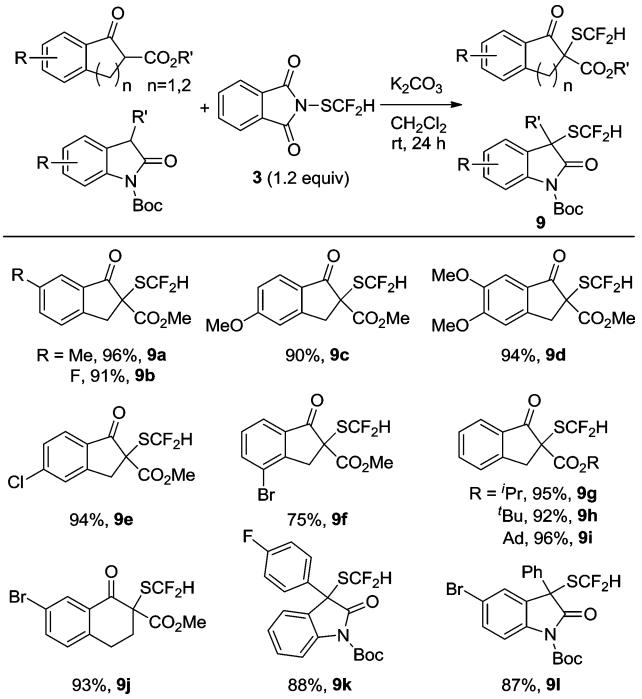
Scheme 7. Scope for Difluoromethylthiolation of β-Ketoesters and 2-Oxindoles with Reagent 3[a,b]



[a]Reaction conditions: β-ketoester or 2-oxindole (0.7 mmol), reagent **3** (0.84 mmol), K_2CO_3 (0.77 mmol) in dichloromethane (4.0 mL) at room temperature for 24 h. [b]Isolated yields.

difluoromethylthiolate indoles, pyrroles, and other electron-rich heteroarenes such as 1*H*-pyrrolo[2,3-*b*]pyridine, imidazo[1,2-*a*]-pyridine, aminothiazole, and isoxazole effectively. In addition, an efficient procedure for direct difluoromethylthiolation of Pyriprole precursor was developed to afford pesticide Pyriprole in high yield. Likewise, in the presence of a copper catalyst, functionalized aryl/vinyl boronic acids and alkynes were able to couple with reagent **3** to generate difluoromethylthiolated arenes and alkynes in good to excellent yields. Furthermore, general nucleophiles such as amines, thiols, β-ketoesters, and oxindoles reacted with reagent **3** smoothly in the absence of any transition-metal catalyst to afford the corresponding difluoromethylthiolated compounds in high yields. The excellent functional group tolerance in these reactions underlines the great potential of reagent **3** as a general reagent for the preparation of more complicated, densely functionalized drug-like molecules. Expanding the scopes of this reagent is underway and will be reported in the near future.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of *N*-(Chlorosulfenyl)-phthalimide 2. Phthalimide (14.7 g, 100 mmol) was dissolved in THF (300 mL) and triethylamine (16.7 mL, 120 mmol). The mixture was cooled in a NaCl/ice bath, and then sulfur monochloride (4.0 mL, 50 mmol) was added dropwise. The mixture was stirred for 2 h and then quenched with H_2O (300 mL). The resulting precipitate was filtered and washed with diethyl ether. Crystallization from $CHCl_3$:MeOH (2:1, v:v) yielded di(1-phthalimidy1)disulfane as a white solid (15.1 g, 85%).

Di(1-phthalimidy1)disulfane (25 g, 70 mmol) was suspended in $CHCl_3$ (200 mL). The reaction was heated at 55 °C, and Cl_2 gas was bubbled for 12 h. Nitrogen was bubbled through the solution to remove the residue Cl_2, and the solvent was evaporated *in vacuo*. The residue was recrystallized from CCl_4 to give *N*-(chlorosulfenyl)-phthalimide as a yellow solid (24 g, 80%).

Alternatively, to a solution of di(1-phthalimidy1)disulfane (25 g, 70 mmol) and 700 mL of HPLC-grade CH_2Cl_2 were added anhydrous pyridine (3.0 mL) and sulfuryl chloride (56.2 g, 33.8 mL, 420 mmol) via a dropping funnel at room temperature. The yellow mixture was stirred at room temperature for 2 days. The solvent and excess sulfuryl chloride were removed under vacuum to give *N*-(chlorosulfenyl)-phthalimide as a yellow solid (27 g, 90%).[24]

General Procedure for the Preparation of *N*-(Difluoromethylthio)-phthalimide 3. To a mixture of *N*-(chlorosulfenyl)phthalimide (5.0 g, 23.6 mmol) and [(SIPr)Ag(CF_2H)] (13.0 g, 23.6 mmol) in a flask was added anhydrous toluene (50.0 mL) under argon atmosphere. The mixture was stirred at room temperature for 4 h and then filtered through a funnel. Dichloromethane (50.0 mL) and petroleum ether (100 mL) were added to the residue. The undissolved [(SIPr)AgCl] (9.0 g, 85%) was filtered, which was recycled to be used for the preparation of [(SIPr)Ag(CF_2H)]. The solvent in the filtrate was evaporated *in vacuo*, and the residue was purified by flash chromatography on silica gel to give *N*-(difluoromethylthio)phthalimide **3** as a white solid (3.6 g, 67%).

General Procedure for Difluoromethylthiolation of Heteroarenes with *N*-(Difluoromethylthio)phthalimide 3. To a 25 mL Schlenk tube charged with heteroarenes (0.5 mmol) and *N*-(difluoromethylthio)phthalimide **3** (0.6 mmol) in $ClCH_2CH_2Cl$ (3.0 mL) was added Me_3SiCl (0.75 mmol). The mixture was stirred at 80−120 °C for 16 h. The solvent was removed under vacuum, and the residue was purified by flask column chromatography to give difluoromethylthiolated heteroarenes.

General Procedure for Copper-Catalyzed Difluoromethylthiolation of Aryl/Vinyl Boronic Acids with *N*-(difluoromethylthio)-phthalimide 3. Aryl boronic acids or vinyl boronic acids (0.7 mmol), *N*-(difluoromethylthio)phthalimide **3** (193 mg, 0.84 mmol), Li_2CO_3 (25.9 mg, 0.35 mmol), CuI (6.7 mg, 0.035 mmol), and 2,2′-bipyridine (5.5 mg, 0.035 mmol) were placed into an oven-dried Schlenk tube that was equipped with a stirring bar under argon. Freshly distilled diglyme (4.0 mL) was added, and the reaction was stirred at 60 °C for 15 h. Distilled water (25.0 mL) and Et_2O (50.0 mL) were added, and the organic phase was separated. The aqueous phase was extracted with Et_2O (3 × 15 mL), and the combined organic layer was washed with distilled water (50.0 mL) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel to give the difluoromethylthiolated arene or alkene.

General Procedure for Copper-Catalyzed Difluoromethylthiolation of Alkyne with *N*-(Difluoromethylthio)phthalimide 3. Alkyne (0.6 mmol), *N*-(difluoromethylthio)phthalimide **3** (178.8 mg, 0.78 mmol), Li_2CO_3 (22.2 mg, 0.30 mmol), CuTc (5.8 mg, 0.030 mmol), and 2,2′-bipyridine (4.7 mg, 0.030 mmol) were placed into an oven-dried Schlenk tube that was equipped with a stirring bar under argon. Freshly distilled diglyme (3.0 mL) was added, and the reaction was stirred at 60 °C for 15 h. Distilled water (25.0 mL) and Et_2O (50.0 mL) were added, and the organic phase was separated. The aqueous phase was extracted with Et_2O (3 × 15 mL), and the combined organic layer was washed with distilled water (50.0 mL) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel to give the difluoromethylthiolated alkynes.

General Procedure for Difluoromethylthiolation of Amines with *N*-(Difluoromethylthio)phthalimide 3. A 25 mL Schlenk tube was charged with amines (0.7 mmol), and *N*-(difluoromethylthio) phthalimide **3** (1.05 mmol) was added to toluene (4.0 mL). The mixture was stirred at 80 °C for 16−24 h. The solvent was removed under vacuum, and the residue was purified by flask column chromatography to give difluoromethylthiolated amines.

General procedure for Difluoromethylthiolation of Thiols with *N*-(Difluoromethylthio)phthalimide 3. To a 25 mL Schlenk tube charged with thiols (0.7 mmol) and *N*-(difluoromethylthio) phthalimide **3** (1.05 mmol) was added 1,2-dichloroethane (4.0 mL). The mixture was stirred at 80 °C for 16−24 h. The solvent was removed under vacuum, and the residue was purified by flask column chromatography to give difluoromethylthiolated thiols.

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General procedure for Difluoromethylthiolation of β-Ketoesters or Oxindoles with *N*-(Difluoromethylthio)phthalimide 3. To a 25 mL Schlenk tube charged with β-ketoesters or oxindoles (0.7 mmol), K_2CO_3 (0.77 mmol), and *N*-(difluoromethylthio)phthalimide **3** (0.84 mmol) was added dichloromethane (4.0 mL). The mixture was stirred at room temperature for 24 h. The solvent was removed under vacuum, and the residue was purified by flask column chromatography to give difluoromethylthiolated β-ketoesters or oxindoles.

■ ASSOCIATED CONTENT

Supporting Information

Synthesis, analytic data, NMR data and X-ray diffraction data of compounds **1**-**9**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b03170.

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Notes

The authors declare no competing financial interest.

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(21) A new species with a chemical shift at −97.2 ppm in ^{19}F NMR spectroscopy was formed in 15% yield after 6 h at 80 °C for the reaction of *N*-difluoromethylthiophthalimide **3** with Me_3SiCl in 1,2-dichloroethane. Addition of 1.0 equiv of indole into this mixture at room temperature for 0.5 h resulted in the disappearance of the new species and the formation of 3-difluoromethylthioindole in 15% yield. This experiment indicated that the new species is an active intermediate for the difluoromethylthiolation of indole in the presence of Me_3SiCl. We suspected that the active intermediate is HCF_2SCl. However, GC/MS studies of the reaction mixture did not support the formation of such a compound. More experiment is clearly needed to support the formation of HCF_2SCl.

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